Statistical Analysis Plan

Phase 1, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess Potential Interactions Between Intravenous Cocaine and Oral SXC-2023

Name of Investigational Drug:	SXC-2023
Study Number:	SXC-Ph1b-001
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Sponsor:	Division of Therapeutics and Medical Consequences of Drug Abuse National Institute on Drug Abuse National Institutes of Health 11601 Landsdown Street North Bethesda, MD 20852
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APPROVAL PAGE

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Study Title: **Phase 1, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess Potential Interactions Between Intravenous Cocaine and Oral SXC-2023**

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ABBREVIATIONS

Abbreviation	Definition
λ_z	Terminal Rate Constant
ACLS	Advanced Cardiovascular Life Support
AE	Adverse Event(s)
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-time Curve
AUC_{0-12}	AUC from Time 0 to 12 Hours Post-dose
$AUC_{0-\infty}$	AUC from Time 0 to Time Infinity
AUC_{0-t}	AUC from Time 0 to Time t
β-HCG	Beta Human Chorionic Gonadotropin
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BE	Benzoylecgonine
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
BSCS	Brief Substance Craving Scale
BW	Bodyweight
CAP	College of American Pathology
CBC	Complete Blood Cell Count
CHF	Congestive Heart Failure
CI	Confidence Interval
CL	Clearance
CL/F	Clearance from Plasma after Oral Administration
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum Plasma Concentration
$C_{max(ss)}$	Maximum Plasma Concentration at Steady State
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CrCL	Creatinine Clearance
C_{trough}	Trough Plasma Concentration
CUD	Cocaine Use Disorder
CV	Coefficient of Variation

Abbreviation	Definition
CYP	Cytochrome P450
DA	Dopamine
DRF	Dose Range Finding
DSM-V	American Psychiatric Association Diagnostic and Statistical Manual
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EPM	Elevated Plus Maze
ePRO	Electronic Patient Reported Outcomes
FDA	United States Food and Drug Administration
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GLAST	Glutamate-aspartate Transporter
GLT-1	Glutamate Transporter 1
GSH	Glutathione
HBsAg	Hepatitis B Surface Antigen
HCVab	Hepatitis C Antibody
HEK	Human Embryonic Kidney
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug Application
IR	Immediate Release
IRB	Institutional Review Board
i.v.	Intravenous
K2EDTA	Dipotassium Ethylenediaminetetraacetic Acid
LC-MS/MS	Liquid Chromatography-tandem Mass Spectrometry
LN	Natural Logarithm
Max	Maximum
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
mGluR5	Metabotropic Glutamate Receptor Subtype 5
MINI	Mini International Neuropsychiatric Interview
MOP	Manual of Procedures
N	Number of Participants

Abbreviation	Definition
NIDA	National Institute on Drug Abuse
NAC	N-acetylcysteine
NET	Norepinephrine Transporter
NIDA	National Institute on Drug Abuse
NOAEL	No Observed Adverse Effect Level
OATP	Organic Anion Transporting Polypeptide
PCP	Phencyclidine (Phenylcyclohexyl Piperidine)
PK	Pharmacokinetics
PoC	Proof of Concept
PPI	Prepulse Inhibition
QD	Everyday
QTc	Corrected QT Interval
QTcF	QT Interval Corrected by Fridericia's Formula
SAE	Serious Adverse Event
SD	Standard Deviation
SERT	Serotonin Transporter
SOC	System Organ Class
Sxc	System x_c^-
$t_{1/2}$	Half-life
THC	Tetrahydrocannabinol
T_{max}	Time to Maximum Plasma Concentration
UI	Uncertainty Interval
US	United States
VAS	Visual Analog Scale

1. INTRODUCTION

Cocaine use disorder (CUD) represents a serious public health problem. Estimates of cocaine abuse, based on data from 195 countries from 1990 to 2016, indicate that the worldwide age-standardized prevalence of cocaine dependence was 64 per 100,000. Despite progress in the development of psychosocial treatments for CUD, many patients still do not respond to these treatments. Standard treatment for CUD has been associated with high dropout rates, and many patients do not attain substantial periods of cocaine abstinence. This limitation has stimulated the search for pharmacological approaches for the treatment of CUD.

A major obstacle to effective treatment of CUD is relapse following abstinence. Preclinical studies have revealed a critical role for glutamatergic signaling, including metabotropic glutamate receptor type 5 (mGluR5)-mediated signaling, in reinstatement of cocaine seeking behavior. Glutamate projections from dorsal (prelimbic, anterior cingulate) medial prefrontal cortex to nucleus accumbens core are involved in reinstatement induced by cocaine priming. Reinstatement of cocaine seeking behavior also involves glutamatergic signaling-induced reduction in synaptic strength in the nucleus accumbens shell.

Understanding the role of System xc- (Sxc), also known as the cystine-glutamate antiporter, in glutamatergic signaling could provide greater insight into treating CUD. Several clinical studies have demonstrated that increased Sxc activity can restore the glutamatergic system. SXC-2023 is a small molecule that activates Sxc by increasing the cyst(e)ine levels in the brain. It is thought that SXC-2023 activates Sxc indirectly, through metabolism which ultimately increases local levels of the endogenous substrate, cystine. Therefore, the neurochemical impact of Sxc activation by SXC-2023 is to restore low levels of GSH, while simultaneously optimizing glutamate signaling to restore cognitive control and executive function over behaviors.

This Statistical Analysis Plan (SAP) describes the analysis and reporting of the safety, tolerability, and interactions of cocaine and oral SXC-2023 (version 3.0, date 18 June 2024).

2. PURPOSE AND RESPONSIBILITIES

The purpose of this SAP is to ensure that the summary tables, data listings and figures (TLFs) that will be produced, and the statistical methodologies that will be used are complete and appropriate to allow valid conclusions regarding the study objectives.

Technical Resources International, Inc. (TRI) will carry out the analysis as well as perform production and quality control of TLFs related to all statistical analyses for the study.

3. OBJECTIVES

The objectives of this study are as follows:

3.1 Primary Objectives

The primary objective of this study is to determine if there are clinically meaningful interactions between oral SXC-2023 treatment concurrent with 20 and 40 mg i.v. cocaine infusions by measuring adverse events (AEs) and cardiovascular responses including heart rate (HR), blood pressure (BP), and electrocardiogram (ECG) (including corrected QT interval [QTc]).

3.2 Secondary Objectives

Following are the secondary objectives:

- To evaluate whether administration of SXC-2023 alters the pharmacokinetics (PK) of cocaine and/or its major metabolite, benzoylecgonine (BE).
- To determine the PK of SXC-2023 administered at a dose of 800 mg once daily.
- To evaluate whether SXC-2023 treatment alters the subjective effects of cocaine measured by Visual Analog Scales (VAS) and Brief Substance Craving Scale (BSCS).

