TITLE PAGE

Protocol Title: 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

Protocol Number: CS-1103-01

Amendment Number: 2

Compound: CS-1103 Concentrate for Solution for Infusion

Brief Title: A Phase 1a Safety, Tolerability and PK Study of CS-1103 in Healthy Participants

Indication: To lower the level of methamphetamine in the human body

Study Phase: 1a

Sponsor Name: Clear Scientific, Inc.

Legal Registered Address: [redacted]

Regulatory Agency Identifier Number(s): [redacted]

Original Protocol Version and Date: Version 1.0, 01 June 2023

Protocol Amendment 1 Version and Date: Version 2.0 Amendment 1, 25 September 2023

Protocol Amendment 2 Version and Date: Version 3.0 Amendment 2, 03 October 2023

Approval Date: 03 October 2023

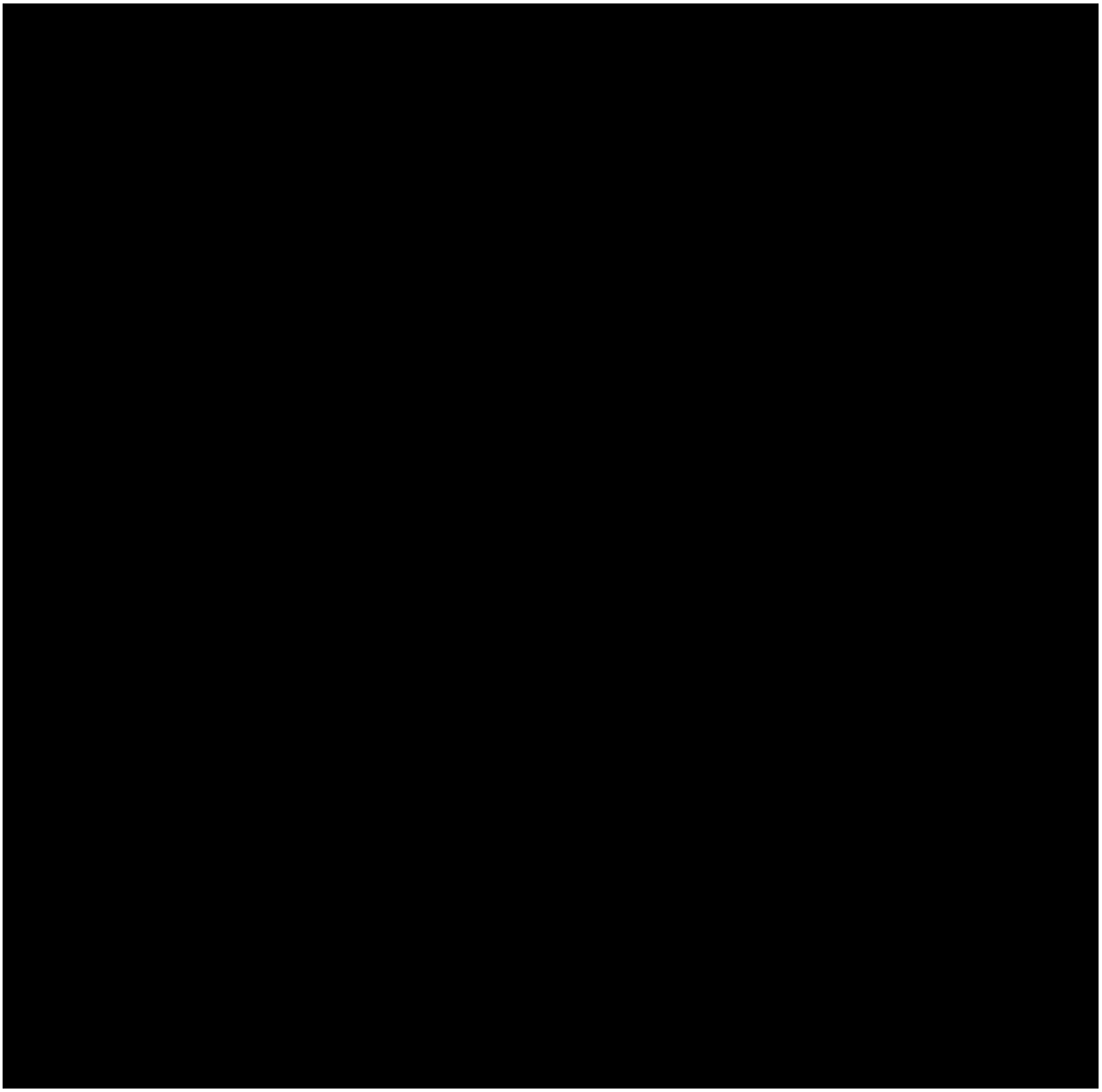
[redacted]

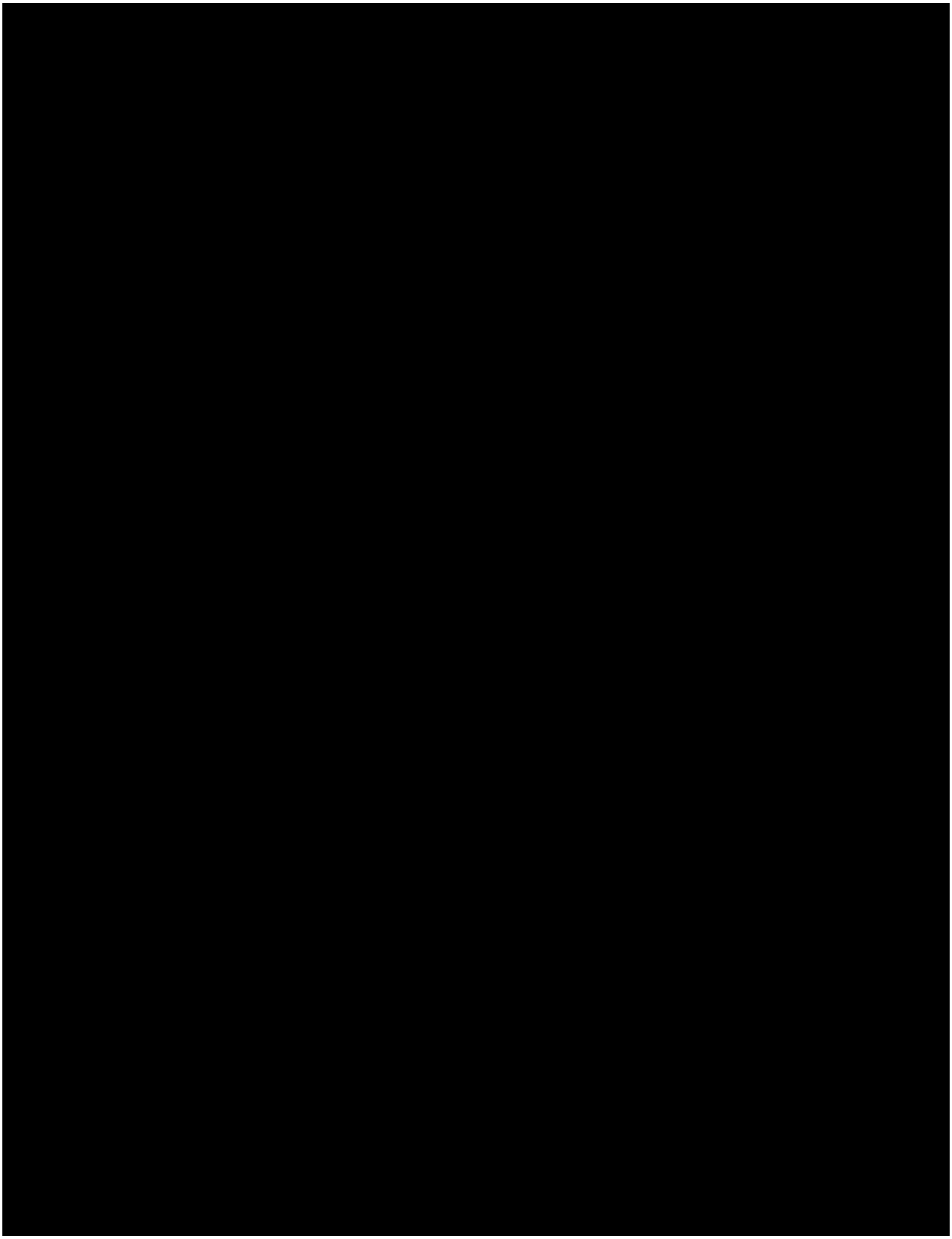
Medical Monitor name and contact information will be provided separately.

