STATISTICAL ANALYSIS PLAN

CS-1103-01

A Phase 1a, Randomized, Double-Blind, Placebo-Controlled, Single Center Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of CS-1103 Following Single, Ascending Intravenous Dose Administration in Healthy Participants

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 09APR2024) for Protocol CS-1103-01.

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates V1.0 (Dated 09APR2024) for Protocol CS-1103-01.

Upon review of this document, the undersigned approves this version of the Output Templates, authorizing that the content is acceptable for the reporting of this study.

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
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TABLE OF CONTENTS

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LIST OF ABBREVIATIONS

$A_{e(t1-t2)}$	By-interval amount excreted in urine during the pooled collection interval from t1 to t2.
$A_{e(0-last)}$	Cumulative amount excreted in urine during the pooled collection intervals.
AE	Adverse event
ASQ	Anxiety Symptoms Questionnaire
AUC	Area under the plasma concentration-time curve
$AUC_{(0-inf)}$	Area under the plasma concentration-time curve from time zero (end of the 10-minute IV infusion) extrapolated to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{(0-last)}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
C_{EOI}	Concentration at the end of the 10-minute intravenous infusion
CL	Systemic clearance
CL_r	Renal clearance
COVID-19	Coronavirus disease 2019
C_0	Plasma drug concentration extrapolated to end of injection in the animal studies
C_{max}	Maximum concentration, obtained directly from the observed concentration versus time data
CV%	Coefficient of variation
dECG	Digital electrocardiogram
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study

$f_{e(0\text{-last})}$	Cumulative fraction of dose excreted in urine during the pooled collection intervals
$f_{e(t1\text{-}t2)}$	By-interval fraction of dose excreted in urine during the pooled collection interval from t1 to t2
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
IV	Intravenous
Max	Maximum
Min	Minimum
N	Total number of subjects
n	Number of subjects in each category
λ_z	Elimination rate constant
PK	Pharmacokinetic
PT	Preferred Term
QTcF	QT corrected for heart rate by Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SoA	Schedule of activities
SOC	System Organ Class
SRC	Safety Review Committee
$t_{½}$	Half-life
t_{max}	Time to C_{max}
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady-state following intravenous dosing

[redacted]

V_z	Volume of distribution following intravenous dosing
WOCBP	Women of childbearing potential

[redacted]

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of safety and pharmacokinetic data for Protocol CS-1103-01. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. Presentation of Holter data and assessment of concentration-QT relationship will be described in a separate analysis plan.

This SAP is based on protocol version 3.0, amendment 2 dated 02 October 2023.

2. STUDY OBJECTIVES

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of CS-1103, administered by IV infusion	Standard safety and tolerability parameters but not limited to: • Adverse Events • Vital signs (blood pressure, pulse rate, respiratory rate, oxygen saturation, and body temperature) • Digital 12-lead ECGs/Holter • Laboratory parameters (clinical chemistry, hematology, coagulation, urinalysis)
Secondary	
• To characterize the PK of CS-1103, administered by IV infusion	Plasma and urine PK parameters including but not limited to: • C_{max}, t_{max}, C_{EOI}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$, $t_{1/2}$, λ_z, CL, V_{ss}, and V_z • By-interval and cumulative CS-1103 excretion in urine (A_e and f_e) • CL_r

[redacted]

Objectives	Endpoints
Exploratory	
• To explore the relationship between CS-1103 plasma concentrations and changes in QT intervals during dosing, if any	• Concentration-QT correlation performed on baseline-corrected QTcF time-matched with PK. Concentration-QT correlation may be reported separately from the clinical study report

- Abbreviations: AE = adverse event; A_e = amount; AUC = area under the concentration versus time curve; $AUC_{(0\text{-inf})}$ = AUC from time zero extrapolated to infinity; $AUC_{(0\text{-last})}$ = AUC from time zero to the last quantifiable concentration; C_{EOI} = concentration at the end of 10-minute IV infusion; CL = systematic clearance; CL_r = renal clearance; C_{max} = maximum concentration; ECG = electrocardiogram; f_e = fraction; IV = intravenous; λ_z = elimination rate constant; PK = pharmacokinetics; $t_{1/2}$ = half-life; QTcF = QT corrected for heart rate by Fridericia's formula; t_{max} = time to C_{max}; V_{ss} = volume of distribution at steady-state following intravenous dosing; V_z = volume of distribution following intravenous dosing.