4. STUDY DESIGN

4.1 Overview

This is a double-blind, placebo-controlled, parallel group study to compare the effects of SXC-2023 vs placebo control on i.v. cocaine's physiological and subjective effects in non-treatment seeking cocaine-experienced volunteers.

Participants will be screened for eligibility as outpatients and inpatients. Outpatient screening will occur between Day -28 and Day -4. On Study Day -3, participants will undergo the clinic intake to screen for continued eligibility. On Study Day -2, participants will be screened for eligibility with a single-blind screening infusion (Infusion Session 1) of 20 mg cocaine, followed by a saline infusion, and followed by a 40 mg cocaine infusion. Each infusion will consist of a 2 mL i.v. push and will be administered 60 minutes apart. Physiological and subjective data (VAS) from these sessions will be part of the eligibility criteria to continue in the study. Participants who cannot differentiate between two cocaine doses will not be enrolled in the study. Participants must have a higher score on the VAS for "HIGH" effect at either the nominal 5 or 10 minute post cocaine infusion assessment after the 40 mg cocaine infusion compared with the 20 mg cocaine infusion, to continue in the study.

Once a participant has been determined to be eligible, the participant will be randomized on Day -1 to receive either SXC-2023 or placebo. On Days 1 and 2, participants will receive baseline infusions of saline and cocaine (Day 1/Infusion Session 2: 20 mg cocaine; Day 2/Infusion Session 3: 40 mg cocaine). The order of the saline and cocaine infusions will be randomized for each session. The participants will receive either SXC-2023 or matched placebo once a day every morning from Days 3 to 9. On Day 8, participants will receive cocaine 20 mg infusion (Infusion Session 4) and on Day 9 participants will receive cocaine 40 mg (Infusion Session 5). Each cocaine infusion will be preceded or followed by saline i.v. infusion. The first infusion on Days 8 and 9 will begin approximately 3 hours after SXC-2023 800 mg or placebo. Each infusion will consist of a 2 mL i.v. push and will be administered 60 minutes apart. The order of the saline and cocaine infusions for each participant for Infusion Sessions 4 and 5 will be the same as the randomized order for Infusion Sessions 2 and 3, respectively. The participants will be discharged from the research clinic on Day 11, 2 days after the last infusion of cocaine (Infusion Session 5), and will have a telephone follow-up call between 7 and 10 days after clinic discharge.

4.2 Sample Size

Twenty participants will be randomized to 2 groups (10 for each group), receiving either SXC-2023 or placebo treatment for 7 days. Study participants who complete all five cocaine infusion sessions will be considered completed participants. This study requires 8 completed participants in each group. It is expected that, if 20 participants are randomized, there should be at least 8 completers in each group.

4.3 Study Population

Male and female non-treatment seeking cocaine-experienced participants, 18 to 59 years of age, who have used cocaine by the smoked or intravenous (i.v.) route at least 6 times over the participant's lifetime prior to clinic intake (Day -3), with at least one use (smoked, i.v., or nasal route) within the past 3 months, and provide a cocaine positive urine sample at least once during screening but must have a negative urine test for cocaine at clinic intake. The inclusion and exclusion criteria can be found in the protocol.

4.4 Stopping Criteria

4.4.1 Study

The study will be halted from further enrollment if any of the following criteria are met at any point during the study:

- Four participants experience a severe AE, such as significant neurological or psychiatric events (e.g., psychosis) or behavioral manifestations of cocaine toxicity
- Two severe AEs related to cocaine toxicity
- Two participants experience a similar SAE that is not clearly unrelated to study drug or cocaine
- Two participants fulfill the following ECG criteria based on the mean of triplicate measures (≥ 1 minute apart), that will be completed once the first ECG demonstrates a prolonged interval: QTcF ≥500 msec or uncorrected QT interval of >600 msec.

4.4.2 Individual Participant

Further participation of the participant in the study is stopped if any of the following criteria are met:

- Acute chest pain
- Systolic BP > 160 mmHg sustained for 5 minutes or more
- Diastolic BP < 40 mmHg or > 100 mmHg sustained for 5 minutes or more
- Heart rate < 40 bpm or > 160 bpm sustained for 5 minutes or more
- QTcF ≥ 500 msec, or uncorrected QT interval > 600 msec
- Clinically significant ECG changes in the opinion of an investigator
- AST > 2 ULN
- ALT > 2 ULN
- BUN > 2 ULN
- Creatinine > 1.5 mg/dL

- Significant neurological or psychiatric events (e.g., psychosis) or any behavioral manifestations of cocaine toxicity
- Any condition that in the clinical judgment of an investigator is of sufficient magnitude to present a danger to the participant
- Participant experiences an SAE that is not clearly unrelated to study drug or cocaine

NIDA and Promentis Pharmaceuticals Inc. alone may suspend dosing at any time for any safety reason. Factors that must be considered for suspension of dosing include the frequency, severity, clinical significance, possible causality, and anticipated reversibility of all observed AEs or laboratory abnormalities. The IRB will be notified if dosing is suspended.

4.5 Study Treatment and Dosing

4.5.1 SXC-2023 or Placebo

Participants randomized to SXC-2023 will take four capsules of 200 mg of SXC-2023 (total 800 mg) once a day from Day 3 to 9. SXC-2023 will be administered to participants before regular breakfast.

Participants randomized to placebo on a dosing schedule identical to that of SXC-2023 and will be administered to participants before regular breakfast.

Table 4-1 summarizes the dose and treatment schedule for SXC-2023 and matching Placebo.

Table 4-1 Dose and Treatment Schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
SXC-2023 200 mg or placebo	800 mg	Once each day from Day 3 – Day 9

The following assessments will be performed daily before dosing:

- adverse events/serious adverse events
- concomitant medications
- vital signs (HR and BP) prior to dosing with SXC-2023
- safety laboratory tests (hematology, clinical chemistry, and urinalysis) will be collected on Day 6.
- blood for SXC-2023 PK will be collected on Day 9 approximately 15 minutes prior to the morning dose and up to 48 hours post-Day 9 dose.

Blood collections will be performed within ± 1 minute for the first 30 minutes after the infusion and ± 5 minutes at all other time points.

The treatment infusion sessions (Sessions 4 and 5 – Study Days 8 and 9) provide cardiovascular effects, subjective responses, and PK data for SXC-2023 at steady state. The schedule of assessments is shown in Table 4-5. The times are nominal times with a window of ± 1 minute for PK blood samples for the first 30 minutes after the infusion and ± 5 minutes at all other time points. When multiple assessments are scheduled at the same time, they should be performed in the order of ECG, vital signs, VAS, then blood draws.

