[redacted]

STATISTICAL ANALYSIS PLAN

A single-dose, randomised, double-blind, controlled, 2-way cross-over study to assess the potential for bronchoconstriction of the new propellant HFA-152a versus the marketed HFA-134a propellant, in adult subjects with mild asthma.

Protocol:	CLI-05993AB6-07 - NCT05472662
[redacted] **Internal Reference:**	BE-80-2100847
Development phase:	IIa
Sponsor:	Chiesi Farmaceutici S.p.A.
SAP version number:	Final 1.0
SAP version date:	22DEC2022

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PROTOCOL HISTORY

Protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the changes on the statistical analysis**
Final 1.0	06APR2022	NAP
Final 2.0	30AUG2022	NAP

Protocol amendments:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the amendment on the statistical analysis**
NAP		

This statistical analysis plan (SAP) only considers the last version of the protocol, and of the protocol amendments, as listed above.

LIST OF ABBREVIATIONS

ACQ-5	Asthma Control Questionnaire©
ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
AUC	area under the curve
$AUC_{0\text{-}xh}$	area under the curve, from 0 to x hours post-dose
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CPU	clinical pharmacology unit
CRF	case report form
DBP	diastolic blood pressure
DRM	data review meeting
DRR	data review report
DY	relative day
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ENR	enrolled set
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
HFA	hydrofluoroalkane
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
KFR	key first results
MedDRA	Medical Dictionary for Regulatory Activities
NAP	not applicable
PEF	peak expiratory flow

pMDI	pressurised metered dose inhaler
PP	per protocol
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
RND	randomised set
SAF	safety set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDTM	study data tabulation model
SE	standard error
[redacted] CR	[redacted] Clinical Research
SOP	standard operating procedure
STAT	Statistics
TEAE	treatment-emergent adverse event
TLF	tables, listings and figures
VS	vital signs
WHO	World Health Organisation
WHODrug	WHO drug dictionary
WI	work instruction

DEFINITION OF TERMS

bias	The systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value. Bias introduced through deviations in conduct is referred to as 'operational' bias. The other sources of bias listed above are referred to as 'statistical'.
case report form (CRF)	A printed, optical, or electronic document designed to record protocol required information to be reported to the sponsor for each trial subject.
display	Analysis table, listing or figure
phase	Interval of time in the planned conduct of a study associated with a specific purpose: for example, screening, treatment, follow-up.
significant digit	All digits of a number used to express it to the required degree of accuracy, starting from the first non-zero digit.
standardised unit	unit populating --STRESU in the clinical database

1. INTRODUCTION

This SAP describes the final statistical analysis to be performed for the CLI-05993AB6-07 (BE-80-2100847) study.

This SAP covers the safety, [redacted], and general characteristics parts of the statistical analysis. It specifies the analysis displays to be presented and describes the methods and procedures in a more elaborated way than in the statistical methods section of the protocol.

The statistical analysis will process and present the results following the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards, in particular the ICH-E3, ICH-E6(R2), and ICH-E9 guidelines.

1.1 STUDY OBJECTIVES

According to the protocol, the primary objective of this study is:

- To compare the potential for bronchoconstriction [redacted] of the HFA-152a propellant versus [redacted] the HFA-134a propellant when administered alone (not in combination with other active compounds).

According to the protocol, the secondary objective of this study is:

- To evaluate the general safety and tolerability of the two different propellants.

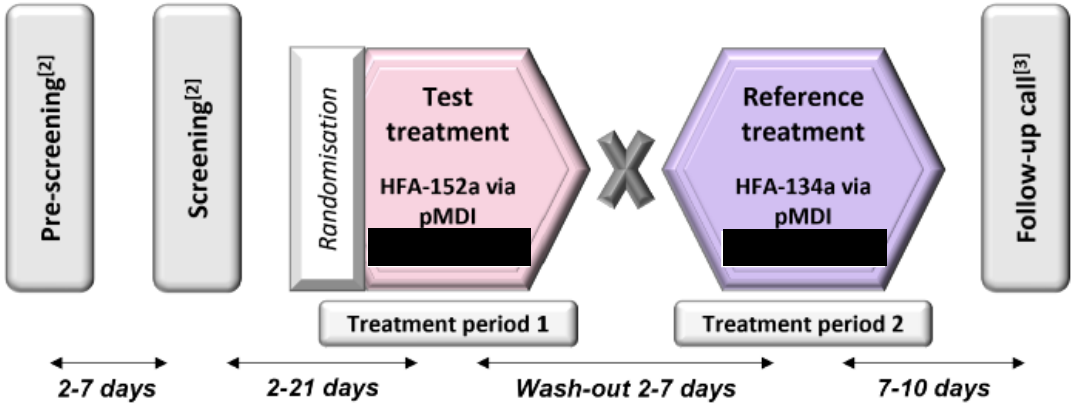
[redacted]

1.2 STUDY DESIGN

This is a Phase IIa, multicentre, single-dose, randomised, double-blind, controlled, 2-way cross-over study to evaluate the potential for bronchoconstriction of the new HFA-152a propellant (single dose, [redacted]) versus the marketed HFA-134a propellant (single dose, [redacted]) in adult subjects with mild asthma.

A double-blind design was chosen for this study to minimise the risk of bias in the study outcomes.

The study design [1] is shown in the below figure:



HFA = Hydrofluoroalkane; pMDI = Pressurised metered dose inhaler.

[1] The study design proposed in the figure is just an example of one of the possible sequences.

[2] The pre-screening and screening visits can be combined in one visit if the study restrictions and wash-out requirements are respected at pre-screening.

[3] A follow-up visit can be performed, if deemed necessary by the Investigator.

The schedule of assessments is in appendix 9.2.

1.3 EXPECTED SAMPLE SIZE

The sample size has been calculated to verify equivalence between the test treatment (HFA-152a) and the reference treatment (HFA-134a) for the relative change from baseline in FEV_1 at the 15 min post-dose time point, with equivalence defined as a difference between the two treatments within the 10% (i.e. [-10%; +10%]).

A total of 20 evaluable subjects will ensure a 95% power to provide a 95% confidence interval (CI) of the mean difference of the relative change from baseline in FEV_1 at 15 min post-dose within the above-mentioned equivalence limits (i.e. [-10%; +10%]) assuming a within-subject standard deviation (SD) of 8%.

Estimating a non-evaluable rate of 16%, a total of 24 subjects will be randomised.

1.4 RANDOMISATION AND BLINDING

A balanced block randomisation list will be prepared using a computerised system. Each subject will be assigned to one of the two possible treatment sequences arranged in a 2x2 William design.

Each subject will be identified by a unique five-digit code assigned at screening.

At randomisation (TP1), each eligible subject will be assigned the lowest randomisation number available at the investigational centre according to a pre-established randomisation list.

1.5 INTERIM ANALYSIS

No interim analyses are foreseen.

1.6 SOFTWARE

SAS version 9.4 or later (SAS Institute Inc., Cary, NC, USA) will be used for programming.

1.7 VALIDATION MODEL

[redacted] Statistics (STAT) standard operating procedures (SOPs) and work instructions (WIs) as effective at the time of the activity will be followed throughout the project, provided the applicable regulatory requirements are still met.

The analysis tables/figures/listings will be validated according to model B (review by an independent person; see SOP.STAT.020).

2. SAFETY ANALYSES

2.1 ADVERSE EVENTS

2.1.1 Available data

Adverse events (AEs) are coded into system organ classes and preferred terms using the medical dictionary for regulatory activities (MedDRA). For each AE, start and stop date(time)s are collected as well as severity, a seriousness flag, treatment-relationship, action taken towards the study drug and outcome.

2.1.2 Derivation rules

Pre-treatment AEs are defined as AEs starting between date of informed consent with 00:00 added as time part and the date(time) of first study drug administration – 1 minute, extremes included.

Treatment-emergent adverse events (TEAE) are defined as AEs starting on or after first administration of any study drug.

Adverse drug reactions (ADRs) are defined as TEAEs related to study drug or with missing relationship.