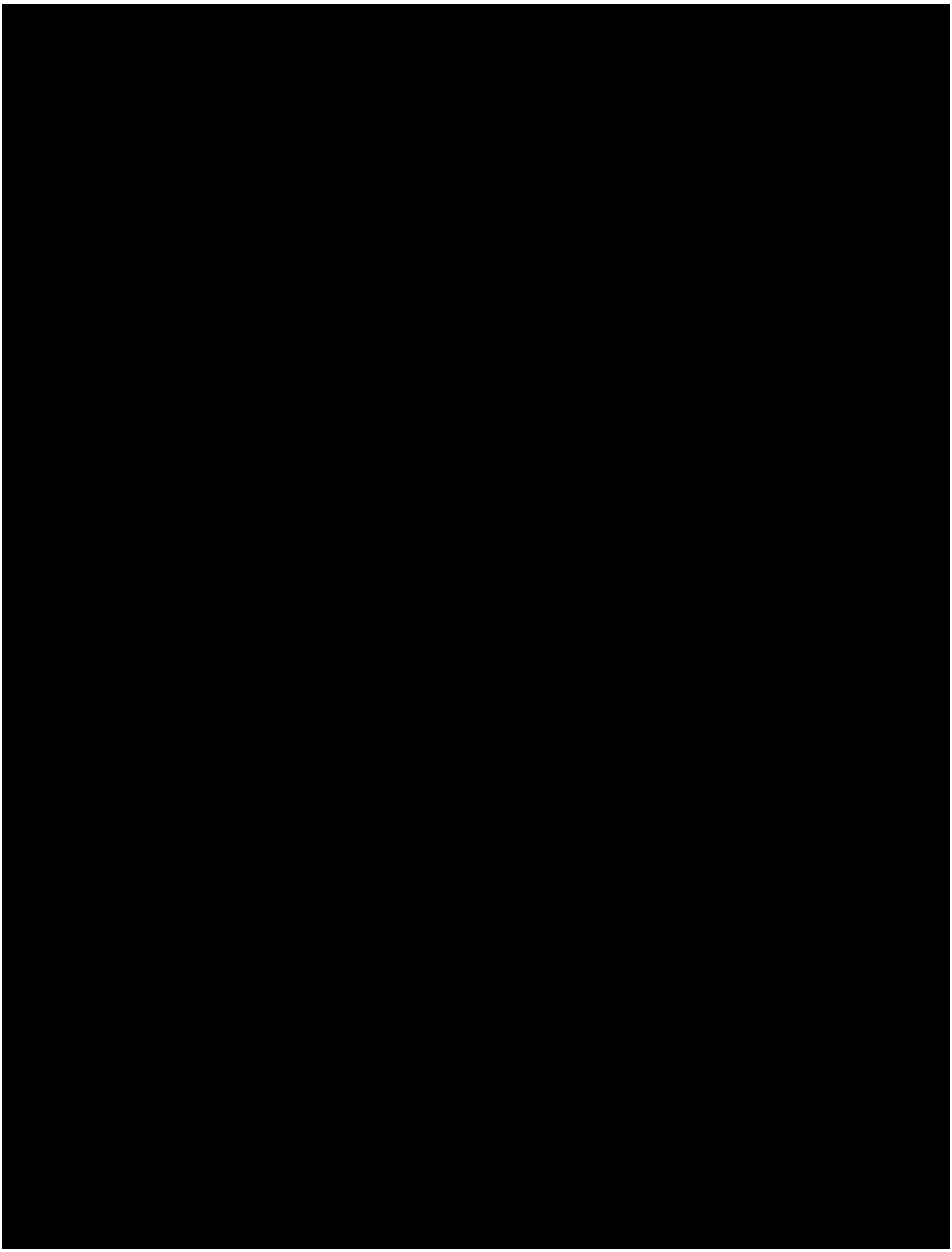
PROTOCOL AMENDMENT SUMMARY OF CHANGES

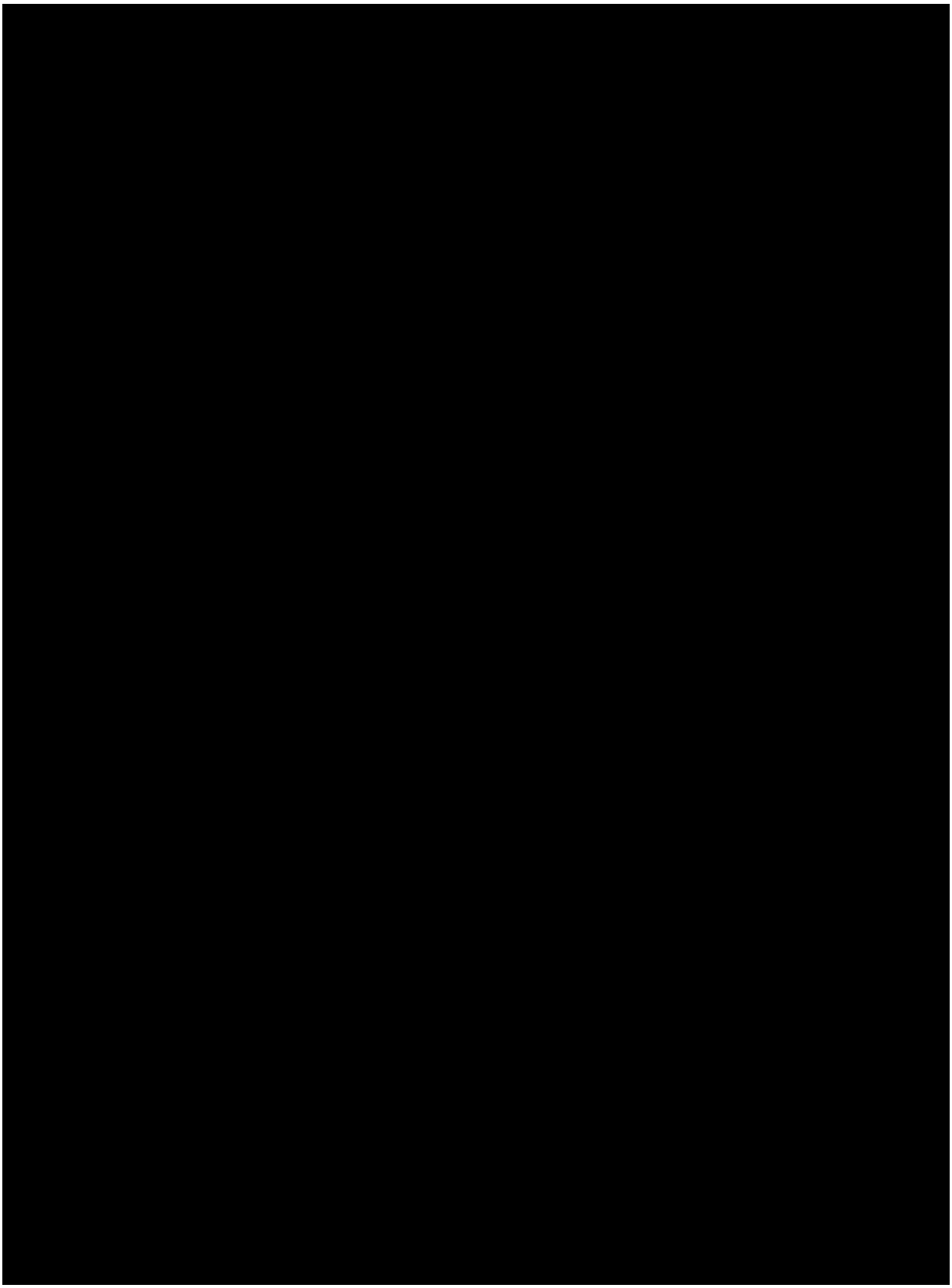
Table 1 Document History

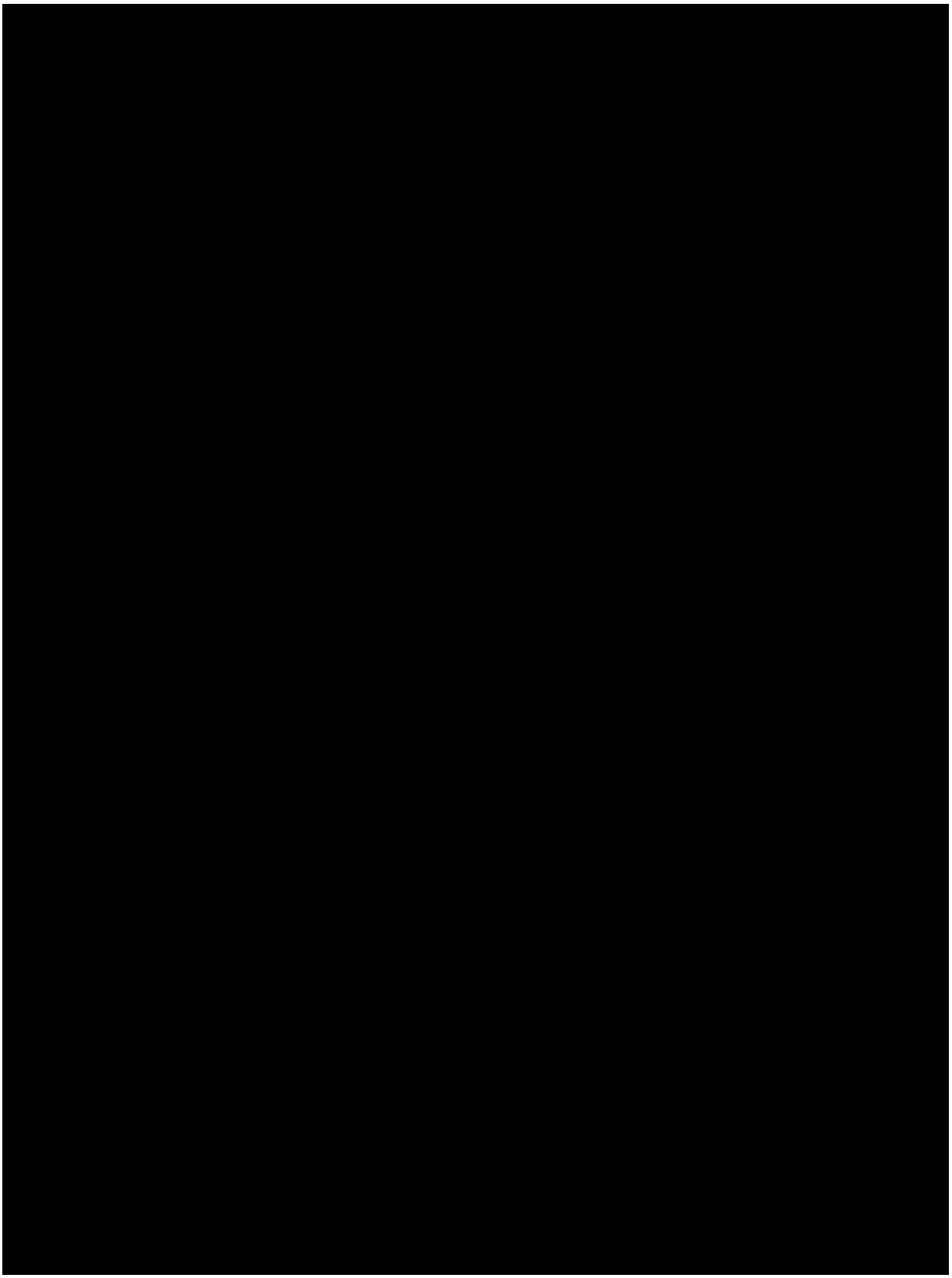
Document	Date	Substantial	Region
Amendment 2	02-Oct-2023	No	Global
Amendment 1	25-Sep-2023	Yes	Global
Original Protocol	01-Jun-2023	-	-

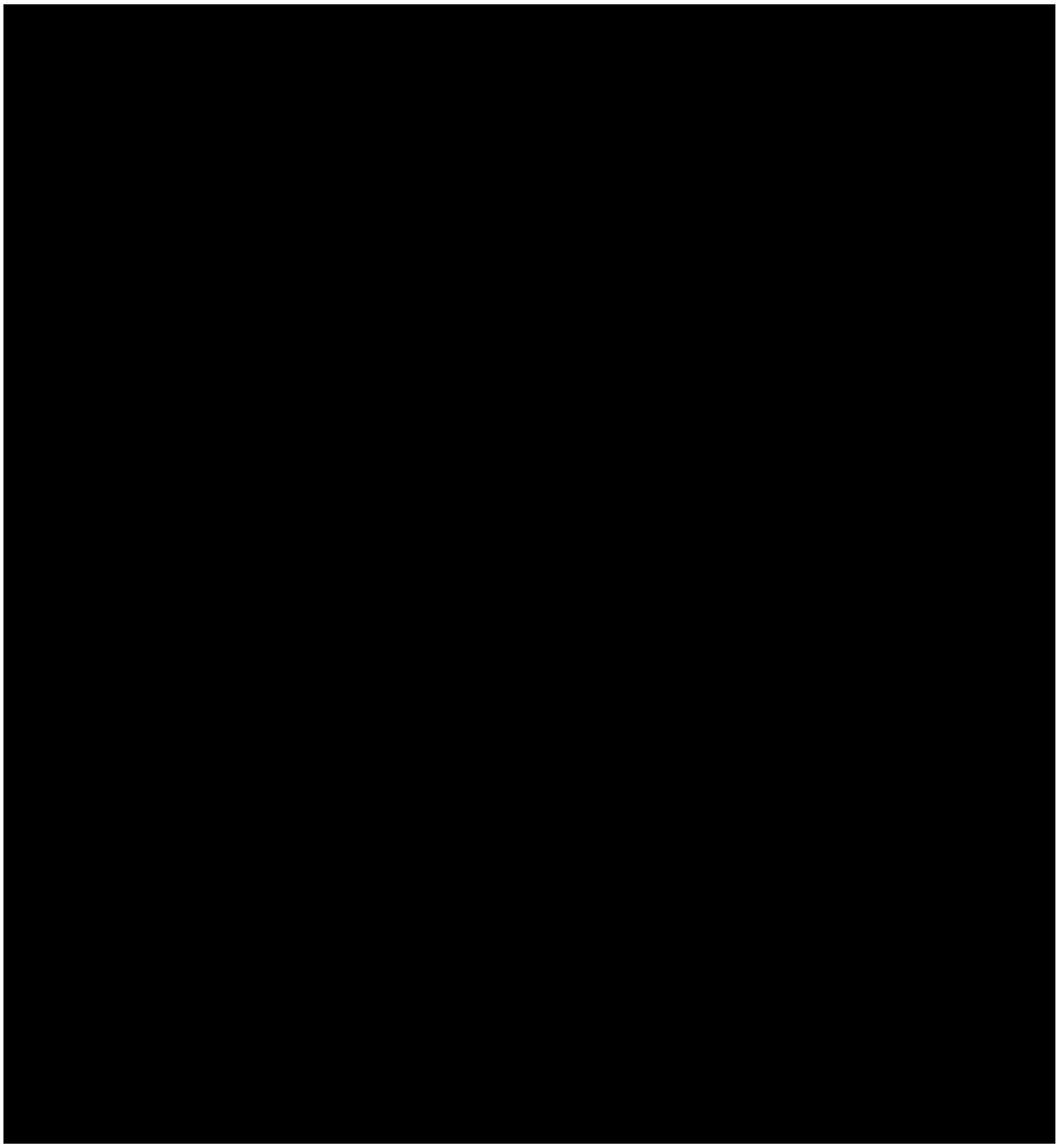












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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Registry ID: IND 155105

Principal Investigator: Steven G. Hull, M.D., FCCP, FAASM

Indication: To lower the level of methamphetamine in the human body

Rationale:

The purpose of the study is to evaluate safety, tolerability, and pharmacokinetics (PK) of single, ascending doses of CS-1103, administered by intravenous (IV) infusion in healthy participants.