4.5.2 Cocaine

Participants will undergo cocaine/saline i.v. challenge sessions according to the following schedule and doses (Table 4-2):

Table 4-2 Schedule of Infusion Sessions

Study Phase	Session Number	Study Day	Infusions (2 mL over 1 minute)
Screening	1	-2	20 mg cocaine, followed by a saline infusion, followed by 40 mg cocaine*
Baseline	2	1	Saline or 20 mg cocaine followed by either 20 mg cocaine or saline*
Baseline	3	2	Saline or 40 mg cocaine followed by either 40 mg cocaine or saline*
Treatment	4	8	Saline or 20 mg cocaine followed by either 20 mg cocaine or saline*[a]
Treatment	5	9	Saline or 40 mg cocaine followed by either 40 mg cocaine or saline*[b]

* Infusions will be administered 60 minutes apart.
a The order of cocaine or saline with match the order established during Infusion Session 2 (Day 1).
b The order of cocaine or saline with match the order established during Infusion Session 3 (Day 2).

4.6 Study Time and Event Schedule

The Assessment Schedule (Table 4-3) lists the assessments and when they are performed.

Table 4-3 Assessment Schedule

Study Phase	Screening	Intake	Screening Infusion		Baseline Infusions		Treatment + Treatment Infusions								Discharge	Follow- up visit[j]
Study Day	**-28 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**18 to 21**
Informed consent	X															
Medical history/current medical conditions	X	X														
Drug history	X	X														
COVID-19 Test [a]		X														
Infectious disease serology	S															
Pregnancy test [b]	X	X			X	X						X	X		X	
Urine toxicology screen	X	X														
Locator form/Demographics	X															
Cocaine use by timeline follow back	X															
MINI (version 7.0)	X															
Body height	X															
Body weight	X	X														
BMI	X															
Inpatient																
Eligibility (Inclusion/Exclusion)	X	X	X	X												
Randomization				X												
Physical exam	S	S													S	
C-SSRS	X	X													X	
VAS Training [c]		X														
VAS [d]			X		X	X						X	X			
BSCS [d]					X	X						X	X			
12-lead ECG [e]	X	X	X		X	X						X	X		X	
Telemetry			X		X	X						X	X			
Vital Signs [e, f]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Safety laboratory tests [g]	X	X								X					X	

Study Phase	**Screening**	**Intake**	**Screening Infusion**		**Baseline Infusions**		**Treatment + Treatment Infusions**								**Discharge**	**Follow- up visit[j]**
SXC-2023/placebo administration							X	X	X	X	X	X	X			
Adverse events/serious adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior & concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion Session #:			**1**		**2**	**3**						**4**	**5**			
20 mg cocaine IV/saline infusion [h]			X		X							X				
40 mg cocaine IV/saline infusion [h]			X			X							X			
Cocaine blood PK [i]						X							X			
SXC-2023 blood PK [i]													X	X	X	
Beck Depression Inventory (BDI)															X	
Beck Anxiety Inventory (BAI)															X	
Mental status exam															X	

S = Assessment to be recorded in source documentation only
X = Assessment to be recorded in the clinical database or received electronically from a vendor

a Will be performed on Day-3

b The serum pregnancy test will be done in all females at screening and intake. Urine pregnancy test will be done prior to each infusion session 2-5 and at discharge.

c Retraining may be performed as needed.

d On infusion days, times for collection of VAS and BSCS are nominal times ± 3 minutes for the first 30 minutes after the infusion and ± 5 minutes at all other time points.

e On infusion days, times for collection of ECG and vital signs (in this order) are nominal times ± 3 minutes for the first 30 minutes after the infusion and ± 5 minutes at all other time points.

f Vital signs include HR and BP. Vital signs will be measured after semi-supine for approximately 3 min. During the screening infusion Session 1, semi-supine BP and HR will be recorded at the time points relative to the first infusion of the day. Out of range BP and HR collected during the first 180 minutes post-dose will be repeated if deemed necessary by an investigator. During the baseline and treatment infusions (Sessions 2 to 5), BP and HR will be recorded at the time points relative to the first infusion of the day. Out of range BP and HR collected during the first 180 minutes post-dose will be repeated if deemed necessary by an investigator.

g Safety laboratory tests include hematology, clinical chemistry panel, and urinalysis. Safety laboratory tests during active treatment will be done on Day 6 and at discharge.

h Participants will undergo cocaine/saline IV challenge sessions according to the schedule and doses described. Infusions will be administered approximately 60 minutes apart.

i Blood collections will be performed after vital signs and ECG are performed and when at the same nominal time within ±1 minute for the first 30 minutes after the infusion and ±5 minutes at all other time points. Order of assessments: ECG, vital signs, VAS, blood draws. On Day 9, blood draws will be approximately 15 minutes prior to SXC-2023/placebo dosing and up to 48 hours post-Day 9 dose according to the study defined time points.

j By phone call.

4.7 Cocaine Infusions

4.7.1 Infusion Session 1 (Day -2)

Table 4-4 shows the series of activities that occur on the day of the screening cocaine infusion. The times are nominal times with a window of ± 3 minutes up to 30 minutes after each infusion otherwise they are ± 5 minutes.

For a participant to receive the first screening cocaine and saline infusions (Session 1 – Study Day -2), s/he must have a urine drug toxicology screen that is negative for drugs of abuse (except marijuana) at Day -3. The participant's semi supine blood pressure must be ≤ 140 mm Hg (systolic) and ≤ 90 mm Hg (diastolic), heart rate must be ≤ 100 beats per minute taken in the half-hour prior to receiving any cocaine infusion. If blood pressure is elevated, it may be repeated one time to determine if the participant meets these criteria to receive an infusion. The participant's ECG taken within 30 minutes prior to receiving any cocaine infusion must not have any clinically significant abnormal arrhythmia or interval changes. The screening infusions are to ensure that Participants are responsive to and safely tolerate the cocaine test doses. Only Participants who are able to distinguish between a 20 mg and 40 mg dose of cocaine i.v. will be randomized. The highest score on VAS for "HIGH" effect at the 5 or 10 minute time point after cocaine infusion will be used to discriminate those individuals who can discern the differences between the two cocaine doses.

Participants who cannot safely tolerate the cocaine test doses and/or are unable to distinguish between a 20 mg and 40 mg dose of cocaine i.v. will not be eligible for the study. These participants will stay overnight for observation and be discharged from the unit the next day after their vital signs are assessed by the PI.

