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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 AND DEFINITIONS

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
CYP	Cytochrome P450

Abbreviation	Definition
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
NIDA	National Institute on Drug Abuse

Abbreviation	Definition
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 SYNOPSIS

Protocol Number:	NIDA-SXC-Ph1b-001
Protocol Title:	Phase 1, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess Potential Interactions Between Intravenous Cocaine and Oral SXC-2023
Principal Investigator:	Debra J. Kelsh, M.D.
Study Site:	Altasciences Clinical Kansas, Inc., Overland Park, Kansas
Study Drug:	SXC-2023
Number of Participants:	Approximately twenty participants will be randomized to 2 groups (approximately 10 for each group), receiving either SXC-2023 or placebo treatment for 7 days. Study participants who complete all 5 cocaine infusion sessions will be considered completed participants. This study requires 8 completed participants in each group. It is expected that, if approximately 20 participants are randomized, there should be least 8 completers in each group.
Study Population:	Non-treatment seeking cocaine-experienced volunteers 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. Participants must provide a cocaine positive urine sample at least once during screening but must have a negative urine test for cocaine at clinic intake.
Objectives:	**Primary:** The primary objective of this study is to determine if there are significant 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 [QTcF]). **Secondary:** 1. To evaluate whether administration of SXC-2023 alters the pharmacokinetics (PK) of cocaine and/or its major metabolite, benzoylecgonine (BE) 2. To determine the PK of SXC-2023 administered at a dose of 800 mg once daily 3. To evaluate whether SXC-2023 treatment alters the subjective effects of cocaine measured by Visual Analog Scales (VAS) and Brief Substance Craving Scale (BSCS)
Primary Endpoints:	**Safety and Tolerability:** AEs and cardiovascular responses including HR, BP, and ECG (including QTcF).
Secondary Endpoints:	**Safety:** Clinical laboratory **PK:** PK of cocaine and BE; PK of SXC-2023 **Subjective Effects:** VAS and BSCS

Design:

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.

Study Drugs and Dosing:

Participants will be randomized to receive either SXC-2023 or placebo.

SXC-2023: Participants will take 800 mg SXC-2023 once a day every morning from Days 3 to 9.

Placebo: Participants will take matched placebo with the dosing schedule identical to that of SXC-2023.

Cocaine: Participants will undergo cocaine/saline i.v. challenge sessions according to the following schedule and doses (the order of cocaine/saline administration will be randomized for Sessions 2 and 3):

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* †

	<table><tr><td>Treatment</td><td>5</td><td>9</td><td>Saline or 40 mg cocaine followed by either 40 mg cocaine or saline*‡</td></tr></table> * Infusions will be administered 60 minutes apart. † The order of cocaine or saline will match the order established during Infusion Session 2 (Day 1). ‡ The order of cocaine or saline will match the order established during Infusion Session 3 (Day 2).
PK Assessments:	**Cocaine:** Blood samples (4 mL) will be collected during infusion Sessions 3 (Day 2) and 5 (Day 9) at 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. **SXC-2023:** On Day 9, blood samples will be collected at pre-dose, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours post-dose. Blood collections will be 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. **Bioanalytics:** Cocaine, BE and SXC-2023 in plasma samples will be analyzed by a bioanalytical laboratory using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods. **PK Parameters:** The following PK parameters will be determined for cocaine, BE, and SXC-2023 (as appropriate): C_{max}, AUC_{0-t}, AUC_{0-12}, $AUC_{0-\infty}$, T_{max}, C_{trough}, λz, $t_{1/2}$, CL, and CL/F. Weight-adjusted parameters may be determined when necessary.
Safety Assessments:	**Screening Infusion Session:** During Screening Infusion Session 1, 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, 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 the Investigator. Continuous telemetry monitoring will be performed beginning approximately 60 minutes before the first infusion until 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, 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 (in this order) 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. **Baseline and Treatment Infusion Sessions:** 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 the Investigator. During Infusion Sessions 2 to 5, continuous telemetry monitoring will be performed beginning 60 minutes before the first infusion until 4 hours after the last infusion. Safety laboratory tests will be repeated on Day 6. Pregnancy testing (urine) will be done prior to each infusion session. Infusion will proceed only if the testing result is negative. Twelve-lead ECG measurements will be recorded at -30 minutes and at 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 (in this order) are nominal times ± 3 minutes for the first 30 minutes after the infusion and ± 5 minutes at all other time points.
Subjective Effects	**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 "drug liking." On a 100 mm Likert Scale with 0 being "Not at all" and 100 being "Extremely". VAS will be administered 30 minutes prior to cocaine 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. **BSCS:** BSCS will be administered at pre-infusion and 125 minutes after the start of the cocaine infusion for infusion Sessions 2 to 5. 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.
Analysis Plan:	**Primary Endpoints:** 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. The severity, frequency, and relationship of AEs to study drug will be presented by preferred term by SOC grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Vital signs data (HR and BP) will be presented as summary statistics of maximum (max) absolute values, max change from baseline, and time to max value during the 1-hour period after each cocaine infusion. Data will be compared between groups and within groups by study day by Wilcoxon rank sum statistic. Effects will be considered statistically significant at a two-sided $p < 0.05$. In addition, summary statistics for vital signs at each study time point will also be presented. Changes in ECG intervals during saline infusion as compared to those taken during cocaine infusions will be reported as summary statistics. Clinically significant ECG changes will be presented as counts and percentages. **Secondary Endpoints:** 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)].

	Plasma concentration-time profiles of SXC-2023 on Day 9 (40 mg cocaine + saline infusion session) will be analyzed to obtain PK parameter estimates. Individual participant and group summary statistics will be presented. To assess the effect of SXC-2023 on the PK of cocaine and BE, an analysis of variance (ANOVA) will be performed on the natural logarithms (LN) of AUC_{0-t}, $AUC_{0-\infty}$ and CL, with treatment group as a fixed effect. In addition, an analysis may be conducted with the LN of 70 kg weight adjusted parameters [C_{max}*bodyweight (BW)/70 kg, AUC_{0-t} *BW/70 kg, $AUC_{0-\infty}$ *BW /70 kg, and CL/BW*70 kg] when necessary. Within this ANOVA framework, comparisons of SXC-2023 versus placebo groups will be performed for baseline (Day 2) and Day 9 cocaine challenge sessions (40 mg). The effect of saline/cocaine versus cocaine/saline randomized administration sequence will also be examined. The 90% CI for the ratio of the least squares means of SXC-2023 versus placebo AUC and C_{max} parameters will be determined. The 90% CI will be obtained by exponentiation of the 90% confidence intervals for the difference between the least squares means on the LN scale. Subjective effects VAS will be presented as summary statistics of maximum absolute values, maximum change from baseline, and time to maximum value over the 1-hour period after cocaine infusions. Data will be compared between groups and within groups between study days by Wilcoxon rank sum statistic. BSCS scores will be presented for each item as n, mean, SD, median, minimum, and maximum values at each scheduled assessment. Group scores will be compared using Wilcoxon rank sum statistic for pre- and post- cocaine infusion assessments. The concentrations of each clinical chemistry 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 screening. The number of excursions outside the normal laboratory limits will be presented.

2 INTRODUCTION AND RATIONALE

2.1 Background and Rationale for the Study

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 population (95% uncertainty interval [UI] 57–71; 5.0 million people [4.5–5.6 million]) (Farrell *et al*., 2019). Globally, an estimated 0.32% (95% UI 0.21–0.45) of all-cause deaths were associated with cocaine dependence. In the United States (US) there are approximately 4.8 million regular users of cocaine and 1.4 million individuals with CUD in 2021 (Substance and Mental Health Services Administration, 2022). From 2012 through 2018, the rate of drug overdose deaths involving cocaine more than tripled (from 1.4 to 4.5) (Hedegaard *et al*., 2020). No medications have been approved for the treatment of CUD, psychosocial treatment is currently the standard treatment (Kampman, 2019). 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. Relapse is often preceded by intense craving that is precipitated by re-exposure to cocaine, or exposure to cocaine-associated contextual cues (Jaffe *et al*., 1989; Ehrman *et al*., 1992; Childress *et al*., 1999). This clinical scenario has been studied extensively by using a preclinical animal model for reinstatement (reviewed in Bossert *et al*., 2013; Shaham *et al*., 2003). 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 (Cornish and Kalivas, 2000; Kalivas and McFarland, 2003). Reinstatement of cocaine seeking behavior also involves glutamatergic signaling-induced reduction in synaptic strength in the nucleus accumbens shell (Jedynak *et al*., 2016; Ebner *et al*., 2018).

