PROMENTIS
PHARMACEUTICALS, INC.

CLINICAL PROTOCOL

An Exploratory, Placebo-Controlled, Crossover Study to Examine the Safety and Activity of SXC-2023 to Improve Behavioral Dynamics in Non-Treatment Seeking Adults Undergoing Acute Nicotine Withdrawal

Protocol No.:	PRO-202
US IND No.:	140669
Phase:	2A
Amendment 3:	**15 April 2019**
Previous versions	
Amendment 2:	26 November 2018
Amendment 1:	05 November 2018
Original Protocol Date:	24 July 2018

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

PROTOCOL REVISION HISTORY

Date/Name	Description
12 Apr 2019/ P. Cotter	Design change from outpatient to inpatient study design (subjects confined at Celerion during treatment days of both Periods of the crossover) Administrative changes throughout document Clinical laboratory location change Principal Investigator change Changed from 1 site to 2 sites. Change in Baylor site status, addition of Celerion site Added fasting requirements for Day 1 of Period 1 and Period 2 Glutathione testing requirements for assay updated Number of subjects changed from up to 32 to up to 36 total subjects exposed to SXC-2023. Celerion to run subjects in two groups Cue reactivity images from MUSC instead of MD Anderson Inclusion criteria: change in starting age from 28yo to 25yo, addition of BMI, clarifications on remaining inclusion requirement timepoints, added requirements for female of non-childbearing potential subjects and included Aricept drug requirement. Exclusion criteria: Change requirement for hepatitis- must be active, SSRI/SNRI requirement change allowing for subjects to be included if they have been on stable dose 30 days prior to screening, and clarified other requirements with examples. Change to Figure 1, Diagram of study design with number of subjects Removed all monetary incentives notations Added section on Confinement, Return visits and Follow up Change in max study duration from 61 days to 59 days Added items to contraceptive requirements for female subjects Schedule of assessments: Increased number of timepoints for physical exams, safety labs, urine drug screens and ECG. Change in requirements for subjects returning on Day 1 of Period 2 Added requirement for replacement of subjects in Group 1 of study Appendix J: Added FTND questionnaire
26 Nov 2018/ P. Cotter	Added exclusion criteria stipulating that subjects will be excluded for any clinically significant laboratory, ECG, or vital sign abnormality. Vital signs assessment added at each study day. Included laboratory, VS, and ECG-based discontinuation criteria. Added exclusion criteria: Removal of allowance of subjects to re-enter the study after a relapse.
02 Nov 2018/ P. Cotter	Included US IND No. Included Dr. Thomas Kosten as Co-PI Addition of 90-day toxicology data in rats and dogs Addition of MAD safety, PK data and Stopping Rules criteria

	Update to Rationale for dose selection Removal of two treatment pair doses Screening window change from -28 days to -30 days Clarification of Adverse event collection at screening Deleted in Section 6.2.3.1 "However, if a subject relapses during Period 1, he/she would be allowed one more chance to participate in this study by enrolling in the future, assuming that he/she meets the eligibility criteria upon re-screening." Update to Statistics (Section 12.1), deletion of "There will be 6 within-subject differences for each pairwise treatment contrast. Twelve difference scores are powered to detect differences approximately twice the within-subject standard deviation."

PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

An Exploratory, Placebo-Controlled, Crossover Study to Examine the Safety and Activity of SXC-2023 to Improve Behavioral Dynamics in Non-Treatment Seeking Adults Undergoing Acute Nicotine Withdrawal

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1 SYNOPSIS

Compound No.

SXC-2023 – a novel small molecule activator of the cystine-glutamate antiporter (System xc- or Sxc)

Study Protocol Title

An Exploratory, Placebo-Controlled, Crossover Study to Examine the Safety and Activity of SXC-2023 to Improve Behavioral Dynamics in Non-Treatment Seeking Adults Undergoing Acute Nicotine Withdrawal

Sites

2 sites: Baylor College of Medicine (site closed); Celerion

Phase of Development

Phase 2A

Dosage and Administration

Double-blinded study drug:

- SXC-2023 200 mg (4 x 50 mg capsules) dosed once per day (QD),
- SXC-2023 800 mg (4 x 200 mg capsules) QD, or
- Matching placebos QD

On Day 1 of each Period, dosing will occur in the morning under fasted conditions. For all other days, dosing will occur at least 2 hours after breakfast.