Table 4-4 Screening Cocaine Infusion (Session 1) Schedule of Activities

Timepoint relative to start of first infusion	Timepoint relative to start of last infusion	HR, BP	ECG	VAS
-30 min	-30 min	X	X	X
-15 min	-15 min	X		
-10 min	-10 min			
Time 0	**Time 0 20 mg cocaine i.v.**	**20 mg cocaine i.v.**		
5 min	5 min	X	X	X
10 min	10 min	X	X	X
15 min	15 min	X	X	X
20 min	20 min	X		
25 min	25 min	X		
30 min	30 min	X	X	X
45 min	45 min	X	X	X
55 min	55 min	X		X
60 min	**Time 0**	**Saline i.v.**		
65 min	5 min	X	X	X
70 min	10 min	X	X	X
75 min	15 min	X	X	X
80 min	20 min	X		
85 min	25 min	X		
90 min	30 min	X	X	X
105 min	45 min	X	X	X

Timepoint relative to start of first infusion	Timepoint relative to start of last infusion	HR, BP	ECG	VAS
115 min	55 min	X		X
120 min	**Time 0**	**40 mg cocaine i.v.**		
125 min	5 min	X	X	X
130 min	10 min	X	X	X
135 min	15 min	X	X	X
140 min	20 min	X		
145 min	25 min	X		
150 min	30 min	X	X	X
165 min	45 min	X	X	X
180 min	60 min	X	X	X
210 min	90 min	X		
240 min	120 min	X		
270 min	150 min	X		
300 min	180 min	X		
330 min	210 min	X		
360 min	240 min	X	X	

4.7.2 Infusion Sessions 2-5

4.7.2.1 Infusion Session 2

The baseline infusion sessions (Sessions 2 and 3 – Study Days 1 and 2) provide cardiovascular effects, subjective responses, and PK data of cocaine in the absence of SXC-2023.

During each baseline infusion session, each session will administer both cocaine and saline in a randomized order. Sessions 2 and 3 are randomized independently of one another. The participant's semi-supine blood pressure must be ≤ 140 mm Hg (systolic) and ≤ 90 mm Hg (diastolic), heart rate must be ≤ 100 beats per minute taken 15 and 30 minutes prior to the first cocaine infusion. If blood pressure or heart rate is elevated, it may be repeated one time to determine if the participant meets these criteria to receive an infusion. The participant's ECG taken in the half-hour (-30 minutes) prior to receiving any cocaine infusion must not have any clinically significant abnormal arrhythmia or interval changes. The pregnancy test must be negative before infusion.

The schedule of activities for infusion sessions are shown in Table 4-5.

Table 4-5 Infusion Sessions 2-5 (Days 1, 2, 8 and 9) Schedule of Activities

Timepoint relative to start of first infusion	Timepoint relative to start of most recent infusion	HR, BP	ECG	VAS	BSCS	Cocaine PK (Days 2 and 9 Only)	SXC-2023 / Placebo Admin (Day 8 and 9 Only)	SXC-2023 Blood PK (Days 9-11 Only)
-180 min	-180 min						X	X[a]
-135 min	-135 min							
-120 min	-120 min							X (1 hr)[a]
-60 min	-60 min							X (2 hr)[a]
-30 min	-30 min	X	X	X				
-15 min	-15 min	X						
-15 min	-15 min					X		
-10 min	-10 min							
-5 min	-5 min				X			X (~3 hr)[a]

Timepoint relative to start of first infusion	Timepoint relative to start of most recent infusion	HR, BP	ECG	VAS	BSCS	Cocaine PK (Days 2 and 9 Only)	SXC-2023 / Placebo Admin (Day 8 and 9 Only)	SXC-2023 Blood PK (Days 9-11 Only)
Time 0	**Time 0**	**Saline or Cocaine i.v.**						
5 min	5 min	X	X	X		X		
10 min	10 min	X	X	X				
15 min	15 min	X	X	X		X		
20 min	20 min	X						
25 min	25 min	X						
30 min	30 min	X	X	X		X		
45 min	45 min	X	X	X				
55 min	55 min	X		X				X (~4 hr)[a]
60 min	**Time 0**	**Saline or Cocaine i.v.**						
65 min	5 min	X	X	X		X		
70 min	10 min	X	X	X				
75 min	15 min	X	X	X		X		
80 min	20 min	X						
85 min	25 min	X						
90 min	30 min	X	X	X		X		
105 min	45 min	X		X				
120 min	60 min	X	X	X		X		
125 min	65 min				X			
150 min	90 min	X	X			X		
180 min	120 min	X	X			X		X (6 hr)[a]
210 min	150 min	X						
240 min	180 min	X				X		
270 min	210 min	X						
300 min	240 min	X	X					X (8 hr)[a]
480 min	420 min					X		
540 min	480 min							X (12 hr)[a]
720 min	660 min					X		
780 min	720 min							X (16 hr)[a]
21 hr	20 hr							X (24 hr)[b]
33 hr	32 hr							X (36 hr)[b]
45 hr	44 hr							X (48 hr)[b]

a Day 9 only.
b These PK samples will be collected on Days 10 and 11

This infusion session 2 is performed as described above, with participants receiving one infusion of 20 mg of cocaine and one infusion of saline (in a randomized order).

Participants will be monitored for safety (vital signs, ECG) and administered subjective assessments (VAS, BSCS) at the timepoints shown.

The times are nominal times with the following windows:

- PK blood draws: ± 1 minute up to 30 minutes after each infusion and ± 5 minutes at all other time points.
- ECG, vital signs, and subjective assessments: ± 3 minutes up to 30 minutes after each infusion and ± 5 minutes at all other time points.

ECG, then vital signs will be collected first when multiple assessments are scheduled at the same nominal time.

Continuous cardiac monitoring by telemetry will be performed from one hour prior to starting transfusions until 4 hours after the last infusion. Participants will be monitored for at least 1 hour after the cocaine infusion by study personnel and staff. Thereafter, study personnel will monitor participants and take vital signs at the times specified in Table 4-5.

4.7.2.2 Infusion Session 3 (Day 2)

This infusion session is performed as described above, with participants receiving one infusion of 40 mg of cocaine and one infusion of saline (in a randomized order). The participant's semisupine blood pressure must be ≤ 140 mm Hg (systolic) and ≤ 90 mm Hg (diastolic), heart rate must be ≤ 100 beats per minute taken in the half-hour prior to receiving any cocaine infusion. If blood pressure or heart rate is elevated, it may be repeated one time to determine if the participant meets these criteria to receive an infusion. The participant's ECG taken in the half hour (-30 minutes) prior to receiving any cocaine infusion must not have any clinically significant abnormal arrhythmia or interval changes. Pregnancy test must be negative prior to infusion.

Blood is collected to assess the PK of cocaine, according to the schedule shown in Table 4-5.

Continuous cardiac monitoring by telemetry from one hour prior to starting infusions until 4 hours after the last infusion. Participants will be monitored for at least 1 hour after the cocaine infusion by study personnel and staff. Thereafter, study personnel will monitor participants and take vital signs at the times specified in Table 4-5.

