STATISTICAL ANALYSIS PLAN

Open label, prospective study to evaluate the effect of step-up from non-extra fine ICS/LABA DPI to extra fine triple therapy with CHF5993 DPI on airway geometry and lung ventilation using FRI in subjects with advanced COPD

Protocol:	CLI-05993BA1-08
PPD **number:**	PPD
Sponsor:	Chiesi Farmaceutici S.p.A
SAP version number:	Final 1.0
SAP version date:	29MAR2022

PROTOCOL HISTORY

Protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the changes on the statistical analysis**
Final 1.0	24NOV2020	NAP
Final 2.0	02FEB2021	NAP
Final 3.0	11FEB2021	NAP
Final 4.0	26MAY2021	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
ALT	alanine transaminase
anti-HBc	hepatitis B core antibody
AST	aspartate transaminase
BMI	body mass index
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CAT	COPD assessment test
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
CV	coefficient of variation
DRR	data review report
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ENR	enrolled set
FRC	functional residual capacity
FRI	functional respiratory imaging
FSH	follicle-stimulating hormone
HBsAG	hepatitis B surface antigen
HIV1	Human Immunodeficiency Virus 1
HIV2	Human Immunodeficiency Virus 2
HR	heart rate
ICF	informed consent form

ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
LLL	left lower lobe
LUL	left upper lobe
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NAP	not applicable
PP	per protocol
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
RLL	right lower lobe
RML	right middle lobe
RUL	right upper lobe
SAF	safety set
SAP	statistical analysis plan
SD	standard deviation
SDTM	study data tabulation model
SE	standard error
siRaw	specific airway resistance
Siva	specific airway volume
SOP	standard operating procedure
STAT	Statistics
TEAE	treatment-emergent adverse event
TLF	tables, listings and figures
TLC	total lung capacity
VS	vital signs
WHO	World Health Organisation
WHO-DD	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.
standardized unit	unit populating --STRESU in the clinical database
investigational product (IP)	Pharmaceutical form of an active ingredient or placebo, being tested or used as a reference in a clinical study.

TABLE OF CONTENTS

1. INTRODUCTION

This SAP describes the final statistical analysis to be performed for the CLI-05993BA1-08 (PPD) study.

This SAP covers the efficacy, safety, and general characteristics parts of the statistical analysis. It specifies the analysis displays to be presented and provides additional description to the methods and procedures of statistical analysis 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, and ICH-E9 guidelines.

1.1 STUDY OBJECTIVES

In line with the protocol, the study objectives of this study are:

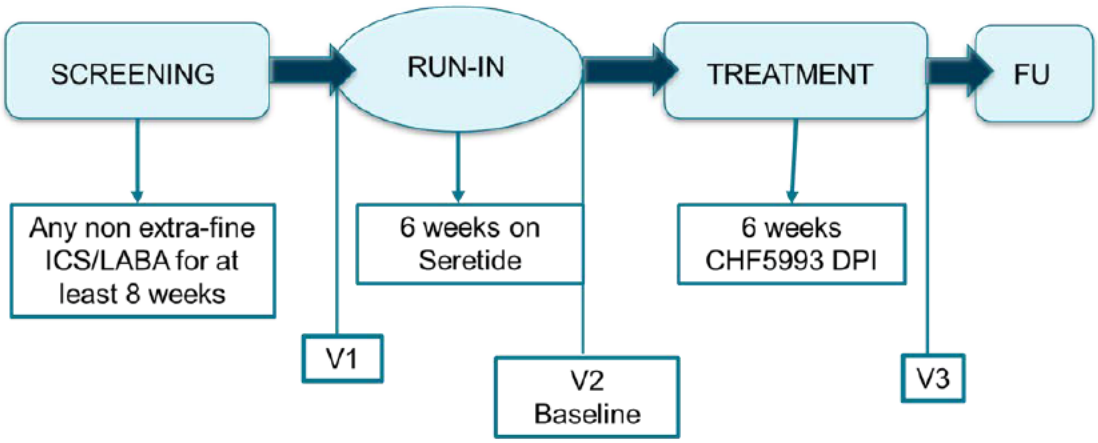
- primary objective: to assess the effect of stepping-up from SERETIDE™ DISKUS™ (fluticasone propionate/salmeterol or FP/SLM 500/50 µg) DPI to extra fine CHF 5993 (BDP/FF/GB 100/6/12.5 µg) DPI on airway geometry and lung ventilation;
- secondary objectives: to assess therapeutic aerosol particles deposition and lung function following a switch from FP/SLM 500/50 µg (SERETIDE™ DISKUS™) DPI to extra fine BDP/FF/GB 100/6/12.5 µg (CHF5993) DPI.

1.2 STUDY DESIGN

This is a multicentre, open-label, single arm study.

After the screening visit that will be performed 6 weeks ± 2 days before Visit 2, eligible subjects will undergo a 6 weeks run-in period with FP/SLM 500/50 µg (SERETIDE™ DISKUS™).

At the end of the run-in period (Visit 2), subjects will be switched to the treatment period with BDP/FF/GB DPI (CHF5993) for 6 weeks (until Visit 3).



The end of the trial is defined as the last visit/last call of the last subject in the trial.

The schedule of assessments is in appendix 9.2.

1.3 EXPECTED SAMPLE SIZE

No formal sample size calculation has been performed since the nature of the study (i.e., exploratory study).

30 subjects will be enrolled in the study in order to have at least 25 completed subjects.

1.4 RANDOMISATION AND BLINDING

This is an open-label, non-randomized study.

1.5 INTERIM ANALYSIS

No interim analyses are foreseen.

1.6 SOFTWARE

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

1.7 VALIDATION MODEL

PPD 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. EFFICACY ANALYSES

Efficacy analyses will be performed on the Per Protocol (PP) Analysis Set.

2.1 PRIMARY EFFICACY ENDPOINT

2.1.1 Multidetector Computed Tomography (MDCT) and FRI endpoints

Scan of the thorax multi-slice with multidetector computed tomography (inspiratory at TLC and expiratory at FRC) will be performed pre-dose and within 60– 120 min post-dose at Visit 2 and Visit 3. At Visit 2, upper airway will be also scanned at TLC, pre-dose. Functional Respiratory Imaging (FRI) is a non-invasive quantification imaging methodology that provides detailed measurement, visualization, and evaluation of the lungs and airways, both regionally and in totality. FRI uses low-dose, high-resolution volumetric computerized tomography (CT) scans and quantitative imaging technology based on computational fluid dynamics (CFD) to model airflow and measure structural and functional characteristics of the respiratory system. FRI provides quantifiable measures of drug performance, contributing to clinical proof of concept and dose selection. Additional details on each FRI parameter that will be used as primary endpoints in this study is provided in the study protocol, sections 7.2.1.1 and 7.2.1.2 (while sections from 7.2.1.3 to 7.2.1.10 for secondary endpoints).

The visible airway generations that comprise the lobes can vary over time. The airway related FRI measurements can thus be performed in two ways:

1) for each segment use all the generations visible at the particular study visit scan ("untrimmed", identified in SUPPRE with QVAL = 'FULL'), or

2) for each segment use only generations of airways that are visible in the baseline scan and in the post scan ("trimmed", identified in SUPPRE with QVAL = 'V2PREV3PRE' 'V2PREV3POST' 'V2PREV2POST' 'V3PREV3POST' 'V2POSTV3POST' depending on the comparison considered).

Data will be analysed for the central lung region, total lung region, overall distal lung region and for each lobe (Right Upper Lobe (RUL), Right Middle Lobe (RML), Right Lower Lobe (RLL), Left Upper Lobe (LUL) and Left Lower Lobe (LLL)) and combined lobes (Upper Lobes (UL) and Lower Lobes (LL)). The primary region is the distal region.

Analysis will be done for the 2 lung levels separately: Functional Residual Capacity (FRC) and Total Lung Capacity (TLC), with the latter one representing the lung level of interest for the primary endpoints.

It is possible for subjects to have regional pathophysiology, thus unusual resistance values can be observed in one region while only normal assessments observed in another. When there is no evidence that the unusual resistance values are indicative of systematic errors in the scans themselves or analyses thereof (which would be addressed by appropriate actions, such as exclusion of all regions in case of scan systematic errors'), they will be considered as outliers and excluded from the analysis. As a general rule, the values that are larger than the third quantile + 3 times the interquartile range will be excluded from the descriptive statistics, MMRM and correlation analyses. The determination was made to exclude outlier resistance values

on a lobar level from analysis as this approach was deemed physiologically plausible due to the way resistance is summed. Specifically, $R = \frac{1}{R_1} + \frac{1}{R_2} + \cdots + \frac{1}{R_j}$, where j is the number of lobes, thus the contribution of a given outlying value to the total resistance approaches 0.

Infinite values for resistance are possible and these will be listed but will be removed from the data before statistical analysis.

2.1.2 Available data

The following parameters were captured and will be included in the primary efficacy analysis:

- Specific Image-Based Airway Volume (at TLC) (siVaw)
- Specific Image-Based Airway Resistance (at TLC) (siRaw)

The primary outcome parameters are:

- percentage change from baseline (pre-dose V2) to pre-dose in untrimmed siVaw upon inspiration (at TLC) at Visit 3
- percentage change from baseline (pre-dose V2) to pre-dose in trimmed siRaw upon inspiration (at TLC) at Visit 3

2.1.3 Derivation rules

2.1.3.1 General Rules

The possibility exists that for some patients no distinction can be made between the different lung lobes, which results for the values of siVaw and siRaw to be non-existent for these lobes but instead are given for a combination of these lobes. These combinations will be removed from the per lobe analysis (descriptive statistics and statistical models).

