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Statistical Analysis Plan

Chiesi Farmaceutici S.p.A.

Protocol: CCD-01535BA0-01

A 12-week, multicenter, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® 100/6µg NEXThaler®, 2 inhalations b.i.d., versus Foster® 100/6µg pMDI, 2 puffs b.i.d., in patients with controlled asthma

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Contents

List of Abbreviations

ACQ	Asthma Control Questionnaire
ADR	Adverse Drug Reaction
ADaM	Analysis Data Model
AE	Adverse Event
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BDP	Beclometasone dipropionate
BID	Bis In Die (twice a day)
BMI	Body Mass Index
Ca	Calcium
CAT	COPD Assessment Test
CI	Confidence Interval
Cl	Chlorine
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DPI	Dry Powder for Inhalation
DRM	Data Review Meeting
DRP	Data Review Plan
DRR	Data review Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoT	End of Treatment
ETV	Early Termination Visit
FEV1	Forced Expiratory Volume in the first second
FF	Formoterol Fumarate
FVC	Forced Vital Capacity
γ-GT	Gamma-glutamyl transpeptidase
Hb	Haemoglobin
Hct	Hematocrit
HR	Heart Rate
ICS	Inhaled corticosteroid
ID	Identification
IRT	Interactive Response Technology
ITT	Intention to Treat
K	Potassium
L	Liter
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarinic antagonist
MAR	Missing At Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities

min	Minute
Min	Minimum
MMRM	Mixed Model for Repeated Measures
ms	Millisecond
µg	Microgram
Na	Sodium
PEF	Peak Expiratory Flow
pMDI	pressurised Metered Dose Inhaler
PLT	Platelet
PP	Per Protocol
PR	Time interval between the beginning of the P wave and the beginning of the QRS complex in 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	Fridericia – Corrected QTc
RBC	Red Blood Cell
RR	Time interval between two consecutive R waves
SABA	Short-acting β2 agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings, Figures
TOC	Table of Contents
V	Visit
WBC	White Blood Cell
WHO-DD	World Health Organization - Drug Dictionary

Revision History

Version # (date)	Page/Section/Appendix	Description of Changes	Reason For change
SAP V1.0 (23Oct2020)		Not applicable	
SAP V2.0 (10Sept2021)	***Section 6.2 Intention-to-treat***	Restored the definition of ITT set reported in the study protocol.	Misalignment of the ITT set between SAP V1.0 and study protocol
	Section 7.3 Handling of missing data	Addition of a clarification about missing clinic visit	During the COVID-19 pandemic, clinic visit could be replaced by a phone call
		Addition of a clarification about missing data for the primary endpoint	To strengthen the validity of the MAR (Missing AT Random) assumption in handling COVID-19 related missing data.
	Section 7.4 Covariates	Sites reclassified into regions	Reclassification based on official source: https://en.wikipedia.org/wiki/List_of_regions_of_China).
	Section 7.9 Data re-allocation	Addition of an algorithm for the reallocation of Diary data for discontinued patients due to COVID-19 pandemic	The number of days between last visit performed and Early Termination Visit can be split into more than one inter-visit period
	Section 7.12 Coding	New MedDRA and WHO-DD dictionaries	Updated to the most recent versions
	Section 7.13.2 Handling impact of COVID-19 in the Statistical Analysis	Removal of the models including COVID-19 factor	The impact of the COVID-19 on the treatment effect is already evaluated by the analysis within the two subgroups of patients (before vs during-after COVID-19 pandemic)
	Section 8 Compliance	Minor updates	Clarification on treatment compliance Clarification on eDiary compliance Clarification on the formula for the treatment period duration
	Section 7.10.1 / 2 exclusion of data from all Statistical Analysis / Per Protocol Analysis ***Section 8.6.3 PEF measurement validity*** ***Section 9.1.1 / 9.2.2 Change from baseline over the entire treatment period in average pre-dose morning / evening PEF***	Validity of PEF measurement updated: 1) PEF measurement performed after IMP intake is kept in the ITT analysis but removed from PP evaluation 2) Only sessions with only 1 PEF measurement or with only 1 PEF measurement in the range 50-900 L/min) will be removed from all analysis	To include as much collected data as possible in the ITT analysis.
	Section 9.2.2 change from baseline in average pre-dose evening PEF	Analysis described in section 9.2.2 will be performed on ITT and PP set (and not on ITT only)	Evening PEF measurement performed after IMP intake will be kept in the ITT analysis but removed from PP evaluation

1 Introduction

This document presents the Statistical Analysis Plan (SAP) for Chiesi Farmaceutici S.p.A. protocol CCD-01535BA0-01: "A 12-week, multicenter, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® 100/6µg NEXThaler®, 2 inhalations b.i.d., versus Foster® 100/6µg pMDI, 2 puffs b.i.d., in patients with controlled asthma". This analysis plan is based on the protocol (version 7.0, dated 31 August 2020), on the electronic Case Report Form (eCRF) (version 7.0, dated 31 December 2019) and on Non-CRF Data Guideline for diary data (version 2.0, dated 23 October 2017), for PEF data (version 2.0, dated 23 October 2017) and for spirometry data (version 2.0, dated 03 November 2017).

2 Study Design

This is a phase III, double-blind, double-dummy, randomised, multicentre, 2-arm parallel-group, active-controlled non-inferiority study preceded by a 4-week run-in period, in adult asthmatic patients. Approximately 1000 patients will be screened and a total of about 490 patients will be randomised in about 50 sites, according to a 1:1 ratio, to Foster® NEXThaler® 100/6µg (245 patients) or Foster® pMDI 100/6µg (245 patients).

During the run-in period, all patients will receive 2 puffs of Foster® 100/6µg pMDI in the morning and 2 puffs of Foster® 100/6µg pMDI in the evening (daily dose of BDP 400 µg plus FF 24 µg).

Eligible patients will then be randomised to one of the following treatments:

- **Treatment A (Test Product):**
  - 2 inhalations of Foster® 100/6µg NEXThaler® plus 2 puffs of pMDI matched placebo in the morning AND
  - 2 inhalations of Foster® 100/6µg NEXThaler® plus 2 puffs of pMDI matched placebo, in the evening

  (total daily dose: BDP 400 µg plus FF 24 µg).

- **Treatment B (Reference Product):**
  - 2 puffs of Foster® 100/6µg pMDI plus 2 inhalations of NEXThaler® matched placebo in the morning AND
  - 2 puffs of Foster® 100/6µg pMDI plus 2 inhalations of NEXThaler® matched placebo, in the evening

  (total daily dose: BDP 400 µg plus FF 24 µg).

A total of 10 clinic visits (Visit 0 to Visit 9) will take place during the study:

- a pre-screening visit (Visit 0) will be carried out in order to fully explain the study to potential patients and to obtain their written informed consent from the patient and to instruct the patient on screening visit procedures (such as medication restrictions);
- a screening visit (Visit 1, no more than 7 days after Visit 0, and 4 weeks before randomisation) will help establish the eligibility of patients for inclusion in the study

(including routine haematology and blood chemistry, medical history, physical examination, vital signs, a 12-lead ECG, FEV_1 reversibility test, and training for the use of inhalers). All previous treatments should be stopped accordingly to the non-permitted concomitant medications section of the study protocol (section 5.2). This visit will be followed by a 4-week open-label run-in period (including V2, Week -2). During the run-in period, all patients will receive Foster pMDI 2 puffs BID.

- a randomisation visit (Visit 3, Week 0) where patients will be randomised to one of the two treatment arms;
- six subsequent visits (Visit 4, Week 2 to Visit 9, Week 12) scheduled during the treatment period every two weeks of treatment.
- A follow-up call where patients will be contacted by phone after 7-10 days of last study medication intake or the Early Termination visit in order to check the status of any unresolved Adverse events (AEs) at the last visit and to record any new AEs that have occurred after the last visit as well as the related concomitant medications.

See Clinical Study Protocol, V7.0 for a detailed list of visits and assessments.

3 Study Objective

3.1 Primary Objective

The primary objective of the study is to demonstrate the non-inferiority of Foster® NEXThaler® 100/6 µg versus Foster® pMDI 100/6 µg in terms of lung function (i.e., change from baseline over the entire treatment period in average pre-dose morning Peak Expiratory Flow (PEF)) in asthmatic patients.

3.2 Secondary Objectives

The secondary objective of the study is to evaluate the effect of the test treatments in terms of additional lung function parameters and clinical outcome measures, and to assess the safety and tolerability.

4 Study Variables

4.1 Efficacy Variables

4.1.1 Primary Efficacy Variable

- Change from baseline over the entire treatment period in average pre-dose morning PEF.

4.1.2 Secondary Efficacy Variables

- Change from baseline to each inter-visit treatment period in average pre-dose morning PEF.
- Change from baseline to each inter-visit treatment period and over the entire treatment period in:
    - average pre-dose evening PEF;
    - average daily PEF variability;

  - average use of rescue medication (number of puffs/day);
  - percentage of rescue medication-free days;
  - average total morning asthma symptom score;
  - average total evening asthma symptom score;
  - percentage of asthma symptoms-free days;
  - percentage of asthma control days.
- Change from baseline in pre-dose morning FEV_1 and FVC at each clinic visit.
- Change from baseline to end of treatment (Week 12) in the Asthma Control Questionnaire (ACQ-6) score.

4.2 Safety Variables

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs).
- Vital signs (heart rate, systolic and diastolic blood pressure) at all visits pre-dose.
- 12-lead ECG parameters: Abnormalities on heart rate (HR), PR, QRS, QTcF (pre-dose at Screening and Week 12).
- Moderate / severe asthma exacerbations.
- Standard Haematology and Blood Chemistry at Screening and Week 12 (by local laboratory)

4.3 Other Variables

No other variables defined.

5 Sample Size

A sample size of 220 evaluable patients per group will provide approximately 85% power to demonstrate the non-inferiority of Foster® NEXThaler® compared to Foster® pMDI in terms of change from baseline over the entire treatment period in average pre-dose morning PEF, with a non-inferiority margin of -15 L/min and a one-sided significance level of 0.025, assuming a mean difference of 0 L/min between treatments and a Standard Deviation (SD) of 52 L/min.

The non-inferiority margin of -15 L/min is widely reported in previous studies[1, 2]. Moreover, it is less than the minimal patient perceivable improvement of 18.8 L/min estimated by Santanello et al.[1].

Estimating a non-evaluable rate of 10%, a total of about 490 patients (245 per treatment group) will be randomized.

6 Analysis Sets

The definitions of the analysis sets are summarised below. A final agreement on the patients to be included in or excluded from each analysis set will be reached before breaking the blind during the Data Review Meeting (DRM) and fully documented in the Data Review Report (DRR).

6.1 Safety set
All randomized patients who receive at least one dose of study treatment.

6.2 Intention-to-Treat Set
All randomized patients who receive at least one dose of the study treatment and with at least one available evaluation of efficacy after the baseline.

6.3 Per Protocol Set
All patients from the ITT Set without any major protocol deviations (i.e., wrong inclusions, poor compliance, non-permitted medications).

6.4 Other Sets Defined for Tables and Listings
For the purposes of tables and listings the following sets are defined:

- Enrolled Set: all patients who provided informed consent for the study;
- Randomized Set: all patients randomized to study medication.

7 General Considerations for Statistical Analysis

7.1 Statistical Significance
Unless otherwise specified 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. The non-inferiority hypothesis on the primary endpoint will be evaluated by a one-sided 97.5% confidence interval.

7.2 Multiplicity
No multiplicity adjustment will be performed in this study since one comparison only (Foster® NEXThaler® 100/6 µg versus Foster® pMDI 100/6 µg) will be performed for the primary efficacy variable.

7.3 Handling of Missing Data

Handling of missing clinic visits
Due to the COVID-19 pandemic, in some cases patients were not allowed to attend the clinic visit at site. Whenever possible the clinic visit was replaced by a remote phone call visit. Details are reported in section 7.13.