4.7.2.3 Infusion Session 4 (Day 8)

The infusion session is performed as described previously; cocaine (20 mg) and saline will be administered in the same order in which they were administered during Session 2. The participant's semi-supine blood pressure must be ≤ 140 mm Hg (systolic) and ≤ 90 mm Hg (diastolic), heart rate must be ≤ 100 beats per minute taken in the half-hour prior to receiving any cocaine infusion. If blood pressure or heart rate is elevated, it may be repeated one time to determine if the participant meets these criteria to receive an infusion. The participant's ECG taken in the half-hour (-30 minutes) prior to receiving any cocaine infusion must not have any clinically significant abnormal arrhythmia or interval changes. Pregnancy test will be done and must be negative before infusion.

SXC-2023 will be administered three hours prior to the first cocaine/saline infusion of the day.

4.7.2.4 Infusion Session 5 (Day 9)

The infusion session is performed as described previously; cocaine (40 mg) and saline will be administered in the same order in which they were administered during Session 3. The participant's semi-supine blood pressure must be ≤ 140 mm Hg (systolic) and ≤ 90 mm Hg (diastolic), heart rate must be ≤ 100 beats per minute taken in the half-hour prior to receiving any cocaine infusion. If blood pressure or heart rate is elevated, it may be repeated one time to determine if the participant meets these criteria to receive an infusion. The participant's ECG taken in the half-hour (-30 minutes) prior to receiving any cocaine infusion must not have any clinically significant abnormal arrhythmia or interval changes. Pregnancy test must be negative before infusion.

SXC-2023 will be administered three hours prior to the first cocaine/saline infusion of the day. This is the last dose to be administered in this study.

The full PK sampling for SXC-2023 is performed at this infusion session (pre-dose and 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours post-dose).

5. STUDY ENDPOINTS

5.1 Primary Endpoints

The primary endpoints are adverse events (AEs) and cardiovascular responses including HR, BP, and ECG (including QTcF).

5.1.1 Adverse Events

Adverse events (AEs) will be assessed daily. An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational product or clinically significant. Sources of information about adverse events include reports by the participant, concomitant medications, and clinically significant abnormal findings on physical examination, vital signs, ECG, BDI, BAI, and mental status assessments.

All AEs, recorded during the inpatient portion of the study regardless of severity, will be followed by study Investigator until satisfactory resolution. AEs must be reported up to the date of final follow-up following hospital discharge. At the follow-up phone call, AEs will be recorded and followed; they will be followed to resolution only if they are serious, or if the study Investigator assesses them to be clinically significant.

5.1.2 Cardiovascular and Blood Pressure Assessments

Before and after each i.v. infusion, the participant's physiologic responses will be closely monitored using repeated HR, BP, and ECG readings assessed in semi supine position.

During the Screening Infusion Session 1, BP and HR will be recorded at the following nominal time points relative to the first infusion of the day: -30, -15, 5, 10, 15, 20, 25, 30, 45, 55, 65, 70, 75, 80, 85, 90, 105, 115, 125, 130, 135, 140, 145, 150, 165, 180, 210, 240, 270, 300, 330 and 360 minutes. Out of range BP and HR collected during the first 180 minutes post-dose will be repeated if deemed necessary by an investigator. Continuous cardiac monitoring with telemetry will begin approximately 60 minutes before the first infusion and will end 4 hours after the last cocaine infusion. Twelve-lead ECG measurements will be recorded at -30 minutes and at 5, 10, 15, 30, 45, 65, 70, 75, 75, 90, 105, 125, 130, 135, 150, 165, 180, and 360 minutes after the first infusion. Study personnel and staff will monitor participants for at least 1 hour after each infusion. Times for collection of ECG and vital signs are nominal times ± 3 minutes for the first 30 minutes after the infusion and ± 5 minutes at all other time points. ECG, then vital signs will be collected first when multiple assessments are scheduled at the same nominal time.

During the baseline and treatment infusions (Sessions 2 to 5), BP and HR will be recorded at the following time points relative to the first infusion of the day: -30, -15, 5, 10, 15, 20, 25, 30, 45, 55, 65, 70, 75, 80, 85, 90, 105, 120, 150, 180, 210, 240, 270, and 300 minutes. Out of range BP

and HR collected during the first 180 minutes post-dose will be repeated if deemed necessary by an investigator. Continuous cardiac monitoring with telemetry beginning approximately 60 minutes before the first infusion until 4 hours after the second infusion. Twelve-lead ECG measurements will be recorded at -30 minutes and at nominal 5, 10, 15, 30, 45, 65, 70, 75, 90, 120, 150, 180 and 300 minutes after the first infusion. Times for collection of ECG and vital signs are nominal times ± 3 minutes for the first 30 minutes after the infusion and ± 5 minutes at all other time points. ECG, then vital signs will be collected first when multiple assessments are scheduled at the same nominal time.

ECG measurements to be recorded on a CRF include HR, RR, PR, QRS, and QT interval. For data analysis the QT interval will be corrected using the method of Fridericia (1920) (QTcF).

5.2 Secondary Endpoints

5.2.1 Safety

5.2.1.1 Clinical Laboratory Test

5.2.1.1.1 Hematology

Blood will be collected with appropriate anticoagulant and tested for complete blood cell count (CBC) with differential (absolute and percent) and platelets. The laboratory performing these assessments will be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of the current certification. Hematology will be performed during screening, intake, on Day 6, and at discharge.

5.2.1.1.2 Clinical Chemistries

Blood will be collected in serum separation Vacutainer™ tubes and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: glucose, blood urea nitrogen, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT, calcium, sodium, potassium, chloride, and carbon dioxide. The laboratory performing these assessments will be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of the current certification. Blood chemistries will be performed at screening, intake, on Day 6, and at discharge.

5.2.1.1.3 Urinalysis

A dipstick urinalysis test will be performed during screening, intake, Day 6, and at discharge.

5.2.2 Pharmacokinetics (PK)

PK samples will be assayed for cocaine, BE, and SXC-2023 (as appropriate) using validated bioanalytical methods of liquid chromatography with tandem mass spectrometry (LC-MS/MS). For details of sample collection, processing, and shipment to the bioanalytical laboratory see the study Manual of Procedures (MOP). Approximately 179 mL blood will be collected for PK analysis and other clinical tests (Appendix A).

5.2.2.1 Cocaine and BE

Blood samples (4 mL) will be collected during infusion Sessions 3 (Day 2) and 5 (Day 9) at predose (approximately 15 minutes before the first infusion) and at 5, 15, 30, 65, 75, 90, 120, 150, and 180 minutes, and at 4, 8, and 12 hours after the first infusion. Samples will be collected for assessment of cocaine and BE PK in 4-mL Vacutainer™ tubes containing K2EDTA.

5.2.2.2 SXC-2023 Blood PK

On Day 9, blood samples will be collected approximately 15 minutes prior to the morning dose and 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours post-dose. Samples for collection of SXC-2023 PK will be collected in 4-mL Vacutainer™ tubes containing sodium heparin.

