STATISTICAL ANALYSIS PLAN

A Phase Ib, randomised, double-blind, placebo-controlled study to investigate the safety, tolerability, and pharmacokinetics of an intravenous monoclonal antibody (mAb) after single ascending doses in subjects affected by idiopathic pulmonary fibrosis

Protocol:	CLI-10067AA1-01
SGS Internal Reference:	[redacted]
Development phase:	Ib
Sponsor:	Chiesi Farmaceutici S.p.A.
SAP version number:	Final 1.0
SAP version date:	30MAY2024

NCT05513950

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PROTOCOL HISTORY

Protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the changes on the statistical analysis**
Final 1.0	03MAY2022	NAP
Final 2.0	25AUG2022	NAP
Final 3.0	24OCT2022	NAP
Final 4.0	22MAY2023	NAP
Final 5.0	16JUN2023	NAP
Final 6.0	06JUL2023	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 latest 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
ADA	anti-drug antibodies
ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse event
anti-HBc	hepatitis B core antibody
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve, from 0 to the last quantifiable concentration
AUC_{inf}	area under the concentration-time curve, extrapolated to infinity
BLQ	below the limit of quantification
BMI	body mass index
bpm	beats per minute
C_{inf}	concentration at the end of infusion
CI	confidence interval
CL	clearance
C_{max}	maximum observed concentration
eCRF	electronic case report form
CV	coefficient of variation
DBP	diastolic blood pressure
D_{LCO}	diffusing capacity of the lung for carbon monoxide
DRM	data review meeting
DRR	data review report
DY	relative day
ECG	Electrocardiogram
EMA	European Medicines Agency
ENR	enrolled set
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity

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 Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHR	Immediate Hypersensitivity Reaction
IL	Interleukin
IPF	idiopathic pulmonary fibrosis
IRT	interactive responsive technology
IS	immunogenicity
IV	intravenous
KFR	key first result
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralising antibody
NAP	not applicable
PCR	polymerase chain reaction
PK	pharmacokinetic
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
RNA	ribonucleic acid
RND	randomised set
SAF	safety set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDTM	study data tabulation model
SOP	standard operating procedure
STAT	Statistics
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TG2	transglutaminase 2

TLF	tables, listings and figures
t_{max}	time to C_{max}
t_{inf}	time to C_{inf}
TNF-α	tumour necrosis factor-α
UIP	usual interstitial pneumonia
VS	vital signs
Vz	volume of distribution
WBC	white blood cell
WHO	World Health Organisation
WHODrug	WHO drug dictionary

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
missing data	Data that would be meaningful for the analysis of a given endpoint but were not collected. They should be distinguished from data that do not exist.
phase	Interval of time in the planned conduct of a study associated with a specific purpose: for example, screening, treatment, follow-up.
significant digit	All digits of a number used to express it to the required degree of accuracy, starting from the first non-zero digit.
standardised unit	unit populating --STRESU in the clinical database
treatment-emergent abnormality	Any postbaseline abnormality/toxicity that was not present at baseline (e.g., glucose low at baseline and high post-baseline; QTcF]450; 480] ms at baseline and >500 ms post-baseline)

1. INTRODUCTION

This SAP describes the final statistical analysis to be performed for the CLI-10067AA1-01 ([redacted]) study.

This SAP covers the pharmacokinetic (PK), immunogenicity (IS), safety, transglutaminase 2 (TG2) levels, and general characteristics parts of the statistical analysis. It specifies the analysis displays to be presented and describes the methods and procedures in a more elaborated way than in the statistical methods section of the protocol.

The statistical analysis will process and present the results following the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards.

1.1 STUDY OBJECTIVES

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

- to assess the safety and tolerability of single ascending doses of CHF10067 in subjects with IPF.

According to the protocol, the secondary objectives of this study are:

- to evaluate the CHF10067 PK profile in serum;
- to evaluate the CHF10067 immunogenicity profile in terms of anti-drug antibody (ADA) and neutralising antibody (nAb).

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

- to evaluate TG2 levels in plasma.

1.2 STUDY DESIGN

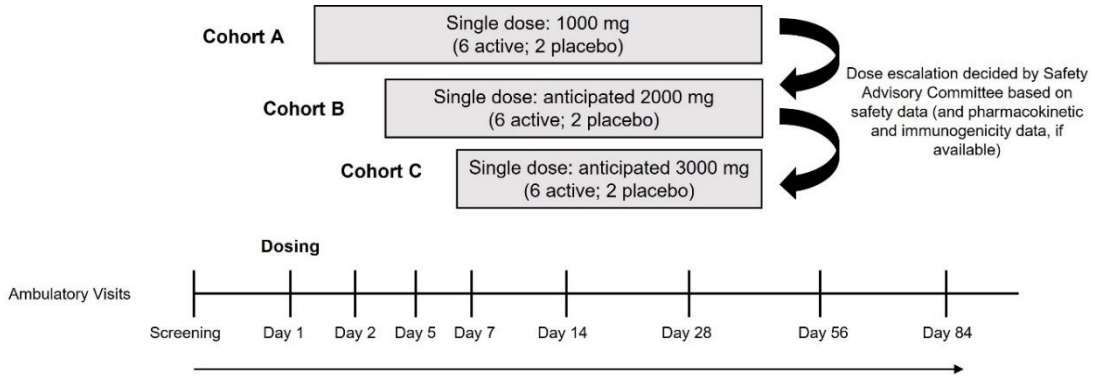
This is a Phase Ib, multi-centre, multi-country, randomised, double-blind, placebo-controlled study to investigate the safety, tolerability, immunogenicity, and PK of single IV doses of CHF10067 in subjects with IPF. The effect of CHF10067 on TG2 levels will also be investigated as an exploratory endpoint.

Overall, 24 subjects will be enrolled in 3 cohorts (Cohorts A [1000 mg], B [anticipated 2000 mg], and C [anticipated 3000 mg]) consisting of 8 subjects per cohort. In each cohort, 6 subjects will receive CHF10067, and 2 subjects will receive placebo.

The doses will be administered according to an escalation scheme designed to ensure sufficient safety conditions for subjects. In each cohort, subjects will be divided into 2 sub-groups, with each sub-group being dosed at least 24 hours apart. The first sub-group will comprise 2 subjects, with 1 subject receiving CHF10067 and 1 subject receiving placebo. The second sub-group will comprise 6 subjects, with 5 subjects receiving CHF10067 and 1 subject receiving placebo. Continuation to dose the remaining 6 subjects will be evaluated by at least the Medical Monitor and Sponsor Clinical Research Physician based on the safety data provided by the Investigator(s) where the first-sub-group have been dosed. The decision to escalate to the next dose will be made by the Safety Advisory Committee when safety data until Day 14 have been collected for all subjects at the previous dose level. Pharmacokinetic and

immunogenicity data will also be included in the safety evaluation for dose escalation (if available) but are not mandatory to escalate to the next dose.

An overview of the study design is shown in the figure below.



The schedule of assessments is in appendix 10.1.

1.3 EXPECTED SAMPLE SIZE

This study is designed to explore the safety and tolerability of CHF10067 for the first time in subjects affected by IPF, while exposing a minimum number of subjects; therefore, no formal power calculation was performed.

A sample size of 24 subjects (8 subjects per cohort; 6 treated with CHF10067 and 2 with placebo) is deemed adequate to assess safety and tolerability of CHF10067. In each cohort, a minimum of 2 subjects are required to be not receiving antifibrotic treatment (including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening).

1.4 RANDOMISATION AND BLINDING

An interactive responsive technology (IRT) system will be used for randomisation and assignment to blind treatment (CHF10067 or placebo).

The Investigator, or designee, at the sites will use the IRT system to screen and randomise subjects and to assign treatment kits according to the randomisation list. Subjects will be randomised in a 3:1 ratio within each cohort to receive either CHF10067 or placebo. Randomisation will require a minimum of 2 subjects within each cohort not receiving antifibrotic treatment (including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening). In each cohort, at least 24 hours must elapse between dosing of the first 2 subjects (1 CHF10067; 1 placebo) and the remaining 6 subjects. The IRT system will be used to coordinate the scheduling of Day 1 visits to be sure that this procedure is followed.

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.

Phoenix WinNonlin 8.3 or later (Certara, NJ, USA) will be used for calculations of PK parameters.

1.7 VALIDATION MODEL

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

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

PK analysis will be validated according SOP.PK.001.

2. PHARMACOKINETIC, AND IMMUNOGENICITY ANALYSES

2.1 PHARMACOKINETIC ANALYSES

2.1.1 Available data

Blood samples will be collected for the determination of CHF10067 in serum at the following time points: pre-dose (within 75 minutes from start of infusion), at the end of infusion, and 2, 4, 8, and 20 hours after the end of the infusion and 5, 7, 14, 28, 56 and 84 days post-dose.

2.1.2 Endpoints and derivation rules

The following PK parameters will be derived for serum CHF10067:

- AUC_{0-t}, AUC_{inf}, C_{max}, t_{max}, C_{inf}, t_{inf}, CL, Vz, $t_{1/2}$.

Standard non-compartmental methods will be used for the calculation of the PK parameters from the individual serum concentration – time profiles using actual sampling time points from start of infusion. If actual sampling time is not available, nominal time will be used (see also section 6.1.3.1). The analysis will consider time only in hours and minutes. Any seconds in the time part of a record will be imputed by zero. The area under the serum concentration-time curve (AUC) will be calculated according to the linear trapezoidal method.

PK parameters definition

- AUC_{0-t}: AUC from 0 to the last quantifiable concentration;
- AUC_{inf}: AUC from 0 to infinite time calculated as:AUC extrapolated to infinity will be calculated as the sum of AUC_{0-t} and a residual part extrapolated to infinite time. The residual area from the last concentration data point to infinite time is calculated using the approximation:

$$\int_t^{\infty} C_t dt = C_t/\lambda z$$

  where λz is the first order terminal rate constant, estimated by linear regression of the terminal loglinear segment of the plasma log concentration curve, and C_t is the last quantifiable concentration data point;
- C_{max} and t_{max}: the value and time of the maximum serum concentration will be obtained directly from the experimental data without interpolation;
- C_{inf} and t_{inf}: the value and time of the serum concentration at end of infusion;
- CL: clearance will be calculated as:

$$Dose/AUC_{inf}$$

- Vz: volume of distribution will be calculated as:

$$Dose/(\lambda z * AUC_{inf})$$

- $t_{1/2}$: terminal half-life, associated with negative slope (-λz), will be calculated as 0.693/λz from the individual drug concentration time profiles

Criteria for $t_{1/2}$ estimation

- At least three time points (excluding t_{max}) should be used for the determination of the elimination rate constant (λz), otherwise the $t_{1/2}$ as well as the derived parameters (AUC_{inf}, CL and Vz) cannot be estimated and will be presented as "NE" (not estimated) in the tables.
- The adjusted correlation coefficient of the linear regression should be ≥0.85, otherwise the $t_{1/2}$ as well as the derived parameters (AUC_{inf}, CL and Vz) are not reliably estimated and will not be reported (presented as "NR" (not reported) in the tables).