Primary Objectives

- To explore the safety and tolerability of SXC-2023 when dosed for 5 days in adults diagnosed with tobacco use disorder (i.e., cigarette smokers) who voluntarily abstain from the use of cigarettes.
- To test the activity of SXC-2023 when dosed for 5 days on measures of abstinence-induced impulsivity and inhibitory control, urge for cigarettes, and mood.

Exploratory Objectives

- To explore the effects of 5 days of tobacco abstinence on levels of total and/or reduced glutathione (GSH) in blood/plasma.
- To test the possible effects of SXC-2023 on levels of total and/or reduced GSH deficits via assay of blood/plasma GSH levels.

Study Design

This randomized, double-blinded, placebo-controlled, two-period crossover study will evaluate the effect of two doses of SXC-2023 on measures of impulsivity and inhibitory control, urge for cigarettes, and mood in non-treatment seeking smokers who are abstaining from smoking. To be eligible, subjects must meet the protocol-specified eligibility criteria which include a score of ≥4 on the Fagerstrom Test of Nicotine Dependence (FTND) and an expelled carbon monoxide (CO) level of ≥10 ppm at screening and Day 1 of Period 1, prior to dosing.

To date, four (4) total subjects have been dosed at Baylor College of Medicine (BCM). At Celerion, two groups of 14 subjects, a total of 28 subjects will be assigned to receive two treatment regimens: SXC-2023 200 mg QD and matching placebo or SXC-2023 800 mg QD and matching placebo, in a 2-treatment crossover design. Subjects will receive one treatment regimen per 5-day treatment period of the crossover with a 9-day washout between treatment periods (after the last study day of Period one and prior to first day of Period 2) where subjects will be able to smoke as usual. Subjects will be randomized to treatment pair comparison (SXC-2023 200 mg QD and matching placebo, or SXC-2023 800 mg QD and matching placebo and to treatment sequence within each pair). Seven (7) subjects will be randomized to each of the 4-treatment pair sequence combinations. Subjects who complete Period 1 in Group 1 but do not return on Day 1 of Period 2 of the crossover will be replaced in Group 2. A total of 4 subject replacements may be enrolled in Group 2.

Subjects will be allowed to smoke until they enter the Celerion facility at the start the study on Period 1, Day 1. Subjects will abstain from nicotine ingestion each day of the treatment period starting at Day 1, and CO testing and Urine cotinine testing will be performed on Day 1 and Day 5 of both periods of the crossover and, at the discretion of the PI, may be performed each day (Days 2 through 4) of the treatment period to confirm nicotine abstinence.

Measurements of neurocognitive control will be performed in the morning on Day 1 of both Periods, prior to study drug administration and on Day 5 (4-5 hours post dose) to assess the effect of SXC-2023 on abstinence-induced measures of impulsivity and inhibitory control. Additional assessments will include measures of urge for cigarettes. Testing will include the Stop Signal Task (SST), Cambridge Gambling Task (CGT), Paired Associates Learning (PAL), Reaction Time (RTI), Questionnaire on Smoking Urges (QSU), Positive and Negative Affect Schedule (PANAS), the Fagerstrom Test for Nicotine Dependence (FTND) and the Cigarette Evaluation Questionnaire (CEQ). Cue reactivity will be evaluated using the International Affective Picture System (IAPS) images and those validated in the TRAIN lab at MUSC (PI Froeliger) (for neutral and positive images) and smoking images on Day 2 (following 24 hours of abstinence) and on Day 5, and two Likert scale assessments will also be performed on Days 2 and 5. Levels of GSH (either total GSH or reduced forms) will be collected in blood and/or plasma at baseline (prior to dosing on Day 1) and after 5 days of tobacco abstinence (4-5 hours after dosing on Day 5). Following the completion of the first 5 days of treatment with SXC-2023 200 mg QD, SXC-2023 800 mg QD, or placebo, subjects will be allowed to smoke *ad lib* during a 9-day washout period. Following the washout period, subjects will crossover into Period 2 of this study and will receive a different study drug or placebo and will repeat the study procedures and assessments employed in Period 1, unless noted otherwise.

A follow-up visit will be scheduled to occur approximately 7-10 days after the last dose of study drug (SXC-2023 200 mg, SXC-2023 800 mg, or placebo) is administered.

Study Duration

The maximum anticipated subject participation will be approximately 59 days (30 days for the screening period, 5 days for Period 1 of the crossover, 9 days for the washout, 5 days for Period 2 of the crossover, and maximum of 10 days until the follow-up visit).