2.2 Rationale for Study Intervention

2.2.1 SXC-2023

Understanding the role of System x_c- (Sxc), also known as the cystine-glutamate antiporter, in glutamatergic signaling could provide greater insight into treating CUD (Kau *et al*., 2008). Many cell types of the central nervous system (*e.g*., neurons, astrocytes, microglia, vascular endothelial cells, ependymal cells of the choroid plexus, and leptomeninges) express detectable levels of Sxc (reviewed in Niciu *et al.,* 2012). Astrocytes, which constitute 40-50% of all glial cells, have been implicated in controlling the clearance of extracellular glutamate concentrations

in the brain (Danbolt 2001; Lee and Pow, 2012; Murphy-Royal *et al*., 2017). Sxc, glutamate transporter-1 (GLT-1), and glutamate-aspartate transporter (GLAST) have roles in regulating glutamate homeostasis in astrocytes (Williams *et al*., 2005). Under physiological conditions, Sxc transports cystine into cells while glutamate is exported in a 1:1 stoichiometric ratio (Massie *et al*., 2016). In particular, Sxc contributes to exporting glutamate from astrocytes into the extracellular space, provides the majority of non-synaptic glutamate levels in the nucleus accumbens core, and has reduced activity following the extinction from cocaine self-administration (Baker *et al*., 2002; Baker *et al*., 2003; Knackstedt *et al*., 2010) Preclinical studies have demonstrated that repeated cocaine use reduces Sxc activity in the nucleus accumbens core, nucleus accumbens shell, and prefrontal cortex (Madayag *et al*., 2007; Hammad *et al*., 2017; Knackstedt *et al*., 2010). Additional preclinical studies have shown the reversal of cocaine-induced blunting of Sxc activity through the administration of N-acetylcysteine (NAC) and N-acetylcysteine amide (NACA) (prodrugs for cysteine) and ceftriaxone (Madayag *et al*., 2007; Kau *et al*., 2008; Knackstedt, *et al*., 2010; Jastrzebska *et al*., 2016; Logan *et al*., 2018). Several clinical studies have demonstrated that increased Sxc activity can restore the glutamatergic system, however, there is limited clinical information determining the treatment of CUD by increasing or restoring Sxc activity.

Promentis Pharmaceuticals has developed SXC-2023, a small molecule that activates Sxc by increasing the cyst(e)ine levels in the brain (Investigator's Brochure, 2024). SXC-2023, formulated as an oral, enteric capsule, is currently under investigation for the treatment of impulse control-related neuropsychiatric disorders and neurodegenerative diseases marked by altered glutamate signaling. It is thought that SXC-2023 activates Sxc indirectly, through metabolism which ultimately increases local levels of the endogenous substrate, cystine. The functional consequence of this increase in cystine concentrations is two-fold: (1) it modulates synaptic glutamate neurotransmission via Sxc-mediated glutamate release into the extrasynaptic compartment; and (2) it promotes the synthesis of glutathione (GSH) by increasing intracellular levels of the rate-limiting precursor molecule, cysteine. 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.

2.2.1.1 Pharmacology

Pharmacokinetics

Seven pharmacokinetic (PK) studies of SXC-2023 (dose range 3 mg/kg to 100 mg/kg) have been conducted in mice, Sprague-Dawley rats, Beagle dogs, and Cynomolgus monkeys. SXC-2023 was rapidly absorbed in all species following oral administration with peak plasma concentrations occurring within one hour in dogs and up to four hours in monkeys. NAC and *p*-toluic acid, the metabolites of SXC-2023, demonstrated short plasma half lives (< 6 hours) in all nonhuman species tested (Investigator's Brochure, 2024).

Safety and toxicity of SXC-2023 was evaluated in rats and dogs following chronic dosing for 7, 28, and 90 days (Investigator's Brochure, 2024). Results from 28- and 90-day dose range finding (DRF) studies in rats determined the no observed adverse effect level (NOAEL) as 1000 mg/kg/day. Based on the 90-day DRF study in rats, the mean SXC-2023 peak C_{max} and AUC values were 43,800 ng/mL and 118,000 ng*hr/mL, respectively, in males and 82,500 ng/mL and 177,000 ng*hr/mL respectively, in females. In an embryo-fetal developmental toxicity study in pregnant rats, no SXC-2023-related changes were observed in maternal body weights, body weight gains, or food consumption for concentrations up to 1000 mg/kg/day. Additionally, no changes were observed in ovarian, uterine, or litter parameters, including embryo-fetal survival and mean fetal body weights, nor any external, visceral, or skeletal fetal changes related to SXC-2023. In a fertility study also conducted in rats, there were no SXC-2023-related clinical observations, effects on body weight, body weight gain, food consumption, estrous cyclicity, mating and fertility, ovary weights, ovarian and uterine parameters or maternal gross necropsy findings at doses up to 1000 mg/kg/day (the highest dose tested).

Based on 7- and 28-day DRF studies in dogs, the NOAEL was established at 250 mg/kg/day (Investigator's Brochure, 2024). The NOAEL corresponds to mean sex-combined C_{max} and $AUC_{0\text{-}24}$ of 27,100 ng/mL and 155,000 ng*hr/mL. In dogs, SXC-2023 was well-tolerated up to 300 mg/kg/day in a 90-day study, with a 28-day recovery arm to assess the reversibility, persistence, or delayed SXC-2023-related effects.

Pharmacodynamics

In vitro studies assessed the effects of SXC-2023 on glutamate, cysteine, and glutathione (GSH) (Investigator's Brochure, 2024). SXC-2023 was shown to stimulate ^{3}H-glutamate release as well as increase intracellular cysteine and GSH concentrations. This activity was confirmed by investigating SXC-2023 in various cell systems.

First, by employing a human astrocytoma cell system, application of SXC-2023 was shown to stimulate ^{3}H-glutamate release, with a significant increase in release at 90 and 180 minutes at a concentration of 300 μM (Investigator's Brochure, 2024). Next, in primary mouse cortical cells, SXC-2023 (30 and 100 μM) application effectively increased intracellular cysteine concentrations compared to vehicle controls following a 90-minute incubation of SXC-2023. Additionally, under *in vitro* conditions that mimic lower GSH levels and potential conditions of oxidative stress, the effects of SXC-2023 on mixed neuronal and glial cortical cultures exposed to diethylmaleate were evaluated. Under conditions where diethylmaleate exposure significantly decreased GSH levels, SXC-2023 administration was capable of reversing and restoring GSH back to normal levels. Lastly, SXC-2023, in a real-time glutamate release assay, did not itself display any direct substrate or inhibitory antiporter activity.

This suite of *in vitro* results suggests that SXC-2023, not through a direct mechanism but instead likely through increasing local levels of the endogenous substrate, cystine, is capable of activating System x_c^- (Investigator's Brochure, 2024).

Oral activity of SXC-2023 was characterized across several *in vivo* rodent models of CNS behaviors including: prepulse inhibition (PPI), which tests behavior that is dependent on cortical glutamatergic transmission; elevated plus maze (EPM), which is used to measure anxiety (a symptom of many psychiatric disorders and a clear indication of CNS penetration); and a cocaine reinstatement model measuring compulsive behavior in a model of chemical addiction (conducted following acute and repeat administration of SXC-2023) (Investigator's Brochure, 2024). In these studies, oral administration of SXC-2023 was found to improve measures of anxiety, sensorimotor gating, and addictive behaviors. The effects of SXC-2023 on reversing sensorimotor deficits in the PPI model were completely abolished in transgenic rats lacking a functional cystine-glutamate antiporter, confirming the mechanism of action of SXC-2023.

2.2.1.2 Safety

As of October 2019, three Phase I and two Phase II clinical studies were completed in which 225 healthy volunteers were exposed to SXC-2023 (Investigator's Brochure, 2024):

Phase I

- A single ascending dose and food effect study of SXC-2023 (dose range 50 to 1600 mg) in 48 healthy, adult male and female participants (PRO-101)
- An open-label drug-drug interaction study with oral contraceptives (1 mg norethindrone / 0.035 mg ethinyl estradiol [Ortho-Novum 1/35]) and a single oral dose of SXC-2023 (800 mg) in 28 healthy oral contraceptive-naive females (PRO-103)
- A multiple ascending dose study of SXC-2023 (200 mg QD, 400 mg QD, 400 mg BID, and 800 mg QD) for 14 days in 40 healthy, adult male and female participants (PRO-104)

Phase II

- A double blind, placebo-controlled study of SXC-2023 (50 mg, 200 mg, and 800 mg QD) for 6 weeks in 128 adults with moderate to severe trichotillomania (PRO-201)
- A placebo-controlled, crossover study of SXC-2023 (200 mg QD and 800 mg QD) for 5 days in 32 non-treatment seeking adults undergoing acute nicotine withdrawal (PRO-202)

These clinical studies demonstrated that SXC-2023 was safe and well-tolerated at single doses (50 mg to 1600 mg), in combination with oral contraceptives (800 mg), and in multiple doses (50 mg to 800 mg). The following were assessed to determine safety: adverse events (AEs), physical examinations, 12-lead electrocardiograms (ECGs), vital signs (heart rate, blood pressure, respiratory rate, and temperature), and clinical laboratory evaluations (hematology, serum chemistry, and urinalysis). The most common AEs in patients from the completed studies were

frontal, generalized, occipital, or temporal headache (9.6%), nausea (4.5%), diarrhea (3%), somnolence (3%), upper respiratory tract infections (3%) and urinary tract infections (3%). To date, no serious AEs or deaths have been reported (Investigator's Brochure, 2024). AEs following treatment with SXC-2023 were classified as "possibly related" (33%), "probably related" (6%), and "unlikely related" or "unrelated" (61%). The frequency of AEs following dosing with SXC-2023 were mild (Grade 1, 77%), moderate (Grade 2, 21%), severe (Grade 3, 2%), life-threatening (Grade 4, 0%), and death (Grade 5, 0%). In one Phase I study (PRO-104) and the two Phase II studies (PRO-201 and PRO-202), there were no investigator concerns regarding cognitive safety, cognitive performance, or CNS function (Investigator's Brochure, 2024).

2.2.1.3 Rationale for Dose/Regimen, Route of Administration, and Duration of Treatment

The dose selected (800 mg QD Oral) for evaluation in this study has been chosen based on the safety, tolerability of dose, regimen and pharmacokinetic (PK) data from completed healthy volunteer and patient studies including modeling and simulation of PK and receptor occupancy (RO) profiles. A total of 225 study participants have been exposed to SXC-2023 in a total of five completed human studies, of which three were Phase I and two were Phase II studies.

