[redacted]

STATISTICAL ANALYSIS PLAN

Open-label, randomised, controlled, 2-way cross-over study to assess the effect of multiple doses of the new HFA-152a propellant versus the marketed HFA-134a propellant on mucociliary clearance in healthy volunteers

NCT05875025

Protocol:	CLI-05993AB6-06
[redacted] **Internal Reference:**	[redacted]
Development phase:	I
Sponsor:	Chiesi Farmaceutici S.p.A.
SAP version number:	Final 1.0
SAP version date:	05OCT2023

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PROTOCOL HISTORY

Protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the changes on the statistical analysis**
Final 1.0	16FEB2023	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

Ab-HCV	hepatitis C virus antibody
Ab-HIV1	human immunodeficiency virus 1 antibody
Ab-HIV2	human immunodeficiency virus 2 antibody
ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse event
AIMTM	aerosol inhalation monitor
ALT	alanine transaminase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
AST	aspartate transaminase
AUC	area under the curve
AUC0-4h	area under the tracheobronchial particle retention curve between 0 and 4 hours
ATC	anatomical therapeutic chemical
BMI	body mass index
bpm	beats per minute
BID	Twice daily
CI	confidence interval
eCRF	electronic case report form
DBP	diastolic blood pressure
DRM	data review meeting
DRR	data review report
DY	relative day
ECG	Electrocardiogram
FEV1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
γ-GT	Gamma-Glutamyl Transpeptidase
Hb	haemoglobin
HBsAG	hepatitis B surface antigen
Hct	haematocrit
HFA	hydrofluoroalkane

HIV1	Human Immunodeficiency Virus 1
HIV2	Human Immunodeficiency Virus 2
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	intention-to-treat
MCC	mucociliary clearance
MedDRA	Medical Dictionary for Regulatory Activities
NAP	not applicable
PCR	polymerase chain reaction
pH	potential of hydrogen
PLT	platelet
pMDI	pressurised metered dose inhaler
PP	per protocol
PPR	Percent Particle Retention
PPR2	Percent Particle Retention at 2 hours after the Inhalation of Radiolabelled Particles
PPR4	Percent Particle Retention at 4 hours after the Inhalation of Radiolabelled Particles
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
RNA	ribonucleic acid
RND	randomised set
SAF	safety set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDTM	study data tabulation model
SOP	standard operating procedure
SpO2	Oxygen Saturation Levels
STAT	Statistics
TEAE	treatment-emergent adverse event

TLF	tables, listings and figures
TP	treatment period
VS	vital signs
WBC	white blood cell
WHO	World Health Organisation
WHODrug	WHO drug dictionary
WI	work instruction
WOCBP	women of childbearing potential

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-05993AB6-06 ([redacted]) study.

This SAP covers the study variables, safety, 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.

1.1 STUDY OBJECTIVES

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

- To assess the effect of multiple doses of the HFA-152a propellant and the HFA-134a propellant (when administered not in combination with active compounds) on Mucociliary Clearance (MCC).

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

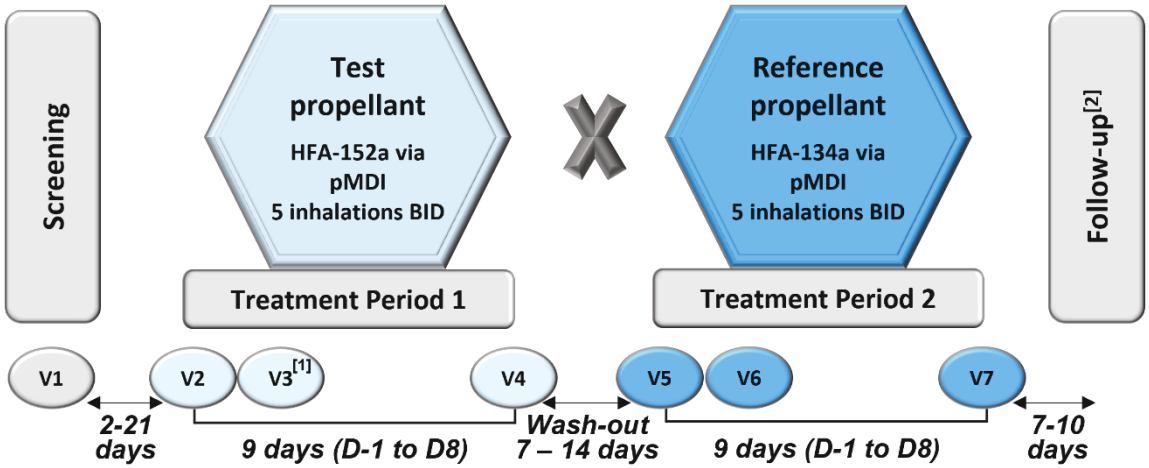
- To evaluate the general safety and tolerability of the two different propellants.

1.2 STUDY DESIGN

This is a Phase I, single-centre, multiple-dose, randomised, open-label, controlled, 2-way cross-over study to assess the effect on MCC of the new HFA-152a propellant (5 inhalations BID for 8 days) *versus* the marketed HFA-134a propellant (5 inhalations BID for 8 days) in adult (aged 18 to 55 years old [inclusive]) healthy volunteers.

The study design is shown in Figure 1.

Figure 1. Study design



BID=Twice daily; D=Day; HFA=Hydrofluoroalkane; pMDI=Pressurised metered dose inhaler; V=Visit.
The study design proposed in the figure is just an example of one of the possible sequences.
[1] Randomisation performed at this visit.
[2] A follow-up visit (instead of a call) can be performed, if deemed necessary by the Investigator.

Study treatment

Approximately 20 subjects fulfilling the study eligibility criteria (see Clinical Protocol) will be randomised to receive multiple doses (5 inhalations BID for 8 days) of each of the following treatments, according to an order determined by the randomisation list:

- **HFA-152a propellant** (also referred to as "test treatment"): placebo HFA-152a propellant (not in combination with other active compounds) via pMDI;
- **HFA-134a propellant** (also referred to as "reference treatment"): placebo HFA-134a propellant (not in combination with other active compounds) via pMDI.

Study visits

A total of 7 ambulatory study visits (Visit 1 [V1] to Visit 7 [V7]) and a follow-up call will be performed during the study.

A full description of study design and study plan is included in the sections 3 and 7.1 of study protocol.

The schedule of assessments is in appendix 9.2.