Infinite values for siRaw parameter will be excluded from the statistical analysis.

For the trimmed parameters (not only for the primary endpoints but for all FRI endpoints), a matching on VISCPSCD will be done when calculating the (percent) change from baseline.

VISIT 2, PRE-DOSE	VISIT 2, 60-120MIN	VISIT 3, PRE-DOSE	VISIT 3, 60-120MIN
Change from baseline			
V2 PRE AND V2 POST	V2 PRE AND V2 POST		
V2 PRE AND V3 POST			V2 PRE AND V3 POST
	V2 POST AND V3 POST		V2 POST AND V3 POST
V2 PRE AND V3 PRE		V2 PRE AND V3 PRE	
Change from V3 PRE			
		V3 PRE AND V3 POST	V3 PRE AND V3 POST

More specifically, in the table above, the records with the same colour will be matched in the calculation (except V2 POST AND V3 POST). So the (percent) change from baseline will be calculated using V2 PRE AND V2 POST V2 PRE AND V3 POST and V2 PRE AND V3

PRE; while the calculation of (percent) change from V3 pre-dose will use V3 PRE AND V3 POST. In the selection of baseline, the V2 PRE AND V3 PRE records will be considered.

In the analysis, V2 PRE AND V2 POST V2 PRE AND V3 POST V2 PRE AND V3 PRE and V3 PRE AND V3 POST will be used in the descriptive tables; V2 PRE AND V2 POST V2 PRE AND V3 POST and V2 PRE AND V3 PRE will be used in the MMRM tables; V2 PRE AND V3 PRE will be used for the correlation tables; and V2 POST AND V3 POST will not be included in the analysis.

2.1.3.2 Descriptive Statistics

For descriptive statistics the original data will be used.

The data will be summarized by following descriptive statistics by timepoint

- Actual values at each timepoint
- Change and percent change from baseline (V2 pre-dose) at V3 pre-dose and V3 post-dose
- Change and percent change from period pre-dose (V2 pre-dose and V3 predose) at V2 post-dose and V3 post-dose respectively

2.1.3.3 Inferential Statistics

When using statistical models, data will be transformed using the natural log and back transformed. For zero values, the log-transformation will result in an error. In that case, half of the minimum value of the corresponding parameter that is observed for any subject at any visit for any region will be imputed.

2.1.4 Inferential statistics

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

Overall distal region value for primary endpoints will be log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM) model. The model will include the logarithm of baseline (V2 pre-dose, but not for trimmed parameters) at TLC and visit (Visit 2 post-dose [V2POST], Visit 3 pre-dose [V3PRE], Visit 3 post-dose [V3POST]) as covariates, and the interaction between visit and logarithm of baseline (for untrimmed parameters). The model parameters will be estimated using the restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. In case there is a convergence problem in the MMRM with the unstructured variance covariance matrix, the following matrix will be considered until a convergence is reached: UNR, TOEPH, ARH(1), CSH, TOEP, AR, compound symmetry. The adjusted % change from baseline to pre-dose at Visit 3 will be back transformed and presented with its 95% CI.

For the trimmed parameters, the records matching on VISCPSCD with values "V2 PRE AND V2 POST" "V2 PRE AND V3 POST" and "V2 PRE AND V3 PRE" will be considered in the model, like described in section 2.1.3.1.

The MMRM model will be performed separately for each parameter. Multiple data on lobar regions for primary endpoints will be analysed using the same model as for the overall distal region.

2.1.5 Presentation of results

Primary efficacy endpoints will be presented using descriptive statistics on actual values, change from baseline and percent change from baseline at each timepoint.

For the MMRM model, % change from baseline to pre-dose at Visit 3 and its 95% confidence interval (CI) and related p-values will be provided. This table will also include the type III p-values associated to model effects.

All primary efficacy endpoints will be listed.

2.2 SECONDARY EFFICACY ENDPOINT

2.2.1 Multidetector Computed Tomography (MDCT) and FRI endpoints, spirometry, plethysmography and CAT

The secondary efficacy endpoints will cover both FRI related as well as non-FRI related endpoints.

Details on the FRI procedure were already provided in section 2.1.1.

For the non-FRI related procedures, only pre-dose assessments were performed during the study treatment phase. In particular, a forced spirometry was carried out under medical supervision both at V2 and V3 and recorded using computer-operated spirometer, following the ATS/ERS standards (see protocol section 7.2.6).

Also, plethysmography test was performed at both V2 and V3 during breathing at rest and following ERS/ATS recommendations (see protocol section 7.2.4).

To assess symptoms, the 8-items questionnaire 'COPD Assessment Test' (CAT) was provided to the patients for completion.

2.2.2 Available Data

2.2.2.1 FRI

For FRI, the evaluation of the percentage change from baseline (V2 pre-dose) to post-dose at Visit 3, the percentage change from pre-dose to post-dose at Visit 2, and the percentage change from pre-dose to post-dose at Visit 3 on primary endpoints (i.e. siVaw and siRaw upon inspiration (at TLC) will be considered.

In addition, the FRI parameters included in the table below will be evaluated following the same primary endpoints strategy on the changes from baseline/pre-dose. The second column describes which overall region should be considered. The third column describes which lobes are considered (variable RELOCXCD). The fourth column provides the lung level, if applicable.

Parameter (RETESTCD)	**Overall lung regions**	**Lobes** (RELOCXCD)	**Applicable Lung levels**
siVaw (SIVAW)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	FRC (TLC covered in primary endpoint)

siRaw (SIRAW)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	FRC (TLC covered in primary endpoint)
Ventilation mapping (VENTMAP)	N/A	RUL, RML, RLL, LUL, LLL, UL, LL	N/A
Perfusion Mapping (considering separately BV5; BV510; BV5PR; BV5_10PR; BV10; BV10PR)	Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	N/A
Image-Based Airway Wall Volume (IVAWW)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
Specific Image-Based Airway Wall Volume (SIVAWW)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
Image-Based Lobar Volume (IVLOBE)	Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC, FRC
Image-Based Airway Volume (IVAW)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC, FRC
Air trapping (AT)	Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	FRC
Low Attenuation Score (LAS)	Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
15th percentile density (PD15)	Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
Image-Based Airway Resistance (IRAW)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC, FRC
Image-based Airway Vol percent predicted (IVAWPP)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC, FRC
Image-based lobar volume percent predicted (IVLOBEPP)	Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC, FRC
Spec image-based airway resist percent predicted (SIRAWPP)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC

Spec image-based airway volume percent predicted (SIVAWPP)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC, FRC
Aerosol Deposition (DEPOSIT, each analyte will be considered as a separate parameter: • BECLOMETHASONE DIPROPIONATE • FORMOTEROL FUMARATE • GLYCOPYRRONIUM BROMIDE)	Central Lung Region Distal Lung Region Total Lung Region Peripheral Lung region	RUL_DISTAL RML_DISTAL RLL_DISTAL LUL_DISTAL LLL_DISTAL UL_DISTAL LL_DISTAL RUL_PERIPHERAL RML_PERIPHERAL RLL_PERIPHERAL LUL_PERIPHERAL LLL_PERIPHERAL UL_PERIPHERAL LL_PERIPHERAL	TLC

All the rest of the FRI parameters below will be included in the listing.

Parameter (RETESTCD)	**Overall lung regions**	**Lobes** (RELOCXCD)	**Applicable Lung levels**
Internal Lobar Airflow Distribution (IAD)	N/A	RUL, RML, RLL, LUL, LLL, UL, LL	N/A
Int Lobar Airflow Distribution Distal to Normal (IADNN)	N/A	RUL, RML, RLL, LUL, LLL, UL, LL	N/A
Image-Based Airway Resistance Percent Predicted (IRAWPP)	Central Lung Region Distal Lung Region Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
Blood Vessel Volume (IVBV)	Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
Ventilation/Perfusion Matching (IVQ)	N/A	RUL, RML, RLL, LUL, LLL, UL, LL	N/A
Square Root of the Wall Area for a Theoretical Airway With an Internal Perimeter of 10 mm (PI10)	Distal Lung Region		TLC
Blood Vessel Density (SIVBV)	Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC

Blood Vessel Density Percent Predicted (SIVBVPP)	Total Lung Region	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
Wall area adjusted for BSA (Mosteller) (WABSA)	Distal Lung Region		TLC
Wall Area as a Percentage of the Sum of Wall Area and Airway Area (WAPERC)	Distal Lung Region		TLC

Values that are more than 3*IQR away from the third quartile will be considered as outliers and excluded from the descriptive; MMRM and correlation analyses.

2.2.2.2 SPIROMETRY

For spirometry, the following variables will be collected:

- Forced Expiratory Volume in 1 second (FEV_1)
- Forced Vital Capacity (FVC)
- Peak Exploratory Flow (PEF)
- Maximal Expiratory Flow at 50% of expired vital capacity (MEF50)
- Maximal Expiratory Flow at 25% of expired vital capacity (MEF25)

2.2.2.3 PLETHYSMOGRAPHY

For plethysmography, the following variables will be collected:

- Vital Capacity (VC)
- Inspiratory Capacity (IC)
- Functional Residual Capacity (FRC)
- Residual Volume (RV)
- Total Lung Capacity (TLC)
- Airway resistance (Raw)
- Specific conductance (sGaw)

2.2.2.4 COPD ASSESSMENT TEST

With regards to symptoms, CAT score will be calculated based on the questionnaire responses.