During clinical development, a majority of the studies were conducted using enteric capsules containing 50 mg or 200 mg of SXC-2023 (supplied in Size 0 white capsules). In addition to SXC-2023, the capsules contained the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, methocel E3, croscarmellose sodium, and magnesium stearate.

2.2.1.4 Pharmacokinetics (PK) and Metabolism

In the single oral dose Phase I study (PRO-101), the pharmacokinetics (PK) of SXC-2023 in healthy volunteer participants were observed using doses ranging from 50 mg to 1600 mg. Under fasted conditions, the mean geometric peak plasma concentration (C_{max}) of SXC-2023 ranged from 758.2 ng/mL for the 50 mg dose to 33,700 ng/mL for the 1600 mg dose and occurred approximately 2.5 to 4.0 hours post-dose (T_{max}). The elimination half-life ($T_{1/2}$) for SXC-2023 for the tested dose range (50 mg to 1600 mg) was 3 to 6 hours. Administration of SXC-2023 (800 mg) with a high-fat meal lowered mean C_{max} and delayed T_{max} by ~3.5 hours compared to the same dose administered under fasted conditions. For doses ranging from 50 mg to 1600 mg, the area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) was 3213 ng*hr/mL to 239,700 ng*hr/mL. Following the consumption of a high-fat meal, the overall exposure ($AUC_{0-\infty}$) was slightly increased following administration of SXC-2023 (Investigator's Brochure, 2024).

The PK of SXC-2023 in a multiple ascending dose study was conducted at 200 mg QD, 400 mg QD, 800 mg QD, and 400 mg BID. The C_{max} of SXC-2023 (at Day 14, under fasted conditions) ranged from 7990 ng/mL (200 mg QD dose) to 30,540 ng/mL (800 mg QD dose). The median

T_{max} ranged from 2 to 6 hours for the tested doses. For the 200 mg to 800 mg dose range, the $T_{1/2}$ of SXC-2023 was ~3.4 to 5.2 hours and 9.4 to 11.7 hours on Days 1 and 14, respectively. Following single and multiple doses of SXC-2023 (200 mg to 800 mg, fasted conditions), the PK parameters for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} was dose proportional to AUC and C_{max} on Day 1 and Day 14.

Overall, the food effect of SXC-2023 (800 mg with a high-fat meal) resulted in a lower, delayed C_{max}, a slight increase of AUC, and a delayed T_{max} (Investigator's Brochure, 2024).

In human liver microsomes, the IC_{50} of SXC-2023 (concentration range 4 to 4000 µM) was determined to be 570 µM for CYP2C8 and >4000 µM for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. *In vitro* evaluation of substrate and inhibitor activity (conduced in HEK293 cells) indicated that SXC-2023 is a likely substrate for drug transporters OATP1B1 (substrate, 10 µM; 96% inhibition at 4000 µM; and IC_{50} = 272 µM) and OATP1B3 (substrate, 10 µM; 66% inhibition at 4000 µM; and IC_{50} = 3180 µM). Very little of SXC-2023 (<0.2%) was detected in urine from doses 200 mg to 800 mg (Investigator's Brochure, 2024).

2.2.1.5 Clinical Efficacy

In the six-week Promentis PRO-201 study, change from baseline in average daily time spent pulling hair was identified and validated as the primary efficacy endpoint for future clinical trials (Investigator's Brochure, 2024). In the preliminary efficacy results, several measures of TTM disease activity after the 6-week treatment with SXC-2023 showed improvement or alleviation in TTM symptoms as well as improvement in measures of impulsivity in these patients. In particular, subjects with moderate to severe TTM in all treatment groups (including placebo) showed a reduction in average daily time spent pulling hair after 6 weeks of study treatment.

Additionally, 70% of the patients in the 800-mg group had an improvement of at least 30 minutes compared with 41% in the placebo group (Investigator's Brochure, 2024). The median minutes spent pulling hair also decreased in all treatment groups after 6 weeks of study treatment, with the largest median decrease seen in the 800-mg group.

In a post hoc analysis using a Target Population consistent with a population that would be seen in future clinical trials, SXC-2023 800-mg treatment showed statistical significance in the least squares mean treatment difference from the pooled placebo/50-mg group in reductions in average daily time spent pulling hair as well as the percentage of hairpulling urges resisted (Investigator's Brochure, 2024). Also in this Target Population, SXC-2023 treatment (800 mg) showed a statistically significant difference in the proportion of patients with 30 minutes or more of reduction in average daily time spent hair pulling as compared with the pooled placebo/50-mg group and a higher percentage of subjects with complete resolution of hair pulling episodes at Week 6. Neurocognitive (CANTAB) findings showed a significant improvement in motor impulsivity and improvement in impulsive decision-making at 800 mg versus placebo in TTM

patients. Overall, these findings are consistent with the activity of SXC-2023 in a previously conducted biomarker study in impulsive smokers.

Study PRO-202 evaluated the safety, tolerability, and PK as well as on measures of abstinence-induced impulsivity and inhibitory control, urge for cigarettes, and mood of multiple oral doses of SXC-2023 (200 mg QD and 800 mg QD) over 5 days (Investigator's Brochure, 2024). Thirty-two (32) volunteers with tobacco use disorder were dosed. Drug was administered as enteric capsules in 200 mg unit dose strengths orally as multiple doses. Generally, SXC-2023 was safe and well tolerated at all doses. Results as assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) showed beneficial effects of SXC-2023 on measurements of impulsivity across two distinct cognitive domains. Firstly, smoking abstinence was associated with a significant increase in delay aversion impulsivity under placebo conditions, and this effect was not observed following treatment with SXC-2023 at either dosing level. Secondly, treatment with the higher dose of SXC-2023 (800 mg group) was associated with a significant reduction in motor impulsivity on the Stop-Signal Task using paired t-tests. Using Cohen's D to compare effect size of SXC-2023 in the current study to published data with psychiatric medicines, the observed effect size with SXC-2023 was large by conventional norms indicating that it was likely to be a clinically meaningful effect. Overall, the current CANTAB findings suggest that 800 mg SXC-2023 improved two important aspects of impulsivity.

2.2.2 Cocaine

2.2.2.1 Pharmacology

Cocaine is a potent inhibitor of monoamine transporters including dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) (Fleckenstein *et al*., 2000; Miller *et al*., 2001). Cocaine binds at the DAT and inhibits neurotransmitter reuptake, leading to a build-up of extracellular dopamine (DA) levels and potentiation of mesolimbocortical pathways (Kuhar *et al*., 1991). Neuroimaging (positron emission tomography) studies of human volunteers who regularly abuse cocaine indicate that doses used by cocaine abusers lead to a significant brain DAT blockade, which is associated with subjective effects of cocaine (self-reported "high") (Volkow *et al*., 1997). Single gene knockout studies in mice of DAT, SERT, and NET indicated that any one of these transporters might be able to mediate cocaine reward in the other's absence (Sora *et al*., 1998; Xu *et al*., 2000). Sora *et al*. (2001) found that cocaine reward depends on both DAT and SERT blockade and that serotonin, as well as DA, plays a critical role in the development of cocaine addiction. The effects of transporter gene copy numbers on the cocaine place preference test indicated a greater role for DAT than SERT in cocaine reward/reinforcement in mice, consistent with previous pharmacological studies. Thus, mice with even a single DAT gene copy and no SERT copies still experienced reward/reinforcement behavior following cocaine administration, while cocaine-induced reward/reinforcement behavior was totally blocked in mice with no DAT gene and either half-normal or absent SERT.

Cocaine affects nearly every organ and system, with the most dramatic changes being observed in the cardiovascular system and the brain. An important factor of cocaine-induced toxicity is vasoconstriction of coronary arteries and cerebral blood vessels combined with increased platelet aggregation, which can lead to focal or general ischemic episodes and myocardial and cerebral infarctions. In the cardiovascular system, tachycardia, hypertension, ruptures of blood vessels, arrhythmias, and arteriosclerotic lesions are typical complications of cocaine abuse that often precede myocardial ischemia and infarction (Karch, 1993). Chronic use of cocaine can result in serious neuropathies, including optic nerve neuropathy, and can lead to seizures, cerebral infarction, cerebral hemorrhage, multifocal cerebral ischemia, and cerebral atrophy (Majeska *et al*.,1996). Psychiatric impairments associated with cocaine abuse include cognitive deficits, particularly in attention, problem solving, abstraction, arithmetic performance and short-term memory (Majeska *et al*.,1996). The most significant psychopathologies observed in cocaine addicts include anhedonia, anxiety, anergy, paranoia, depression, and bipolar mood disorder, which may predispose to suicide and are believed to contribute to cocaine craving and relapse. Cocaine seems to be hepatotoxic in humans (Marks and Chapple, 1967; Kloss *et al*., 1984); this hepatotoxicity is enhanced by drugs such as barbiturates, alcohol and cocaine adulterants.

Cocaine also induces pulmonary disorders, which are particularly severe in cocaine smokers. These disorders include barotrauma, inflammation and lung infections, pulmonary congestion, edema, hypertrophy of pulmonary arteries, and pulmonary necrosis (Karch, 1993).