1.3 EXPECTED SAMPLE SIZE

No formal sample size calculation has been performed for this study, considering its exploratory nature. A total of 20 subjects will be randomised in the study in order to reach at least 18 evaluable subjects.

1.4 RANDOMISATION AND BLINDING

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

Each subject will be identified by a unique 4-digit code (SXXX) assigned at screening.

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 reviewed by an independent person (validated according to model B; see [redacted]).

2. STUDY VARIABLES

2.1 MCC

2.1.1 Available data

The following parameters will be collected from the MCC measurements on Day -1 and on Day 8 of each treatment period: Percent Particle Retention (PPR) in whole lung; PPR in central lung region; PPR in peripheral lung region and central/peripheral ratio. All 4 parameters will be measured for 3 different lung areas: left lung, right lung and whole lung, so in total 12 different MCC measurements will be available.

MCC assessments are performed as follow:

- Co-57 transmission scan and background scan: Day -1 of TP 1 only, prior to the assessment of MCC;
- Administration of radiotracer and image acquisition: subjects will be administered a radiotracer and image acquisitions will be performed at 0 (immediately), 15 minutes, 30 minutes, 1 hour, 1 hour 30 minutes, 2 hours, 2 hours 30 minutes, 3 hours and 4 hours after the administration of the radiotracer. On Day 8 of each treatment period, the radiotracer will be administered approximately 2 hours after the administration of the last dose of the propellant, whereafter the image acquisitions will be performed on Day -1 and on Day 8 of each treatment period (*Note: On Day 8, the radiotracer will be administered at post-dose, approximately 2 hours after administration of the last dose of the propellant.*)

2.1.2 Endpoints and derivation rules

1) Change from baseline in PPR_2 (right whole lung) at Day 8

2) Change from baseline in PPR_4 (right whole lung) at Day 8

3) $AUC_{0\text{-}4}$: Area Under the Tracheobronchial Particle Retention Curve Between 0 and 4 hours after the inhalation of radiolabelled particles (to be calculated only for PPR parameter on right whole lung region)

The area under the result vs. time curve observed from time 0 up to the last measurable value (i.e., 4h) 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:

- $AUC_{0\text{-}4}$ normalised by time =

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

- Change from baseline in AUC = $AUC_{0\text{-}4}$ normalised by time at Day 8 – baseline ($AUC_{0\text{-}4}$ normalised by time at Day -1).

where:

- t_0 is the actual time of administration of radiotracer,
- for i = 15 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, and 4h, PPR_i is the actual PPR 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_{4h}.

Per analysis window, only the time point 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 $AUC_{0\text{-}4h}$ calculation:

- In case the last measurement for the $AUC_{0\text{-}4h}$ (i.e. 4h) is missing, the entire curve will be considered missing;
- Single, isolated missing values (different from 0h 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.

2.1.3 Inferential statistics

All statistical comparisons will be made using two-sided tests at the 0.05 significance level unless specifically stated otherwise.

The change from baseline in PPR_2 and PPR_4 at Day 8 will be analysed using an analysis of covariance (ANCOVA) model, including treatment, subject and period as fixed effects, and PPR_2 (or PPR_4) at baseline (i.e., Day -1) as a covariate. The adjusted mean change from baseline obtained with each treatment and the adjusted mean difference between HFA-152a and HFA-134a with their 95% confidence intervals (CIs) and p-values will be estimated by the model.

2.1.4 Presentation of results

All MCC variables in right whole lung (PPR in right whole lung region (%), PPR in right central lung region (%), PPR in right peripheral lung region (%) and Right Central/Peripheral Ratio) (including $AUC_{0\text{-}4}$ only for right whole lung region) will be summarised by means of descriptive statistics by treatment. Actual values (with their 95% CI) and changes from baseline (with their 95% CI) will be tabulated separately.

The ANCOVA model will be performed for change from baseline of PPR_2 and PPR_4 at Day 8. The results will be tabulated, including the estimates (mean, 95% CI, p-value) of the model estimated changes from baseline and difference between HFA-152a and HFA-134a in change from baseline.

Graphs of the mean actual values and the mean changes from baseline over time will be prepared for PPR (in right whole lung region, right central lung region and right peripheral lung region) by treatment.

All MCC data will be listed. All MCC data for the whole and the left lung will be listed only.

3. SAFETY ANALYSES

3.1 ADVERSE EVENTS

3.1.1 Available data

Adverse events (AEs) are coded into system organ classes and preferred terms using the medical dictionary for regulatory activities (MedDRA, see section 9.3). For each AE, start and stop date(time)s are collected as well as intensity, a seriousness flag, seriousness criteria, treatment-relationship, action taken towards the study treatment and outcome.

3.1.2 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 treatment administration – 1 minute, extremes included.

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

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

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 treatment 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 5.3.3) =
  - 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".

3.1.3 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

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. AEs started on or after the date of the follow-up call/visit will be flagged as 'Follow-

up'. COVID-19 related AEs will be flagged. Separate listings will be prepared for the categories presented in the summary tables.

3.2 CLINICAL LABORATORY EVALUATION

3.2.1 Available data

Per protocol, the following safety laboratory parameters are expected:

- Chemistry: creatinine, urea, aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [γ-GT], total bilirubin, alkaline phosphatase, sodium, potassium, albumin, fasting glucose
- Haematology: red blood cell [RBC] count, white blood cell [WBC] count and differential, total haemoglobin [Hb], haematocrit [Hct], platelets [PLT] count
- Urinalysis: bilirubin, urobilinogen, ketones, glucose, proteins, blood, nitrite, potential of hydrogen (pH), specific gravity, and leukocytes.
- Serum and urine pregnancy test and FSH.

Normal ranges are available as provided by the laboratory.

3.2.2 Derivation rules

The following abnormality categories will be defined:

- Low: value < lower limit of normal range
- Normal: lower limit of normal range ≤ value ≤ upper limit of normal range
- High: value > upper limit of normal range

Notes:

- Classification will be done in standardised units, by using non-imputed values and limits as reported in standardized units in the clinical database: a value <X where X equals the lower limit of normal range will be classified as low. A value X with normal range <X will be classified as high.
- If not straightforward how to categorize results, e.g. when results are reported as ranges, a worst-case approach will be used. A value of '4 to 6' with normal range '0 to 5' will thus be classified as normal for pre-dose assessments but as high for post-dose assessments.

3.2.3 Presentation of results

All laboratory data will be listed.