Objectives and Endpoints

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: • AEs • 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

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.

Overall Design:

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.

Number of Participants:

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

Intervention Cohorts and Duration:

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])
- 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])

The study 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

Statistical Methods:

Descriptive statistics will be used as applicable to summarize the study data unless otherwise specified. Continuous variables: Sample size (n), mean, standard deviation (SD), median,

minimum (min), and maximum (max). Summaries for plasma CS-1103 concentrations will include the coefficient of variation and PK parameter summaries will also include the geometric mean (except for t_{max}, which will only be presented as min, median, max). Categorical variables: Frequencies and percentages. Individual participant data will be presented in listings.

The sample size for this study is based upon precedent set by other Phase 1 studies to gain preliminary measure of safety and CS-1103 PK characteristics in a healthy participant population and not on statistical considerations of power while exposing as few participants as possible to the study treatment and procedures. A sample size of 8 participants per dose level (6 active: 2 placebo) in this study design is expected to be sufficient to meet the objectives of this study.

Safety:

Analysis of safety data will be performed for all participants receiving at least one dose of study treatment (CS-1103 or placebo). The frequency of all treatment emergent adverse events (TEAEs), TEAEs by maximum severity, TEAEs by relationship to study treatment, serious adverse events (SAEs), TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated by Preferred Term (PT) and System Organ Class (SOC) for each treatment cohort. Summary statistics, including change from baseline, for vital signs, laboratory parameters, and electrocardiograms (ECGs) intervals will be provided by treatment, visit, and time point, as appropriate. For ECG results, appropriate outlier tabulations for QT and QT corrected for heart rate by Fridericia's formula (QTcF) will also be presented by treatment. Results of the physical examinations and the Anxiety Symptoms Questionnaire (AQS) will be listed and if appropriate, summarized by treatment.

Pharmacokinetics:

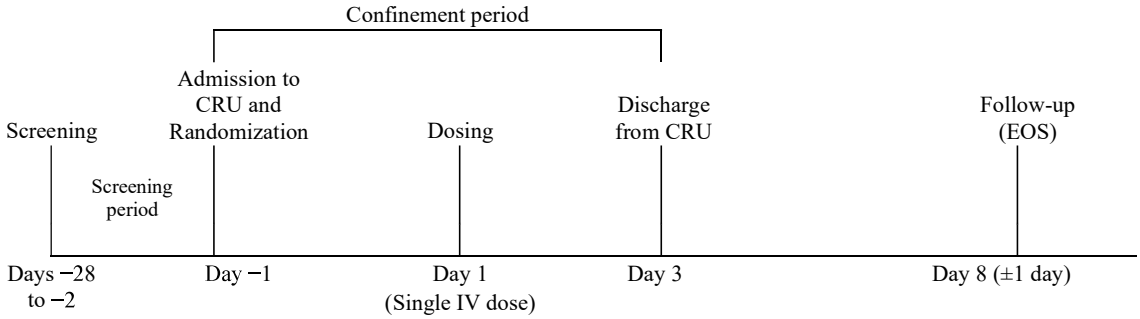
Analysis of PK data will be performed for all participants receiving at least one dose of CS-1103 and have at least 1 quantifiable postdose concentration, without protocol deviations or events expected to affect PK results. CS-1103 concentrations and calculated PK parameters will be listed and descriptively summarized by treatment and scheduled time point, as applicable. Arithmetic mean ±SD and individual CS-1103 plasma concentration versus time curves will be plotted on linear and semilogarithmic scale and percent of dose recovered in urine over time will be presented graphically, as appropriate. Dose proportionality will be explored graphically and by using a power model, as appropriate.

Data Monitoring/Other Committee: Yes

Dose escalation, and other decisions related to safety and PK will be made by the Sponsor in consultation with a Safety Review Committee (SRC).

1.2 Schema

Figure 1 Study Schema



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

Up to 40 participants randomized to 5 cohorts of 8 participants each (6 active, 2 placebo participants per cohort).
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.

1.3 Schedule of Activities

Table 3 Schedule of Activities

Visit type:	Screening[a]	Admission to CRU[a]	In-CRU	In-CRU	Discharge	Follow-up/ EOS[b]
Procedure:	**−28 to −2**	**Admission/ Day −1**	**Day 1**	**Day 2**	**Day 3**	**Day 8 ±1 day**
Informed Consent	X					
Demographics	X					
Medical History	X					
COVID-19 test[c]		X				
Drug of Abuse/Alcohol Screen	X	X				
HIV/HBsAg/HCV Serology	X					
FSH (females only)	X					
Serum Pregnancy Test (females only)	X					
Urine Pregnancy Test (females only)		X				X
Weight; Height/BMI (screening only)	X	X				X
Inclusion/Exclusion criteria	X	X				
Previous/Concomitant Medications[d]	X	X	X	X	X	X
Clinical Laboratory Evaluations[e]	X	X	X[e]	X		X
Safety ECG[f]	X	X	X	X	X	X
Holter Monitoring[g,h]		X[g]	X[h]	X[h]		
Vital Signs[i]	X	X	X	X	X	X
Physical Examinations[j]	X	X		X	X	X
Injection Site Assessment[k]			X	X	X	
ASQ[l]	X	X	X			
AE/SAE events[m]	X	X	X	X	X	X
Randomization		X				
Administer Dose in-CRU[n]			X			
PK Blood Samples[o]			X	X	X	
Pooled Urine Collection[o]		X	X	X	X	

Abbreviations: AE = adverse event; ASQ = Anxiety Symptoms Questionnaire; BMI = body mass index; COVID-19 = coronavirus disease 2019; CRU = clinical research unit; ECG = electrocardiogram; EOS = end of study; FSH = follicle stimulating hormone; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IV = intravenous; PK = pharmacokinetic; SAE = serious adverse event; SoA = schedule of activities.

[a] All participants within a given cohort may check-in on the day prior to sentinel dosing and remain confined to the study center until their discharge day. Two participants will be randomized for dosing in the sentinel group, and the remaining participants may be eligible to participate in the main cohort group without repeating the admission evaluations, provided they were in confinement the entire time. The remaining participants will have a set of vital signs and AE/concomitant medication review performed on the day prior to their dosing day. For remaining participants, Admission/Day −1 may span 2 days in the CRU. Note: Screening may end on Day −3 for participants with Admission Day spanning 2 days in the CRU.

[b] Participants who discontinue from the study prematurely should perform the Follow-up/EOS Visit as soon as possible after discontinuation.

[c] A COVID-19 test will be performed at Admission and for which a negative result must be available prior to study treatment administration.

[d] Includes over-the-counter medications, herbal medications/supplements, and other supplements.

[e] Clinical laboratory tests: hematology, clinical chemistry (including liver and renal function), coagulation, and urinalysis with microscopic examination to be performed at screening, on Admission/Day −1, Day 2 and EOS. In addition, urinalysis will be performed for each urine sample collected on Day 1. Protocol-required laboratory tests are detailed in Section 10.2, Table 6.

[f] Triplicate 12-lead ECGs will be obtained following at least 5 minutes remaining in a supine position and collected before other simultaneously scheduled procedures, i.e., vital signs and blood collections. Single ECGs may be collected during the first 30 minutes post-EOI to allow completion of all simultaneously scheduled procedures (see Table 2).

[g] On Admission/Day −1, continuous Holter Monitoring will be performed for 4 hours. If needed, any repeat ECG needs to be performed in triplicate.

[h] On Day 1, continuous Holter Monitoring will commence approximately 1 hour prior to study treatment administration and continue through 24 hours postdose. The ECGs will be extracted from Holter to be time-matched with PK samples (see Table 2).

[i] Vital signs (Systolic, diastolic, and mean blood pressure, pulse rate, respiratory rate, oxygen saturation, and body temperature) will be measured following at least 5 minutes remaining in a supine position following ECG collection (see Table 2 and Section 8.2.2 for details). If needed, repeat vital signs may be performed.

[j] Complete physical examination at screening and at end of study. Brief physical examination on Admission/Day −1 at check-in, Day 2, and Day 3.

[k] On Day 1, the injection site will be evaluated prior to study treatment administration and again immediately after study treatment administration, in approximately (+15 minutes) hourly intervals for up to 6 hours postdose. Injection site assessment also occurs any time on Day 2, and any time prior to discharge from the CRU on Day 3. (see Section 8.2.1.1 for details on the 4-point scale injection site assessment).

[l] On Day 1, ASQ will be completed predose (within 60 minutes prior to dosing) and approximately 10 minutes (+15 minutes), 1 hour (+15 minutes), and 2 hours (+15 minutes) postdose. This assessment will be performed after completion of all other simultaneously scheduled procedures to avoid interference with scheduled vital sign, ECG, and PK evaluation (see Section 8.2.4).

[m] All SAEs will be collected from the signing of the ICF until the last study visit at the timepoints specified in the SoA. All AEs will be collected from the start of study treatment until the last study visit at the timepoints specified in the SoA.

[n] Study Treatment will be administered on Day 1 in the morning after at least a 10 hour overnight fast with an approximately 4 hour fast following dose administration. Note: All scheduled postdose assessments listed in Table 1 and Table 2 are relative to the start of the IV infusion.

[o] PK blood and urine collection timepoints (see Table 2).

Table 4 Detailed Schedule of PK, Urine, dECG, Safety ECG, ASQ, Injection Site Assessment and Vital Signs During Single IV Administration Days −1 to Day 3