2.2.2.2 Safety

Intravenous (i.v.) cocaine administration spanning the doses proposed for use in this study (20 mg and 40 mg) has been previously investigated in human laboratory clinical trials (Johnson *et al*., 1998; Walsh *et al.,* 1994). Johnson and colleagues conducted continuous non-invasive cardiovascular monitoring in eight healthy cocaine addicts receiving i.v. doses of cocaine 0.325 mg/kg or 0.650 mg/kg. They demonstrated dose dependent increases in pulse and mean arterial pressure following cocaine administration that peaked 5 minutes post-cocaine infusion with a maximal response being sustained for a further 15 and 35 minutes afterwards, respectively. Cocaine administration had no significant effect on peripheral oxygen saturation, and no clinical abnormalities of rhythm or conductivity were seen on ECG. These doses of cocaine (20 mg and 40 mg) and the method of single-dose i.v. cocaine administration as well as procedures for cardiovascular monitoring appear to be relatively safe for laboratory studies of healthy cocaine addicts with no pre-existing cardiovascular disease. Importantly, in a Phase 1 clinical trial study of fluoxetine, i.v. cocaine doses of 20 mg and 40 mg did not produce any adverse physiological or subjective reactions in 5 healthy adult male volunteers with histories of cocaine abuse (Walsh *et al.*, 1994). These doses of cocaine (20 mg and 40 mg i.v.) were also used in a recent drug-drug interaction study of cocaine and lorcaserin (NIDA, 2016). No severe AEs were reported in that study. Only one moderate AE was reported, a case of euphoria experienced subsequent to cocaine infusion and considered to be related to cocaine. The most frequent cocaine-related AEs experienced across the entire safety population (N=26) were euphoric mood (25 participants,

96%), abnormal feelings (11 participants, 42%), hyperhidrosis (10 participants, 38%), feeling hot (10 participants, 38%), tachycardia (6 participants, 23%), and paraesthesia (5 participants, 19%). These events coincided with cocaine infusion and were consistent with the risk profile of low-dose cocaine administration.

Study PRO-201 was a placebo-controlled phase II study evaluating the safety, tolerability, and activity of SXC-2023 (50 mg, 200 mg, and 800 mg QD) in 97 adults with trichotillomania when dosed for a period of six weeks. SXC-2023 was administered as enteric capsules in 50 and 200 mg unit dose strengths orally as multiple doses. Generally, SXC-2023 was safe and well tolerated at all doses. AEs were reported in 38% (37/97) of volunteer subjects following treatment with SXC-2023 and in 32% (10/31) of subjects dosed with placebo. The most common AEs in the SXC-2023 group were headache, urinary tract infections, and nausea. Out of 63 AEs reported in the SXC-2023 group, 25% (16/63) were judged to possibly be related to study treatment, and 17% (11/63) were judged to probably be related to study treatment. Out of 63 AEs, 57% (36/63) were judged to be unrelated to study treatment. Of the 16 AEs possibly related to study treatment, 69% (11/16) of them were considered to be mild, and 31% (5/16) were considered moderate. Of the 11 AEs probably related to study treatment, 73% (8/11) of them were considered to be mild, 18% (2/11) were considered moderate, and 9% (1/11) were considered severe. The only severe AE observed and judged to be probably related to study treatment was a case of insomnia, observed in the 800 mg QD cohort.

2.2.2.3 Pharmacokinetics and Metabolism

The distribution half-life of cocaine from an i.v. dose is about 10 minutes and the elimination half-life of cocaine was found to be about 1 hour (50-80 minutes) by Jeffcoat *et al*., 1989, although subsequently a half-life of about 4 hours was reported by Cone (1995).

Cocaine is primarily metabolized by esterases in the plasma and liver to inactive metabolites, benzoylecgonine (BE), ecgonine methyl ester and ecgonine (Stewart *et al*., 1977; Kloss *et al*., 1984; Dean *et al*., 1991; Kolbrich *et al*., 2006). A very small portion of cocaine is metabolized by hepatic microsomal enzyme CYP3A to an active metabolite, norcocaine (N-demethyl metabolite) (Ladona *et al*., 2000); however norcocaine is a minor metabolite that accounts for only 2 to 6% of the administered cocaine dose (Inaba *et al*., 1978). In the presence of ethanol, liver carboxylesterase catalyzes the ethyl transesterification of cocaine to form cocaethylene plus methanol (Dean *et al*., 1991).

3 STUDY OBJECTIVES

3.1 Primary

The primary objective of this study is to determine if there are significant interactions between oral SXC-2023 treatment concurrent with 20 and 40 mg intravenous (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 [QTcF]).

3.2 Secondary

1. To evaluate whether administration of SXC-2023 alters the pharmacokinetics (PK) of cocaine and/or its major metabolite, benzoylecgonine (BE).
2. To determine the PK of SXC-2023 administered at a dose of 800 mg once daily.
3. 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 SPONSOR

The Division of Therapeutics & Medical Consequences, National Institute on Drug Abuse, National Institutes of Health will be the IND sponsor for this study.

5 STUDY SITE

This will be a single site study conducted at Altasciences Clinical Kansas, Inc., 10103 Metcalf Avenue, 10183 Metcalf Avenue, and 10203 Metcalf Avenue, Overland Park, Kansas 66212, USA.

6 STUDY DESIGN

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 be a 2 mL i.v. push and 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 800 mg 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 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 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.

The study schema is illustrated in Figure 1 and the schedule of infusion sessions is shown in Table 1.

Table 1: 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* †
Treatment	5	9	Saline or 40 mg cocaine followed by either 40 mg cocaine or saline* ‡

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

Figure 1: Study Schema

Study Day	Study Procedures
Days -28 to -4	Screening
Day -3	Clinic intake
Day -2	Screening Infusion Session #1: 20 mg cocaine → Saline → 40 mg cocaine
Day -1	Randomization
Day 1	Baseline Infusion Session #2: Session #2: Saline & 20 mg cocaine
Day 2	Baseline Infusion Session #3: Saline & 40 mg cocaine
Days 3 to 9	SXC-2023 or placebo administration QD
Day 8	Infusion Session #4: Saline & 20 mg cocaine
Day 9	Infusion Session #5: Saline & 40 mg cocaine
Day 11	Clinic Discharge
Days 18 to 21	Final Follow-up

7 PARTICIPANT SELECTION

7.1 Inclusion Criteria

In order to participate in the study, participants must:

1. Be participants who are cocaine-experienced and not seeking treatment for cocaine use disorder.
2. Males and females between 18 and 59 years of age, inclusive.
   - The masculine / feminine gender is used without any discrimination and with the aim to lighten the text.
3. Have a body mass index (BMI) within a range of 17.0 to 36.0 kg/m^2 and a minimum weight of at least 50.0 kg at screening.
4. Have experience using cocaine by the smoked or i.v. route at least 6 times over the participant's lifetime prior to clinic intake (Day -3) and at least one use (smoked, i.v., or nasal route) within the past 3 months.
5. Provide a urine sample positive for cocaine at least once during screening (Days -28 to -4) and a urine test negative for cocaine at clinic intake.
6. Be able to verbalize understanding of consent form, able to provide written informed consent, and verbalize willingness to complete study procedures.
7. A female study participant must meet one of the following criteria:
   - If of childbearing potential – agrees to use one of the accepted contraceptive regimens from at least 30 days prior to the first administration of the study medication, during the study, and for at least 30 days after the last dose of the study medication. An acceptable method of contraception includes one of the following:
     i. Abstinence from heterosexual intercourse
     ii. Hormonal contraceptives (oral/injectable/implant/insertable hormonal birth control products, transdermal patch)
     iii. Intrauterine device (with or without hormones)

     OR agrees to use a double barrier method (*e.g.,* condom and spermicide) during the study and for at least 30 days after the last dose of the study medication.
   - If a female of non-childbearing potential – should be surgically sterile (*i.e.,* has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation/occlusion) or in a menopausal state (at least 1 year without menses), as confirmed by FSH levels (≥ 40 mIU/mL).

   A male study participant that engages in sexual activity that has the risk of pregnancy must agree to use a double barrier method (*e.g.,* condom and spermicide) and agree to not donate sperm during the study and for at least 90 days after the last dose of the study medication.
8. Be able to comply with protocol requirements, rules and regulations of the study site, and be likely to complete all the study treatments.

7.2 Exclusion Criteria

In order to participate in the study, participants must not:

1. Have a current or past history of seizure disorder, including alcohol- or stimulant-related seizure, febrile seizure, or significant family history of idiopathic seizure disorder.
2. Have any previous medically adverse reaction to cocaine, including loss of consciousness, chest pain, paranoid reaction, or seizure.
3. Have clinically significant findings in the opinion of an investigator based on the MINI (version 7.0) neuropsychiatric interview.
4. Be pregnant or lactating.
5. Have a sitting systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg and heart rate > 100 beats per minute at screening and clinic intake.*
6. Have current or lifetime past history of cardiac illness, including, but not limited to:
    a) Uncontrolled arrythmia
    b) Congestive heart failure (CHF)
    c) Myocardial infarction
    d) Uncontrolled symptomatic angina
    e) QTcF >450 msec for males and females or history of prolonged QT syndrome.
7. Have a history of liver disease or current elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), 2 × the upper limit of normal.*
8. Have a lifetime history of renal disease or current renal function test values* as follows:
    - blood urea nitrogen (BUN) > 2 × the upper limit of normal, or
    - creatinine > 1.5 mg/dL
9. Blood donation (excluding plasma donation) of approximately 500 mL within 56 days prior to screening.
10. Plasma donation within 7 days prior to screening.
11. Treatment with an investigational drug within 30 days or 5 times the half-life (whichever is longer) prior to screening.
12. Have any clinically significant finding on medical history, physical examination, clinical laboratory test, vital signs or ECGs that contraindicate participation in the study.
13. Have a history of suicide attempts or current or recent evidence of suicidal ideation in the past 12 months based on the Columbia-Suicide Severity Rating Scale (C-SSRS).
14. Have a positive urine drug screen upon clinic intake (Day -3) for any of the following drugs: alcohol, amphetamine/methamphetamine, barbiturates, benzodiazepines, buprenorphine, cocaine, fentanyl, 3,4-methylenedioxymethamphetamine (MDMA), methadone, phencyclidine/phenylcyclohexyl piperidine (PCP), propoxyphene, and opioids (*e.g.*, codeine, heroin, morphine, oxycodone, etc.). If a participant presents with a positive urine drug screen for cocaine or alcohol at clinic intake (Day -3), the participant may be rescheduled one time at the discretion of an investigator or designee as long as

clinic intake is within the total screening window. A positive tetrahydrocannabinol (THC) test is not exclusionary, but participant must show no impairment.