Criteria for AUC_{inf} estimation

- When for a profile the $AUC_{extrapolated}$ / $AUC_{0-\infty}$ > 20%, this AUC_{inf} as well as the derived parameters (CL and Vz) will be excluded from the statistical analyses.

All PK parameters will be estimated, if feasible, and presented in the TLFs, unless specified differently (e.g., unreliable $t_{1/2}$). PK parameters that cannot be estimated will be specified in the Data Review Report (DRR) (*prior* to database lock and disclosure of the bioanalytical data) and/or PK DRR (*after* database lock and disclosure of the bioanalytical data). PK data that is excluded from PK analysis will be discussed in the DRR and/or PK DRR, and marked in the relevant tables, accompanied with a footnote.

2.1.3 Inferential statistics

Dose proportionality in terms of CHF10067 AUC_{0-t}, AUC_{inf}, and C_{max} will be evaluated using the power model, including the log-transformed PK parameters as dependent variables, and the log-transformed CHF10067 dose as a covariate. The slope for log-transformed dose will be estimated with its 90% confidence interval (CI) to examine dose proportionality.

There will be no evidence for deviation of dose proportionality in case the 90% CI of the fixed slope for log-dose contains 1.

SAS code is provided in section 10.1.

2.1.4 Presentation of results

Listing

The actual sampling date/time and the actual time of end of infusion will be listed per subject, dose level and analysis time point. For samples that are reallocated to another analysis time point window, the new analysis time point window will be presented in "Analysis Time Window" column. Additionally, individual PK concentrations will be presented. PK concentrations excluded from PK parameter estimation and/or descriptive statistics will be marked and clarified with a remark. Important time deviations will be reported with elapsed time from planned timepoint in "Remarks" column.

Subjects that are excluded from the PK set and/or PK data that is excluded from PK parameter estimation, descriptive statistics and/or inferential statistics will be listed per subject, dose level and concentration time point or PK parameter, with the reason for exclusion. If this reason is due to an important protocol deviation, it will be marked too.

Tables

Individual actual sampling time points relative to end of infusion will be tabulated, per dose level. Important time deviations will be marked in the table with appropriate footnoting. Missing sampling times will be reported as “NT” (no time). Missing samples will be reported as “NS” (no sample).

Individual serum concentration data together with descriptive statistics will be tabulated, per dose level at each allocated analysis time point window. A footnote will be added to specify that a time windowing approach was considered to assign samples to the analysis time point. Missing samples or samples missing in an analysis time point window due to reallocated to another analysis time point window will be reported as “NRS” (no sample or reallocated sample). Samples for which no result is available will be reported as “NR” (no result). Exclusion of PK concentrations from descriptive statistics is described in section 6.1.3.1.

Individual PK parameters together with descriptive statistics will be tabulated, per dose level. Not estimable PK parameters will be reported as “NE” (not estimated). Exclusion of PK parameters from descriptive statistics is described in section 2.1.2 and section 6.1.3.1.

For the dose proportionality assessment on CHF10067 $AUC_{0\text{-}t}$, AUC_{inf}, and C_{max}, the slope and 90% CI of the power model will be tabulated.

Figures

Serum concentration - time profiles will be presented in linear/linear and log/linear scales. Mean (±SD for linear/linear scale) graphs will be presented with all dose levels on the same graph. Individual graphs will be presented per dose level, with all subjects on the same graph. The graphs will be presented over the full-time scale (i.e., up to Day 84).

The following attributes will be used in the concentration – time profiles:

- Dose levels (mean graphs)
  - A different colour, line pattern and symbol per dose level.
- Subjects (individual graphs with all subjects on the same graph, i.e., spaghetti plot)
  - A different line pattern and symbol per subject, and a unique colour for ADA positivity or negativity (see definitions in Section 2.2.2).

The individual and geometric mean values (log-transformed) of CHF10067 $AUC_{0\text{-}t}$, AUC_{inf}, and C_{max} will be presented graphically versus log-transformed dose. In addition, the linear regression line fitted will be displayed on each plot. The individual values will have the same colour and symbol as used in the concentration – time profiles. Only individual values used in the analysis will be plotted.

2.2 IMMUNOGENICITY

2.2.1 Available data

Serum samples for anti-drug antibody (ADA) assessments will be conducted utilizing a tiered approach (i.e., screen, confirm, titer), and ADA data will be collected pre-dose and at Days 14, 28, 56, and 84 and in case of early termination visit.

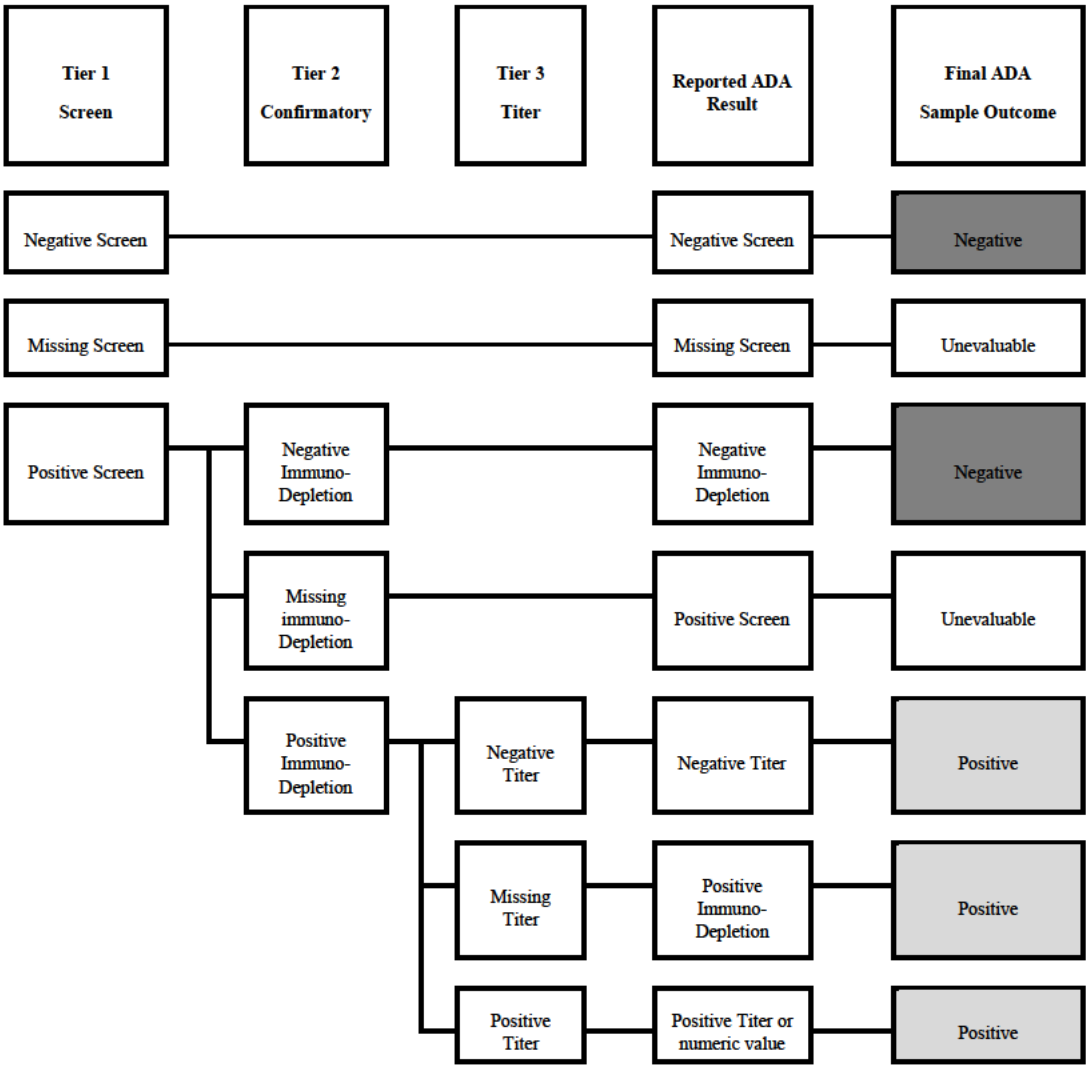
ADA result from each sample will be reported as either:

- ADA-positive: when ADA is detected at both screening and confirmatory tests in a sample, the sample is considered positive.
- ADA-negative: when ADA is not detected at screening test OR ADA is detected at screening but not detected at confirmatory test, the sample is considered negative.
- ADA-unevaluable: when a sample could not be tested for ADA status ("un-assayed sample") due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc. ..., either at screening or confirmatory test.

If the confirmatory sample is positive (i.e., ADA-positive sample), the ADA titer will be reported as well. ADA titer is a quasi-quantitative expression of the level of ADA in the sample.

In addition, the presence of neutralizing antibody (nAb) will be tested for all ADA -positive samples using a ligand-binding assay. The nAb results will be reported as either positive or negative.

ADA sample results



2.2.2 Derivation rules

No data imputation will be performed for missing and/or unevaluable samples.

Using the sample ADA status, subjects will be classified using the following definitions:

- ADA evaluable subject: A subject with baseline sample and at least one sample taken after drug administration during the treatment periods that are appropriate for ADA testing (i.e., with reportable result).
- ADA unevaluable subject: A subject without an evaluable sample at baseline OR with reportable baseline result but without a single sample taken (or without a reportable result) after drug administration during the treatment period.
- ADA-positive subject (ADA+): A subject with at least one treatment-induced or treatment-boosted ADA-positive sample at any time during the treatment period. See definitions of treatment-induced and treatment-boosted ADA in Section 2.2.3.
- ADA-negative subject (ADA-): A subject without a treatment-induced or treatment-boosted ADA-positive sample during the treatment period.

2.2.3 Presentation of results

The number and percentage of subjects who fulfil the below criteria will be presented by treatment.

- Baseline ADA-positive
  For this group of subjects, titer range (median and interquartile range (IQR)) of the baseline ADA-positive samples will be reported.
- ADA positive at any visit (ADA prevalence)
  A subject with at least one positive ADA result available at any time, including baseline (i.e., pre-existing ADA) and post-baseline measurements (i.e., ADA+). For this group of subjects, peak positive titer and range (median, IQR) will be reported.
- ADA incidence
  - Treatment-induced ADA, defined as ADA developed de novo (seroconversion) following drug administration (i.e., formation of positive ADA any time after the drug administration in subjects with ADA-negative baseline).

