NCT04886999

STATISTICAL ANALYSIS PLAN

STUDY CODE No.: CLI-01535AA0-02

AN EXPLORATORY, DOUBLE-BLIND, RANDOMISED, MULTICENTER, PSYCHOPHARMACOLOGICAL STUDY IN ADULT PATIENTS WITH MODERATE TO SEVERE ASTHMA TO COMPARE TWO PRESSURISED METERED-DOSE INHALERS (pMDIS) ON PATIENTS' PERCEPTION OF ASTHMA SYMPTOMS

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Contents

List of Abbreviations

ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
ANOVA	Analysis of Variance
AQLQ(S)	Standardised Asthma Quality of Life Questionnaire
ATC	Anatomical Therapeutic Chemical Classification
b.i.d.	Bis In Die (twice daily)
BMI	Body Mass Index
CI	Confidence Interval
cm	Centimeter
COVID-19	Corona Virus Disease appeared in 2019
(e)CRF	(Electronic) Case Report Form
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DRM	Data Review Meeting
DRR	Data Review Report
ED	Early Discontinuation
ETV	Early Termination Visit
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
ITT	Intention-To-Treat
kg	Kilogram
LABA	Long-acting β2 agonist
m	Meter
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
µg	Microgram
pMDI	Pressurised Metered Dose Inhaler
PP	Per Protocol
PR	Pulse Rate
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
WHO-DD	World Health Organisation Drug Dictionary

VERSION HISTORY

Version	Date	Change History
1.0	*13 April 2023*	*First version*

1 Introduction

This document presents the Statistical Analysis Plan (SAP) for Chiesi Farmaceutici S.p.A. protocol CLI-01535AA0-02: An exploratory, double-blind, randomised, multicenter, psychopharmacological study in adult patients with moderate to severe asthma to compare two pressurised Metered-Dose Inhalers (pMDIs) on patients' perception of asthma symptoms.

This analysis plan is based on the final protocol (version 2.0, 14 October 2021) and the final electronic case report form (eCRF) (1.0, 06 July 2021).

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

PPD will perform the statistical analyses and is responsible for the production and quality control of all outputs described in this document.

2 Study Design

This is a phase IIIb, exploratory, double-blind, randomised, multicenter, psychopharmacological, 2x2 cross-over study conducted in Italy with approximately 75 subjects randomised in 10 sites.

The whole study will last approximately 6 weeks for each subject and a total of 4 study visits (V1 to V4) will be performed during the study, as follows (See also Figure 1):

2 face-to-face clinic visits:

- Screening/randomisation visit (Visit 1),
- Visit 4 at Day 43.

2 remote video contact visits:

- Visit 2 at Day 15,
- Visit 3 at Day 29.

Subjects who have signed an informed consent will be screened at the investigational site during the Screening/Randomisation Visit (V1).

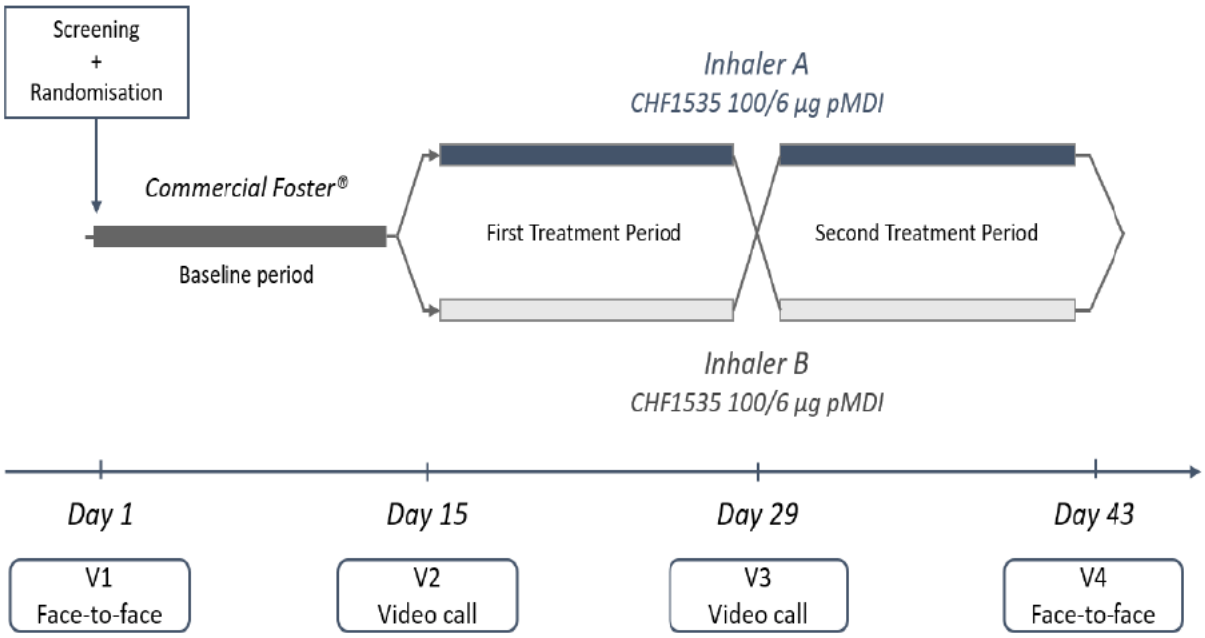
When all the inclusion and exclusion criteria have been checked, eligible subjects will be randomised on the same day.

The subject will follow the study treatment sequence as described below:

- Subjects will be treated with the commercial Foster® during the Baseline Period of 14 days;
- Subjects will be instructed to take CHF1535 100/6 µg pMDI inhalers A and B during 2 consecutive periods of 14 days each (First and Second Treatment Periods) in a sequential way as per the randomisation:
    - Either CHF1535 100/6 µg pMDI with Inhaler A then CHF1535 100/6 µg pMDI with Inhaler B,
    - Or CHF1535 100/6 µg pMDI with Inhaler B then CHF1535 100/6 µg pMDI with Inhaler A

The study design is shown in the diagram below:

Figure 1: Study design



The study plan and scheduled tests are summarised in Table 1 and also described below.

The study plan includes 4 study visits (Visit 1 to Visit 4), as follows:

- Visit 1 at Day 1 / Face to face clinic visit: Screening/randomisation visit, for eligible subjects, this visit will be followed by a 2-week Baseline Period, where the subjects will receive the Baseline treatment, i.e. the commercialised Foster® 100/6 µg pMDI
- Visit 2 at Day 15 / Remote video call: 14 days (± 1 day) after the screening/randomisation visit, to switch study treatment to the corresponding randomised treatment for Treatment Period 1, i.e. CHF 1535 100/6 µg pMDI in Inhaler A or Inhaler B, and for any adverse events (AEs) and concomitant treatment collection
- Visit 3 at Day 29 / Remote video call: 14 days (± 1 day) after Visit 2, to switch study treatment to the corresponding randomised treatment for Treatment Period 2, i.e. CHF 1535 100/6 µg pMDI in Inhaler A or Inhaler B, and for any AEs and concomitant treatment collection
- Visit 4 at Day 43 / Face to face clinic visit: 14 days (± 1 day) after Visit 3, to return the study treatments, to collect any AEs and concomitant treatments and proceed to the study Exit Interview.

Table 1: Schedule of Events

	Baseline	Treatment Period		
Visits	**Visit 1 Screening/ Randomisation**	**Visit 2**	**Visit 3**	**Visit 4 or ED[1]**
Type of visit	**Face to face**	**Remote video call**	**Remote video call**	**Face to face[8]**
Time (days)	**Day 1**	**Day 15**	**Day 29**	**Day 43**
Visits' window (days)		**± 1 day**	**± 1 day**	**± 1 day**
Informed Consent Form	✓			
Inclusion and Exclusion Criteria	✓			
Asthma Diagnosis History (including Asthma exacerbation history)	✓			
Medical History/Previous Medications (including Asthma medication history)	✓			
ACT	✓			
Smoking status	✓			
Demographic Data	✓			
Physical Examination	✓			
Vital Signs	✓			
Body weight	✓			
Height	✓			
Body temperature	✓			
Urine pregnancy test[2]	✓			✓
Adverse Events assessment	✓	✓	✓	✓
Concomitant medications	✓	✓	✓	✓
Randomisation	✓			
Training to treatment kit content and administration schedule[3]	✓			
Treatment kits dispensation[3]	✓			
Treatment administration[4]	✓			
Instruction to subject for treatment kit switch[3]		✓	✓	
Treatment kits return[3]				
Treatment kit accountability[3]	✓	✓	✓	✓
e-Diary app download on subject's device and training	✓			
Check of e-Diary completion by the investigator[5]		✓	✓	✓
AQLQ(S)[6]		✓	✓	✓
e-Diary completion by subjects[7]				
Daily questionnaire: Asthma symptom perception and medication intake	Daily completion			
Psychopharmacological and preference questions		✓	✓	✓
Exit Interview[9]				✓

[1] ED stands for Early Discontinuation visit to be performed in lieu of the V4 for randomised subjects withdrawn from study treatment before Day 43.
[2] For females of childbearing potential only. Urine pregnancy test performed locally.
[3] Assessments to be performed by a Unblinded site personnel, delegated by the Principal Investigator.
[4] This refers to the first drug administration at V1, except in case the subject has taken his/her morning dose of maintenance treatment at home before the visit.
[5] To be checked regularly, at least during scheduled visits and remote video calls. Investigator should retrain subjects on e-Diary timely completion if needed.
[6] Interviewer-administered questionnaire.
[7] Refer to Appendix 1 for the list of questions to be answered at each study time point.
[8] In case the subject is unable to physically come to the investigational site to attend the face to face visit, it is possible to replace it by a remote video call.
[9] The Exit Interview is conducted by the Unblinded Site Personnel.

3 Study Objectives

In subjects with moderate to severe asthma, the following objectives will be assessed and compared:

- The perception of asthma symptoms;
- The psychopharmacological aspects;
- The subjects' preference and perception of the devices;
- The use of reliever medication;
- The quality of life,

after the use of two inhalers of CHF1535 100/6 µg pMDI.

4 Study Variables

4.1 Efficacy Variables

- Change from baseline in average visual analogue scale (VAS) score evaluating subject perceptions of asthma symptoms over the entire 14 days treatment period;
- Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over the first 7 days of treatment;
- Summary measures (descriptive statistics) for questions with continuous outcome covering subjects' psychopharmacological aspects;
- Percentages of subjects to questions covering subjects' preference and perception of the devices;
- Change from baseline in reliever medication use over the entire 14 days treatment period;
- Change from baseline in standardised asthma quality of life questionnaire (AQLQ(S)) score after 14 days of treatment.

4.2 Safety Variables

Occurrence of

- Treatment emergent adverse events (TEAEs),

- Adverse drug reactions (ADRs),
- Severe ADRs,
- Serious ADRs,
- Serious TEAEs (SAEs),
- Non-serious TEAEs,
- Severe TEAEs,
- TEAEs leading to discontinuation from study treatment,
- TEAEs leading to death

4.3 Other Variables

No other variables defined.