AEs of particular interest will be selected based on the following algorithms:

- Bronchospasm: to select preferred terms or lowest level terms including the word “bronchospasm”
- Cough: to select preferred terms or lowest level terms including the words “cough” or “coughing”
- Dysphonia: to select preferred terms including the word “dysphonia” (excluding lowest level terms containing the word “hoarseness”)
- Hoarseness: to select lowest level terms containing the word “hoarseness”

Based on their start date(time), AEs will be allocated to the phase and period during which they started. Phases and periods are defined in section 5.2.1. In case the AE start date(time) is incomplete or missing and the AE could consequently be allocated to more than one phase or period, a worst-case allocation will be done as detailed below:

- Treatment phase vs. non-treatment phase: AE will be allocated to the treatment phase.
- Multiple treatment periods: AE will be allocated to all treatment periods, except periods for which the available parts of the AE start or stop date(time) provides evidence the AE did not occur during that period.

A fatal AE is defined as an AE with outcome ‘fatal’.

An AE for which the study drug was discontinued is defined as an AE with action taken ‘drug permanently withdrawn’.

AE onset and duration will be calculated as follows:

- AE onset day (vs. first administration) =
    - AE start date < date of first administration: AE start date – date of first administration
    - AE start date ≥ date of first administration: AE start date – date of first administration + 1 day
- AE onset day (vs. start of period) = AE start date – analysis period start date + 1 day
- AE duration (rounded as detailed in section 5.3.4) =
    - If start and stop date/time are available:
        - AE end date/time – AE start date/time + 1 minute

  Note: If AE duration is less than 1 hour, the duration will be presented in minutes. If the AE duration is 1 hour or more, but less than 1 day, it will be presented in hours. If AE duration is 1 day or more, it will be presented in days.
    - If only start and stop dates are available:
        - AE end date – AE start date + 1 day
        - date of last contact – AE start date + 1 day (when the AE start date is fully known but the AE is not resolved at the end of the study); in this case the duration will be presented as ">x days".

2.1.3 Presentation of results

Tables will present TEAEs only. Pre-treatment AEs will only be listed.

An overview table will show the number and percentage of subjects with at least one event and the number of events by treatment and overall for the following:

- TEAEs
- Serious TEAEs
- Non-serious TEAEs
- ADRs
- Serious ADRs
- Severe TEAEs
- TEAEs leading to study drug discontinuation
- TEAEs leading to death
- TEAEs of particular interest

Separate summary tables by MedDRA system organ class and preferred term will show the number and percentage of subjects with at least one event and the number of events by treatment and overall for the aforementioned categories. Each AE record in the clinical database is considered as a distinct adverse event and is counted as such. Blank system organ classes and preferred terms, if any, will be shown as 'Not Available' in the tables and listings.

All AEs, including pre-treatment events and all coding information will be listed. COVID-19 related AEs will be flagged. Separate listings will be prepared for the categories presented in the summary tables.

2.2 CLINICAL LABORATORY EVALUATION

2.2.1 Available data

Per protocol, the following safety laboratory parameters are expected:

- Biochemistry: creatinine, urea, phosphate, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, alkaline phosphatase, total cholesterol, triglycerides, sodium, potassium, calcium, chloride electrolytes.

  Note: only abnormal clinically significant results will be entered in the eCRF.
- Haematology: red blood cells count, white blood cells count and differential count (absolute value and %), total haemoglobin, haematocrit, platelets count.

  Note: only abnormal clinically significant results will be entered in the eCRF.
- Urinalysis: quantitative (proteins) and qualitative (proteins, ketones, microscopic examination of the sediment).

  Note: only abnormal clinically significant results will be entered in the eCRF.
- Serum and urine pregnancy test and FSH.

Normal ranges are available as provided by the laboratory.

2.2.2 Presentation of results

All laboratory data will be listed.

2.3 VITAL SIGNS

2.3.1 Available data

The following vital signs parameters are collected:

- Systolic (SBP) and diastolic blood pressure (DBP) in supine position

2.3.2 Derivation rules

Mean values of the duplicates will be calculated per time point and rounded as detailed in section 5.3.4. Records belonging to the same duplicate will be identified using the visit and time point. In case of only one assessment available for the specific time point, its result will be considered. Throughout the analysis the mean values will be used. Individual duplicate values will only be listed.

Potential exclusion of vital signs parameters will be discussed during the review of the data by the Chiesi team. Decisions on whether values are to be excluded from the analysis will be fully documented in the DRR.

2.3.3 Presentation of results

Vital signs parameters will be summarised by means of descriptive statistics at each analysis time point by treatment. Actual values and changes from baseline will be tabulated.

All vital signs data will be listed.

2.4 ELECTROCARDIOGRAMS

2.4.1 Available data

The following electrocardiogram (ECG) parameters will be collected:

- Triplicate local 12-lead ECG at Screening: heart rate (HR), PR interval, QRS interval, QT interval, corrected QT interval (Fridericia) and the corresponding interpretation
- Local 12-lead single ECG: HR, PR interval, QRS interval, QT interval, corrected QT interval (Fridericia) and the corresponding interpretation

2.4.2 Derivation rules

For QTcF interval (ms), the following abnormality categories are defined:

- Actual values:
  - >450 ms (males) or >470 ms (females)
  - >480 ms (males)
  - >500 ms
- Changes from pre-dose:
  - Increase from pre-dose >30 ms
  - Increase from pre-dose >60 ms

Note: The worst-case, as defined in section 5.2.5, is the highest value and associated change.

Potential exclusion of ECG parameters will be discussed during the review of the data by the Chiesi team. Decisions on whether values are to be excluded from the analysis will be fully documented in the DRR.

2.4.3 Presentation of results

Local 12-lead single ECG parameters (HR, PR, QRS and QTcF) will be summarised by means of descriptive statistics at each analysis time point by treatment. Actual values (with their 95% CI) and changes from pre-dose (with their 90% CI) will be tabulated.

For QTcF, the number and percentage of subjects with abnormal actual values will be presented at each post-dose analysis time point and at the worst-case post-dose analysis window by treatment. In addition, the number and percentage of subjects with abnormal changes from pre-dose will be presented at each post-dose analysis window and at the worst-case analysis time point by treatment.

All local 12-lead ECG parameters will be listed. Uncorrected QT interval and the investigator's interpretation will only be listed.

2.5 LUNG FUNCTION

2.5.1 Available data

The following lung function (spirometry) parameters are collected: Forced Expiratory volume in 1 second (FEV_1), percent predicted FEV_1, forced vital capacity (FVC), percent predicted FVC, FEV_1/FVC ratio, percent predicted FEV_1/FVC ratio, peak expiratory flow (PEF) and forced expiratory flow 25-75%.

2.5.2 Derivation rules

Pre-dose:

The mean values of the two measurements at 45 min and 15 min will be calculated in each treatment period and rounded as detailed in section 5.3.4. In case only one assessment is available, its result will be used as pre-dose. Throughout the analysis the mean values will be used. Individual duplicate values will only be listed.

FEV_1 $AUC_{0\text{-}3h}$ calculation:

The area under the result vs. time curve observed from time 0 up to the last measurable value (i.e., 3h) will be computed using the linear trapezoidal rule.

The change from baseline in area under the curve (AUC) normalised by time will be calculated as follows, using the trapezoidal summation rule:

- AUC normalised by time =

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

- Change from baseline in AUC = AUC normalised by time – baseline ($FEV1_0$).

where:

- for t_0, $FEV1_0$ is the pre-dose average of $t_{-45'}$ and $t_{-15'}$ before study drug administration of each treatment period.
- t_0 is the actual time of first study drug administration,
- for i = 5 min, 15 min, 30 min, 1h, 1.5h and 3h, $FEV1_i$ is the actual FEV_1 value at each time point and t_i is the actual time of sample i.
- *time* is the actual elapsed time from t_0 until t_{3h}.

Per analysis window, only the timepoint closest to the target time will be considered for AUC calculation (as per analysis windows rules reported in section 5.2.4).

The following rules will be applied for the AUC_{0-3h} calculation:

- In case only one pre-dose measurement is available, it will be used as pre-dose value (corresponding to time 0 for the calculation of the area under the concentration-time curve [AUC]);
- In case no pre-dose measurements are available, the entire curve will be considered missing;
- In case the last measurement for the AUC_{0-3h} (i.e. 3h) is missing, the entire curve will be considered missing;
- Single, isolated missing values (different from pre-dose or last value) will be replaced by linear interpolation using adjacent values;
- In case of two or more consecutive missing time points, the entire curve will be considered missing;
- In case of three or more missing time points, the entire curve will be considered missing.
- If the date(time) is missing or incomplete for a specific post-dose time point, then it will be imputed as the date(time) of the previous time point + the theoretical time interval between the two time points.
- If 2 or more consecutive post-dose time points have a missing or incomplete date(time), then the AUC will also be set to missing.