2.2.3 Derivation rules

2.2.3.1 FRI RELATED

For descriptive statistics the original data will be used.

The data will be summarized by following descriptive statistics by timepoint

- Actual values at each timepoint
- Change and percent change from baseline (V2 pre-dose) at V3 pre-dose and V3 post-dose
- Change and percent change from period pre-dose (V2 pre-dose and V3 pre-dose) at V2 post-dose and V3 post-dose respectively

When using statistical models, data will be transformed using the natural log and back transformed. For zero values, the log-transformation will result in an error. In that case, half of the minimum value of the corresponding parameter that is observed for any subject at any visit for any region will be imputed.

2.2.3.2 NON-FRI RELATED

For descriptive statistics the original data will be used.

The data will be summarized by following descriptive statistics by timepoint

- Actual values at each timepoint
- Change and percent change from baseline (V2 pre-dose) at V3 pre-dose for lung function and plethysmography parameters, change from baseline (V2 pre-dose) at V3 pre-dose for CAT score.

When using statistical models, data will not be transformed.

2.2.4 Inferential statistics

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

2.2.4.1 FRI RELATED

Selected secondary FRI parameters will be analysed using the same model as for the primary endpoints, with the appropriate selection of the baseline (i.e. at TLC or FRC depending on the lung level selected). The FRI parameters listed in the table below will be included in the MMRM analysis. For 15th percentile density (PD15), not like the rest of the parameters, the original value will be used instead of the log transformed values as the response of the MMRM.

Parameter (RETESTCD)	**Overall lung regions**	**CT Scan Visit Comparison**	**Lobes** (RELOCXCD)	**Applicable Lung levels**
siVaw (SIVAW)	Central Lung Region Distal Lung Region Total Lung Region	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	FRC (TLC covered in primary endpoint)
siRaw (SIRAW)	Central Lung Region Distal Lung Region	Trimmed	RUL, RML, RLL, LUL, LLL, UL, LL	FRC (TLC covered in primary endpoint)

	Total Lung Region			
Ventilation mapping (VENTMAP)	N/A	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	N/A
Perfusion Mapping (BV5; BV510; BV10)	Total Lung Region	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	N/A
Image-Based Airway Wall Volume (IVAWW)	Central Lung Region Distal Lung Region Total Lung Region	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
Specific Image-Based Airway Wall Volume (SIVAWW)	Central Lung Region Distal Lung Region Total Lung Region	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
Image-Based Lobar Volume (IVLOBE)	Total Lung Region	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	TLC, FRC
Image-Based Airway Volume (IVAW)	Central Lung Region Distal Lung Region Total Lung Region	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	TLC, FRC
Air trapping (AT)	Total Lung Region	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	FRC
Low Attenuation Score (LAS)	Total Lung Region	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
15th percentile density (PD15)	Total Lung Region	Untrimmed	RUL, RML, RLL, LUL, LLL, UL, LL	TLC
Aerosol Deposition (DEPOSIT), each analyte will be considered as a separate parameter: • BECLOMETHASONE DIPROPIONATE • FORMOTEROL FUMARATE • GLYCOPYRRONIUM BROMIDE	Central Lung Region Distal Lung Region Total Lung Region Peripheral Lung region		RUL_DISTAL RML_DISTAL RLL_DISTAL LUL_DISTAL LLL_DISTAL UL_DISTAL LL_DISTAL RUL_PERIPHERAL RML_PERIPHERAL RLL_PERIPHERAL LUL_PERIPHERAL LLL_PERIPHERAL UL_PERIPHERAL LL_PERIPHERAL	TLC

For the trimmed parameters, the records matching on VISCPSCD with values "V2 PRE AND V2 POST" "V2 PRE AND V3 POST" and "V2 PRE AND V3 PRE" will be considered in the model, like described in section 2.1.3.1.

2.2.4.2 NON-FRI RELATED

For non-FRI endpoints, change from baseline (V2 pre-dose) to pre-dose at Visit 3 will be analysed presenting 95% CI of the mean change and using a paired t-test.

2.2.4.3 CORRELATIONS BETWEEN FRI AND NON-FRI VARIABLES

Relevant correlations between FRI and non-FRI variables will be evaluated using Spearman's rank correlation coefficient. In particular, Spearman's rank correlation coefficient will be calculated of the % change from baseline (FRI-related variables) versus the changes from baseline (non-FRI related variables) considering the following:

- FRI related:
  - siRaw at lung level (TLC and FRC)
  - siVaw at lung level (TLC and FRC)
  - Untrimmed Air Trapping at FRC
  - Untrimmed Perfusion Mapping (BV5, BV510, BV5PR, BV5_10PR, BV10 and BV10PR) at TLC
  - Trimmed Image-Based Airway Resistance at lung level (TLC and FRC)
  - Image-Based Airway Volume at lung level (TLC and FRC)
  - Image-Based Airway Wall Volume at TLC
  - Untrimmed Image-Based Lobar Volume at lung level (TLC and FRC)
  - Untrimmed Low Attenuation Score at TLC
  - Untrimmed 15th percentile density at TLC
  - Specific Image-Based Airway Wall Volume at TLC
  - Untrimmed Ventilation mapping
  - Aerosol Deposition at TLC
- Non-FRI related:
  - Dynamic lung volume parameters: FEV_1, FVC, PEF, MEF25 and MEF50
  - Static lung volume parameters: VC, IC, FRC, TLC and RV
  - Airway resistance: sGaw and Raw
  - CAT total score

2.2.5 Presentation of results

2.2.5.1 FRI RELATED

Similarly to the primary endpoints, also for FRI related secondary endpoints the change from baseline (V2 pre-dose) to pre-dose at Visit 3 as well as change from pre-dose to post-dose at Visit 2 and Visit 3 will also be presented using descriptive statistics. The MMRM model for secondary FRI parameters will present % change from baseline to pre-dose at Visit 3 and its 95% confidence interval (CI) and related p-values will be provided. The MMRM model table will also include the type III p-values associated to model effects.

2.2.5.2 NON-FRI RELATED

Change and percent change from baseline to pre-dose at Visit 3 will be presented for:

- spirometry parameters
- plethysmography parameters
- CAT score

In the table the change from baseline to pre-dose Visit 3 will be presented with the 95% confidence interval (CI) and the p-value from the paired t-test.

2.2.5.3 CORRELATIONS BETWEEN FRI AND NON-FRI VARIABLES

For the analysis of correlations, four tables reporting the Spearman's rank correlation coefficient will be created considering:

1. FRI related: siVaw, siRaw / Non-FRI related: dynamic lung volume parameters, static lung volume parameters
2. FRI related: siVaw, siRaw / Non-FRI related: airway resistance, CAT total score
3. FRI related: Untrimmed Air Trapping at FRC; Untrimmed Perfusion Mapping (BV5, BV510, BV5PR, BV5_10PR, BV10 and BV10PR) at TLC; Trimmed Image-Based Airway Resistance at lung level (TLC and FRC); Image-Based Airway Volume at lung level (TLC and FRC); Image-Based Airway Wall Volume at TLC; Untrimmed Image-Based Lobar Volume at lung level (TLC and FRC); Untrimmed Low Attenuation Score at TLC; Untrimmed 15th percentile density at TLC; Specific Image-Based Airway Wall Volume at TLC; Untrimmed Ventilation mapping and Aerosol Deposition at TLC / Non-FRI related: dynamic lung volume parameters, static lung volume parameters
4. FRI related: Untrimmed Air Trapping at FRC; Untrimmed Perfusion Mapping (BV5, BV510, BV5PR, BV5_10PR, BV10 and BV10PR) at TLC; Trimmed Image-Based Airway Resistance at lung level (TLC and FRC); Image-Based Airway Volume at lung level (TLC and FRC); Image-Based Airway Wall Volume at TLC; Untrimmed Image-Based Lobar Volume at lung level (TLC and FRC); Untrimmed Low Attenuation Score at TLC; Untrimmed 15th percentile density at TLC; Specific Image-Based Airway Wall Volume at TLC; Untrimmed Ventilation mapping and Aerosol Deposition at TLC / Non-FRI related: airway resistance, CAT total score

The Spearman's rank correlation coefficient will be calculated of the % change from baseline (V2 pre-dose) to Visit 3 pre-dose for FRI-related variables versus the changes from baseline (V2 pre-dose) to Visit 3 pre-dose for non-FRI related variables.

All secondary efficacy endpoints will be listed.

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). For each AE, start and stop date(time)s are collected as well as severity, a seriousness flag, treatment-relatedness, action taken towards the study drug and outcome.

3.1.2 Derivation rules

Pre-treatment AEs are defined as AEs starting between date of informed consent and the date(time) of first study drug (CHF 5993 DPI) administration – 1 minute (e.g. events starting in Screening and Run-in phases).

Treatment-emergent adverse events (TEAE) are defined as AEs starting on or after first administration of study drug (CHF 5993 DPI).

Based on their start date(time), AEs will be allocated to the phase during which they started. Phases 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, a worst-case allocation will be done as detailed below:

- Treatment phase vs. non-treatment phase: AE will be allocated to the treatment phase.