Handling of missing data for the primary endpoint
The primary analysis of the primary endpoint will be based on Analysis of Covariance (ANCOVA) model. No imputation of missing data will be done (only data recorded from the patient fulfilling the rules reported in section 9.1.1 will be considered for this analysis).

Sensitivity analysis with a different statistical model (MMRM - under the same assumption of primary model) will be conducted on the primary efficacy variable to investigate the robustness of the conclusions of the study. A detailed description of these analyses is provided in section 9.1.1.

The linear mixed model for repeated measures (MMRM) is based on a Missing At Random (MAR) assumption. These models provide an unbiased estimate of the treatment effect that could have been observed if all patients had continued the treatment for the full study duration [2]. This means that the MAR assumption in a non-inferiority study is a conservative approach because it does not favour the non-inferiority hypothesis.
Moreover the MAR assumption is also applicable for the subjects who discontinue the study due to reasons directly or indirectly related to COVID-19 pandemic (for example: early withdrawal because of patient refusal to go to the hospital due to COVID-19 pandemic or restricted by COVID-19 outbreak). As mentioned also in a recent paper by Meyer et al "most data that are missing due to pandemic reasons may be argued to be MCAR or MAR, especially if missingness is due to structural reasons" [3].

Handling of missing data for secondary endpoints
For secondary endpoints measured repeatedly over time, missing data will be handled using the same MMRM approach as described for the primary endpoint.

Handling of partial / missing dates
In order to calculate the duration of smoking for ex-smokers, the following rules will be applied for the partial dates of start/stop of smoking:

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

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

- the first day of the month will be assumed;
- if the day and the month are missing, January 1st will be assumed.

If the date of the last randomised 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 missing: min (date of last randomised study medication intake in the diaries, date of completion/discontinuation);
- if partial: evaluation of partial date of last randomised study medication intake will be performed case by case during the DRM and decision will be documented in the DRR.

In case of missing or incomplete dates not directly allowing allocation to any of the following four categories of medications:

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

a worst-case allocation will be done according to the available parts of the start and the end dates.

In case of missing or incomplete dates not directly allowing allocation to any of the four categories of procedures:

- concomitant procedure;
- procedure maintained during the randomised treatment period;
- post-study procedures;
- previous procedures,

a worst-case allocation will be done according to the available parts of the start and the end dates.

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

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

Descriptive statistics

The number of patients 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 summarised, only the non-missing values will be evaluated for calculating summary statistics.

For ACQ-6 questionnaire, the total score will be calculated only if all the scores derived from all the six items are recorded. The ACQ-6 total and mean scores for the analysis will be derived in ADaM dataset.

Missing data from e-Diary

The following rules are applied for variables based on eDiary data:

- For the daily variables recorded by the patients on the e-diary, the availability of at least 7 valid measurements will be required in each inter-visit period (including baseline period (i.e., the last 14 days before date of start of randomised treatment period)) to consider the following variables as non-missing: average pre-dose morning PEF, average pre-dose evening PEF, average daily PEF variability, average use of rescue medication, average total morning asthma symptom scores, average total evening asthma symptom scores, percentage of rescue medication free-days, percentage of asthma symptom free-days, percentage of asthma control days. For the entire treatment period the availability of at least one valid inter-visit period will be required.

- For the calculation of the daily intake of rescue medication, if one session (morning/evening) is missing the rescue medication intake of the day will be missing.

- The average rescue medication and the percentage of rescue-medication free-days will be derived on the data collected in the e-Diary. In case of missing day (i.e missing answer) the day will be excluded by the average calculation and won't be considered for the % of rescue medication free-days.

- If the answer to the question MQ9 (EQ9) of the e-Diary "*Have you already taken the Foster® pMDI this morning (evening)?*" is missing, the morning (evening) PEF session of that day will be discarded from the valid sessions of the run-in period.

- If the answer to the question MQ10 (EQ10) of the e-Diary "Have you already taken the Foster® pMDI or NEXThaler® this morning (evening)?" is missing the morning (evening) session of that day will be discarded from the valid sessions of the randomised treatment period.

7.4 Covariates

All ANCOVA models and linear MMRM will include the baseline value of the variable as covariate and region and sex as fixed effects.

Linear MMRM will also include visit/inter-visit period, the treatment by visit/inter-visit period interaction and the baseline by visit/inter-visit period interaction.

In the analyses stratified by one of the factors included in the statistical model used for the non-stratified analysis, the factor will be removed from the model (e.g., in the analysis stratified by the sex, the sex will not be included as a factor in the model).

Due to a high number of sites with a limited number of randomised patients (i.e., lower than 10) included in the ITT set, the sites have been grouped on the basis of their regional proximity.

Region	Cities and provinces	Site number
North China	Beijing, Tianjin, Hebei, Shanxi, part of inner Mongolia	11, 25, 34, 36, 42, 50, 59, 63, 72, 82
Northeast of China	Heilongjiang, Jilin, Liaoning, part of inner Mongolia	21, 60, 76, 78
East China	Shanghai, Jiangsu, Zhejiang, Anhui, Jiangxi, Shandong, Fujian, Taiwan	19, 28, 30, 31, 37, 41, 43, 54, 64, 65, 74
Central China	Henan, Hubei, Hunan	13, 14, 61, 75, 79, 81
South China	Guangdong, Guangxi, Hainan, HK, Macao	07, 08, 10, 51, 56, 62, 66, 67, 68, 71, 73, 77, 83
Western China	Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang	26, 33, 38, 69, 70, 80

In all statistical models the factor "site" will be replaced by the factor "region".

7.5 Interim Analyses

No interim analysis is planned for this study.

7.6 Examinations of Subgroups

As exploratory purpose, the analysis of primary efficacy variable (change from baseline of average pre-dose morning PEF over the entire treatment period, and to each inter-visit period as well) will be also performed on the ITT set stratifying by:

- Sex (male or female);
- BMI (<25 kg/m^2, ≥25 kg/m^2)
- Time since first Asthma diagnosis in years ([1-5) years, ≥ 5 years);

The following primary/secondary efficacy variables:

- Change from baseline to each inter-visit period and over the entire treatment period in average pre-dose morning PEF;
- Change from baseline to each inter-visit period and over the entire treatment period percentage of asthma control days;
- Change from baseline in pre-dose morning FEV_1 at each clinic visit;
- Change from baseline to end of treatment (Week 12) in the Asthma Control Questionnaire (ACQ-6) score,

will also be evaluated in subgroups of patients defined according to the COVID-19 pandemic periods (See section 7.13.2 for the definition of the subgroups)

7.7 Descriptive Statistics

Descriptive statistics for quantitative variables will include n (the number of non-missing values), mean, SD, median, minimum and maximum values. The 95% Confidence Interval (CI) of the mean will also be presented for the lung function parameters

Categorical variables will be summarised by using frequency count and percent distributions.

7.8 Definitions

7.8.1 Baseline and Change from Baseline

The baseline value for each efficacy and safety variable is defined as follows:

- For variable recorded at Clinic Visit the baseline is the value recorded at Visit 3, or at Visit 1 for variables not recorded at Visit 3 (ECG and Laboratory parameters).
- For all the derived efficacy variables (listed in section 4.1.1 and 4.1.2) based on information recorded daily in the e-diary, the baseline:
    - will be calculated if there are at least 7 available assessments in the last 14 days before the start of randomised treatment period;
    - will not be calculated otherwise and will be set at missing.

Additional specifications for the calculation of baseline value for each efficacy and safety variables are reported in the relevant sections in chapter 9 and 10 respectively.

For each of the efficacy and safety variables, **change from baseline** is defined at each visit (or at each inter-visit period/entire treatment period for the variables derived from e-Diary data) as:

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

7.8.2 Date of First and Last Randomised Study Medication Intake

The date of first randomised study medication intake is the earliest date of randomised study medication intake considering the eCRF data. This date corresponds to the date part of the variable RFSTDTC in the SDTM dataset DM.

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

7.8.3 Study day

For the e-Diary data, the study day will be calculated as: (date of the day – date of start of randomised treatment period +1).

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

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

7.8.4 Visit dates

For each visit (either clinic or performed remotely due to the COVID-19 pandemic), 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 Visit 9 (or Early Termination Visit) if the start date is lower than the end date, the end date of the Visit 9 (or Early Termination Visit) should be considered.

7.8.5 Date of Start/End of Randomised Treatment Period

Since many algorithms used in the statistical analyses require the start and/or the end of the randomised treatment period to be identified, ad-hoc variables specifying these dates will be defined.

- In general, the date of start of randomised treatment period should coincide with the date of Visit 3, the randomisation date and the date of first randomised study medication intake. However, discrepancies between these dates may arise and the most appropriate date to be used in such situations requires a case-by-case evaluation. The date of start of randomised treatment period will be initially set equal to the date of first randomised study medication intake for all patients. The need for deviations from this rule in single cases will be evaluated during the data review and documented in the DRR.
- The date of end of randomised treatment period will be initially set according to the following rule:
  - If Visit 9 or early termination visit was performed, then the date of end of randomised treatment period will be set equal to the date of Visit 9 or date of early termination visit;

- If Visit 9 or early termination visit was not performed, then the date of end of randomised treatment period will be defined as max [dates of clinic visits (including unscheduled visits), date of last randomised study medication intake (see the previous section)]; Clinic visits includes the visits performed at site or remotely due to COVID-19 pandemic, therefore follow-up visits (and unscheduled follow-up visits) have not to be considered.

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

7.9 Data Re-allocation

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

Data Collected at Visit 9

- 12-lead ECG and laboratory data recorded at the study termination visit for discontinued patients will be always re-allocated to Visit 9.

Data Collected at multiple visits

- Data collected at multiple visits (lung function, vital signs, physical examinations) and recorded at the early termination visit for discontinued patients will be re-allocated by selecting the visit following the last one performed before the early termination visit with the expected date, calculated starting from the date of randomization, closest to the date of the early termination visit. For example if the last visit performed before the early termination visit was Visit 5, the data recorded at the study termination visit will be re-allocated to Visit 6, 7, 8 or 9 depending on the date of the early termination visit.

  An example:
  Date of Randomisation (V3): 08Jul2020
  Date of last Visit (V5): 05Aug2020
  Date of ETV: 18Sept2020

  Expected date for V6: 19Aug2020 (V3 + 42 days)
  Expected date for V7: 02Sept2020 (V3 + 56 days)
  Expected date for V8: 16Sept2020 (V3 + 70 days)
  Expected date for V9: 30Sept2020 (V3 + 84 days)

  Decision: ETV re-allocated to V8

  If the early termination visit was performed less than 7 days after the preceding visit, data recorded at the study termination visit will not be re-allocated and they will be excluded from the statistical analysis. For each assessment, only the visits at which the assessment was scheduled will be considered for re-allocation;

Reallocation of Data Collected in the Diary to inter-visit periods

- in case of **missing intermediate visit** not due to the re-allocation of data collected at the early termination visit (e.g., Visit 5 missing, but Visits 4 and 6 performed), the

expected date for the missing intermediate visit will be derived through the following algorithm:

i. the number of days between the last available date before the missing intermediate visit and the first available date after the missing intermediate visit will be divided by the number of missing inter-visit periods;

ii. The date for the missing intermediate visit = date of the visit before the missing intermediate visit + the integer part of the result derived at the previous bullet point.

This algorithm can be easily applied when more than one intermediate visit is missing. Below a couple of examples:

Example 1: one intermediate visit missing (V4)
Date V3: 3 Apr
Date V5: 8 May
Date V5 – Date V3 = 35 days
(Date V5 - Date V3)/2 = 17.5 days
Date V4 (imputed) = Date V3 + 17 days = 20 Apr
Date V5 - Date V4 (imputed) = 18 days (35-17)

Example 2: two intermediate visits missing (V4 and V5)
Date V3: 3 Apr
Date V6: 20 May
Date V6 – Date V3 = 47 days
(Date V6 - Date V3)/3 = 15.7 days
Date V4 (imputed) = Date V3 + 15 days = 18 Apr
Date V5 (imputed) = Date V4(imputed) + 15 days = 3 May
Date V6 - Date V5(imputed) = 17 days

- For **discontinued patients with early termination visit available**, **missing intermediate visit** might result after re-allocation of the early termination visit (e.g. Visit 5 is the last Visit performed, Visit 6 and 7 missing, Visits 8 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 visit and the resulting inter-visit periods will be derived through the same algorithm reported above.
- study medication intake data recorded in the diaries from the last visit performed before the date of last randomised study medication intake onwards will be reallocated on the basis of the inter-visit periods defined above.
- **For discontinued patients with no early termination visit available**, diary data recorded in the diaries from the last visit performed onwards will be reallocated to the next expected inter-visit period.