For FEV_1, the following abnormality categories are defined:

- Relative changes from baseline:
    - Decrease from Baseline >15 %

Potential exclusion of lung function parameters based on time window not respected will be discussed during the review of the data by the Chiesi team. Decisions on whether values are to be excluded from the analysis will be fully documented in the DRR.

2.5.3 Inferential statistics

Primary objective (i.e. evaluation of the potential for bronchoconstriction of each propellant):

- The relative change from baseline in FEV_1 at the 15 min post-dose time point will be analysed using an analysis of covariance (ANCOVA) model, including treatment group, subject and period as fixed effects, and FEV_1 baseline (mean of the two measurements at 45 min and 15 min pre-dose in each treatment period) as a covariate.

  The adjusted mean relative change from baseline obtained with each treatment and the adjusted mean difference between HFA-152a and HFA-134a with their 95% CIs and p-values will be estimated by the model.

Other variables completing the evaluation of the potential for bronchoconstriction of each propellant:

- The relative changes from baseline in FEV_1 at all the other post-dose time points (5 min, 30 min, 1 h, 1 h 30 min and 3 h) will be analysed using the same model used for the relative change from baseline in FEV_1 at 15 min post-dose;
- The absolute changes from baseline in FEV_1 at all post-dose time points (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h) will be analysed using the same model used for the relative change from baseline in FEV_1 at 15 min post-dose.

2.5.4 Presentation of results

Lung function parameters will be summarised by means of descriptive statistics at each analysis time point by treatment. Actual values, absolute and relative changes from baseline (FEV_1 and PEF only) will be tabulated.

For the ANCOVA models, adjusted mean in each treatment and the adjusted mean difference between HFA-152a and HFA-134a, their 95% CIs and related p-values will be provided and tabulated from the ANCOVA. This tables will also include the type III p-values associated to model effects.

The number and percentage of subjects with FEV_1 abnormal relative changes from baseline will be presented at each post-dose time point and at the worst-case analysis visit by treatment.

The change from baseline in FEV_1 $AUC_{0\text{-}3h}$ will be summarised by means of descriptive statistics by treatment.

All lung function parameters will be listed.

Graphs of the mean changes (both absolute and relative) from baseline over time will be prepared for FEV_1 and PEF by treatment.

2.6 USE OF RESCUE MEDICATION

2.6.1 Available data

For each administration of rescue medication, the start and end date(time) and the number of puffs will be recorded.

2.6.2 Derivation rules

The following parameters will be derived:

- Mean use of rescue medication (puffs) = total number of puffs of rescue medication during the first 3h post-dose

2.6.3 Presentation of results

The number and percentage of subjects with use of rescue medication in the first 3h post-dose will be presented by treatment using frequency tabulations.

Mean use of rescue medication in the first 3h post-dose will be summarised by means of descriptive statistics by treatment.

All rescue medication data will be listed.

2.7 PHYSICAL EXAMINATIONS

Abnormal physical examination findings will be listed.

[redacted]

4. GENERAL CHARACTERISTICS ANALYSES

4.1 SUBJECT DISPOSITION

The following subject data will be tabulated by treatment sequence:

- The number of screen failures
- The number and percentage of subjects who completed or discontinued the study as documented on the study termination page and the number and percentage of subjects for each study discontinuation reason
- The number of subjects in each analysis set per period
- The number of subjects enrolled, randomised, completed, and discontinued by site
- The number and percentage of subjects who entered, completed, or discontinued each study period

All information collected in the CRF concerning allocation, code breaking, study discontinuation (discontinuations due to COVID-19 will be flagged) and information on phases and periods, dates of first signed informed consent, last visit and last contact (over the whole study) will be listed.

4.2 PROTOCOL DEVIATIONS AND ELIGIBILITY

The number and percentage of subjects with important protocol deviations, per category and type, will be tabulated, by treatment and overall.

All available information concerning protocol deviations (protocol deviations related to COVID-19 will be flagged), violations on eligibility criteria (only violated eligibility criteria having DV.DVCAT = 'INCLUSION/EXCLUSION CRITERIA') and restrictions will be listed.

4.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

4.3.1 Available data

The following parameters will be available:

- Demographics: women of childbearing potential (yes / no / post-menopausal), age, sex, race, BMI, height and weight at screening, date of birth, and date of signing informed consent form (ICF), smoking status, duration and number of pack-years
- Screening tests: vital signs, local 12-lead ECG, lung function, reversibility test and ACQ-5
- Baseline disease characteristics: date of first diagnosis, asthma medication at study entry, exacerbation history (number of exacerbations in the 12 months before screening and date of the most recent exacerbation ended, treatment, hospitalisation, emergency room)

4.3.2 Derivation rules

The following parameters will be derived:

- Age categories:
  - >=18 and <65 years
  - >=65 and <85 years
- Time since first diagnosis (years): (date of ICF – date of first diagnosis)/365.25

  Note: Partially missing dates will be imputed as specified in section 5.3.2
- Time since most recent exacerbation (months): (date of ICF – date of most recent exacerbation ended)/30.4375

  Note: Partially missing dates will be imputed as specified in section 5.3.2
- Mean values of the duplicates (blood pressure parameters) will be calculated and rounded as detailed in section 5.3.4. Records belonging to the same duplicate will be identified using the visit and time point. In case of only one assessment available for the specific time point, its result will be considered.
- Mean values of the triplicates (ECG parameters) will be calculated and rounded as detailed in section 5.3.4. Records belonging to the same triplicate will be identified using the visit and time point. All records of the triplicate will be used to calculate the mean, even if less or more than the expected three.

4.3.3 Presentation of results

Demographics will be presented by treatment sequence and overall using descriptive statistics for age, height, weight, BMI, smoking duration and number of pack-years (current and ex-smokers only) and frequency tabulations for sex, race, age category and smoking status.

Baseline disease characteristics will be presented by treatment sequence and overall using descriptive statistics for time since first diagnosis, time since most recent exacerbation ended and number of exacerbations in the last 12 months and frequency tabulations for asthma medication category at study entry, number of exacerbations in the last 12 months, last exacerbation treatments, hospitalization and emergency room.

In addition, the following parameters will be presented by treatment sequence and overall using descriptive statistics:

- vital signs at screening and Period 1 Day 1 pre-dose;
- local 12-lead ECG at screening and Period 1 Day 1 pre-dose;
- lung function at screening and Period 1 Day 1 pre-dose;
- reversibility test at screening (FEV_1 Reversibility (mL) and FEV_1 Reversibility (%));
- ACQ-5 at screening and Period 1 Day 1 pre-dose.

All demographic data, baseline disease characteristics and screening tests (except when listed in the safety part, i.e. vital signs, local 12-lead ECG, lung function) will be listed.

4.4 MEDICAL HISTORY AND CONCOMITANT DISEASES

4.4.1 Available data

Medical history and concomitant diseases findings are coded using the medical dictionary for regulatory activities (MedDRA) into system organ classes and preferred terms. For each finding (MH.MHCAT is 'GENERAL MEDICAL HISTORY'), a start and stop date or ongoing flag is collected.

The following selection will be performed:

- Medical history finding: not ongoing at informed consent (MH.MHENRTPT is 'BEFORE')
- Concomitant disease finding: still ongoing at informed consent (MH.MHENRTPT is 'ONGOING' or missing)

4.4.2 Presentation of results

Medical history and concomitant diseases will be tabulated separately by treatment sequence and overall. Each table will show:

- The number and percentage of subjects with findings
- The number and percentage of subjects with findings by system organ class and preferred term

All medical history and concomitant diseases data will be listed separately.

4.5 PROCEDURES AND MEDICATIONS

4.5.1 Available data

All procedures are coded into system organ classes and preferred terms using the medical dictionary for regulatory activities (MedDRA). For each procedure, start and stop dates or ongoing flag are collected.