5.2.3 Subjective Effects

5.2.3.1 Brief Substance Craving Scale (BSCS)

The BSCS is a self-administered assessment that asks the participant to rate his or her craving for cocaine. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire. Participants will use an electronic patient reported outcomes (ePRO) system provided by Technical Resources International, Inc, to answer BSCS. BSCS will be administered at pre-infusion and 125 minutes after the start of the cocaine infusion.

5.2.3.2 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a measure of suicidal ideation and behavior. At Screening, the “Baseline” version will be administered; on Days -3 and 12 and at the Follow-up visit (Days 19 to 26), the “Since Last Visit” version will be administered.

5.2.3.3 Subjective Response – Visual Assessment Scale (VAS)

The VAS is a self-administered assessment evaluating the subjective effects of cocaine. Participants will use an ePRO system provided by Technical Resources International, Inc., to answer VAS. The participant should be instructed to respond to the questions with regards to how they feel at the moment of the assessment on a 100 mm Likert Scale with 0 being “Not at all” and 100 being “Extremely”. For the VAS, participants will report the degree to which they feel “any effects”, “high”, “good effects”, “bad effects”, “desire for cocaine”, “depressed”, “anxious”, “over- stimulated”, and “cocaine liking.”

VAS will be administered 30 minutes prior to the first infusion and at 5, 10, 15, 30, 45, 55, 65, 70, 75, 90, 105, 115, 125, 130, 135, 150, 165 and 180 minutes after the first infusion for screening infusion 1, and at -30, 5, 10, 15, 30, 45, 55, 65, 70, 75, 90, 105 and 120 minutes after the first infusion for baseline and treatment infusion Sessions 2 to 5. Windows for collection of VAS are nominal times ± 3 minutes for the first 30 minutes after the infusion and ± 5 minutes at all other time points.

6. STUDY POPULATION

6.1 Full Analysis Set (FAS)

The FAS population will include all randomized participants.

6.2 Safety Population

The safety population will include all participants who are included in the FAS population and who received any study drug.

6.3 Pharmacokinetic Population

The pharmacokinetic (PK) population will include all participants who completed the Day 9 12-hour cocaine PK sample. The PK concentration dataset will include all participants who have at least 1 quantifiable concentration of SXC-2023, cocaine, or cocaine metabolite, benzoylecgonine (BE). The PK analysis dataset will include all participants who have sufficient concentration-time data for a given analyte to calculate PK parameters.

6.4 Evaluable for Subjective Effects Analysis Population

The Evaluable analysis set will include all participants who completed all 5 infusion sessions.

7. STATISTICAL ANALYSES

Descriptive statistics will be used to present study data. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. Categorical variables will be presented as counts and percentages. All data will be presented separately by treatment group. All data will be presented in listings, except for the assessments done to determine eligibility.

All the analyses of safety data for this study will be performed using SAS® statistical software package, version 9.4 or later. Additional software, such as R (version 4.5.1, The R foundation for Statistical Computing), may also be used for input data and TLFs generation if necessary.

Missing data will not be imputed for any analysis, except for partial dates for determining treatment emergent AEs and prior and concomitant medication (see Section 7.1). The numbers of data points reflected in summary statistics will be indicated by presenting the number of observations.

The pharmacokinetics data will be analyzed using Phoenix WinNonlin (Version 8.6 or later, Certara). Additional software such as R (version 4.3.3 or later, The R foundation for Computing) may also be used for input data and Tables, Listings, and Figures (TLFs) generation if necessary.

7.1 Handling of Partial Dates

It is common to allow the entry of partial dates for adverse events and concomitant medications. For dates where incomplete month and/or day values are allowed, the partial dates will be imputed as follows:

For adverse event and concomitant medications start dates:

- If the month and year are provided, the day is missing, and the month and year is the same as the month and year of the first dose/infusion of any study drug, then the day of the date of the first dose/infusion will be used for the missing day.
- If the month and year are provided, the day is missing, and the month and year is different from the month and year of the first dose/infusion of any study drug, then the 1st of the month will be used for the missing day.
- If the year is provided, the day and month are missing, and the year is the same as the year of the first dose/infusion of any study drug, then the day and month of the date of the first dose/infusion will be used for the missing day and month.
- If the year is provided, the day and month are missing, and the year is different from the year of the first dose/infusion of any study drug, then the 1st of January will be used for the missing day and month.
- If the day and year is provided, the month is missing, and the year is the same as the year of the first dose/infusion of any study drug, then the month of the date of the first dose/infusion will be used for the missing month.
- If a start date is missing all date parts then first date of dose/infusion will be used.

For adverse event and concomitant medications end dates:

- If the month and year are provided, the day is missing, and the month and year is the same as the month and year of the first dose/infusion of any study drug, then the day of the date of the first dose/infusion will be used for the missing day.
- If the month and year are provided, the day is missing, and the month and year is different from the month and year of the last dose/infusion of any study drug, then the last day of the month will be used for missing day.
- If the year is provided, the day and month are missing, and the year is the same as the year of the first dose/infusion of any study drug, then the day and month of the date of the first dose/infusion will be used for the missing day and month.
- If the year is provided, the day and month are missing, and the year is different from the year of the first dose/infusion of any study drug, then the 31st of December will be used for missing day and month.
- If the day and year is provided, the month is missing, and the year is the same as the year of the first dose/infusion of any study drug, then the month of the date of the last dose will be used for the missing month.
- If end date is missing and ongoing is not missing then the adverse event or medication will be assumed to be ongoing and the end date will remain missing.
- If the imputation rules for an end date makes the end date less than the start date for an adverse event or medication, then the start date will be used for the end date.

The imputed dates will be used to determine treatment emergent adverse events and prior and concomitant medications. In their respective listings, imputed dates will be flagged. The value for the derived variable of duration for adverse events or medication will be missing if either start or end date are imputed.

7.2 Demographic and Baseline Characteristics

7.2.1 Subject Disposition and Withdrawals

The number of participants included in each population will be summarized by treatment and along with the reason for exclusion and discontinuations.

7.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, gender, ethnicity, race, height, weight, and BMI) will be summarized by population, treatment group and overall.

7.2.3 Medical History and Physical Examination Findings

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group for the safety population. Listings will also be provided.

7.2.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the World Health Organization drug dictionary (WHO DD). A summary of concomitant medications will be provided for the safety population by Anatomic Therapeutic Class (ATC), WHO DD Level 4, and treatment. A listing of prior and concomitant medication will also be provided.

7.3 Exposure

The summary of study drug exposure by dose day (Day 1-9) of SXC-2023 or placebo and by cocaine infusion session (1-5) will be summarized for the safety population of descriptive statistics (counts and percentages). A listing will also be provided.