5 Sample Size

The sample size calculation is not based on a formal statistical hypothesis, since this is an exploratory study. A total of 75 randomised subjects is deemed sufficient to assess the objectives of the study.

As per our knowledge at the time of the protocol redaction, this is the first psychopharmacological study in adult patients with moderate to severe asthma based on patients' perception of asthma symptoms. At the time of the sample size considerations, no scientific article from previous experiences was available to obtain at a minimum a rough indication of the key parameters (effect size and variability) needed for a proper sample size calculation.

In this study, and in general in every psychopharmacological study which aims at evaluating the "patients' perception", there is not a single formal primary variable to be used as outcome for the sample size calculation.

For these reasons it was decided to proceed with an exploratory study. The present study can be considered as a "pilot" to check for signals to be quantified and potentially used as reference in future studies.

The choice of the sample size, based on the scientific advice received from a Key Opinion Leader in the psychopharmacological and neurobiological field, was in line with previous psychopharmacological studies performed in other therapeutic areas [1][2][3][4][5][6]and is deemed sufficient to ensure for the study outcomes a clinically acceptable degree of precision.

Below are listed some considerations on this regard.

Degree of precision for categorical outcomes:

The categorical outcomes are quantified as proportion of subjects reporting, at the end of the Visit 4 (end of study) the preference on the inhalers used during the study and the changes/differences between them (items 11-16 of the e-diary). By using the formula for the approximation of the binomial distribution to the normal distribution, the degree of precision for the proportion is estimated by the half-width of the 95% confidence interval (CI). In case of a proportion equal to 50% (worst case) the half-width of the 95% CI would be 11.3%. For

proportions greater or lower than 50% the half-with of the 95% CI would be smaller and the precision higher [7].

Degree of precision for "change from baseline in average VAS score":

In the present study the VAS scales measure asthma symptoms in a range 0-100. Based on symptom data from a previous Chiesi cross-over study in asthmatic subjects (TRISKEL, NCT02127866 [8]), an estimate of the within-subject standard deviation (SD) of 5.4 units was obtained for change from baseline in average VAS score. By assuming 75 evaluable subjects, the above estimate of within subject SD leads to a 95% CI with an expected precision (i.e., half width) of ±1.8 units for the mean difference between treatments.

6 Analysis Sets

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

Since the study has a cross-over design, the inclusion in the sets for analysis will be defined on a per-period basis.

6.1 Safety Set

Safety set includes all randomised subjects who receive at least one dose of study treatment in a period. Analyses based on the Safety set will be based on the actual treatment received per period. The Safety set will be used in the analysis of all safety variables.

For Tables presented by Sequence, in case of early discontinuation, the planned sequence will be displayed.

6.2 Intention-to-Treat Set

Intention-To-Treat (ITT) Set includes all randomised subjects who receive at least one dose of the study treatment and with at least one analysable evaluation of efficacy after the baseline (i.e. meaning that for VAS analysis, subject must have average over 14 days (respectively 7 days) available for both periods to be included in the model).

Using this definition, subjects with analysable data just in one treatment period will not be taken into account by the statistical models for the calculation of the treatments difference.

The ITT set analyses will be based on the randomised treatment for each period. The ITT set will be used in the analysis of all efficacy variables.

6.3 Per Protocol Set

Per-protocol (PP) set includes all subjects from the ITT set without any important protocol deviations (i.e., wrong inclusions, poor compliance, non-permitted medications) leading to the exclusion of the subject from the PP analysis. Exact definition of important protocol deviations leading to the exclusion of the subject from the PP analysis will be discussed by the study team during the blind review of the data and described in the DRR before breaking the blind. Since this is a cross-over study, the inclusion in each set will be defined on a per-period basis.

- The efficacy endpoints will be analysed both in the ITT and in the PP set unless otherwise specified.
- The Safety set will be used in the analysis of safety endpoints.

6.4 Other Sets Defined for Tables and Listings

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

- Enrolled set: all subjects who provided informed consent for the study;
- Randomised set: all randomised subjects regardless if study drug received or not.

7 General Considerations for Statistical Analysis

7.1 Statistical Significance

All tests of hypotheses will be two-sided and conducted at the 0.05 significance level. All confidence intervals will be two-sided at the 95% confidence level.

7.2 Multiplicity

Since there is no hypothesis testing involved, no multiplicity adjustment will be performed.

7.3 Handling of Missing Data

Missing efficacy data will not be imputed.

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

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

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

Duration of Smoking

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

- For start date if the day is missing then the first day of the month will be assumed;
- For stop date if the day is missing then the last day of the month will be assumed;
- If the month of start date is missing, January 1st will be assumed;
- If the month of stop date is missing, December 31st will be assumed;
- If the stop date imputed based on the above rules is after the date of informed consent, the date of informed consent, will be assumed as stop date;
- For ex-smokers, if the stop date is missing, the duration of smoking will not be calculated.

Time since Asthma Diagnosis

For the calculation of time since first asthma diagnosis, following rule applies:

- The missing day of first diagnosis is imputed by the first day of the month.

- The missing month of first diagnosis is imputed to January 1st

Time since most recent exacerbation:

For the calculation of time since most recent Asthma exacerbation, following rule applies:

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

Procedures: Missing/Incomplete Date

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

1. Concomitant procedure;
2. Maintained procedure;
3. Prior procedure

Medications: Missing/Incomplete Date

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

1. Concomitant medication;
2. Maintained medication;
3. Prior medication

AEs: Missing/Incomplete Date

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

1. Treatment emergent;
2. Pre-treatment

AEs: Missing Severity

In case of missing severity, the severity will be imputed to the maximum severity possible and will be reported as “Severe”.

AEs: Missing Seriousness

In case of missing seriousness, it will be reported as “Serious”.

Reliever (Rescue) Medications: Number of Inhalations

Data collected in eDiary:

If the number of inhalations is missing, then the number of inhalations will not be imputed.

Data collected during visit at the clinic:

If the number of inhalations is missing but a rescue medication has been administrated, then the number of inhalations will be set to 1.

7.4 Covariates

Not applicable.

7.5 Interim Analyses

No interim analysis will be performed.

7.6 Examinations of Subgroups

No subgroup analysis will be performed.

7.7 Descriptive Statistics

Descriptive statistics will be provided in summary tables by study treatment (except for baseline characteristics, which will be summarised by sequence and overall), according to the type of variable summarised.

General descriptive statistics for quantitative variables will include n (the number of non-missing values), mean, standard deviation (SD), median, minimum (min) and maximum values (max).

For categorical variables, number (n) and percentage (%) of subjects with a specific level of the variable will be presented.

7.8 Definitions

7.8.1 Baseline and Change from Baseline

- **VAS Scores**

VAS daily score will be entered daily by the subject. The assessment/question will always refer to the day before the entry date (i.e. STDTC will be date of completion – 1).

Baseline value is defined as the average of the VAS scores collected during the baseline period: e-Diary collection will start the day after V1 (Study Day 2) to V2 (Study Day 15). Data collected will be covering the symptoms occurred from the Study Day 1 to Study Day 14.

First week value within each treatment period is defined as the average of the VAS scores collected during the first week of treatment within each treatment period (i.e. from Day 1 to Day 7 under treatment collected from Day 2 to Day 8 on e-Diary).

Second week value within each treatment period is defined as the average of the VAS scores collected during the first week of treatment within each treatment period (i.e. from Day 8 to Day 14 under treatment collected from Day 9 to Day 15 on e-Diary).

Overall value each treatment period is defined as the average of the VAS scores collected during the 2 weeks of treatment for each treatment period (i.e. from Day 1 to Day 14 under treatment collected from Day 2 to Day 15 on e-Diary).

The average VAS score during each period defined above will be obtained as follows:

Average VAS score = ∑ non missing VAS score / number of days with non-missing VAS score

Missing VAS score will not be imputed.

Change from baseline will be done over the first week of treatment, over the second week of treatment and overall (14 days of treatment) for each treatment period.

- **Reliever medication**

A day will be considered without intake of rescue medication if the number of puffs on that day is 0.

Missing #puffs will not be imputed. If the number of puffs is missing, then the day will be excluded from the analysis.

eDiary data collected after last treatment visit or after the early discontinuation visit should not be considered in the calculation of the variable. For subjects discontinued without performing the early discontinuation visit, data recorded after the date of discontinuation from the study will not be considered in the calculation of the variable.

Average reliever medication use (puffs/day)

Baseline value is defined as the average value (number of puff/day) collected during the baseline period.

Average value for each treatment period is defined as the average of the value (number of puff/day) collected over the entire 14 days treatment period (i.e. from Day 1 to Day 14 under treatment collected from Day 2 to Day 15 on e-Diary).

The average use (puffs/day) during each period defined above will be obtained as follows:Average #puffs/day = ∑ non missing puffs / number of days with non-missing puffs

Percentage of days without intake of reliever medication

Baseline percentage of days without intake of reliever will be calculated on daily eDiary data collected during the baseline period.

Percentage of days without intake of reliever will be calculated on daily eDiary data collected over the entire 14 days treatment period for each treatment period (i.e. from Day 1 to Day 14 under treatment collected from Day 2 to Day 15 on e-Diary).

The percentage of days without intake of reliever during each period defined above will be obtained as follows:

% of rescue-free days = [(Number of days with no rescue medication use) / (Number of days with non-missing puff)] x 100.

- **AQLQ(S) score**

For AQLQ(S) score, baseline value is defined as the last available value of the AQLQ(S) score collected at the end of the baseline period, during Visit 2 (i.e. study day 15)

AQLQ score will also be collected at Visit 3 and Visit 4 at the end of each treatment period.

For each of the efficacy variables described above, **change from baseline** is defined at each visit (or at each week within a period/entire treatment period) as:

Value at the visit (or week within a 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 (InhalerA/InhalerB) considering the CRF data corresponding to the date part of the variable RFSTDTC in the study data tabulation model (SDTM) dataset DM

The date part of RFXSTDTC will be used to identify the first intake of commercial Foster during the baseline period in the SDTM dataset DM.

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

7.8.3 Study Day

For the purpose of this SAP and the analyses proposed, the first day of study medication administration is referred to as Day 1 i.e. the day on which randomised medication was first taken and not the Day 1 of baseline period and randomisation.

- If the date of the assessment is prior to the first study drug administration date, then

  Study Day = Date of assessment – First study drug administration date.
- If the date of the assessment is on or after the first study drug administration date, then

  Study Day = (Date of assessment – First study drug administration date) + 1.

Treatment period 1 is defined from Study day 1 to Study Day 14, and treatment period 2, from Study day 15 to Study Day 28.

Treatment period 1 - first week is defined from Study Day 1 to Study Day 7, and treatment period 2 - first week, from Study day 15 to Study Day 21.

Treatment period 1 – second week is defined from Study day 8 to Study Day 14 and treatment period 2– second week, from Study day 22 to Study Day 28.

7.8.4 Study Day per Treatment Period

The first day of randomised study medication administration in a particular period is referred to as Day 1. Day -1 is the day that precedes Day 1 within a treatment period.

- If the date of the assessment is prior to the first study drug administration date in a period, then

  Study Day = (Date of assessment in a particular period X – First study drug administration date of the period X), where X=1, 2.