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 when start and stop dates are fully known:

- 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 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
    - Study discontinuation date – 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 for the following:

- TEAEs
- Serious TEAEs
- Non-serious TEAEs
- ADRs
- Serious ADRs
- 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 for the aforementioned categories. 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 after date of last study medication intake (including follow-up) 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 laboratory parameters are expected:

- Biochemistry: creatinine, BUN (if BUN cannot be assessed it is acceptable that carbamide will be assessed instead), glucose (fasting), phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), total bilirubin, alkaline phosphatase, total cholesterol, triglycerides and sodium, potassium, calcium.
- Haematology: red blood cells count (RBC), white blood cells count (WBC) and differential count (absolute value and %), total haemoglobin (Hb), haematocrit (Hct), platelets count (PLT).
- Urinalysis: pH, specific gravity, proteins, glucose, ketones, bilirubin, nitrites and microscopic examination of the sediment (casts, erythrocytes, leucocytes).
- 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 predose 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:

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

3.3.2 Derivation rules

Mean values of the duplicates (if less than two measurements are available, the available measurement will be considered) will be calculated per visit and rounded as detailed in section 5.3.4. Throughout the analysis, including the derivation of baseline, the mean values will be used. Individual duplicate values will only be listed.

3.3.3 Presentation of results

Blood pressure parameters will be summarised by means of descriptive statistics at each analysis time point by treatment. Actual values and changes from baseline to pre-dose Visit 3 will be tabulated.

All vital signs data will be listed.

3.4 ELECTROCARDIOGRAMS

3.4.1 Available data

The following electrocardiogram (ECG) parameters will be collected:

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

3.4.2 Presentation of results

All ECG results will be listed.

3.5 PHYSICAL EXAMINATIONS

Abnormal physical examination findings will be listed.

4. GENERAL CHARACTERISTICS ANALYSES

4.1 SUBJECT DISPOSITION

The following subject data will be tabulated:

- The number of screen failures
- The number of subjects in each analysis set
- The number and percentage of subjects for each analysis visit
- 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

All information collected in the CRF concerning allocation, study discontinuation and information on phases, 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.

All available information concerning protocol deviations, violations on eligibility criteria (only violated eligibility criteria having DV.DVCAT = 'INCLUSION/EXCLUSION) 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: biochemistry and haematology, vital signs, local 12-lead ECG, serology (Human Immunodeficiency Virus Antibody (Ab-HIV1 and 2), Hepatitis B Surface Antigen (HBsAg), hepatitis B core antibody (anti-HBc) and Hepatitis C Virus Antibody (Ab-HCV), urine drug screen (cannabinoids, opiates, cocaine, benzodiazepines, amphetamines, morphine, barbiturates) and urine cotinine test
- Baseline disease characteristics: date of first diagnosis, medication category at study entry, exacerbation history (number moderate or severe of exacerbations in the 12 months before screening and end date and treatment (systemic corticosteroids, antibiotics, hospitalisation, emergency room) of the most recent moderate/severe exacerbation)

4.3.2 Derivation rules

The following parameters will be derived:

- Mean values of the duplicates (blood pressure parameters, if less than two measurements are available, the available measurement will be considered) will be calculated and rounded as detailed in section 5.3.4.
- Time since first COPD diagnosis (years): (date of ICF – date of diagnosis)/365.25

Note: Partially missing dates will be imputed as specified in section 5.3.2

- Time since most recent moderate/severe exacerbation (months): (date of ICF – date of last documented asthma exacerbation)/30.4375

Note: Partially missing dates will be imputed as specified in section 5.3.2

4.3.3 Presentation of results

Demographics will be presented by treatment using descriptive statistics for age, height, weight, BMI, smoking duration and number of pack-years and frequency tabulations for sex, race and smoking status.

Baseline disease characteristics will be presented by treatment using descriptive statistics for time since first COPD diagnosis, time since most recent moderate/severe exacerbation and number of moderate or severe exacerbations in the 12 months before screening and frequency tabulations for treatment of most recent exacerbation.

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

- biochemistry and haematology at screening
- vital signs at screening
- local 12-lead ECG at screening

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

4.4 MEDICAL HISTORY AND CONCOMITANT DISEASES

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 screening (MH.MHENRTPT is 'BEFORE')
- Concomitant disease finding: still ongoing at screening (MH.MHENRTPT is 'ONGOING' or missing)

4.4.1 Presentation of results

Medical history and concomitant diseases will be tabulated separately. 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 date(time)s 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 and stop date or ongoing flag are collected.

4.5.2 Derivation rules

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

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

Based on their start and stop date 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 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 that match the worst-case allocated category.

4.5.3 Presentation of results

Procedures:

The number and percentage of subjects with procedures and the number and percentage of subjects with procedures by system organ class and preferred term alphabetically sorted will be tabulated per category (prior, maintained, and concomitant). Blank system organ classes and preferred terms, if any, will be shown as 'Not Available' in the tables.

Subjects having more than one procedure allocated to the same category within the same treatment, system organ class and preferred term will be counted only once.

All procedures data will be listed. Procedures started after date of last study medication intake (including the follow-up) will be flagged.

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 generic term will be tabulated per category (prior, maintained, and concomitant). Blank ATC levels and generic terms, 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, anatomical main group, therapeutic subgroup, chemical subgroup, and generic term will be counted only once.

All medications data will be listed. Medications started after date of last study medication intake (including the follow-up) will be flagged.

4.6 COVID-19 TEST RESULTS

4.6.1 Available data

COVID-19 test results will be recorded.

4.6.2 Presentation of results

Data on COVID-19 tests will only be listed.

4.7 EXPOSURE TO STUDY DRUG AND TREATMENT COMPLIANCE

4.7.1 Available data

For run-in medication (FP/SLM DPI) and study drug medication (CHF 5993 DPI) administrations, the start and end date(time)s, the dose to be administered and actual number of correct and incorrect inhalations and coughing (occurrence and clinical significance) will be recorded in the eCRF and number of inhalations will be recorded in the diary. In addition, data on training with inhalers is collected.

4.7.2 Derivation rules

The following parameters will be derived:

- Total treatment duration (days) = date of last administration – date of first administration + 1 day
- Total number of administered doses: sum of all administrations
- Total number of scheduled doses: sum of all scheduled doses
  - FP/SLM DPI: 2 * total treatment duration (days)
  - CHF 5993 DPI: 4 * total treatment duration (days) – 2 (if the subject did not discontinue the treatment)
- Compliance = 100 * (total number of administered doses)/(total number of scheduled doses)
- Compliance category: <75%, 75-125%, >125%

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

If for a dosing occasion both diary and site data are available (e.g., for the morning dose on the days of the scheduled clinic visits), the site data only will be considered for the calculation of compliance.

In case of multiple entries in the same day derived from different diaries (i.e., last day with data recorded in a diary is the first day of the next diary), the data recorded in the new diary only will be considered for the calculation of compliance.

The compliance will only be calculated when (at least one record) of diary data is available.

The parameters above will be derived for both FP/SLM DPI and CHF 5993 DPI separately.

4.7.3 Presentation of results

Exposure information will be presented separately for FP/SLM DPI and CHF 5993 DPI using descriptive statistics for total treatment duration, total number of

administered doses and treatment compliance and frequency tabulations by treatment for compliance category.

All exposure, compliance and training with inhalers 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
Safety Set (SAF):	subjects who *received at least one dose of study drug (CHF 5993 DPI)*
Per Protocol (PP) Analysis Set:	all subjects from the safety population, except subjects without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the analysis populations

Notes:

- Having signed an informed consent is defined as having a complete informed consent signature date in the database.
- Having received at least one dose of study drug is defined as having an exposure date or any information confirming exposure (CHF 5993 DPI).
- Exact definition of important protocol deviations impacting the primary study endpoints concerning the PP Analysis Set (i.e., wrong inclusions, poor compliance, non-permitted medications) will be discussed by the study team during the review of the data and described in the DRR

Unless stated otherwise, the SAF will be used for the safety tables, listings and figures and general characteristics listings. The PP set will be used for efficacy tables, listings and figures. In addition, the PP set (and SAF, if relevant) will be used for general characteristics tables.

In case of protocol deviations impacting only specific time point, only the affected data at the specific time point will be excluded from the applicable analysis sets.

5.1.2 As planned versus as actual analysis

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

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

5.2 PHASES AND TIME POINTS

5.2.1 Phases

Adverse events, medications, and procedures will be allocated to phases. For assessments, the visit and time point labels indicated on the subject's case report form (CRF) will be used to allocate to the correct treatment.

When both date and time are collected:

Phase	Start	End
Screening	Date of signing the ICF, with 00:00 added as time part	First FP/SLM DPI administration date(time) – 1 minute
Run-in	First FP/SLM DPI administration date(time)	First CHF 5993 DPI administration date(time) – 1 minute
Treatment	First CHF 5993 DPI administration date(time)	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 ends on the date of last contact, with 23:59 added as time part.

When only date is collected:

Phase	Start	End
Screening	Date of signing the ICF	First FP/SLM DPI administration date – 1 day
Run-in	First FP/SLM DPI administration date	First CHF 5993 DPI administration date – 1 day
Treatment	First CHF 5993 DPI administration date	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 ends on the date of last contact.

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

5.2.2 Baseline and change from baseline

The baseline value for the efficacy endpoints is the non-missing value at pre-dose of Visit 2.

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.

Percentage 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 drug (CHF 5993 DPI).

5.2.4 Analysis visits

The analysis will use the visits and time points indicated on the subject's CRF.