    For this group of subjects, the following additional parameters will be presented:
    - Peak positive titer and range (median, IQR);
    - Onset of ADA
      Time to onset of ADA (i.e., time period between the initial administration of the drug and the first instance of treatment-induced ADA);
    - Duration of ADA
      - *Persistently positive ADA*
        Subjects having a treatment-induced ADA detected at

least two non-consecutive time points, with the last ADA-positive measurement (irrespective of any negative samples in between first and last positive measurements) being detected at the end of the study period (i.e., day 84) for completer subjects or at the last available sampling time point for prematurely discontinued subjects.

- *Transiently positive ADA*
  Subjects having a treatment-induced ADA not fulfilling the above condition for persistently positive.

- Treatment-boosted ADA, defined as a baseline positive ADA titer (i.e., pre-existing ADA) that was boosted to a 4-fold or higher level following drug administration.

  For this group of subjects, the fold increase in titer (ratio of peak post-administration titer to baseline titer) and range of titer increases (median, IQR) will be presented.

The combination of both treatment-induced and treatment-boosted ADA (i.e., the percentage of patients fulfilling this criterion) is defined as ADA incidence.

- nAb positive at any visit (including baseline and all post-baseline measurements).

All immunogenicity data will be listed.

Only if immunogenicity data will allow (i.e., if the number of ADA+ subjects will be ≥3), the effect of immunogenicity on PK and safety will be evaluated:

- **PK**: Serum concentration/time curves will be presented in linear/linear and log/linear scale. Plots will be presented by dose level and subject ADA status (i.e., ADA+ or ADA-), based on arithmetic means;
- **Safety**: The number and percentage of patients with treatment-emergent AEs will be summarized by subject ADA status (i.e., ADA+ or ADA-), in line with the summary reported in Section 3.1.3.

3. SAFETY ANALYSES

3.1 ADVERSE EVENTS

3.1.1 Available data

Adverse events (AEs) are coded into system organ classes and preferred terms using the medical dictionary for regulatory activities (MedDRA, see section 10.3). For each AE, start and stop date(time)s are collected as well as intensity, a seriousness flag, seriousness criteria, treatment-relationship, action taken towards the study treatment and outcome.

Immediate hypersensitivity reactions (IHRs) are collected in a dedicated eCRF and are coded according to MedDRA dictionary (see section 10.3). For each IHR, start and stop date(time)s are collected as well as associated signs/symptoms, severity and suspected anaphylaxis.

3.1.2 Derivation rules

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

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

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

Based on their start date(time), AEs will be allocated to the phase during which they started. Phases are defined in section 6.2.1. 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 treatment was discontinued is defined as an AE with action taken ‘drug permanently withdrawn’.

AE onset and duration will be calculated as follows:

- AE onset day (vs. first administration) =
  - AE start date < date of first administration: AE start date – date of first administration
  - AE start date ≥ date of first administration: AE start date – date of first administration + 1 day
- AE duration (rounded as detailed in section 6.3.4) =
  - If start and stop date(time)s are available:
    - AE end date(time) – AE start date(time) + 1 minute

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

3.1.3 Presentation of results

Tables will present TEAEs and IHRs 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
- Grade 3 or 4 TEAEs
- TEAEs leading to study treatment discontinuation
- TEAEs leading to death
- Immediate hypersensitivity reactions

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 (except for IHRs). Each AE record in the clinical database is considered as a distinct adverse event and is counted as such. Blank system organ classes and preferred terms, if any, will be shown as 'Not Available' in the tables and listings.

All AEs, including pre-treatment events and all coding information will be listed. All IHR, including all reaction details will be listed. Separate listings will be prepared for the categories presented in the summary tables.

3.2 CLINICAL LABORATORY EVALUATION

3.2.1 Available data

Per protocol, the following safety laboratory parameters are expected to be collected at Screening, at Day 1 pre-dose, at Day 2, 7, 14, 28, 56 and 84:

- Biochemistry: creatinine, urea, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, alkaline phosphatase, sodium, potassium, chlorine, and fasting glucose.
- Haematology: red blood cells count, white blood cells count and differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils; % and values), total haemoglobin, haematocrit, and platelets count.
- Urinalysis (at Screening only): quantitative (proteins) and urinalysis – qualitative (ketones, microscopic examination of the sediment), will only be listed.
- Serum and urine pregnancy test and FSH (at Screening, Day 1, Day 28, Day 56, and Day 84 only), will only be listed.

Normal ranges are available as provided by the laboratory.

3.2.2 Derivation rules

Since not all the clinical sites involved in the study are able to provide WBC differential results but rather WBC absolute count results only, the WBC differential values at the given timepoint/assessment will be derived according to the following formula:

$$WBC\ type\ differential\ (\%) = \left(\frac{WBC\ type\ (count)}{WBC\ total\ (count)}\right) * 100$$

where WBC types are: neutrophils, eosinophils, lymphocytes, monocytes and basophils.
Derived differential values will be used for analysis purposes, while observed differential values (when available) will be listed only.

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:

- No normal ranges will be available for the derived WBC type differentials.

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

3.2.3 Presentation of results

The statistical analysis will present results in standardised units.

Continuous laboratory parameters (biochemistry and haematology) will be summarised by means of descriptive statistics at each analysis visit by treatment. Actual values and changes from baseline will be tabulated. Categorical parameters will be listed only.

Laboratory abnormalities will be presented by treatment as cross-tabulations of the abnormality at each post-dose analysis visit and at the worst-case analysis visit versus the baseline abnormality.

All laboratory data will be listed.

3.3 VITAL SIGNS

3.3.1 Available data

The following vital signs parameters are collected:

- duplicate systolic (SBP) and diastolic blood pressure (DBP) in supine position.
- pulse rate.
- respiratory rate.
- body temperature.
- oxygen saturation.

Vital signs (blood pressure, pulse rate, respiratory rate, body temperature): systolic and diastolic blood pressure will be evaluated in duplicate after 5 minutes in supine position. Vital signs will be measured at the following timepoints: screening, pre-dose, every 15 minutes during the infusion (e.g., 15, 30, 45, 60, 75, 90, 105, etc.), at the end of the infusion and 30 min, 1, 2, 3, 4, 6, 8, and 20 hours after the end of the infusion and 5, 7, 14, 28, 56, and 84 days post-dose.

Oxygen saturation: will be measured at screening and continuous monitoring will occur from pre-dose to 10 hours post-dose at the following timepoints: pre-dose, every 15 minutes during the infusion (e.g., 15, 30, 45, 60, 75, 90, 105, etc.), at the end of the infusion and 30 min, 1, 2, 3, 4, 6, 8, hours after the end of infusion. Oxygen saturation will also be measured at 20 hours after the end of infusion, and 5, 7, 14, 28, 56 and 84 days post-dose and in case of early termination visit.

3.3.2 Derivation rules

Mean values of the duplicates will be calculated per time point and rounded as detailed in section 6.3.4. Records belonging to the same duplicate will be identified using variable VSREFID. All records of the duplicate will be used to calculate the mean, even if less or more than the expected two. The date and time of the first member of the duplicate will be assigned to this mean value. Throughout the analysis, including the derivation of baseline and abnormalities, the mean values will be used. Individual duplicate values will only be listed.

The following change from baseline abnormality categories will be defined:

- Changes from baseline:
  - Diastolic blood pressure
    - Decrease from baseline >10 mmHg
    - Increase from baseline >10 mmHg
  - Systolic blood pressure
    - Decrease from baseline >20 mmHg
    - Increase from baseline >20 mmHg

3.3.3 Presentation of results

Vital signs and oxygen saturation parameters will be summarised by means of descriptive statistics at each analysis time point by treatment. Actual values (with 2-sided 95% CI) and changes from baseline (with 2-sided 95% CI) will be tabulated.

For the blood pressure parameters, the number and percentage of subjects with abnormal changes from baseline will be presented at each post-baseline time point and at the worst-case analysis visit by treatment.

All vital signs data will be listed.

Graphs of the mean changes from baseline over time will be prepared for the vital signs and oxygen saturation parameters by treatment. In addition, individual graphs of the changes from baseline over time will be presented by treatment for the vital signs and oxygen saturation parameters.

3.4 ELECTROCARDIOGRAMS

3.4.1 Available data

The following electrocardiogram (ECG) parameters will be collected:

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

ECGs will be performed at Screening visit, at pre-dose on Day 1, and Days 2, 7, 28, and 84 days post-dose and in case of early termination visit.

3.4.2 Derivation rules

Mean values of the triplicates will be calculated at Screening and rounded as detailed in section 6.3.4. Records belonging to the same triplicate will be identified using variable EGREFID. All records of the triplicate will be used to calculate the mean, even if less or more than the expected three. Throughout the analysis, including the derivation of baseline and abnormalities, the mean values will be used. Individual triplicate values will only be listed.

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

- Actual values:
  - Males:
    - > 450 ms
    - > 480 ms
    - > 500 ms
  - Females:
    - > 470 ms
    - > 500 ms
- Changes from baseline:
  - Increase from baseline >30 ms
  - Increase from baseline >60 ms

Note: The worst-case, as defined in section 6.2.5, is the highest value and associated change.

3.4.3 Presentation of results

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

For QTcF, the number and percentage of subjects with abnormal actual values will be presented at each post-dose time point and at the worst-case post-baseline analysis visit by treatment.

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

All ECG data will be listed.

Graphs of the mean changes from baseline over time will be prepared for the continuous ECG parameters by treatment. In addition, individual graphs of the changes from baseline over time will be presented by treatment.

3.5 LUNG FUNCTION

3.5.1 Available data

The following lung function parameters are collected:

- Spirometry: Forced Expiratory volume in 1 second (FEV_1), predicted FEV_1, percent predicted FEV_1, forced vital capacity (FVC), predicted FVC, percent predicted FVC and FEV_1/FVC ratio.
  Spirometry will be assessed at the following timepoints: screening, 7, 28, 56, and 84 days post-dose and in case of early termination visit.
- Diffusing capacity: D_{LCO} [unadjusted], D_{LCO} % predicted, D_{LCO} corrected for haemoglobin, D_{LCO} corrected for haemoglobin % predicted, carbon monoxide transfer coefficient [KCO], and alveolar volume [VA].
  Diffusing capacity will be assessed at the following timepoints: screening, 28, 56, and 84 days post-dose and in case of early termination visit.

3.5.2 Presentation of results

Spirometry:

Spirometry parameters will be summarised by means of descriptive statistics (with their 95% CI) at each analysis time point by treatment. Actual values, changes from baseline and relative changes from baseline will be tabulated.

Graphs of the absolute and relative mean changes from baseline over time will be prepared by treatment.

All spirometry parameters will be listed.

Diffusing capacity:

Diffusing capacity parameters will be summarised by means of descriptive statistics (with their 95% CI) at each analysis time point by treatment. Actual values, changes from baseline and relative changes from baseline will be tabulated.