3.3 VITAL SIGNS

3.3.1 Available data

The following vital signs parameters are collected:

- duplicate systolic (SBP) and diastolic blood pressure (DBP) in supine position
- body temperature
- SpO_2

3.3.2 Derivation rules

Mean values of the duplicates will be calculated per time point and rounded as detailed in section 5.3.3. Records belonging to the same duplicate will be identified using variable VSGRPID. All records of the duplicate will be used to calculate the mean, even if less or more than the expected two. The date and time of the first member of the duplicate will be assigned to this mean value. Throughout the analysis, including the derivation of Baseline and abnormalities, the mean values will be used. Individual duplicate values will only be listed.

3.3.3 Presentation of results

Vital signs parameters (SBP, DBP and SpO_2) will be summarised by means of descriptive statistics at each analysis window by treatment. Actual values (with their 95% CI) and changes from baseline (with their 95% CI) will be tabulated separately.

All vital signs data will be listed.

3.4 ELECTROCARDIOGRAMS

3.4.1 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 at Day 1 and Day 8 of each period: heart rate (HR), PR interval, QRS interval, QT interval, corrected QT interval (Fridericia) and the corresponding interpretation

3.4.2 Derivation rules

Mean values of the triplicates will be calculated for screening and rounded as detailed in section 5.3.3. Records belonging to the same triplicate will be identified using variable EGGRPID. All records of the triplicate will be used to calculate the mean, even if less or more than the expected three. Individual triplicate values will only be listed.

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

- Actual values:
  - For male subjects: QTcF interval > 450 ms and <=480 ms, > 480 and <=500 ms, and > 500 ms;
  - For female subjects: QTcF interval > 470 ms and <=500 ms, > 500 ms;
- Changes from Baseline:
  - Increase from Baseline >30 ms and <=60 ms
  - Increase from Baseline >60 ms

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

3.4.3 Presentation of results

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

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

All local 12-lead ECG parameters will be listed. Uncorrected QT interval and the investigator's interpretation will only be listed. Any post-baseline abnormality that was not present at baseline (e.g., QTcF]450; 480] ms at baseline and >500 ms post-baseline for male subjects) will be flagged.

3.5 LUNG FUNCTION

3.5.1 Available data

The following lung function (spirometry) parameters are collected: Forced Expiratory volume in 1 second (FEV_1), predicted FEV_1, percent predicted FEV_1, forced vital capacity (FVC), and FEV_1/FVC ratio.

3.5.2 Presentation of results

Lung function parameters (FEV_1 and FVC) will be summarised by means of descriptive statistics (with their 95% CI) at each analysis window by treatment. Actual values, changes from baseline, and relative changes from baseline will be tabulated separately.

All lung function parameters will be listed.

3.6 PHYSICAL EXAMINATIONS

Abnormal physical examination findings will be listed.

4. GENERAL CHARACTERISTICS ANALYSES

4.1 SUBJECT DISPOSITION

The following subject data will be tabulated by treatment sequence and overall:

- 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 and percentage of subjects who entered, completed or discontinued each study period

All information collected in the eCRF concerning allocation, 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 important 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 reported in the relative listings.

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, year of birth, and date of signing informed consent form (ICF), smoking status, duration and number of pack-years
- Screening tests: chemistry and haematology, vital signs, local 12-lead ECG (HR, PR, QRS and QTcF), lung function, serology (Human Immunodeficiency Virus Antibody (Ab-HIV1 and 2), Hepatitis B surface Antigen (HBsAg), Hepatitis B core antibody (anti-HBc) Hepatitis C Virus Antibody (Ab-HCV) and HCV-RNA PCR), ethanol and urine drug screen (methamphetamine, cocaine, cannabis, amphetamines, morphine/opiates, benzodiazepines, methylenedioxymethamphetamine, methadone, tramadol and ketamine) and cotinine test

4.3.2 Derivation rules

The following parameters will be derived:

- Smoking duration will be calculated as the sum of smoking years for each reported tobacco category.
- Mean values of the duplicates (blood pressure parameters) will be calculated and rounded as detailed in section 5.3.3. Records belonging to the same duplicate will be identified using variable VSGRPID. All records of the duplicate will be used to calculate the mean, even if less or more than the expected two. The date and time of the first member of the duplicate will be assigned to this mean value.
- Mean values of the triplicates (12-lead ECG parameters at screening) will be calculated and rounded as detailed in section 5.3.3. Records belonging to the same triplicate will be identified using variable EGGRPID. All records of the triplicate will be used to calculate the mean, even if less or more than the expected three. The date and time of the first member of the triplicate will be assigned to this mean value.

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, and smoking status.

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

- vital signs at screening, Period 1 Day -1 (temperature only) 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.

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

4.4 MEDICAL/SURGICAL HISTORY AND CONCOMITANT DISEASES

4.4.1 Available data

Medical/surgical history and concomitant diseases findings are coded using the medical dictionary for regulatory activities (MedDRA, see section 9.3) into system organ classes and preferred terms. For each finding, 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, see section 9.3). For each procedure, start and stop dates or ongoing flag are collected.

All medications are coded using WHODrug (see section 9.3). 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 date(time)s 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 treatment administration
- Maintained: the procedure/medication started before first study treatment administration and was ongoing at first study treatment administration
- Concomitant: the procedure/medication started at or after first study treatment administration

For procedures/medications with (partially) missing date(time)s not allowing allocation to one unique category, 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. Procedures started on or after the date of the follow-up call/visit will be flagged as ‘Follow-up’.

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. Medications started on or after the date of last follow-up call/visit will be flagged as ‘Follow-up’.

4.6 EXPOSURE TO STUDY TREATMENT, TREATMENT COMPLIANCE

4.6.1 Available data

For each study treatment administration at visit, the start date(time)s, the total number of correct and incorrect inhalations taken and reason for incorrect inhalations will be recorded in eCRF. In addition, data on training with inhalers (AIM™ Vitalograph®

and pMDI Placebo) is collected. For all other study treatment administrations (i.e. from the evening of Day 1 to the evening of Day 7), the intake of the study propellant (i.e., number of puffs only) will be daily recorded by the subject in the diary cards.