Day	~~Time Relative to IV Infusion Dose (T=0)[a] and PK windows~~	Time relative to End of Infusion[b] (EOI)	PK Blood [b]	Urine[c]	dECG[d] and Safety ECG[e] (triplicates)	Vital Signs[f]	ASQ[g]	Injection Site Assessment[h]
Admission/ Day −1	~~4 hour Holter*~~			−12 to 0 hr (±15 min)	X[d,e] (4 hour Holter)	X[f]	X	
Day 1	~~Predose (within 60 minutes of dose)~~	Predose	X (Within 60 mins of start of infusion)		X[d,e] (Holter to start approx. 60 mins before start of infusion)	X (within 60 mins of start of infusion)	X (within 60 mins of start of infusion)	X (within 60 mins of start of infusion)
		5 minutes into Infusion		0 to 2 hr (±15 min)		X[j] (±2.5 min)		
	~~End of IV infusion (+1 minute)~~	At End of Infusion (EOI)	X[i] (+1 min)			X[j] (1 to 4 min post EOI)		X (+15 min)
	~~15 min (±1 minutes)~~	5 minutes	X[i] (+1 min)					
	~~20 min (±1 minutes)~~	10 minutes	X[i] (±1 min)		X[e] (±5 min)		X (+15 min)	
	~~30 min (±2 minutes)~~	20 minutes	X[i] (±2 min)			X[j] (±5 min)		
	~~40 min (±2 minutes)~~	30 minutes	X[i] (±2 min)		X[e] (±5 min)			
	~~50 min (±4 minutes)~~	40 minutes	X[i] (±4 min)			X (±5 min)		
	~~1 hr, 10 minutes (±4 minutes)~~	1 hr	X[i] (±4 min)		X[e] (±10 min)	X (±10 min)	X (+15 min)	X (+15 min)
	~~1 hour, 40 minutes (±10 minutes)~~	1.5 hr	X[i] (±10 min)					
	~~2 hr, 10 minutes (±10 minutes)~~	2 hr	X[i] (±10 min)		X[e] (±10 min)	X (±10 min)	X (+15 min)	X (+15 min)
	~~2 hr, 40 minutes (±10 minutes)~~	2.5 hr	X[i] (±10 min)	2 to 4 hr (±15 min)				
	~~3 hr, 10 minutes (±10 minutes)~~	3 hr	X[i] (±10 min)		X[e] (±10 min)	X (±10 min)		X (+15 min)
	~~4 hr (±15 minutes)~~	4 hr	X (±15 min)					X (+15 min)
	~~5 hr (±15 minutes)~~	5 hr		4 to 6 hr (±15 min)				X (±15 min)
	~~6 hr (±15 minutes)~~	6 hr	X (±15 min)		X[e] (±10 min)	X (±10 min)		X (+15 min)
	~~8 hr (±15 minutes)~~	8 hr	X (±15 min)	6 to 12 hr (±15 min)	X[e] (±10 min)	X (±10 min)		
	~~12 hr (±15 minutes)~~	12 hr	X (±15 min)					
Day 2	~~24 hr (±30 minutes)~~	24 hr	X (±30 min)	12 to 24 hr (±15 min)	X[d,e] (Holter to end after 24-hr)	X (±10 min)		X (+12 hr)
	~~36 hr (±30 minutes)~~	36 hr	X (±30 min)	24 to 36 hr (±15 min)		X (±10 min)		
Day 3	~~48 hr (±30 minutes)~~	48 hr	X (±30 min)	36 to 48 hr (±15 min)	X[e] (±10 min)	X (±10 min)		X (any time prior to discharge)

Abbreviations: ASQ: Anxiety Symptoms Questionnaire; CRU = clinical research unit; dECG: Digital electrocardiogram; EOI = end of infusion; hr = hour; IV = intravenous; min = minutes; PK: pharmacokinetics; (T=0) = Time equals 0.

* Continuous Holter performed during the day of admission

a. All predose procedures and PK blood samples may be taken up to 60 minutes prior to start of the 10 minute IV infusion on Day 1. All postdose procedures and PK blood samples will be collected relative to the end of the IV infusion unless otherwise indicated or there is a significant extension of the infusion duration (see footnote [b] below).
b. The following windows will be allowable for PK samples: a ±1 minute window will be allowed for samples taken up to and including 10 minutes postdose, a ±2 minute window will be allowed for samples at 20 and 30 minutes postdose, a ±4 minute window will be allowed for samples at 40 minutes, 50 minutes, and 1 hour postdose, a ±10 minute window for samples taken between 1.5 hours and 3 hours postdose; a ±15 minute window is acceptable for samples taken at >3 hours postdose, and a ±30 minute window is acceptable for samples taken at >12 hours postdose.
c. A small amount of urine will be removed at each interval for urinalysis. Removal of urine will occur after the volume of the pooled urine has been recorded.
d. ECGs to be extracted from the continuous Holter on Days 1 and 2 as listed in Table 2 and will be time-matched with PK sample collections from predose to 24-hour postdose. Digital ECG assessments will be extracted at a time prior to the PK sample collection. Participants will remain in supine position for at least 5 minutes before each of the planned ECG extraction.
e. Scheduled safety ECG by site for in-time evaluation of ECGs. Timepoints will be from the start of the triplicate assessment as indicated. Single ECG will be collected at the 10 and 30 minutes post EOI timepoints.
f. Vital signs can be taken any time prior to randomization on Admission/Day −1.
g. On Day 1, ASQ will be completed predose (within 60 minutes prior to dosing) and approximately 10 minutes (+15 minutes), 1 hour (+15 minutes), and 2 hours (+15 minutes) postdose. This assessment will be performed after completion of all other simultaneously scheduled procedures to avoid interference with scheduled vital sign, ECG, and PK evaluation (see Section 8.2.4).
h. On Day 1, the injection site will be evaluated prior to study treatment administration and again immediately after study treatment administration, in approximately hourly (+15 minutes) intervals for up to 6 hours postdose. Injection site assessment also occurs any time on Day 2, and any time prior to discharge from the CRU on Day 3 (see Section 8.2.1.1 for details on the 4 point scale injection site assessment).
i. If the duration of the short 10 minute infusion exceeds 15 minutes, or an interruption occurs that exceeds the duration of infusion to more than 15 minutes, for PK blood collection (postdose) up and including 3 hours, every effort should be made to follow the time relative to the end of infusion.
j. Blood pressure measurements for 5 minutes post start of infusion, at EOI, and 20 minute post EOI timepoints will be single readings.

The timing of PK (both plasma and urine), safety ECG, and vital sign assessments may be adjusted based on emerging data. Furthermore, in case that CS-1103 half-life is less than 4 hours, Holter recording may be discontinued at a time earlier than 24 hours post IV infusion. Furthermore, up to 2 additional blood collections may be added on Day 1, Day 2, or Day 3; pooled urine collections may be extended, and discharge may be delayed for up to 8 hours to optimize PK assessment without preparation of an amendment.

2.0 INTRODUCTION

2.1 Study Rationale

The purpose of the study is to evaluate safety, tolerability, and pharmacokinetics (PK) of single, ascending doses of CS-1103, administered by intravenous (IV) infusion in healthy participants.

2.2 Background

There is an urgent need for a rapidly acting reversal agent for methamphetamine (meth) intoxication. Meth is the fastest growing drug of abuse in the U.S., representing nearly 800,000 annual emergency room visits,[1] with deaths increasing 14-fold since 2015 (32,856 deaths in 2021 alone),[2,3] yet no current therapeutics are available for treating meth intoxication.

Clear Scientific is developing CS-1103 to treat acute toxic effects of meth. CS-1103 lowers the level of meth in the body by sequestering it in the central compartment, and accelerating its renal clearance into urine, therefore mitigating its toxic effects. [redacted]

[redacted]

Clear Scientific has completed a nonclinical program in compliance with guidelines published by the Food and Drug Administration (FDA).[10] The results are summarized in the current Investigator's Brochure (IB).

[redacted]

The purpose of the planned Phase 1a clinical trial is to evaluate the safety, tolerability, and PK of CS-1103 following a single, ascending IV dose administration in healthy participants. The proposed route of administration in humans is IV.

[redacted]

[redacted]

2.3 Benefit/Risk Assessment

The benefit of the present study is that it will provide important human data on the safety, tolerability and PK of CS-1103, however there is no benefit to the healthy study participants. This study will provide a base of information for further development of this molecule, which has the potential to treat participants with meth intoxication. CS-1103 has been extensively evaluated in nonclinical studies. The development of hypersensitivity reactions in human participants is a potential risk. See Section 2.2.1 for additional information. More detailed information about the known and anticipated benefits as well as the risks, and reasonably expected AEs of CS-1103 may be found in the current IB.

For the justification of the starting dose and provisionary dose range, see Sections 4.3 and 4.5. A comprehensive set of safety assessments have been implemented (see Section 8.2) along with well-defined study stopping criteria (see Section 4.6) to ensure participant safety.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements.

3.0 OBJECTIVES AND ENDPOINTS

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: • AE • 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
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.

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 1a, single center, double-blind, placebo-controlled, randomized, single ascending-dose first-in-human (FIH) study. The study will recruit up to 40 healthy normal participants, aged 18 to 55 years inclusive, with standard inclusion/exclusion criteria for healthy participant studies. 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).

All participants will be screened within 28 days of dose administration and participants will check-in to the inpatient clinical research unit (CRU) on Admission/Day −1. Participants will be randomized on Day −1, the day prior to their schedule CS-1103 administration (after meeting all eligibility criteria). Participants are scheduled to remain in the CRU for up to 48 hours postdose for safety and PK assessments. Participants will be discharged on Day 3 after completion of all scheduled assessments and will be asked to return to the CRU on Day 8 for the end of study (EOS) visit. Note: Discharge from the CRU may be delayed for up to 8 hours to optimize PK assessment (see Section 8.4.1). The study duration will be approximately 37 days.

All participants for a dose level may check-in to the CRU on the same date. However, each dose level will include 2 sentinel participants (1 active, 1 placebo) who will be dosed first and monitored by an Investigator for a minimum of 24 hours. The available safety and tolerability data from the sentinel participants, up to 24 hours post dose, will be reviewed by an Investigator. Following this safety data review, dosing of the remaining participants in the cohort may proceed (see Section 10.1.7.1). The remaining participants for each dose level will be randomized the day prior to dosing and will dose on Day 1, provided there are no safety or tolerability concerns, using a 5:1 randomization ratio to active or placebo study treatment separately for each dose level. A randomization list will be prepared for each cohort. See Section 4.5 for dose escalation details.

Eligible participants will be randomized to 5 cohorts of 8 participants each. Each cohort will receive a single IV infusion of CS-1103 or placebo at one dose level. At each dose level, 6 participants will receive CS-1103 and 2 participants will receive matching placebo. The starting dose and provisional subsequent dose levels are provided below:

- 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])
- 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])

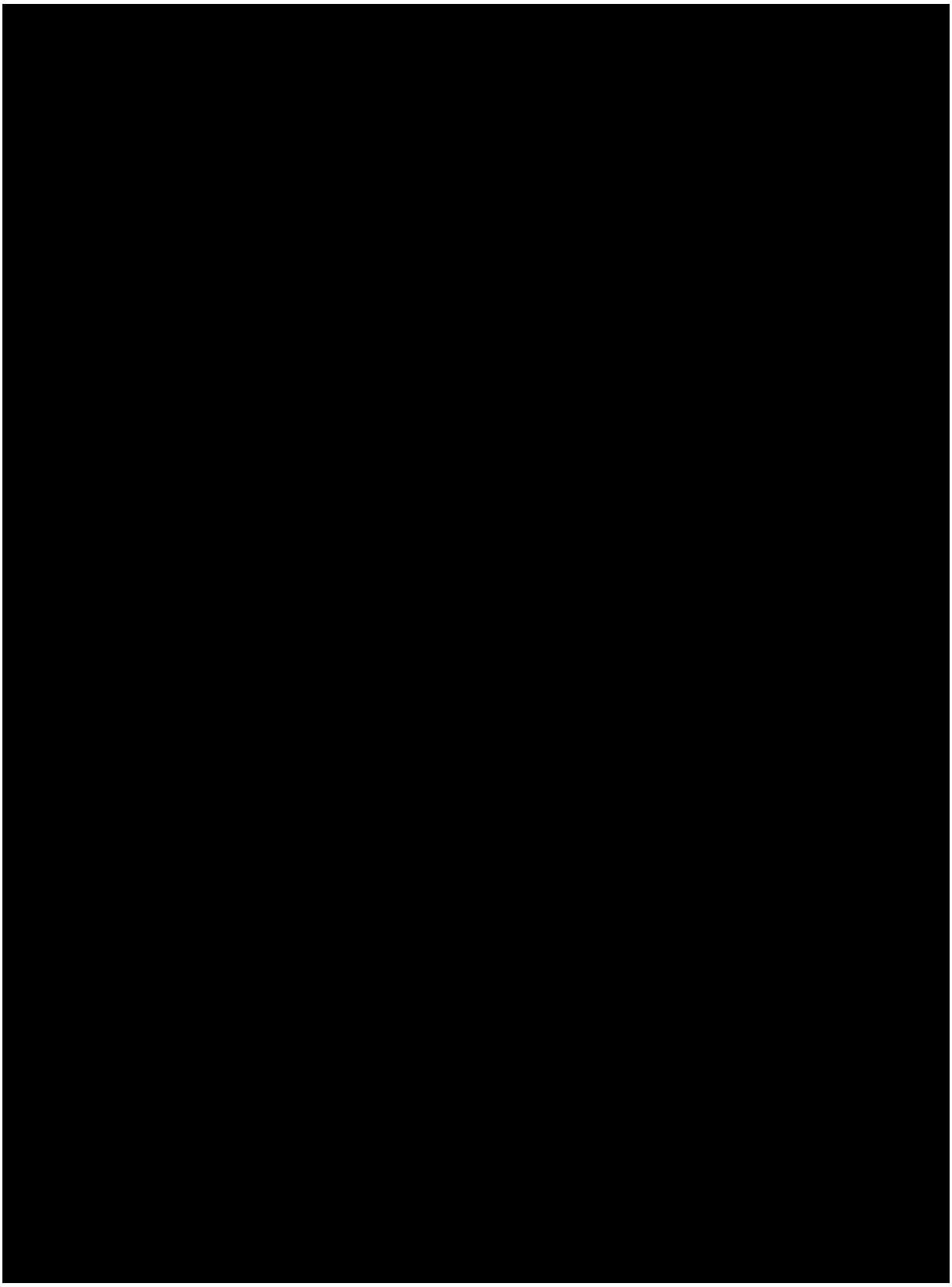
- Note: The dose will be capped at 3000 mg.