- If the date of the assessment is on or after the first study drug administration date in a period, then

  Study Day = (Date of assessment in a particular period X – First study drug administration date of the period X) + 1, where X=1, 2.

For all assessments performed on Visit 2 and Visit 3, the study day will be derived based on the first study drug administration of the first treatment period. For Visit 4, the study day will be derived based on the first study drug administration of the treatment second period.

For analyses purpose, each week within treatment period will be defined as Week 1 (first week of each Treatment Period) and Week 2 (second week of each Treatment Period). In case a subject stops the study before having the second period study drug administration, then all the study days will be based on the first study drug administration of the first treatment period.

7.8.5 Visit dates

For each visit, the variable SVSTDTC in the SDTM.SV dataset will be considered as the visit date in all the algorithms and the listings. SVSTDTC corresponds to the minimum of all assessments dates performed for a visit.

In case of visit end date (SVENDTC) after the visit start date (SVSTDTC) and if the subject is still under randomised treatment, the end of randomised treatment date will be SVENDTC.

7.8.6 Duration of Adverse Events or Medications

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

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

7.8.7 Study Period Completion and Discontinuation

A subject will be considered as completer for the treatment period 1 if the subject has performed the Visit 3. A subject will be considered as discontinued from period 1 if the subject receives the randomised study drug administration at Visit 2 but stops before Visit 3 or does not perform Visit 3.

A subject will be considered as completer for the treatment period 2 if the subject has performed the Visit 4 and if the subject status is noted "Completed" in the study termination form. A subject will be considered as discontinued if the subject receives the randomised study drug administration at Visit 3 and if the subject status is noted "Early Withdrawal" in the study termination form.

As the V4 will be used to collect data related to the early termination Visit (ETV), we will distinguish:

- V4 – Completer
- V4 – ETV P1
- V4 – ETV P2

According to this distinction, data collected in the case of a V4 – ETV – P1 will be excluded from Period 2 analysis and will be considered in Period 1 analysis.

For the 2 others cases (V4 – Completer or V4 – ETV P2), data collected will be considered in Period 2 analysis.

7.9 Diary Data

At screening Visit 1 subject e-Diary app will be downloaded on subject's own electronic device and training will be conducted. A comprehensive training will be performed at Screening/randomisation (Visit 1) by the Investigator using the training module built-in the e-Diary app. Subjects will be asked to answer specific questions at specific time points.

e-Diary will be used to record study specific subject's questionnaire which includes 16 questions. Some questions are asked on daily basis whereas some questions have to be completed on specific visits (Visit 2, Visit 3 or Visit 4, refer APPENDIX I for details).

7.10 Data Re-allocation

7.11 Exclusion of Data from the Statistical Analyses

7.11.1 Exclusion of Data from All Statistical Analyses

As a general rule, all data collected in the database will be used in all statistical analyses.
For the data recorded in e-Diary, any records related to data occurred after the date of end of randomised treatment period/end of the study will not be considered in the calculation of compliance and of the efficacy variables. In case of duplicate e-diary data (more than one set of answers on the same day), the set of answers entered first will be considered in the analysis.

If for any reason the subject is filling the e-diary after Day 14, the data collected after will not be used in the efficacy analysis.

7.11.2 Exclusion of Data from Per Protocol Analyses

Important protocol deviations leading to the exclusion of the whole subject from the PP analysis, or to the exclusion of isolated data from the PP analysis will be documented in the DRR before breaking the blind.

7.12 Listings

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

Data collected in eDiary after the study completion will not be presented.

All the variables derived from the diaries used in the analyses will be presented in the listings. All listings will be presented for the randomised analysis set, unless specified otherwise.

7.13 Coding

Medical and surgical history, concomitant diseases, procedures and adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher.
Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version March 2021 or later.

7.14 Other Considerations

7.14.1 Impact of COVID-19 Pandemic

Since this study has been conducted during the COVID-19 pandemic, impact on the assessments on the subjects have to be evaluated:

- No impact is expected on efficacy endpoints.
- No spirometry endpoints are planned in the study that could be significantly impacted by the COVID-19 pandemic.

In conclusion no subgroup analysis, no specific summary tables or flag will be applied.

8 Study Population

8.1 Disposition of Subjects and Discontinuations

8.1.1 Disposition of Subjects

The number of enrolled subjects, the number of randomised subjects, the number of screen failures and the reasons for screen failure will be presented (overall) based on Enrolled Set.

8.1.2 Discontinuation from the Study

The number of subjects who completed the study, discontinued the study, the reasons for withdrawal from the study will be presented by sequence and overall using the Randomised Set.
The number of subjects who completed the treatment periods, discontinued the treatment periods will be presented by treatment using the Randomised set.

The number of subjects randomised, completed the treatment period, discontinued the treatment period, completed the study and discontinued the study will be presented by treatment and by site using the Randomised set.

Discontinuations during treatment are allocated to the treatment period during which discontinuation occurred.

An individual subject listing will be provided for the disposition data. A flow chart of study disposition will be presented.

8.1.3 Protocol Deviations and Analysis Sets

Important protocol deviations will be categorised according to following categories:

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

Trial ProceduresOther categories may be added and will be discussed during the DRM and documented in the DRR before breaking the blind.

Important protocol deviations will be summarized by treatment using the ITT Set. Important protocol deviations occurring during the baseline period will be reported only in the overall column.

The number of subjects included in each of the ITT, Safety and PP sets will be summarized for each treatment and overall using the Randomised Set.

A flow chart of analysis sets will also be presented.

8.2 Demographic and Baseline Characteristics

No formal comparison between treatments on demographic and baseline characteristics will be performed. As a general rule, for all the assessments performed more than once during the screening period, the last available data will be used as demographic variable.

8.2.1 Demographic Characteristics

Demographics variables will be summarised by sequence and overall using descriptive statistics for the ITT set.

The following variables will be presented: age (years), age category (years), sex, race, height (cm), weight (kg), and body mass index (BMI, kg/m^2).

Analysis will be presented for the Safety set (if different from the ITT set) and the PP set (if different from the ITT set) for the same variables.

Notes:

- Age categories are: < 18 years; 18-64 years; 65-84 years; >= 85 years. All categories must be reported even if there are no subjects under a particular category.

8.2.2 Smoking Status

Smoking status, duration of smoking (years) and number of pack-years recorded at Visit 1 will be presented by sequence and overall using the Safety set. Separate summaries will be produced using the ITT and PP sets if different.

Notes:

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

8.2.3 Asthma History

Time since first asthma diagnosis (years), asthma medication category at pre - trial (Foster 100/6 µg maintenance (2 puffs BID), Foster 100/6 µg maintenance (1 puff BID), Foster 100/6 µg maintenance (2 puffs once a day), Foster 100/6 µg MART (1 puff BID + puffs as needed), Foster 100/6 µg MART (2 puffs BID + puffs as needed), other), number of exacerbations in the 12 months prior to Screening and time since most recent exacerbation will be summarised by sequence and overall. Separate summaries will be produced using the Safety, ITT and PP sets if different.

Notes:

- Time since first asthma diagnosis (years) will be calculated as (date of Visit 1 – date of first asthma diagnosis)/365.25;
- Time since most recent exacerbation (months) will be calculated as (date of Visit 1 – date of most recent exacerbation end)/30.4375.

8.2.4 Asthma Control Test (ACT)

ACT total score at Visit 1 will be summarised using descriptive statistics by sequence and overall based on the Safety set. The domain scores will also be summarised.

Separate summaries will be produced using the ITT, Safety and PP sets if different.

8.3 Medical History and Concomitant Diseases

Medical/surgical history will be summarised by System Organ Class (SOC), Preferred Term (PT), sequence and overall. Concomitant diseases will be summarised by SOC, PT, Sequence and overall respectively using the Safety set.

Notes:

- Medical/surgical history is defined as conditions in the medical/surgical history and concomitant diseases eCRF form which are not ongoing at Visit 1 (even if end date is missing);
- Concomitant diseases are defined as conditions in the medical/surgical history and concomitant diseases eCRF form which are ongoing at Visit 1.

In addition, medical, surgical and concomitant diseases data will be listed.

8.4 Medications

Prior medications will be summarised by sequence and overall using Safety set. Medications maintained during the randomised treatment period, concomitant medications will be summarised by treatment using Safety set. Table will be presented 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, alphabetically sorted.

The medications will be classified according to the following rules:

- Prior medication: start date < date of first randomised study medication intake (study-level) and medication stop date ≤ date of first randomised study medication intake (study-level);
- Medication maintained during the randomised treatment period: start date < date of first randomised study medication intake (study-level) and medication stop date > date of first randomised study medication intake (study-level) or ongoing at the end of study;
- Concomitant medication: date of first randomised study medication intake (study-level) ≤ start date < date of last randomised study medication intake (study-level);

Since this is a cross-over study, for the purpose of inclusion in tables, the following rules will be applied for assigning medications to a specific treatment:

- Prior medications will not be assigned to treatments since they will be summarised by sequence/overall.
- Maintained and concomitant medications will be assigned to the treatment(s) received by the subject whilst using the medication, by comparing the start and stop date of medication and the date of each dose. A concomitant/maintained medication could be assigned to more than one treatment.
- Where a medication, start and/or stop date is fully or partially missing, so that it's unclear as to which treatment the medication is associated, the medication will be assigned to all treatments.

In the summaries, subjects experiencing more than one medication classified in the same category (prior medications, maintained medications during the treatment period, concomitant medications) within the same anatomical main group, therapeutic subgroups, chemical subgroup and preferred name will be counted only once.

Asthma medications and non-asthma medications will be summarised separately.

Any medications with an indication 'ASTHMA' will be considered as asthma medication. Classification of medications in asthma medication and non-asthma medications will be reviewed during the DRM and documented in the DRR.

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

8.5 Procedures

Prior procedures will be summarised by sequence and overall using Safety set. Procedures maintained during the randomised treatment period, concomitant procedures will be summarised by treatment using Safety set. The table will be summarised for the Safety set through frequency distributions and percentages by MedDRA SOC and PT.

The procedures will be classified according to the following rules:

- Prior procedures: start date < date of first randomised study medication intake (study-level) and procedure end date ≤ date of first randomised study medication intake (study-level);
- Procedures maintained during the randomised treatment period: start date < date of first randomised study medication intake (study-level) and end date > date of first randomised study medication intake (study-level) or flagged as "Ongoing";
- Concomitant procedures: date of first randomised study medication intake (study-level) ≤ start date < date of last randomised study medication intake (study-level);

For the purpose of inclusion in tables, the following rules will be applied for assigning procedures to a specific treatment:

- Prior procedures will not be assigned to treatments since they will be summarised by sequence.
- Maintained and concomitant procedures will be assigned to the treatment(s) received by the subject whilst procedure has taken the place, by comparing the start and stop date of procedure and the date of each dose. A concomitant/maintained procedure could be assigned to more than one treatment.
- Where a procedure start and/or end date is fully or partially missing, so that it's unclear as to which treatment the medication is associated, the procedure will be assigned to all treatments.