4.6.2 Derivation rules

The following parameters will be derived:

- If clinic visit at Day 8 (V4/V7) is performed (so treatment period has been completed):
  - Total treatment duration (days) = Date of Day 8 (V4/V7) – Date of Day 1 (V3/V6) + 1 day
  - Total number of administered inhalations: sum of all inhalations (correct and incorrect) of study drug between Date of Day 8 (V4/V7) and Date of Day 1 (V3/V6) (both included)

    Note: at the visit, information on the number of correct and incorrect inhalations is captured, on the other days (i.e., from the evening of Day 1 to the evening of Day 7) only the information on the number of puffs (total number) is recorded in the diary card.
  - Total number of scheduled inhalations: sum of all scheduled inhalations of study drug defined as: 5*(2*total treatment duration (days) – 1)
- If clinic visit at Day 8 (V4/V7) is not performed (so treatment period has not been completed):
  - Date of last study drug administration for each treatment period = date of last study drug administration (maximum date of either site or diary in the specific treatment period)
  - Total treatment duration (days) = max(date of last study drug administration, date of last visit performed in the treatment period (ET and FU visits excluded)) – Date of Day 1 (V3/V6) + 1 day
  - Total number of administered inhalations: sum of all inhalations of study drug (correct and incorrect) between max(date of last study drug administration, date of last visit performed in the treatment period (ET and FU visits excluded)) and Date of Day 1 (V3/V6) (both included)
  - Total number of scheduled inhalations: sum of all scheduled inhalations of study drug defined as: 5*2*total treatment duration (days)
- Compliance = 100 * (total number of administered inhalations)/(total number of scheduled inhalations)
- Compliance category: <80%, 80-100%, >100%

The above parameters will be evaluated on the basis of the inhalations administered at site and recorded in the eCRF and on the information recorded daily by the subject on the diary card.

If for the morning dose on the days of the scheduled clinic visits both diary and site data are available (in case for any reason should the subject report in the diary the already administered morning dose at the site), the site data only will be considered for the calculation of compliance.

4.6.3 Presentation of results

Exposure information will be presented using descriptive statistics by treatment for total treatment duration and compliance and frequency tabulations by treatment for compliance category.

All exposure, compliance 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:

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 treatment* (analysed as treated)
Intent-to-Treat (ITT) Analysis Set:	subjects who were randomised and *received at least one dose of study treatment* (analysed as randomised)
Per Protocol (PP) Analysis Set:	subjects from the ITT, excluding the subjects with any important protocol deviations leading to data exclusion

Notes:

- 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 treatment is defined as having an exposure date or any information confirming exposure.
- Exact definition of important protocol deviations impacting the analysis sets (e.g. wrong inclusions, poor compliance, non-permitted medications) will be discussed by the study team during the review of the data and described in the Data Review Report.

Unless stated otherwise, the ITT will be used for the general characteristics and SAF for safety tables and the RND will be used for listings. ITT and PP Analysis Set will be used for the study variables tables and figures.

5.1.2 As planned versus as actual analysis

For the safety analyses the actual treatment of the subject will be considered. The general characteristics and study variable analyses will be by planned treatment (sequence). In the listings the actual treatment (sequence) will be presented.

5.1.3 Exclusion of data from the statistical analyses

The important/non-important protocol deviation definitions are defined in the Protocol Deviation Criteria List and will be used to identify cases that will be discussed by Chiesi during the DRM. Decisions on whether subjects are to be excluded from the analysis set and/or values are to be excluded from the analysis will be fully documented in the Open-Label DRR.

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.

5.2 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 electronic case report form (eCRF) 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 the first available period – 1 minute
Treatment	Period 1	First administration date(time) in period 1	First administration date(time) in the next available period – 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 the first available period – 1 day
Treatment	Period 1	First administration date in period 1	First administration date in the next available period – 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 rather than periods.

AEs, medications and procedures will be allocated to phases and periods as described in sections 3.1.2 and 4.5.2 respectively.

5.2.2 Baseline and change from baseline

The baseline value is the last non-missing value, including unscheduled assessments, before the first administration of any study treatment of each treatment period.

The following table summarizes the baseline definition for each parameter:

Parameter	**Baseline**
Vital signs	Day 1 pre-dose (of each treatment period)
12-lead ECG parameters	Day 1 pre-dose (of each treatment period)
Lung function	Day 1 pre-dose (of each treatment period)
Study Variables (PPR_i [right lung])	Matched CRF time-point at Day-1 (of each treatment period) e.g.: baseline for PPR_2 at Day 8: PPR_2 at Day -1
Study Variables ($AUC_{0\text{-}4h}$)	Day -1 $AUC_{0\text{-}4h}$ (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 both baseline value and value at time point t are zero: not calculated
- When baseline value is zero and value at time point t is not 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 treatment (in the study and in each period).

5.2.4 Analysis visits

The analysis will use the visits indicated on the subject's eCRF, while for the time points related to study variables, vital signs, ECG, and lung function 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 as screening value, or per time window definitions below.

The unscheduled assessments will be checked during the data review meeting before database lock, and any different approach to the rule defined above will be documented in the data review report.

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.

The analysis visit labels will be assigned using the following rules:

- All planned screening, re-screening, eligibility recheck, 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)

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

- Pre-dose time points will be presented as 'Pre-dose'
- Time points expressed in minutes in SDTM will be presented as 'Xmin' (e.g.: '10min', '30min', '45min', etc.)
- Time points expressed in hours in SDTM will be presented as 'Xh' (e.g.: '1h', '12h', '24h', etc.)
- Time points expressed in ranges in SDTM will be presented using the same ranges (e.g.: '-75min-6h', 'Within 1.5h', '0-12h', etc.)
- Unscheduled time points will be blank unless the decision to reallocate the time point is fully documented in the DRR. In case of reallocation, the unscheduled time point will be presented with the same label as the replaced planned time point (see rules above)
- Other time points not covered by the rules above will be presented using similar labels to the ones used in SDTM (XX.XXTPT)

The analysis time point labels for study variables, vital signs, ECG parameters, and lung function parameters will be assigned using the following time windowing rules. All assessments, including unscheduled assessments, will be allocated to time windows. Tables will present the time windows as defined below and listings will present the time windows, as well as the eCRF time point labels.

Allocation of time assessments will be done according to the following tables:

Study variables:

Analysis time point window	**Target time after end of radiotracer inhalation per assessment day per period (minutes)**	**Time interval (minutes)**
0 (immediately)	0	[0,7]
15min	15	[8;22]
30min	30	[23;45]
1h	60	[46;75]
1h 30min	90	[76;105]
2h	120	[106;135]
2h 30min	150	[136;165]
3h	180	[166;210]
4h	240	[211;360]

Vital signs and Electrocardiogram:

Analysis time point window	**Target time after first dose (last inhalation) of study treatment per assessment day per period (minutes)**	**Time interval (minutes)**
Pre-dose	<0	Last day 1 (or day 8), pre-dose assessment
5min	5	[0;10]
15min	15	[11;45]
1h 45min	105	[46;180]

Note: The reference time for Pre-dose is the first inhalation of study treatment per assessment day per period (minutes).