The following general rules to handle unscheduled/optional assessments during the randomised treatment period (i.e., from Visit 3 to Visit 9) will be considered:

- two or more lung function measurements valid for the same timepoint (with the timepoint checked vs. the time of medication intake):

- FEV_1: the highest value from the measurements with BTR grade "acceptable" or "borderline acceptable" will be considered. If BTR grade = "unacceptable" for all measurements, the highest value will be considered;
- FVC: same approach as for FEV_1;
- for post-salbutamol spirometry at Visit 1 / re-scheduled Visit 1 / Visit 2, the assessment originally flagged as "post PFT" will always be used also in case of additional post-salbutamol measurements. The rationale for this exception is that the original values were considered for the assessments of eligibility;

- 12-lead ECG:
  - in case of multiple measurements associated to the same timepoint (with the time point checked vs. the time of medication intake), the average value will be considered for HR, QTcF, PR and QRS.

- Vital signs:
  - in case of multiple measurements associated to the same timepoint (with the time point checked vs. the time of medication intake), the average value will be considered for HR, systolic and diastolic blood pressure.

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.

7.10 Exclusion of Data from the Statistical Analyses

7.10.1 Exclusion of Data from All Statistical Analyses

Diary Data

The data recorded in the diaries before Visit 1 or after the date of end of randomised treatment period will not be considered in the calculation of compliance, efficacy and, in general, the diary derived variables.

If "date of end of randomised treatment period" = "Date of Visit 9", 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 randomised treatment period, 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

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

- the sessions with only 1 PEF measurement available;
- the sessions with at least two measurements available but with only one measurement in the range [50-900] L/min.

Lung Function parameters

All lung function parameters values will be considered in the statistical analysis, even those classified as "Unacceptable" by the over-reader.

If inclusion criteria no. 2 was not met at Visit 1 and the spirometry was repeated before Visit 2 or at Visit 2, the 2nd assessment 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.

12-lead ECG numerical parameters:

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

- Patients with a pacemaker inserted before study entry will be identified by the presence of at least one of the following Preferred Terms in the medical/surgical history or concomitant diseases: "Cardiac pacemaker battery replacement", "Cardiac pacemaker evaluation", "Cardiac pacemaker insertion", "Cardiac pacemaker replacement", "Electrocardiogram pacemaker spike", "Pacemaker generated arrhythmia", "Pacemaker generated rhythm", "Pacemaker syndrome", "Cardiac assistant device user".
- Patients with a pacemaker inserted during study will be identified by the presence of the Preferred Term "Cardiac pacemaker insertion" in the procedures (other relevant cases may be identified during DRM). In these cases, data will be excluded from the analysis from the day of pacemaker insertion onwards.
- Patients with atrial fibrillation will be identified by the presence of at least one of the following Preferred Terms in the concomitant diseases: "Atrial fibrillation", "Cardiac fibrillation".

At each timepoint/visit, 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 timepoint will be excluded).

In case of data excluded from the statistical analysis, 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

7.10.2 Exclusion of Data from Per Protocol Analyses

In case of major protocol deviation, the patient will be excluded from the PP set and therefore from all PP analyses.

In case of local major protocol deviation, only the affected data at the specific time point/visit will be excluded from the PP analyses.

PEF

The PEF morning and evening sessions performed after the study medication intake and evaluable on the bases of the criteria reported in section 7.10.1 will be included in the ITT analysis but excluded from the PP analysis as local major deviations. These will be reported and described in the DRR.

7.11 Listings

All data collected in the eCRF will be presented in the listings.

All the single data recorded in the diary as well as the variables derived and used in the analyses will be presented in the listings.

7.12 Coding

Medical and surgical history, concomitant diseases, procedures and adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. Medications will be coded using the World Health Organisation Drug Dictionary (WHO-DD), version 02Sep2020.

7.13 Other considerations: Handling impact of COVID-19 Pandemia

At the time of the beginning of the COVID-19 pandemic in China there was no guideline to face the impact of the pandemic on methodological aspects of ongoing trials. Below are described the actions that were put in place by the Sponsor on this regard.

7.13.1 Guidance and Contingency Plan from Sponsor to sites

On the 22nd of January the local CRO communicated by email to Sponsor the increasing risk of an impact on the study activities due to the spread of the COVID-19 pandemic. By that date 7 cities (Wuhan, Beijing, Guangzhou, Shanghai, Zhejiang, Tianjin, Henan, Chongqing) having sites participating to this study reported COVID-19 cases. CRO communicated that "patients might refuse to visit hospitals and/or sites staff might be busy handling patients affected by the pneumonia". Since it was foreseeable that the COVID-19 pandemic would have interfere with the conduct of the trial, the Sponsor promptly elaborated a contingency plan to address the possible issues related to pandemic.

Several actions were immediately decided and communicated by email to face the evolving situation. The measures can be summarised as follows:

- ***Flexibility in the time-windows visits:***
  - Between V1 (start of Run-in) and V3 (Randomisation visit) a maximum of 7 weeks was accepted instead of 4 weeks (as per protocol).
    - If V2-V1 = 2 weeks, then V3-V2 maximum of 5 weeks
    - If V2-V1 = 3 weeks, then V3-V2 maximum of 4 weeks
    - If V2-V1 = 4 weeks, then V3-V2 maximum of 3 weeks
    - If V2-V1 = 5 weeks, then V3-V2 maximum of 2 weeks;
  - If Randomisation Visit (V3) could not be arranged in a due date, patient was considered as run-in failure and possibly re-screened when the outbreak would have been off;

- V9 (End of Study) could be postponed at site with an allowed time window of 15 days; subjects that performed the End of study Visit (V9) over the allowed time window were considered as completing the study with their own collected data, with time deviation to be discussed at the Data Review Meeting. If visit could not be performed patient was considered as « discontinued » with the reason "Restricted due to COVID-19 outbreak";
- Visits between V4 and V8, during treatment period, a delay of 15 days was allowed and, in the case the clinic visit was not done despite of the delay, a remote phone call was foreseen;
- For V4, V6 and V8, where no IMP dispensation was planned, in the case the visit was not performed even remotely (e.g: sites staff too busy in handling patients affected by the pneumonia), the visit could have been skipped.

- ***Study medication dispensation:*** At V5 and V7, where IMP dispensation was planned, study medication (and rescue medication) was shipped directly at patient home by qualified vendor.

- In case of **visit performed remotely** by phone call (visits that could not be performed at site), site staff had to call the patients to:
    - Check the patient safety and collect all AE/SAE;
    - Check and remind the patient to perform the PEF and fill in the AM device;
    - Remind the patient to correctly take the study medication (in the morning and in the evening);
    - Collect the change in concomitant treatment, if any;
    - Remind the patient to call the site in case of issue;
    - Enter the patient status in IWRS.

There was the awareness that in case of remote visit nothing could be done for pre-dose spirometer measurement.

All this process was requested to be described in the patient source data.

7.13.2 Handling impact of COVID-19 in the Statistical Analysis

All deviations related to the COVID-19 pandemic and resulting from the measures described in the Sponsor's contingency plan will be captured and discussed during the DRM and decisions will be documented in the DRR.

Additional analyses have been planned to investigate whether the COVID-19 pandemic impacted on the measurement of:

- the primary endpoint, selected secondary endpoints and AEs
- the efficacy of the FOSTER® NEXThaler®.

The date of 22nd of January, as mentioned in the section 7.13.1, identifies the group of patients that completed their study period before the implementation of the containment measures due to COVID-19 outbreak (date of completion/discontinuation before 22nd of January). Considering that at the time of the finalisation of the present document (September 2021) emergency due to COVID-19 is still ongoing worldwide and that the containment measures are still active in several sites, no date of end of containment measure is estimable. Therefore only two phases (pre/during pandemic) have been taken into consideration and only two groups were finally defined as follows:

- patients whose study participation was not affected by COVID-19 outbreak (study participation completed before 22nd January 2020 included);
- patients whose study participation was potentially affected by COVID-19 outbreak (study participation completed after 22nd January 2020).

Subgroup analysis have been planned on primary and selected secondary efficacy variables (see section 7.6 and section 9.2.12) and AEs. Upfront it can be stated that:

- no impact or minor impact is expected on primary endpoint (change from baseline over the entire treatment period in average pre-dose morning PEF) and related secondary endpoints (morning PEF at each inter-visit period, evening PEF and daily PEF variability) since PEF measurements were downloaded daily from the AM device used by the patient to the eRT portal. These data were automatically collected regardless of the study phase (before/during COVID-19 pandemic) and the type of visit performed (clinic/remote/skipped visit) therefore it is expected that no data was lost. Moreover, in case of visits performed remotely, investigators were instructed to remind the patient to perform the PEF and to take correctly the study medication.
- minor impact is expected on rescue medication endpoints. This information was recorded on e-Diary by the patients at home regardless of the study period. As study medication, the rescue medication during the COVID-19 pandemic was delivered at patient home if needed and in case of visits performed remotely, investigators were instructed to remind the patient to take correctly the study medication and rescue/concomitant medication.
- No impact or minor impact is expected on endpoints based on asthma symptoms score. This information was recorded daily on e-Diary by the patients at home regardless of the study phase and type of visit;
- significant impact on spirometry endpoints. Patients that replaced clinic visit with the remote one or skipped at all the visit not performed spirometry. For these patients FEV_1 and FVC were not available at the missing clinic visit. As reported in section 7.3 missing data for variable repeatedly measured over time will be handled by MMRM model. It can be expected that in the phase "during COVID-19" a large part of the timepoints have missing spirometry data.
- There is no reason to expect any worsening in patient safety.

By considering the "COVID-19" factor at patient level through the Flag:

- "N" = "completed/discontinued before 22nd January 2020" included,
- "Y" = "completed/discontinued after 22nd January 2020",

subgroup analysis will consist in performing, within groups of patients COVID-19="Y" and COVID-19="N", the same statistical models planned for the selected primary/secondary efficacy variables. Treatment effect will be estimated within each group of COVID-19.

Descriptive tables for AEs will also be provided for the two subgroups.

8 Study Population

8.1 Disposition of Patients and Discontinuations

8.1.1 Disposition of Patients

The number of patients screened, the number of screen failures and the number of patients with each reason for screen failure will be presented (overall). These summaries will be based on the enrolled set.

The number of patients randomised at Visit 3, who attended Visits 4, 5, 6, 7 and 8, who completed Visit 9, who discontinued and performed Early Termination visit and with follow-up contact available will be presented by treatment group using the Randomised set.

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

8.1.2 Discontinuation from the Study

The number and percentage of patients who completed the study, withdrew from the study after randomisation and the number and percentage of patients with each reason for discontinuation from the study will be presented by treatment group using the Randomised set.

Time to discontinuation from the study after randomisation will be analysed using the Kaplan-Meier method for the Randomised set.

Time to discontinuation from the study (weeks) will be calculated as (date of completion/discontinuation – date of start of randomised treatment period + 1)/7. For patients randomised, but not treated, time to discontinuation from study will be assumed = 0.

In the Kaplan-Meier analysis of time to discontinuation, patients who complete the study will be censored at the date of completion.

For the study periods [0-2) weeks, [2-4) weeks, [4-6) weeks, [6-8) weeks, [8-10) weeks, [10-12) weeks, [12-14) weeks and [14 weeks-End of Treatment (EoT)], the number of patients in study at the beginning of the period, the cumulative number of discontinued patients at the end of the period and the probability of discontinuation at the end of the period with the associated 95% CIs will be presented by treatment group. Comparisons between treatments will also be performed by means of the log-rank test.