15. Have used any prescription drugs within 14 days of clinic intake or non-prescription drugs or herbal remedies within 7 days of clinic intake.
16. Be unable to distinguish between a 20 mg and 40 mg dose of cocaine i.v. based on the high effects VAS at either the 5 or 10 minute time point during the screening infusion.
17. Have a positive serology for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCVab), or human immunodeficiency virus (HIV).
18. Have positive results for a coronavirus disease 2019 (COVID-19) test performed on Day -3 after screening is complete and participant is confirmed, but prior to admission.

* Participants with an out-of-range laboratory test or vital signs may have the assessment repeated once, at the discretion of the PI.

8 INVESTIGATIONAL PRODUCT

8.1 SXC-2023

SXC-2023 is manufactured and supplied by Promentis Pharmaceuticals. The product is supplied as enteric capsules containing 200 mg of SXC-2023 (supplied in Size 0 white capsules). In addition to SXC-2023, the capsules contained the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, methocel E3, croscarmellose sodium, and magnesium stearate.

Initial stability evaluations of the drug substance and drug product indicate that SXC-2023 is stable at room temperature and requires no special protection or handling; special protection from light is not required. The bottled drug product should be stored at 20-25°C with excursions allowed between 10°C and 30°C.

Participants will take four capsules of 200 mg SXC-2023 (total 800 mg) orally QD as described in Section 6. SXC-2023 will be administered to participants before regular breakfast. Any unused drug will be disposed according to standard practices.

8.2 Placebo

Matching placebo capsules will be supplied by Promentis Pharmaceuticals. The capsules should be stored at 20-25°C with excursions permitted to 10°C to 30°C.

8.3 Cocaine

Cocaine hydrochloride solution, 20 mg/mL in 4 mL vial (*i.e.,* 80 mg/vial) is manufactured by Murty Pharmaceuticals Inc. (Lexington, KY) under a contract with NIDA. The cocaine hydrochloride solutions should be stored in a securely locked refrigerator within the pharmacy. Standard controlled substance procedures will govern access to the drug. Cocaine will be

administered by 2 ml i.v. push over 60 seconds by an investigator or qualified designee (such as a licensed registered nurse). Any unused drug will be disposed according to standard practices.

8.4 Dietary and Other Restrictions

Diet. Food and drink will be provided by the site. From Days 3 to 9, SXC-2023 capsules will be administered to patients before regular breakfast. The first infusions of cocaine on Days 8 and 9 will be started 3 hours after SXC-2023 dosing. During infusion Sessions 1 to 5, caffeinated beverages are not permitted from 1 hour prior to and until 4 hours after cocaine administration; other beverages are allowed. Eating is not allowed during infusion to avoid risk of nausea/vomiting. A meal can be given at the end of an infusion session if they are stable without restriction.

Exercise. Participants will be instructed to refrain from participation in contact sports and weightlifting from 48 hours before inpatient period until completion of the study.

Tobacco Products. Participants will be allowed to smoke during the study in designated areas and accompanied by site staff at scheduled times according to the rules of the site. Smoking is permitted *ad libitum* and there is no restriction on the number of cigarettes smoked daily. However, during infusion sessions, smoking is not permitted from at least 1 hour prior to the first cocaine/saline infusion to until 4 hours after the second infusion.

Alcohol. Participants will be questioned about their estimated daily intake of alcohol during the pre- study evaluation of eligibility. Any participant who shows physiological dependence on alcohol requiring medical detoxification will be excluded. Alcoholic beverages are not permitted from 48 hours before the inpatient period until the discharge from the study. Participants will have a urine alcohol test on admission (Day -3). If a participant has a urine alcohol result greater than zero, the participant may be retested one time prior to screening infusion.

8.5 Prior and Concomitant Medications

No prescription medications for 14 days and non-prescription medications (including herbal remedies) for 7 days are to be taken by participants prior to clinic intake with the exception of contraceptive hormones. Female participants may use oral contraceptives, Depo-Provera, Norplant, Patch or intrauterine progesterone contraceptive system during the study. The addition of any medication during the course of the study must be discussed with the NIDA medical monitor prior to administration. Should there be a clinical indication for any additional medication during the course of the study, the name of the drug, dosage, reason for administration, and duration of administration must be recorded on the appropriate electronic case report form (eCRF).

9 STUDY PROCEDURES

Table 2 provides a detailed table of the timing of study activities.

Table 2: Time and Events 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	
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

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**
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.

9.1 Screening (Study Day -28 to Day -4)

Prospective participants will meet with the study staff and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the local site's Institutional Review Board (IRB). After providing informed consent, the participant proceeds to the screening/baseline assessments phase of the study.

Screening of participants to establish eligibility will occur initially before inpatient clinic intake and be completed after intake. Participants with an abnormal laboratory test or vital sign may have the assessment repeated once, to confirm the abnormal value per discretion of the PI.

Assessments performed at screening visit include:

- informed consent
- medical history and current medical conditions
- drug, alcohol and smoking history
- infectious disease serology (recorded in source documentation only)
- serum β-HCG (pregnancy test)
- urine toxicology screening
- collection of demographic information
- timeline follow back interview for cocaine use for the past 30 days
- MINI version 7.0 and C-SSRS
- body height and weight
- BMI
- eligibility (inclusion/exclusion)
- physical examination
- 12-lead ECG
- vital signs (HR and BP)
- safety laboratory tests (hematology, clinical chemistry panel, and urinalysis)
- prior medication use

A urine drug toxicology screen will also be conducted for drugs of abuse. The urine toxicology screen must be positive for cocaine at least once during screening (Day -28 to -4). Screening visits may be repeated until the participant has a cocaine positive urine; however, the urine toxicology screen must be negative for cocaine at clinic intake (Day -3; see Section 9.2), and negative for all other substances listed in Exclusion Criterion #12, to be eligible to receive the first cocaine infusion.

Participants will be administered the MINI (version 7.0) neuropsychiatric interview and the C-SSRS by a trained medical staff to determine if there are any underlying psychiatric conditions that might exclude the potential participant from participation. These assessments must be completed before clinic intake.

Participants will be instructed that no prescription/nonprescription medications or herbal remedies with the exception of contraceptive hormones in female participants are to be taken within 14 and 7 days of clinic intake, respectively. Participants will also be instructed to refrain from using any alcohol or any other substances listed in Exclusion Criterion #12 from 48 hours before clinic intake until discharge from the study. Participants will also be instructed to refrain from participation in contact sports and weightlifting from 48 hours before the inpatient period until study completion.

Women participating in the study will be tested for serum beta-human chorionic gonadotropin (β-HCG) to detect pregnancy at screening and admission intake. In the case of a positive or borderline serum β-HCG pregnancy test at the screening visit, the participant will not enter the study.

Enrolled participants may receive treatment referral information for drug abuse at the end of their study involvement.

9.2 Intake Screening (Day -3)

Potential candidates whose screening assessment results do not exclude them from study participation will complete intake procedures and reside full-time as inpatients until discharge or completion of the study. Screening procedures on Day -3 include the following:

- Update medical history/current medical conditions
- Update drug, alcohol history
- COVID-19 test
- serum β-HCG (pregnancy test)
- urine toxicology screening (must be negative for all substances listed below, including alcohol and cocaine)
- body weight
- eligibility (inclusion/exclusion)
- physical exam
- C-SSRS (since last visit)
- VAS Training
- 12-lead ECG
- vital signs (HR and BP)
- safety laboratory assessments (hematology, clinical chemistry panel and urinalysis)
- adverse events/serious adverse events

- prior & concomitant medications

The drug toxicology screen on this day must be negative for the substances listed in Exclusion Criterion #12. If a positive urine toxicology screen for cocaine or alcohol is found at clinic intake, it may be repeated once and rescheduled for admission at the PI's discretion.

9.3 Screening Cocaine Infusion (Day -2)

Participants will be screened for eligibility with a single-blind screening infusion (Infusion Session 1, see below) of 20 mg cocaine, followed by a saline infusion, followed by a 40 mg cocaine infusion. Each infusion will consist of a 2 mL i.v. push and will be administered approximately 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. To continue 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. Additional procedures on Day -2 include the following:

- eligibility (inclusion/exclusion)
- VAS
- 12-lead ECG
- telemetry
- vital signs (HR and BP)
- adverse events and serious adverse events
- prior and concomitant medications

9.3.1 Infusion Session 1 (Day -2)

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 as listed in Exclusion #12 and alcohol. 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 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 and found to be clinically stable.

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.

Table 3 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. ECG then vital signs will be collected first when multiple assessments are scheduled at the same nominal time.

Table 3: Screening Cocaine Infusion (Session 1) Schedule of Activities

Time point relative to start of first infusion	Time point 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.**		
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
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	

9.4 Blinding and Randomization (Day -1)

This is a double-blind, placebo-controlled, parallel group study. Eligibility criteria are re-reviewed on Day -1. A prospective participant who meets all of the study inclusion criteria and does not meet any of the exclusion criteria may be enrolled onto the study. After completing screening cocaine infusions (Session 1), participants will be randomized to receive either SXC-

2023 (10 participants) or matched placebo (10 participants). Participants will also be randomized to the order of the baseline and treatment cocaine and saline infusions.