3. STUDY DESIGN

3.1. General Description

CS-1103-01 is a Phase 1a, single center, double-blind, placebo-controlled, randomized, single ascending-dose first in-human (FIH) study. All participants will be screened within 28 days of dose administration and participants will check-in to the inpatient clinical research unit (CRU) on their Admission/Day −1. Participants will be randomized on Day −1, the day prior to dosing, after meeting all eligibility criteria. Participants are scheduled to remain in the CRU for up to 48 hours postdose for safety and PK assessments.

Up to 40 healthy participants, aged 18 to 55 years will be randomized.

Up to 5 cohorts of 8 participants (6 active, 2 placebo participants per cohort) will be enrolled with each participant assigned to receive a single dose of CS 1103 or placebo on 1 occasion (Day 1). Note: The dose will be capped at 3000 mg.

- Cohort 1: Dose level 1 (CS-1103 2.7 mg/kg, [redacted]) or placebo ([redacted])
- Cohort 2: Dose level 2 (CS-1103 8.0 mg/kg, [redacted]) or placebo ([redacted])

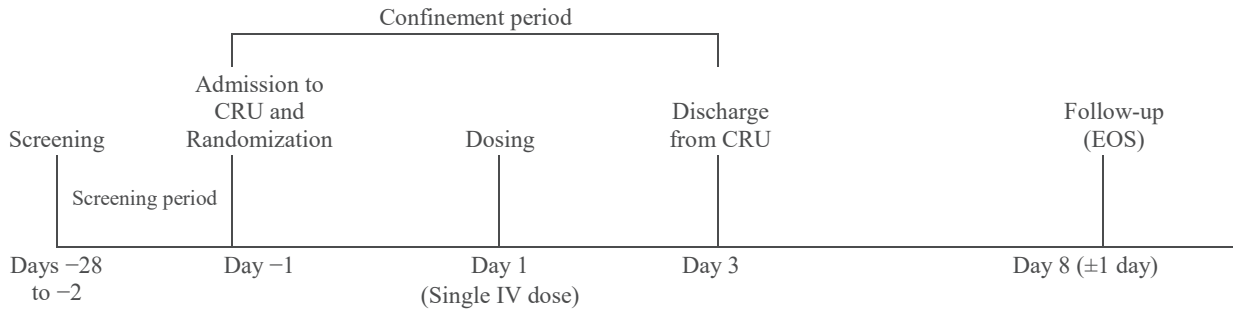
[redacted]

- Cohort 3: Dose level 3 (CS-1103 16.0 mg/kg, [redacted]) or placebo ([redacted])
- Cohort 4: Dose level 4 (CS-1103 26.7 mg/kg, [redacted]) or placebo ([redacted])
- Cohort 5: Dose level 5 (CS-1103 40.0 mg/kg, [redacted]) or placebo ([redacted])

Each cohort duration will be approximately 37 days.

- Screening Period: up to 28 days
- CRU confinement period: 4 days
- Treatment administration: 1 day
- CRU discharge through follow-up/end of study period: 5 days

Table A: Study Schema



Abbreviations: CRU = clinical research unit; EOS = end of study, IV = intravenous.

Note: Admission/Day −1 may span 2 days in the CRU, in that case screening will end on Day −3 for participants with Admission Day spanning 2 days in the CRU.

3.2. Schedule of Events

Schedule of events can be found in Section 1.3 Table 1 of the protocol.

3.3. Changes to Analysis from Protocol

Serious adverse events (SAEs), TEAEs leading to death and TEAEs leading to discontinuation from study will be listed.

[redacted]

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analysis for Safety Review Committee (SRC)
- Final Analysis

4.1. Safety Review Committee

The SRC will review safety results and preliminary plasma PK data. For additional details pertaining to these data reviews and analyses, refer to the SRC Charter. Preliminary PK parameters will be calculated by using available quality-controlled CS-1103 concentrations and scheduled sampling times to support dose-escalation decisions, as applicable.

4.2. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, and Unblinding of Treatment.

5. ANALYSIS SETS

5.1. All Participants Screened Set

The all participants screened set will contain all participants who provide informed consent for this study.

5.2. Safety Analysis Set

The safety analysis set will contain all participants who receive study treatment (CS-1103 or placebo). Participants will be classified according to treatment received.