7.4 Primary Outcome Measures

7.4.1 Adverse Events

AE data will be compiled for the SXC-2023 and placebo groups and presented as summary statistics for the safety population. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and will be grouped by system, organ, class (SOC) designation. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.

- by treatment, primary system organ class, preferred term, and maximum severity.

Separate summaries will be provided for related (definitely, probably, or possibly) adverse events for treatment emergent adverse events and serious adverse events (separately for SXC-2023 and cocaine). Listings of all adverse events and serious adverse events will be provided. Additionally, a listing will be provided for adverse events leading to death, withdrawal or discontinuation.

7.4.2 Cardiovascular Responses

Summary statistics (n, mean, standard deviation, median, minimum and maximum) of HR and BP by treatment, cocaine dose, infusion session, and timepoint will be presented. Maximum, maximum change and time to maximum from pre-infusion during the first hour after each infusion will be summarized by treatment, cocaine dose, and infusion session.

The maximum value and maximum change from pre-infusion values will be analyzed using an analysis of covariance (ANCOVA) model to compare the treatment groups (SXC-2023 versus placebo). The ANCOVA model will include the baseline (i.e., prior to SXC-2023/placebo treatment) maximum value or the baseline maximum change from pre-infusion as a covariate. The analyses for the 20mg and 40mg cocaine infusions will be performed separately. Effects will be considered statistically significant at a two-sided $p < 0.05$.

The distribution of the maximum value and maximum change for HR and BP will be explored. If not deemed normal or if right skewed, an ANCOVA analysis will be performed on the log-transformed HR and BP maximum value and maximum change. If the log-transformed data distribution is not normal then a Wilcoxon rank sum test will be used to compare treatment groups.

Time to maximum value will be analyzed using a Kaplan-Meier estimator. A log-rank test will be used to compare the time to maximum value by treatment groups (SXC-2023 vs Placebo). The analyses for the 20mg and 40mg cocaine infusions will be performed separately. Effects will be considered statistically significant at a two-sided $p < 0.05$.

ECG parameters extracted from Holter and their changes from pre-infusion (mean of the 3 pre-infusion ECGs) will be presented with summary statistics by visit and timepoint. Changes in ECG intervals during saline infusion as compared to those taken during cocaine infusions will be also reported as summary statistics. A listing of clinically significant ECG changes will be presented.

Pulse will be summarized by infusion session, timepoint, and treatment group.

Clinically significant ECG values will be presented in listings.

A listing of repeated assessments will be presented.

7.5 Secondary Outcome Measures

7.5.1 Safety

7.5.1.1 Clinical Laboratory Parameters

The parameters of each clinical test will be presented for each group as n, mean, SD, median, minimum and maximum values at each scheduled assessment, as well as change from baseline. Baseline value will be the last value prior to dosing (SXC-2023/Placebo). Summary data (counts and % of patients) of clinically significant laboratory parameters and listings of all results will be presented.

7.5.1.2 C-SSRS

A listing of the C-SSRS responses will be presented.

7.5.2 Pharmacokinetic Analyses

The following PK parameters will be determined for cocaine, BE, and SXC-2023 (as appropriate): maximum plasma concentration (Cmax), area under the concentration-time curve (AUC) from time 0 to time t (AUC0-t), AUC from time 0 to 12 hours post-dose (AUC0-12), AUC from time 0 to time infinity (AUC0-∞), time to maximum plasma concentration (Tmax), trough plasma concentration (Ctrough), terminal rate constant (λz), half-life (t1/2), clearance (CL) and clearance from plasma after oral administration (CL/F). Weight-adjusted parameters may be determined when necessary.

PK parameters will be calculated using noncompartmental analysis (NCA) implemented within a validated installation of Phoenix® WinNonlin®. Additional software may be used, if necessary. All softwares used will be documented in the PK section of the CSR.

7.5.2.1 Plasma PK of Cocaine and BE

PK parameters for plasma cocaine and BE will be calculated as described in Table 7-1 using noncompartmental methods. Plasma concentration-time profiles of cocaine and BE after infusion Sessions 3 and 5 will be analyzed to obtain PK parameter estimates and will be presented by participant and group summary statistics [N, mean, standard deviation (SD), % coefficient of variation (CV), median, minimum, maximum, geometric mean, CV% of geometric mean, and 90% confidence intervals (CI)]. Actual sampling times relative to the start of the cocaine infusion will be used in the NCA, where available, otherwise nominal sampling times will be used. Additionally, individual participant profiles will be plotted by day using actual times on linear and log-linear scales and mean profiles will be plotted by day using nominal sampling times on linear and log-linear scales.

7.5.2.2 Plasma PK of SXC-2023

Plasma SXC-2023 concentration data for all participants in the PK concentration dataset will be summarized by day, treatment, and nominal sampling time, regardless of their inclusion in the PK analysis dataset. Summary statistics will include N, mean, standard deviation (SD), %

coefficient of variation (CV), median, minimum, maximum, geometric mean, and CV% of geometric mean. Individual participant and mean profiles of the concentration-time data will be plotted by day and treatment. Individual participant profiles will be plotted by day using actual times on linear and log-linear scales and mean profiles will be plotted by day using nominal sampling times on linear and log-linear scales.

PK parameters for plasma SXC-2023 will be calculated as described in Table 7-1 using noncompartmental methods.

Table 7-1 Pharmacokinetic Parameters

Parameter	Description
For Plasma Cocaine and BE	
C_{max}	Maximum observed plasma concentration
T_{max}	Time of the maximum observed plasma concentration
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration (Ct) calculated by the linear-up/log-down trapezoidal rule.
$AUC_{(0-11)}$	Area under the plasma concentration-time curve from time 0 to 11 hours post-dose calculated by the linear-up/log-down trapezoidal rule. **Note:** This parameter was not requested in the protocol but it will be reported because only subjects randomized to cocaine→saline will have a 12 hr. sample.
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from time 0 to 12 hours post-dose calculated by the linear-up/log-down trapezoidal rule. This requires extrapolation for subjects randomized to saline→cocaine, for which the last timepoint is 11 hrs.
AUC_{inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity. The terminal area from Ct to infinity was calculated by using the approximation as Ct/ λz thus $AUC_{inf} = AUC_{last} + Ct/\lambda z$
AUC%extrap	Percent of AUC_{inf} extrapolated from Ct to infinity
λz	The terminal-phase exponential rate constant as calculated from the negative slope of the regression line for the terminal linear portion of the LN transformed plasma concentration versus time curve
$t_{½}$	The apparent terminal exponential half-life, calculated as ln(2)/λz
CL	Total body clearance estimated as the drug dose divided by the plasma AUC_{0-inf} (cocaine only)
C_{max}/70	C_{max} for a 40 mg dose of cocaine normalized to 70 kg body weight (Cmax*70/BW)
AUC_{0-11}/70 and AUC_{0-12}/70	AUC_{0-11} and AUC_{0-12} for a 40 mg dose of cocaine normalized to 70 kg body weight (AUC_{0-11}*70/BW)
AUC_{inf}/70	AUC_{inf} for a 40 mg dose of cocaine normalized to 70 kg body weight (AUC_{inf}*70/BW)