Number of Subjects (Planned Exposure)

To date, 4 subjects have been dosed at BCM. At Celerion, two groups of 14 subjects (a total of 28 subjects) will be enrolled on the study. Subjects who complete Period 1 in Group 1 but do not return on Day 1 of Period 2 of the crossover will be replaced in Group 2. A total of 4 subjects will be allowed as replacements in Group 2. With a 2-treatment crossover design, 16 possible subjects will be exposed to SXC-2023 200 mg vs. placebo, and 16 possible subjects to SXC-2023 800 mg vs. placebo during each period (n=32).

Including an anticipated 10% dropout rate at Celerion, no more than 32 subjects will be exposed to SXC-2023. At both sites, no more than 36 subjects will be exposed to SXC-2023 in this study.

Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for the study:

1. Adult, female or male, 25-55 years of age, inclusive at screening.
2. BMI ≥ 16.0 and ≤ 35.0 kg/m^2 at screening.
3. Has provided signed written informed consent and has willingness and ability to comply with all aspects of the protocol, including abstaining from the use of tobacco/nicotine products for two 5-day periods.
4. Non-treatment seeking smokers regularly using tobacco with a FTND score ≥4 at screening and self-reported use of ≥10 cigarettes/day at screening.
5. Has smoked for >5 years at screening.
6. Meets Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria for tobacco use disorder.
7. Must have a score of ≥4 on the FTND and an expired-air CO level ≥10 ppm during initial screening and prior to first dose.
8. For a female of childbearing potential: either be sexually inactive (abstinent as a life style) for 28 days prior to the first dosing and throughout the study or be using acceptable birth control methods as described in Section 5.2.2.4 of the protocol.
9. Female of non-childbearing potential: must have undergone one of the following sterilization procedures, at least 6 months prior to the first dose:
    a. hysteroscopic sterilization;
    b. bilateral tubal ligation or bilateral salpingectomy;
    c. hysterectomy;
    d. bilateral oophorectomy;

    Or be postmenopausal with amenorrhea for at least 1 year prior to the first dose with serum follicle stimulating hormone levels consistent with postmenopausal status or have medically documented history of biological or congenital sterility.

10. Has not used Aricept (a cholinersterase inhibitor) 30 days prior to screening.

Exclusion Criteria

Subjects meeting ANY of the following criteria must NOT be enrolled in this study.

1. Subject is mentally or legally incapacitated or has significant emotional problems or clinically significant abnormality at the time of the screening visit or expected during the conduct of the study.
2. Subject suffered a concussion 6 months or less prior to screening.
3. Females who are pregnant or breastfeeding.
4. Positive for active hepatitis, human immunodeficiency virus, coagulopathy, or hepatic illness.

5. Use of Selective Serotonin or Norepinephrine Reuptake Inhibitors (SSRI/SNRI) for psychiatric illness (e.g. depression, anxiety, etc.), unless subject has been on a stable dose for at least 30 days prior to screening
6. Use of antipsychotics or use of antiepileptics within 30 days prior to screening.
7. Use of N-acetylcysteine within 30 days prior to screening.
8. Use of Chantix or related smoking cessation medications (e.g., NicoDerm patch, Nicorette gum, etc) within 30 days prior to the first dose.
9. Use of sulfasalazine (Azulfidine®) within 30 days prior to the first dose.
10. DSM-5 criteria for alcohol/substance use disorder (except for tobacco use disorder).
11. History or presence of clinically significant psychiatric condition (except for tobacco use disorder) or disease in the opinion of the Principal Investigator (PI) or designee.
12. History of any illness that, in the opinion of the PI or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
13. History of seizures.
14. Any history of psychiatric hospitalization in the past year.
15. Currently participating in a clinical study.
16. Previously participated in any Phase 1 Promentis studies or dosed in this Phase 2A study.
17. FTND score <4 and expelled CO levels <10 ppm at screening and prior to first dose.
18. Any clinically significant laboratory, ECG and/or vital sign abnormalities at screening.
19. Unable to read/understand/speak English.