Plot of time to discontinuation by treatment group will also be presented.

8.1.3 Protocol Deviations and Analysis Populations

Major protocol deviations may include wrong inclusions, poor compliance and non-permitted concomitant medications. Deviations will be classified according to the following categories:

- Violation of Inclusion Criterion;
- Violation of Exclusion Criterion;
- Non Adequate Compliance to the Run-In;
- Non Adequate Compliance to the Study Drug;

- Treatment Administration Deviation;
- Non Permitted Medication;
- Assessment Performed Outside the Allowed Time Window;
- Visit Performed Outside the Allowed Time Window;
- Study Procedure Deviation;
- Randomisation Code Broken;
- Wash-Out Period Not Respected.

These categories may be amended, or other categories may be added, but any changes will be made prior to database lock and will be discussed during the DRM and documented in the DRR. In addition, it is anticipated that data may be excluded from the PP analysis on a by-visit basis or also on a by-session basis (i.e: sessions with PEF measurement performed after the study medication intake, see section 7.10.2).

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

The number of patients included in each of the Randomised, Safety, ITT and PP sets will be summarised for each treatment group and overall. The summary will also be presented by region and site.

Local major deviations (data excluded from the PP analysis on a by-visit / by-session basis) will only be listed.

8.2 Demographic and Baseline Characteristics

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

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

8.2.1 Demographic Characteristics

Demographic characteristics will be summarised by treatment group and overall. This will include age, Age in class, sex, race, height, weight and Body Mass Index (BMI). Separate summaries will be produced using the Safety, ITT and PP sets.

Notes:

- height and weight recorded at Visit 1 will be presented;
- BMI will be calculated as: weight (kg) / height $(m)^2$.
- Age in class will be defined as <65 years old and >=65 years old

8.2.2 Asthma History

Time since first Asthma diagnosis (years), Time since first Asthma diagnosis by category (< 5 years, [5-20) years, ≥ 20 years), Asthma medication category at study entry (ICS alone, ICS/LABA fixed combination, ICS+LABA free combination, Other) and Spacer Device at entry and randomisation will be presented by treatment group and overall. Separate summaries will be produced using the Safety, ITT and PP sets.

Notes:

- Time since first Asthma diagnosis (years) will be calculated as (date of Visit 1 – date of first Asthma diagnosis)/365.25;

8.2.3 Smoking Status

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

Notes:

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

8.2.4 Lung function test at Visit 1 and baseline

The following lung function parameters at Visit 1 and Baseline (Visit 3) will be summarised by treatment group and overall: FEV_1 (L), FEV_1 % of predicted normal value, FVC (L).
In case Spirometry at Visit 1 was repeated before Visit 2 or at Visit 2 for the re-check of the inclusion criteria #3, the 2nd assessment was considered as the Visit 1. In case Spirometry at Visit 3 was repeated within 2 days after the Visit for the re-check of the inclusion criteria #3, the 2nd assessment was considered as the Visit 3. Separate summaries will be produced using the Safety, ITT and PP sets.

8.2.5 Reversibility Test at Visit 1

Reversibility test as change in FEV_1 measured before and after salbutamol intake was assessed at Visit 1. The test was performed only on subjects without any documented reversibility test or bronchial provocation test/challenge test within the last 24 months.

In case the test at Visit 1 was repeated before Visit 2 or at Visit 2 for the re-check of the inclusion criteria #2, the 2nd assessment was considered as the Visit 1.

FEV_1 pre- and post-salbutamol, delta FEV_1 (ml) and %delta FEV_1 will only be listed on Randomised Set.

8.2.6 ACQ-6 score at Visit 1 and baseline

The ACQ-6 mean score at Visit 1 and Baseline (Visit 3) will be summarised by means of descriptive statistics by treatment group and overall using the ITT set.

8.2.7 PEF, use of rescue medication and asthma symptoms scores at baseline

Average morning and evening PEF, daily PEF variability, average use of rescue medication, percentage of rescue medication-free days, average total morning asthma symptom scores, average total evening asthma symptom scores, percentage of asthma symptom-free days and percentage of asthma control days at baseline will be summarised by treatment group and overall using the ITT population.

8.2.8 COVID-19

The COVID-19 variable will be identified during the study according to the definition given in section 7.13.2. Il will be summarised by means of descriptive statistics by randomised group and overall and will be included in the table of the demographic characteristics.

The variable will also be listed in the listings of demography.

8.3 Medical History and Concomitant Diseases

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

Notes:

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

8.4 Medications

Previous medications, medications maintained during the randomised treatment period and concomitant medications will be summarised by treatment group and overall (except for concomitant medications) for the ITT set through frequency distributions and percentages by Anatomical Main Group [1st level of the Anatomical Therapeutic Chemical (ATC) classification], Therapeutic Subgroup (2nd level of the ATC classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.

The medications will be classified according to the following rules:

- previous medication: start date < date of start of randomised treatment period and stop date ≤ date of start of randomised treatment period;
- medication maintained during the randomised treatment period: start date < date of start of randomised treatment period and stop date > date of start of randomised treatment period or ongoing;
- concomitant medication: date of start of randomised treatment period ≤ start date < date of completion/discontinuation;
- post-study medication: start date ≥ date of completion/discontinuation.

If a patient has multiple occurrences of a medication, the patient is presented only once in the respective patient count.

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

The following tables will be provided:

- previous medications
- medications maintained during the randomised treatment period
- concomitant medications.

Each table will be presented separately for asthma medications and non-asthma medications. Any medications with an indication equal to 'ASTHMA' or 'ASTHMA EXACERBATION' will be considered as asthma medications. A full review of the medications to identify medication taken for asthma will be performed during the Data Review Meeting.

Post-study medications will only be presented in a listing.

8.5 Procedures

The procedures will be classified according to the following rules:

- previous procedures: start date < date of start of randomised treatment period and end date ≤ date of start of randomised treatment period;
- procedures maintained during the randomised treatment period: start date < date of start of randomised treatment period and end date > date of start of randomised treatment period;
- concomitant procedures: date of start of randomised treatment period ≤ start date < date of completion/discontinuation;
- post-study procedures: start date ≥ date of completion/discontinuation.

All procedures (previous / maintained /concomitant / post-study) will only be presented in a listing, with proper SOC and PT.

8.6 Compliance

8.6.1 Treatment Compliance

Treatment compliance will be evaluated on the bases of the information recorded daily by the patient on the diary. If for a dosing occasion both diary and eCRF data is available (e.g., for the morning dose on the days of the clinic visits), the eCRF data will be considered.

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

For these subjects, the duration of the treatment period will be reduced by the number of sessions during which the settings were incorrect.

The information recorded at the study clinic will always be considered in the calculation (i.e. the session will be considered in calculation if exposure is recorded at clinic in a session where diary has an incorrect setting).

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

8.6.1.1 Treatment Compliance During Run-in Period

Treatment exposure (days) is calculated as: date of last run-in study medication intake – date of first run-in study medication intake +1.

The date of first and last run-in study medication intake will be derived on the bases of the information recorded on the diary and the eCRF.

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

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

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

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

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

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

- [0%-50%)
- [50%-75%)
- [75-100%)
- [100%-125%]
- >125%

8.6.1.2 Treatment Compliance during Randomised Treatment Period

Extent of exposure (days) is calculated as: date of last randomised study medication intake - date of first randomised study medication intake + 1.

The date of first and last randomised study medication intake are defined in section 7.8.2.

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

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

The total number of administered doses will be calculated as the total number of inhalations recorded from the evening session of the day of first randomised study medication intake (reporting the dose taken in the morning) to the day of last randomised study medication intake, inclusive.

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

- # scheduled doses = Extent of exposure (days)*8 (4 inhalations b.i.d.).

If the last day considered in the formula is the date of Visit 9 (date of last randomised study medication intake = Date of Visit 9), the number of scheduled doses on this day will be 4 (4 inhalations) as study medication will be administered only in the morning. Therefore the total number of scheduled doses will be:

- (Date of last randomised study medication intake - Date of first randomised study medication intake)*8 + 4

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

For patients with date of discontinuation = date of Visit 3, then:

- # scheduled doses = 4 (2 inhalations of Foster® 100/6 µg NEXTHaler® active or placebo + 2 inhalations of Foster® 100/6 µg pMDI active or placebo);
- the information on study medication intake will be taken from the eCRF.

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

A range of 75-125% will be taken into account for a satisfactory level of compliance.

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

- [0%-50%)
- [50%-75%)
- [75-100%)
- [100%-125%]
- >125%

8.6.2 Diary Compliance

Diary data will be dispensed and filled in twice a day: morning and evening session.

Each question refers to the previous session:

- Morning questions [MQx] refer to the prior evening
- Evening questions [EQx] refer to the morning

The diary comprises 7 and 8 questions for the run-in and treatment period respectively:

Run-in Period:

- One question on number of inhalations from the Foster pMDI taken in the previous session [EQ1 / MQ1] (SDTM.EC.ECDOSE and SDTM.EC.ECOCCUR, where ECTRT=" FOSTER PMDI 100/6" and EPOCH=" RUN-IN")
- Four questions about asthma symptoms score between previous and current session [EQ4 – EQ7 / MQ4 – MQ7] (SDTM.QS.QSTESTCD in ("ASS0101", "ASS0102", "ASS0103", "ASS0104") and
EPOCH=" RUN-IN"

- One question on number of puffs rescue medications between previous and current session [EQ8 / MQ8] (SDTM.EC.ECDOSE, where XRTRT=" SALBUTAMOL" and EPOCH=" RUN-IN")
- One question asking whether Foster pMDI had already been taken in the current session [EQ9 / MQ9] (SDTM.QS.QSTESTCD= "ASS0105" and EPOCH=" RUN-IN")

Treatment Period:

- One question on number of inhalations from the Foster pMDI taken in the previous session [EQ2 / MQ2] (SDTM.EC.ECDOSE and SDTM.EC.ECOCCUR, where ECTRT=" FOSTER® PMDI/PLACEBO" and EPOCH="TREATMENT")
- One question on number of inhalations from the Foster NEXTHaler taken in the previous session [EQ3 / MQ3] (SDTM.EC.ECDOSE and SDTM.EC.ECOCCUR, where ECTRT=" FOSTER® NEXTHALER®/PLACEBO" and EPOCH="TREATMENT")
- Four questions about asthma symptoms score between previous and current session [EQ4 – EQ7 / MQ4 – MQ7] (SDTM.QS.QSTESTCD in ("ASS0101", "ASS0102", "ASS0103", "ASS0104") and EPOCH="TREATMENT"
- One question on number of puffs rescue medications between previous and current session [EQ8 / MQ8] (SDTM.EC.ECDOSE, where XRTRT=" SALBUTAMOL" and EPOCH="TREATMENT")
- One question asking whether Foster pMDI or NEXThaler had already been taken in the current session [EQ10 / MQ10] (SDTM.QS.QSTESTCD= "ASS0106" and EPOCH=" TREATMENT)

Diary will be considered as compliant if all information as listed above are present.

In case of patients with an incorrect setting of electronic diary at randomisation (questions on run-in medication asked during the randomised treatment period or vice versa), the calculation of the Diary Compliance will not be modified but it will be calculated only on the sessions (morning/evening) with the correct setting.
The above rules will be applied to patients switching from the questions on run-in medication to the ones on the correct randomised study medication only once. The handling of more complex cases (i.e., with more than one switch) will be defined in the DRR.

Compliance of diary at session level will be calculated and reported at ADaM level.

For both periods, diary compliance will be summarised on the 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 randomised treatment period will be considered as data of the run-in period.

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

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

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

- [0%-50%]
- (50%-60%]
- (60%-70%]
- (70%-80%]
- (80%-90%]
- (90%-100%].

8.6.2.2 Diary Compliance during Randomised Treatment Period

Sessions recorded from the evening of the day of start of randomised treatment period to the day of end of randomised treatment period will be considered as data of the randomised treatment period.