The screening value is the last available and non-missing value before Visit 2. 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 an unscheduled assessment was done to replace not available/reliable data. The decision whether an unscheduled assessment should be used instead of the original assessment will be taken during the data review meeting before database lock. The selection of the unscheduled assessments to be included in the analysis instead of the original assessments will be done in the corresponding ADaM datasets using appropriate values for AVISIT(N) and ATPT(N). Hard coding (documented in the data review report and by a Note to File signed off by both PPD and Chiesi Farmaceutici S.p.A) will be implemented in the impacted analysis programs by including a comment.

Baseline is defined in section 5.2.2

Data collected at multiple visits (spirometry, CAT, vital signs and full physical examination) recorded at the study termination visit for discontinued patients will be re-allocated to Visit 3 in case the Early Termination visit was performed at least 7 days after the preceding visit; otherwise, data recorded at the study termination visit will not be re-allocated and this data will be excluded from the statistical analysis.

All scheduled and unscheduled assessments will be listed.

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 'Visit x' (x = 2 or 3.)
- Early termination visits will be presented as 'Early Termination'
- Follow-up visits and follow-up call visit 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, 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.)
- Unscheduled time points performed as re-test of a specific planned time point will be presented with the same label as the planned time point (see rules above)
- Unscheduled time points performed on a day different than a planned visit will be blank
- Other time points not covered by the rules above will be presented using similar labels to the ones used in SDTM (XX.XXTPT)

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*

Partially missing date of first COPD diagnosis and last documented COPD exacerbation will be imputed as follows for the calculation of time since event:

- Missing day will be imputed with 1
- Missing day and month will be imputed with 1JAN

5.3.3 *Values below or above a threshold*

Safety or efficacy 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 to the appropriate number of decimals at TLF level:

- AE duration will be presented with 1 decimal.
- Mean of duplicates and mean scores will be rounded to the nearest integer.

Note: since the rounding is applied at TLF level, in the listings, the change from baseline could be slightly different to the listed value at time point t – baseline value

- Change from baseline for FRI, lung function and body plethysmography parameters will be presented with 3 decimals, while for CAT score will be presented with 1 decimal.
- Percent change from baseline will be presented with 2 decimals.
- Compliance will be rounded to 1 decimal.
- Time since first diagnosis and last exacerbation will be presented with 1 decimal.
- Log-transformed values will not be rounded.

Rounding will be done using the round half away from zero tie-breaking rule (see Definition of terms).

5.3.5 *Rounding of FRI variables*

FRI variables will be rounded to the appropriate number of decimals based on the following table:

Parameter (RETESTCD)	**Number of digits**
siVaw (SIVAW)	3
siRaw (SIRAW)	3
Ventilation mapping (VENTMAP)	3
Perfusion Mapping (considering separately BV5; BV510; BV5PR; BV5_10PR; BV10; BV10PR)	3

Image-Based Airway Wall Volume (IVAWW)	3
Specific Image-Based Airway Wall Volume (SIVAWW)	3
Image-Based Lobar Volume (IVLOBE)	3
Image-Based Airway Volume (IVAW)	3
Air trapping (AT)	3
Low Attenuation Score (LAS)	3
15th percentile density (PD15)	3
Image-Based Airway Resistance (IRAW)	3
Image-based Airway Vol percent predicted (IVAWPP)	3
Image-based lobar volume percent predicted (IVLOBEPP)	3
Spec image-based airway resist percent predicted (SIRAWPP)	3
Spec image-based airway volume percent predicted (SIVAWPP)	3
Aerosol Deposition (DEPOSIT, each analyte will be considered as a separate parameter: • BECLOMETHASONE DIPROPIONATE • FORMOTEROL FUMARATE • GLYCOPYRRONIUM BROMIDE)	4
Internal Lobar Airflow Distribution (IAD)	3
Int Lobar Airflow Distribution Distal to Normal (IADNN)	3
Image-Based Airway Resistance Percent Predicted (IRAWPP)	3
Blood Vessel Volume (IVBV)	3
Ventilation/Perfusion Matching (IVQ)	3
Square Root of the Wall Area for a Theoretical Airway With an Internal Perimeter of 10 mm (PI10)	3
Blood Vessel Density (SIVBV)	3
Blood Vessel Density Percent Predicted (SIVBVPP)	3
Wall area adjusted for BSA (Mosteller) (WABSA)	3
Wall Area as a Percentage of the Sum of Wall Area and Airway Area (WAPERC)	3

5.3.6 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.

With regards to FRI parameters linked to the lung resistance, rule on how to define an outlier is defined in Section 2.1.1.

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% confidence interval (CI) on the mean (based on t-distribution, without continuity correction).

Descriptive statistics of efficacy parameters will additionally include 95% CI on the mean (based on t-distribution, without continuity correction), geometric mean and 95% CI on the geometric mean. Geometric mean and 95% CI on the geometric mean are calculated as the exponentials of the arithmetic mean and corresponding CI of the log-transformed data.

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.

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).

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 label will be used in the tables and listings:

- CHF 5993 DPI
- FP/SLM DPI

The treatment “FP/SLM DPI” will only be used in the exposure/compliance displays.

5.4.3 Ordering in tables, figures and listings

Tables will be sorted by analysis visit and time point.

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

- Under "Secondary endpoints" on page 8 of the protocol the terminology "airway wall thickness" corresponds to "airway wall volume" and the parameter "IVAWW" in the data transfer agreement.
- MMRM was selected instead of ANCOVA model as the former provide more efficient use of the FRI data collected multiple times for the same patient.
- In the model specification the covariate "logarithm of pre-dose lobar volume at FRC on Visit 3" was omitted, as following further investigations by FLUIDDA it would not improve the model performances.

7. REFERENCES

- ICH Topic E6(R2) Guideline for Good Clinical Practice – Step 4, 9 November 2016.
- Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. Fridericia LS Acta Med Scand 1920 15:469–485.
- Which QT correction formulae to use for QT monitoring? Vandenberk B, Vandael E, Robyns T et al. J Am Heart Assoc. 2016;5:e003264.
- 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	**Screen Failures (Enrolled Set)**	**ENR**	**DST001**
	Tabulation of the reason for screening failures.		
14.1.1.2	**Disposition by Treatment (Safety Set)**	**SAF**	**DST002**
	Tabulation of completion/discontinuation and the reason for discontinuation by treatment period.		
14.1.1.3	**Analysis Sets (Safety Set)**	**SAF**	**DST005**
	Tabulation of the number of subjects in each of the analysis sets defined in the SAP.		
14.1.1.4	**Attendance at Each Visit (Safety Set)**	**SAF**	**SVT001**
	Tabulation of the number and percentage of subjects that attend each visit.		
14.1.1.5	**Important Protocol Deviations Impacting the Analysis Populations (Safety Set)**	**SAF**	**DVT001**
	Tabulation of the important protocol deviations impacting the analysis populations (at least one), deviation category and deviation type by treatment.		
14.1.2.1.1	**Demographic Characteristics (Per Protocol Analysis Set)**	**PP**	**DMT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.1.2	**Demographic Characteristics (Safety Set)**	**SAF**	**DMT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.2.1	**COPD History (Per Protocol Analysis Set)**	**PP**	**SCT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.2.2	**COPD History (Safety Set)**	**SAF**	**SCT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.3.1	**COPD Exacerbation History (Per Protocol Analysis Set)**	**PP**	**SCT003**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.3.2	**COPD Exacerbation History (Safety Set)**	**SAF**	**SCT003**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.4.1	**Smoking Status (Per Protocol Analysis Set)**	**PP**	**SUT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		

Number	Title	Analysis Set	TLFs Library Template Number
14.1.2.4.2	**Smoking Status (Safety Set)**	**SAF**	**SUT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.5.1	**Lung Function at Screening (Per Protocol Analysis Set)**	**PP**	**RET002**
	Descriptive statistics of spirometry results pre- and post-bronchodilator at Screening. Including all parameters.		
14.1.2.5.2	**Lung Function at Screening (Safety Set)**	**SAF**	**RET002**
	Descriptive statistics of spirometry results pre- and post-bronchodilator at Screening. Including all parameters.		
14.1.2.6.1	**Body Plethysmography at Screening (Per Protocol Analysis Set)**	**PP**	**BLT001**
	Descriptive statistics of body plethysmography results at Screening. Including all parameters.		
14.1.2.6.2	**Body Plethysmography at Screening (Safety Set)**	**SAF**	**BLT001**
	Descriptive statistics of body plethysmography results at Screening. Including all parameters.		
14.1.2.7	**Haematology at Screening (Safety Set)**	**SAF**	**BLT002**
	Descriptive statistics of haematology results at Screening.		
14.1.2.8	**Biochemistry at Screening (Safety Set)**	**SAF**	**BLT002**
	Descriptive statistics of biochemistry results at Screening.		
14.1.2.9	**Local 12-Lead ECG at Screening (Safety Set)**	**SAF**	**BLT002**
	Descriptive statistics of all local 12-lead ECG results at Screening.		
14.1.2.10	**Vital Signs at Screening (Safety Set)**	**SAF**	**BLT001**
	Descriptive statistics of SBP and DBP results at Screening.		
14.1.2.11.1	**CAT Total Score at Screening (Per Protocol Analysis Set)**	**PP**	**BLT001**
	Descriptive statistics of CAT total score at Screening.		
14.1.2.11.2	**CAT Total Score at Screening (Safety Set)**	**SAF**	**BLT001**
	Descriptive statistics of CAT total score at Screening.		
14.1.2.12	**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.		
14.1.2.13	**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.		
14.1.2.14	**Prior Procedures (Safety Set)**	**SAF**	**MHT001**
	Tabulation of the number and percentage of subjects with prior procedures and number and percentage of subjects with prior procedures by system organ class and preferred term.		