2 ABBREVIATIONS

AE	Adverse event
AUC	Area under the concentration-time curve
BIS	Barratt Impulsiveness Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
CEQ	Cigarette Evaluation Questionnaire
CFR	Code of Federal Regulations
CGT	Cambridge Gambling Task
Cm	Centimeter
C_{max}	Maximum observed concentration
CNS	Central nervous system
CO	Carbon monoxide
CRF/eCRF	Case report form/electronic case report form
CRO	Contract research organization
DG	Days of gestation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	Electrocardiogram
EDC	Electronic Data Capture
EE2	Ethinyl estradiol
FAS	Full Analysis Set
FE	Food effect
FTND	Fagerstrom Test of Nicotine Dependence
GCP	Good Clinical Practice(s)
GLP	Good Laboratory Practice
GSH	Glutathione
HIV	Human immunodeficiency virus
HR	Heart rate
Hr	hour(s)
IAPS	International Affective Picture System
ICD	Impulse control disorder
ICF	Informed Consent Form

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
IRB	Institutional review board
ITT	Intent-to-Treat
Kg	Kilogram
m^2	Meters squared
MAD	Multiple ascending dose
MedDRA®	Medical Dictionary for Regulatory Activities®
Mg	Milligram
mL	Milliliter
mmHg	Millimeters of mercury
NAC	N-acetylcysteine
NET	Norethindrone
No.	Number
NOAEL	No observed adverse effect level
OC/DDI	Oral contraceptive/drug-drug Interaction
OTC	Over-the-counter
PAL	Paired Associates Learning
PANAS	Positive and Negative Affect Schedule
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per Protocol
Ppm	parts per million
PT	Preferred term
QA	Quality assurance
QD	Once per day
QSU	Questionnaire on Smoking Urges
QTcF	Corrected QT Fridericia's
RBC	Red blood cell
RTI	Reaction Time
SAD	Single ascending dose

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
SST	Stop Signal Task
SXC	System xc-
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum observed concentration
TTM	Trichotillomania
UA	Urinalysis
US	United States
VS	Vital signs
WHODD	World Health Organization Drug Dictionary

3 BACKGROUND AND RATIONALE

3.1 Background

Impaired cortical control over impulses, mood and urges is a hallmark feature of several disorders of the central nervous system (CNS), specifically, impulse control disorders (ICDs) such as trichotillomania (TTM), excoriation (skin picking) disorder, obsessive compulsive disorder, and various addictions. Dysfunction in areas of the brain responsible for regulating cortical control over urges and motor habits are purported to underlie the pathological progression of ICDs (Froeliger et al., 2017, Froeliger et al., 2015). Evidence supporting this contention arises out of functional magnetic resonance imaging studies linking behavioral dysfunction to abnormal signaling and connectivity in the brain's inhibitory control circuitry namely, the cortico-striatal pathway that originates in the frontal cortex and innervates the lower limbic areas responsible for movement and reward.

Several clinical studies (e.g., LaRowe et al., 2007; Amen et al., 2011; Froeliger et al., 2015) in non-treatment-seeking nicotine or cocaine addicts have shown that following a brief abstinence period, subjects in acute withdrawal exhibit deficits in inhibitory control, measurements of executive function (e.g., impulsiveness) and mood. Therefore, short periods of nicotine abstinence in otherwise healthy volunteers represent a consistent approach to evaluate and further characterize the ability of novel therapeutic agents designed to restore cortical function and overall behavioral control by reversing deficits in impulsive behavior.

Promentis Pharmaceuticals is developing SXC-2023, a novel small molecule designed to activate System xc^- (also known as the cystine-glutamate antiporter). By increasing cyst(e)ine levels, SXC-2023 increases the activity of System xc- in the brain. System xc- is expressed within the brain's inhibitory pathway, namely the cortico-striatal pathway (Lutgen et al., 2014), and more specifically, on astrocytes within this area of the brain and throughout the CNS. The primary function of System xc- is to couple the uptake of one extracellular molecule of cystine to the release of one intracellular molecule of glutamate. As alterations in glutamate neurotransmission and/or oxidative imbalances in the CNS are proposed to contribute to the pathogenesis and maintenance of various ICD behaviors (e.g., TTM), this mechanism of activating System xc- may represent an important pathway to modulate glutamatergic neurotransmission and restore imbalances in oxidative stress to restore control of various pathological behaviors.

SXC-2023 is currently under investigation for the treatment of TTM in adults (Investigational New Drug [IND] No. 133689).

This current study is being performed to evaluate SXC-2023 on measures of abstinence-induced impulsivity and inhibitory control impairment, urge, and mood in smokers who have abstained from smoking.

Refer to the Investigator's Brochure, Version 5.0 (SXC-2023, 2018) for detailed background information on SXC-2023.