If the day of end of randomised treatment period is the day of a clinic visit, the following formula will be used:

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

Otherwise, the following formula will be used:

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

Compliance to the use of diaries during the randomised treatment period will be summarised by treatment group by means of descriptive statistics. The number and the percentage of patients will also be presented in the same categories defined for the run-in period (section 8.6.2.1).

8.6.3 Compliance to the PEF measurement

Since the AM device only offers the possibility to perform PEF measurements after the Diary is answered and saved, it is expected that the compliance to the PEF measurement is equal or lower than the diary compliance.
For both periods, compliance to the PEF measurement will be summarised on the ITT set.

8.6.3.1 Run-in Period

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

On a per patient basis, the overall and morning compliance to the PEF measurement during the run-in period will be calculated using the following formulae:

- Overall Compliance to the PEF measurement during run-in (%) = [((# valid morning sessions during run-in) + (# valid evening sessions during run-in)) / ((Date of start of randomised treatment period – Date of Visit 1)*2)]*100
- Morning Compliance to the PEF measurement during run-in (%) = [(# valid morning sessions during run-in) / (Date of start of randomised treatment period – Date of Visit 1)]*100.

For the sake of the compliance to the PEF measurement the rules reported in section 7.10.1 will be considered. The following sessions are considered not valid and not included for the analysis of PEF parameters:

- the sessions with only 1 PEF measurement available;
- the sessions with at least two measurements available but with only one measurement in the range [50-900] L/min.

Compliance to the PEF measurement during run-in period, quantifies the amount of data from run-in period, which the efficacy analysis will be based on.

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

- [0%-50%]
- (50%-60%]
- (60%-70%]
- (70%-80%]
- (80%-90%]
- (90%-100%].

8.6.3.2 Treatment Period

Data recorded from the evening of the date of start of randomised treatment period to the date of end of randomised treatment period will be considered as data of the treatment period.

On a per patient basis, the overall and morning compliance to the PEF measurement during the randomised treatment period will be calculated using the following formula:

- If the date of end of randomised treatment period is the day of a scheduled clinic visit, the following formula will be used:
  - Overall Compliance to the PEF measurement during treatment (%) = [(# valid morning sessions during treatment) + (# valid evening sessions during treatment) / ((Date of end of randomised treatment period – Date of start of randomised treatment period)*2)]*100
  - Morning Compliance to the PEF measurement during treatment (%) = [(# valid morning sessions during treatment) / (Date of end of randomised treatment period – Date of start of randomised treatment period)]*100.

- If the date of end of randomised treatment period isn't the day of a scheduled clinic visit, the following formula will be used:
  - Overall Compliance to the PEF measurement during treatment (%) = [(# valid morning sessions during treatment) + (# valid evening sessions during treatment) / (((Date of end of randomised treatment period – Date of start of randomised treatment period)*2) +1)]*100
  - Morning Compliance to the PEF measurement during treatment (%) = [(# valid morning sessions during treatment) / (Date of end of randomised treatment period – Date of start of randomised treatment period)]*100.

For the sake of the compliance to the PEF measurement the rules reported in section 7.10.1 will be considered. The following sessions are considered not valid and not included for the analysis of PEF parameters:

- the sessions with only 1 PEF measurement available;
- the sessions with at least two measurements available but with only one measurement in the range [50-900] L/min.

In case of sessions with more than one assessment recorded, only the first assessment will be considered for the calculation of compliance (and of the efficacy variables derived from the electronic peak flow meter).

Compliance to the PEF measurement during treatment period, quantifies the amount of data from treatment period which the efficacy analysis will be based on.

Overall and Morning Compliance to the PEF measurement during the randomised treatment period will be summarised by treatment group by means of descriptive statistics. The number and the percentage of patients will also be presented in the same categories defined for the run-in period (section 8.6.3.1).

9 Efficacy Analyses

Summary and analysis on the primary efficacy variable will be performed on ITT and PP sets. Since the study is based on a non-inferiority hypothesis, for the primary efficacy analysis the ITT and the PP sets will have equal importance.
Sensitivity and subgroup analysis on the primary efficacy variable will be performed on ITT set.

Summaries and analyses on each secondary efficacy variable will be performed on ITT set only (with the exclusion of analysis described in section 9.2.1 and 9.2.2 performed on ITT and PP sets).

9.1 Primary Efficacy Variable

9.1.1 Change from baseline over the entire treatment period in average pre-dose morning PEF

Stated:
CFB_{NEXT}=(average pre-dose morning PEF over the entire treatment period - average pre-dose morning PEF at baseline) for patients under Foster® NEXThaler® treatment

CFB_{pMDI}=(average pre-dose morning PEF over the entire treatment period - average pre-dose morning PEF at baseline) for patients under Foster® pMDI treatment

Null hypothesis of the study: $CFB_{NEXT} - CFB_{pMDI} \leq -15$ L/min
Alternative hypothesis of the study: $CFB_{NEXT} - CFB_{pMDI} > -15$ L/min

The following algorithms should be considered for the pre-dose morning PEF:

Variable	Definition
Pre-dose morning Best PEF	All morning sessions during **run-in** are **valid for PEF measurement,** with the exception of the sessions listed in section 7.10.1 (see also 8.6.3.1). All morning sessions during **treatment period** are **valid for PEF measurement,** with the exception of the sessions listed in section 7.10.1 (see also 8.6.3.2). Under these conditions the **pre-dose morning Best PEF** for the statistical analysis will be calculated as the highest morning PEF. Note: as reported in section 7.10.2, the PEF morning sessions performed after the study medication intake and evaluable on the basis of the criteria reported in section 7.10.1 will be taken into account in the ITT analysis but excluded from the PP analysis as local major deviations.
Baseline average pre-dose morning PEF	The mean of all pre-dose morning Best PEF values recorded during the baseline (run-in) period. Baseline (run-in) period: the last 14 days before the start of randomised treatment period (i.e., only the morning sessions performed in the last 13 days before the date of start of randomised treatment period and in the morning of the date of start of randomised treatment period). Availability of at least 7 valid morning sessions during the baseline period are required to make the baseline evaluable.
Average pre-dose morning PEF at each inter-visit period	The mean of all pre-dose morning Best PEF values recorded in each inter-visit period. Inter-visit period: 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 randomised treatment period for last 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. For the period Visit 3 – Visit 4 (first inter-visit period), the date of start of randomised treatment period will be considered as reference point instead of date of Visit 3. *Note: This adjustment is valid and will have to be applied for all endpoints based on inter-visit periods (up to section 9.2.9 included).*
Average pre-dose morning PEF over entire treatment period	The mean of all pre-dose morning Best PEF values recorded all over the entire treatment period. Entire treatment period: Time interval from the morning session of the day after the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period. Availability of at least 1 evaluable inter-visit period is required over all treatment period to make the entire treatment period evaluable.
Mean change from baseline day by day	The mean of the change from baseline of pre-dose morning Best PEF of all patients included in each study day.

Average pre-dose morning PEF values at baseline and over entire treatment period will be summarised by treatment group using descriptive statistics. Changes from baseline over the entire treatment period will also be summarised by treatment group.

Change from baseline over the entire treatment period in average pre-dose morning PEF will be analysed using an ANCOVA model including treatment, region and sex as fixed effects, and baseline value as covariate.
The number of patients considered in the model will be provided by treatment group. P-values of the fixed effects and covariate will also be presented. The adjusted means in each treatment group and the adjusted mean difference between treatments will be estimated by the model with their 95% CIs.
Non-inferiority will be demonstrated if the null hypothesis will be rejected with a lower confidence limit of the 95% CI of the adjusted mean difference between Foster® NEXThaler® and Foster® pMDI ≥ -15 L/min.

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

Sensitivity analysis of the primary efficacy variable

A sensitivity analysis based on a different statistical model (MMRM) will be performed on the ITT and PP set. Change from baseline over the entire treatment period in average pre-dose morning PEF will be estimated using a linear MMRM with change from baseline to each inter-visit period in average pre-dose morning PEF as dependent variable, with treatment, inter-visit period, treatment by inter-visit period interaction, region and sex as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates. The model will estimate the only comparison between treatment over the entire treatment period (estimates of the change from baseline to each inter-visit period, also provided by the model, will be considered as secondary efficacy variable and described in the section 9.2.1). An unstructured covariance matrix will be assumed, and the Kenward-Roger adjustment will be used for the degrees of freedom. The adjusted means in each treatment group, the adjusted

mean difference between treatments, their 95% CIs and associated p-values for entire treatment period will be derived by the model.

9.2 Secondary Efficacy Variables

9.2.1 Change from baseline to each inter-visit treatment period in average pre-dose morning PEF

Average pre-dose morning PEF values at baseline, at each inter-visit period will be summarised by treatment group using descriptive statistics. Changes from baseline to each inter-visit period will also be summarised by treatment group.

Change from baseline to each inter-visit period in average pre-dose morning PEF will be analysed using the same linear MMRM described in the section 9.1.1 for the sensitivity analysis of the primary efficacy variable.

The model will estimate comparison between treatments at each inter-visit period.

Descriptive statistics and MMRM to be performed on ITT and PP sets.

The number of patients considered in the model will be provided by treatment group. P-values of the fixed effects and covariates will also be presented. The adjusted means in each treatment group, the adjusted mean difference between treatments, their 95% CIs and associated p-values at each inter-visit period will be estimated by the model.

The same descriptive statistics and the same statistical model will also be provided in subgroups of Sex, BMI and Time to first diagnosis of asthma (ITT set only).

The following figures will have to be provided:

- Forest plot: adjusted mean difference between Foster® NEXThaler® and Foster® pMDI in change from baseline over the entire treatment period for average pre-dose morning PEF, summarizing the results from ANCOVA and MMRM models on ITT and PP sets, as well as the results from MMRM in subgroups of COVID-19 (Y/N), sex (M/F), BMI (<25 kg/m^2, ≥25 kg/m^2), Time since first Asthma diagnosis in years ([1-5) years, ≥ 5 years);
- adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM (ITT and PP sets);
- change from baseline of the pre-dose morning Best PEF day by day for each treatment group (ITT set);

9.2.2 Change from baseline to each inter-visit treatment period and over the entire treatment period in average pre-dose evening PEF

The following algorithms should be considered for the pre-dose evening PEF:

Variable	Definition

Pre-dose evening Best PEF	All evening sessions during **run-in** are **valid for PEF measurement** with the exception of the sessions listed in section 7.10.1 (see also 8.6.3.1). All evening sessions during **treatment period** are **valid for PEF measurement** with the exception of the sessions listed in section 7.10.1 (see also 8.6.3.2). Under these conditions the **pre-dose evening Best PEF** for the statistical analysis will be calculated as the highest evening PEF. Note: as reported in section 7.10.2, the PEF evening sessions performed after the study medication intake and evaluable on the basis of the criteria reported in section 7.10.1 will be taken into account in the ITT analysis but excluded from the PP analysis as local major deviations.
Baseline average pre-dose evening PEF	The mean of all pre-dose evening Best PEF values recorded during the baseline (run-in) period. Baseline (run-in) period: the last 14 days before the start of randomised treatment period (i.e., only the evening sessions performed in the last 14 days before the date of start of randomised treatment period). Availability of at least 7 valid evening sessions during the baseline period are required to make the baseline evaluable.
Average pre-dose evening PEF for each inter-visit period	The mean of all pre-dose evening Best PEF values recorded in each inter-visit period Inter-visit period: time interval from the evening session of the day of clinic visit to the evening session of the day before next clinic visit (or the date of end of randomised treatment period for last 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.
Average pre-dose evening PEF over entire treatment period	The mean of all pre-dose evening Best PEF values recorded all over the entire treatment period. Entire treatment period: Time interval from the evening session of the date of start of randomised treatment period to the evening session of the day of end of randomised treatment period. Availability of at least 1 evaluable inter-visit period is required over all treatment period to make the entire treatment period evaluable.
Mean change from baseline day by day	The mean of the change from baseline of pre-dose evening Best PEF of all patients included in each study day

Change from baseline to each inter-visit treatment period and entire treatment period in average pre-dose evening PEF (MMRM)

Changes from baseline to each inter-visit treatment period and over the entire treatment period in average pre-dose evening PEF will be analysed using the same descriptive statistics and the same statistical model (linear MMRM) provided for the average pre-dose morning PEF (9.2.1).