Number	Title	Analysis Set	TLFs Library Template Number
14.1.2.15	**Maintained Procedures (Safety Set)**	**SAF**	**MHT002**
	Tabulation of the number and percentage of subjects with maintained procedures and number and percentage of subjects with maintained procedures by system organ class and preferred term.		
14.1.2.16	**Concomitant Procedures (Safety Set)**	**SAF**	**MHT002**
	Tabulation of the number and percentage of subjects with concomitant procedures and number and percentage of subjects with concomitant procedures by system organ classes and preferred terms.		
14.1.2.17	**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.		
14.1.2.18	**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.		
14.1.2.19	**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.		
14.1.2.20	**Extent of Exposure (days) (Safety Set)**	**SAF**	**EXT001**
	Descriptive statistics of extent of exposure as defined in section 4.7.2.		
14.1.2.21	**Treatment Compliance (Safety Set)**	**SAF**	**EXT002**
	Descriptive statistics of treatment compliance and frequency tabulations for compliance category as defined in section 4.7.2.		
EFFICACY			
14.2.1.1	**Descriptive Statistics per Time Point in Specific Airway Volume at TLC (siVaw) (Per Protocol Analysis Set)**	**PP**	**LBT001**
	Descriptive statistics per parameter (considering scan condition; CT scan visit comparison and location, the same for the similar table descriptions below) per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.		
14.2.1.2	**Adjusted % Change From Baseline/pre-dose in Specific Airway Volume at TLC (siVaw) (Per Protocol Analysis Set)**	**PP**	**ANT001**
	Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) at TLC and visit as covariates.		
14.2.2.1	**Descriptive Statistics per Time Point in Specific Airway Resistance at TLC (siRaw) (Per Protocol Analysis Set)**	**PP**	**LBT001**
	Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.		

Number	Title	Analysis Set	TLFs Library Template Number
14.2.2.2	**Adjusted % Change From Baseline/pre-dose in Specific Airway Resistance at TLC (siRaw) (Per Protocol Analysis Set)** Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) at TLC and visit as covariates.	**PP**	**ANT001**
14.2.3.1	**Correlation of Primary Endpoints versus Dynamic and Static Lung Volume Parameters, Airway Resistance and CAT Total Score (Per Protocol Analysis Set)** The Spearman's rank correlation coefficient will be calculated of the % change from baseline (V2 pre-dose) to Visit 3 pre-dose for FRI-related variables versus the changes from baseline (V2 pre-dose) to Visit 3 pre-dose for non-FRI related variables. The following FRI-related variables were considered: Specific Airway Volume at TLC (siVaw) and Specific Airway Resistance at TLC (siRaw). The table is sorted by parameter, lung level and lung region/lobes.	**PP**	**ANT003**
14.2.4.1	**Descriptive Statistics per Time Point in Specific Airway Volume at FRC (siVaw) (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.	**PP**	**LBT001**
14.2.4.2	**Adjusted % Change From Baseline/pre-dose in Specific Airway Volume at FRC (siVaw) (Per Protocol Analysis Set)** Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) at FRC and visit as covariates.	**PP**	**ANT001**
14.2.5.1	**Descriptive Statistics per Time Point in Specific Airway Resistance at FRC (siRaw) (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.	**PP**	**LBT001**
14.2.5.2	**Adjusted % Change From Baseline/pre-dose in Specific Airway Resistance at FRC (siRaw) (Per Protocol Analysis Set)** Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) at FRC and visit as covariates.	**PP**	**ANT001**
14.2.6.1	**Descriptive Statistics per Time Point in Ventilation mapping (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.	**PP**	**LBT001**
14.2.6.2	**Adjusted % Change From Baseline/pre-dose in Ventilation mapping (Per Protocol Analysis Set)** Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) and visit as covariates.	**PP**	**ANT001**
14.2.7.1	**Descriptive Statistics per Time Point in Perfusion mapping (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.	**PP**	**LBT001**

Number	Title	Analysis Set	TLFs Library Template Number
14.2.7.2	**Adjusted % Change From Baseline/pre-dose in Perfusion mapping (Per Protocol Analysis Set)** Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) and visit as covariates.	**PP**	**ANT001**
14.2.8.1	**Descriptive Statistics per Time Point in Image-Based Airway Wall Volume at TLC (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.	**PP**	**LBT001**
14.2.8.2	**Adjusted % Change From Baseline/pre-dose in Image-Based Airway Wall Volume at TLC (Per Protocol Analysis Set)** Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) and visit as covariates.	**PP**	**ANT001**
14.2.9.1	**Descriptive Statistics per Time Point in Specific Image-Based Airway Wall Volume at TLC (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.	**PP**	**LBT001**
14.2.9.2	**Adjusted % Change From Baseline/pre-dose in Specific Image-Based Airway Wall Volume at TLC (Per Protocol Analysis Set)** Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) and visit as covariates.	**PP**	**ANT001**
14.2.10.1	**Descriptive Statistics per Time Point in Image-Based Lobar Volume (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.	**PP**	**LBT001**
14.2.10.2	**Adjusted % Change From Baseline/pre-dose in Image-Based Lobar Volume (Per Protocol Analysis Set)** Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) and visit as covariates.	**PP**	**ANT001**
14.2.11.1	**Descriptive Statistics per Time Point in Image-Based Airway Volume (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.	**PP**	**BLT001**
14.2.11.2	**Adjusted % Change From Baseline/pre-dose in Image-Based Airway Volume (Per Protocol Analysis Set)** Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) and visit as covariates.	**PP**	**ANT001**
14.2.12.1	**Descriptive Statistics per Time Point in Air Trapping at FRC (Per Protocol Analysis Set)**	**PP**	**LBT001**

Number	Title	Analysis Set	TLFs Library Template Number
	Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.		
14.2.12.2	**Adjusted % Change From Baseline/pre-dose in Air Trapping at FRC (Per Protocol Analysis Set)**	**PP**	**ANT001**
	Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) and visit as covariates.		
14.2.13.1	**Descriptive Statistics per Time Point in Low Attenuation Score at TLC (Per Protocol Analysis Set)**	**PP**	**LBT001**
	Descriptive statistics per parameter per time point for actual value, change and % change from baseline/pre-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.		
14.2.13.2	**Adjusted % Change From Baseline/pre-dose in Low Attenuation Score at TLC (Per Protocol Analysis Set)**	**PP**	**ANT001**
	Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) and visit as covariates.		
14.2.14.1	**Descriptive Statistics per Time Point in 15th Percentile Density at TLC (Per Protocol Analysis Set)**	**PP**	**LBT001**
	Descriptive statistics per parameter per time point for actual value, change and % change from baseline/post-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.		
14.2.14.2	**Adjusted % Change From Baseline/post-dose in 15th Percentile Density at TLC (Per Protocol Analysis Set)**	**PP**	**ANT001**
	Result from MMRM model including the logarithm of baseline (Visit 2 pre-dose) and visit as covariates.		
14.2.15	**Descriptive Statistics per Time Point in Image-Based Airway Resistance (Per Protocol Analysis Set)**	**PP**	**LBT001**
	Descriptive statistics per parameter per time point for actual value, change and % change from baseline/post-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.		
14.2.16	**Descriptive Statistics per Time Point in Image-based Airway Volume Percent Predicted (Per Protocol Analysis Set)**	**PP**	**LBT001**
	Descriptive statistics per parameter per time point for actual value, change and % change from baseline/post-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.		
14.2.17	**Descriptive Statistics per Time Point in Image-based Lobar Volume Percent Predicted (Per Protocol Analysis Set)**	**PP**	**LBT001**
	Descriptive statistics per parameter per time point for actual value, change and % change from baseline/post-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.		
14.2.18	**Descriptive Statistics per Time Point in Specific Image-based Airway Resistance Percent Predicted at TLC (Per Protocol Analysis Set)**	**PP**	**LBT001**
	Descriptive statistics per parameter per time point for actual value, change and % change from baseline/post-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.		