5.3. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will consist of all participants who receive active study treatment (CS-1103) and

[redacted]

have at least 1 measured plasma or urine concentration at a scheduled PK time after start of dosing for at least 1 PK analyte without protocol deviations or events with potential to affect the pharmacokinetic concentrations. Participants in this population will be used for all PK analyses.

6. GENERAL CONSIDERATIONS

Derivation of the PK parameters will be the responsibility of the clinical pharmacokineticist at IQVIA. The PK and safety summaries, data listings and figures as well as the statistical analysis of the PK variables will be the responsibility of the study biostatistician at IQVIA.

6.1. Summary Statistics

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative safety variables will be summarized using descriptive statistics, including N, n, mean, standard deviation (SD), coefficient of variation (CV%) as appropriate, median, minimum, and maximum values. Geometric mean and geometric CV% will be included for PK parameters, where applicable. CV will not be presented for change from baseline results.

6.2. Treatment Summarization

In general, data will be presented for each active treatment group, with placebo participants from all dose groups combined into a single, overall placebo group. Data for all study participants combined or all active-treated subjects will also be presented when appropriate.

6.3. Precision

Safety variables (ie, clinical laboratory values, vital signs, and ECG intervals), including derivations thereof, will be reported to the same precision as the source data.

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bio-analytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by-participant listings. The rounded derived PK data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK

parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (eg, Cmax) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (eg, tmax) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics, the mean (arithmetic or geometric), standard deviation, standard error and confidence intervals will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place.

6.4. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. It will appear in every listing where an assessment date or event date appears.
Reference start date is defined as the day of study drug administration (Day 1 is the day of study drug administration).

- If the date of the event is on or after the reference date, then:
- Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
- Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.5. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline if the assessment is planned per protocol to take place prior to study treatment administration, otherwise, that measurement will be considered post-baseline. Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline

unless otherwise indicated based on available start date/time combination or collected eCRF information that identifies the individual event/medication as starting prior to study treatment administration.

6.6. Retests, Unscheduled Visits and Early Termination Data

Unscheduled measurements will not be included in post-baseline summary statistics but will contribute to the assessment of clinical outliers where applicable. Early termination results will be recorded as such and included with the end of study summaries.

In the case of a retest of a scheduled assessment, the earliest available measurement for that scheduled time (i.e., the original assessment) will be used for summaries unless flagged as invalid.

Listings will include all scheduled, unscheduled, retest, and early discontinuation data.

6.7. Common Calculations

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

6.8. Software Version

Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 8.3 or higher (Certara, Princeton, New Jersey) or SAS Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). All other derivations, summaries, and listings will be generated using the same version of SAS. Graphics will be prepared using the same version of SAS.

7. STATISTICAL CONSIDERATIONS

7.1. Missing Data

Missing safety data will not be imputed.
Missing PK data will be handled as described in Section 15 of this analysis plan.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The output shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

9. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent will be accounted for in this study. Participant disposition will be tabulated for each study treatment and for all participants combined with the number of participants who are randomly assigned to treatment, dosed, complete the study, prematurely discontinue, and the reason for early discontinuation. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each participant.

Listings of study eligibility with inclusion/exclusion criteria responses, treatment randomization, and study treatment administration will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics such as age, sex, race, ethnicity, height, weight (assessed at Screening), and body mass index (BMI) will be summarized and tabulated by treatment and for all subjects overall. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex, race, and ethnicity. No statistical testing will be carried out for demographic or other baseline characteristics.

Individual subject demographics and results from viral serology, drug of abuse/alcohol screening, COVID-19 testing, pregnancy tests, and follicle-stimulating hormone (FSH) test will be presented in listings.

11. PROTOCOL DEVIATIONS

11.1. Deviations Related to Study Conduct

A deviation from a protocol occurs when Investigator site staff or a study participant does not adhere to the protocol's stipulated requirements, whether inadvertently or planned. Protocol deviations will be listed and will include a classification of minor or major, as determined by clinical staff.

11.2. Deviations Related to PK Analysis

Changes to the procedures or events, which may impact the quality of the PK data, will be considered important protocol deviations and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing on the day of PK sampling. In the case of an important protocol deviation or event, PK data collected during the affected treatment period will be excluded from the study results. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered important protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviations from blood collection times.

12. SURGICAL AND MEDICAL HISTORY

Medical History coded using Medical Dictionary for Regulatory Activities (MedDRA), the latest version, will be listed for the safety analysis set.