Lung function:

Analysis time point window	Target time after first dose (last inhalation) of study treatment per assessment day per period (minutes)	Time interval (minutes)
Pre-dose	<0	Last day 1 (or day 8), pre-dose assessment
20min	20	[0;60]

Note: The reference time for Pre-dose is the first inhalation of study treatment per assessment day per period (minutes).

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.

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-baseline 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 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.

5.3.3 Rounding of derived variables

Derived variables will be rounded at display level:

- AE duration will be presented with 1 decimal.
- Mean of duplicates/triplicates 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
- Relative change from baseline will be presented with 1 decimal.
- Compliance will be rounded to 1 decimal.

5.3.4 Outliers

Potential other 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 Open-Label 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 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, with a maximum of 4 decimal places. Minimum and maximum will be presented with the same number of decimal places as the individual values, with a maximum of 3 decimal places.

For graphs showing mean values, a 95% CI flag will be shown (based on t-distribution, without continuity correction).

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.

For tabulations by planned treatment, subjects who discontinued the study early will not be included in the denominator of the treatment periods they did not attend.

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), ratios with three decimal places 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:

- T: HFA-152a Propellant
- R: HFA-134a Propellant

When presented by treatment sequence:

- T-R
- R-T

If possible, the long labels (i.e. HFA-152a Propellant, HFA-134a Propellant, etc.) should be used for tables, listings and figures. If needed for layout purposes, the short labels (i.e. HFA-152a or T, HFA-134a or R) will be used instead.

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 treatments will be shown in following order: T, R.

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

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

In tables and figures 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

According to the study protocol, the statistical analysis of MCC variables in whole lung region would be required, but the MCC measurements done in the left lung can be biased due to an overlap of signal from the stomach; therefore, only the right whole lung should be considered and included in the statistical analysis of the MCC data (inferential and descriptive statistics). Moreover, differently from what stated in the study protocol, where descriptive statistics would be provided for the whole lung region only, descriptive statistics for PPR in right central lung region (%), PPR in right peripheral lung region (%), Right Central/Peripheral Ratio and AUC0-4H in right whole lung will be provided as well. Also the figures will be provided for PPR in right central lung region and PPR in right peripheral lung region, in addition to the PPR in the right whole lung.

7. REFERENCES

- ICH Topic E6(R2) Guideline for Good Clinical Practice – Step 5 (EMA/CHMP/ICH/135/1995), 1 December 2016.
- ICH guideline E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (R3) – questions and answers, January 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	**Disposition by Treatment Sequence (Randomised Set)** Tabulation of completion/discontinuation and the reason for discontinuation.	**RND**	**DST002**
14.1.1.2	**Disposition by Treatment (Randomised Set)** Tabulation of completion/discontinuation and the reason for discontinuation by treatment period.	**RND**	**DST003**
14.1.1.3	**Analysis Sets per Period by Treatment (Randomised Set)** Tabulation of the number of subjects per period in each of the analysis sets defined in the SAP.	**RND**	**DST006**
14.1.1.4	**Attendance at Treatment Periods by Sequence (Randomised Set)** Tabulation of the number and percentage of subjects that entered, completed or discontinued each treatment period.	**RND**	**SVT002**
14.1.1.5	**Important Protocol Deviations (ITT Analysis Set)** Tabulation of the important protocol deviations (at least one), deviation category and deviation type by treatment and overall.	**ITT**	**DVT001**
14.1.1.6	**Important Protocol Deviations Leading to Exclusion from PP Analysis Set (ITT Analysis Set)** Tabulation of the important protocol deviations (at least one) leading to exclusion from the PP analysis set compared to the ITT analysis set, deviation category and deviation type by treatment and overall.	**ITT**	**DVT001**
14.1.2.1.1	**Demographic Characteristics (ITT Analysis Set)** Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.	**ITT**	**DMT001**
14.1.2.1.2	**Demographic Characteristics (PP Analysis Set)** Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.	**PP**	**DMT001**
14.1.2.2	**Smoking Status (ITT Analysis Set)** Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.	**ITT**	**SUT001**
14.1.2.3	**Vital Signs at Screening, Period 1 Day -1 and Period 1 Day 1, Pre-dose (ITT Analysis Set)** Descriptive statistics of vital signs (DBP, SBP, SpO_2 and body temperature) results at Screening, Period 1 Day -1 (temperature only) and Period 1 Day 1, pre-dose (baseline).	**ITT**	**BLT002**

Number	Title	Analysis Set	TLFs Library Template Number
14.1.2.4	**Local 12-Lead ECG at Screening and Period 1 Day 1, Pre-dose (ITT Analysis Set)** Descriptive statistics of all local triplicate 12-lead ECG results at Screening and single 12-lead ECG result at Period 1 Day 1, pre-dose (baseline).	**ITT**	**BLT002**
14.1.2.5	**Lung Functions at Screening, and Period 1 Day 1 Pre-dose (ITT Analysis Set)** Descriptive statistics of all lung function results at Screening and Period 1 Day 1 pre-dose (baseline).	**ITT**	**RET002**
14.1.2.6	**Medical History (ITT Analysis Set)** 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.	**ITT**	**MHT001**
14.1.2.7	**Concomitant Diseases (ITT Analysis Set)** 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.	**ITT**	**MHT001**
14.1.2.8	**Prior Medications (ITT Analysis Set)** Tabulation of the number and percentage of subjects with prior medications and number and percentage of subjects with prior medications by ATC class (level 1), ATC class (level 2), ATC class (level 4) and preferred name.	**ITT**	**CMT001**
14.1.2.9	**Maintained Medications (ITT Analysis Set)** 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.	**ITT**	**CMT001**
14.1.2.10	**Concomitant Medications (ITT Analysis Set)** 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.	**ITT**	**CMT002**
14.1.2.11	**Treatment Compliance (ITT Analysis Set)** Descriptive statistics of treatment compliance and frequency tabulations for compliance category as defined in section 4.6.2.	**ITT**	**EXT002**
14.1.2.12	**Extent of Exposure (ITT Analysis Set)** Descriptive statistics of total treatment duration as defined in section 4.6.2.	**ITT**	**EXT001**