Number	Title	Analysis Set	TLFs Library Template Number
14.2.19	**Descriptive Statistics per Time Point in Specific Image-based Airway Volume Percent Predicted (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline/post-dose. The table is sorted first by parameter and lung level, lung region/lobes then by time point.	**PP**	**LBT001**
14.2.20.1	**Descriptive Statistics per Time Point in Aerosol Deposition at TLC (Per Protocol Analysis Set)** Descriptive statistics per analyte per time point for actual value, change and % change from baseline. The table is sorted first by analyte and lung level, lung region/lobes then by time point.	**PP**	**LBT001**
14.2.20.2	**Adjusted % Change From Baseline in Aerosol Deposition at TLC (Per Protocol Analysis Set)** Result from MMRM models including the logarithm of appropriate selection of the baseline and visit as covariates. Separate models will be used for each analyte.	**PP**	**ANT001**
14.2.21.1	**Descriptive Statistics per Time Point in Spirometry Parameters (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline. The table is sorted first by parameter then by time point.	**PP**	**LBT001**
14.2.21.2	**Statistical Analysis of Change From Baseline in Spirometry Parameters (Per Protocol Analysis Set)** Result from paired T-test assessing the change from baseline to pre-dose Visit 3.	**PP**	**ANT001**
14.2.22.1	**Descriptive Statistics per Time Point in Plethysmography Parameters (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline. The table is sorted first by parameter then by time point.	**PP**	**LBT001**
14.2.22.2	**Statistical Analysis of Change From Baseline in Plethysmography Parameters (Per Protocol Analysis Set)** Result from paired T-test assessing the change from baseline to pre-dose Visit 3.	**PP**	**ANT001**
14.2.23.1	**Descriptive Statistics per Time Point in COPD Assessment Test (Per Protocol Analysis Set)** Descriptive statistics per parameter per time point for actual value, change and % change from baseline. The table is sorted by time point.	**PP**	**LBT001**
14.2.23.2	**Statistical Analysis of Change From Baseline in COPD Assessment Test (Per Protocol Analysis Set)** Result from paired T-test assessing the change from baseline to pre-dose Visit 3.	**PP**	**ANT001**
14.2.24.1	**Correlation of Selected Secondary Endpoints versus Dynamic and Static Lung Volume Parameters, Airway Resistance and CAT Total Score (Per Protocol Analysis Set)**	**PP**	**ANT003**

Number	Title	Analysis Set	TLFs Library Template Number
	The Spearman's rank correlation coefficient will be calculated of the % change from baseline (V2 pre-dose) to Visit 3 pre-dose for FRI-related variables versus the changes from baseline (V2 pre-dose) to Visit 3 pre-dose for non-FRI related variables. The following FRI-related variables were considered: Specific Airway Volume at FRC (siVaw); Specific Airway Resistance at FRC (siRaw); Untrimmed Air Trapping at FRC; Untrimmed Perfusion Mapping (BV5, BV510, BV5PR, BV5_10PR, BV10 and BV10PR) at TLC; Trimmed Image-Based Airway Resistance at lung level (TLC and FRC); Image-Based Airway Volume at lung level (TLC and FRC); Image-Based Airway Wall Volume at TLC; Untrimmed Image-Based Lobar Volume at lung level (TLC and FRC); Untrimmed Low Attenuation Score at TLC; Untrimmed 15th percentile density at TLC; Specific Image-Based Airway Wall Volume at TLC; Untrimmed Ventilation mapping and Aerosol Deposition at TLC. The table is sorted by parameter, lung level and lung region/lobes.		
SAFETY			
ADVERSE EVENTS			
14.3.1.1	**Summary of TEAEs (Safety Set)**	**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.		
14.3.1.7	**TEAEs Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Safety Set)**	**SAF**	**AET003**
	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.		

Number	Title	Analysis Set	TLFs Library Template Number
14.3.1.8	**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 actual values and changes from baseline at V3 in vital signs (DBP and SBP) results per parameter and analysis time point. Table sorted by analysis time point. Each parameter will begin on a new page.	**SAF**	**VST001**

8.2 LISTINGS

Number	Title	Analysis Set	TLFs Library Template Number
GENERAL CHARACTERISTICS			
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	**Subject Disposition (Safety Set)**	**SAF**	**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. The disposition due to COVID-19 will be flagged.		
16.2.1.3	**Subject Disposition: Analysis Phases With Time (Safety Set)**	**SAF**	**DSL008**
	Listing of the phases in the study (definition with time for adverse events), together with the start and end date(time)s.		
16.2.1.4	**Subject Disposition: Analysis Phases Without Time (Safety Set)**	**SAF**	**DSL008**
	Listing of the phases in the study (definition without time for procedures and medications), together with the start and end dates.		
16.2.1.5	**Study Visits (Safety Set)**	**SAF**	**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 (Safety Set)**	**SAF**	-
	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 (Safety Set)**	**SAF**	**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 (Safety Set)**	**SAF**	**DVL002**
	Listing of all important protocol deviations information		
16.2.3.1	**Analysis Set Disposition (Safety Set)**	**SAF**	**DSL006**
	Listing of all subjects and analysis set indicators.		
16.2.3.2	**Subjects Excluded from Safety/PP Analysis Set (Safety Set)**	**SAF**	**DSL007**
	Listing of all subjects that were excluded from SAF/PP.		
16.2.4.1	**Demographic Characteristics (Safety Set)**	**SAF**	**DML001**
	Listing of all demographic parameters		
16.2.4.2	**COPD History (Safety Set)**	**SAF**	**SCL001**
	Listing of all baseline disease characteristics. Adjust the columns of SCL001 according to the available data.		

Number	Title	Analysis Set	TLFs Library Template Number
16.2.4.3	**Serology at Screening (Safety Set)**	**SAF**	**SCL002**
	Listing of all results of serology tests done at screening		
16.2.4.4	**Urine Drug Screen and Cotinine Tests (Safety Set)**	**SAF**	**SCL002**
	Listing of all results of urine drug screen tests performed For layout purposes, template SCL003 could be used instead.		
16.2.4.5	**Smoking Status (Safety Set)**	**SAF**	**SUL001**
	Listing of all smoking data available in the CRF		
16.2.4.6	**Medical/Surgical History (Safety Set)**	**SAF**	**MHL001**
	Listing of the medical history data findings available in the CRF		
16.2.4.7	**Concomitant Diseases (Safety Set)**	**SAF**	**MHL002**
	Listing of the concomitant diseases data findings available in the CRF		
16.2.4.8	**Procedures (Safety Set)**	**SAF**	**PRL001**
	Listing of all data on prior, maintained and concomitant procedures		
16.2.4.9	**Medications (Safety Set)**	**SAF**	**CML001**
	Listing of all data on prior, maintained and concomitant medications		
16.2.4.10	**COVID-19 Test Results (Safety Set)**	**SAF**	**SCL002**
	Listing of all results of COVID-19 tests		
16.2.4.11	**Comments (Safety Set)**	**SAF**	**COL001**
	Listing of all remarks and comments written in the CRF		
16.2.5.1	**Training with Inhalers (Safety Set)**	**SAF**	
	Listing of all data related to training with inhalers		
16.2.5.2	**Exposure and Compliance (Safety Set)**	**SAF**	
	Listing of all data related to exposure (study medication intake at sites, including time of start-end inhalations, correct/incorrect inhalations and issues during inhalations etc.) and treatment compliance		
EFFICACY			
16.2.6.1	**FRI Endpoints: Full Listing (Per Protocol Analysis Set)** Listing of all primary FRI parameters results.	**PP**	**LBL001**
16.2.6.2	**Spirometry: Full Listing (Per Protocol Analysis Set)** Listing of all Spirometry parameters results.	**PP**	**LBL001**
16.2.6.3	**Plethysmography: Full Listing (Per Protocol Analysis Set)** Listing of all Plethysmography parameters results.	**PP**	**LBL001**
16.2.6.4	**COPD Assessment Test: Full Listing (Per Protocol Analysis Set)** Listing of all COPD assessment test results.	**PP**	**LBL001**

Number	Title	Analysis Set	TLFs Library Template Number
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.		
16.2.7.2	**Treatment Emergent Adverse Events (Safety Set)**	**SAF**	**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. TEAEs related to COVID-19 will be flagged.		
16.2.7.3	**Serious Treatment Emergent Adverse Events (Safety Set)**	**SAF**	**AEL002**
	Same as listing 16.2.7.2, but listing serious TEAEs only		
16.2.7.4	**Non-Serious Treatment Emergent Adverse Events (Safety Set)**	**SAF**	**AEL002**
	Same as listing 16.2.7.2, but listing non-serious TEAEs only		
16.2.7.5	**Adverse Drug Reactions (Safety Set)**	**SAF**	**AEL002**
	Same as listing 16.2.7.2, but listing ADRs only		
16.2.7.6	**Serious Adverse Drug Reactions (Safety Set)**	**SAF**	**AEL002**
	Same as listing 16.2.7.2, but listing serious ADRs only		
16.2.7.7	**Treatment Emergent Adverse Events Leading to Study Drug Discontinuation (Safety Set)**	**SAF**	**AEL002**
	Same as listing 16.2.7.2, but listing TEAEs leading to study drug discontinuation only		
16.2.7.8	**Treatment Emergent Adverse Events Leading to Death (Safety Set)**	**SAF**	**AEL002**
	Same as listing 16.2.7.2, but listing TEAEs leading to death only		
16.2.7.9	**Physical Examination Abnormalities (Safety Set)**	**SAF**	**PEL001**
	Listing of all data on abnormal physical examinations findings		
LABORATORY DATA			
16.2.8.1	**Laboratory Results: Haematology Full Listing (Safety Set)**	**SAF**	**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 (Safety Set)**	**SAF**	**LBL001**
	Listing of all abnormal haematology results. The (non-imputed) values will be shown, as well as normal ranges, abnormality flags (L/H), clinical significance flag and fasted flag.		
16.2.8.3	**Laboratory Results: Biochemistry Full Listing (Safety Set)**	**SAF**	**LBL001**
	Same as listing 16.2.8.1, but listing biochemistry results instead		
16.2.8.4	**Laboratory Results: Biochemistry Abnormalities (Safety Set)**	**SAF**	**LBL001**
	Same as listing 16.2.8.1, but listing all abnormal biochemistry results instead		

Number	Title	Analysis Set	TLFs Library Template Number
16.2.8.5	**Laboratory Results: Urinalysis (Safety Set)**	**SAF**	**LBL001**
	Listing of all urinalysis results. The (non-imputed) values will be shown, as well as normal ranges, abnormality flags (L/H/A), and clinical significance flag.		
16.2.8.6	**Laboratory Results: Urinalysis Abnormalities (Safety Set)**	**SAF**	**LBL001**
	Same as listing 16.2.8.1, but listing all abnormal urinalysis results instead		
16.2.8.7	**Laboratory Results: Pregnancy Test (Safety Set)**	**SAF**	**LBL005**
	Listing of all serum and urine pregnancy and FSH results.		
VITAL SIGNS			
16.2.9.1	**Vital Signs: Full Listing (Safety Set)**	**SAF**	**VSL001**
	Listing of all vital signs results. The values will be shown, as well as changes from pre-dose and change abnormalities.		
ECG			
16.2.10.1	**Local 12-Lead ECG: Full Listing (Safety Set)**	**SAF**	**EGL001**
	Listing of all local 12-lead ECG results and the corresponding interpretation.		