13. MEDICATIONS

Medication usage, coded using the World Health Organization (WHO) Drug Dictionary, the latest version, will be categorized as Prior or Concomitant and listed for the safety analysis set:

- 'Prior' medications are medications which started and stopped prior to the administration of study medication.
- 'Concomitant' medications are medications which were taken during the treatment period, or specifically:
    - started on or after the administration of study treatment

[redacted]

- started prior to the administration of study medication and were continued after the administration of study treatment

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified as concomitant.

14. STUDY MEDICATION EXPOSURE

Study treatment administration will be listed.

15. PHARMACOKINETIC ANALYSIS

15.1. Plasma Concentration Data

Participants with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.
A listing of PK blood sample collection times as well as derived sampling time deviations will be provided.

Plasma concentrations will be summarized using descriptive statistics for each active treatment using the PK Analysis Set. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics.

A subject listing of all concentration-time data for each treatment will be presented. Figures of arithmetic mean concentration-time data (±SD, as appropriate) will be presented for each treatment on linear and semi-logarithmic scales. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales.

15.2. Pharmacokinetic Parameters

For PK parameter calculations, predose samples that are BLQ or missing will be assigned a numerical value of zero. Any anomalous concentration values observed at predose will be identified in the study report and used for the computation of PK parameters. Pharmacokinetic parameters will be computed if the anomalous concentration is not greater than 5% of the observed maximum concentration (C_{max}). If the anomalous concentration is greater than 5%

of C_{max}, the PK parameters for the given subject will be calculated and reported in the listing, but excluded from statistical summaries and analyses.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.
The following plasma PK parameters will be estimated for CS-1103 by non-compartmental methods using actual elapsed time from the end of infusion. A minimum of 3 quantifiable postdose concentrations will be required for calculation of PK parameters.

C_{max}	Maximum concentration, obtained directly from the observed concentration versus time data
C_{EOI}	Concentration at the end of the 10-minute IV infusion
t_{max}	Time to C_{max}
$AUC_{(0\text{-inf})}$	Area under the plasma concentration-time curve from time zero (end of the 10-minute IV infusion) extrapolated to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{(0\text{-last})}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
CL	Systemic clearance, calculated as dose divided by $AUC_{(0\text{-inf})}$
V_z	Volume of distribution following intravenous dosing (L), calculated as dose divided by $[\lambda_z \cdot AUC_{(0\text{-inf})}]$
V_{ss}	Volume of distribution at steady state following intravenous dosing (L), calculated as mean residence time (MRT) extrapolated to infinity multiplied by clearance

[redacted]

	(MRT_{inf}*CL)
$t_{1/2}$	Apparent terminal half-life (h), determined as $\ln 2/\lambda_z$.
λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. A minimum of 3 data points will be used for determination.

Dose normalized C_{max}, $AUC_{(0\text{-}inf)}$, and $AUC_{(0\text{-}last)}$ will also be determined. Additional plasma parameters may be calculated if deemed appropriate.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized.

$t_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine λ_z.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used for determination.
Rsq adj	Goodness of fit statistic for calculation of λ_z (Regression coefficient). If the Rsq_adj is less than 0.800, then λ_z and associated parameters ($AUC_{(0\text{-}inf)}$, t1/2, CL, and Vz (Vss)) will be listed but not included in summary and inferential statistics.
$\%AUC_{ex}$	Percentage of $AUC_{(0\text{-}inf)}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{(0\text{-}inf)}\times 100]$. If the $\%AUC_{ex}$ is greater than 30% of $AUC_{(0\text{-}inf)}$, then $AUC_{(0\text{-}inf)}$, CL, V_z, and V_{ss} will be listed but not included in summary and inferential statistics.

Pharmacokinetic parameters will be summarized by treatment using descriptive statistics. Geometric mean will not be calculated for t_{max}. A subject listing of individual PK parameters for each treatment will be provided.

Scatter plots of individual values and geometric means of PK parameters, $AUC_{(0\text{-}inf)}$ (or $AUC_{(0\text{-}last)}$, if $AUC_{(0\text{-}inf)}$ is not calculable in most participants (75% or more per dose level)), C_{max} (and C_{EOI}, if appropriate) as well as dose-normalized exposure parameters versus dose will be presented.