All medications are coded using WHO Drug. ATC coding up to level 5 is available in the clinical database. For each medication, a start date(time) and stop date(time) or ongoing flag are collected.

4.5.2 Derivation rules

Based on their start and stop date(time), procedures and medications will be allocated to each phase / period during which they were performed/administered. A procedure/medication can therefore be reported in more than one phase or period.

Phases and periods are defined in section 5.2.1. Procedures/medications with (partially) missing dates will be allocated to each phase / period unless the available parts of the procedure/medication start or stop date(time) provide evidence that the procedure/medication was not performed/taken during that phase / period.

Based on their start and stop date(time) procedures and medications will be allocated to one of the following categories:

- Prior: the procedure/medication stopped prior to first study drug administration
- Maintained: the procedure/medication started before first study drug administration and was ongoing at first study drug administration
- Concomitant: the procedure/medication started at or after first study drug administration

For procedures/medications with (partially) missing date(time)s not allowing allocation to any of the categories, a worst-case allocation will be done based on the available parts of the medication/procedure start or stop date(time). The medication/procedure will be allocated to the first category allowed by the available data, according to the following order:

- Concomitant
- Maintained
- Prior

Note: these procedures/medications will only be allocated to the phases / periods that match the worst-case allocated category.

4.5.3 Presentation of results

Procedures:

All procedures data will be listed.

Medications:

The number and percentage of subjects with medications and the number and percentage of subjects with medications by anatomical main group (level 1), therapeutic subgroup (level 2), chemical subgroup (level 4), and preferred name will be tabulated per category (prior, maintained, and concomitant); by treatment (sequence for prior medications) and overall. Blank ATC levels and preferred names, if any, will be shown as 'Not Available' in the tables.

Subjects having more than one medication allocated to the same category within the same treatment (sequence), anatomical main group, therapeutic subgroup, chemical subgroup, and preferred name will be counted only once.

All medications data will be listed.

4.6 EXPOSURE TO STUDY DRUG

4.6.1 Available data

For each study drug administration, the start date(time)s, the number of correct and incorrect inhalations and the reason for incorrect inhalations. In addition, data on training with inhalers is collected.

4.6.2 Presentation of results

All exposure and training with inhalers data will be listed.

5. GENERAL METHODOLOGY

5.1 ANALYSIS SETS

5.1.1 Analysis sets

The following analysis sets will be considered in the statistical analysis:

Enrolled Set (ENR):	subjects who *signed an informed consent* to participate in this study
Randomised Set (RND):	subjects who were *randomised* into this study
Safety Set (SAF):	subjects who were randomised and *received at least one dose of study drug*
Per Protocol (PP) Analysis Set:	subjects from the SAF, excluding the subjects having important protocol deviations impacting the analysis set

Notes:

- Having signed an informed consent is defined as having a complete informed consent signature date in the database.
- Randomised is defined as having a randomisation date in the database or any information to confirm randomisation.
- Having received at least one dose of study drug is defined as having an exposure date or any information confirming exposure.
- Exact definition of important protocol deviations concerning PP will be discussed by the clinical team and described in the DRR. The subjects to be excluded from PP analysis set will be defined in the DRR.

Unless stated otherwise, the SAF will be used for the general characteristics, safety [redacted] tables, listings and figures. The variables assessing the primary study objective will also be analysed considering the PP, for sensitivity purposes.

Since a cross-over design will be used, the inclusion in the analysis sets will be defined at subject level on a per-period basis and at subject level overall (in case all periods are affected). In case of important protocol deviations impacting specific time points, only the affected data at the specific time point will be excluded from the applicable analysis sets. These cases will be documented in the DRR.

5.1.2 As planned versus as actual analysis

For analyses done on the safety analysis set and on PP analysis set (excluding general characteristics analyses), the actual treatment of the subject will be considered. In addition, the actual treatment will be presented in all listings.

For all other analyses, the planned treatment (sequence) will be used.

5.2 PHASES, PERIODS AND TIME POINTS

5.2.1 Phases and periods

Adverse events, medications, and procedures will be allocated to phases and periods. All other analyses will not be allocated to phases and periods. Instead, the visit and time point labels indicated on the subject's case report form (CRF) will be used to allocate the assessments to the correct treatment. Early termination and follow-up visit assessment will be allocated to the last administered treatment.

Adverse events and medications:

Phase	Period	Start	End
Screening		Date of signing the informed consent form (ICF), with 00:00 added as time part	First administration date(time) in period 1 – 1 minute
Treatment	Period 1	First administration date(time) in period 1	First administration date(time) in period 2 – 1 minute
	Period 2	First administration date(time) in period 2	Date of last contact, with 23:59 added as time part

Per definition, and for each subject, the first phase starts on the date of the earliest available ICF signature, with 00:00 added as time part. The last available phase/period ends on the date of last contact, with 23:59 added as time part.

Procedures:

Phase	Period	Start	End
Screening		Date of signing the informed consent form (ICF)	First administration date in period 1 – 1 day
Treatment	Period 1	First administration date in period 1	First administration date in period 2 – 1 day
	Period 2	First administration date in period 2	Date of last contact

Per definition, and for each subject, the first phase starts on the date of the earliest available ICF signature. The last available phase/period ends on the date of last contact.

All tables and figures will present treatments/sequences rather than periods.

AEs, medications and procedures will be allocated to phases and periods as described in sections 2.1.2 and 4.5.2 respectively.

5.2.2 Baseline and change from baseline

The baseline value is a non-missing value before the first administration of any study drug.
The following table summarizes the baseline definition for each parameter:

Parameter	Baseline
Vital signs	Day 1 pre-dose (of each treatment period)
ECG parameters	Day 1 pre-dose (of each treatment period)
Lung function	Day 1 pre-dose (average of 45 min and 15 min pre-dose measurements of each treatment period)

Note: decisions on whether a different baseline should be used in the analysis will be fully documented in the DRR.

Change from baseline is defined as:

Change from baseline at time point t = value at time point t – baseline value.

Relative change from baseline at time point t is defined as follows:

- When baseline value is not zero: 100*((value at time point t – baseline value) / baseline value)
- When baseline value is zero: not calculated

5.2.3 Relative day

Relative days (DY) will be calculated according to the following rule:

- Concerned date < reference date: DY = concerned date – reference date
- Concerned date ≥ reference date: DY = concerned date – reference date + 1

The reference date is the date of first administration of study drug (in the study and in each period).

5.2.4 Analysis visits

The analysis will use the visits and time points indicated on the subject's CRF, while for the timepoints related to the vital signs, ECG and spirometry assessments a windowing approach will be used (see time window definitions below).

The screening value is the last available and non-missing value before Period 1 Day 1. This value corresponds to the screening visit, except in case of retesting. Reason for this approach is the use of retest results for subject eligibility assessment.

Unscheduled assessments will not be used in the analysis unless it is selected as screening value, or per time window definitions below.

The unscheduled assessments will be checked during the DRM before database lock, and any different approach to the rule defined above will be documented in the DRR.

Baseline is defined in section 5.2.2.

All scheduled and unscheduled assessments will be listed. Early termination and follow-up visits will be listed only, unless otherwise specified.

Except when defined by time windows, the analysis visit labels will be assigned using the following rules:

- All planned screening, re-screening, eligibility re-check, etc. visits occurred during the screening phase will be presented as 'Screening'.
- All planned visits occurred during a scheduled day, will be presented as 'Day x' (x = study day, e.g. 'Day -1', 'Day 1', etc.)
- Early termination visits will be presented as 'Early Termination'
- Follow-up visits will be presented as 'Follow-up'
- Unscheduled visits will be presented as 'Unscheduled' unless the decision to reallocate the visit is fully documented in the DRR. In case of reallocation, the unscheduled visit will be presented with the same label as the replaced planned visit (see rules above)
- Other visits not covered by the rules above will be presented using similar labels to the ones used in SDTM (XX.VISIT)

The analysis time point labels for spirometry, vital signs and ECG parameters, will be assigned using the following time windowing rules.