Parameter	Description
CL/70	Clearance for a 40 mg dose of cocaine normalized to 70 kg total body weight (cocaine only) (CL*70/BW)
For Plasma SXC-2023	
C_{max}	Maximum observed plasma concentration
T_{max}	Time of maximum observed plasma concentration
$AUC_{(0-24)}$ = AUCtau	Area under the plasma concentration-time curve from 0 to 24 hours post-dose. **Note**: the protocol requested $AUC_{(0-12)}$ but $AUC_{(0-24)}$ is more appropriate because SXC-2023 was dosed once per day.
AUC_{inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity. The terminal area from Ct to infinity is calculated by using the approximation as Ct/ λz thus $AUC_{inf} = AUC_{lasr} + Ct/\lambda z$
λz	The terminal-phase exponential rate constant as calculated from the negative slope of the regression line for the terminal linear portion of the LN transformed plasma concentration versus time curve. A minimum of 3 time points are required to calculate λz.
t½	The apparent terminal exponential half-life, calculated as ln(2)/λz
C_{trough}	Trough (predose) concentration
CL/F	Apparent oral clearance estimated as the drug dose divided by the plasma $AUC_{(0-24)}$ at steady-state (Day 9/10)
C_{max}/70	C_{max} normalized to 70 mg body weight
$AUC_{(0-24)}$/70	$AUC_{(0-24)}$ normalized to 70 mg body weight
AUC_{inf}/70	AUC_{inf} normalized to 70 kg body weight
CL/F/70	CL/F normalized to 70 kg body weight

PK parameters values will be listed for each participant in the PK analysis dataset by day and treatment, and the following descriptive statistics will be provided: N, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean and geometric CV% will be calculated for continuous PK parameters. Tmax will be presented as median, minimum, and maximum.

7.5.2.3 Imputation of BLQ Values

For calculation of mean concentrations and generation of mean concentration versus time profiles, all BLQ values will be set to zero except when an individual BLQ value falls between 2 quantifiable values, in which case it will be treated as missing data.

For the PK analysis and individual concentration versus time plots, a concentration that is BLQ is assigned a value of zero if it occurs in a profile before the first measurable concentration. If a BLQ value occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantification, then the BLQ value is treated as missing data. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it is treated as missing data. If 2 BLQ values occur in succession after Cmax, the profile is deemed to have

terminated at the first BLQ value, and any subsequent concentrations are omitted from PK calculations.

In circumstances where alternative approaches to handling BLQ data are necessary, the relevant modifications will be appropriately documented in the clinical study report or final PK report.

7.5.2.4 Imputation of Concentration at Dosing Time for AUC Calculation

For all analytes, the last pre-dose concentration will be used as the concentration at the dosing time (i.e., at time =0).

7.5.2.5 Significant Digits

Concentration data and PK parameters will be generally reported to 3 significant figures. All associated summary statistics for these parameters will also be reported to 3 significant figures, except for N which will be reported as an integer. Discrete time parameters (such as Tmax and Tlast) and associated summary statistics will be reported to 2 decimal places.

7.5.2.6 Statistical Analysis of PK Parameters

To assess the effect of SXC-2023 on the PK of cocaine and BE, an analysis of covariance (ANCOVA) will be performed on the natural logarithms (LN) of Cmax, $AUC_{(0\text{-}11)}$, $AUC_{(0\text{-}12)}$, AUC_{last}, AUC_{inf}, CL, and their weight-normalized values, with treatment group, baseline LN of the parameter, and their interaction as a fixed effects. A second model including the Day 9 cocaine/saline infusion order as a fixed effect will also be fit. Following FDA guidance, normality of residuals will not be checked or expected.

The 95% confidence interval (CI) for the ratio of the least squares means of SXC-2023 versus placebo will be determined. The 95% CI will be obtained by exponentiation of the lower and upper bounds of the 95% CI of the difference between the least squares means of the LN of the parameter.

7.5.3 Subjective Effects Analyses

The VAS and BSCS analyses described below will be conducted on the Evaluable Population.

7.5.3.1 VAS Responses

Subjective effects VAS will be presented as summary statistics of maximum values, change from baseline and time to maximum values over 1-hour from the start of the cocaine infusion by treatment group for each question. Data will be compared between groups by Wilcoxon rank sum test. Additionally, within groups comparisons between study days will be done by Wilcoxon signed-rank test. Time to maximum VAS score will be analyzed using a Kaplan-Meier estimator. A log-rank test will be used to compare the time to maximum value by treatment groups (SXC-2023 vs Placebo). Comparisons will be considered statistically significant at a two-sided $p < 0.05$. The analyses for the 20mg and 40mg cocaine infusions will be performed separately.

7.5.3.2 BSCS Scores

BSCS scores will be presented for each item as n, mean, SD, median, minimum, and maximum values at each scheduled assessment by treatment group. Group scores will be compared using Wilcoxon rank sum statistic for pre- and post- cocaine infusion assessments.

7.6 Other Outcome Measures

7.6.1.1 BDI Scores

BDI scores will be presented for each item in a listing.

7.6.1.2 BAI Scores

BAI scores will be presented for each item in a listing.

7.6.1.3 Mental Status

Mental status exam findings will be presented in a listing.

7.6.2 Tobacco Consumption

A listing of the cigarette consumption during the trial will be presented.

8. TABLES, FIGURES, LISTINGS, AND APPENDICES

The proposed listing of tables, figures, and listings to be generated with the analysis and included in clinical study report is presented in a separate document.

APPENDIX A

Table A-1 Schedule and Volume of Blood Collections

	Per sample		Study Day																
			-28 to -4	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**18 to 21**	**Total Volume (mL)**
Chemistries (including pregnancy testing and FSH, if needed)	5 mL	S	1	1								1					1		15
Hematology	4 mL	P	1	1								1					1		12
PK Samples for cocaine*	4 mL	P						13							13				104
PK Samples for SXC-2023*	4 mL	P													9	2†	1††		48
Total (mL)			**9**	**9**				**52**				**9**			**88**	**8**	**13**		**188**

S = Serum, P = Plasma
Additional 1 mL of blood will be added to every in-house collection as potential waste due to use of catheter.
*For collection, storage, and shipping of PK samples see the study Manual of Procedures (MOP).
†24 and 36 hours after SXC-2023 dosing on Day 9
††48 hours after SXC-2023 dosing on Day 9