8.6 Compliance

Compliance during baseline period (i.e. compliance to commercial Foster ® 100/6 µg pMDI) and during treatment period (i.e. compliance to Inhaler A and Inhaler B) will be evaluated on the basis of the information recorded daily by the subject on the intake of the study medication in the eDiary based on questions #1 of the study specific subject's questionnaire (see APPENDIX I for the list of questions).

8.6.1 Commercial Foster ® compliance (baseline period)

Compliance to commercial Foster ® 100/6 µg pMDI taken during baseline period will be evaluated on the basis of the information recorded daily by the subject in the eDiary (except if the subject will take the first dose during the clinic visit, the information will be collected then in eCRF directly). The evaluation of compliance will be done using the following formula:

% of administered drug during Baseline = (Total number of administered doses during baseline period / Total number of scheduled doses during Baseline period) x100

The total number of scheduled doses will be calculated on the basis of the extent of exposure (days) of each subject. A range of 80-120 % will be taken into account for a satisfactory level of compliance.

Note: The first administration of the baseline treatment will take place at the clinic visit unless subject has already taken his morning dose of maintenance treatment before the PIS/ICF signature at study site. In this latter case, subject will be instructed to take the first dose of study baseline medication provided by the unblinded site personnel at subject's home in the evening of the Visit 1, preferably before 10.00 pm.

In case of first dose at the clinic visit, this dose will be taken into account for exposure and for compliance calculation.

- The total number of administered doses will be calculated as the total number of inhalations taken during the baseline period.
- The total number of scheduled doses will be calculated on the basis of the treatment exposure (days) of each subject:

  Total number of scheduled doses = Treatment exposure (days) x 4 (2 inhalations b.i.d. = 4 inhalations).
- Treatment exposure (days) will be calculated as:

  Treatment exposure of baseline period (days) = (Date of last baseline medication intake - Date of first baseline medication intake + 1)

Compliance to commercial Foster ® 100/6 µg pMDI taken during baseline period, will be presented by sequence and overall on ITT Set.

Compliance during the baseline period will be also presented for the following categories: <80%, ≥80% and ≤120%, >120%.

8.6.2 Treatment compliance

Treatment compliance will be evaluated on the basis of the information recorded daily by the subject in the eDiary. The evaluation of compliance will be done using the following formula within each period:

% of administered drug during period X = (Total number of administered doses during that period / Total number of scheduled doses during that period) x100, where X = 1,2

The total number of scheduled doses will be calculated on the basis of the extent of exposure (days) of each subject within each period. A range of 80-120 % will be taken into account for a satisfactory level of compliance.

For all subjects, the last dose collected in the study termination visit form recorded in EDC will be assumed to be 2 puffs except if study discontinuation date is not equal to last study treatment dose date (i.e. no additional puff to add).

Notes:

- The total number of administered doses will be calculated as the total number of inhalations taken within each period (collected on eDiary).
- The total number of scheduled doses will be calculated on the basis of the treatment exposure (days) of each subject within each period:

  For subject who completed treatment period 1 and for subject who discontinued during treatment period 1 and where study discontinuation date is not equal to last study treatment dose date: Total number of scheduled doses = Treatment exposure during Period 1 (days) * 4

  For all other cases: Total number of scheduled doses = [Treatment exposure (days) * 4] -2
- Treatment exposure (days) within each period will be calculated as:

  Treatment exposure of period X (days) = (Date of last randomised study medication intake of that period - Date of first randomised study medication intake of that period + 1), where X= 1, 2.

Treatment interruptions are not taken into account for treatment exposure.

Treatment compliance will be summarised by treatment group on ITT set. Descriptive summaries of treatment compliance (%) will be presented by treatment. Treatment compliance during the randomised study period will be also presented for the following categories: <80%, ≥80% and ≤120%, >120%.

8.6.3 eDiary compliance

eDiary compliance during baseline and treatment period will be evaluated on the basis of the information recorded daily from Visit 1 to Visit 4 by the subject in the eDiary. The evaluation of compliance will be done using the following formula:

- For baseline period:

% of days of completed eDiary = (The total number of days eDiary is completed during baseline period/Total number of days eDiary is expected to be completed) x100

The total number of days eDiary expected will be calculated on the basis of the extent (days) of exposure of each subject.

- For each Treatment Period:

% of days of completed eDiary = (The total number of days eDiary is completed during each Treatment period/Total number of days eDiary is expected to be completed within each period) x100.

The total number of days eDiary expected will be calculated on the basis of the extent (days) of exposure of each subject.

eDiary compliance during baseline period, will be presented by sequence and overall on ITT Set.

eDiary compliance during treatment period, will be presented by treatment on ITT Set.

eDiary compliance will also be tabulated using frequency number (n) and percentage (%) using [0%-50%], (50%-60%], (60%-70%], (70%-80%], (80%-90%], (90%-100%] as categories.

Summaries will be presented in ITT Set.

9 Efficacy Analyses

9.1 Efficacy Variables

9.1.1 Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over the entire 14 days treatment period

This analysis will be performed on the ITT and PP sets using a linear mixed model for repeated measures including subject, period, treatment, timepoint (i.e. from Day 1 to Day 7 and from Day 8 to Day 14 of each treatment period), period by timepoint interaction, and treatment by timepoint interaction as fixed effects. Baseline value will not be included as covariate because it is common for the two periods and the inter-subject differences are already accounted for by the subject effect. An unstructured covariance matrix within period 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 and their 95% CIs will be estimated by the model (this analysis will assign equal weights to the two timepoints). Statistically significant difference between treatments is defined as $p<0.05$. Missing data will not be imputed. This analysis will be applied on questions #3, #4, #5 and #6 of the study specific subject's questionnaire collected daily using a VAS score (see APPENDIX I for the list of questions). Each question will be analysed separately.

Adjusted mean change from baseline at each timepoint by treatment group estimated by the model will be plotted using line graph for mean ± 95% CI.

Additionally, average VAS scores and change from baseline at each timepoint and over the entire 14 days period will also be summarised using descriptive statistics.

9.1.2 Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over the first 7 days of treatment

This analysis is already included in the model presented in 9.1.1. The analysis will be performed separately for each question collected daily in the first 7 days of each period. Missing data will not be imputed.

Additionally, daily scores and change from baseline at each day will also be summarised using descriptive statistics and the mean change on VAS score will be plotted using line graph for mean ± SD.

9.1.3 Summary measures for questions with continuous outcome covering subjects' psychopharmacological aspects

Summary statistics will be presented on the ITT and PP sets by treatment group. This analysis will be applied on questions #7, #8, #9 and #10 of the study specific subject's questionnaire collected at baseline and over 14 days of treatment. Each question will be analysed separately. The list of all the questions is reported in APPENDIX I.

9.1.4 Percentages of subjects to questions covering subjects' preference and perception of the devices

Number and percentage of subjects will be reported on the ITT and PP sets by treatment group along with their 95%CI. This analysis will be applied on questions #11, #12, #13, #14, #15 and #16 of the study specific subject's questionnaire collected only at V4. Each question will be analysed separately. The list of all the questions is reported in APPENDIX I.

9.1.5 Reliever medication use over the entire 14 days treatment period

Those analyses will be applied on questions #2 of the study specific subject's questionnaire collected daily (see APPENDIX I for the list of questions).
Average reliever medication use (puff/day) and percentage of days without intake of reliever medication will be presented.

9.1.6 Change from baseline in average reliever medication use (puffs/day) over the entire 14 days treatment period

Average use (puffs/day) during baseline, average use (puffs/day) during treatment period (over the entire 14 treatment days) and change from baseline will be derived as described in section 7.8.1.

Actuals values and change from baseline will be summarized on the ITT set by treatment group.

9.1.7 Change from baseline in percentage of days without intake of reliever medication over the entire 14 days treatment period

Percentage of days without intake of reliever medication during baseline, percentage of days without intake of reliever medication during treatment period (over the entire 14 treatment days) and change from baseline will be derived as described in section 7.8.1.

Actuals values and change from baseline will be summarized on the ITT set by treatment group.

9.1.8 Change from baseline in AQLQ(S) score after 14 days of treatment

The standardised AQLQ scoring system is used to assess quality of life of asthma subjects in this study. It consists of 32 questions divided in 4 domains and has a 7-point scale to assess subject's condition. Only one response is allowed per question and a subject must answer all the questions.

The domains and the items in each domains are:

Activity limitation	Items: 1 to 5,11,19,25,28,31,32
Symptoms	Items: 6,8,10,12,14,16,18,20,22,24,29,30
Emotional function	Items: 7,13,15,21,27
Environmental stimuli	Items: 9,17,23,26

The domain scores as well as the overall AQLQ(S) score will be derived as follows:

Domain score = $\sum$ score of each item/ number of available items in that domain

Overall AQLQ(S) score = ∑ score of each 32 domains/ number of available items in overall AQLQ

Handling missing AQLQ(S) score:

The developer suggests no more than 10% of missing data. This means no more than 3 missing responses for the overall score and no more than 1 missing response per domain. For symptoms and activity domain scores, one missing value per domain is allowed. For the emotional function and environmental stimuli domain scores, no missing values are allowed. If these limits for missing questions are exceeded, the variable will be considered missing and will not be imputed [10].

Change from baseline in AQLQ(S) score after 14 days of treatment in each of the randomised treatment periods, will be analysed on the ITT set by an analysis of variance (ANOVA) model including treatment, period and subject as fixed effect.

Baseline value is defined as in section 7.8.1.

Overall AQLQ(S) score at each visit and change from baseline in overall AQLQ(S) score and domains will be summarised by treatment using descriptive statistics on ITT set.

Change in overall AQLQ(S) score at each visit may be plotted using mean ± SD.

Domain scores will be summarised and listed. Raw scores will only be included in the derived SAS dataset.

AQLQ(S) response will be categorised as:

Improved:	Change in AQLQ(S) score ≥ 0.5
Worsened:	Change in AQLQ(S) score ≤ -0.5
No change:	-0.5 < Change in AQLQ(S) score < 0.5

Number and percentage of subjects with each AQLQ(S) response after 14 days of treatment will be presented for overall score and for each domain.

10 Safety Analyses

Safety endpoints will be presented using descriptive statistics (section 7.7). Safety analysis will be based on the Safety set using actual treatment received.

10.1 Extent of Exposure

Descriptive statistics of treatment exposure (days) as described in section 8.6.2 and 8.6.2 will be presented by treatment on the Safety set for the randomised treatment period.

10.2 Adverse Events

An AE will be classified as pre-treatment AE if it starts after the informed consent signature and before the first randomised study medication intake (AE onset date < date of first randomised study medication intake).

All adverse events starting on or after the time of first study drug intake will be classified as TEAE. Pre-Treatment Adverse Events will only be listed.

In the study, for the purpose of inclusion in tables, TEAEs will be classified on a per period basis as follows (refer section 7.3 in case of missing data):

- If first administration date/time of treatment period 1 ≤ AE onset date/time < first administration date/time of treatment period 2, then the AE will be assigned to the 1st treatment of the sequence;
- If first administration date/time of treatment period 2 ≤ AE onset date/time, then the AE will be assigned to the 2nd treatment of the sequence;

Any adverse events started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse event.