Number	Title	Analysis Set	TLFs Library Template Number
STUDY VARIABLES			
14.2.1.1.1	**MCC Variables: Summary of Actual Values (ITT Analysis Set)** Descriptive statistics of study variables (right whole lung: PPR and AUC_{0-4}) results per parameter and analysis visit and time point window. Table sorted by analysis window. Each parameter will begin on a new page.	**ITT**	**TPT002**
14.2.1.1.2	**MCC Variables: Summary of Actual Values (PP Analysis Set)** Descriptive statistics of study variables (right whole lung: PPR and AUC_{0-4}) results per parameter and analysis visit and time point window. Table sorted by analysis window. Each parameter will begin on a new page.	**PP**	**TPT002**
14.2.1.2.1	**MCC Variables: Summary of Changes from Baseline (ITT Analysis Set)** Descriptive statistics of changes from baseline in study variables (right whole lung: PPR and AUC_{0-4}) results per parameter and analysis window. Table sorted by analysis window. Each parameter will begin on a new page.	**ITT**	**TPT003**
14.2.1.2.2	**MCC Variables: Summary of Changes from Baseline (PP Analysis Set)** Descriptive statistics of changes from baseline in study variables (right whole lung: PPR and AUC_{0-4}) results per parameter and analysis window. Table sorted by analysis window. Each parameter will begin on a new page.	**PP**	**TPT003**
14.2.1.3.1	**MCC Variables: Statistical Analysis of Changes from Baseline in PPR_2 in Right Whole Lung Region (ITT Analysis Set)** Results from the ANCOVA model on change from baseline at Day 8 for PPR_2 as described in section 2.1.3	**ITT**	**ANT001**
14.2.1.3.2	**MCC Variables: Statistical Analysis of Changes from Baseline in PPR_2 in Right Whole Lung Region (PP Analysis Set)** Results from the ANCOVA model on change from baseline at Day 8 for PPR_2 as described in section 2.1.3	**PP**	**ANT001**
14.2.1.4.1	**MCC Variables: Statistical Analysis of Changes from Baseline in PPR_4 in Right Whole Lung Region (ITT Analysis Set)** Results from the ANCOVA model on change from baseline at Day 8 for PPR_4 as described in section 2.1.3	**ITT**	**ANT001**
14.2.1.4.2	**MCC Variables: Statistical Analysis of Changes from Baseline in PPR_4 in Right Whole Lung Region (PP Analysis Set)** Results from the ANCOVA model on change from baseline at Day 8 for PPR_4 as described in section 2.1.3	**PP**	**ANT001**
SAFETY			
ADVERSE EVENTS			
14.3.1.1	**Summary of TEAEs (Safety Set)** 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.	**SAF**	**AET001**

Number	Title	Analysis Set	TLFs Library Template Number
14.3.1.2	**TEAEs by System Organ Class and Preferred Term (Safety Set)** 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.	**SAF**	**AET003**
14.3.1.3	**Serious TEAEs by System Organ Class and Preferred Term (Safety Set)** 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.	**SAF**	**AET003**
14.3.1.4	**Non-Serious TEAEs by System Organ Class and Preferred Term (Safety Set)** 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.	**SAF**	**AET003**
14.3.1.5	**ADRs by System Organ Class and Preferred Term (Safety Set)** 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.	**SAF**	**AET003**
14.3.1.6	**Serious ADRs by System Organ Class and Preferred Term (Safety Set)** 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.	**SAF**	**AET003**
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**
VITAL SIGNS			
14.3.2.1	**Vital Signs: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of vital signs (DBP, SBP and SpO_2) actual values and changes from baseline per parameter and analysis window. Table sorted by analysis visit and analysis time window. Each parameter will begin on a new page.	**SAF**	**VST001**

Number	Title	Analysis Set	TLFs Library Template Number
ECG			
14.3.3.1	**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 parameter and analysis visit and analysis time window. Each parameter will begin on a new page.	**SAF**	**EGT002**
14.3.3.2	**QTcF: Abnormalities (Safety Set)** Tabulation of the abnormalities as defined in section 3.4.2 at each post-baseline analysis window and at the worst-case analysis window. Table sorted by analysis window. post-baseline analysis time point windows are shown.	**SAF**	**EGT007**
14.3.3.3	**QTcF: Abnormal Changes from Baseline (Safety Set)** Tabulation of the QTcF change abnormalities as defined in section 3.4.2 at each post-baseline analysis window and at the worst-case analysis window. Table sorted by analysis window. Only post-baseline analysis windows are shown.	**SAF**	**EGT008**
LUNG FUNCTION			
14.3.4.1	**Lung Function: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of FEV_1 and FVC actual values and changes from baseline per parameter, analysis visit and time point window. Table sorted by analysis window. Each parameter will begin on a new page.	**SAF**	**TPT001**
14.3.4.2	**Lung Function: Summary of Relative Changes from Baseline (Safety Set)** Descriptive statistics of relative changes from baseline in FEV_1 and FVC results per parameter and analysis window. Table sorted by analysis visit and analysis time window. Only post-baseline analysis windows are shown.	**SAF**	**TPT004**

8.2 LISTINGS

Number	Title	Analysis Set	TLFs Library Template Number
GENERAL CHARACTERISTICS			
16.1.7	**Randomisation Schedule (Randomised Set)** Listing of subject numbers and randomisation information All discrepancies (as-randomised versus as-treated) will be presented.	**RND**	**DSL001**
16.2.1.1	**Study Discontinuation After Randomisation (Randomised Set)** Listing of all subjects that discontinued after randomisation. The study discontinuation reason will also be listed.	**RND**	**DSL003**

Number	Title	Analysis Set	TLFs Library Template Number
16.2.1.2	**Subject Disposition (Randomised Set)**	**RND**	**DSL004**
	Listing of the reasons for completion / discontinuation and the number of days since first study treatment 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 eCRF, this will also be presented in this listing.		
16.2.1.3	**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.		
16.2.1.4	**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.		
16.2.1.5	**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.		
16.2.1.6	**First and Last Contact in the Study (Randomised Set)**	**RND**	
	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. Template DVL002 is used, excluding the ‘Category’ column.		
16.2.2.3	**Restrictions (Randomised Set)**	**RND**	
	Listing of all restrictions data available in the eCRF.		
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/ITT/PP Analysis Set (Randomised Set)**	**RND**	**DSL007**
	Listing of all subjects that were excluded from SAF/ITT/PP.		
16.2.4.1	**Demographic Characteristics (Randomised Set)**	**RND**	**DML001**
	Listing of all demographic parameters		
16.2.4.2	**Serology at Screening (Randomised Set)**	**RND**	**SCL002**
	Listing of all results of serology tests done at screening		