The dose proportionality of the primary PK parameters, $AUC_{(0\text{-}inf)}$ (or $AUC_{(0\text{-}last)}$, if $AUC_{(0\text{-}inf)}$ is not calculable in most participants (75% or more per dose level)) and C_{max}, over the administered dose range will be investigated using the following power model:

[redacted]

log (PK parameter) = a + b * log (dose)
where ‘a’ is the intercept and ‘b’ is the slope.

The power model parameters will be estimated using least-squares (LS) regression or an equivalent method. A minimum of 3 values per dose must be available for a given parameter to estimate dose proportionality with the power model. Dose proportionality analysis will not be performed for the secondary PK parameters.

15.3. Analysis of Urine PK Data

A listing of individual PK urine sample collection start and stop dates/times as well as urine volumes will be provided for each urine collection. Amounts of urine excreted over each planned collection interval for each treatment will be summarized using descriptive statistics for the PK Analysis Set.

The following parameters will be calculated from the urine data:

$A_{e(t1-t2)}$	By-interval amount excreted in urine during the pooled collection interval from t1 to t2 over the following intervals: 0-2 hr, 2-4 hr, 4-6 hr, 6-12 hr, 12-24 hr, 24-36 hr and 36-48 hr
$A_{e(0-last)}$	Cumulative amount excreted in urine during the pooled collection intervals
$f_{e(t1-t2)}$	By-interval faction of dose (reported as percent) excreted in urine during the pooled collection interval from t1 to t2
$f_{e(0-last)}$	Cumulative fraction of dose (reported as percent) excreted in urine during the pooled collection intervals
CL_r	Renal clearance (L/h), calculated as $A_{e(0-last2)}$ divided by $AUC_{(0-last)}$.

Urine PK parameters will be summarized by treatment using descriptive statistics for the PK Analysis Set. A participant listing of individual urine PK parameters for each treatment will be provided. Geometric mean and individual cumulative percent CS-1103 excreted in urine versus time curves by dose will also be presented on linear scale.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified within the relevant section.

16.1. Adverse Events

Adverse Events (AEs) will be coded Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, the latest version.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the date/time of study treatment administration.

Pretreatment AEs are defined as AEs occurring and ending prior to dosing or occurring prior to dosing and continuing into the treatment period without worsening. These events will be presented in the listings only and are not included in the tabular summary of AEs. See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.

16.1.1. All TEAEs

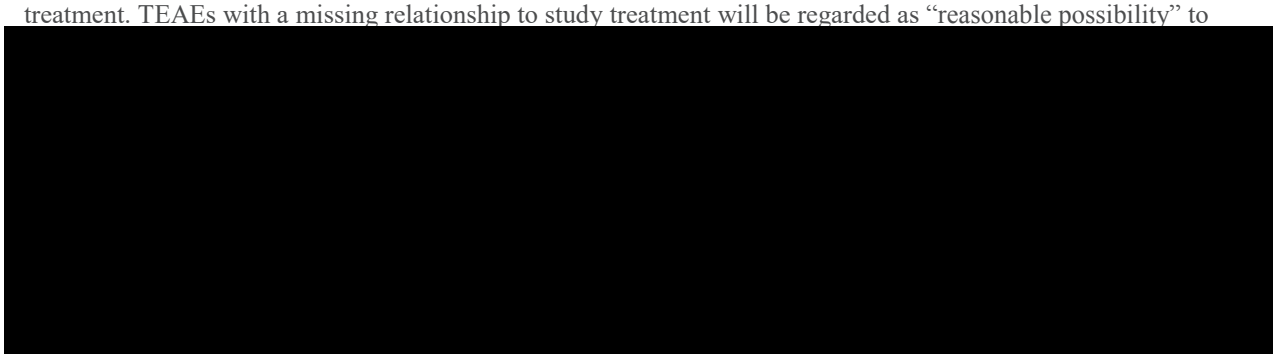
Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication.