Where an AE start and/or end date is fully or partially missing, so that it's unclear as to which treatment the AE is associated, the AE will be assigned to all treatments.

The number of TEAEs, serious TEAEs (SAEs), adverse drug reactions (ADRs), severe ADRs, serious ADRs, non-serious TEAEs, severe TEAEs, TEAEs leading to discontinuation from study treatment, TEAEs leading to death and the number and percentage of subjects experiencing TEAEs, SAEs, ADRs, severe ADRs, serious ADRs, non-serious TEAEs, severe TEAEs, TEAEs leading to discontinuation from study treatment, TEAEs leading to death will be summarised by treatment.

The SOC and PT will also be used for tabulation. The number and percentage of subjects with at least one TEAE and the number of TEAEs will be presented by SOC and PT by treatment group for TEAEs, Serious TEAEs, ADRs, severe ADRs, serious ADRs, non-serious TEAEs, severe TEAEs, TEAEs leading to discontinuation from study treatment and TEAEs leading to death.

10.3 Vital Signs

Vital signs parameters, body temperature (ºC), systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg) and pulse rate (beats/min) collected at Visit 1 will be summarised on Safety set.

10.4 Pregnancy Test

Results of urine pregnancy test will only be listed.

10.5 Physical Examination

Physical examination results at Visit 1 will only be listed.

11 Other Analyses

No other analyses planned.

12 Changes in the Planned Analyses from Study Protocol

Following changes are made to protocol specified analyses:

- Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms will be presented also for PP set.
- Percentage of days without use of reliever medication has been added.
- Categorical summary for AQLQ(S) response has also been added.

13 Output

13.1 Software

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

13.2 Reporting Conventions

13.2.1 Treatment, Visit and Subgroup Descriptors

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

Descriptor for treatment	Treatment group
Commercial Foster®	CHF 1535 100/6 µg pMDI 2 inhalations b.i.d. during baseline period
Inhaler A	CHF1535 100/6 µg pMDI 2 inhalations b.i.d. using inhaler A
Inhaler B	CHF1535 100/6 µg pMDI 2 inhalations b.i.d. using inhaler B

Treatment sequence (as displayed in the outputs)	Descriptor for treatment
Inhaler A//Inhaler B	CHF1535 100/6 µg pMDI 2 inhalations b.i.d. using inhaler A // CHF1535 100/6 µg pMDI 2 inhalations b.i.d. using inhaler B
Inhaler B//Inhaler A	CHF1535 100/6 µg pMDI 2 inhalations b.i.d. using inhaler B // CHF1535 100/6 µg pMDI 2 inhalations b.i.d. using inhaler A

Output	Descriptor for visits
Tables	Baseline, Visit 1 (Day 1), Visit 2 (Day 15), Visit 3 (Day 29), Visit 4 (Day 43) Periods will be presented as Baseline, First Week, and Second Week, Overall

Listings	Just the visit name (Visit 1, Visit 2, Visit 3 and Visit 4) will be presented in the "Visit" column. Periods will be presented as Baseline, Period 1, Period 2, Week 1, Week 2 and Overall. Daily measure will be presented as Day 1, Day 2 […].
Figures	V1, V2, V3, …

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):

- Duration of smoking (years), time since initial diagnosis of asthma (years): whole numbers;
- BMI, compliance, percentage of days without intake of rescue medication, average use of rescue medication (daily mean number of puffs), % of days of completed eDiary, AQLQ scores, Average for VAS scores: 1 decimal place;
- Change from baseline: 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;
- adjusted mean and its confidence limits, adjusted difference between means and its confidence limits, SD, median, first and third quartiles: actual data + 1 decimal place;
- percentage: 1 decimal place;
- odds ratio and its confidence limits: 3 decimal places;

p-values will be presented to 3 decimal places. If the p-value is less than 0.001, it will be presented as <0.001.

13.2.3 Other reporting conventions

Treatments will be presented with the following order in the tables: commercialised Foster® 100/6 µg pMDI, CHF1535 100/6 µg pMDI (Inhaler A), CHF1535 100/6 µg pMDI (Inhaler B).

Unless otherwise stated, listings will be sorted by Subject ID.

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

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

In the top left portion of each table/listing, a table/listing number followed by the title of the table/listing will be presented. After the title line, optional sub-title or analysis set information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. Footnotes will be put under the main body of text at the bottom of the page.

The sponsor name, protocol number, status of the table/listing (i.e. draft or final) and SAS program name will appear bottom left in a string and the page number will appear on the bottom right corner of each table/listing. The date and time of creation of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

Tables and listings will be produced in rich text format (i.e., they will tabular in format).

A landscape layout will be used for both tables and listings.

The left and right margins of all tables and listings 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.

A 9-point font size for tables and 7 or 8-point font size for listings will be used using Courier New font. A maximum SAS line size=141 and page size=44 for 8-point font size, and line size=161 and page size=50 for 7-point will be used so as to fit on both UK and US paper sizes.

A portrait layout will be used for figures.

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

The size of the figures (except forest plot) will be: width=16.3 cm height=12.2 cm. The size of forest plot figures will be: width=16.3 cm height=20 cm. The resolution will be set using the option IMAGE_DPI=400.

All tables, listings and figures will be collated into three Microsoft Word complete documents. If the listings are too large to be included in one file, they will be separated into manageable sized files. The Microsoft Word documents will be subsequently converted in PDF format. Both, Word and PDF documents will include a table of contents with hyperlinks.

13.4 Quality Control

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

14 SAS Code

14.1 Mixed model for repeated measures for change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over 7 days and 14 days of treatment:

```
PROC MIXED DATA = dataset;
    CLASS tmt period atpt subject;
    MODEL change = subject period tmt atpt period*atpt tmt*atpt / DDFM=KR;
    REPEATED atpt/SUBJECT=subject*period TYPE=UN;
    LSMEANS tmt tmt*atpt/ cl;
    LSMESTIMATE tmt*atpt
    'Inhaler A vs. Inhaler B over Week 1'  1 0 -1 0  ,
    'Inhaler A vs. Inhaler B over Week 2'  0 1 0 -1/ CL,
LSMESTIMATE tmt  'Inhaler A vs. Inhaler B: Overall'       1 -1 / cl;

RUN;
```

Notes:

- *"change": change from baseline to each visit/timepoint of the variable;*
- *"tmt": treatment group (treatment order: 1 = Inhaler A, 2 = Inhaler B);*
- *"atpt": timepoint of interest;*
- *"period": treatment period (1 and 2);*
- *"subject": subject number;*

14.2 ANOVA model for change from baseline in AQLQ(S) score after 14 days of treatment:

```
PROC MIXED DATA = dataset;
    CLASS tmt period subject;
    MODEL change = tmt period subject / DDFM=KR;
    LSMEANS tmt / om at means cl;
LSMESTIMATE tmt
    'Inhaler A vs. Inhaler B'   1 -1 / CL;
RUN;
```

Notes:

- *"change": change from baseline to Day 14*
- *"tmt": treatment group (treatment order: 1 = Inhaler A, 2 = Inhaler B);*
- *"period": treatment period (1 and 2);*
- *"subject": subject number;*

14.3 Tables that need descriptive statistics – continuous variables:

PROC MEANS DATA=dataset 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;

Notes:

- *"varn": variable for which summary statistics will be presented;*
- *"byvar": list of "by" variables;*

14.4 Tables that need frequency counts:

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

Notes:

- *"byvar": list of "by" variables;*
- *"var1 and var2": variables for which counts and percentages will be presented;*

14.5 Tables that need 95%CI on frequency counts:

PROC FREQ DATA=dataset NOPRINT;
BY tmt
TABLES var/ OUT= cnt binomial;
EXACT binomial;
ODS OUTPUT binomial=bin (where=(name1 in ('XL_BIN', 'XU_BIN')));
RUN;

Notes:

- *"tmt": treatment group (treatment order: 1 = Inhaler A, 2 = Inhaler B);*
- *var: variable of interest*
- *XL_BIN: 95% lower Conf Limit*
- *XU_BIN: 95% Upper Conf Limit*

15 References

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10. AQLQ Background October 2018

16 List of Tables, Listings and Figures

16.1 Tables

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

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.1	Subject Disposition: Screening Failures (Enrolled Set)	DST001	- Only 'Overall' column will be displayed	Source: Listing 16.2.1.1
Table 14.1.1.2	Disposition by Sequence (Randomised Set)	DST002	- This table will be presented by sequence. - Overall column should be displayed. - Display 'Randomised' 'Completed the Study', 'Discontinued the Study', 'Primary Reason for Study Discontinuation'.	Source: Listing 16.2.1.2

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.3	Disposition by Treatment (Randomised Set)	DST003	- This table will be presented by treatment. - If a subject discontinues during Period 1 then the reason of end of study will be displayed in the column of treatment received during first period. - If a subject discontinues during Period 2 then the reason of end of study will be displayed in the column of treatment received during second period. - Use the V4 status to distinguish V4/ETV as noted in section 7.8.7 -Add as first line 'Randomised'.	Source: Listing 16.2.1.2 Add the footnotes: [1] Treatment period 1 starts at Visit 2 and stops at Visit 3. Treatment period 2 starts at Visit 3 and stops at Visit 4. [2] A subject will be considered as Completer in period 1 if Visit 3 is performed. A subject will be considered as Completer in period 2 if Visit 4 is performed and if the status of the subject is "Completed". [3] Visit 4 could be used as an early termination Visit, if the subject is discontinued before the start of the second period, the data collected at Visit 4 are not analysed as from the period 2.
Table 14.1.1.4	Disposition by Site (Randomised Set)	DST004	- This table will be presented by treatment. - 'Overall' column should be displayed - Do not display Enrolled - Display: 'Randomised', 'Treatment Completed', 'Treatment Discontinued', 'Study Completed', 'Study Discontinued'. - Replace 'Country' with 'Site'.	Source: Listing 16.2.1.2

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.5	Attendance at Treatment Periods by Sequence (Randomised Set)	SVT002	- Overall column should be displayed. - Study Period to be displayed: • Treatment Period 1 • Treatment Period 2	Source: Listing 16.2.1.4 Footnote: [1] a subject will be considered as entering a treatment period if he takes at least one dose of the study treatment period.
Table 14.1.1.6	Important Protocol Deviations (Intention-To-Treat Set)	DVT001	- This table will be presented by treatment. - 'Overall' column should be displayed. - Important protocol deviations which cannot be linked to a specific treatment period (i.e. occurred during baseline period) will be reported in overall column only. Deviation Category is DVSCAT. Deviation Type is DVDECOD.	Source: Listing 16.2.2.1 Footnote: [1] Important protocol deviations occurring during the baseline period are reported in the overall column.
Table 14.1.1.7	Important Protocol Deviations Leading to the Exclusion from the PP Analysis (Intention-To-Treat Set)	DVT001	Same as Table 14.1.1.6	Same as Table 14.1.1.6