Number	Title	Analysis Set	TLFs Library Template Number
16.2.4.3	**Ethanol, Urine Drug Screen and Cotinine Tests (Randomised Set)**	**RND**	**SCL002**
	Listing of all results of urine drug screen tests performed For layout purposes, template SCL003 could be used instead.		
16.2.4.4	**Smoking Status (Randomised Set)**	**RND**	**SUL001**
	Listing of all smoking data available in the eCRF		
16.2.4.5	**Medical/Surgical History (Randomised Set)**	**RND**	**MHL001**
	Listing of the medical history data findings available in the eCRF		
16.2.4.6	**Concomitant Diseases (Randomised Set)**	**RND**	**MHL002**
	Listing of the concomitant diseases data findings available in the eCRF		
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 eCRF		
16.2.5.1	**Training with Inhalers (Randomised Set)**	**RND**	
	Listing per subject number of all data related to training with inhalers		
16.2.5.2	**Exposure and Compliance (Randomised Set)**	**RND**	
	Listing of all data related to exposure and treatment compliance		
STUDY VARIABLES			
16.2.6.1	**MCC Variables: Listing (ITT Analysis Set)** Listing of all study variable results (MCC on whole lung, central region, peripheral region and central/peripheral ratio in the different regions: the whole lung region, left region and right region), including AUC_{0-4} for PPR (right lung). Changes from baseline will be included for results on the right lung only (including AUC_{0-4}).	**ITT**	
SAFETY			
ADVERSE EVENTS			
16.2.7.1	**Pre-Treatment Adverse Events (Randomised Set)**	**RND**	**AEL001**
	Listing of all pre-treatment AE information collected in the eCRF and of the onset day and duration. All information of one AE will be presented on the same line.		
16.2.7.2	**Treatment Emergent Adverse Events (Randomised Set)**	**RND**	**AEL002**
	Listing of all AE information collected in the eCRF 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		

Number	Title	Analysis Set	TLFs Library Template Number
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	**Physical Examination Abnormalities (Randomised Set)**	**RND**	**PEL001**
	Listing of all data on abnormal physical examinations findings		
LABORATORY DATA			
16.2.8.1	**Laboratory Results: Haematology Full Listing (Randomised Set)**	**RND**	**LBL001**
	Listing of all haematology results. The (non-imputed) values will be shown, as well as normal ranges, abnormality flags (L/H), clinical significance flag and fasted flag.		
16.2.8.2	**Laboratory Results: Haematology Abnormalities (Randomised Set)**	**RND**	**LBL001**
	Same as listing 16.2.8.1, but listing abnormal results only		
16.2.8.3	**Laboratory Results: Chemistry Full Listing (Randomised Set)**	**RND**	**LBL001**
	Same as listing 16.2.8.1, but listing chemistry results instead		
16.2.8.4	**Laboratory Results: Chemistry Abnormalities (Randomised Set)**	**RND**	**LBL001**
	Same as listing 16.2.8.2, but listing chemistry abnormal results instead		
16.2.8.5	**Laboratory Results: Urinalysis (Randomised Set)**	**RND**	**LBL001**
	Listing of all urinalysis results. The (non-imputed) values will be shown, as well as normal ranges, abnormality flags (A), and clinical significance flag.		
16.2.8.6	**Laboratory Results: Pregnancy Test (Randomised Set)**	**RND**	**LBL005**
	Listing of all serum and urine pregnancy results and FSH results.		
VITAL SIGNS			
16.2.9.1	**Vital Signs: Full Listing (Randomised Set)**	**RND**	**VSL001**
	Listing of all vital signs results. The values will be shown, as well as the changes from baseline.		

Number	Title	Analysis Set	TLFs Library Template Number
ECG			
16.2.10.1	**Local 12-Lead ECG: Full Listing (Randomised Set)** Listing of all local 12-lead ECG results and the corresponding interpretation. The values will be shown, as well as changes from baseline, abnormality categories (for QTcF) and treatment emergent abnormality flag and change abnormalities.	**RND**	**EGL001**
LUNG FUNCTION			
16.2.11.1	**Lung Function: Full Listing (Randomised Set)** Listing of all lung function results. The values will be shown, as well as absolute and relative changes from baseline. Template VSL001 is used, presenting the lung function parameters instead.	**RND**	**VSL001**

8.3 FIGURES

Number	Title	Analysis Set	TLFs Library Template Number
STUDY VARIABLES			
14.2.1.1.1	**Mean Change from Baseline in PPR (right lung) (ITT Analysis Set)**	**ITT**	**TPF002**
	Graph of mean changes, with "time" (0h – 4h) on the horizontal axis and a different line colour, line style and plot symbol for each treatment.		
14.2.1.1.2	**Mean Change from Baseline in PPR (right lung) (PP Analysis Set)**	**PP**	**TPF002**
	Graph of mean changes, with "time" (0h – 4h) on the horizontal axis and a different line colour, line style and plot symbol for each treatment.		
14.2.1.2.1	**Mean Actual Values in PPR (right lung) (ITT Analysis Set)**	**ITT**	**TPF002**
	Graph of mean actual values, with "time" (0h – 4h) on the horizontal axis and a different line colour for each treatment and different line style for Day -1 and Day 8. A different plot symbol will be used for combinations of treatment and Day.		
14.2.1.2.2	**Mean Actual Values in PPR (right lung) (PP Analysis Set)**	**PP**	**TPF002**
	Graph of mean actual values, with "time" (0h – 4h) on the horizontal axis and a different line colour for each treatment and different line style for Day -1 and Day 8. A different plot symbol will be used for combinations of treatment and Day.		

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.