16.1.1.1. SEVERITY

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the study treatment administration with a missing severity will be classified as severe. If a participant reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

16.1.1.2. RELATIONSHIP TO STUDY MEDICATION

Relationship, as indicated by the Investigator, is classed as “reasonable possibility” or “not a reasonable possibility”. A “related” TEAE is defined as a TEAE with a relationship to study treatment as “reasonable possibility” to study treatment. TEAEs with a missing relationship to study treatment will be regarded as “reasonable possibility” to



study treatment. If a participant reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

All AE tabulations will be performed by treatment, including all placebo and active-treated subjects combined when applicable. Incidence of TEAEs will be tabulated by the following:

- An overall summary across all SOC and PT, any TEAE, any related TEAE, severe, serious, leading to study discontinuation, leading to death, and TEAEs by maximum severity
- By SOC and PT
- By SOC and PT for related TEAEs
- By SOC, PT and Maximum Severity
- By SOC, PT and Maximum Severity for related TEAEs

16.1.2. TEAEs Leading to Discontinuation from Study

Treatment emergent adverse events leading to discontinuation from study will be identified by using the response to the question “Did the AE cause the subject to discontinue from the study?” on the AE page of the electronic Case Report Form (eCRF) and listed

16.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as “Serious” on the Adverse Events page of the (e)CRF and will be listed.

16.2. Deaths

If any participants die during the study as recorded on the “deaths” page of the (e)CRF, the information will be presented in a data listing.

16.3. Laboratory Evaluations

Laboratory results, with units provided by the local laboratory, will be included in the reporting of this study for hematology, clinical chemistry, coagulation, and urinalysis. A list of laboratory assessments to be included in the outputs is included in Table 5 of the protocol.

Protocol-specified clinical laboratory tests will be listed and summarized using descriptive statistics. Clinical laboratory data collected during study conduct, which were not required per protocol, such as for special testing to evaluate an AE, will be listed separately and not summarized.

Quantitative laboratory measurements reported as '< X', i.e., below the lower limit of quantification, or '> X', i.e., above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e., as '< X' or '> X' in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit and treatment (for quantitative measurements)
- Shift from baseline according to normal range criteria at each post-baseline visit
- Listing of laboratory results outside the normal range

16.3.1. Laboratory Reference Ranges

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges by the laboratory vendor and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

Clinical laboratory reference/normal ranges will be listed.

16.4. ECG Evaluations

The following ECG data will be reported for this study: PR, QRS, QT, QTcF, and HR. Replicate measurements will be averaged for use in summary tables.

Assessment of ECG (Investigator's judgment) for each parameter will be recorded as following:

- Normal
- Abnormal, Not Clinically Significant (NCS)
- Abnormal, Clinically Significant (CS)

[redacted]

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit, timepoint and treatment
- Number (%) of subjects with clinically noteworthy values postdose
- Listing of subjects with clinically noteworthy values

16.4.1. Clinically Noteworthy ECG Criteria

Clinically noteworthy quantitative ECG measurements will be identified in accordance with the following criteria:

- Absolute values for QTcF will be classified as:
  - 450 msec and <=480 msec
  - > 480 msec and <=500 msec
  - > 500 msec
- Change from Baseline for QTcF will be classified as:
  - Increase from baseline >30 msec and <=60 msec
  - Increase from baseline >60 msec

16.5. Vital Signs

The following Vital Signs measurements will be reported for this study: systolic and diastolic blood pressure, pulse rate, respiratory rate, heart rate, oxygen saturation, and body temperature.

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit and treatment

16.6. Physical Examination

Physical examination results will be listed. Clinically significant findings will be recorded under Medical/Surgical History up to screening and under Adverse Events post screening.

16.7. Injection Site Assessment

Result of injection site assessment will be listed.

16.8. Anxiety Symptoms Questionnaire

Anxiety Symptoms Questionnaire (ASQ) results will be listed.

17. DATA NOT SUMMARIZED OR PRESENTED

Comments will not be summarized or presented but will be available in clinical study database.

18. REFERENCES

There are no references.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the IQVIA Global Biostatistics Standard Output Conventions, which is available upon request.

Dates & Times

Depending on data availability, if not otherwise specified, dates will take the format DDMMMYYYY; times will take the format hh:mm; combined dates and time will take the format DDMMMYYYY/hh:mm.

Spelling Format

English US.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows, as appropriate:
Placebo, CS-1103 xx mg/kg, All Active (when applicable), All Subjects.

Presentation of Visits

For outputs, visits will be represented as collected on eCRF, as appropriate.

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Cohort/Treatment (cohort only presented when applicable)
- Subject number
- Date and Time (where applicable) of assessment
- For listings where non-randomized subjects are included (if applicable), these will appear in a category after the randomized treatment groups labeled ‘Not Randomized’

[redacted]

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

[redacted]

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

[redacted]