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.8	Analysis Sets per Period by Treatment (Randomised Set)	DST006	- Display count for ITT, PP and Safety sets. - Table will be presented by treatment and 'Overall' column should be displayed	Source: Listing 16.2.3.1 Footnotes: [1] Safety Set includes all randomised subjects who receive at least one dose of study treatment in a period. [2] Intention-To-Treat (ITT) Set includes all randomised subjects who receive at least one dose of the study treatment and with at least one available evaluation of efficacy after the baseline. [3] Per Protocol (PP) Set includes all subjects from the ITT set without any major protocol deviations (e.g. wrong inclusions, poor compliance, non-permitted medications).
Table 14.1.2.1	Demographic Characteristics (Safety Set)	DMT001	- Present 'Age (years)', 'Age Category (years)', 'Sex, 'Race', 'Height (cm)', 'Weight (kg)' and 'Body Mass Index (BMI, kg/m^2)' at V1. - Table will be presented by sequence and 'Overall' column should be displayed. - In case of discontinuation between 2 treatment period, please display the planned treatment in the subject sequence.	Source: Listing 16.2.4.1
Table 14.1.2.2	Demographic Characteristics (Intention-To-Treat Set)	DMT001	Same as Table 14.1.2.1	Same as Table 14.1.2.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.2.3	Demographic Characteristics (Per Protocol Set)	DMT001	Same as Table 14.1.2.1	Same as Table 14.1.2.1
Table 14.1.3.1	Asthma Control Test (ACT) (Intention-To-Treat Set)	BLT001	- Present table by sequence and 'Overall' column should be displayed - First present summary statistics for 'ACT Total Score' (*ACT test results* from the eCRF) - Next present number and percentage of subjects in each category for each of the questions as recorded on the eCRF.	Source: Listing 16.2.4.2
Table 14.1.3.2	Asthma Control Test (ACT) (Safety Set)	BLT001	Same as Table 14.1.3.1 - In case of discontinuation between 2 treatment period, please display the planned treatment in the subject sequence.	Same as Table 14.1.3.1
Table 14.1.3.3	Asthma Control Test (ACT) (Per Protocol Set)	BLT001	Same as Table 14.1.3.1	Same as Table 14.1.3.1
Table 14.1.4.1.1	Asthma History (Intention-To-Treat Set)	SCT002	- Present' Time since First Asthma Diagnosis (years)', 'Asthma Medication Category at Study Entry)', 'Number of Asthma Exacerbations in the 12 months Before Screening', and 'Time since Most Recent Exacerbation (months)' - Table will be presented by sequence and 'Overall' column should be displayed	Source: Listing 16.2.4.3 Footnotes: [1] Time since first asthma diagnosis (years) has been calculated as (date of Visit 1 – first diagnosis date + 1) /365.25. [2] Time since most recent exacerbation (months) has been calculated as (date of Visit 1 – date of most recent exacerbation end)/30.4375.
Table 14.1.4.1.2	Asthma History (Safety Set)	SCT002	Same as Table 14.1.4.1.1 - In case of discontinuation between 2 treatment period, please display the planned treatment in the subject sequence.	Same as Table 14.1.4.1.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.4.1.3	Asthma History (Per Protocol Set)	SCT002	Same as Table 14.1.4.1.1	Same as Table 14.1.4.1.1
Table 14.1.4.2.1	Smoking Status (Intention-To-Treat Set)	SUT001	- Present 'Smoking Status at Screening' (*Non-Smoker*, E*x-Smoker or Current Smoker),* 'Tobacco Categories' *(i.e. Cigarettes, Cigar etc.)*, 'Duration of Smoking (years)', and 'Number of Pack-Years' - Table will be presented by sequence and 'Overall' column should be displayed	Source: Listing 16.2.4.4 Footnotes: [1] For ex-smokers, duration of smoking (years) has been calculated as (stop date – start date + 1)/365.25. [2] For current smokers, duration of smoking (years) has been calculated as (date of informed consent signature – start date + 1)/365.25.
Table 14.1.4.2.2	Smoking Status (Safety Set)	SUT001	Same as Table 14.1.4.2.1 - In case of discontinuation between 2 treatment period, please display the planned treatment in the subject sequence.	Same as Table 14.1.4.2.1
Table 14.1.4.2.3	Smoking Status (Per Protocol Set)	SUT001	Same as Table 14.1.4.2.1	Same as Table 14.1.4.2.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.4.3	Summary of Vital Signs at Screening (Safety Set)	VST002	- Include parameters 'Body Temperature (°C)', 'Systolic Blood Pressure (mmHg)', and 'Diastolic Blood Pressure (mmHg)', 'Pulse Rate (beats/min)' by treatment. - Display summary by Sequence and include Overall column - In case of discontinuation between 2 treatment period, please display the planned treatment in the subject sequence.	Source: Listing 16.2.8.1
Table 14.1.5.1	Medical and Surgical History (Safety Set)	MHT001	Present table by sequence and 'Overall' column should be displayed - In case of discontinuation between 2 treatment period, please display the planned treatment in the subject sequence.	Source: Listing 16.2.4.6 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.1.5.2	Concomitant Diseases (Safety Set)	MHT001	- Present table by sequence and 'Overall' column should be displayed - In case of discontinuation between 2 treatment period, please display the planned treatment in the subject sequence.	Source: Listing 16.2.4.7 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.5.3	Prior Procedures (Safety Set)	MHT001	Present table by treatment sequence. Include 'Overall' column. - In case of discontinuation between 2 treatment period, please display the planned treatment in the subject sequence.	Source: Listing 16.2.4.8 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.1.5.4	Procedures Maintained during the Randomised Treatment Period (Safety Set)	MHT002	- Present table by treatment. Include 'Overall' column	Source: Listing 16.2.4.8 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.5.5	Concomitant Procedures (Safety Set)	MHT002	- Present table by treatment. Include 'Overall' column	Source: Listing 16.2.4.8 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.1.6.1	Prior Medications (Safety Set)	CMT001	- Present the summary by treatment sequence. Include 'Overall' column. First display Asthma medications then non-Asthma medications. - Add first line for this categorization with following labels: 'Asthma medication', 'Non-Asthma Medications'. - In case of discontinuation between 2 treatment period, please display the planned treatment in the subject sequence.	Source: Listings 16.2.4.9 and 16.2.4.10 Footnote: [1] ATCs and Preferred Name are coded using WHO-DD March 20xx.
Table 14.1.6.2	Medications Maintained during the Randomised Treatment Period (Safety Set)	CMT002	Same as Table 14.1.6.1 but present the summary by treatment. Include 'Overall' column.	Source: Listings 16.2.4.9 and 16.2.4.10 Footnote: [1] ATCs and Preferred Name are coded using WHO-DD March 20xx.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.6.3	Concomitant Medications (Safety Set)	CMT002	- Present the summary by treatment and first display Asthma medications then non-Asthma medications. - Add first line for this categorization with following labels: 'Asthma medication', 'Non-Asthma Medications'. - 'Overall' column will be included.	Source: Listings 16.2.4.9 and 16.2.4.10 Footnote: [1] ATCs and Preferred Name are coded using WHO-DD March 20xx.
Table 14.1.7.1	Treatment Compliance during Baseline Period – Commercial Foster (Intention-To-Treat Set)	EXT002	- Present summary statistic for Commercial Foster by Sequence and Overall. - Compliance categories to be presented are: <80%, ≥80% and ≤120%, >120%	Source: Listing 16.2.5.2
Table 14.1.7.2	Treatment Compliance (Intention-To-Treat Set)	EXT002	- Present summary statistic by Treatment - Compliance categories to be presented are <80%, ≥80% and ≤120%, >120%.	Source: Listing 16.2.5.2 Footnotes: [1] Treatment compliance is calculated as % of administered drug during period X = (Total number of administered doses during that period / Total number of scheduled doses during that period) x100, where X = 1,2 [2] For subjects who completed treatment period 1: Total number of scheduled doses during period 1 = Treatment exposure during period 1 (days) * 4 and for all other cases: Total number of scheduled doses = [Treatment exposure (days) * 4] -2

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.7.3	eDiary Compliance during Baseline Period (Intention-To-Treat Set)	EXT002	- Present summary statistic by Sequence and Overall. - Compliance categories to be presented are: [0%-50%], (50%-60%], (60%-70%], (70%-80%], (80%-90%], (90%-100%]	Source: Listing 16.2.5.2
Table 14.1.7.4	eDiary Compliance during Study Treatment Period (Intention-To-Treat Set)	EXT002	- Present summary statistic by treatment group - Compliance categories to be presented are: [0%-50%], (50%-60%], (60%-70%], (70%-80%], (80%-90%], (90%-100%]	Source: Listing 16.2.5.2
Table 14.2.1.1	Absolute Values and Change from Baseline in Average and Daily VAS Scores Evaluating Subject Perceptions of Asthma Symptoms (Intention-To-Treat Set)	TPT001	- Present summary statistic (actual values and Change form baseline) for VAS score recorded in eDiary daily and average. - Display values for 'Day1', 'Day2' […] 'Day 14', 'Week 1' 'Week 2' and 'Over the 14 Days' under 'Timepoint' header. - Questions 3 to 6 from the eDiary will be summarised in this table. Each question will be summarised separately and starting on new page, refer to **Appendix I**. - Include n, Mean (SD), Median, Minimum, Maximum - Present questions as follows as sub-header: *Q3: Asthma Symptoms Score* *Q4: Asthma Burden* *Q5: Improvement in Asthma Symptoms* *Q6: Worsening of Asthma Symptoms*	Source: Listing 16.2.6.1.2

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.2***	Statistical Analysis of Change from Baseline in Average VAS Scores Evaluating Subject Perceptions of Asthma Symptoms Over 14 Days of Treatment (Intention-To-Treat Set)	ANT001	- Treatment comparison is Inhaler A vs. Inhaler B. - Use model as described in 'footnote [2]' for 'change from baseline in average VAS score' – Timepoints are first week, second week and add the overall treatment effect. Questions 3 to 6 from eDiary will be analysed in this table, refer to **Appendix I**. Present each question separately starting on a new page. - Present questions as follows as sub-header: *Q3: Asthma Symptoms Score* *Q4: Asthma Burden* *Q5: Improvement in Asthma Symptoms* *Q6: Worsening of Asthma Symptoms*	Source: Listing 16.2.6.1.2 Footnote: [1] n is the number of subjects included in the model. [2] Linear mixed model for repeated measure including subject, period, treatment, timepoint (i.e. during week 1, week 2), period by timepoint interaction, and treatment by timepoint interaction as fixed effects.
Table 14.2.1.3	Absolute Values and Change from Baseline in Average and Daily VAS Scores Evaluating Subject Perceptions of Asthma Symptoms (Per Protocol Set)	TPT001	- Present summary statistic for VAS score recorded in eDiary daily and average. - Display values for 'Day1', 'Day2' […] 'Day 14', 'Week 1' 'Week 2' and 'Over the 14 Days' under 'Timepoint' header. - Questions 3 to 6 from the eDiary will be summarised in this table. Each question will be summarised separately and starting on new page, refer to **Appendix I**. - Include n, Mean (SD), Median, Minimum, Maximum - Present questions as follows as sub-header: *Q3: Asthma Symptoms Score* *Q4: Asthma Burden* *Q5: Improvement in Asthma Symptoms* *Q6: Worsening of Asthma Symptoms*	Source: Listing 16.2.6.1.2