Graphs of the absolute mean changes from baseline over time will be prepared by treatment for D_{LCO} % predicted and D_{LCO} corrected for haemoglobin.

All diffusing capacity parameters will be listed.

3.6 SYSTEMIC MARKERS FOR EVALUATION OF IMMEDIATE HYPERSENSITIVITY REACTIONS

3.6.1 Available data

Following systemic markers for evaluation of immediate hypersensitivity reactions will be collected: Cytokine markers (IFN-γ, TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 (p70), and IL-13), mast cell tryptase, complement markers (C3a, C5a, CH50, and SC5b-9), and CHF10067 IgE.

3.6.2 Presentation of results

The statistical analysis will present results in standardised units.

Systemic markers will be summarised by means of descriptive statistics, if data is available for at least 3 subjects, at each timepoint by treatment. Actual values and changes from baseline will be tabulated.

3.7 PHYSICAL EXAMINATIONS

Abnormal physical examination findings will be listed.

4. OTHER VARIABLES

4.1 TG2 IN PLASMA

According to the protocol, the exploratory endpoint of this study is:

- TG2 levels in plasma

4.1.1 Available data

TG2 levels in plasma samples be collected pre-dose and on Days 14, 28, 56, and 84.

4.1.2 Presentation of results

The statistical analysis will present results in standardised units.

TG2 levels in plasma will be summarised by means of descriptive statistics at each analysis visit by treatment. Actual values (with their 95% CI) and changes from baseline (with their 95% CI) will be tabulated.

Graphs of the mean changes from baseline over time will be prepared by treatment. In addition, individual graphs of the changes from baseline over time will be presented by treatment and ADA positivity/negativity (see definitions in Section 2.2.2).

5. GENERAL CHARACTERISTICS ANALYSES

5.1 SUBJECT DISPOSITION

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

- The number of screen failures
- The number and percentage of subjects who completed or discontinued the study as documented on the study termination page and the number and percentage of subjects for each study discontinuation reason
- The number of subjects in each analysis set
- The number and percentage of subjects for each analysis visit

All information collected in the eCRF concerning allocation, code breaking, study discontinuation and information on phases, dates of first signed informed consent, last visit and last contact (over the whole study) will be listed.

5.2 IMPORTANT PROTOCOL DEVIATIONS AND ELIGIBILITY

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

All available information concerning important protocol deviations violations on eligibility criteria (only violated eligibility criteria having DV.DVCAT = 'INCLUSION/EXCLUSION CRITERIA') and restrictions will be listed.

5.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

5.3.1 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: serology (Human Immunodeficiency Virus Antibody (Ab-HIV1 and 2), Hepatitis B surface Antigen (HBsAg), Hepatitis B core antibody (anti-HBc), immunoglobulin M Hepatitis B core antibody (IgM anti-HBc), Hepatitis C Virus Antibody (Ab-HCV)) and Hepatitis C Virus RNA PCR, ethanol and urine drug screen (cannabinoids, opiates, cocaine, benzodiazepine, amphetamines and barbiturates) and cotinine test
- Baseline disease characteristics: date of diagnosis, type of diagnosis (usual interstitial pneumonia (UIP) pattern, possible UIP pattern, probable UIP pattern), IPF diagnosis confirmation, biopsy, antifibrotic treatment for IPF (Nintedanib or Pirfenidone), SoC treatment (Nintedanib or Pirfenidone) well tolerated, exacerbation history (number of exacerbations in the 3 months before screening and end date of the most recent exacerbation)

5.3.2 Derivation rules

The following parameters will be derived:

- Age categories:
  - >=40 and <65 years
  - >=65 and <85 years
  - >=85 years
- Time since diagnosis (years): (date of ICF – date of diagnosis)/365.25

Note: Partially missing dates will be imputed as specified in section 6.3.2

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

Note: Partially missing dates will be imputed as specified in section 6.3.2

5.3.3 Presentation of results

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

Baseline disease characteristics will be presented by treatment and overall using descriptive statistics for continuous parameters and frequency tabulations for categorical parameters.

All demographic data, baseline disease characteristics and screening tests will be listed.

5.4 MEDICAL HISTORY AND CONCOMITANT DISEASES

5.4.1 Available data

Medical history and concomitant diseases findings are coded using the medical dictionary for regulatory activities (MedDRA, see section 10.3) 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.

5.4.2 Derivation rules

The following selection will be performed:

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

5.4.3 Presentation of results

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

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

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

5.5 PROCEDURES AND MEDICATIONS

5.5.1 Available data

All procedures are coded into system organ classes and preferred terms using the medical dictionary for regulatory activities (MedDRA, see section 10.3). For each procedure, start and stop dates or ongoing flag are collected.

All medications are coded using WHODrug (see section 10.3). ATC coding up to level 5 is available in the clinical database. For each medication, a start date(time) or prior flag and stop date(time) or ongoing flag are collected.

5.5.2 Derivation rules

Based on their start and stop date(time), 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 6.2.1. Procedures/medications with (partially) missing date(time)s will be allocated to each phase unless the available parts of the procedure/medication start or stop date(time) provide evidence that the procedure/medication was not performed/taken during that phase.

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

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

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

- Concomitant
- Maintained
- Prior

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

5.5.3 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); by treatment and overall. 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.

Medications:

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

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

All medications data will be listed.

5.6 EXPOSURE TO STUDY TREATMENT

5.6.1 Available data

For each study treatment administration, the start and end date(time)s, kit number, the dose, the infusion rate, the reason for interruption or rate change and the action taken during the infusion will be recorded.

5.6.2 Presentation of results

All exposure data will be listed.

6. GENERAL METHODOLOGY

6.1 ANALYSIS SETS

6.1.1 Analysis sets

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

Enrolled Set (ENR):	subjects who *signed an informed consent* to participate in this study
Randomised Set (RND):	subjects who were *randomised* into this study
Safety Set (SAF):	all randomised subjects who receive a dose of study treatment, including partial dose
PK Set:	all subjects from the safety set excluding subjects without any valid PK measurement or with important protocol deviations significantly affecting PK, for example, use of non-permitted medications.

Notes:

- Having signed an informed consent is defined as having a complete informed consent signature date in the database.
- Randomised is defined as having a randomisation date in the database or any information to confirm randomisation.
- Having received at least one dose of study treatment is defined as having an exposure date or any information confirming exposure.
- Exact definition of important protocol deviations significantly affecting PK evaluations will be discussed by the Chiesi team during the Data Review Meeting (DRM) and described in the DRR and/or PK DRR. The PK set will be defined in the DRR and/or PK DRR. See section 6.1.3.1 for further details. Subjects will not be excluded on the basis of statistical analysis or for PK reasons, except in the cases defined in the European Medicine Agency guideline on the Investigation of Bioequivalence

Unless stated otherwise, the SAF will be used for the general characteristics, demographics and baseline characteristics, immunogenicity and safety tables and figures and the RND will be used for the general characteristics and safety listings. In addition, the PK set will be used for demographics and baseline characteristics tables, if different than the SAF. PK set will be used for the PK tables, listings and figures.

6.1.2 As planned versus as actual analysis

For the safety, immunogenicity, other variables (TG2) and PK analyses the actual treatment of the subject will be considered. The general characteristics analyses will be by planned treatment. In the listings the actual treatment will be presented.

6.1.3 Exclusion of data from the statistical analyses

The important/non-important protocol deviation definitions are defined in the Protocol Deviation Criteria List and will be used to identify cases that will be

discussed by Chiesi during the DRM. Decisions on whether subjects are to be excluded from the analysis set and/or values are to be excluded from the analysis will be fully documented in the DRR and/or PK DRR.

In case of important protocol deviations impacting specific time points, only the affected data at the specific time point will be excluded from the applicable analysis sets. These cases will be documented in the DRR and/or PK DRR.

6.1.3.1 EXCLUSION OF DATA FROM PK ANALYSIS

Subjects and/or PK data can be excluded from the PK set or PK analysis based on the important protocol deviations with potential impact on PK. Below, the rules for handling PK assessments not performed, or performed out of the allowed window, or not reportable are described. In addition to the important protocol deviations, PK data can be excluded based on specific rules after disclosure of the bioanalytical data or specific criteria for PK parameters. The criteria of the latter are described in section 2.1.2.

Important protocol deviations

The impact of PK assessments not performed, or performed out of the allowed window, or not reportable will depend on the number of deviations per profile and the timing of the deviation:

At predose

The impact of serum PK assessments performed out of allowed window or taken after start of infusion will be evaluated during the DRM.

For serum PK assessments not performed or not reportable at pre-dose, see section 6.3.1 for proper imputation rules for PK parameter estimation.

At t_{max}

For serum PK assessments not performed, or performed out of allowed window, or not reportable at the expected t_{max}, the general rule is the following: the resulting estimation of C_{max}, t_{max} and AUCs could not be accurately determined, and these parameters will be excluded from PK analyses. This deviation will have no impact on the estimation of $t_{1/2}$. The expected t_{max} of CHF10067 is within 1 hour from the end of infusion.

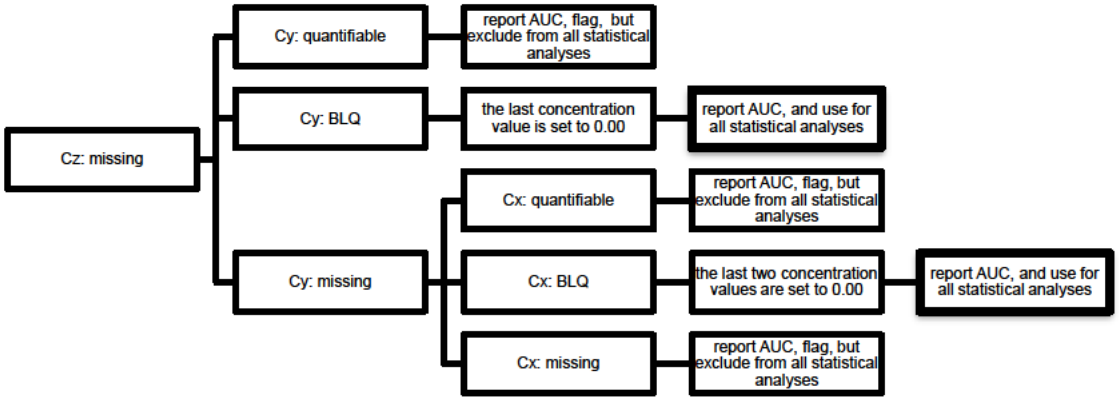
At t_{inf}

For serum PK assessments not performed, or performed out of allowed window, or not reportable at the expected t_{inf}, the general rule is the following: the resulting estimation of C_{inf} could not be accurately determined, and this parameters will be excluded from PK analyses. This deviation will have no impact on the estimation of $t_{1/2}$.