Next to the screening value, all assessments, including unscheduled assessments, will be allocated to analysis windows. Tables will present the analysis windows as defined below and listings will present the analysis windows, as well as the CRF visits. Allocation of assessments will be done according to the following tables:

Spirometry:

Analysis time point window	**Target time from dose of study drug per period (minutes)**	**Time interval (minutes)**
45min Pre-dose	<0	Day 1, before study drug
15min Pre-dose	<0	Day 1, before study drug
5min	5	[3 ; 10)
15min	15	[10 ; 23)
30min	30	[23 ; 45)
1h	60	[45 ; 75)
1.5h	90	[75 ; 135)
3h	180	[135 ; 240]

Notes:

- Target time and time interval will be calculated in each treatment period from the first inhalation for pre-dose assessments and from the last inhalation for post-dose assessments.
- The 45min pre-dose and 15min pre-dose assessments will first be allocated to analysis windows before calculation of the pre-dose mean value.

Vital signs and ECG:

Analysis time point window	Target time from dose of study drug per period (minutes)	Time interval (minutes)
Pre-dose	<0	Day 1, before study drug
45min	45	[15 ; 75)
1h 45min	105	[75 ; 135)
2h 45min	165	[135 ; 240]

Note: Target time and time interval will be calculated in each treatment period from the first inhalation for pre-dose assessments and from the last inhalation for post-dose assessments.

Per parameter and analysis window, the value closest to the target time will be used in analysis tables and figures, other values will only be listed. If more than one value is located at the same distance from the target, then the latest in time will be selected. The value latest in time will be identified using, in order of preference, the assessment time, the visit and time point label or the group identifier. Missing values are removed before the selection is made.

Partially missing assessment dates or times disabling allocation to analysis windows will not be imputed and thus these assessments will not be considered in the per-time point analysis, except for the derivation of the worst-case.

5.2.5 Worst-case

A worst-case analysis visit (presented in the analysis as 'At Any Time Point', or similar) will be created for parameters for which abnormalities are defined to summarise values considered as the worst-case.

The worst-case analysis visit will be derived within each treatment period, including scheduled and unscheduled assessments as well as the early termination and follow-up visit assessments. Only post-dose assessments will be considered for the worst-case analysis visit.

5.3 IMPUTATION AND ROUNDING RULES

5.3.1 Missing values

No imputation of missing values will be done (i.e. observed cases analysis).

5.3.2 Handling partially or completely missing dates in calculations

In case of missing date(time)s for FEV_1 assessments, needed for the calculation of $AUC_{0\text{-}3h}$, these cases will be discussed and documented in the DRR.

Partially missing date of first diagnosis event will be imputed as follows for the calculation of time since event:

- Missing day will be imputed with the first day of the month
- Missing day and month will be imputed with 1st JAN

Partially missing date of most recent exacerbation event will be imputed as follows for the calculation of time since event:

- Missing day will be imputed with the last day of the given month
- Missing day and month will be imputed with 31st DEC

5.3.3 Values below or above a threshold

Safety values expressed as below (or above) the limit of quantification will be imputed by the value of the quantification limit itself. Listings will always show the non-imputed values.

5.3.4 Rounding of derived variables

Derived variables will be rounded at display level:

- AE duration will be presented with 1 decimal.
- Mean of duplicates (blood pressure)/triplicates (ECG) will be rounded to the nearest integer.

  Note: since the rounding is applied at display level, in the listings, the change from baseline could be slightly different to the listed value at time point t – baseline value
- Mean of duplicates (lung function) will be rounded to same number of decimal places as the individual values.

  Note: since the rounding is applied at display level, in the listings, the change from baseline could be slightly different to the listed value at time point t – baseline value
- FEV_1 $AUC_{0\text{-}3h}$ will be rounded to the same number of decimal places as the actual FEV_1 values.
- Relative change from baseline will be presented with 1 decimal.
- Time since first diagnosis and most recent exacerbation will be presented with 1 decimal.

5.3.5 Outliers

Potential outliers will be discussed during the review of the data by the Chiesi team. Decisions on whether values are to be excluded from the analysis will be fully documented in the DRR.

5.4 PRESENTATION OF RESULTS

5.4.1 Calculation of descriptive statistics and percentages

For continuous parameters, full descriptive statistics will only be presented if there are at least 2 non-missing observations. Alternatively, only the number of non-missing data points and mean are shown.

Descriptive statistics will include the number of non-missing data points, the arithmetic mean, the standard deviation (SD), the median, minimum and maximum.

Descriptive statistics of safety parameters will additionally include 95% (or 90%) confidence interval (CI) on the mean (based on t-distribution, without continuity correction).

Mean, median, SD and CI will be presented with one more decimal place than the individual values. Minimum and maximum will be presented with the same number of decimal places than the individual values.

For event-type data, the denominator will be all subjects in the analysis set and phase and period. All treatments will be shown, even if no events are present.

P-values will be presented with three decimal places (Note: any p-value less than 0.001 will be presented as <0.001 and any p-value greater than 0.999 will be presented as >0.999) and test statistics with two decimal places.

For frequency tabulations, missing values will not be included in the denominator count when computing percentages.

Percentages will be shown with one decimal place.

5.4.2 Presentation of treatments

The following treatment labels will be used in the tables, listings and figures:

When presented by treatment:

- HFA-152a
- HFA-134a

When presented by treatment sequence:

- HFA-152a-HFA-134a
- HFA-134a-HFA-152a

Unless specified otherwise, an overall column, to summarise all subjects over treatments, will be presented only in tables showing data that are not affected by the study treatment, as well as in the AEs summaries. The overall column will be shown last.

5.4.3 Ordering in tables, listings and figures

If the treatments are presented as columns, tables will be sorted by analysis visit and time point. Otherwise, tables will be sorted first by treatment, then by analysis visit and time point.

The test treatment will be shown first, and then reference treatment: HFA-152a, HFA-134a.

In the analysis of general characteristics, results will be presented by treatment sequence except where stated otherwise. For all other analyses (safety, [redacted]), results will be presented by treatment.

All listings will be ordered by subject and then by analysis visit and time point (chronologically), unless specified otherwise.

In tables showing several parameters, each parameter will begin on a new page and parameters will be sorted alphabetically, within the parameter category if applicable.

5.4.4 Raw SAS output

In addition to the statistical output as described in section 8, raw SAS output will be delivered in separate files as ‘Appendix to Table 14.x.x.x’ for all tables presenting

inferential statistics. The layout of the appendices will be similar to the table (study identifier, SAS program name, production date, page count); presenting the raw SAS output in the body section.

6. CHANGES TO THE PLANNED ANALYSIS

6.1 CHANGES NOT COVERED BY PROTOCOL AMENDMENTS BEFORE UNBLINDING

Not applicable

7. REFERENCES

- ICH Topic E6(R2) Guideline for Good Clinical Practice – Step 4, 9 November 2016.
- ICH Topic E9 Statistical Principles for Clinical Trials – Step 5 – Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96), September 1998.

8. LIST OF TABLES, LISTINGS AND FIGURES

8.1 TABLES

Number	Title	Analysis Set	TLFs Library Template Number
GENERAL CHARACTERISTICS			
14.1.1.1	**Screen Failures (Enrolled Set)**	**ENR**	**DST001**
	Tabulation of the reason for screening failures.		
14.1.1.2	**Disposition by Treatment Sequence (Randomised Set)**	**RND**	**DST002**
	Tabulation of completion/discontinuation and the reason for discontinuation.		
14.1.1.3	**Disposition by Treatment (Randomised Set)**	**RND**	**DST003**
	Tabulation of completion/discontinuation and the reason for discontinuation by treatment period.		
14.1.1.4	**Disposition by Site (Randomised Set)**	**RND**	**DST004**
	Tabulation of completion/discontinuation and the reason for discontinuation per site.		
14.1.1.5	**Analysis Sets per Period by Treatment (Randomised Set) [KFR]**	**RND**	**DST006**
	Tabulation of the number of subjects per period in each of the analysis sets defined in the SAP.		
14.1.1.6	**Attendance at Treatment Periods by Sequence (Randomised Set)**	**RND**	**SVT002**
	Tabulation of the number and percentage of subjects that entered, completed or discontinued each treatment period.		
14.1.1.7	**Important Protocol Deviations (Safety Set)**	**SAF**	**DVT001**
	Tabulation of the important protocol deviations (at least one), deviation category and deviation type by treatment and overall.		
14.1.1.8	**Important Protocol Deviations Leading to Exclusion from PP Analysis Set (Safety Set)**	**SAF**	**DVT001**
	Tabulation of the important protocol deviations (at least one) leading to exclusion from the PP analysis set, deviation category and deviation type by treatment and overall.		
14.1.2.1.1	**Demographic Characteristics (Safety Set) [KFR]**	**SAF**	**DMT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.1.2	**Demographic Characteristics (PP Analysis Set)**	**PP**	**DMT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.2.1	**Asthma History (Safety Set)**	**SAF**	**SCT002**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		