The data-coordinating center will supply the Research Pharmacist with a randomization list. The Research Pharmacist will dispense the investigational agent for the participant to an investigator each day during treatment and infusion sessions.

Study participants who complete all 5 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 (10 for each group), there should be at least 8 completers in each group. Should there be 3 or more participants terminated in either group, replacement participant(s) will be assigned to that specific group.

9.5 Infusion Session 2 (Day 1)

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.

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

Time point relative to start of first infusion	Time point 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]
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.

Please refer to Sections 9.7, 10.3.1, and 10.3.2 for complete lists of SXC-2023 and cocaine PK timepoints.

9.6 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 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 prior to infusion.

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

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.

9.7 Treatment Period (Days 3-9)

Participants will begin receiving 800 mg SXC-2023 or placebo once daily (QD, mornings) from Day 3 to 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, described below) provide cardiovascular effects, subjective responses, and PK data for SXC-2023 at steady state. The schedule of assessments is shown in Table 4. 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.

9.7.1 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.

9.7.2 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).

9.8 Clinic Discharge (Day 11) and Follow-up (Day 18-21)

The participants will be discharged from the unit 2 days after the last infusion of cocaine (Infusion Session 5) on Day 11.

Clinic Discharge Criteria:

Participants' vital signs and mental status will be assessed by the clinician.

- Vital signs must be within what those were at baseline or the normal parameters (a sitting systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg and heart rate < 100 beats per minute).
- Mental status must be assessed with the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and mental status assessment by the clinician examining thought content and processing to exclude psychosis.
- Mental status must be deemed acceptable for the discharge, as judged by the clinician[1].

Participants will be requested to complete the Follow-Up Visit 7 to 10 days after the day of discharge; this visit will consist of a phone call to the participant. Assessments to be performed at discharge and the follow-up visit are shown in Table 2.

[1] In the case where the mental status of the participant would not allow for the study discharge, the participant will be referred to an appropriate mental health provider and the appointment will be made.

9.9 Safety Monitoring

An investigator or designee will perform the infusions and will be present at least 1 hour after the completion of the infusions. Thereafter, the investigator will remain on site and be available by telephone for prompt response, if needed, for at least 4 hours post-infusion. If a participant demonstrates a significant adverse reaction to cocaine, the cocaine administration will be halted, appropriate medical response will be implemented per site's standard operating procedures, and the participant will be discontinued from the remainder of the study.

Emergency medical coverage at the clinical research unit will be available to the participants. The clinical site will provide emergency medical coverage and services to manage potentially serious and life-threatening medical emergencies should they arise at any point during the clinical trial. Advanced Cardiovascular Life Support (ACLS) trained personnel, including but not limited to physicians and paramedics, will be available at all times during the inpatient component of this clinical trial. Further, an investigator's presence will be required at all times during and immediately after cocaine infusions to ensure additional safety. An investigator will be present on-site during and for at least 1 hour after infusion and will be on site for at least 4 hours after completion of the infusion. Completely equipped and regularly monitored crash carts will be readily available should they be required at any point. Also, the study site will be located in close proximity to a major medical center.

9.10 Individual Participant Stopping Criteria

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

1. Acute chest pain
2. Systolic BP > 160 mmHg sustained for 5 minutes or more
3. Diastolic BP < 40 mmHg or > 100 mmHg sustained for 5 minutes or more
4. Heart rate < 40 bpm or > 160 bpm sustained for 5 minutes or more
5. QTcF ≥ 500 msec, or uncorrected QT interval > 600 msec
6. Clinically significant ECG changes in the opinion of an investigator
7. AST > 2 ULN
8. ALT > 2 ULN
9. BUN > 2 ULN
10. Creatinine > 1.5 mg/dL
11. Significant neurological or psychiatric events (*e.g.,* psychosis) or any behavioral manifestations of cocaine toxicity
12. Any condition that in the clinical judgment of an investigator is of sufficient magnitude to present a danger to the participant
13. 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.

9.11 Participant Discontinuation

Participants will be excluded or discharged if their behavior is disruptive, non-compliant with study procedures, or otherwise not in compliance with remaining on the Unit.

Study participants can withdraw from the study at any time for any reason. Subjects can be discontinued if they withdraw consent, are unable to remain under medical supervision, are noncompliant or have a major deviation from the protocol, pregnancy, experience an SAE or severe AE, if the site PI feels that continuation would not be in the best interest of the subjects, or if the trial is discontinued. If discharged from the clinic early, all assessments scheduled for Day 11 will be performed.

9.12 Study Stopping Criteria

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 participants experience a similar SAE that is not clearly unrelated to study drug or cocaine
- Two severe AEs related to cocaine toxicity
- 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.

10 ASSESSMENT METHODS

10.1 Adverse Events

Reports of AEs will be elicited by a verbal probe (*e.g.,* "How are you feeling?") administered starting with the first cocaine screening infusion on Day -2. Any events spontaneously reported by the participant or observed by the investigative staff will also be recorded. AEs will be assessed for severity and relationship to the study drug in accordance with the criteria in APPENDIX B.

10.2 Urine Toxicology Test

A urine toxicology test will be administered at screening and intake to assess for the following drugs: alcohol, amphetamine/methamphetamine, barbiturates, benzodiazepines, buprenorphine, cocaine, fentanyl, MDMA, methadone, PCP, propoxyphene, THC, and opioids (*e.g.*, codeine, heroin, morphine, oxycodone, etc.).

10.3 Blood Sample Collections for Pharmacokinetic (PK) Determinations

An i.v. catheter will be inserted for each infusion session and may be maintained in place for the 2 days of infusion sessions in one week, if the participant wishes. PK blood samples will be obtained by either direct venipuncture or use of an indwelling catheter. If a catheter is used, two i.v. catheters will be placed for infusion sessions that involve repeated blood draws; one will be for cocaine administration, the other for blood sample collection.

Approximately 179 mL blood will be collected for PK analysis and other clinical tests (APPENDIX A). 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).

10.3.1 Cocaine and BE

Blood samples (4 mL) will be collected during infusion Sessions 3 (Day 2) and 5 (Day 9) at pre-dose (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.

10.3.2 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.

10.4 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 (Mezinskis *et al*., 1998). 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 (Sessions 2 to 5).

10.5 Cardiovascular Assessments During Infusion Sessions

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 beginning approximately 60 minutes before the first infusion until 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, 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).

10.6 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.

10.7 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.

10.8 Urinalysis

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

10.9 Pregnancy Test

A serum pregnancy test designed to measure β-HCG will be performed during screening and at intake. A urine pregnancy test will be done prior to cocaine infusion sessions 2-5 and at discharge.

10.10 Infectious Disease Serology

Blood will be collected for HBsAg, HCVab, and HIV serology at Screening. These data will not be collected in the study database.

10.11 Cocaine Use by Timeline Follow Back Method

Detailed histories of cocaine use over the past 30 days prior to screening will be obtained using the timeline followback method. In addition, the route of self-administration will also be collected. Participants must report administration by the i.v., nasal, or smoked routes to be eligible for the study. The timeline followback method was described and validated by Sobell *et al*., (1986) for reporting alcohol use. It has also been found to be a reliable method for assessing the history of psychoactive substance use in drug-abusing populations (Fals-Stewart *et al*., 2000).

10.12 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a measure of suicidal ideation and behavior. At Screening, the "Screening/Baseline" version will be administered; on Days -3 and 11, the "Since Last Visit" version will be administered.

10.13 Beck Depression Inventory (BDI)

This scale is a self-report measure of depression consisting of 21 items. The scale was developed to measure the behavioral manifestations of depression.

10.14 Beck Anxiety Inventory (BAI)

This scale is a self-report measure of anxiety consisting of 21 items.

10.15 Concomitant Medications

Concomitant medications will be assessed once a day by an investigative staff member. Any medications to be taken during the study must be approved by a site investigator/study physician.

10.16 Participant Disposition

The Participant Disposition eCRF will be completed at the end of screening, treatment and follow-up that reports the status of the participant at each of these study periods.

10.17 Eligibility Checklist

The Eligibility Checklist source document must be completed at the end of screening prior to make the decision for clinic intake and on the day of clinic intake prior to randomization and enrollment. This information will be used to determine whether the participant may be enrolled in the study. This form will document final eligibility and, if applicable, the reason the participant was not enrolled in the study. An inclusion/exclusion eCRF will be completed for screen failures to document the reason the participant was not eligible for the study.

10.18 Medical History

A medical history will be taken on all potential study participants to assure medical fitness including questions about current and past opioid use, abuse, and dependence and recent smoking history. Women will be asked about their choice of method for birth control. Participants will be queried about recent alcohol and xanthine containing products consumption to assure eligibility.

10.19 MINI Neuropsychiatric Interview

A MINI neuropsychiatric interview (version 7.0) (Sheehan *et al.*, 1998) will be administered during screening to rule out any major psychiatric disorders (*e.g.*, affective disorders, schizophrenia).

10.20 Physical Examination

A physical exam of the oral cavity, head, eyes, ears nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during screening. Height and weight will be recorded during screening. A symptom directed physical exam will be performed at clinic intake and clinic discharge. Weight will be recorded at clinic intake.

10.21 Subjective Responses 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 cocaine 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.

10.22 Vital Signs

Vital signs (HR and BP) will be measured at screening and daily during inpatient stay. Additional vital signs will be monitored on cocaine infusion days (see Section 10.5, Table 3, and Table 4). Vital signs are assessed in semi-supine position.