Descriptive statistics and MMRM to be performed on ITT and PP sets.

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided. An additional figure describing the change from baseline of the pre-dose evening Best PEF day by day for each treatment group will also be presented.

9.2.3 Change from baseline to each inter-visit treatment period and over the entire treatment period in average daily PEF variability

The following algorithms should be considered for the daily PEF variability:

Variable	Definition
Daily PEF variability	Daily PEF variability will be calculated for each day using the following formula: $Daily\ PEF\ variability\ (day\ x) = \frac{Best\ PEF\ evening\ (day\ x) - Best\ PEF\ morning\ (day\ x)}{\frac{Best\ PEF\ evening\ (day\ x) + Best\ PEF\ morning\ (day\ x)}{2}} \times 100$ Daily PEF variability will be calculated only for days with both pre-dose morning Best PEF and pre-dose evening Best PEF available. In the analysis of daily PEF variability, a day will be constituted by the data recorded in the morning session of that day plus the data recorded in the evening session of the same day.
Baseline average daily PEF variability	The mean of all daily PEF variability values recorded during the baseline (run-in) period. Baseline (run-in) period: the last 14 days before the start of randomised treatment period. Availability of at least 7 days with both morning and evening sessions valid during the baseline period are required to make the baseline evaluable.
Average daily PEF variability for each inter-visit period	The mean of all daily PEF variability values recorded in each inter-visit period. Inter-visit period: time interval from the day of clinic visit to the day before next clinic visit (or the date of end of randomised treatment period for last inter-visit period). Availability of at least 7 valid daily PEF variability values are required to make the inter-visit period evaluable.

Average daily PEF variability over entire treatment period	The mean of all daily PEF variability values recorded all over the entire treatment period. Entire treatment period: Time interval from date of start of randomised treatment period to the date of end of randomised treatment period. Availability of at least 1 evaluable inter-visit period is required over the treatment period to make the entire treatment period evaluable.
Mean change from baseline day by day	The mean of the change from baseline of daily PEF variability of all patients included in each study day

Changes from baseline to each inter-visit treatment period and over the entire treatment period in average daily PEF variability will be analysed using the same descriptive statistics and the same statistical model (linear MMRM) described for the average pre-dose evening PEF (9.2.2).

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided. An additional figure describing the change from baseline in average daily PEF variability day by day for each treatment group will also be presented.

9.2.4 Change from baseline to each inter-visit treatment period and over the entire treatment period in average use of rescue medication (number of puffs/day)

The following algorithms should be considered for the use of rescue medication:

Variable	Definition
Use of rescue medication	For each day, the "daily use of rescue medication" will be calculated as the sum of the number of puffs taken during the day-time (i.e., recorded in the evening session of that day on question EQ8 of the diary questionnaire) and taken during the night-time (recorded in the morning session of the next day on question MQ8 of the diary questionnaire). A day will be therefore constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day and the daily use of rescue medication will be calculated only if data at evening session and morning session of the next day are available.
Baseline average use of rescue medication	The mean of all daily use of rescue medication recorded during the baseline (run-in) period. Baseline (run-in) period: the last 14 days before the start of randomised treatment period. Data on rescue medication use recorded in the morning session of the date of start of randomised treatment period will be considered as a measurement of the baseline period.

Average use of rescue medication at each inter-visit period	The mean of all daily use of rescue medication values recorded in each inter-visit period Inter-visit period: 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 randomised treatment period for last inter-visit period). Data of rescue medications recorded in the morning session of the day of each clinic visit will be considered as a measurement of the inter-visit period before that clinic visit.
Average use of rescue medication over entire treatment period	The mean of all daily use of rescue medication values recorded all over the entire treatment period Entire treatment period: Time interval from the evening session of the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period.
Mean change from baseline day by day by treatment group	The mean of the change from baseline of daily use of rescue medication of all patients included in each study day.

Changes from baseline to each inter-visit treatment period and over the entire treatment period in average use of rescue medication will be analysed using the same descriptive statistics and the same statistical model (linear MMRM) described for the average pre-dose evening PEF (9.2.2).

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided. An additional figure describing the change from baseline in average use of rescue medication day by day for each treatment group will also be presented.

9.2.5 Change from baseline to each inter-visit treatment period and over the entire treatment period in percentage of rescue medications-free days

The following algorithms should be considered for the percentage of rescue medication-free days:

Variable	Definition
Rescue medication-free days	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.
Baseline percentage of rescue medication-free	100*(no. of rescue medication-free days during baseline (run-in) period / no. of days with available daily use of rescue medication during baseline (run-in) period)

days	Baseline (run-in) period: the last 14 days before the start of randomised treatment period. Data on rescue medication use recorded in the morning session of the date of start of randomised treatment period will be considered as a measurement of the baseline period.
Average percentage of rescue medication-free days at each inter-visit period	100*(number of rescue medication-free days during the inter-visit period / number of days with available daily use of rescue medication during the inter-visit period) Inter-visit period: 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 randomised treatment period for last inter-visit period).
Average percentage of rescue medication-free days over entire treatment period	100*(number of rescue medication-free days over entire treatment period / number of days with available daily use of rescue medication over entire treatment period) Entire treatment period: Time interval from the evening session of the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period.

Changes from baseline to each inter-visit treatment period and over the entire treatment period in percentage of rescue medication-free days will be analysed using the same descriptive statistics and the same statistical model (linear MMRM) provided for the average pre-dose evening PEF (9.2.2).

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided.

9.2.6 Change from baseline to each inter-visit treatment period and over the entire treatment period in average total morning asthma symptom scores

The following algorithms should be considered for the average total morning asthma symptom scores:

Variable	Definition
Total morning asthma symptom score	Symptoms to be considered are cough, wheeze, chest tightness, breathlessness. Total morning (day-time) asthma symptom score will be calculated as sum of the four asthma symptom scores recorded in the evening session (Min=0; Max=12).
Baseline average total morning asthma symptom score	The mean of all total morning asthma symptom score recorded during the baseline (run-in) period. Baseline (run-in) period: the last 14 days before the start of randomised treatment period (i.e., only the evening sessions performed in the last 14 days before the date of start of randomised treatment period have to be taken into account).

Average total morning asthma symptom score at each inter-visit period	The mean of all total morning asthma symptom score recorded at each inter-visit period. Inter-visit period: time interval from the evening session of the day of clinic visit to the evening session of the day before next clinic visit (or date of end of randomised treatment period for last inter-visit period).
Average total morning asthma symptom score over entire treatment period	The mean of all total morning asthma symptom score recorded over the entire treatment period. Entire treatment period: Time interval from the evening session of the date of start of randomised treatment period to the evening session of the date of end of randomised treatment period.
Mean change from baseline day by day by treatment group	The mean of the change from baseline of total morning asthma symptom score of all patients included in each study day.

Changes from baseline to each inter-visit treatment period and over the entire treatment period in average total morning asthma symptom scores will be analysed using the same descriptive statistics and the same statistical model (linear MMRM) provided for the average pre-dose evening PEF (9.2.2).

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided. An additional figure describing the change from baseline in average total morning asthma symptom scores day by day for each treatment group will also be presented.

9.2.7 Change from baseline to each inter-visit treatment period and over the entire treatment period in average total evening asthma symptom scores

The following algorithms should be considered for the average total evening asthma symptom scores:

Variable	Definition
Total evening asthma symptom score	Symptoms to be considered are cough, wheeze, chest tightness, breathlessness. Total evening (night-time) asthma symptom score will be calculated as sum of the four asthma symptom scores recorded in the morning session of the next day (Min=0; Max=12).
Baseline average total evening asthma symptom score	The mean of all total evening asthma symptom score recorded during the baseline (run-in) period Baseline (run-in) period: the last 14 morning sessions performed before the start of randomised treatment period (i.e., only the morning sessions performed in the last 13 days before the date of start of randomised treatment period and in the morning of the date of start of randomised treatment period). Data of asthma symptom scores recorded in the morning session of the

	date of start of randomised treatment period will be considered a measurement of the baseline period.
Average total evening asthma symptom score at each inter-visit period	The mean of all total evening asthma symptom score recorded at each inter-visit period. Inter-visit period: time interval from the morning session of the day after clinic visit to the morning session of the day of next clinic visit (or date of end of randomised treatment period for last inter-visit period).
Average total evening asthma symptom score over entire treatment period	The mean of all total evening asthma symptom score recorded over the entire treatment period. Entire treatment period: Time interval from the morning session of the day after the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period.
Mean change from baseline day by day by treatment group	The mean of the change from baseline of total evening asthma symptom score of all patients included in each study day.

Changes from baseline to each inter-visit treatment period and over the entire treatment period in average total evening asthma symptom scores will be analysed using the same descriptive statistics and the same statistical model (linear MMRM) provided for the average pre-dose evening PEF (9.2.2).

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided. An additional figure describing the change from baseline in average total evening asthma symptom scores day by day for each treatment group will also be presented.

9.2.8 Change from baseline to each inter-visit treatment period and over the entire treatment period in percentage of asthma symptoms-free days

The following algorithms should be considered for the percentage of asthma symptom-free days:

Variable	Definition
Asthma symptom-free days	An asthma symptom-free day is a day with both total morning and total evening asthma symptom scores = 0. A day will be constituted by the data recorded in the evening session (total morning asthma symptom score) of that day plus data recorded in the morning session of the next day (total evening asthma symptom score). Only days with both total morning and total evening asthma symptom scores available will be considered in the calculation of asthma symptom-free day.
Baseline percentage of	100*(number of asthma symptom-free days during baseline (run-in) period / number of days with available data during baseline (run-in)

asthma symptom-free days	period). Baseline (run-in) period: only data recorded in the last 14 days before the start of randomised treatment period. Data of asthma symptom scores recorded in the morning session of the date of start of randomised treatment period will be considered a measurement of the baseline period.
Average percentage of asthma symptom-free days at each inter-visit period	100*(number of asthma symptom-free days during inter-visit period / number of days with available data during inter-visit period) Inter-visit period: 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 randomised treatment period for last inter-visit period).
Average percentage of asthma symptom-free days over entire treatment period	100*(number of asthma symptom-free days over entire treatment period / number of days with available data over entire treatment period) Entire treatment period: Time interval from the evening session of the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period.

Changes from baseline to each inter-visit treatment period and over the entire treatment period in percentage of asthma symptoms-free days will be analysed using the same descriptive statistics and the same statistical model (linear MMRM) provided for the average pre-dose evening PEF (9.2.2).

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided.

9.2.9 Change from baseline to each inter-visit treatment period and over the entire treatment period in percentage of asthma control days

The following algorithms should be considered for the percentage of asthma control days:

Variable	Definition
Asthma control days	An asthma control day is a rescue medication-free day and an asthma symptom-free day (i.e., total morning asthma symptom score = 0, total evening asthma symptom score = 0 and daily use of rescue medication = 0). A day will be constituted by the data recorded in the evening session of that day plus data recorded in the morning session of the next day. Only days with both evening and morning sessions available will be considered in the calculation of asthma control day.
Baseline percentage of asthma control days	100*(number of asthma control days during baseline (run-in) period / number of days with available data during baseline (run-in) period) Baseline (run-in) period: last 14 days before the start of randomised treatment period. Data recorded in the morning session of the date of start of randomised

	treatment period will be considered a measurement of the baseline period.
Average percentage of asthma control days at each inter-visit period	100*(number of asthma control days during inter-visit period / number of days with available data during inter-visit period) Inter-visit period: 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 randomised treatment period for last inter-visit period).
Average percentage of asthma control days over entire treatment period	100*(number of asthma control days over entire treatment period / number of days with available data over entire treatment period) Entire treatment period: Time interval from the evening session of the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period.