4.2 Scientific Rationale for Study Design

This is the FIH study to be conducted with CS-1103. It is designed to evaluate the safety, tolerability, and PK of CS-1103 in healthy participants at increasing doses when given as a single IV infusion. The study will be conducted in healthy participants who are free of underlying comorbidities to allow evaluation of CS-1103-related response. The schedule of safety and PK assessments and planned 48-hour in-house observation are targeted to an expected short half-life ($t_{1/2}$) based on the nonclinical species evaluated. The 7-day follow-up period is consistent with that of other FIH studies.

Scheduled activities during the Phase 1a clinical trial include careful monitoring of vital signs (systolic, diastolic, and mean blood pressure, pulse rate, respiratory rate, oxygen saturation, body temperature) and electrocardiogram (ECG) monitoring before, during, and after dosing. The proposed monitoring plan mitigates any potential risk for the Phase 1a clinical trial associated with respiratory or cardiovascular effects.

4.3 Justification for Dose



Additional details are provided in the current IB.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities (SoA) (Section 1.3), whichever is later.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA Section 1.3.

4.5 Dose Escalation

This initial dose will be a single IV infusion. An expected dose escalation will proceed with maximum incremental increase in dose not exceeding 3-fold at the lowest dose. Subsequent dose escalation will not exceed a 2-fold increase in dose and the incremental dose escalations are planned to decrease in size as CS-1103 dose rises. See Section 4.1 for the provisional CS-1103 doses for the subsequent cohorts and for additional details on screening and admission/discharge from the inpatient CRU.

Dose escalation to the next dose level(s) will not proceed until the safety and tolerability of CS-1103 over at least 48 hours and plasma PK results scheduled over at least the 24 hour in-clinic assessment period have been evaluated for at least 6 of the 8 participants in the preceding dose cohort by the Safety Review Committee (SRC) (see Section 10.1.7.1).

[2] At a dose of 40.0 mg/kg CS-1103 in humans, the C_0 is estimated at 340 µg/mL (220 µM) and $AUC_{[0\text{-tlast}]}$ is estimated at 318 µg·hr/mL.

4.6 Study Stopping Criteria

4.6.1 Criteria for Stopping Dose Escalation

Dose escalation will be stopped if any of the following study stopping rules are met:

- One or more participants who received CS-1103 report a serious adverse events (SAEs) considered at least possibly related to the study treatment
- Two or more participants who received CS-1103 experience a moderate AE in the same organ system that are at least possibly related to the study treatment
- One or more participants who received CS-1103 fulfill Hy's law defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] >3 × the upper limit of normal (ULN) and total bilirubin >2 × ULN in the absence of significant increase (>2 × ULN) in alkaline phosphatase (ALP) and in the absence of an alternative diagnosis that explains the increase in total bilirubin, to be assessed from the first administration of study treatment up to and including follow-up/EOS Visit. The event must be considered at least possibly related to study treatment
- Two or more participants, who receive CS-1103, have QTc prolongation defined as QT corrected for heart rate by Fridericia's formula (QTcF) >500 msec, or an increase of QTcF >60 msec above baseline to a value >480 msec on the 12-lead ECG, confirmed (persistent for >5 min) on a repeat 12-lead ECG.
- Any other event in CS-1103-treated participants occurs and is deemed by the SRC to pose an unacceptable risk to participants
- Any participant exceeds predicted exposures equivalent to exposure limits [redacted]); $AUC_{(0\text{-last})}$ (456 µg·h/mL). If the predefined exposure limits are reached and there are no safety or tolerability concerns, a lower dose may be investigated. If any of these criteria are met, the SRC will stop further dose escalation. The SRC will determine whether a lower dose should be tested or whether the study should be terminated

4.6.2 Criteria for Stopping the Study

If the Sponsor, Investigator, clinical monitor, or FDA officials discover conditions during the study that indicate that the study or a study site should be terminated, this action may be taken after appropriate consultation between the Sponsor, Investigator, and clinical monitor.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Provision of signed and dated, written informed consent prior to any study specific procedures.
2. Healthy male and/or female participants aged 18 to 55 years, inclusive.
3. A body mass index between 18.0 to 30.0 kg/m^2, inclusive, and a minimum body weight of 50 kg.
4. Females must be of nonchildbearing potential, must not be lactating, must have a negative serum pregnancy test at the Screening Visit, and must have a negative urine pregnancy test on admission to the study site CRU. The nonchildbearing potential of the female participant will be confirmed at the Screening Visit by fulfilling 1 of the following criteria (see Section 10.4.1 for additional information):
    - Postmenopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle stimulating hormone (FSH) levels in the laboratory defined postmenopausal range.
    - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
5. Male participants should be willing to use double barrier contraception, i.e., condoms and spermicide, from the day of dosing until at least 90 days after dosing with the study treatment (see Section 10.4.2 for additional information).
6. Male participants must agree not to donate sperm from the day of dosing until at least 90 days after dosing with the study treatment.
7. Considered generally healthy upon completion of medical history, physical examination, vital sign measurements, ECG, and clinical laboratory test results in the opinion of an Investigator at Screening and Admission/Day −1.
8. Must agree to abstain from alcohol intake 48 hours before administration of the study treatment, during the confinement period of the study until after the final Follow-up/EOS Visit.
9. Able to comply with the protocol and attend all scheduled visits.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of any clinically important disease or disorder which, in the opinion of an Investigator, may either put the participant at risk because of participation in the study, or influence the results or the participant's ability to participate in the study.
2. History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of drugs.
3. Estimated glomerular filtration rate <90 mL/min/1.73 m^2 based on Modification of Diet and Renal Disease formula during Screening and on Admission/Day −1 (Table 6).
4. Any current active infections, including localized infections, or any recent history (within 1 week prior to study treatment administration) of active infections (including severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), cough or fever, or a history of recurrent or chronic infections.
5. Administration of any vaccine (live and inactivated [e.g., inactivated influenza vaccines or SARS-CoV-2 vaccines]) are not allowed within 2 weeks of dosing and while on study is prohibited.
6. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of study treatment or planned surgical procedure during the study period.
7. Blood donation/blood loss greater than 500 mL during the 56 days prior to screening.
8. Any positive result at the Screening Visit for serum hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, and human immunodeficiency virus (HIV).
9. Abnormal vital signs, after at least 5 minutes remaining in the supine position at the Screening Visit and on Admission/Day −1, defined as any of the following:
    - Systolic blood pressure >145 mmHg
    - Diastolic blood pressure >95 mmHg
    - Heart rate <45 or >100 bpm
10. Any clinically significant abnormalities in rhythm, conduction or morphology of the resting ECG, and any clinically important abnormalities in the 12-lead ECG as considered by the Investigator that may interfere with the interpretation of QTc interval changes.
11. Prolonged Fridericia QTcF >450 msec in males or >470 in females or shortened QTcF <340 msec or family history of long QT syndrome at the Screening Visit and on Admission/Day −1
12. ALT and/or AST >1.0 × ULN at the Screening Visit and on Admission/Day −1.
13. Current smokers, or those who have smoked or used nicotine products (including nicotine patches) within 1 month prior to dose administration (see Section 5.3.2 for additional details).
14. History of alcohol abuse or excessive intake of alcohol as defined in Section 5.3.2.

15. Positive screen for drugs of abuse or cotinine at the Screening Visit or admission to the study site CRU or positive screen for alcohol on admission to the study site CRU prior to the first administration of study treatment (see Table 6).
16. Positive test results for coronavirus disease 2019 (COVID-19) performed at admission to the CRU.
17. History of severe allergy/hypersensitivity/anaphylaxis or ongoing clinically important allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to any components in the study treatment.
18. Excessive intake of caffeine containing drinks or food (more than 6 cups of coffee or equivalent per day) (see Section 5.3.2 for definition of excessive).
19. Treatment with prescription or nonprescription medications (including over-the-counter [OTC] medications, supplements, and herbal preparations such as St. John's Wort extract) within 14 days prior to start of study treatment, unless in the opinion of an Investigator and Sponsor the medication will not interfere with the study. See Section 6.6 for additional details.
20. Has received an Investigational Product within 30 days or a biologic within 90 days (or 5 half-lives for both, whichever is longer) prior to screening.
21. Consumption of poppy seeds, red wine, Seville oranges, Seville orange marmalade, grapefruit, or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices within the 7 days prior to Admission/Day −1 (see Section 5.3.1).
22. Previous randomization to treatment in the present study.
23. Involvement in the planning and/or conduct of the study (applies to the Sponsor, contract research organizations, and study site staff, etc.).
24. Participants who are unlikely to cooperate with the requirements of the study.
25. Judgment by the Investigator that the participant should not participate in the study if they have any ongoing or recent (i.e., during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions and requirements.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

- Refrain from consumption of poppy seeds, red wine, Seville oranges, Seville orange marmalade, grapefruit, or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to Admission/Day −1 and through the duration of the study (see Section 5.2, exclusion criteria 21).
- At least a 10 hour overnight fast (with water ad libitum) is required prior to study treatment administration and a 4 hour fast is required following study treatment administration

- Participants will be asked to drink 360 mL of water after completion of their final predose urine void. After that no water is allowed until 1 hour after dose administration, after which time, water is allowed ad libitum. At 2 hours postdose, participants will be encouraged to drink another 360 mL of water. Participants are encouraged to drink at least 1 L of water over the first 12 hours post drug administration (inclusive of the 2 × 360 mL of water specified above). If participants are unable to drink the complete 360 mL of water, the reason why and the exact amount consumed will be documented.

5.3.2 Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting excessive caffeine- or xanthine-containing products (e.g., coffee, tea, red bull, cola drinks, and chocolate [more than 6 cups of coffee or equivalent per day]) within 7 days prior to study treatment administration and through the final Follow-up/EOS Visit
    - One caffeine unit is contained in the following items: 1 (6 oz) cup of coffee, 2 (12 oz) cans of cola, 1 (12 oz) cup of tea, ½ (4 oz) cup of energy drink (e.g., Red Bull), or 3 (1 oz) chocolate bars
- Participants will abstain from alcohol intake 48 hours prior to study treatment administration and until after the final Follow-up/EOS Visit. History of alcohol abuse or excessive intake of alcohol defined as:
    - an average weekly intake of >14 drinks/week for men or >7 drinks/week for women. One drink is equivalent to (12 g alcohol) = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of 80 proof distilled spirits
- Use of tobacco products will not be allowed within 1 month prior to study treatment administration and through the final Follow-up/EOS Visit.