10.23 Clinic Discharge/Final Participant Disposition

The participant disposition CRF will document all data relevant to participant discharge from the clinic: reason for discharge (*i.e.*, completion of inpatient portion of the study, or early termination from the study) and date of discharge.

11 REGULATORY AND REPORTING REQUIREMENTS

11.1 Good Clinical Practice

This study will be conducted in accordance with the most current version of the International Council for Harmonisation (ICH) Guidance Document *E6 (R2): Good Clinical Practices: Consolidated Guideline*. An Operations Manual will be provided to all investigational sites as a study quality assurance tool.

11.2 Form FDA 1572

The Principal Investigator will sign a Statement of Investigator (Form FDA 1572) prior to initiating this study. The Form FDA 1572 will be updated as needed.

11.3 IRB Approval

Prior to initiating the study, the Principal Investigator will obtain written approval from the IRB of record to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the local IRB by the site Principal Investigator for IRB approval prior to implementation. In addition, NIDA and the local IRB will approve all advertising materials used for participant recruitment and any educational materials given to the

participant. Progress reports will be submitted to the local IRB annually or at a frequency requested by the IRB. The Investigator will report to the IRB all changes in research activity and all unanticipated problems involving risks to human participants or others.

11.4 Informed Consent

All candidates for the study will be given the current IRB-approved Informed Consent Form (ICF) to read. The principal investigator or other study investigator will explain all aspects of the study, including its risks and benefit, in lay language and answer all of the candidate's questions regarding the study, and will ensure that each candidate understands the study prior to obtaining the participant's signature. If the candidate desires to participate in the study, s/he will be asked to sign the ICF. A copy of the consent form will be given to the participant. No study procedure will be performed prior to signing the ICF. Candidates who refuse to participate or participants who withdraw from the study will be regarded without prejudice.

11.5 Outside Monitoring

Medical Monitor: A medical monitor has been appointed for the study. The medical monitor will be available for making recommendations to the Investigator and the Sponsor on the severity of any SAEs, the relatedness to the study interventions, and for determining if the SAE should be reported to the FDA in a 7 or 15 day expedited report or an annual report. The medical monitor will also be responsible for tracking and assessing trends in the AEs reported. In the event that the medical monitor and Investigator do not concur on SAE evaluations, both opinions will be reported to the FDA.

Clinical Monitors: All Investigators will allow representatives of the Sponsor to periodically monitor, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each participant. These monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study and to inform the Sponsor of potential problems. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that the investigational product is properly stored and accounted for, verify that participants' consent for study participation has been properly obtained and documented, confirm that research participants entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by GCP guidelines are appropriately filed.

Monitors will conduct a study initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training Investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities and staff are available to conduct the study.

Routine monitoring visits by NIDA's representatives will be scheduled at appropriate intervals but probably more frequently at the beginning of the study. At these visits, the monitors will

verify that study procedures are being conducted according to the protocol guidelines and will review AEs and SAEs and drug accountability. At the end of the study, they will advise on storage of study records and return of unused investigational products. All sites should anticipate visits by NIDA and the FDA.

11.6 Adverse Events Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the Investigator or sub-Investigators according to the specific instructions detailed in this section of the protocol and in APPENDIX B. The occurrence of AEs will be assessed starting when the participant receives the first dose of study drug, then daily during the inpatient portion of the study until clinic release, and at the final follow-up telephone contact.

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. For this study, events reported by the participant, as well as clinically significant abnormal findings on physical examination, vital signs, ECG, or laboratory evaluation will be recorded on the AE CRF. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

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.

11.7 Serious Adverse Events

Each adverse event or reaction will be classified by a study Investigator as being serious or non-serious. Based on the seriousness of the adverse event or reaction, appropriate reporting procedures will be followed. The Code of Federal Regulations Title 21 part 312.32 and ICH *Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (ICH-E2A), as implemented by the U.S. Food and Drug Administration (March 1995), defines a serious adverse event (SAE) or serious adverse drug experience as any untoward medical occurrence at any dose that:

- results in death;
- is life-threatening; *(NOTE: 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.)*

- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug reaction, when based on appropriate medical judgment that may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

An unexpected AE is one that is not described with respect to nature, severity, or frequency in the current product package insert.

Reporting of AEs and SAEs is described in APPENDIX B. There can be serious consequences including, ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs. The Investigators in this study have the responsibility of promptly reporting all SAEs to the designated Medical Monitor at NIDA in order that the NIDA can comply with these regulations.

If a study participant withdraws from the study or if an investigator decides to discontinue the participant from the study because of an SAE, the participant must have appropriate follow-up medical monitoring including, if necessary, hospitalization. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

12 ANALYSIS PLAN

12.1 Study Endpoints

12.1.1 Primary Endpoint

- **Safety and Tolerability:** AEs and cardiovascular responses including HR, BP, and ECG (including QTcF).

12.1.2 Secondary Endpoints

- **Safety:** Clinical laboratory assessments
- **PK:** PK of cocaine and BE; PK of SXC-2023
- **Subjective Effects:** VAS and BSCS

12.2 Study Populations

12.2.1 Safety Population

The safety population will include all participants who receive any administration of study drug.

12.2.2 Evaluable Population

Any participant who completed all 5 infusion sessions will be considered evaluable for primary endpoints.

12.3 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.

12.4 Safety Data Analyses

12.4.1 Adverse Events (AEs)

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. The severity, frequency, and relationship of AEs to study drug will be presented by preferred term by SOC grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided.

12.4.2 Vital Signs and ECG Changes

Vital signs data (HR and BP) will be presented as summary statistics of maximum (max) absolute values, max change from baseline, and time to max value during the 1-hour period after each cocaine infusion. Data will be compared between groups and within groups by study day by Wilcoxon rank sum statistic. Effects will be considered statistically significant at a two-sided $p < 0.05$. In addition, summary statistics for vital signs at each study time point will also be presented. Changes in ECG intervals during saline infusion as compared to those taken during cocaine infusions will be reported as summary statistics. Clinically significant ECG changes will be presented as counts and percentages.

12.4.3 Clinical Laboratory Parameters

The concentrations of each clinical chemistry 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 screening. The number of excursions outside the normal laboratory limits will be presented.

12.5 PK Data Analyses

The following PK parameters will be determined for cocaine, BE, and SXC-2023 (as appropriate): maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC) from time 0 to time t (AUC_{0-t}), AUC from time 0 to 12 hours post-dose (AUC_{0-12}), AUC from time 0 to time infinity ($AUC_{0-\infty}$), time to maximum plasma concentration (T_{max}), trough

plasma concentration (C_{trough}), terminal rate constant (λ_z), half-life ($t_{1/2}$), clearance (CL) and clearance from plasma after oral administration (CL/F). Weight-adjusted parameters may be determined when necessary.

12.5.1 Parameters and Definitions

PK parameters for plasma cocaine and BE as shown in Table 5 will be calculated using noncompartmental methods.

Table 5: Pharmacokinetic Parameters for Plasma Cocaine and BE

PK Parameter	Definition
C_{max}	Maximum observed plasma concentration
t_{max}	Time of the maximum observed plasma concentration
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time 0 to the time (t) of last quantifiable concentration (Ct) calculated by the linear-up/log-down trapezoidal rule
$AUC_{(0-\infty)}$	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 $AUC_{(0-\infty)} = AUC_{(0-t)} + Ct/\lambda z$
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from time 0 to 12 hours post-dose
AUC%extrap	Percent of $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ (cocaine only)
C_{max}*BW /70 kg	C_{max} for a 40 mg dose of cocaine normalized to 70 kg body weight
AUC_{0-t} *BW /70 kg	AUC_{0-t} for a 40 mg dose of cocaine normalized to 70 kg body weight
$AUC_{0-\infty}$ *BW /70	$AUC_{0-\infty}$ for a 40 mg dose of cocaine normalized to 70 kg body weight
CL/BW*70 kg	Clearance for a 40 mg dose of cocaine normalized to 70 kg total body weight (cocaine only)

Plasma concentration-time profiles of SXC-2023 on Day 9 (40 mg cocaine + saline infusion session) will be analyzed to obtain PK parameter estimates for SXC-2023 as shown in Table 6.

Table 6: Pharmacokinetic Parameters for Plasma SXC-2023

PK Parameter	Definition
C_{max}	Maximum observed plasma concentration
T_{max}	Time of the maximum observed plasma concentration
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from time 0 to 12 hours post-dose.
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.
$t_{½}$	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 $AUC_{(0-12)}$ at steady-state (of Day 10)
C_{max}*BW/70 kg	C_{max} normalized to 70 mg body weight
$AUC_{(0-1t)}$*BW /70 kg	AUC_{0-t} normalized to 70 mg body weight
$AUC_{(0-\infty)}$*BW /70 kg	$AUC_{0-\infty}$ normalized to 70 mg body weight
CL/F/ BW*70 kg	CL/F normalized to 70 kg total body weight

12.5.2 Statistical Analysis of PK Parameters

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)].

Plasma concentration-time profiles of SXC-2023 on Day 9 (40 mg cocaine + saline infusion session) will be analyzed to obtain PK parameter estimates.

Individual participant and group summary statistics will be presented.