At last planned sampling time point

For serum PK assessments performed out of allowed window at the last planned sampling time point, in order to minimise the risk to under- or overestimate AUC_{0-t}, AUC_{0-t} will be calculated using the theoretical time of the last planned timepoint instead of the actual time. Note that in case the last sample is taken before the planned sampling time point, this AUC_{0-t} can only be estimated if λz is reliably measurable.

For serum PK assessments not performed or not reportable at the last planned sampling time point, the following schema will be used to determine the handling of impacted AUCs (C_x, C_y and C_z are adjacent concentration samples at the end of the profile, with $t_x < t_y < t_z$; thus t_z being the last planned sampling time point of the profile):



Multiple missing PK assessments

The impact of multiple PK assessments not performed or not reportable, i.e., at least 2 adjacent intermediate values are missing, or more than 3 intermediate values are missing, the PK profiles will be discussed case by case in the DRR and/or PK DRR. If 1, or 2 non adjacent intermediate values are missing, no impact on PK parameter estimation is expected.

Two serum samples at the same actual time

The Phoenix WNL software cannot handle two identical actual sampling time points in a profile. Therefore, if two serum samples are taken at the same time, the sample taken closest to the planned sampling time point will be used while the other will be excluded from PK parameter estimation.

Rules after disclosure of the bioanalytical data

After disclosure of the bioanalytical data, subjects and/or PK data will not be excluded based on post-hoc statistical analysis or for pharmacokinetic reasons, except for certain cases described below (in line with the EMA guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 2010).

All BLQ values

When plasma concentrations are BLQ at all time points, no PK parameters will be estimated and the subject will be excluded from the PK set.

Non-zero baseline concentration > 5% of C_{max}

Subjects with Day 1 pre-dose values exceeding 5% of the C_{max} will be excluded from the PK set.

AUC_{0-t} lower than 5% of the corresponding geometric mean AUC_{0-t}

Subjects with an AUC_{0-t} lower than 5% of the corresponding geometric mean AUC_{0-t} (calculated without inclusion of data from the outlying subject) will be excluded from the PK set.

Abnormal PK concentrations or profiles

Abnormal PK concentrations or profiles will be discussed case by case in the PK DRR.

6.1.3.2 EXCLUSION OF DATA FROM SAFETY ANALYSIS

Not applicable

6.2 PHASES AND TIME POINTS

6.2.1 Phases

Adverse events, medications, and procedures will be allocated to phases. All other analyses will not be allocated to phases. Instead, the visit and time point labels indicated on the subject's electronic case report form (eCRF) will be used to allocate the assessments. Early termination assessments will be allocated to the treatment phase.

Adverse events and medications:

Phase	Start	End
Screening	Date of signing the ICF, with 00:00 added as time part	First administration date(time) – 1 minute
Treatment	First 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.

Procedures:

Phase	Start	End
Screening	Date of signing the ICF	First administration date – 1 day
Treatment	First 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 5.5.2 respectively.

All PK records (PK concentrations and PK parameters) and IHRs will be allocated to the treatment phase.

6.2.2 Baseline and change from baseline

The baseline value is the last non-missing value, including unscheduled assessments, before the administration of the study treatment. In case this results in more than one record with the same date and time, the unscheduled record is selected as baseline.

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

Change from baseline is defined as:

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

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

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

6.2.3 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 administration of study treatment.

6.2.4 Analysis visits

The analysis will use the visits indicated on the subject's eCRF, while for the time points related to the PK concentration data and the vital signs and oxygen saturation assessments a windowing approach will be used (see time window definitions below). For PK parameter calculation the actual sampling time will be considered, as reported in section 2.1.2.

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

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

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

Baseline is defined in section 6.2.2.

All scheduled and unscheduled assessments will be listed.

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

- All planned screening, re-screening, eligibility recheck, etc. visits occurred during the screening phase will be presented as 'Screening'.
- All planned visits occurred during a scheduled day, will be presented as 'Day x' (x = study day, e.g. 'Day -1', 'Day 1', etc.)
- Early termination visits will be presented as 'Early Termination'
- 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)

For PK data, AVISIT(N) will be assigned per PK profile of interest and will be based on the eCRF visit of the corresponding study treatment administration.

The analysis time point labels for pharmacokinetic concentration data, vital signs and oxygen saturation, will be assigned using the following time windowing rules.

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

Pharmacokinetics:

Analysis time point window	**Target time after end of infusion (hours)**	**Time interval (hours)**
Pre-dose	<0	Last day 1, pre-dose assessment
EOI	0	[0 min;10 min=0.1667]
2h	2	[11min=0.1833;3]
4h	4	[3.0167;6]
8h	8	[6.0167;14]
20h	20	[14.0167;58]
Day 5	96	[58.0167;120]
Day 7	144	[120.0167;228]
Day 14	312	[228.0167; 480]

Day 28	648	[480.0167;984]
Day 56	1320	[984.0167;1656]
Day 84	1992	[1656.0167;∞)

Vital signs and oxygen saturation:

Before and during infusion:

Analysis time point window	**Target time vs. start of infusion (minutes)**	**Time interval (minutes)**
Pre-dose	<0	Last day 1, pre-dose assessment
0.25h	15	[1;22]
0.5h	30	[23;37]
0.75h	45	[38;52]
1h	60	[53;67]
1.25h	75	[68;82]
1.5h	90	[83;97]
1.75h	105	[98;112]
2h	120	[113;127]
2.25h	135	[128;142]
2.5h	150	[143;157]
2.75h	165	[158;172]
3h	180	[173;187]
3.25h	195	[188;202]
3.5h	210	[203;217]
3.75h	225	[218;232]
4h	240	[233;247]
4.25h	255	[248;262]
4.5h	270	[263;277]
4.75h	285	[278;292]

5h	300	[293; 307]
5.25h	315	[308; 322]
5.5h	330	[323; end of infusion]

After infusion:

Analysis time point window	**Target time vs. end of infusion (minutes)**	**Time interval (minutes)**
0h	0	[End of infusion; 5]
0.5h	30	[6;45]
1h	60	[46;90]
2h	120	[91;150]
3h	180	[151;210]
4h	240	[211;300]
6h	360	[301;420]
8h	480	[421;840]
20h	1200	[841;1560)

Systemic markers:

Analysis time point window	Target time vs. end of infusion (pre-dose) or start of hypersensitivity reaction (post-dose) (minutes)	Time interval (minutes)
Pre-dose	<0	Last day 1, pre-dose assessment
1h	60	[1;90]
2h	120	[91;∞)

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

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

6.2.5 Worst-case

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

The worst-case analysis visit will be derived within the treatment phase, including scheduled and unscheduled assessments as well as the early termination visit assessments. Only post-baseline assessments will be considered for the worst-case analysis visit.

6.3 IMPUTATION AND ROUNDING RULES

6.3.1 Missing values

No imputation of missing values will be done (i.e., observed cases analysis), except missing pre-dose concentrations will be imputed per rules below for PK parameter derivation only:

- The missing pre-dose PK concentration will be set to 0 for PK parameter derivation.

6.3.2 Handling partially or completely missing dates in calculations

Partially missing date of date of diagnosis or end date of the most recent 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

6.3.3 Values below or above a threshold

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

PK concentrations below the quantification limit will be flagged as BLQ in the concentration and parameters tables. All BLQ values will be considered as 0.00 for PK and descriptive statistical analyses.

6.3.4 Rounding of derived variables

Derived variables will be rounded at display level:

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

  Note: since the rounding is applied at display level, in the listings, the change from baseline could be slightly different to the listed value at time point t – baseline value
- Relative change from baseline will be presented with 1 decimal.
- Time since diagnosis, last exacerbation will be presented with 1 decimal.
- Derived laboratory differential values will be presented with 1 decimal.
- Log-transformed values will not be rounded.
- PK concentrations and parameters (as well as descriptive statistics) will be presented in tables with 3 significant digits except values >1000, which will be presented without decimals and t_{max} which will be presented with 2 decimals.

6.3.5 Outliers

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

6.4 PRESENTATION OF RESULTS

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

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

Mean, median, SD and CI will be presented with one more decimal place than the individual values, with a maximum of 4 decimal places. Minimum and maximum will be presented with the same number of decimal places as the individual values, with a maximum of 3 decimal places.

Descriptive statistics of PK concentrations will include the number of non-missing data points, the arithmetic mean, SD, the median, minimum and maximum and the coefficient of variation (CV) % of arithmetic mean. If more than half of values are BLQ at a specific timepoint, then SD and CV% will not be calculated and reported as "NC" (not calculated) in the tables.

Descriptive statistics on PK parameters will additionally include geometric mean and geometric CV%, except t_{max} for which the descriptive statistics will include the number of non-missing data points, the median, minimum and maximum.

The descriptive statistics on PK data will be presented as described in section 6.3.4.

The slopes and their 90%CI from the power model on PK parameters will be presented with two decimals.

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

For frequency tabulations and cross-tabulations, missing values will not be included in the denominator count when computing percentages. For cross-tabulations of post-baseline results versus baseline results, a 'missing' category will be shown for baseline results if applicable.

Percentages will be shown with one decimal place.

6.4.2 Presentation of treatments

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

- CHF10067 1000 mg
- CHF10067 2000 mg
- CHF10067 3000 mg
- CHF10067 Total [+]
- Placebo [*]
- Overall [#]

[+] "CHF10067 Total" is the combination of "CHF10067 1000mg", "CHF10067 2000mg" and "CHF10067 3000mg" treatment groups, will be shown for all demographics and safety tables (with the exception of disposition, analysis set, protocol deviations and PK).

[*] All placebo subjects (from all cohorts) will be pooled into one "Placebo" group for presentation in tables and figures.

[#] Unless specified otherwise, an "Overall" column, to summarise all subjects over treatments (including placebo), will be presented only in tables showing data that are not affected by the study treatment (i.e., general characteristics analyses). The overall column will be shown last.

6.4.3 Ordering in tables, listings and figures

If the treatments are presented as columns, tables will be sorted by analysis visit and time point. Otherwise, tables will be sorted first by treatment, then by analysis visit and time point. The active treatments will be shown first in ascending dose order, and then placebo: CHF10067 1000 mg, CHF10067 2000 mg, CHF10067 3000 mg, CHF10067 Total and then placebo.

All tables and figures will be presented per treatment, unless specified otherwise.

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

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

6.4.4 Raw SAS output

In addition to the statistical output as described in section 9, 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.

6.4.5 eCTD tables

Additional tables will be delivered in separate files as 'Appendix to Table 14.x.x.x' for all tables presenting PK parameters: they will be created separately for each

analyte and will present the subjects/profiles (if any), per treatment, showing AUC_{0-t}/ $AUC_{0-\infty}$ <0.8, C_{max} as the first point and pre-dose sample >5% C_{max} per treatment.