Changes from baseline to each inter-visit treatment period and over the entire treatment period in percentage of asthma control days will be analysed using the same descriptive statistics and the same statistical model (linear MMRM) provided for the average pre-dose evening PEF (9.2.2).

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided.

9.2.10 Change from baseline in pre-dose morning FEV_1 and FVC at each clinic visit

Pre-dose morning FEV_1 will be summarised by treatment group at baseline and at each visit using descriptive statistics. Changes from baseline at each visit will also be summarised by treatment group.

Baseline is the pre-dose morning FEV_1 recorded at Visit 3.

Change from baseline in pre-dose morning FEV_1 at each visit will be analysed using the same MMRM described for the average pre-dose morning PEF (9.2.1). "Visits" will be considered instead of "inter-visits". Overall change from baseline will also be estimated by the model.

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

Pre-dose morning FVC will be analysed analogously.

9.2.11 Change from baseline to end of treatment (Week 12) in the ACQ-6 score

ACQ-6 mean score will be summarised by treatment group at baseline and at each visit using descriptive statistics. Changes from baseline at each visit will also be summarised by treatment group.

Baseline is the ACQ-6 total score recorded at Visit 3.

Change from baseline in ACQ-6 mean score at V9 will be analysed using an ANCOVA model including treatment, region and sex as fixed effects, and baseline value as covariate. The number of patients considered in the model will be provided by treatment group. P-values of the fixed effects and covariate will also be presented. The adjusted means in each

treatment group and the adjusted mean difference between treatments will be estimated by the model with their 95% CIs and p-value.

9.2.12 Subgroup analysis to investigate the impact of COVID-19

9.2.12.1 Change from baseline to each inter-visit treatment period and over the entire treatment period (MMRM) in average pre-dose morning PEF

The same descriptive statistics reported in section 9.2.1 will be summarised for subgroups of patients based on COVID-19 variable ("Y", "N") and will be performed on ITT set.

The same MMRM model reported in section 9.2.1 will also be performed on subgroups of patients based on COVID-19 variable ("Y", "N").

The statistical models will be performed on ITT set.

9.2.12.2 Change from baseline to each inter-visit treatment period and over the entire treatment period in percentage of asthma control days

Same analysis described in 9.2.12.1

9.2.12.3 Change from baseline in pre-dose morning FEV_1 at each clinic visit

The same descriptive statistics reported in section 9.2.10 will be summarised for subgroups of patients based on COVID-19 variable ("Y", "N") and will be performed on ITT set.

The same MMRM model reported in section 9.2.10 will also be performed on subgroups of patients based on COVID-19 variable ("Y", "N").

The statistical models will be performed on ITT set.

9.2.12.4 Change from baseline to end of treatment (Week 12) in the ACQ-6 score

The same descriptive statistics reported in section 9.2.11 will be summarised for subgroups of patients based on COVID-19 variable ("Y", "N") and will be performed on ITT set.

The same ANCOVA model reported in section 9.2.11 will also be performed on subgroups of patients based on COVID-19 variable ("Y", "N").

The statistical models will be performed on ITT set.

10 Safety Analyses

All analyses of safety variables will be performed on the Safety set.

10.1 Extent of Exposure

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

- Extent of exposure (days) = date of last randomised study medication intake - date of first randomised study medication intake +1.

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

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

Descriptive statistics of extent of exposure (days) will be provided by treatment group.
The number and the percentage of patients with the following 2-week categories of extent of exposure will also be presented:

- [0-2)
- [2-4)
- [4-6)
- [6-8)
- [8-10)
- [10-12)
- ≥ 12

10.2 Adverse Events

The AEs will be classified according to the following rules:

- Pre-treatment AE: AE onset date < date of first randomised study medication intake;
- Treatment-Emergent AE (TEAE): date of first randomised study medication intake ≤ AE onset date ≤ date of completion/discontinuation;
- post-study AE: start date > date of completion/discontinuation.

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

The AEs will also be classified in the following categories:

- A Serious AE (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".

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

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

The duration of an AE will be calculated as follows:

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

- missing (when the AE onset date is incomplete or unknown, or when the AE has resolved but with an incomplete or unknown end date, or when the AE onset date is > date of completion/discontinuation and the AE is not resolved).

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

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

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

The number of AEs and the number and percentage of patients experiencing at least one treatment-emergent AEs, SAEs, non-serious AEs, ADRs, serious ADRs, severe AEs, AEs leading to study drug discontinuation and AEs leading to death will be summarised overall by treatment group and also by treatment group, SOC and PT.

Two AEs with the same PT and classified in the same category (pre-treatment AE, TEAE or post-study AE) will be considered as two different events when calculating the "number of events" in the tables.

A table presenting the number of AEs and the number and percentage of patients with at least one AE for the most common TEAEs (reported in ≥ 3% of patients in any treatment group) will be provided by treatment group. PTs will be used for tabulation, sorted by decreasing overall frequency.

The descriptive statistics for treatment-emergent AEs, will be performed for subgroups of patients based on COVID-19 periods.

10.3 Vital signs

Pre-dose vital signs (Heart Rate, systolic and diastolic blood pressure) at each visit and their changes from baseline (from Visit 4 onwards) will be summarised by treatment group using descriptive statistics and the 95% CI of the mean.
Baseline is the vital signs value recorded at Visit 3.

10.4 12-lead ECG

12-lead ECGs will be performed prior to the bronchodilator or study medication administration at Visit 1 and Visit 9.

For 12-lead ECG parameters (HR, QTcF, PR and QRS), the absolute values and the changes from baseline (Visit 1) will be summarised by treatment group using descriptive statistics and the CI of the mean (95% CI for absolute values and 90% CI for the changes from baseline).
Baseline is the 12-lead ECG parameters value recorded at Visit 1 (screening).

The number and the percentage of patients with:

- QTcF >450 ms, >480 ms and >500 ms for males and QTcF >470 ms and >500 ms for females;
- change from baseline in QTcF >30 ms and >60 ms;

- normal, abnormal non clinically significant and abnormal clinically significant;

at Visit 9 will be presented by treatment group.

ECG with QRS > 120 msec and/or PR > 210 msec and/or HR < 45 bpm and/or HR > 110 bpm and/or QTcF > 450 ms for males or QTcF > 470 ms for female, will be flagged as "abnormal" in the listing.

Patients with pacemaker or atrial fibrillation as concomitant disease and ECGs with PR=0 will be excluded from the analysis of 12-lead ECG parameters (see section 7.10.1).

10.5 Asthma exacerbations

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

Only asthma exacerbations started between the date of first randomised study medication intake and the date of completion/discontinuation will be considered in the analysis (i.e., date of first randomised study medication intake ≤ start date ≤ date of completion/discontinuation).

The number of moderate/severe asthma exacerbations and the number and percentage of patients experiencing moderate/severe asthma exacerbations will be summarised by treatment group.
The same statistics will be provided separately for severe asthma exacerbations and moderate asthma exacerbations.

10.6 Laboratory Findings

The following laboratory parameters wil l be recorded at Visit 1 (Screening), and Visit 9 (Week 12/ETV):

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

Biochemistry:
Creatinine, blood urea nitrogen (BUN), fasting serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GT), total bilirubin, alkaline phosphatase, sodium (Na), potassium (K), calcium (Ca), and chloride (Cl) electrolytes.
In addition, only for females of childbearing potential, a serum and urine pregnancy test (β-HCG) will be performed at Visit 1 and Visit 9.

Shift tables from screening 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 of the laboratory parameters.
All laboratory data will be listed with abnormal values flagged.

Pregnancy test results will be only listed.

11 Other Analyses

No other analyses planned.

12 Changes in the Planned Analyses from Study Protocol

The following changes from study protocol have been considered in the SAP V1.0:

Baseline and demographic characteristics

- demographics characteristics, asthma history, smoking status and lung function tests at Visit 1 and Baseline will be presented on Safety, ITT and PP sets, instead of ITT and PP sets as reported in the study protocol.
- Medical/surgical history and concomitant disease will be presented on Safety set, instead of ITT and PP sets as reported in the study protocol.
- Medications will be presented on ITT set only, instead of ITT and PP sets as reported in the study protocol.
- ACQ-6 scores, PEF, use of rescue medication, and asthma scores variables during run-in period will also be presented at baseline.
- In each statistical model the covariate "site" has been replaced by the covariate "region" according to the following categorization:

Region	Cities and provinces	Site number
North China	Beijing, Tianjin, Hebei, Shanxi, part of inner Mongolia	11, 25, 34, 36, 42, 50, 59, 63, 72, 82
Northeast of China	Heilongjiang, Jilin, Liaoning, part of inner Mongolia	21, 60, 76, 78
East China	Shanghai, Jiangsu, Zhejiang, Anhui, Jiangxi, Shandong, Fujian, Taiwan	19, 28, 30, 31, 37, 41, 43, 54, 64, 65, 74
Central China	Henan, Hubei, Hunan	13, 14, 61, 75, 79, 81
South China	Guangdong, Guangxi, Hainan, HK, Macao	07, 08, 10, 51, 56, 62, 66, 67, 68, 71, 73, 77, 83
Southwest of China	Chongqing, Sichuan, Guizhou, Yunnan, Tibet	33, 38, 70, 80
Northwest of China	Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang, part of inner Mongolia	26, 69

Primary and secondary efficacy variables

- For the daily variables recorded by the patients on the e-Diary, the availability of at least seven measurements will be required in each inter-visit period instead of the availability of at least 50% of the measurements as reported in the study protocol.

- A definition of valid Best PEF has been introduced for the analysis of the primary and secondary endpoints based on PEF (described in section 9.1.1 and sections 9.2.1-9.2.3).
- A sensitivity analysis for the primary efficacy variable based on the MMRM model has been added (sensitivity analysis not planned in the study protocol). This analysis is described in paragraph 9.1.1.
- For all the secondary efficacy variables measured repeatedly during the randomised treatment period:
    - Average pre-dose evening PEF;
    - Average daily PEF variability;
    - Average use of rescue medication (number of puffs/day);
    - Percentage of rescue medication-free days;
    - Average total morning asthma symptom score;
    - Average total evening asthma symptom score;
    - Percentage of asthma symptoms-free days;
    - Percentage of asthma control days,

  the "change from baseline over the entire treatment period" will be estimated by the same MMRM model used to estimate the "change from baseline at each inter-visit period". On this regard no ANCOVA model (as, instead, previously stated in the study protocol) will be performed.

Additional Subgroup analysis

- As exploratory analysis, the change from baseline over the entire treatment period and over each inter-visit period in terms of pre-dose morning PEF will be also evaluated by a MMRM model in the following subgroups:
    - Sex (male or female);
    - BMI (<25 kg/m^2, ≥25 kg/m^2)
    - Time since first Asthma diagnosis in years ([1-5) years, ≥ 5 years).

Safety analysis

- Confidence interval for 12-leads ECG parameters (HR, QTcF, PR and QRS): change from baseline will be described with its 90% CI instead of the 95% CI (as reported in the study protocol).
- Abnormalities in ECG:
    - evaluated by QTcF absolute values (by sex) and deviation from baseline:
        - QTcF >450 ms, >480 ms and >500 ms for males and QTcF >470 ms and >500 ms for females;
        - change from baseline in QTcF >30 ms and >60 ms;

      this criteria was not present in the study protocol.
    - Abnormal ECG (i.e., QRS > 120 msec and/or PR > 210 msec and/or HR < 45 bpm and/or HR > 110 bpm and/or QTcF > 450 ms for males or QTcF > 470 ms for female) will be summarised at Visit 9 only (at Visit 1 all ECG parameters should be normal (fulfilling exclusion criterion no.16).
- Descriptive statistics on haematology and blood chemistry parameters (shift table from screening to Week 12) have been added in the Safety section (analysis not planned in the study protocol).

Evaluation of the impact of the COVID-19 Pandemic

- A new variable COVID-19 has been created and stored in ADaM dataset to classify patients as "before" or "during" COVID-19 outbreak, according to EMA guidelines (section 7.13.2)
- Subgroups and sensitivity analysis to check the impact of COVID-19 have been planned (sections 9.2.12).