To assess the effect of SXC-2023 on the PK of cocaine and BE, an analysis of variance (ANOVA) will be performed on the natural logarithms (LN) of AUC_{0-t}, $AUC_{0-\infty}$ and CL, with treatment group as a fixed effect. In addition, an analysis may be conducted with the LN of 70 kg weight adjusted parameters [C_{max} * bodyweight (BW)/70 kg, AUC_{0-t} * BW/ 70 kg, $AUC_{0-\infty}$ * BW /70 kg, and CL/BW*70 kg] when necessary. Within this ANOVA framework, comparisons of SXC-2023 versus placebo groups will be performed for baseline (Day 2), and Day 9 cocaine

challenge sessions (40 mg). The effect of saline/cocaine versus cocaine/saline randomized administration sequence will also be examined. The 90% CI for the ratio of the least squares means of SXC-2023 versus placebo AUC and C_{max} parameters will be determined. The 90% CI will be obtained by exponentiation of the 90% confidence intervals for the difference between the least squares means on the LN scale.

12.6 Subjective Assessment Analyses (VAS and BSCS)

Subjective effects VAS will be presented as summary statistics of maximum absolute values, maximum change from baseline, and time to maximum value over the 1-hour period after cocaine infusions. Data will be compared between groups and within groups between study days by Wilcoxon rank sum statistic.

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

12.7 Missing Data

Missing data will not be imputed for any analysis. The numbers of data points reflected in summary statistics will be indicated by presenting the number of observations.

13 DATA MANAGEMENT AND CASE REPORT FORMS

13.1 Data Collection

Data will be collected at the study sites on source documents, which will be transcribed at the site into case report forms (CRFs). The CRFs will be supplied by the Data Management Center. CRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. Completed CRFs will be collected by clinical monitors after monitoring against the source documents on a regular basis throughout the trial. The Investigator is responsible for maintaining accurate, complete and up-to-date records for each participant. The Investigator is also responsible for maintaining any source documentation related to the study, including clinical laboratory data, ECG tracings, *etc*.

13.2 Case Report Form Completion

Electronic CRFs (eCRFs) will be provided for each participant. The participant identifiers and actual date (and time, if applicable) of each assessment should always be entered in the eCRFs. The final, completed eCRF for each participant must be signed and dated by the Investigator on the appropriate CRF page to signify that he/she has reviewed the report and certifies it to be complete and accurate.

13.3 Data Editing and Control

Automated edit checks for missing, discrepant, and out-of-range data will be programmed into the study electronic data capture system (EDC). The identified discrepancies will be presented to the site user for resolution or justification. A TRI Data Manager will review the justification for all unresolvable discrepancies and will close or re-query them. Once all discrepancies and queries have been resolved, the PI will review the eCRFs in the EDC and confirm their accuracy with his/her electronic signature.

13.4 Data Monitoring

The PI agrees to routine data audits by the sponsor's designated Site Monitors. Monitors will periodically visit the site to assure that data entered in the EDC are in agreement with source documents. Monitor reviews may also be accomplished remotely (off-site), by comparing EDC data with de-identified source documents submitted by the site for this purpose. Any inconsistencies will be resolved, and any changes to the data forms will be made using the procedures specified in the Study Operations Manual.

13.5 Data Processing

A database will be constructed from the eCRFs that captures each item of data from each eCRF. All eCRFs will undergo a single-data entry process into the main study database with 100% quality control verification of all data entered into the eCRF. After entry, the data will be validated both manually and electronically. The database will undergo 100% quality assurance audit before locking and release for statistical analysis.

All AE information will be entered into the main study database from the AE CRF. 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. The severity, frequency, and relationship of AEs to study drug will be presented by preferred term by SOC grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided.

13.6 Study Documentation and Records Retention

Study documentation includes all eCRFs, data correction forms (if used), workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (*e.g.*, signed protocol and amendments, IRB correspondence and approved consent form, signed ICFs, Statement of Investigator form, and clinical supplies receipts and distribution records).

Source documents include recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, if applicable, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, patient diaries, biopsy reports, ultrasound photographs,

patient progress notes, charts or pharmacy records, and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

FDA regulations require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of two years after discontinuation of the IND or 2 years after the approval of a New Drug Application and finalization of all marketing strategies. In all instances, permission must be obtained from NIDA prior to disposition of any study documentation and materials.

13.7 Confidentiality

13.7.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical Investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical Investigator and IRB.

By signing this protocol, the Investigator affirms to NIDA that information furnished to the Investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

13.7.2 Confidentiality of Records

To maintain participant confidentiality, all laboratory specimens, CRFs, reports and other records will be identified only by a coded study participant identification number. Research and clinical records will be stored securely. Only research staff and sponsor or sponsor's representative will have access to the records. Participant information will not be released without written permission, except as necessary for monitoring by the FDA, sponsor, or sponsor's representative. Release of personal health information will be in accordance with current Standards for Privacy of Individually Identifiable Health Information (45 CFR parts 160 and 164) of the Health Insurance Portability and Accountability Act (HIPAA).

By signing the protocol, the PI also agrees that within local regulatory restrictions and ethical considerations, the sponsor, sponsor representative, or any regulatory agency may consult and/or copy study documents in order to verify CRF data.

14 SIGNATURES

NIDA DESIGNATED REPRESENTATIVES

Typed Name	Signature	Date
Jason Sousa, Ph.D. NIDA Project Officer	_____	_____
Shwe Gyaw, M.D. NIDA Medical Monitor	_____	_____

PRINCIPAL INVESTIGATOR

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 11.6 of this protocol.

Typed Name	Signature	Date
Debra Kelsh, M.D. Principal Investigator	_____	_____

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APPENDIX A: Schedule and Volume of Blood Sample Collections

Table 7: 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

Blood Drawing Procedure:

Blood drawn from all participants should be considered infectious and extreme caution should be used to avoid needle sticks and direct contact with blood or plasma.

Blood drawn for safety labs will be handled according to the procedures of the treating site and local analytical laboratory.

Blood drawn for plasma PK analysis will be handled as described in the study MOP. Plasma samples will be divided into two aliquots (one main and one backup).

APPENDIX B: Instructions for Evaluating and Reporting Adverse Events and Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. AEs will be recorded after the first dose of study drug is administered.
2. AEs will be reported on an AE CRF.
3. Report the severity of the event following the guidance in section B below.
4. Report the relatedness of the event to the investigational product administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild:	Awareness of symptom, but easily tolerated.
Moderate:	Discomfort enough to cause interference with usual activity.
Severe:	Incapacitating with inability to work or do usual activity.

C. DEFINITIONS – RELATEDNESS OF EVENTS

The study Investigator is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the investigational product. The degree of certainty for which the AE/SAE is attributed to the investigational product or alternative causes (*e.g.,* natural history of the underlying disease, concomitant therapies, *etc*.) should be determined by how well the experience can be understood in terms of one or more of the following:

- ***Exposure:*** Is there evidence that the participant was actually exposed to the investigational product?
- ***Timing of the administration of investigational product:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the investigational product?
- ***Consistency with investigational product safety profile:*** Known pharmacology and toxicology of the investigational product in animals and man; reaction of similar nature having been previously described with the investigational product.
- ***Alternative explanations*** for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.
- ***Response to discontinuation*** of the investigational product.

Terms and definitions to be used in assessing the investigational product relationship to the AE/SAE are:

- ***Unknown:***
  Use this category only if the cause of the AE/SAE is not possible to determine.
- ***Definitely Not Related:***
  The participant did not receive investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.
- ***Unlikely Related:***
  There is evidence of exposure to the investigational product or there is another more likely cause of the AE/SAE.
- ***Possibly Related:***
  There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.
- ***Probably Related:***
  There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.
- ***Definitely Related:***
  There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

A laboratory or ECG AE is any clinically significant worsening in a test variable that occurs during the course of the study, whether or not considered to be investigational product related. For each such change, provide the information requested on date of test, severity, likelihood of a relationship to investigational product, change in investigational product dosage due to the AE, and treatment required.

All laboratory AEs should be specified as an increased or decreased test result (*e.g.,* "increased glucose", "decreased potassium") or as a term that implies an abnormality (*e.g.,* hyperkalemia, azotemia, hypokalemia, or bradycardia). Any abnormal laboratory value that is considered not clinically significant will be recorded as such on the clinical laboratory report CRF along with a comment providing justification for that determination.

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any participant from the time of admission through discharge whether or not related to the investigational product, must be reported within 24 hours to the NIDA Medical Monitor and the NIDA Project Officer via email.

NIDA Medical Monitor:
Shwe Gyaw, M.D.
Phone: (301) 827-5924
Email: shwe.gyaw@nih.gov

NIDA Project Officer:
Jason Sousa, Ph.D.
Phone: (301) 827-5919
Email: jason.sousa@nih.gov

The following information must be provided with the initial report of an SAE or unexpected AE:

- Name of person reporting the SAE/unexpected AE
- Participant's I.D. number
- Name of the principal Investigator and institution
- Date the participant signed informed consent
- Date(s) of administration of investigational products
- Description of the SAE/unexpected AE
- Date and time of onset
- Date/time of administration of last dose of investigational product prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to investigational product (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the investigational product, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor/Alternate and the NIDA Project Officer within 3 days of reporting the event. Required documents that must be submitted include the following:

- SAE Form
- Concomitant Medication CRF pages
- Adverse Events CRF pages
- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the Investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor

These documents may be submitted as email attachments, or via overnight courier.

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended hospitalization period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the participant was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected AEs occurring up to the final safety evaluation must be reported. All follow-up Day 24 AEs will be recorded and followed to resolution only if they are serious, or if the study Investigator assesses them to be clinically significant.

The Investigator is required to provide the Medical Monitor and the IND Sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the investigational product.

Reporting to the FDA

The IND Sponsor is required to report SAEs to the FDA:

- in **7 days** if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the investigational product, with a follow-up written report in 8 days;
- in **15 days** if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening;
- in an annual report in all other cases.