ANCOVA

```
proc mixed data=model;
   class usubjid treatment period;
   model chg = base treatment period usubjid;
   lsmeans treatment / cl alpha=0.05 diff;
   ods output lsmeans=lsmeans diffs=diffs;
run;
```

9.2 SCHEDULE OF ASSESSMENTS

	Screening visit (V1)	Investigational Phase (TP1 and TP2) [1]				Early termination visit	Follow-up call [2]
		V2/V5	V3/V6	V3 to V4 V6 to V7	V4/V7		
Date	2-21 days before V2	Day -1	Day 1 (morning)	Day 1 (evening) to Day 7 (evening)	Day 8 (morning)		7-10 days after last intake of study treatment
Informed consent	X						
Randomisation			X *(TP1 only)*				
Ambulatory visit	X	X	X		X	X	X[2]
Treatment intake							
Treatment administration [3]			X	X	X		
Training							
Placebo training	X						
Training with AIM™	X						
Subject health evaluation							
Inclusion/Exclusion criteria	X	X *(TP1 only)*	X *(TP1 only)*				
Medical history and previous medications	X						
Demographic data	X						
Height and weight	X						
Body temperature	X	X	X		X	X	
Physical examination	X		X		X (*TP2 only*)	X	
Alcohol breath test	X	X			X	X	
Adverse events recording	X	X	X	X	X	X	X
Restrictions	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X

	Screening visit (V1)	Investigational Phase (TP1 and TP2) [1]				Early termination visit	Follow-up call [2]
		V2/V5	V3/V6	V3 to V4 V6 to V7	V4/V7		
Date	2-21 days before V2	Day -1	Day 1 (morning)	Day 1 (evening) to Day 7 (evening)	Day 8 (morning)		7-10 days after last intake of study treatment
Safety assessments in blood							
Clinical chemistry	X				X (*TP2 only*)	X	
Serology	X						
Haematology	X				X (*TP2 only*)	X	
Fasting glucose	X				X (*TP2 only*)	X	
FSH or pregnancy test[4]	X						
Generic assessments in urine							
Urinalysis	X						
Cotinine test	X	X			X	X	
Drug panel test	X	X			X	X	
Pregnancy test [4]		X			X (*TP2 only*)	X	
Cardiac assessments [5]							
12-lead ECG	X		X		X	X	
Vital signs	X		X		X	X	
Pulmonary assessment							
Lung function [6]	X		X		X		
MCC assessment [7]							
Co-57 transmission scan and background scan		X *(TP1 only)*					
Administration of radiotracer and image acquisition		X			X		

	Screening visit (V1)	Investigational Phase (TP1 and TP2) [1]				Early termination visit	Follow-up call [2]
		V2/V5	V3/V6	V3 to V4 V6 to V7	V4/V7		
Date	2-21 days before V2	Day -1	Day 1 (morning)	Day 1 (evening) to Day 7 (evening)	Day 8 (morning)		7-10 days after last intake of study treatment
Other assessments							
Daily record card [8]				X			

BID=Twice daily; Co-57=57-Cobalt; DBP=Diastolic blood pressure; ECG=Electrocardiogram; eCRF=Electronic case report form; FEV_1=Forced expiratory volume in 1 second; FSH=Follicle-stimulating hormone; FVC=Forced vital capacity; MCC=Mucociliary clearance; SBP=Systolic blood pressure; SpO_2=Oxygen saturation levels; TP=Treatment Period; V=Visit; WOCBP=Women of childbearing potential.

[1] TP1 and TP2 will be separated by a 7- to 14-day wash-out period.

[2] A follow-up visit (instead of a call) can be performed, if deemed necessary by the Investigator. A follow-up call (or visit) will be performed in case of early termination as well, if the early termination visit is performed less than 7 days after the intake of the last dose of the study treatment.

[3] A total of 5 inhalations BID for 8 consecutive days, starting from the morning of Day 1 until the morning of Day 8. The first and last dose of the study treatment will be administered at the investigational site.

[4] For logistical reasons, both the pregnancy test (in blood and urine) and FSH test will be performed for samples collected from all female subjects. However, only the relevant results will be recorded in the eCRF (i.e. pregnancy tests for WOCBP and FSH tests for post-menopausal women).

[5] Cardiac assessments will be performed before the lung function assessments and the blood tests, and as described below:

- Vital signs:
  At screening, SBP and DBP (in duplicate, made within a 5-minute interval) will be evaluated after 5 minutes in supine position.
  On the morning of Day 1 and Day 8 of each treatment period, SBP, DBP (in duplicate) and SpO_2 (in single) will be evaluated at the following timepoints:
  - Pre-dose: within 1 hour before the intake of the first inhalation of the propellant;
  - Post-dose: 5 minutes, 15 minutes, 1 hour 45 minutes after the intake of the last inhalation of the propellant.
- Local 12-lead safety ECG: a triplicate ECG will be performed to assess eligibility at screening (V1) and a single ECG will be evaluated on the morning of Day 1 and Day 8 of each treatment period, at the same timepoints (before or after) as the vital signs.

In case of early termination, SpO_2 (single), SBP and DBP (duplicate) will be assessed and a single local 12-lead ECG will be measured during the early termination visit.

	Screening visit (V1)	Investigational Phase (TP1 and TP2) [1]				Early termination visit	Follow-up call [2]
		V2/V5	V3/V6	V3 to V4 V6 to V7	V4/V7		
Date	2-21 days before V2	Day -1	Day 1 (morning)	Day 1 (evening) to Day 7 (evening)	Day 8 (morning)		7-10 days after last intake of study treatment

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

- Screening: single spirometry to assess the subject's eligibility;
- On the morning of Day 1 and Day 8 of each treatment period, spirometry assessments will be performed as follow:
  - Pre-dose: within 30 minutes before the intake of the first inhalation of the propellant;
  - Post-dose: 20 minutes after the intake of the last inhalation of the propellant.

[7] MCC assessments will be performed as follow:

- Co-57 transmission scan and background scan: Day -1 of TP 1 only, prior to the assessment of MCC;
- Administration of radiotracer and image acquisition: subjects will be administered a radiotracer and image acquisitions will be performed at 0 (immediately), 15 minutes, 30 minutes, 1 hour, 1 hour 30 minutes, 2 hours, 2 hours 30 minutes, 3 hours and 4 hours after the administration of the radiotracer. The analysis of these images will provide a measurement of MCC.
  On Day 8 of each treatment period, the radiotracer will be administered approximately 2 hours after the administration of the last dose of the propellant.

[8] Subjects will use a daily record card (one for each treatment period) to record the intake of the study propellant, the occurrence of adverse events or the intake of concomitant medications. The daily record card will be given to the subjects on Day 1 of each treatment period and will be collected on Day 8 of each treatment period. In case of early discontinuation, if discontinuation occurs during a treatment period, the daily record card will be collected during the early termination visit.

9.3 DICTIONARY VERSIONS

Data	Dictionary
Adverse Events	MedDRA version 26.0
Concomitant Therapy	WHO-DD version 01 Mar 2023 (Global) Format B3
Anatomical-Therapeutic-Chemical (ATC) selection	WHO-DD version 01 Mar 2023 (Global) Format B3
Medical History	MedDRA version 26.0
Procedures	MedDRA version 26.0