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, to accommodate different variables' names.

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

  The approach described below will ensure that the least squares means calculated by SAS will be based on:
  - effects of quantitative covariates set equal to their mean values in the group of patients analysed.

  The analysis is based on the following steps:
  1. generate a dataset by selecting all the post-randomisation records for patients with at least one available and valid post-randomisation measurement and no missing covariates;
  2. in case of repeated post-randomisation measurements, add to the dataset generated in step 1 the records for missing post-randomisation visits of the patients included in the dataset. In the added records the value of the response variable will be missing, but the full information on covariates has to be included;
  3. use the dataset obtained as the input dataset for the MIXED procedure, specifying the options AT MEANS in the LSMEANS statement.

  Example: analysis of change from baseline (Visit 2 pre-dose) at all visits/timepoint (Visits 2 pre-dose, Visit 3 pre-dose and Visit 3 post-dose 5) based on a mixed model for repeated measures including the effects of visit (categorical variable), baseline and another covariate. Visit 1 represents the screening visit.

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

Patient	Covariate	Baseline	Visit	Timepoint	Change from baseline
1	X	X	1	-	.
1	X	X	2	Pre-dose	.
1	X	X	2	Post-dose	X
1	X	X	3	Pre-dose	X
1	X	X	3	Post-dose	X
2	X	X	1	-	.
2	X	X	2	Pre-dose	.
2	X	X	2	Post-dose	X
3	X	X	1	-	.
3	X	X	2	Pre-dose	.
3	X	X	2	Post-dose	X

3	X	X	3	Pre-dose	.
3	X	X	3	Post-dose	X
4	X	X	1	-	.
4	X	X	2	Pre-dose	.
5	.	X	1	-	.
5	.	X	2	Pre-dose	.
5	.	X	2	Post-dose	X

Step 1 (visits 1 and 2 pre-dose not selected since pre-study treatment administration, PPD not selected due to missing post-Visit 2 pre-dose measurements, PPD not selected due to missing covariate):

Patient	Covariate	Baseline	Visit	Timepoint	Change from baseline
1	X	X	2	Post-dose	X
1	X	X	3	Pre-dose	X
1	X	X	3	Post-dose	X
2	X	X	2	Post-dose	X
3	X	X	2	Post-dose	X
3	X	X	3	Pre-dose	.
3	X	X	3	Post-dose	X

Step 2 (added records in *italic*):

Patient	Covariate	Baseline	Visit	Timepoint	Change from baseline
1	X	X	2	Post-dose	X
1	X	X	3	Pre-dose	X
1	X	X	3	Post-dose	X
2	X	X	2	Post-dose	X
2	*X*	*X*	*3*	*Pre-dose*	.
2	*X*	*X*	*3*	*Post-dose*	.
3	X	X	2	Post-dose	X
3	X	X	3	Pre-dose	.
3	X	X	3	Post-dose	X

- **SAS code example for MMRM:**

For untrimmed variables:

```
proc mixed data=eff(where=(RELOCXCD='DISTAL')) method=reml;
   class avisitn usubjid;
   model logPCHG = logBASE avisitn logBASE*avisitn / solution
ddfm=kr;
   repeated avisitn /subject=usubjid type=un;
   lsmeans avisitn / cl alpha=0.05;
   estimate 'V3 Post-dose vs V3 Pre-dose' avisitn 0 -1 1 / cl;
   ods output lsmeans=lsmeans estimates=estimate;
run;
/* Backtransformation of results */
data back_trans;
      set lsmeans estimate;
      geolow=exp(lower);
      geomean=exp(estimate);
      geoupper=exp(upper);
run;
```

For trimmed variables:

```
proc mixed data=eff(where=(RELOCXCD='DISTAL')) method=reml;
   class avisitn usubjid;
   model logPCHG = avisitn / solution ddfm=kr;
   repeated avisitn /subject=usubjid type=un;
   lsmeans avisitn / cl alpha=0.05;
   estimate 'V3 Post-dose vs V3 Pre-dose' avisitn 0 -1 1 / cl;
   ods output lsmeans=lsmeans estimates=estimate;
run;
/* Backtransformation of results */
data back_trans;
      set lsmeans estimate;
      geolow=exp(lower);
      geomean=exp(estimate);
      geoupper=exp(upper);
run;
```

- SAS code example for paired T-Test:

```
proc ttest data=eff alpha=0.05;
   paired V3*Base;
   ods output ttests=ttests;
run;
```

- SAS code example for correlation analysis:

```
proc corr data=eff spearman;
   by lunglevel;
   var var1 var2;
run;
```

9.2 SCHEDULE OF ASSESSMENTS

	V0	Screening Visit (V1) -6weeks	Visit 2 6 weeks ±2 days	Visit 3 6 weeks ±2 days	Follow-up 2 weeks ±2 days
Informed consent form	✓				
Medical history		✓			
Incl/Excl criteria check and/or confirmation		✓	✓		
Demographic data		✓			
Vital Signs (blood pressure)[1]		✓	✓	✓	✓*
Hematology and Chemistry[2]		✓			
Serology		✓			
COVID-19 test[3]		✓	✓	✓	✓*
Physical examination[4]		✓		✓	✓*
Local safety ECG[5]		✓			
Training with In-check dial		✓			
Urinalysis		✓			
Urine pregnancy test[6]		✓	✓	✓	✓*
Urine sample for drug test[7]		✓	✓		
Body plethysmography[8]		✓	✓	✓	
CAT test		✓	✓	✓	
Spirometry[9]		✓	✓	✓	
Drug intake[10]		✓	✓	✓	
MDCT[11]			✓	✓	
Diary dispensation[12]		✓	✓		
Diary collection[13]			✓	✓	
Concomitant medication		✓	✓	✓	✓
Adverse events assessment		✓	✓	✓	✓

* A follow-up phone call will be done 14 days after Visit 3. For WOCBP the follow-up visit will occur 30 days after Visit 3

Footnotes for schedule of events:

1. **Vital signs (BP)**: duplicate measurements at screening for checking inclusion/exclusion criteria; At Visit 2, Visit 3 and at follow-up visit, if applicable. BP after at least 5 min rest in sitting or supine. Duplicate assessment with at least 5 min in between
2. The **blood samples** will be collected after overnight fasting (i.e. at least 10 h fasting, water allowed).
3. **COVID-19 test**: a molecular swab at screening and serological test at V2, V3 and Follow-up (if applicable). In case a serologic test for COVID-19 antibodies is positive, a molecular test must be performed.
4. **Physical Examination**: Full physical examination at screening visit for checking the inclusion/exclusion criteria; at Visit 3 and follow-up visit (if applicable).
5. **Safety ECG (single ECG)**: At screening visit pre-dose for checking the inclusion/exclusion criteria; ECG will be always recorded after at least 5 minutes of resting in supine position
6. **Pregnancy test**: for WOCBP a urine pregnancy test to be performed at screening, Visit 2, Visit 3 and at Follow-up visit
7. **Urine drug screen:** at screening visit for checking the inclusion/exclusion criteria and at Visit 2.

8. **Body plethysmography**: at screening, at Visit 2 and Visit 3 pre-dose
9. **Spirometry**: at screening pre- and post-bronchodilator, at Visit 2 and Visit 3 pre-dose between 7:00 and 10:00 a.m. preferably
10. **Drug intake**: Run-in medication dispensation at screening, the first dose will be taken at investigational site at Visit 1 in the morning. Study drug dispensation at Visit 2. Morning dose of Visit 2 and Visit 3 will be taken at the investigational site.
11. **MDCT**: multi-slice with multidetector computed tomography (inspiratory at TLC and expiratory at FRC) will be performed pre-dose and within 60– 120 min post-dose at Visit 2 and Visit 3. At Visit 2, Upper airway will be also scanned at TLC, pre-dose.
12. **Diary**: the paper subject diary will be dispensed at screening for the run-in medication and at Visit 2 for the IMP. Information on concomitant medications and adverse events occurrences and study drug intake will be recorded. Diaries will be checked by the Investigator at Visit 2 and Visit 3.

Statistical Analysis Plan Approval Form	

Protocol title:	**Open label, prospective study to evaluate the effect of step-up from non-extra fine ICS/LABA DPI to extra fine triple therapy with CHF5993 DPI on airway geometry and lung ventilation using FRI in subjects with advanced COPD**
Protocol reference:	CLI-05993BA1-08
PPD internal reference:	PPD
Sponsor:	Chiesi Farmaceutici S.p.A.
SAP version number:	Final 1.0
SAP version date:	29/MAR/2022

Name and function	**Date** (dd/MMM/yyyy HH:mm)	**Signature**
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Approved by the Sponsor:		
PPD , Statistician		PPD