13 Output

13.1 Software

All statistical analyses and data processing will be performed using Statistical Analysis Systems (SAS®) Software (release 9.4 or later).

13.2 Reporting Conventions

13.2.1 Treatment and Subgroup Descriptors

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

Treatment group	***Descriptor***
Foster® NEXThaler® 100/6 µg, 2 inhalations b.i.d.	Foster NEXThaler
Foster® pMDI 100/6 µg, 2 puffs b.i.d.	Foster pMDI

Output	***Descriptor for visits***
Tables	Visit 1 (Week -4), Visit 2 (Week -2), Visit 3 (Week 0), …
Listings	Just the visit number (1, 2, …) will be presented in the "Visit" column.
Figures	V1, V2, V3, …

Variable	***Subgroups***	***Descriptor***
Sex	"Males"	Males
	"Females"	Females
BMI	"<25"	BMI<25 kg/m^2
	"≥25"	BMI≥25 kg/m^2
Age	"<65"	Age <65 years old
	">=65"	Age >=65 years old
Time since first Asthma diagnosis	"[1-5)"	Time since first Asthma diagnosis <5 years
	"≥5"	Time since first Asthma diagnosis ≥5 years
COVID-19	"N"	Completed/discontinued before COVID-19 outbreak (≤22-Jan-2020)
	"Y"	Completed/discontinued during COVID-19 outbreak (>22-Jan-2020)

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):

- exposure (days), duration of AE (days): whole numbers;
- duration of smoking (years), Time since first Asthma diagnosis (years), treatment compliance, diary compliance, extent of exposure (weeks), average pre-dose morning PEF, average pre-dose evening PEF, average daily PEF variability, average total morning asthma symptom scores, average total morning asthma symptom scores, percentage of rescue medication-free days, percentage of asthma symptom-free days, percentage of asthma control days, average HR (bpm), average QTcF (ms), average PR (ms), average QRS (ms): 1 decimal place;
- average use of rescue medication (number of puffs/day): 2 decimal places;
- change from baseline/screening same as the variable considered.

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

- min, max: same as actual data;
- mean and its confidence limits (unadjusted and adjusted), adjusted difference between means and its confidence limits, SD, median actual data: + 1 decimal place;
- percentage: 1 decimal place;

P-values, if applicable, will be presented with 3 decimal places. If the p-value is less than 0.001 then it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.

13.2.3 Other reporting conventions

Treatments will be presented with the following order in the tables: Foster® NEXThaler® 100/6 µg, Foster® pMDI 100/6 µg.

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

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

Unless otherwise stated, listings will be sorted by patient ID and will have the Study Data Tabulation Model (SDTM) and/or ADaM source data referenced in a footnote.

In a listing, in the case that a patient's record has been continued to the next page, an appropriate identification (e.g., the patient ID number) must be presented at the beginning of that page.

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

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

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

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.

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 arm 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 of 0.8 cm.

13.4 Quality Control

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 from the SDTM datasets by a second statistician/programmer and outputs will be compared
- Listings will be checked by comparing the data in the listings to the SDTM/ADaM datasets.
- All outputs will be compared to the shells.
- Related outputs will be compared for consistency.

14 SAS Code

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

PROC UNIVARIATE DATA=dset NOPRINT;
VAR var1 var2 var3 …varn;
BY byvar; (optional)
OUTPUT OUT=outname
N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std;
RUN;

- **Tables that need frequency counts:**

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

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

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

- **Tables for Time to Discontinuation: Kaplan-Meier estimate and Log-Rank test:**

PROC LIFETEST DATA=ds_in TIMELIST=(0 1.9999 3.9999 5.9999 7.9999 9.9999 11.9999 13.9999 EoT) alpha=.05;
WHERE var1;
*TIME time*status(0);*
STRATA tmt;
RUN;

Notes:

- Time represents the time from baseline to completion/discontinuation;
- Status indicates the censoring indicator (0 = censored);
- Tmt represents the randomised groups;
- Var1 represents the indicator(s) to select the chosen population
- Treatment order: 1 = Foster® NEXThaler® 100/6 µg, 2 = Foster® pMDI 100/6 µg.
- Ds_in= dataset used to perform the analysis.
- EoT should be replaced by the last time to event >12 weeks (if any).

- **Tables that require ANCOVA model for changes from baseline over entire treatment period for Primary Analysis and change from baseline to end of treatment in ACQ-6 and 95% CIs of differences between treatments:**

PROC MIXED data = dataset;
CLASS tmt region sex;
MODEL change = tmt region sex baseline / ddfm=kr;
LSMEANS tmt / om cl;
LSMESTIMATE tmt 'A vs B' 1 -1 / cl;
RUN;

Notes:
- Change represents the change from baseline of the variable;
- Tmt represents the treatment group;
- Region represents the region (pooled sites as per rule reported in section 12);
- Sex represents the patient sex;
- Baseline represents the baseline value of the variable;
- Treatment order: 1 = Foster® NEXThaler® 100/6 µg, 2 = Foster® pMDI 100/6 µg.

- **Tables that require linear MMRM for sensitivity analysis on primary efficacy variable and 95% CIs of differences between treatments:**

PROC MIXED data = dataset;
CLASS tmt visit region sex patient;
*MODEL change = tmt visit tmt*visit region sex baseline baseline*visit / ddfm=kr;*
REPEATED visit / subject=patient type=un;
LSMEANS tmt / om at means cl;
LSMESTIMATE tmt 'A vs B: Overall' 1 -1 / cl;
RUN;

Notes:
- Change represents the change from baseline to each inter-visit period of the variable;
- Tmt represents the treatment group;
- Visit represents the inter-visit period;
- Region represents the region (pooled sites as per rule reported in section 12);
- Sex represents the patient sex;
- Baseline represents the baseline value of the variable;
- Patient represents the Patient Number;
- Treatment order: 1 = Foster® NEXThaler® 100/6 µg, 2 = Foster® pMDI 100/6 µg.

- **Tables that require linear MMRM for diary data (PEF data, rescue medication, asthma symptoms) and pre-dose lung function and 95% CIs of differences between treatments:**

PROC MIXED data = dataset;
CLASS tmt visit region sex patient;
*MODEL change = tmt visit tmt*visit region sex baseline baseline*visit / ddfm=kr;*
REPEATED visit / subject=patient type=un;
*LSMEANS tmt tmt*visit / om at means cl;*
*LSMESTIMATE tmt*visit*
'A vs B: IV Weeks 0-2' 1 0 0 0 0 0 -1 0 0 0 0 0,
'A vs B: IV Weeks 2-4' 0 1 0 0 0 0 0 -1 0 0 0 0,
'A vs B: IV Weeks 4-6' 0 0 1 0 0 0 0 0 -1 0 0 0,
'A vs B: IV Weeks 6-8' 0 0 0 1 0 0 0 0 0 -1 0 0,
'A vs B: IV Weeks 8-10' 0 0 0 0 1 0 0 0 0 0 -1 0,
'A vs B: IV Weeks 10-12' 0 0 0 0 0 1 0 0 0 0 0 -1 / cl;
LSMESTIMATE tmt
'A vs B: Overall' 1 -1 / cl;
RUN;

Notes:
- Change represents the change from baseline to each visit of the variable;
- Tmt represents the treatment group;
- Visit represents the inter-visit period (with the exception of pre-dose lung function parameters where visit represent the clinic visit);
- Region represents the region (pooled sites as per rule reported in section 12);
- Sex represents the patient sex;
- Baseline represents the baseline value of the variable;
- Patient represents the Patient Number;
- Treatment order: 1 = Foster® NEXThaler® 100/6 µg, 2 = Foster® pMDI 100/6 µg.

- *In the model for change from baseline to each inter-visit period in morning PEF, the estimates over the entire treatment period will not be produced*

Labels to be used for pre-dose lung function parameters:
*LSMESTIMATE tmt*visit*
'A vs B: Week 2' 1 0 0 0 0 0 -1 0 0 0 0 0,
'A vs B: Week 4' 0 1 0 0 0 0 0 -1 0 0 0 0,
'A vs B: Week 6' 0 0 1 0 0 0 0 0 -1 0 0 0,
'A vs B: Week 8' 0 0 0 1 0 0 0 0 0 -1 0 0,
'A vs B: Week 10' 0 0 0 0 1 0 0 0 0 0 -1 0,
'A vs B: Week 12' 0 0 0 0 0 1 0 0 0 0 0 -1 / cl;

- **Calculation of adjusted means (least squares means):**

The approach described above will ensure that the least squares means calculated by SAS will be based on:
- coefficients for classification effects (i.e., the effects of categorical covariates) proportional to the margins observed in the group of patients analysed;

– effects of quantitative covariates set equal to their mean values in the group of patients analysed.

The analysis is based on the following steps:

1. generate a dataset by selecting:
   – in case of repeated post-randomisation measurements (e.g., pre-dose FEV_1 at each visit, analysed using a linear MMRM): all the post-randomisation records for patients with at least one available and valid post-randomisation measurement and no missing covariates;
   – in case of single post-randomisation measurement (e.g., average pre-dose morning PEF during the entire treatment period, analysed using an ANCOVA model): all the patients with available and valid response and no missing covariates;
2. in case of repeated post-randomisation measurements, add to the dataset generated in step 1 the records for missing post-randomisation visits of the patients included in the dataset. In the added records the value of the response variable will be missing, but the full information on covariates has to be included;
3. use the dataset obtained as the input dataset for the MIXED or the GENMOD procedure, specifying the following options in the LSMEANS statement:
   – in case of repeated post-randomisation measurements: OM AT MEANS;
   – in case of single post-randomisation measurement: OM.

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

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

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

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

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

Step 2 (added records in *italic*):

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

15 References

1. Santanello N.C., et al., What are minimal important changes for asthma measures in a clinical trial? European Respiratory Journal, 1999. 14: p. 23-27.
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf
3. Meyer et al, Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic. Statistics in Biopharmaceutical Research, 2020, VOL. 12, NO. 4, 399–411

16 List of Tables, Listings and Figures

Raw SAS output of all tables based on statistical models will be also provided.

Flagged tables below (*) will be provided for Key First Results presentation.

Notes for Efficacy Analysis

1) all MMRM models titled as "Change from baseline in <<variable>>"" (i.e: Tables from 14.2.2.2.1.2 to 14.2.10.2 and tables 14.2.14.1.2, 14.2.14.2.2) include change from baseline to each inter-visit period and change from baseline over the entire treatment period.
2) all descriptive tables titled as "Change from baseline in <<variable>>"" (i.e: Tables from 14.2.2.2.1.1 to 14.2.10.1 and tables 14.2.14.1.1, 14.2.14.2.1) include both change from baseline to each inter-visit period and change from baseline over the entire treatment period
3) all MMRM models for pre-dose lung function parameters (FEV_1 and FVC) (i.e: Tables 14.2.11.2, 14.2.12.2, 14.2.14.3.2, include change from baseline to each clinic visit and change from baseline overall.

16.1 Tables

Study Populations, Demography And Baseline Characteristics	
Table No.	***Title***
Table 14.1.1.1	Disposition of Subjects: Screening Failures (Enrolled Set)
Table 14.1.1.2 *	Disposition of Subjects: Randomized Subjects (Randomized Set)
Table 14.1.1.3	Disposition of Subjects by Region and Site (Enrolled Set)
Table 14.1.2	Time to Discontinuation from the Study (Randomized Set)
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16.2 Listings

For each listing: At patient level a flag to highlight the COVID-19 period of the patient:
"before COVID-19"
§ "during COVID-19"

For listings where TLF library code is "Not Available" please refer to external document "MOCK_UP missing in TLFs Chiesi library"

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Listing 16.2.7.2.6	Treatment-Emergent Severe Adverse Events (Randomized Set)
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16.3 Figures

Use the following colors: blue for pMDI and red for the DPI.

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Figure 14.2.1.2-b*	Adjusted Mean Change from Baseline to each Inter-Visit Period in Average Pre-Dose Morning PEF (L/Min) - MMRM Model (Per-Protocol Set)
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