Number	Title	Analysis Set	TLFs Library Template Number
14.1.2.2.2	**Asthma History (PP Analysis Set)**	**PP**	**SCT002**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.3.1	**Exacerbation History (Safety Set)**	**SAF**	**SCT003**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.3.2	**Exacerbation History (PP Analysis Set)**	**PP**	**SCT003**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.4	**Smoking Status (Safety Set)**	**SAF**	**SUT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.5	**Vital Signs at Screening and Period 1 Day 1 Pre-dose (Safety Set)**	**SAF**	**BLT002**
	Descriptive statistics of vital signs (DBP and SBP) results at Screening and Period 1 Day 1 pre-dose.		
14.1.2.6	**Local 12-Lead ECG at Screening and Period 1 Day 1 Pre-dose (Safety Set)**	**SAF**	**BLT002**
	Descriptive statistics of all local triplicate 12-lead ECG results at Screening and single ECG at Period 1 Day 1 pre-dose.		
14.1.2.7.1	**Lung Functions at Screening and Period 1 Day 1 Pre-dose (Safety Set)**	**SAF**	**BLT002**
	Descriptive statistics of lung function parameters at Screening and Period 1 Day 1 pre-dose.		
14.1.2.7.2	**Lung Functions at Screening and Period 1 Day 1 Pre-dose (PP Analysis Set)**	**PP**	**BLT002**
	Descriptive statistics of lung function parameters at Screening and Period 1 Day 1 pre-dose.		
14.1.2.8.1	**Reversibility Test (Safety Set)**	**SAF**	**RET001**
	Descriptive statistics of reversibility test at Screening.		
14.1.2.8.2	**Reversibility Test (PP Analysis Set)**	**PP**	**RET001**
	Descriptive statistics of reversibility test at Screening.		
14.1.2.9	**ACQ-5 at Screening and Period 1 Day 1 Pre-dose (Safety Set)**	**SAF**	**BLT002**
	Descriptive statistics of ACQ-5 (overall score) at Screening and Period 1 Day 1 pre-dose.		
14.1.2.10	**Medical History (Safety Set)**	**SAF**	**MHT001**
	Tabulation of the number and percentage of subjects with medical history findings and number and percentage of subjects with medical history findings by system organ class and preferred term.		
14.1.2.11	**Concomitant Diseases (Safety Set)**	**SAF**	**MHT001**
	Tabulation of the number and percentage of subjects with concomitant diseases and number and percentage of subjects with concomitant diseases by system organ class and preferred term.		

Number	Title	Analysis Set	TLFs Library Template Number
14.1.2.12	**Prior Medications (Safety Set)**	**SAF**	**CMT001**
	Tabulation of the number and percentage of subjects with prior medications and number and percentage of subjects with medications by ATC class (level 1), ATC class (level 2), ATC class (level 4) and preferred name.		
14.1.2.13	**Maintained Medications (Safety Set)**	**SAF**	**CMT001**
	Tabulation of the number and percentage of subjects with maintained medications and number and percentage of subjects with maintained medications by ATC class (level 1), ATC class (level 2), ATC class (level 4) and preferred name.		
14.1.2.14	**Concomitant Medications (Safety Set)**	**SAF**	**CMT002**
	Tabulation of the number and percentage of subjects with concomitant medications and number and percentage of subjects with concomitant medications by ATC class (level 1), ATC class (level 2), ATC class (level 4) and preferred name.		
SAFETY			
ADVERSE EVENTS			
14.3.1.1	**Summary of TEAEs (Safety Set) [KFR]**	**SAF**	**AET001**
	Tabulation of the number and percentage of subjects with at least one of the events described in the SAP. The number of events will also be shown.		
14.3.1.2	**TEAEs by System Organ Class and Preferred Term (Safety Set)**	**SAF**	**AET003**
	Tabulation of the number and percentage of subjects with TEAEs by MedDRA system organ class and preferred term. The number of events will also be shown.		
14.3.1.3	**Serious TEAEs by System Organ Class and Preferred Term (Safety Set)**	**SAF**	**AET003**
	Tabulation of the number and percentage of subjects with serious TEAEs by MedDRA system organ class and preferred term. The number of events will also be shown.		
14.3.1.4	**Non-Serious TEAEs by System Organ Class and Preferred Term (Safety Set)**	**SAF**	**AET003**
	Tabulation of the number and percentage of subjects with non-serious TEAEs by MedDRA system organ class and preferred term. The number of events will also be shown.		
14.3.1.5	**ADRs by System Organ Class and Preferred Term (Safety Set)**	**SAF**	**AET003**
	Tabulation of the number and percentage of subjects with ADRs by MedDRA system organ class and preferred term. The number of events will also be shown.		
14.3.1.6	**Serious ADRs by System Organ Class and Preferred Term (Safety Set)**	**SAF**	**AET003**
	Tabulation of the number and percentage of subjects with serious ADRs by MedDRA system organ class and preferred term. The number of events will also be shown.		

Number	Title	Analysis Set	TLFs Library Template Number
14.3.1.7	**Severe TEAEs by System Organ Class and Preferred Term (Safety Set)** Tabulation of the number and percentage of subjects with severe TEAEs by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
14.3.1.8	**TEAEs Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Safety Set)** Tabulation of the number and percentage of subjects with TEAEs leading to study drug discontinuation by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
14.3.1.9	**TEAEs Leading to Death by System Organ Class and Preferred Term (Safety Set)** Tabulation of the number and percentage of subjects with TEAEs leading to death by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
14.3.1.10	**TEAEs of Particular Interest (Safety Set)** Tabulation of the number and percentage of subjects with TEAEs of particular interest (as defined in section 2.1.2) by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
VITAL SIGNS			
14.3.5.1	**Vital Signs: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of vital signs actual values and changes from baseline per parameter and analysis time point. Table sorted by analysis time point. Each parameter will begin on a new page.	**SAF**	**VST001**
ECG			
14.3.6.1	**Local 12-Lead ECG: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of continuous 12-lead ECG (HR, PR, QRS, QTcF) actual values and changes from baseline per analysis time point. Table sorted by analysis time point. Each parameter will begin on a new page.	**SAF**	**EGT002**
14.3.6.2	**QTcF: Abnormalities (Safety Set)** Tabulation of the abnormalities as defined in section 2.4.2 at baseline and each post-dose analysis time point and at the worst-case analysis time-point. Table sorted by analysis time point. Only baseline and post-dose analysis time points are shown.	**SAF**	**EGT007**
14.3.6.3	**QTcF: Abnormal Changes from Baseline (Safety Set)** Tabulation of the QTcF change abnormalities as defined in 2.4.2 at each post-dose analysis time point and at the worst-case analysis time point. Table sorted by analysis time point. Only post-dose analysis time points are shown.	**SAF**	**EGT008**