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.4***	Statistical Analysis of Change from Baseline in Average VAS Scores Evaluating Subject Perceptions of Asthma Symptoms Over 14 Days of Treatment (Per Protocol Set)	ANT001	- Treatment comparison is Inhaler A vs. Inhaler B. - Use model as described in 'footnote [2]' for 'change from baseline in average VAS score' – Timepoints are first week, second week and add the overall treatment effect. Questions 3 to 6 from eDiary will be analysed in this table, refer to **Appendix I**. Present each question separately starting on a new page. - Present questions as follows as sub-header: *Q3: Asthma Symptoms Score* *Q4: Asthma Burden* *Q5: Improvement in Asthma Symptoms* *Q6: Worsening of Asthma Symptoms*	Source: Listing 16.2.6.1.2 Footnote: [1] n is the number of subjects included in the model. [2] Linear mixed model for repeated measure including subject, period, treatment, timepoint (i.e. during week 1, week 2), period by timepoint interaction, and treatment by timepoint interaction as fixed effects.
Table 14.2.2.1	Summary of Response to Questions Covering Subjects' Psychopharmacological Aspects (Intention-To-Treat Set)	TPT002	- Present summary statistic for question 7, question 8, question 9 and question 10 from **Appendix I**. - Present for each visit on which these questions are collected. - Include n, Mean (SD), Median, Minimum and Maximum. - Present questions as follows as sub-header: *Q7: Expected Improvement in Asthma Symptoms* *Q8: Expected Worsening of Asthma Symptoms* *Q9: Improvement in Overall Asthma Symptoms* *Q10: Worsening of Overall Asthma Symptoms*	Source: Listing 16.2.6.1.1
Table 14.2.2.2	Summary of Response to Questions Covering Subjects' Psychopharmacological Aspects (Per Protocol Set)	TPT002	Same as Table 14.2.1.3.1	Same as Table 14.2.2.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.3.1	Summary of Response to Questions Covering Subjects' Preference and Perception of the Devices (Intention-To-Treat Set)	TPT006	- Present number and percentage of subjects for each category under question 11, question 12, question 13, question 14, question 15 and question 16 at the visit the response to these questions is collected. Please refer to **Appendix I** for details of categories and the visits. - Each category will be presented in place of 'Criterion'. - Do not present summary for 'At Any Timepoint' - Present questions as follows: *Q11: Visual Preference* *Q12: Use Preference* *Q13: Inhaler Changes were made to Inhaler* *Q14: Inhaler Changes Impacted Asthma Symptoms* *Q15: Information Received Impacted Perception of Asthma Symptoms* *Q16: Inhaler with Biggest Impact on Perception of Asthma Symptoms* - Add 95% CI for each category's percentages.	Source: Listing 16.2.6.1.1
Table 14.2.3.2	Summary of Response to Questions Covering Subjects' Preference and Perception of the Devices (Per Protocol Set)	TPT006	Same as Table 14.2.2.3.1	Same as Table 14.2.3.1
Table 14.2.4.1	Actual Values and Change from Baseline in Average Reliever Medication Use (puffs/day) over the Entire 14 Days Treatment Period (Intention-To-Treat Set)	TPT001	- Present summary statistic by treatment - Summary will be presented for actual values and change from baseline over the entire 14 days treatment period. - Include n, Mean (SD), Median, Minimum, Maximum	Source: Listing 16.2.5.3

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.4.2	Actual Values and Change from Baseline in Percentage of Days without Intake of Reliever Medication over the Entire 14 Days Treatment Period (Intention-To-Treat Set)	TPT001	- Present summary statistic by treatment - Summary will be presented for actual values and change from baseline over the entire 14 days treatment period. - Include n, Mean (SD), Median, Minimum, Maximum	Source: Listing 16.2.5.3
Table 14.2.5.1	Actual Values and Change from Baseline in Overall and Domains Standardised Asthma Quality of Life Questionnaire -(AQLQ(S)) Score (Intention-To-Treat Set)	TPT001	- Present summary statistic by treatment - Summary will be presented for each of the domain scores – 'Activity Limitation', 'Symptoms', 'Emotional Function' and 'Environmental Stimuli' - and 'Overall AQLQ(S) Score' at each visit, and for Overall and domains score change from baseline for post-baseline visits in that period. Present domain scores each starting on new page, similarly present overall score starting on a new page. - Include n, Mean (SD), Median, Minimum, Maximum	Source: Listing 16.2.6.2
Table 14.2.5.2	Statistical Analysis of Change from Baseline in Overall Standardised Asthma Quality of Life Questionnaire -(AQLQ(S)) Score after 14 Days of Treatment (Intention-To-Treat Set)	ANT001	- Treatment comparison is Inhaler A vs. Inhaler B. - Use model as described in section 9.1.6 of the SAP text – Timepoint to be included visits 3 and 4.	Source: Listing 16.2.6.2 Footnote: [1] Analysis of variance model (ANOVA) including treatment, period and subject as fixed effects.
Table 14.2.5.3	AQLQ(S) Response (Intention-To-Treat Set)	TPT006	- Present at each post-baseline visit AQLQ(S) response categories: 'Improved', 'Worsened', 'No Change'. - Number and percentage of subjects with each AQLQ(S) response will be presented. - Present the summary for each domain and for the overall Score	Source: Listing 16.2.6.2 Footnote: [1] Improved: Change in AQLQ(S) score $\geq$ 0.5; Worsened: Change in AQLQ(S) score $\leq$ -0.5; No change: -0.5 < Change in AQLQ(S) score < 0.5.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.1	Treatment Exposure (Safety Set)	EXT001	Summarize 'Exposure (days)' using descriptive statistics by treatment. Display exposure for commercial Foster during Baseline period, then for each Inhaler: Inhaler A and Inhaler B. No category to be display.	Source: Listing 16.2.5.2
Table 14.3.2.1	Summary of Treatment Emergent Adverse Events (Safety Set)	AET001	- Include rows for TEAEs, Serious TEAEs, non-Serious TEAEs, ADRs, serious ADRs, severe ADRs, severe TEAEs, TEAEs Leading to Discontinuation from Study Drug and TEAEs Leading to Death. - Include 'Overall' column.	Source: Listing 16.2.7.2
Table 14.3.2.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003	Include 'Overall' column.	Source: Listing 16.2.7.2 Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x..
Table 14.3.2.3	Serious Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003	Include 'Overall' column. SAEs are Serious TEAEs.	Source: Listing 16.2.7.3 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.2.4	Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003	Include 'Overall' column.	Source: Listing 16.2.7.4 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.5	Severe Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003	Include 'Overall' column.	Source: Listing 16.2.7.4 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.2.6	Serious Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003	Include 'Overall' column.	Source: Listing 16.2.7.4 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.2.7	Severe Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003	Include 'Overall' column.	Source: Listing 16.2.7.2 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.2.8	Treatment Emergent Adverse Events Leading to Discontinuation from Study Drug by System Organ Class and Preferred Term (Safety Set)	AET003	Include 'Overall' column.	Source: Listing 16.2.7.5 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Table 14.3.2.9	Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Set)	AET003	Include 'Overall' column.	Source: Listing 16.2.7.6 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.10	Non-Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003	Include 'Overall' column.	Source: Listing 16.2.7.2 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.

16.2 Listings

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.1.7	Randomisation Schedule (Randomised Set)	DSL001	Replace 'Randomised Treatment' by 'Randomised Sequence'. Replace 'Actual Treatment' by 'Actual Sequence' Replace 'Randomised Treatment Misallocation during Study" by 'Randomised Sequence Misallocation during Study'.	
Listing 16.2.1.1	Screening Failures (Enrolled Set)	DSL002	Include only subjects who discontinued before the randomisation.	
Listing 16.2.1.2	Subjects Disposition (Randomised Set)	DSL004	Replace 'Randomised Treatment' by 'Randomised Sequence'. - Last two columns should be presented. - Replace 'Date/Time of First Dose' And 'Date/Time of Last Dose' by 'Date f First Dose' and 'Date of last Dose' as we do not collect the time.	Footnotes: [1] [Day 1] is the study Day at Date of Study Discontinuation calculated with reference to the Informed Consent Date [2] [Day 2] is the study Day at Date of Study Discontinuation calculated with reference to the First Dose Date in that period. [3] [Day 3] is the study Day at Date of Study Discontinuation calculated with reference to the Last Dose Date in that period
Listing 16.2.1.3	Randomisation Code Broken (Randomised Set)	DSL005	Change 'Randomised Treatment' to 'Randomised Sequence'.	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.1.4	Study Visits (Randomised Set)	SVL001	- Remove the word 'Retest' in header. - Replace 'Treatment' with 'Sequence'	Footnotes: [1] [Study Day] is the study Day at Visit calculated with reference to the First Dose at study level. [2] [Study Day in period] is the study Day at Visit calculated with reference to the First Dose in the associated period.
Listing 16.2.2.1	Important Protocol Deviations (Randomised Set)	DVL002	Include all Important deviations from DV. DVCAT/DVSCAT/DVDECOD and DVTERM to be presented.	
Listing 16.2.2.2	Violation of Inclusion/Exclusion Criteria (Randomised Set)	DVL001	Only deviations from DV in relation to inclusion/exclusion criteria to be included Replace 'Treatment' with 'Sequence'	
Listing 16.2.3.1	Analysis Set Disposition (Randomised Set)	DSL006	List Safety, ITT and PP.	
Listing 16.2.3.2	Subjects Excluded from Analysis Sets (Randomised Set)	DSL007	Present for Safety, ITT and PP.	
Listing 16.2.4.1	Demographic Characteristics (Randomised Set)	DML001	- 'Replace 'Treatment' with 'Sequence' - Include 'Age (years)', 'Sex', 'Race', 'Height (cm)', 'Weight (kg)' and 'Body Mass Index (BMI, in kg/m2)', 'Childbearing Potential'. - Add column for 'Post-Menopausal'	
Listing 16.2.4.2	Asthma Control Test (Randomised Set)		The following columns will be presented: - Subject ID - Randomised Sequence - COVID-19 related Visit - Assessment Date - Question *<Present questions 1 to 5 in this column>* - Response *<Present subject's response to each of the questions 1 to 5 in this column>* - ACT Test Result	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.3	Asthma History (Randomised Set)		The following columns will be presented: - Subject ID - Randomised Sequence - Date of First Diagnosis - Time since first Diagnosis (Years) - Asthma Medication Category at Study Entry/Specify, if Other - Number of Exacerbations in the 12 Months before Screening - Date of Most Recent Exacerbation End - Time since Most Recent Exacerbation (Months) - Ongoing at Screening	
Listing 16.2.4.4	Smoking Status (Randomised Set)	SUL001	- Replace 'Randomised Treatment' with 'Randomised Sequence' - The following columns need to be added: 'Tobacco category (Cigarettes, Cigars or spliffs, etc.)' and 'Average Number per Day', - Do not present 'CHANGE IN SMOKING STATUS ' nor 'Number of Cigarettes/Day'	
Listing 16.2.4.5	Training and Diary Dispensation (Randomised Set)		The following columns will be presented: - Subject ID - Randomised SequenceVisit - All Trainings Completed <Reason> - Diary Application Installed and Training Performed <Reason>	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.6	Medical and Surgical History (Randomised Set)	MHL001	Replace 'Randomised Treatment' with 'Randomised Sequence'	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Listing 16.2.4.7	Concomitant Diseases (Randomised Set)	MHL002	Replace 'Randomised Treatment' with 'Randomised Sequence'	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Listing 16.2.4.8	Procedures (Randomised Set)	PRL001	- Replace 'Randomised Treatment' with 'Randomised Sequence'. - [CAT] Prior, Maintained, Concomitant - Do not display last column last column 'Indication'	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.
Listing 16.2.4.9	Asthma Medications (Randomised Set)	CML001	- Replace 'Randomised Treatment' with 'Randomised Sequence'. - [CAT] Prior, Maintained, Concomitant	Footnotes: [1] ATCs and Preferred Name are coded using WHO-DD March 20xx. [2] [Day] is the study Day at Start Date calculated with reference to the First Dose Date in the associated period.
Listing 16.2.4.10	Non-Asthma Medications (Randomised Set)	CML001	- Replace 'Randomised Treatment' with 'Randomised Sequence'. - [CAT] Prior, Maintained, Concomitant	Footnotes: [1] ATCs and Preferred Name are coded using WHO-DD March 20xx. [2] [Day] is the study Day at Start Date calculated with reference to the First Dose Date in the associated period.