7. CHANGES TO THE PLANNED ANALYSIS

7.1 CHANGES NOT COVERED BY PROTOCOL AMENDMENTS BEFORE UNBLINDING

- **"Immunogenicity Analysis": Section 2.2 of the SAP to clarify section '12.3.5.3 Immunogenicity' of the study protocol.**
  Section 2.2 of this SAP, compared to Section 12.3.5.3 of the study protocol, provides clear definitions and a corresponding summary table on the whole Safety Set for: ADA evaluable subject, ADA positive subjects, ADA prevalence, ADA incidence (i.e., treatment-induced and treatment-boosted ADA) and nAb positive subject. As a consequence of the above update, the two summary tables on the subset of ADA positive subjects, initially foreseen in Section 12.3.5.3 of the study protocol, have been translated into a listing (see Listing 16.2.6.1 at Section 9.2 of the present document).

- **"Vital signs": Section 3.3 of the SAP to clarify section '12.3.5.4.3 Oxygen saturation' of the study protocol.**
  While per protocol, individual time profile plots are not requested for oxygen saturation, these will be produced to be in line with the vital signs analysis.

- **"Lung function": Section 3.5 of the SAP to clarify section '12.3.5.4 Pulmonary assessments' of the study protocol.**
  The following summary analysis is described in the protocol:

  "The frequency of subjects with FEV1% and FVC% below the lower limit of normal at each timepoint will be listed and summarised with descriptive statistics."

  Since no normal ranges are available for the aforementioned parameters, this summary will not be produced.

- **"Placebo-corrected change from baseline": Section 3.4 of SAP to clarify Section '12.3.5.5 ECG' of the study protocol.**
  Placebo-corrected change from baseline is erroneously mentioned in the protocol but it is not applicable for this study design. Therefore, none of the analyses related to placebo-related change from baseline will be produced.

- **Section "12.3.6.1 TG2 in plasma" of the study protocol.**

  The below text was erroneously included in the study protocol. Therefore, the related analyses will not be produced.

  "The TG2 levels in plasma obtained from healthy subjects will be summarised using descriptive statistics.

  Box-plots summarising the pre-dose levels for treated subjects in the study, the healthy subjects' external group, and each post-dose levels for the different doses for treated subjects will be presented."

- **"By dose level": SAP to clarify Section 12 of the study protocol.**

  While across the study protocol 'dose level' could be equivalent to 'cohort', and across section 12 of the protocol analyses are defined to be performed by 'dose level', in the SAP all analyses have been defined as 'by treatment', separating the subjects receiving active study treatment and placebo as defined in section 6.4.2 of this SAP.

8. REFERENCES

- ICH Topic E6(R2) Guideline for Good Clinical Practice – Step 5 (EMA/CHMP/ICH/135/1995), 1 December 2016.
- ICH guideline E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (R3) – questions and answers, January 2016.
- ICH Topic E9 Statistical Principles for Clinical Trials – Step 5 – Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96), September 1998.
- D419QC00001-SAP-ed-4_Final Redacted_15Sep21.pdf, available at https://clinicaltrials.gov/ct2/show/NCT03043872.
- El-Khoueiry A. et al, Immunogenicity of durvalumab: analysis of pooled pan-tumor data, J Immunother Cancer 2022;10(Suppl 2):A1–A1603.
- Shankar G. et al, Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations, The AAPS Journal, Vol. 16, No. 4, July 2014.

9. LIST OF TABLES, LISTINGS AND FIGURES

9.1 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 (Randomised Set) [KFR]**	**RND**	**DST002**
	Tabulation of completion/discontinuation and the reason for discontinuation.		
14.1.1.3	**Analysis Sets (Randomised Set)**	**RND**	**DST005**
	Tabulation of the number of subjects in each of the analysis sets defined in the SAP.		
14.1.1.4	**Attendance at Study Visits (Randomised Set)**	**RND**	**SVT001**
	Tabulation of the number and percentage of subjects per analysis visit.		
14.1.1.5	**Important Protocol Deviations (Safety Set)**	**SAF**	**DVT001**
	Tabulation of the important protocol deviations (at least one), deviation category and deviation type by treatment and overall.		
14.1.1.6	**Important Protocol Deviations Leading to Exclusion from PK Set (Safety Set)**	**SAF**	**DVT001**
	Tabulation of the important protocol deviations (at least one) leading to exclusion from the PK set, deviation category and deviation type by treatment and overall.		
14.1.2.1.1	**Demographic Characteristics (Safety Set) [KFR]**	**SAF**	**DMT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.1.2	**Demographic Characteristics (PK Set)**	**PK**	**DMT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.2.1	**IPF History (Safety Set) [KFR]**	**SAF**	**SCT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters. Template SCT001 is used, using the IPF parameters instead.		
14.1.2.2.2	**IPF History (PK Set)**	**PK**	**SCT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters. Template SCT001 is used, using the IPF parameters instead.		

Number	Title	Analysis Set	TLFs Library Template Number
14.1.2.3.1	**IPF Exacerbation History (Safety Set)**	**SAF**	**SCT003**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters. Template SCT003 is used, using the IPF exacerbation parameters instead.		
14.1.2.3.2	**IPF Exacerbation History (PK Set)**	**PK**	**SCT003**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters. Template SCT003 is used, using the IPF exacerbation parameters instead.		
14.1.2.4	**Smoking Status (Safety Set)**	**SAF**	**SUT001**
	Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.		
14.1.2.5	**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.		
14.1.2.6	**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.		
14.1.2.7	**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.		
14.1.2.8	**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.		
14.1.2.9	**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.		
14.1.2.10	**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.		
14.1.2.11	**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.		

Number	Title	Analysis Set	TLFs Library Template Number
14.1.2.12	**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.		
PHARMACOKINETICS			
14.2.2.1	**Actual Blood Sampling Times for PK Assessments (PK Set)**	**PK**	**PCT001**
	Individual actual sampling times of blood samples per dose level		
14.2.2.2	**CHF10067 Serum Concentrations (ng/mL) by Scheduled Time (PK Set)**	**PK**	**PCT002**
	Individual values and descriptive statistics of CHF10067 serum concentrations per dose level		
14.2.2.3	**CHF10067 Serum PK Parameters (PK Set)**	**PK**	**PKT001**
	Individual values and descriptive statistics of CHF10067 serum PK parameters, per dose level		
14.2.2.4	**Dose Proportionality Assessment of CHF10067 Serum PK Parameters (Power Model) (PK Set)**	**PK**	
	The slope and 90% CI of the power model will be tabulated by PK parameter of CHF10067 (AUC_{0-t}, AUC_{inf}, and C_{max})		
IMMUNOGENICITY			
14.2.4.1	**Summary of ADA Responses (Safety Set) [KFR]**	**SAF**	
	Tabulation of the number and percentage of subjects as classified in section 2.2.3.		
14.2.4.2	**Summary of TEAEs by Subject ADA Status (Safety Set)**	**SAF**	**AET001**
	Tabulation of the number and percentage of subjects with at least one TEAE by subject ADA status (ADA+ or ADA-). Note: if the number of ADA+ subjects is less than 3, this table will be generated without results. Instead, an informative message will be printed in this output.		
SAFETY			
ADVERSE EVENTS			
14.3.1.1	**Summary of TEAEs (Safety Set) [KFR]**	**SAF**	**AET001**
	Tabulation of the number and percentage of subjects with at least one of the events described in the SAP. The number of events will also be shown.		
14.3.1.2	**TEAEs by System Organ Class and Preferred Term (Safety Set)**	**SAF**	**AET003**
	Tabulation of the number and percentage of subjects with TEAEs by MedDRA system organ class and preferred term. The number of events will also be shown.		

Number	Title	Analysis Set	TLFs Library Template Number
14.3.1.3	**Serious TEAEs by System Organ Class and Preferred Term (Safety Set)** Tabulation of the number and percentage of subjects with serious TEAEs by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
14.3.1.4	**Non-Serious TEAEs by System Organ Class and Preferred Term (Safety Set)** Tabulation of the number and percentage of subjects with non-serious TEAEs by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
14.3.1.5	**ADRs by System Organ Class and Preferred Term (Safety Set) [KFR]** Tabulation of the number and percentage of subjects with ADRs by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
14.3.1.6	**Serious ADRs by System Organ Class and Preferred Term (Safety Set)** Tabulation of the number and percentage of subjects with serious ADRs by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
14.3.1.7	**Grade 3 or 4 TEAEs by System Organ Class and Preferred Term (Safety Set)** Tabulation of the number and percentage of subjects with grade 3 or 4 TEAEs by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
14.3.1.8	**TEAEs Leading to Study Treatment Discontinuation by System Organ Class and Preferred Term (Safety Set)** Tabulation of the number and percentage of subjects with TEAEs leading to study treatment discontinuation by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
14.3.1.9	**TEAEs Leading to Death by System Organ Class and Preferred Term (Safety Set)** Tabulation of the number and percentage of subjects with TEAEs leading to death by MedDRA system organ class and preferred term. The number of events will also be shown.	**SAF**	**AET003**
LABORATORY DATA			
14.3.2.1	**Haematology: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of haematology results and changes from baseline by treatment, parameter and analysis visit. Table sorted first by parameter, then by analysis visit. Each parameter will begin on a new page.	**SAF**	**LBT001**
14.3.2.2	**Haematology: Shift from Baseline (Safety Set) [KFR]** Shift table of the abnormality at each analysis visit versus the baseline abnormality per parameter. Each parameter will begin on a new page.	**SAF**	**LBT005**