Number	Title	Analysis Set	TLFs Library Template Number
LUNG FUNCTION			
14.3.7.1.1	**Lung Functions: Summary of Actual Values and Changes from Baseline (Safety Set) [KFR]** Descriptive statistics of actual values and changes from baseline in FEV_1 and PEF results per parameter and analysis time point. Table sorted by analysis time point. Each parameter will begin on a new page.	**SAF**	**TPT001**
14.3.7.1.2	**Lung Functions: Summary of Actual Values and Changes from Baseline (PP Analysis Set)** Descriptive statistics of actual values and changes from baseline in FEV_1 and PEF results per parameter and analysis time point. Table sorted by analysis time point. Each parameter will begin on a new page.	**PP**	**TPT001**
14.3.7.2.1	**Lung Functions: Summary of Relative Changes from Baseline (Safety Set) [KFR]** Descriptive statistics of relative changes from baseline in FEV_1 and PEF results per parameter and analysis time point. Table sorted by analysis time point. Only post-baseline analysis time points are shown.	**SAF**	**TPT004**
14.3.7.2.2	**Lung Functions: Summary of Relative Changes from Baseline (PP Analysis Set) [KFR]** Descriptive statistics of relative changes from baseline in FEV_1 and PEF results per parameter and analysis time point. Table sorted by analysis time point. Only post-baseline analysis time points are shown.	**PP**	**TPT004**
14.3.7.3.1	**Primary Objective: Statistical Analysis of Relative Change from Baseline in FEV_1 at 15 Min Post-dose (Safety Set) [KFR]** Results from the primary objective ANCOVA on relative change from baseline in FEV_1 at the 15 min post-dose time point as described in section 2.5.3.	**SAF**	**ANT001**
14.3.7.3.2	**Statistical Analysis of Relative Change from Baseline in FEV_1 at 15 Min Post-dose (PP Analysis Set) [KFR]** Results from the ANCOVA on relative change from baseline in FEV_1 at the 15 min post-dose time point as described in section 2.5.3.	**PP**	**ANT001**
14.3.7.4	**Statistical Analysis of Relative Change from Baseline in FEV_1 at Other Time Points (Safety Set) [KFR]** Results from the ANCOVA on relative change from baseline in FEV_1 at all other post-dose time points (5 min, 30 min, 1 h, 1 h 30 min and 3 h) as described in section 2.5.3.	**SAF**	**ANT002**
14.3.7.5	**Statistical Analysis of Change from Baseline in FEV_1 (Safety Set) [KFR]** Results from the ANCOVA on absolute change from baseline in FEV_1 at all post-dose time points (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h) as described in section 2.5.3.	**SAF**	**ANT002**

Number	Title	Analysis Set	TLFs Library Template Number
14.3.7.6	**FEV_1: Abnormal Relative Changes from Baseline (Safety Set)**	**SAF**	**EGT008**
	Tabulation of the FEV_1 relative change abnormalities as defined in section 2.5.2 at each post-dose analysis time point and at the worst-case analysis time point. Table sorted by analysis time point. Only post-dose analysis time points are shown. Template EGT008 is used, using the FEV_1 relative change abnormalities instead.		
14.3.7.7	**FEV_1: Changes from Baseline in AUC_{0-3h} (Safety Set)**	**SAF**	**TPT002**
	Descriptive statistics of change from baseline in FEV_1 AUC_{0-3h}.		
USE OF RESCUE MEDICATION			
14.3.8.1	**Rescue Medication Use (Safety Set)**	**SAF**	**XRT001**
	Descriptive statistics of mean use of rescue medication in the first 3h post-dose by treatment and frequency tabulation of use of rescue medication.		

[redacted]

8.2 LISTINGS

Number	Title	Analysis Set	TLFs Library Template Number
GENERAL CHARACTERISTICS			
16.1.7	**Randomisation Schedule (Randomised Set)**	**RND**	**DSL001**
	Listing of subject numbers and randomisation information All discrepancies (as-randomised versus as-treated) will be presented.		
16.2.1.1	**Screening Failures (Enrolled Set)**	**ENR**	**DSL002**
	Listing of all subjects not randomised. The study discontinuation reason and demographic data will be listed.		
16.2.1.2	**Study Discontinuation After Randomisation (Randomised Set)**	**RND**	**DSL003**
	Listing of all subjects that discontinued after randomisation. The study discontinuation reason will also be listed.		
16.2.1.3	**Subject Disposition (Randomised Set)**	**RND**	**DSL004**
	Listing of the reasons for completion / discontinuation and the number of days since first study drug administration at study discontinuation. In case the discontinuation was due to AE, the AE will be presented in this listing. If there is another explanation on the discontinuation reason collected in the CRF, this will also be presented in this listing.		
16.2.1.4	**Randomisation Code Broken (Randomised Set)**	**RND**	**DSL005**
	Listing of the code breaking information. Only subjects for which the code was broken are presented in this listing.		
16.2.1.5	**Subject Disposition: Analysis Phases and Periods With Time (Randomised Set)**	**RND**	**DSL008**
	Listing of the phases and periods in the study (definition with time for adverse events and medications), together with the start and end date(time)s.		
16.2.1.6	**Subject Disposition: Analysis Phases and Periods Without Time (Randomised Set)**	**RND**	**DSL008**
	Listing of the phases and periods in the study (definition without time for procedures), together with the start and end dates.		
16.2.1.7	**Study Visits (Randomised Set)**	**RND**	**SVL001**
	Listing per subject number of all subject visits, together with the start and end date of each visit. Listing is sorted chronologically by visit start date within each subject.		
16.2.1.8	**First and Last Contact in the Study (Enrolled Set)**	**ENR**	
	List of the date of the first signed ICF, last visit date and last date of contact in the study. All dates are presented overall, not by treatment.		
16.2.2.1	**Violation of Eligibility Criteria (Randomised Set)**	**RND**	**DVL001**
	Only violated in- and exclusion criteria will be listed. Only deviations with DVDECOD = “VIOLATION OF INCLUSION CRITERION” or “VIOLATION OF EXCLUSION CRITERION” will be selected.		
16.2.2.2	**Important Protocol Deviation (Randomised Set)**	**RND**	**DVL002**
	Listing of all important protocol deviations information		

Number	Title	Analysis Set	TLFs Library Template Number
16.2.2.3	**Restrictions (Randomised Set)**	**RND**	
	Listing of all restrictions data available in the CRF.		
16.2.3.1	**Analysis Set Disposition (Randomised Set)**	**RND**	**DSL006**
	Listing of all subjects and analysis set indicators.		
16.2.3.2	**Subjects Excluded from Safety/PP Analysis Set (Randomised Set)**	**RND**	**DSL007**
	Listing of all subjects that were excluded from SAF/PP.		
16.2.4.1	**Demographic Characteristics (Randomised Set)**	**RND**	**DML001**
	Listing of all demographic parameters		
16.2.4.2	**Asthma History (Randomised Set)**	**RND**	**SCL001**
	Listing of all baseline disease characteristics. Adjust the columns of SCL001 according to the available data.		
16.2.4.3	**Smoking Status (Randomised Set)**	**RND**	**SUL001**
	Listing of all smoking data available in the CRF		
16.2.4.4	**Reversibility Test (Randomised Set)**	**RND**	**REL001**
	Listing of all reversibility test data available in the CRF		
16.2.4.5	**Medical/Surgical History (Randomised Set)**	**RND**	**MHL001**
	Listing of the medical history data findings available in the CRF		
16.2.4.6	**Concomitant Diseases (Randomised Set)**	**RND**	**MHL002**
	Listing of the concomitant diseases data findings available in the CRF		
16.2.4.7	**Procedures (Randomised Set)**	**RND**	**PRL001**
	Listing of all data on prior, maintained and concomitant procedures		
16.2.4.8	**Medications (Randomised Set)**	**RND**	**CML001**
	Listing of all data on prior, maintained and concomitant medications		
16.2.4.9	**Comments (Randomised Set)**	**RND**	**COL001**
	Listing of all remarks and comments written in the CRF		
16.2.5.1	**Training with Inhalers (Randomised Set)**	**RND**	
	Listing of all data related to training with inhalers		
16.2.5.2	**Exposure (Randomised Set)**	**RND**	
	Listing of all data related to exposure		
SAFETY			
ADVERSE EVENTS			
16.2.7.1	**Pre-Treatment Adverse Events (Enrolled Set)**	**ENR**	**AEL001**
	Listing of all pre-treatment AE information collected in the CRF and of the onset day and duration. All information of one AE will be presented on the same line.		