5.3.3 Activity

- Participants should refrain from strenuous exercise for 72 hours before the screening medical examination, 72 hours before admission, and throughout the residential period in the CRU and again 72 hours before the scheduled Follow-up/EOS Visit.
- Participants will be advised not to donate blood or plasma for at least 3 months after the last dose administration.
- Participants will be asked to remain in the supine position during dose administration and for at least 40 minutes post-EOI
- On days when digital ECG (dECG) Holter measurements are being taken, study participants should be restricted to a low level of physical activity and should refrain from any activities likely to stimulate or excite them (e.g., video games, stimulating movies, or television shows, etc.) during extraction timepoints. Additionally, participants should

refrain from using hand-held electronic or electrical devices (e.g., cell phones, hair dryers, etc.) as these have a potential to interfere with ECG signals.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study does not meet all the eligibility criteria and is not subsequently randomly assigned to study treatment to enter the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5 Criteria for Temporarily Delaying Enrollment/Randomization

Enrollment and randomization can be paused, at the Sponsor's discretion, in the event of restrictions related to the COVID-19 pandemic or a similar national emergency.

As the COVID-19 pandemic may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the Investigator in consultation with the study team and the medical team as needed, while maintaining participant safety and confidentiality as the priority. Management of COVID-19 risk post enrollment will be according to CRU specific procedures.

6.0 STUDY TREATMENT(S) AND CONCOMITANT THERAPY

Study treatment is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. The study treatments that will be administered in the study are provided in Table 3. Refer to the site Pharmacy Manual for additional details.

6.1 Study Treatments Administered

Table 5 Study Treatments Administered

Intervention Name	CS-1103	Placebo
Intervention Description	Administered as solution for infusion by IV	Administered as solution for injection by IV infusion
Type	Drug	Drug
Dose Formulation	[redacted]	0.9% saline (sodium chloride) IV bag for injection
Storage	See Pharmacy Manual	See label instructions
Unit Dose Strength(s)	[redacted]	0.9% saline (sodium chloride) for injection
Dosage Level(s)	Up to 5 CS-1103 dose levels will be evaluated. One single dose will be administered in each cohort as outlined in Section 4.1.	Up to 5 placebo dose levels will be evaluated. One single dose will be administered in each cohort as outlined in Section 4.1.
Route of Administration	IV infusion	IV infusion
Administration Site	Arm (suitable vein to support infusion volume and duration)	Arm (suitable vein to support infusion volume and duration)
Dose Frequency	A single IV infusion To be administered on Day 1 in the morning after at least a 10 hour overnight fast; 4 hour fast following dose administration.	A single IV infusion To be administered on Day 1 in the morning after at least a 10 hour overnight fast; 4 hour fast following dose administration.
Number of Doses to be Administered	1	1
Infusion Duration	10 minutes	10 minutes
Infusion Volume[a,b]	[redacted]	[redacted] Volume administered (mL/kg) will match volume administration of IMP
Use	Experimental	Placebo (to maintain blinding)

Intervention Name	CS-1103	Placebo
Sourcing	Provided centrally by the Sponsor	Provided by clinical site
Packaging and Labeling	[redacted]	The clinical site will provide commercially available 0.9% Sodium chloride for infusion. Each dose will be packaged and labeled per all applicable regulatory requirements. The volume (mL/kg) of the placebo treatment will match that of the CS-1103 treatment.

Abbreviation: IMP = Investigational Medicinal Product; IV = intravenous.
[a] Admission/Day −1 weight will be used for dose calculations.
Note: CS-1103 dose administration will be based on the weight of the tetrasodium salt.
[b] See Pharmacy Manual for specifics for determining IV bag volume.

6.2 Preparation, Handling, Storage, and Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment, and only authorized study site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study site staff.

The Investigator or delegated pharmacy staff is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The Investigator, or delegated pharmacy staff must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Form. These forms must be available for inspection at any time.

Further guidance and information for packaging, storage, study treatment preparation/handling and the final disposition of unused study treatments are provided in the study site Pharmacy Manual outside of this protocol.

6.3 Measures to Minimize Bias: Randomization and Blinding

On Day −1, the day prior to dosing, participants will be assigned a unique number (randomization number) in ascending numerical order at the CRU. The randomization number encodes the participant's assignment to one of the study treatments of the study, according to the randomization schedule generated prior to the study by the Statistics Department at IQVIA. Each participant will be dispensed blinded study treatment, labeled with his/her unique randomization number, throughout the study.

Participants who withdraw from the study for reasons other than AEs may be replaced at the discretion of the Sponsor. If a participant withdraws his/her participation in the study, then his/her randomization number cannot be reused. In the event that a participant is replaced, an unblinded pharmacy delegate at the site will utilize the randomization schedule to determine the appropriate randomization number for the replacement participant so that each replacement participant will be assigned to the appropriate treatment and will receive the same study treatment (CS-1103) or placebo as the participant being replaced. Randomization numbers for replacement participants will be assigned as follows: the original randomization number plus 100 (e.g., if the original participant being replaced had a randomization number of 1001, the replacement randomization number will be 1101).

Sponsor safety staff may unblind the study treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's study treatment assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

In case of a medical emergency, an Investigator or authorized designee is allowed to break the code to determine treatment assignment. The Sponsor will be notified of the unblinding.

After each dose cohort the SRC will determine the dosing regimen(s) for the next cohort (see Sections 6.5 and 10.1.7.1 for additional SRC details). This decision will generally be made without breaking the randomization code. If judged necessary by the SRC, an individual or the complete cohort may be unblinded during evaluation of the study data. Before unblinding, a decision should be made about the action to be taken based on the revealed treatment allocation. All decisions to unblind an individual or the complete cohort will be documented in writing.

6.4 Study Treatment Compliance

Participants will receive study treatment directly from the Investigator or designee, under medical supervision. The start date and time and the end date/time of the IV infusion administered in the clinic will be recorded in the source documents. The volume infused will also be documented. Any interruptions in the infusion (stop/restart time) will also be documented, if applicable. The dose volume of study treatment and study participant

identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.4.1 Study Treatment Strategy

The clinical research facility is staffed 24 hours a day, 7 days a week with a minimum of one Advanced Cardiovascular Life Support certified safety personnel and a Basic Life Support certified personnel on site. Site safety measures for participants include crash cart with 2 jump bags, panic buttons located throughout the facility and strategically placed cameras. The clinical research facility is located within close proximity to multiple emergency rooms and hospitals and always has an Investigator (physician or nurse practitioner) on call 24 hours a day, 7 days a week for medical consultation by clinical staff, if needed.

As this is the first administration of CS-1103 in humans, all effects cannot be reliably predicted. The preclinical data suggest an acceptable safety margin. Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided.

6.4.2 Individual Study Treatment Adjustment/Interruption

If a participant experiences a reaction symptom, the study treatment infusion should be stopped. The infusion may be restarted at a slower rate or halted entirely based on an Investigator's discretion. Any interruptions (stop time/restart time) will be documented.

6.5 Dose Modification

The full details of starting dose selection/dose justification, dose escalation, and study stopping criteria are described in Sections 4.3, 4.5, and 4.6 of this protocol, respectively.

The decision to proceed to the next dose level of CS-1103 will be made by the SRC based on safety and tolerability through at least 48 hours and preliminary PK data through at least 24 hours are obtained at the most recent dose level as well as cumulative data for at least 6 out of the 8 participants. The SRC may decide to increase the dose to the next higher planned dose level, increase the dose by a lesser margin, repeat, or reduce the dose to an intermediate dose level. The decision may also be made to stop dosing.

6.6 Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, recreational drugs, vitamins, minerals, and/or herbal supplements) that the participant is receiving within 1 month of study treatment administration, at the time of enrollment, and receives during the study must be recorded in the electronic case report form (eCRF) along with:

- Reason for use
- Dates of administration including start and end dates

- Dosage information including dose and frequency

Any changes in prior or concomitant medications will also be recorded in the eCRF.

Administration of any vaccine (live and inactivated [e.g., inactivated influenza vaccines or SARS-CoV-2 vaccines]) are not allowed within 2 weeks of dosing and while on study is prohibited.

Participants must abstain from taking prescription or nonprescription drugs (including OTC medications, vitamins, dietary or herbal supplements, such as St John's Wort extract) within 14 days before the start of study treatment until completion of the study (Follow-up/EOS Visit), unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of ≤2 g/24 hours, but <1 g in 4 hours, is permitted for use any time during the study. Other concomitant medications which are considered necessary for the participant's safety and wellbeing, may be considered on a case-by-case basis at the discretion of the Investigator in consultation with the medical monitor, if required, and recorded in the appropriate sections of the eCRF.

6.7 Monitoring and Management of Hypersensitivity Reactions

See Section 2.2.1 and the IB for nonclinical background information related to hypersensitivity to CS-1103.

Participants will be closely monitored and assessed for the development of signs and symptoms of hypersensitivity reactions, including anaphylaxis. For any hypersensitivity reaction, appropriate therapy should be instituted per standard of care. Administration of study treatment is to occur under close supervision of a physician and where full resuscitation equipment is immediately available.

7.0 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific study sites or of the study as a whole are detailed in Section 10.1.11.

The process for dose escalation and the stopping criteria for the study are described in Sections 4.5 and 4.6.

7.1 Discontinuation of Study Treatment

Not applicable as this is a single dose study.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, positive COVID-19 test or suspected SARS-CoV-2 infection, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up (Follow-up/EOS Visit) and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study treatment and the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study site study records.

Should a participant request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Participants withdrawing due to an AE should be followed up according to the follow-up/EOS Visit (see SoA, Section 1.3).

Participants who voluntarily withdraw are termed dropouts. Dropouts and participants withdrawn due to protocol violations may be replaced following discussion with the Principal Investigator and Sponsor.

Participants withdrawn due to an AE will not be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 450 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

When multiple procedures are scheduled at the same visit, the order of assessments will be, ECG procedures, vital signs, PK sample collection (nominal), questionnaire, and injection site assessment. All scheduled postdose times listed for the assessments in the SoA (Section 1.3) are relative to the start of the IV infusion unless there is a significant extension of the infusion duration or infusion interruption (see Table 2).

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

The Investigator will be responsible for safety assessments and review of AEs. The SRC will use reports of AEs to determine if further investigation is required due to possible association with study procedures or study treatment.

8.2.1 Physical Examinations

Physical examination schedule/timepoints are detailed in Section 1.3.

A complete physical examination will include, at a minimum, neurological assessments of the cardiovascular, respiratory, gastrointestinal, renal, and systems. Height/body mass index (BMI) (screening only) and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, renal, and abdomen (liver and spleen).

8.2.1.1 Injection Site Assessment

Injection Site Reactions

Injection site reactions will be monitored and assessed at the time points listed in the SoA (Section 1.3) until resolved. The Investigator will assess the following:

1. Induration
2. Redness
3. Swelling

This will be done on a 4-point scale:

0 = absent
1 = mild
2 = moderate
3 = severe

8.2.2 Vital Signs

Vital signs (to be taken before blood collection for laboratory tests) will be measured after remaining in a supine position for at least 5 minutes, following ECG collection, and will include body temperature, pulse rate, respiratory rate, oxygen saturation, and systolic and diastolic, and mean blood pressure. Three blood pressure measurements (3 consecutive blood pressure readings) will be recorded at intervals of at least 1 minute. The average of the 3 blood pressure, including the mean blood pressure readings will be recorded.

At screening and Admission/Day −1 vital signs may be repeated up to 2 times for meeting inclusion/exclusion criteria.

For detailed vital sign schedule/timepoints, see Table 1 and

Table 2 in Section 1.3.

8.2.3 Electrocardiograms

8.2.3.1 Safety ECGs

Triplicate 12-lead ECG(s) will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Electrocardiograms will be obtained after remaining for 5 minutes in the supine position and collected before other simultaneously scheduled procedures, i.e., vital signs and blood collections.