Listing Number	Listing Title	Template Code	Notes	Footnotes

Listing 16.2.5.1	Study Drug Administration (Randomised Set)		The following columns will be presented:
			- Subject ID
			- Randomised Sequence
			- Period/Actual Treatment
			-
			- Visit or Day within Period
			- Study Drug Dispensed <Reason>-
			- Date of Dispensation/ Date of Administration
			- Number of Inhalations
			- Kit Number
			- First Dose of Baseline Trt Adm. at Clinic <Reason/Specify>
			- Time of Administration
			- Instruction Given to Switch to Trt
			  - #2 <Reason>
			  - #3 <Reason>
			- Study Drugs Returned:
			  - Yes <Date of return>
			  - Kit Number <Reason>
			
			Note: Number of inhalations will come from eDiary data. Other variables are collected on the eCRF.	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.5.2	Randomised Study Medication Extent of Exposure and Compliances (Randomised Set)		The following columns will be presented: - Subject ID - Randomised Sequence - Period - Actual Treatment - Date of Start / End of the Period - Extent of Exposure (days) - Number of Scheduled Doses - Number of Administered Doses, - Compliance (%) - eDiary Compliance (%) Include also Commercial Foster data.	
Listing 16.2.5.3	Reliever (Rescue) Medication (Randomised Set)		The following columns will be presented: - Subject ID - Randomised Sequence - Period - Actual Treatment - Day within Period or Weeks - Date - Number of puffs Derived variables: - Number of Days with Available Data - Total Number of Inhalations - Average Use (puffs/day) - Number Rescue Medication-free Days - % of Days without Rescue Medication - Change from baseline	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.1.1	eDiary Data (Randomised Set)		The following columns will be presented: - Subject ID - Randomised Sequence - Period - Actual Treatment - Visit or Day within Period - Question # concatenated with Question text - Response - Change from Baseline presented as 'CFB [1]' Present CFB only for daily VAS scores Note: Present all the questions (questions 3 to 16, refer Appendix I)	Footnotes: [1] CFB is Change from baseline

Listing 16.2.6.1.2	eDiary Data – Derived data (Randomised Set)		The following columns will be presented:
			- Subject ID
			- Randomised Sequence
			- Period
			- Actual Treatment
			- Question # concatenated with Question text
			- Weeks
			  - Baseline
			  - Week 1
			  - Week 2
			  - Over 2 Weeks
			- Average Value
			- Change from Baseline presented as 'CFB [1]' *(display the change from baseline to Week 1, Week 2, Overall)*
			
			Note: Present the questions (questions 3 to 6, refer Appendix I)
				Footnotes:
				
				[1] CFB is Change from baseline

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.2	Asthma Quality of Life Questionnaire (Randomised Set)		The following columns will be presented: Subject ID - Randomised Sequence - Period - Actual Treatment - Visit - Date - AQLQ(S) Domain (present 'Activity Limitation', 'Symptoms', 'Emotional Function' and 'Environmental Stimuli' and also present 'Overall') - AQLQ(S) Score (Present score of each domain and overall score in this column) - AQLQ(S) Change from Baseline - AQLQ(S) Response <*Improved, Worsened, No Change*>	Footnote: [1] AQLQ(S): Asthma Quality of Life Questionnaire [2] Improved: Change in AQLQ(S) score ≥ 0.5; Worsened: Change in AQLQ(S) score ≤ -0.5; No change: -0.5 < Change in AQLQ(S) score < 0.5
Listing 16.2.7.1	Pre-Treatment Adverse Events (Randomised Set)	AEL001	- Remove 'Pattern' and Ethnicity - Replace 'Randomised Treatment' with 'Randomised Sequence'	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.'

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.7.2	Treatment Emergent Adverse Events (Randomised Set)	AEL002	- Remove pattern and Ethnicity, Starting Dose/Dose at Onset/Weigth - Replace 'Randomised Treatment' with 'Randomised Sequence'	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.' [2] DTH = results in death; LTH = is life-threatening; HSP = requires hospitalization or prolongation of existing hospitalization; DI = results in persistent or significant disability or incapacity; CA = is a congenital anomaly or birth defect; SIG = is a medically significant adverse event. [D1] is the study Day at Onset Date calculated with reference to the First Dose Date at study level; [D2] is the study Day at Onset Date calculated with reference to the First Dose Date at period level; [D3] is the study Day at End Date calculated with reference to the First Dose Date at study level.
Listing 16.2.7.3	Serious Treatment Emergent Adverse Events (Randomised Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2.
Listing 16.2.7.4	Adverse Drug Reactions (Randomised Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2.
Listing 16.2.7.5	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation (Randomised Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.6	Treatment Emergent Adverse Events Leading to Death (Randomised Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.8.1	Vital Signs (Randomised Set)	VSL002	- Present for Body Temperature (ºC), SBP (mmHg), DBP (mmHg), PR (beats/min) under Test <Unit> - Do not present columns 'Analysis period', 'Baseline [1]', 'Use [2]', 'Change from Baseline' and 'Change from Pre-dose' - Add column for 'Location'. This will be populated only when 'Test' = 'Body Temperature (ºC)' - Replace 'Actual Treatment' by 'Actual Sequence' - Replace 'Analysis Timepoint' by 'Visit' - Do not display Study Day in Period	
Listing 16.2.8.2	Urine Pregnancy Test (Randomised Set)	LBL005	- Replace 'Randomised Treatment' with 'Randomised Sequence' - Remove columns 'Childbearing Potential' and 'Test'. -Replace 'Assessment Date/Time' by 'Assessment date'	
Listing 16.2.8.3	Physical Examination Results (Randomised Set)	PEL001	- Replace 'Analysis period' by 'Visit' - Replace 'Actual Treatment' by 'Actual Sequence' - Replace 'Assessment Date/Time' by 'Assessment Date' - Do not display Study Day in Period	
Listing 16.2.8.4	Comments (Randomised Set)	COL001		

16.3 Figures

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.1.1	Disposition Flow Chart (Enrolled Set)	DSF001		Source: Tables 14.1.1.1 and 14.1.1.2
Figure 14.1.2	Flow Chart of Analysis Sets (Randomised Set)	DSF003	Present Safety, ITT and PP Sets.	Source: Table 14.1.1.8
Figure 14.2.1	Adjusted Mean Change from Baseline in Average VAS Score (Intention-To-Treat Set)	TPF001	Adjusted mean change derived from the stats model. One figure per page for each question (Item #3, #4, #5 and #6).	Source: Table 14.2.1.2
Figure 14.2.2	Daily change from Baseline on VAS score (Intention-To-Treat Set)	TPF002	Mean values ± SD. One figure per page for each question (Item #3, #4, #5 and #6).	Source: Table 14.2.1.1
Figure 14.2.3	Mean Change from Baseline in Overall AQLQ(S) Score (Intention-To-Treat Set)	TPF002	Mean values ± SD.	Source: Table 14.2.5.1
Figure 14.2.4	Mean Change from Baseline in Domains AQLQ(S) Score (Intention-To-Treat Set)	TPF002	Mean values ± SD. One figure per page for each domain.	Source: Table 14.2.5.1

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APPENDIX I

List of e-Diary questions to subjects during the study

	Assessments / Questions	V1 (Day 1)	V2 (Day 15)	V3 (Day 29)	V4 (Day 43)
1	"How many puffs of study maintenance treatment have you taken yesterday?" (number of puffs)	Daily collection from V1 to V4			
2	"How many puffs of rescue medication have you taken yesterday?" (number of puffs)	Daily collection from V1 to V4			
3	"How would you score your asthma symptoms yesterday?" (VAS 100, from "no symptoms at all" to "very symptomatic")	Daily collection from V1 to V4			
4	"How burdensome was your asthma yesterday?" (VAS 100, from "no burden at all" to "very burdensome")	Daily collection from V1 to V4			
5	"Did your asthma symptoms improve yesterday?" (VAS 100, from "no improvement" to "maximum improvement")	Daily collection from V1 to V4			
6	"Did your asthma symptoms worsen yesterday?" (VAS 100, from "no worsening" to "maximum worsening")	Daily collection from V1 to V4			
7	"Do you expect any improvement in asthma symptoms with this treatment? (VAS 100, from "none" to "maximum improvement")		X	X	
8	"Do you expect any worsening of your asthma symptoms with this treatment?" (VAS 100, from "none" to "maximum worsening")		X	X	
9	"How much do you think this treatment improved your overall asthma symptoms?" (VAS 100, from "no improvement" to "maximum improvement")			X	X
10	"How much do you think this treatment worsened your overall asthma symptoms?" (VAS 100, from "no worsening" to "maximum worsening")			X	X
11	"Which inhaler did you visually prefer?" [1] (Inhaler A / Inhaler B / No preference)				X
12	"Which inhaler did you prefer to use?" [1] (Inhaler A / Inhaler B / No preference)				X

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	Assessments / Questions	V1 (Day 1)	V2 (Day 15)	V3 (Day 29)	V4 (Day 43)
13	Do you think that changes were made to the inhalers? [1] (Yes / No / I do not know)				X
14	"Do you think the changes we made across the inhalers have impacted your asthma symptoms?" [1,2] (Yes / No / I do not know)				X
15	"Based on the information you've received, did it impact your perception of your asthma symptoms?" [1,3] (Yes / No / I do not know)				X
16	"Which of inhaler A or inhaler B had the biggest impact on the perception of your asthma symptoms?"[1,3] (Inhaler A / Inhaler B / I don't know)				X

[1] *Questions as part of the "Exit Interview"*
[2] *Dynamic question to be asked only if response to question #13 is 'yes'*
[3] *Question to be asked when changes are revealed to the subjects*