Number	Title	Analysis Set	TLFs Library Template Number
16.2.7.2	**Treatment Emergent Adverse Events (Randomised Set)**	**RND**	**AEL002**
	Listing of all AE information collected in the CRF and of the phase / period dates and onset day and duration. All information of one AE will be presented on the same line.		
16.2.7.3	**Serious Treatment Emergent Adverse Events (Randomised Set)**	**RND**	**AEL002**
	Same as listing 16.2.7.2, but listing serious TEAEs only		
16.2.7.4	**Non-Serious Treatment Emergent Adverse Events (Randomised Set)**	**RND**	**AEL002**
	Same as listing 16.2.7.2, but listing non-serious TEAEs only		
16.2.7.5	**Adverse Drug Reactions (Randomised Set)**	**RND**	**AEL002**
	Same as listing 16.2.7.2, but listing ADRs only		
16.2.7.6	**Serious Adverse Drug Reactions (Randomised Set)**	**RND**	**AEL002**
	Same as listing 16.2.7.2, but listing serious ADRs only		
16.2.7.7	**Severe Treatment Emergent Adverse Events (Randomised Set)**	**RND**	**AEL002**
	Same as listing 16.2.7.2, but listing severe TEAEs only		
16.2.7.8	**Treatment Emergent Adverse Events Leading to Study Drug Discontinuation (Randomised Set)**	**RND**	**AEL002**
	Same as listing 16.2.7.2, but listing TEAEs leading to study drug discontinuation only		
16.2.7.9	**Treatment Emergent Adverse Events Leading to Death (Randomised Set)**	**RND**	**AEL002**
	Same as listing 16.2.7.2, but listing TEAEs leading to death only		
16.2.7.10	**Adverse Events of Particular Interest (Randomised Set)**	**RND**	**AEL002**
	Same as listing 16.2.7.2, but listing TEAEs of particular interest only		
16.2.7.11	**Physical Examination Abnormalities (Randomised Set)**	**RND**	**PEL001**
	Listing of all data on abnormal physical examinations findings		
LABORATORY DATA			
16.2.8.1.1	**Laboratory Results: Haematology Abnormalities (Randomised Set)**	**RND**	**LBL001**
	Listing of all abnormal haematology results. The (non-imputed) values will be shown, as well as normal ranges, clinical significance flag and fasted flag.		
16.2.8.1.2	**Laboratory Results: Biochemistry Abnormalities (Randomised Set)**	**RND**	**LBL001**
	Listing of all abnormal biochemistry results. The (non-imputed) values will be shown, as well as normal ranges, clinical significance flag and fasted flag.		
16.2.8.1.3	**Laboratory Results: Urinalysis (Randomised Set)**	**RND**	**LBL001**
	Listing of all available urinalysis results. The (non-imputed) values will be shown, as well as normal ranges, abnormality flags, and clinical significance flag.		

Number	Title	Analysis Set	TLFs Library Template Number
16.2.8.1.4	**Laboratory Results: Pregnancy Test (Randomised Set)**	**RND**	**LBL005**
	Listing of all serum and urine pregnancy and FSH results.		
VITAL SIGNS			
16.2.8.2	**Vital Signs: Full Listing (Randomised Set)**	**RND**	**VSL001**
	Listing of all vital signs results. The values will be shown, as well as changes from baseline.		
ECG			
16.2.8.3	**Local 12-Lead ECG: Full Listing (Randomised Set)**	**RND**	**EGL001**
	Listing of all triplicate local 12-lead ECG results and the corresponding interpretation. The values will be shown, as well as changes from baseline and abnormality categories (for QTcF).		
LUNG FUNCTION			
16.2.8.4	**Lung Function: Full Listing (Randomised Set)**	**RND**	**VSL001**
	Listing of all lung function results, except the reversibility test results. The values will be shown, as well as changes, relative changes from baseline and relative change abnormalities. Template VSL001 is used, presenting the lung function parameters instead. For layout purposes, VSL002 could be used instead.		
USE OF RESCUE MEDICATION			
16.2.8.5	**Rescue Medication Use (Randomised Set)**	**RND**	
	Listing of all data related to rescue medication available in the CRF		

[redacted]

8.3 FIGURES

Number	Title	Analysis Set	TLFs Library Template Number
LUNG FUNCTION			
14.3.7.1	**Mean Change from Baseline in Lung Functions (Safety Set)** Graph of mean absolute changes from baseline in FEV_1 and PEF with "time" on the horizontal axis and a different plot symbol/colour/line pattern for each subject group. Each parameter will be presented separately.	**SAF**	**TPF001**
14.3.7.2	**Mean Relative Change from Baseline in Lung Functions (Safety Set) [KFR]** Graph of mean relative changes from baseline in FEV_1 and PEF with "time" on the horizontal axis and a different plot symbol/colour/line pattern for each subject group. Each parameter will be presented separately.	**SAF**	**TPF001**

9. APPENDICES

9.1 SAS CODE

The SAS code in this section is an example and might differ from the actual code used in the statistical analysis.

Lung function ANCOVA models:

```
proc mixed;
   by param atptn;
   class trtan subjid aperiod;
   model (p)chg = trtan subjid aperiod base;
   lsmeans trtan / diff alpha= 0.05;
run;
```

9.2 SCHEDULE OF ASSESSMENTS

	Pre-screening visit (Visit 0)[1]	Screening visit (Visit 1)[1]	Investigational Phase		Follow-up call[2]	Early Termination visit
			TP1	TP2		
Date	2-7 days before screening	2-21 days before TP1	Day 1	2-7 days after TP1	7-10 days after TP2	
Informed consent	X					
Randomisation			X			
Ambulatory visit	X	X	X	X	X[2]	X
Treatment intake						
Treatment administration[3]			X	X		
Training						
Placebo training		X				
Subject Health Evaluation						
Inclusion/Exclusion criteria		X	X			
Medical history, concomitant diseases and previous medications		X				
Demographic data		X				
Height and weight		X				
Physical examination		X	X	X		X
ACQ-5	X*	X	X			
Adverse events recording		X	X	X	X	X
Restrictions		X	X	X		
Concomitant medications	X	X	X	X	X	X
Safety assessment in blood						
Clinical chemistry		X				
Haematology		X				
FSH or pregnancy test		X				
Generic assessments in urine						
Urinalysis		X				
Pregnancy test			X	X		X
Cardiac assessments[4]						
12-lead ECG		X	X	X		X
Vital signs - Blood pressure		X	X	X		X
Pulmonary Assessments						
Bronchodilator reversibility or bronchial challenge test[5]		X				
Lung function[6]		X	X	X		
Other Assessments						
[redacted]			X	X		

ACQ-5 = Asthma Control Questionnaire©; DBP = Diastolic blood pressure; ECG = Electrocardiogram; FEV_1 = Forced expiratory volume in 1 second; FSH = Follicle-stimulating hormone; h = hour; min = minute; PEF = Peak expiratory flow; SBP = Systolic blood pressure; T0 = Time of the first inhalation of the study treatment; T1 = Time of the last [redacted] inhalation of the study treatment; TP = Treatment period.

[1] Visit 0 and Visit 1 can be combined in a single visit if the study restrictions and wash-out requirements are respected at Visit 0.

[2] A follow-up visit can be performed, if deemed necessary by the Investigator. A follow-up call (or visit) is not required in case of early withdrawal.

[3] A single dose [redacted] will be administered. Subjects must perform the [redacted] inhalations within 12 min. For each subject, the two treatment administrations (at TP1 and TP2) must start at approximately the same time of the day.

[4] Cardiac assessments will be performed as follows:

- Vital signs: duplicate SBP and DBP will be evaluated after 5 min in supine position and before the spirometry assessments and blood tests, at screening (Visit 1), and at the following timepoints on TP1 and TP2:
  - Pre-dose: within 1 h before T0;
  - Post-dose: 45 min, 1 h 45 min and 2 h 45 min after T1.
- Local 12-lead safety ECG: a triplicate ECG will be performed to assess eligibility at screening (Visit 1), before the spirometry assessments and blood tests and a single ECG will be evaluated on TP1 and TP2, at the same timepoints as the vital signs.

[5] The bronchodilator reversibility or bronchial challenge test will be performed to assess a subject's eligibility, in case documented evidence of excessive variability in lung function is not available or in case the documentation is older than 2 years. In case the criterion of excessive lung function variability is not met at screening, the test (bronchodilator reversibility or bronchial challenge) can be repeated once before randomisation (performed at TP1).

[6] Lung function assessments (spirometry [FEV_1 and PEF]) will be performed as follows:

- Screening (Visit 1): single spirometry to assess the subject's eligibility;
- TP1 and TP2:
  - Pre-dose: 45 min and 15 min before T0;
  - Post-dose: 5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1.

[redacted]

* ACQ-5 questionnaire can be administered at pre-screening or at screening visit.