The ECG tracing should clearly identify the patient, include the date and time of the assessment, and include the signature and date of the person who made the local interpretation; the tracing will be archived at the study site. The site Investigator will read and evaluate the standard 12-lead ECG tracings and confirm the result and indicate "clinically significant," or "not clinically significant" along with a date and signature/initials. Review of ECG, at the time of collection, will be entered into the eCRF. Abnormal, clinically significant ECG results will be recorded as AEs (see Section 8.3). Additional details on how ECG data will be managed and recorded will be provided in the Site Study Manual.

During the 24-hour Holter-ECG monitoring, at each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

For detailed ECG timepoints, see Table 1 **and** Table 2 **in Section 1.3.**

8.2.3.2 Holter-ECG Monitoring

Continuous 24-hour Holter-ECG monitoring will be performed as outlined in the SoA Section 1.3. The ECGs will be extracted from Holter at predefined timepoints to be time-matched with PK samples as detailed in Table 1 and Table 2, Section 1.3.

Date and time of intake (start and completion) of any food during the Holter-ECG recording period will be recorded on the source documents and eCRF.

All ECGs for QT evaluation will be recorded by using high resolution (1,000 Hz) 12-lead digital Holter recorders provided by the ECG central laboratory. All Holter recording relevant procedures will be described in a manual provided by the central laboratory.

The CRU staff involved in the recording of the Holter ECGs will receive a training comprising study participant preparation, electrode placement, recording of the Holter-ECG under resting conditions, and data upload from the Holter-ECG recorded.

The same recorder/model will be used for all recordings for a study participant. Prior to each recording, the Holter recorder should be loaded with fresh batteries. The date and time settings must be checked at the start of each study day and synchronized with an official timekeeper for all machines used in the study.

Skin preparation must be thorough and electrode positions must be according to electrode positions recommended by the Laboratory Manual. Electrode positions will be marked with an indelible pen at the start of the study day to ensure exact reposition.

The 12-lead dECGs for concentration QTcF analysis will be extracted by the designated central laboratory after the study participant has remained in the supine position for at least 5 minutes.

Triplicate 12-lead dECGs for safety monitoring will be extracted within a 5-minute window preceding and up to the specified ECG acquisition time point.

Prior to conducting the concentration-QT analysis, a separate analysis plan will be prepared detailing the procedure and analysis.

During extraction periods on days when dECG Holter measurements are being taken, study participants should be restricted to a low level of physical activity and should refrain from any activities likely to stimulate or excite them as outlined in Section 5.3.3 due to potential interference with ECG signals. Food and drink should be restricted as detailed in the protocol (see Section 5.3.1) as this also has the potential to affect ECG signals.

IQVIA Connective Devices Team will provide the Holter monitor equipment, oversight, and central reads for this data. Detailed instructions regarding Holter Monitoring for the study is provided in the Site Study Manual.

8.2.4 Anxiety Symptoms Questionnaire

The Anxiety Symptoms Questionnaire (ASQ) is a brief self-report questionnaire which measures frequency and intensity of symptoms and was developed to improve assessment of anxiety symptoms in a clinical setting. The ASQ will be performed at timepoints outlined in Section 1.3, after completion of all other simultaneously scheduled procedures to avoid interference with scheduled vital sign, ECG, and PK evaluation.

Instructions will be provided to participants related to completing each questionnaire.

8.2.5 Clinical Safety Laboratory Tests

See Table 6 in Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

Local laboratories will be utilized to process and provide results for clinical laboratory tests allowing for immediate participant medical management. The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. All AEs require appropriate follow-up as described in Section 8.3). The laboratory reports must be filed with the source documents.

All laboratory tests with values considered abnormal and clinically significant from the time of study treatment administration to the end of the study should be repeated up to or until the values return to normal or baseline, or are no longer considered clinically significant by the Investigator or medical monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory tests, as defined in Table 6 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.6 Pregnancy Testing

Women of nonchildbearing potential should only be included after a negative highly sensitive serum pregnancy test at screening and urine pregnancy test prior to study treatment administration.

Additional urine pregnancy testing should be performed at times specified in the SoA (Section 1.3) and when pregnancy is otherwise suspected during the study.

8.2.7 Medical History/Demographics

Surgical, and general medication history will be recorded in the eCRF. Medical history will include COVID-19 infection and treatments received, COVID-19 vaccination status (including date and vaccine type received).

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on all AEs (see Section 8.3.3).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the last study visit at the timepoints specified in the SoA (Section 1.3). All AEs will be collected from the start of study treatment until the last study visit at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs. All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of the Investigator's awareness of the event, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of their awareness of the updated information.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event/cause of death to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting safety reports are provided in Section 10.3.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the Institutional Review Board (IRB), if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 10 weeks after dosing with study treatment. If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the female participant or female partner of male participant pregnancy and should follow the procedures outlined in Section 10.4.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication (or elective termination) of a pregnancy for medical reasons will be reported as an AE or SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death)], the Investigator will report according to the SAE reporting procedures described in Section 10.3.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy e.g., until delivery of baby or for longevity. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor or designee.

Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study

participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant after the single dose administration of study treatment, may continue participating in the study to complete required assessments until Follow-up/EOS Visit.

8.4 Pharmacokinetics

8.4.1 Collection of Samples

Blood samples of approximately 2 mL and pooled urine will be collected for measurement of plasma and urine concentrations of CS-1103; respectively, at times as specified in SoA (Section 1.3) and Table 2 during treatment. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to optimize the PK sample collection schedule for PK parameter calculations. Up to 2 additional blood collections may be added, pooled urine collections may be extended, and discharge may be delayed for up to 8 hours to optimize PK assessment without preparation of an amendment. The timing of PK (both plasma and urine) may be adjusted based on emerging data. In case that CS-1103 half-life is less than 4 hours, PK sampling may be discontinued at a time earlier than 48 hours.

Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. On the day of CS-1103 administration, samples should be collected in the contralateral (opposite) arm from the one being used for drug infusion. The actual date and time (24-hour clock time) of each sample will be recorded. Samples will be used to evaluate the PK of CS-1103-01. Each plasma sample will be divided into 2 aliquots (1 each [primary and a back-up]). Samples collected for analyses of CS-1103 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

The window for the blood collections is detailed in Table 2.

Urine samples for the determination of CS-1103-01 will be collected over the pooled intervals as specified in Table 2, Section 1.3. The actual start and stop date/time of each pooled urine collection as well as the volume of each pooled collection will be recorded. The site will also document whether the entire voided urine was collected for each interval (and complete void volume was recorded).

Blood and pooled urine samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.4.2 Determination of Drug Concentration

Samples for the determination of CS-1103 in plasma and urine will be analyzed on behalf of the Sponsor using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report. Reported CS-1103 concentrations will reflect the concentrations of the tetrasodium salt.

All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

Samples collected from participant who received placebo will not be analyzed.

Remaining plasma and pooled urine samples may be subjected to further analysis by the Sponsor or designee for the purpose of the development of additional bioanalytical assays and/or to investigate the presence of CS-1103 metabolic products, if applicable. Samples collected for analyses of CS-1103 (plasma) concentration may also be used to evaluate safety aspects related to concerns arising during or after the study. The bioanalytical laboratory personnel analyzing the PK samples will be unblinded.

8.4.3 Calculation of Derivation of Pharmacokinetic Variables

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.3 or higher (Certara, L.P. Princeton, New Jersey, United States of America [USA]) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA). Actual elapsed time from start of the IV infusion will be used for the final plasma PK parameter calculations. Nominal time from end of the IV infusion will be used for preliminary PK parameter calculations.

The plasma PK parameters in Table 4 will be determined for CS-1103. A minimum of 3 quantifiable postdose concentrations will be required for all calculations.

Table 6 Plasma Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
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 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

V_z	Volume of distribution
V_{ss}	Steady-state volume of distribution
$t_{1/2}$	Half-life; a minimum of 3 points will be used for estimation
λ_z	Elimination rate constant

Abbreviation: IV = intravenous.

Note: No dose correction for the sodium salt will be required for dose-dependent parameters, as both CS-1103 dose and plasma concentrations will be based on the weight of the tetrasodium salt.

For this study, an extrapolation of 30% will be considered acceptable for considering $AUC_{(0\text{-inf})}$ sufficiently well defined. Dose normalized exposure will also be determined. Additional plasma parameters may be calculated if deemed appropriate. Further details with respect to the PK analysis will be provided in the statistical analysis plan (SAP).

Any preliminary plasma PK result for use by the SRC will be reported in a manner that maintains blinding of the treatment the participants have received unless otherwise requested by the SRC. The urine PK parameters in Table 5 will be determined for CS-1103.

Table 7 Urine Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
$A_{e(t1\text{-}t2)}$	By-interval amount excreted in urine during the pooled collection interval from t1 to t2
$A_{e(0\text{-last})}$	Cumulative amount excreted in urine during the pooled collection intervals
$f_{e(t1\text{-}t2)}$	By-interval faction of dose (reported as percent) excreted in urine during the pooled collection interval from t1 to t2
$f_{e(0\text{-last})}$	Cumulative fraction of dose (reported as percent) excreted in urine during the pooled collection intervals
CL_r	Renal clearance calculated as $Ae_{(0\text{-last})}/AUC_{(0\text{-last})}$

Note: No dose correction for the sodium salt will be required for dose-dependent parameters, as both CS-1103 dose and plasma concentrations will be based on the weight of the tetrasodium salt.

Additional urine parameters may be calculated if deemed appropriate. Further details will be provided in the SAP.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and study site study files but will not constitute a protocol amendment. The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Genetics

Genetics are not evaluated in this study.

8.7 Biomarkers

Biomarkers are not evaluated in this study.

8.8 Immunogenicity Assessments

Not applicable

8.9 Health Economics

Health economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal statistical hypotheses are to be tested.

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

- Safety Analysis Set: All participants who have received one dose of study treatment (CS-1103 or placebo)
- Pharmacokinetic Analysis Set: All participants who have received one dose of CS-1103 and have at least 1 quantifiable plasma or urine postdose concentration, without protocol deviations or events expected to affect PK results

9.3 Statistical Analyses

9.3.1 General Considerations

The SAP will be developed and will describe the participant analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section focuses on the summary of the planned statistical analyses of the primary and secondary endpoints.

All analyses, summaries, and listings will be performed using SAS® software (Version 9.4 or higher). Results will be summarized by treatment and overall, where appropriate.

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: Sample size (n), mean, standard deviation (SD), median, minimum (min), and maximum (max)
- Summaries for plasma CS-1103 concentrations will include the coefficient of variation and PK parameter summaries will also include the geometric mean (except for t_{max}, which will only be presented as min, median, max)
- Categorical variables: Frequencies and percentages

Individual participant data will be presented in listings.

All missing or incomplete safety and PK data, including dates and times, are treated as such. Missing test results or assessments will not be imputed. The handling of any missing, unused, and spurious data will be documented in the Clinical Study Report.

9.3.2 Pharmacokinetic Analyses

9.3.2.1 PK Analysis

The PK analysis will be performed on the PK Population. CS-1103 plasma concentrations and calculated plasma and urine PK parameters will be listed and descriptively summarized by treatment and scheduled time point, as applicable. Arithmetic mean (±SD) and individual CS-1103 plasma concentration versus time curves will be plotted on linear and semilogarithmic scale, and percent of dose recovered in urine over time will be presented graphically, as appropriate. Dose proportionality of PK parameters will be explored graphically and by using a power model, as appropriate.

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 participant), C_{max} (and C_{EOI}, if appropriate) as well as dose-normalized exposure parameters versus dose will be presented (PK parameter definitions provided in Table 4). Geometric mean and individual cumulative percent CS-1103 excreted in urine versus time curves will also be presented on linear scale.