3.1.1 Preclinical Trials

3.1.1.1 Pharmacology

In preclinical rodent models, SXC-2023 was found to produce anxiolytic activity as measured by an increase in the time spent in the open arm of the elevated plus maze, which is used to measure anxiety (a symptom of many psychiatric disorders and a clear indication of CNS penetration) and ameliorate N methyl-D-aspartate receptor antagonist (MK-801)-induced deficits in pre-pulse inhibition, which tests behavior that is dependent on cortical glutamatergic transmission. Additionally, acute and chronic (7-day) administration of SXC-2023 significantly lowered the number of lever presses to reinstatement cocaine-seeking behavior. These studies, coupled with a study using rats engineered to lack a functional cystine-glutamate antiporter (specifically the xCT light chain protein), suggest that SXC-2023, through activation of System xc-, reverses deficits associated with glutamatergic dysfunction and heightened levels of oxidative stress implicated in the pathophysiology of ICDs.

3.1.1.2 Pharmacokinetics

Following oral administration of SXC-2023, the absolute bioavailability in dogs, the only species in which this has been studied, is 17.2%.

SXC-2023 is rapidly absorbed in all species following oral administration, with peak plasma concentrations typically occurring within 2 hours post-dose. In whole blood, most of the SXC-2023 and N-acetylcysteine (NAC) (a metabolite of SXC-2023) are present in the plasma, with high protein binding (>96%) at a concentration of 10 μM (2.81 μg/mL). Compared to total plasma concentrations, concentrations of SXC-2023 and metabolites (NAC and *p*-toluic acid) in red blood cells (RBCs) appear to be consistently lower . Metabolism of SXC-2023 was evaluated using rat, monkey, and human hepatocytes. In each species, the primary metabolites were NAC and *p*-toluic acid. Another possible minor pathway of SXC-2023 metabolism includes deamidation followed by cysteine conjugation.

Based on preliminary data, the parent drug and both metabolites appear to have relatively short plasma half-lives (<6 hours). The metabolites are polar, therefore extensive renal clearance and urinary excretion are expected.

Based on *in vitro* studies to assess the potential of SXC-2023 to inhibit, induce, or be metabolized by cytochrome P450 enzymes, it is anticipated that the likelihood of drug-drug interactions with SXC-2023 is minimal, with a possible exception for inhibition of cytochrome P450 P2C8 (showing half-maximal inhibitory concentration of enzyme activity of 570 μM). *In vitro* data indicate that SXC-2023 may be a substrate of organic anion transporting polypeptide 1B1 and 1B3, but not of P-glycoprotein or breast cancer resistance protein.

3.1.1.3 Toxicity

The safety and toxicity associated with chronic SXC-2023 treatment was evaluated in 2 species (rats and dogs) following a 28- or 90-day dosing period. In the 90-day toxicity studies, the

reversibility, persistence, or delayed occurrence of any SXC-2023-related effects was evaluated after a 28-day recovery phase.

Once-daily oral administration of SXC-2023 for 28 days at 500, 1000, and 2000 mg/kg/day was well tolerated in both male and female rats. While non-adverse hematology observations and findings consistent with chronic progressive nephropathy were observed in this 28-day dosing study, no adverse findings were noted. Based on these findings and taking into consideration the overall wellbeing of the animals, the Study Director at the nonclinical contract research organization (CRO) considered the no observed adverse effect level (NOAEL) to be the highest dose tested (2000 mg/kg/day). However, given the increase in kidney weights and greater severity of findings in the kidney tubules at the highest dose in both sexes, Promentis conservatively considers the NOAEL to be 1000 mg/kg/day.

In the 90-day rat toxicity study, SXC-2023 was well tolerated at 100, 300, and 1000 mg/kg/day and resulted in no adverse findings. Reversible, non-adverse clinical pathology findings included a higher incidence of ketones in the urine, mildly higher urine volume, and minimally to mildly lower urinary pH in males administered ≥300 mg/kg/day and females administered 1000 mg/kg/day. Mildly lower T3 and T4 serum levels occurred in males administered 1000 mg/kg/day and were not accompanied by any TSH changes or microscopic correlates. Microscopic findings at the terminal and recovery sacrifices were limited to minimal to moderate basophilic tubules and minimal to slight degeneration of tubules in animals administered 1000 mg/kg/day, which correlated with SXC-2023-related increased kidney weight parameters at the terminal sacrifice. Due to the mild severity of findings and the lack of impact on the health and well-being of animals administered 1000 mg/kg/day, effects for this dose were considered non-adverse. Thus, the NOAEL was determined to be 1000 mg/kg/day.