Number	Title	Analysis Set	TLFs Library Template Number
14.3.2.3	**Biochemistry: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of biochemistry results and changes from baseline by treatment, parameter and analysis visit. Table sorted first by parameter, then by analysis visit. Each parameter will begin on a new page.	**SAF**	**LBT001**
14.3.2.4	**Biochemistry: Shift from Baseline (Safety Set) [KFR]** Shift table of the abnormality at each analysis visit versus the baseline abnormality per parameter. Each parameter will begin on a new page.	**SAF**	**LBT005**
VITAL SIGNS			
14.3.3.1	**Vital Signs and Oxygen Saturation: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of vital signs and oxygen saturation actual values and changes from baseline per parameter and analysis time-point. Table sorted by analysis time-point. Each parameter will begin on a new page.	**SAF**	**VST001**
14.3.3.2	**Blood Pressure: Summary of Abnormal Changes from Baseline (Safety Set) [KFR]** Tabulation of the blood pressure abnormalities as defined in section 3.3.2 at each post-baseline analysis time point and at the worst-case analysis time point per parameter. Table sorted by analysis time point. Each parameter will begin on a new page. Only post-baseline analysis time points are shown.	**SAF**	**VST004**
ECG			
14.3.4.1	**12-Lead ECG: Summary of Actual Values and Changes from Baseline (Safety Set) [KFR]** Descriptive statistics of continuous 12-lead ECG (HR, PR, QRS, QTcF) actual values and changes from baseline per parameter and analysis time point. Table sorted by analysis time point. Each parameter will begin on a new page.	**SAF**	**EGT002**
14.3.4.2	**QTcF: Abnormalities (Safety Set)** Tabulation of the abnormalities as defined in section 3.4.2 at each post-dose analysis time point and at the worst-case analysis time-point. Table sorted by analysis time point. Only baseline and post-dose analysis time points are shown.	**SAF**	**EGT007**
14.3.4.3	**QTcF: Abnormal Changes from Baseline (Safety Set) [KFR]** Tabulation of the QTcF change abnormalities as defined in section 3.4.2 at each post-baseline analysis time point and at the worst-case analysis time point. Table sorted by analysis time point. Only post-baseline analysis time points are shown.	**SAF**	**EGT008**
LUNG FUNCTION			
14.3.5.1	**Spirometry: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of spirometry parameters actual values and changes from baseline per parameter and analysis time point. Table sorted by analysis time point. Each parameter will begin on a new page.	**SAF**	**TPT001**

Number	Title	Analysis Set	TLFs Library Template Number
14.3.5.2	**Spirometry: Summary of Relative Changes from Baseline (Safety Set) [KFR]** Descriptive statistics of relative changes from baseline in spirometry results per parameter and analysis time point. Table sorted by analysis time point. Only post-baseline analysis time points are shown.	**SAF**	**TPT004**
14.3.5.3	**Diffusing Capacity: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of diffusing capacity parameters actual values and changes from baseline per parameter and analysis time point. Table sorted by analysis time point. Each parameter will begin on a new page.	**SAF**	**TPT001**
SYSTEMIC MARKERS			
14.3.6.1	**Systemic Markers: Summary of Actual Values and Changes from Baseline (Safety Set)** Descriptive statistics of systemic markers actual values and changes from baseline per parameter and analysis time-point. Table sorted by analysis time-point. Each parameter will begin on a new page. Note: if systemic reactions are detected in less than 3 subjects, this table will be generated without results. Instead, an informative message will be printed in this output. Template VST001 is used, using the systemic markers.	**SAF**	**VST001**
OTHER VARIABLES			
TG2 IN PLASMA			
14.3.7.1	**TG2 in Plasma: Summary of Actual Values and Changes from Baseline (Safety Set) [KFR]** Descriptive statistics of TG2 plasma levels actual values and changes from baseline per parameter and analysis time-point. Table sorted by analysis time-point. Template VST001 is used, using TG2 plasma levels instead.	**SAF**	**VST001**

9.2 LISTINGS

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

Number	Title	Analysis Set	TLFs Library Template Number
16.2.2.2	**Important Protocol Deviation (Randomised Set)**	**RND**	**DVL002**
	Listing of all important protocol deviations information. Template DLV002 is used, excluding the 'Category' column.		
16.2.2.3	**Restrictions (Randomised Set)**	**RND**	
	Listing of all restrictions data available in the eCRF.		
16.2.3.1	**Analysis Set Disposition (Randomised Set)**	**RND**	**DSL006**
	Listing of all subjects and analysis set indicators.		
16.2.3.2	**Subjects Excluded from Safety/PK Set (Randomised Set)**	**RND**	**DSL007**
	List of all subjects that were excluded from SAF/PK/PD.		
16.2.4.1	**Demographic Characteristics (Randomised Set)**	**RND**	**DML001**
	Listing of all demographic parameters		
16.2.4.2	**IPF History (Randomised Set)**	**RND**	**SCL001**
	Listing of all baseline disease characteristics. Adjust the columns of SCL001 according to the available IPF history data.		
16.2.4.3	**Serology at Screening (Randomised Set)**	**RND**	**SCL002**
	Listing of all results of serology tests done at screening		
16.2.4.4	**Ethanol, Urine Drug Screen and Cotinine Tests (Randomised Set)**	**RND**	**SCL002**
	Listing of all results of urine drug screen tests performed For layout purposes, template SCL003 could be used instead.		
16.2.4.5	**Smoking Status (Randomised Set)**	**RND**	**SUL001**
	Listing of all smoking data available in the eCRF		
16.2.4.6	**Medical/Surgical History (Randomised Set)**	**RND**	**MHL001**
	Listing of the medical history data findings available in the eCRF		
16.2.4.7	**Concomitant Diseases (Randomised Set)**	**RND**	**MHL002**
	Listing of the concomitant diseases data findings available in the eCRF		
16.2.4.8	**Procedures (Randomised Set)**	**RND**	**PRL001**
	Listing of all data on prior, maintained and concomitant procedures		
16.2.4.9	**Medications (Randomised Set)**	**RND**	**CML001**
	Listing of all data on prior, maintained and concomitant medications		
16.2.4.10	**Comments (Randomised Set)**	**RND**	**COL001**
	Listing of all remarks and comments written in the eCRF		
16.2.5.1	**Exposure (Randomised Set)**	**RND**	
	Listing of all data related to exposure		

Number	Title	Analysis Set	TLFs Library Template Number
PHARMACOKINETICS			
16.2.5.2	**Actual Sampling Times and Serum Concentrations (PK Set)** Listing per subject, dose level, and planned time point of actual blood sampling times and serum concentrations (actual date of sampling and end of infusion, 'theoretical sampling time after windowing' (if different from scheduled one), and remarks (if applicable) will be presented too). Exclusions of concentrations will be marked.	**PK**	**PCL001**
16.2.5.3	**PK Data Excluded from PK Analysis (PK Set)** Listing per subject, dose level and PK parameter or concentration time point of the subjects that are excluded from PK set and/or PK data that is excluded from PK analysis, with the reason for exclusion. Exclusions that are due to an IDV are marked too.	**PK**	
IMMUNOGENICITY			
16.2.6.1	**ADA Responses (Safety Set)** Listing for ADA positive subjects presenting at least the following information: subject identifier, actual dose administered, pre-existing ADA (i.e., baseline ADA status and titer), peak ADA titer and corresponding actual and nominal time point, nAb status at nominal time point of peak ADA, time to onset of ADA, ADA status and titer at final ADA assessment / last available time point, pre-dose TG2 level, TG2 level at nominal time point of peak ADA, CHF10067 $AUC_{0\text{-}inf}$; $AUC_{0\text{-}t}$, clearance	**SAF**	
SAFETY			
ADVERSE EVENTS			
16.2.7.1	**Pre-Treatment Adverse Events (Randomised Set)** Listing of all pre-treatment AE information collected in the eCRF and of the onset day and duration. All information of one AE will be presented on the same line.	**RND**	**AEL001**
16.2.7.2	**Treatment Emergent Adverse Events (Randomised Set)** Listing of all AE information collected in the eCRF and of the phase dates and onset day and duration. All information of one AE will be presented on the same line.	**RND**	**AEL002**
16.2.7.3	**Serious Treatment Emergent Adverse Events (Randomised Set)** Same as listing 16.2.7.2, but listing serious TEAEs only	**RND**	**AEL002**
16.2.7.4	**Non-Serious Treatment Emergent Adverse Events (Randomised Set)** Same as listing 16.2.7.2, but listing non-serious TEAEs only	**RND**	**AEL002**
16.2.7.5	**Adverse Drug Reactions (Randomised Set)** Same as listing 16.2.7.2, but listing ADRs only	**RND**	**AEL002**
16.2.7.6	**Serious Adverse Drug Reactions (Randomised Set)** Same as listing 16.2.7.2, but listing serious ADRs only	**RND**	**AEL002**
16.2.7.7	**Grade 3 or 4 Treatment Emergent Adverse Events (Randomised Set)** Same as listing 16.2.7.2, but listing grade 3 or 4 TEAEs only	**RND**	**AEL002**

Number	Title	Analysis Set	TLFs Library Template Number
16.2.7.8	**Treatment Emergent Adverse Events Leading to Study Treatment Discontinuation (Randomised Set)** Same as listing 16.2.7.2, but listing TEAEs leading to study treatment discontinuation only	**RND**	**AEL002**
16.2.7.9	**Treatment Emergent Adverse Events Leading to Death (Randomised Set)** Same as listing 16.2.7.2, but listing TEAEs leading to death only	**RND**	**AEL002**
16.2.7.10	**Immediate Hypersensitivity Reactions (Randomised Set)** Listing IHR along with associated signs/symptoms and suspected anaphylaxis and a reference to the related adverse event(s).	**RND**	**AEL002**
16.2.7.11	**Physical Examination Abnormalities (Randomised Set)** Listing of all data on abnormal physical examinations findings	**RND**	**PEL001**
LABORATORY DATA			
16.2.8.1	**Laboratory Results: Haematology Full Listing (Randomised Set)** 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. Treatment-emergent abnormalities will be flagged.	**RND**	**LBL001**
16.2.8.2	**Laboratory Results: Haematology Abnormalities (Randomised Set)** Same as listing 16.2.8.1, but listing abnormal results only	**RND**	**LBL001**
16.2.8.3	**Laboratory Results: Biochemistry Full Listing (Randomised Set)** Same as listing 16.2.8.1, but listing biochemistry results instead	**RND**	**LBL001**
16.2.8.4	**Laboratory Results: Biochemistry Abnormalities (Randomised Set)** Same as listing 16.2.8.3, but listing abnormal results only	**RND**	**LBL001**
16.2.8.5	**Laboratory Results: Urinalysis (Randomised Set)** 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.	**RND**	**LBL001**
16.2.8.6	**Laboratory Results: Pregnancy Test (Randomised Set)** Listing of all serum and urine pregnancy results.	**RND**	**LBL005**
VITAL SIGNS			
16.2.9.1	**Vital Signs: Full Listing (Randomised Set)** Listing of all vital signs results, including oxygen saturation. The values will be shown, as well as changes from baseline and change abnormalities. Treatment-emergent abnormalities will be flagged.	**RND**	**VSL002**

Number	Title	Analysis Set	TLFs Library Template Number
ECG			
16.2.10.1	**Local 12-Lead ECG: Full Listing (Randomised Set)**	**RND**	**EGL001**
	Listing of all triplicate/single local 12-lead ECG results and the corresponding interpretation. The values will be shown, as well as changes from baseline and abnormality categories (for QTcF). Treatment-emergent abnormalities will be flagged.		
16.2.10.2	**Local 12-Lead ECG: Abnormalities (Randomised Set)**	**RND**	**EGL001**
	Same as listing 16.2.10.1 but listing abnormal results only. Note: results are considered abnormal when the interpretation by the investigator is abnormal.		
LUNG FUNCTION			
16.2.11.1	**Lung Function: Full Listing (Randomised Set)**	**RND**	**VSL002**
	Listing of all lung function results. The values will be shown, as well as changes and relative changes from baseline. Template VSL002 is used, presenting the lung function parameters instead.		
SYSTEMIC MARKERS			
16.2.12.1	**Systemic Markers: Full Listing (Randomised Set)**	**RND**	**VSL001**
	Listing of all systemic markers. The values will be shown, as well as changes from baseline. Template VSL001 is used, presenting the systemic markers instead.		
OTHER VARIABLE			
TG2 IN PLASMA			
16.2.13.1	**TG2 in Plasma: Full Listing (Randomised Set)**	**RND**	**VSL001**
	Listing of TG2 levels in plasma. The values will be shown, as well as changes from baseline. Template VSL001 is used, presenting the TG2 plasma levels instead.		