Further details with respect to the PK analysis will be provided in the SAP.

9.3.2.2 PK-PD Analysis

As an exploratory analysis, concentration-QT relationship will be assessed using linear mixed effects modeling. The details of the model will be provided in the SAP.

9.3.3 Safety Analyses

All safety analyses will be performed on the Safety Analysis Population. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The overall number and percentage of participants with at least one AE (and SAE) will be tabulated. Placebo participants will be combined into 1 treatment cohort. Overall, AE data will be summarized by treatment received. The frequency of all treatment emergent AEs (TEAEs), TEAEs by severity as detailed in Section 10.3. All TEAEs by relationship to study treatment, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of the study will be tabulated by Preferred Term (PT) and System Organ Class (SOC) for each treatment cohort. Summary statistics, including change from baseline, for vital signs, laboratory parameters, and ECG intervals will be provided by treatment, visit, and time point, as appropriate. Shift tables for laboratory parameters at each postbaseline visit will be tabulated against baseline results showing frequency of laboratory parameter observed normal range indicator (Low, Normal, High). For ECG results, appropriate outlier tabulations for QT and QTcF will also be presented by treatment. Outliers for QT and QTcF defined under outcome measures will be summarized using counts and percentages by treatment and sampling time, if appropriate and using participant-level maximum over time by treatment. The following categories will be presented by treatment and overall for CS-1103:

- Outlier QT and QTcF intervals (450-480 ms, 480-500 ms and >500 ms)
- Change from baseline in QT and QTcF intervals (30-60 ms and >60 ms)

Results of the physical examinations (including injection site assessment) and the AQS will be listed and if appropriate, summarized by treatment.

9.4 Interim Analysis

No formal interim analysis is planned. Preliminary PK parameters will be calculated using available quality-controlled CS-1103 concentrations and scheduled sampling times to support dose escalation decisions, as applicable.

9.5 Sample Size Determination

The sample size for this study is based upon precedent set by other Phase 1 studies to gain preliminary measure of safety and CS-1103 PK characteristics in a healthy participant population and not on statistical considerations of power while exposing as few participants as possible to the study treatment and procedures.

A sample size of 8 participants per dose level (6 active: 2 placebo) in this study design is expected to be sufficient to meet the objectives of this study.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs, or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, and all other applicable local regulations

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study site at which the Investigator has not signed the protocol.

10.1.2 Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study site.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

10.1.3 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

10.1.5 Informed Consent Process

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB or study site.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened will sign another ICF and receive a new screening number.

10.1.6 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant

names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.7 Committees Structure

10.1.7.1 Safety Review Committee

A SRC has been appointed for this study. The SRC is a group of clinicians and/or scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations regarding for escalation to the next planned dose level, escalation to an intermediate dose (a dose lower than the next planned dose), repeating a dose level, suspension of the dose escalation until further review of study data can be made, as to whether the stopping rules have been met, or stop dose escalation and termination of the study, etc. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

The SRC will consist, at a minimum, of the Principal or Sub-Investigator, Medical Monitor, and Sponsor's qualified designee. The SRC is responsible for reviewing and evaluating blinded safety and PK data for the most recently dosed cohort, cumulatively obtained data, and subsequently at regularly scheduled meetings and for the dose selection during dose escalation. The committee may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study.

Participant safety will be continuously monitored by the SRC, which includes safety signal detection at any time during the study.

In addition, an early aggregated safety data review will be performed, the goal of which is to allow for a cautious, stepwise approach to study treatment administration/dose escalation. An initial sentinel safety review by an Investigator for this study is planned for the first 2 participants who are dosed in each of the 5 cohorts and have provided safety and tolerability data for 24 hours after administration of a single dose prior to dosing the remaining participants within each cohort (see Section 4.1).

All safety results for at least 48 hours and preliminary PK data through at least Day 2 (24 hours postdose) for at least 6 out of the 8 participants within a cohort will be summarized

and reviewed by the SRC for agreement of next steps in dose escalation, due to the short half-life of the compound.

In particular, data will be reviewed by the Sponsor for identification of events that would potentially contribute to a requirement to pause/stop dose escalation or the study. See Section 4.6 for stopping criteria details.

Enrollment will be paused during the review. If a stopping rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.

Case unblinding may be performed for above reviews if necessary.

The details regarding SRC meeting frequency, data to be reviewed, the data review process, and information dissemination to clinical sites, are included in the SRC charter.

10.1.8 Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to any relevant database a summary of the results of the clinical study within 1 year from the end of the global clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

10.1.9 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- Guidance on completion of eCRFs will be provided in eCRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined in the Integrated Project Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Monitoring Plan.
- Details of study monitoring, including action required due to SARS-CoV-2/COVID-19, will be included in a separate Study Monitoring Plan.

- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.10 Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the monitoring guidelines and eCRF completion guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11 Study and Site Start and Closure

First Act of Recruitment

The study start date and first act of recruitment is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study treatment development

For study site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.12 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of

multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 6 will be performed by the CRU local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.0 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8 Protocol-required Laboratory Tests

Laboratory Assessments	Parameters	
Hematology	Platelet count	White blood cell count with differential (absolute and percent):
	Red blood cell count	Neutrophils
	Hemoglobin	Lymphocytes
	Hematocrit	Monocytes
	Red blood cell indices:	Eosinophils
	Mean corpuscular volume (MCV)	Basophils
	Mean corpuscular hemoglobin (MCH)	
	Mean cell hemoglobin concentration (MCHC)	Red cell distribution width (RDW)
	%Reticulocytes	Mean Platelet Volume (MPV)
Clinical Chemistry[a]	Blood urea nitrogen (BUN)	Triglycerides
	Creatinine	Aspartate aminotransferase (AST)
	Glucose	Alanine aminotransferase (ALT)
	Gamma glutamyl transferase (GGT)	Alkaline phosphatase (ALP)
		Creatine kinase
	Magnesium	Creatine kinase MB fraction will be performed if clinically indicated
	Cholesterol	Chloride
	Potassium	Globulin
	Sodium	Amylase
	Calcium	Total, direct, and indirect bilirubin
	Lactate dehydrogenase	Total protein
	Albumin	Phosphate
	Uric acid	Carbon dioxide (bicarbonate)
	Estimated glomerular filtration rate (eGFR) Modification of Diet and Renal Disease (MDRD): ($eGFR = 175 \times [\text{Serum Creatinine}]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ only if female}] \times [1.212 \text{ only if black}]$)	
Coagulation	International normalized ratio (INR)	Activated partial thromboplastin time (APTT)
	Prothrombin time (PT)	Thrombin time

Laboratory Assessments	Parameters	
		Fibrinogen
Urinalysis, Complete	Color	Ketones
	Appearance	Occult Blood
	Specific Gravity	Protein
	pH	Nitrite
	Glucose	Leukocyte esterase
	Microscopy (if clinically indicated)[b]	
Viral serology[c]	Human immunodeficiency virus (HIV) I and II Ag/Ab	
	Hepatitis B surface antigen (HBsAg)	
	Hepatitis C virus (HCV)	
Drugs of abuse and alcohol	Amphetamine/Methamphetamine	Opiates (morphine, codeine, heroin)
	Ethanol	Benzodiazepines
	Cannabinoids	Methadone metabolites
	Cocaine metabolites	Barbiturates
		Ecstasy (3,4-methylenedioxymethamphetamine)
	Cotinine (urine)	Phencyclidine
Other Tests	• COVID-19 Test • Follicle stimulating hormone (FSH) (as needed in women of nonchildbearing potential only)[c] • Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test[c] • Highly sensitive urine hCG pregnancy test[d] The results of each test must be entered into the (e)CRF.	

NOTES:
[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 4.6.
[b] If protein, blood, nitrites, or leukocyte esterase is abnormal it will reflex to microscopic testing.
[c] Screening only.
[d] Admission/Day −1, Follow-up/EOS Visit, and if pregnancy is suspected after dosing.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Study Treatment

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with that product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected treatment-treatment interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a preexisting condition and the surgery/procedure has been preplanned prior to study entry. However, if the preexisting condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the

deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

- For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

b. Is life-threatening

- The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- The term congenital anomaly/birth defect means there is suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the applicable/required report form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The intensity of an AE is an estimate of the relative severity of the event made by the Investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For causality assessments, events assessed as having a reasonable possibility of being related to study treatment will be considered "related". Events assessed as having no reasonable possibility of being related to study treatment will be considered "unrelated".
- The Investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee. All SAEs shall be considered at least possibly related to the study drug unless there is an obvious alternative explanation for the event.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of the Investigator's awareness of the information.

10.3.3 Reporting of SAEs

SAE Reporting to the Sponsor or Designee via Paper SAE Report Form

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the paper SAE report form. The study site will submit the SAE report form, via email, within 24 hours of the Investigator's awareness of the event. Facsimile transmission may be utilized as an alternative mode of submission, if necessary.

- Notification of SAE information via telephone does not replace the need for the Investigator to complete, sign and submit the paper SAE report form to the Sponsor or designee within 24 hours of the Investigator's awareness of the event.
- Contacts and methods for SAE reporting can be found in Safety Management Plan.

10.4 Appendix 4: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    a) Documented hysterectomy
    b) Documented bilateral salpingectomy
    c) Documented bilateral oophorectomy

NOTE: Documentation can come from the study site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female:
    a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

10.4.2 Contraception Guidance

Male Participants

The following text is required ONLY until it has been determined that WOCBP who are partners of male participants no longer need protection from potential exposure to study treatment in seminal fluid and should be provided by the Sponsor and/or medic. For genotoxic study treatment, or for non-genotoxic study treatment with demonstrated or suspected human teratogenicity/fetotoxicity at subtherapeutic exposure levels where it is theoretically possible that relevant systemic concentrations may be achieved in WOCBP from exposure to seminal fluid, to prevent exposure of an embryo/fetus, the following text is required.

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study and at least 90 days after dosing with the study treatment.

  - Agree to use a male condom with spermicide and have their partner use a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

- In addition, male participants must refrain from donating sperm for the duration of the study and for at least 90 days after dosing with the study treatment.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration from the day of dosing until at least 90 days after dosing with the study treatment.

Female Participants

Female participants of childbearing potential are not eligible to participate.

Pregnancy Testing:

- Pregnancy testing should be performed at times specified in the SoA (Section 1.3) and as required locally.
- Additional pregnancy testing may be performed at any time during the study based on an Investigator's discretion when pregnancy is suspected.
- Pregnancy testing, with a sensitivity of 5 mIU/mL will be performed using the test kit approved by the Sponsor and in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Male Participants With Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive CS-1103.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a

participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the Investigator will report according to the SAE reporting procedures described in Section 10.3.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor or designee as described in Section 10.3. While the Investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant after the single dose administration of the study treatment may continue participating in the study to complete required assessments including Follow-up/EOS Visit.

10.5 Appendix 5: Abbreviations

Abbreviation	Definition
$A_{e(t1-t2)}$	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.
ADL	Activities of Daily Living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AQS	Anxiety Symptoms Questionnaire
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{(0-inf)}$	Area under the plasma concentration-time curve from time zero 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
CFR	Code of Federal Regulations
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
CRF	Case report form
CRU	Clinical Research Unit
dECG	Digital electrocardiogram
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study

Abbreviation	Definition
FDA	Food and Drug Administration
$f_{e(0\text{-last})}$	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
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IV	Intravenous
Max	Maximum
Min	Minimum
λ_z	Elimination rate constant
NOAEL	No-observed-adverse-effect-level
OTC	Over-the-counter
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

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

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Signature of Investigator

PROTOCOL TITLE: 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

PROTOCOL NO: CS-1103-01

VERSION: Version 3.0 Amendment 2

This protocol is a confidential communication of Clear Scientific, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to IQVIA, Inc.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

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