9.3 FIGURES

Number	Title	Analysis Set	TLFs Library Template Number
PHARMACOKINETICS			
14.2.2.1	**Mean CHF10067 Serum Concentration vs. Time Profiles (PK Set)** Mean (±SD, for linear scale) CHF10067 serum concentration vs. time profiles. In linear-linear and log-linear scales, with a different plot symbol, colour, and line pattern for each dose level.	**PK**	**TPF005**
14.2.2.2	**Dose Proportionality Assessment (PK Set)** Individual and geometric mean PK parameter (log values) vs. log dose with regression line together with a 90% confidence band.	**PK**	
16.2.5.1	**Individual CHF10067 Serum Concentration vs. Time Profiles, per Dose Level (PK Set)** Individual CHF10067 serum concentration vs. time profiles, per dose level, all subjects on the same graph. One graph per dose level. In linear-linear and log-linear scales with a different plot symbol and line pattern for each subject, and a different colour for ADA positivity and negativity.	**PK**	**TPF006**
IMMUNOGENICITY			
14.2.4.1	**Mean CHF10067 Serum Concentration vs. Time Profiles by subject ADA status (PK Set)** Mean (±SD, for linear scale) CHF10067 serum concentration vs. time profiles. In linear-linear and log-linear scales, with a different plot symbol for each dose level and ADA subject status. Note: if the number of ADA+ subjects is less than 3, this figure will be generated without results. Instead, an informative message will be printed in this output.	**PK**	**TPF005**
VITAL SIGNS			
14.3.3.1	**Mean Change from Baseline in Vital Signs and Oxygen Saturation (Safety Set)** Graph of mean changes and their 95% confidence interval, with "time" on the horizontal axis and a different plot symbol for each treatment. Each parameter will be presented separately.	**SAF**	**TPF001**
16.2.9.1	**Individual Change from Baseline in Vital Signs and Oxygen Saturation (Safety Set)** Graph of individual changes from baseline, with "time" on the horizontal axis and a different colour or plot symbol for each subject. Each treatment and parameter will be presented separately.	**SAF**	**TPF002**
ECG			
14.3.4.1	**Mean Change from Baseline in Heart Rate and QTcF (Safety Set)** Graph of mean changes, with "time" on the horizontal axis and a different plot symbol for each treatment. Each parameter will be presented separately.	**SAF**	**TPF001**

Number	Title	Analysis Set	TLFs Library Template Number
16.2.10.1	**Individual Change from Baseline in 12-Lead ECG (Safety Set)**	**SAF**	**TPF002**
	Graph of individual changes from baseline, with "time" on the horizontal axis and a different colour or plot symbol for each subject. Each treatment and parameter will be presented separately.		
LUNG FUNCTION			
14.3.5.1	**Mean Absolute Change from Baseline in Spirometry (Safety Set)**	**SAF**	**TPF001**
	Graph of mean absolute changes, with "time" on the horizontal axis and a different plot symbol for each treatment.		
14.3.5.2	**Mean Relative Change from Baseline in Spirometry (Safety Set)**	**SAF**	**TPF001**
	Graph of mean relative changes, with "time" on the horizontal axis and a different plot symbol for each treatment.		
14.3.5.3	**Mean Absolute Change from Baseline in Diffusing Capacity (Safety Set)**	**SAF**	**TPF001**
	Graph of mean absolute and relative changes, with "time" on the horizontal axis and a different plot symbol for each treatment.		
OTHER VARIABLE			
TG2 IN PLASMA			
14.3.6.1	**Mean Actual Values of TG2 in Plasma (Safety Set)**	**SAF**	**TPF001**
	Graph of mean actual values, with "time" on the horizontal axis and a different plot symbol for each treatment.		
16.2.11.1	**Individual Actual Values of TG2 in Plasma (Safety Set)**	**SAF**	**TPF002**
	Graph of individual actual values, with "time" on the horizontal axis and a different colour or plot symbol for each subject. ADA positivity/negativity will be shown using different colours. Each treatment will be presented in a different plot.		

10. APPENDICES

10.1 SAS CODE

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

Dose proportionality on CHF10067 serum PK parameters:

```
proc mixed data=dataset;
      by param
      model logPK = logDOSE;
      estimate 'slope' logDOSE 1 / cl alpha = 0.1;
      ods output estimates = diff;
run;
```

Notes:

- Dataset: analysis dataset of PK parameters. One record per subject per parameter;
- Param (character): PK parameter name and/or identifier;
- LogPK (numeric): log value of PK parameter;
- LogDOSE (numeric): log value of doses (1000mg; 2000mg; 3000mg).

10.2 SCHEDULE OF ASSESSMENTS

	Screening (Days -28 to -3)	Treatment Period					Early Termination
		Day 1	Day 2	Days 5 and 7 (± 1 day)	Days 14, 28, and 56 (± 2 days)	Day 84 (± 2 days)	
Informed consent	X						
Randomisation		X					
Ambulatory visit	X	X	X	X	X	X	X
Treatment Intake							
CHF10067 or placebo administration [a]		X					
Subject Health Evaluation							
In/Ex criteria	X	X [b]					
Medical history	X						
Demographic data	X						
Height and weight	X						
Alcohol breath test	X						
Physical examination	X	X	X	X			X
Abbreviated physical examination					X	X	
Adverse events recording	X	X	X	X	X	X	X
Restrictions	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X
Safety Assessment in Blood							
Fasting clinical chemistry	X	X (pre-dose)	X	X [h]	X	X	X
Haematology	X	X (pre-dose)	X	X [h]	X	X	X
Fasting glucose	X	X (pre-dose)	X	X [h]	X	X	X
FSH (post-menopausal female subjects) and/or pregnancy test (females of childbearing potential)	X						
Serology	X						
Markers for evaluation of immediate hypersensitivity reactions		X [f]					
ADA and nAb (in case of positive ADA)		X (pre-dose)			X	X	X
Other Assessments							
TG2 levels		X (pre-dose)			X	X	
Naso-absorption samples		X (pre-dose)			X [i]		

Proteomic sample (serum)		X (pre-dose)			X [i]		
Proteomic sample (plasma)		X (pre-dose)					
Optional transcriptomic samples		X (pre-dose)			X [i]		
Assessments in Urine							
Urinalysis	X						
Drug screen	X						
Cotinine	X						
Pregnancy test (females of childbearing potential)		X			X [j]	X	
Pharmacokinetic in Blood [c]							
CHF10067		X	X	X	X	X	
Safety Cardiac Assessments							
Vital signs [d]	X	X	X	X	X	X	X
Local 12-lead ECG [e]	X	X	X	X	X	X	X
Safety Pulmonary Assessments							
Oxygen saturation [g]	X	X	X	X	X	X	X
Spirometry	X			X [k]	X [k]	X	X
Diffusing capacity	X				X [l]	X	X

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; FSH = follicle-stimulating hormone; In/Ex = inclusion/exclusion; nAb = neutralising antibody; TG2 = transglutaminase 2.

Footnotes for Evaluation Schedule:

[a] Special attention will be given to immediate hypersensitivity reactions and monitoring up to 8 hours post-dose is required. If the subject has no symptoms, he/she can be discharged. If the subject has symptoms, he/she may remain overnight. An overnight stay is also permitted for logistical reasons and/or site's/subject's preference.

[b] Specific In/Ex criteria will also be checked pre-dose on Day 1 according to study schedule and In/Ex criteria.

[c] Pharmacokinetic blood samples for serum CHF10067 will be collected at the following timepoints: pre-dose (within 75 minutes from start of infusion), at the end of infusion, and 2, 4, 8, and 20 hours after the end of the infusion and 5, 7, 14, 28, 56 and 84 days post-dose.

[d] Vital signs (blood pressure, pulse rate, respiratory rate, body temperature): systolic and diastolic blood pressure will be evaluated in duplicate after 5 minutes in supine position. Vital signs will be measured at screening and at the following timepoints: pre-dose, every 15 minutes during the infusion (e.g., 15, 30, 45, 60, 75, 90, 105, etc.), at the end of the infusion and 30 min, 1, 2, 3, 4, 6, 8, and 20 hours after the end of the infusion and 5, 7, 14, 28, 56, and 84 days post-dose.

[e] Local 12-lead ECG: a triplicate ECG will be performed to assess eligibility and a single ECG will be evaluated at all other timepoints. Electrocardiograms will be measured at screening and at the following timepoints: pre-dose on Day 1, and Days 2, 7, 28, and 84.

[f] Markers for evaluation of immediate hypersensitivity reactions: pre-dose for all subjects. If required (based on subject experiencing symptoms of immediate hypersensitivity reactions), blood samples will be collected at 1 and 2 hours after the onset of the event.

[g] Oxygen saturation: will be measured at screening and continuous monitoring will occur from pre-dose to 10 hours post-dose at the following timepoints: pre-dose, every 15 minutes during the infusion (e.g., 15, 30, 45, 60, 75, 90, 105, etc.), at the end of the infusion and 30 min, 1, 2, 3, 4, 6, 8, hours after the end of infusion. Oxygen saturation will also be measured at 20 hours after the end of infusion, and 5, 7, 14, 28, 56 and 84 days post-dose.

[h] Clinical laboratory evaluations will be conducted on Day 7 only.

[i] Sample(s) will be collected on Day 14 only.

[j] Pregnancy test conducted on Days 28 and 56.

[k] Spirometry conducted on Days 7, 28, and 56 only.

[l] Diffusing capacity conducted on Days 28 and 56 only.

10.3 DICTIONARY VERSIONS

Data	**Dictionary**
Adverse Events	MedDRA version 25.0
Concomitant Therapy	WHO-DD version 01 Mar 2022 (Global) Format B3
Anatomical-Therapeutic-Chemical (ATC) selection	WHO-DD version 01 Mar 2022 (Global) Format B3
Medical History	MedDRA version 25.0
Procedures	MedDRA version 25.0
Clinical Events	MedDRA version 25.0