In Beagle dogs, SXC-2023 had no effect on survival when administered at doses up to 1200 mg/kg/day for 28 days. No CNS safety or measurements of CNS excitotoxicity differences in neuron integrity were noted between controls and animals administered the highest dose of SXC-2023 (1200 mg/kg/day). Emesis/vomitus, excessive salivation, liquid feces, and overall loss of body weight in animals administered 1200 mg/kg/day were observed. Similar findings were occasionally noted in animals administered 250 mg/kg/day and 500 mg/kg/day, and these findings were observed in the control animals as well.

Decreased thymus weight parameters occurred in male dogs at all doses, statistically significantly different from vehicle control at doses of 250 and 1200 mg/kg/day but not 500 mg/kg/day. Decreased cortical lymphocytes were observed in some males and females administered ≥ 250 mg/kg/day. Incidence of decreased cortical lymphocytes was variable, without a clear dose response, with minimal to slight severity in animals administered 250 or 500 mg/kg/day and minimal to marked severity in animals administered 1200 mg/kg/day. Given the lack of clinical pathology correlates and dose response, these findings in the thymus did not impact the function of the organ and could be attributed to stress given the emesis, weight loss, and need for supplementation.

Also, in the high-dose group, lower testis weights in male dogs administered 1200 mg/kg/day were correlated with the microscopic findings of degeneration and atrophy (slight to moderate)

of the seminiferous tubules, which were considered adverse. No effects on seminiferous tubules or testes weight were observed in animals administered 250 mg/kg/day or 500 mg/kg/day. Based on these findings, the Study Director of the nonclinical CRO defined the NOAEL as 500 mg/kg/day; however, based on the similar exposure levels at 500 and 1200 mg/kg/day groups, Promentis conservatively defined the NOAEL in this study to be 250 mg/kg/day for 28 days.

In addition, there is no effect on the male or female reproductive systems in rats or dogs at the NOAELs. At higher doses, sperm granuloma was noted in rats (2000 mg/kg/day) and decreased testes weight with microscopic degeneration and atrophy of the seminiferous tubules were noted in dogs (1200 mg/kg/day). In dogs (the only species tested for these effects), there was no effect on testosterone, prolactin, progesterone, or estradiol.

In the 90-day dog toxicity study, SXC-2023 was well tolerated at 30, 100, and 300 mg/kg/day. No SXC-2023-related findings or adverse microscopic or macroscopic findings were noted in this study. Similarly, no changes in measurements of hematology, immune system, ophthalmic or cardiovascular system were found in this 90-day dog tox study. Therefore, the NOAEL was determined to be 300 mg/kg/day.

Good Laboratory Practice (GLP) development and reproductive toxicology studies have also been completed following chronic SXC-2023 treatment. Doses selected for these studies were based on the results from previous non-GLP dose range finding studies in pregnant rats and rabbits.

In a GLP study to test for effects resulting from SXC-2023 treatment to female Wistar Hannover rats on various fertility parameters, females were orally dosed with SXC-2023 at either 0, 100, 300 or 1000 mg/kg/day (n=22 female rats per dose group) once daily beginning 15 days before cohabitation, during cohabitation and continuing until Day 7 of gestation. All rats survived to scheduled euthanasia. 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. Therefore, the NOAEL of oral SXC-2023 in rats for both maternal toxicity and female fertility and early embryonic development was 1000 mg/kg/day, the highest dose tested.

In a study to detect adverse effects of SXC-2023 on pregnant Wistar Hannover rats and development of the embryo and fetus, female rats were orally dosed with SXC-2023 at either 0, 100, 300 or 1000 mg/kg/day (n=20 rats per group) once daily on Days 7 through 17 of gestation (DGs 7 through 17). All rats survived to scheduled euthanasia on DG 21. There were no SXC-2023-related changes in mean maternal body weights, body weight gains or food consumption up to 1000 mg/kg/day, the highest dose tested. There were no SXC-2023-related changes in ovarian, uterine, or litter parameters, including embryo-fetal survival and mean fetal body weights. Lastly, there were no SXC-2023-related fetal external, visceral, or skeletal malformations or variations observed up to 1000 mg/kg/day, the highest dose tested.

In a GLP study to assess possible adverse effects of SXC-2023 on pregnant New Zealand White rabbits and development of the embryo and fetus following daily oral exposure from

implantation to closure of the hard palate (gestation day 7 to 19 [DG 7 to 19]), pregnant rabbits were orally dosed with SXC-2023 at either 0, 30, 100 and 300 mg/kg/day (n=20/dose group) once daily on DG 7 to 19. One rabbit in the control group and one rabbit in the 300 mg/kg/day group aborted on DG 25. Additionally, one rabbit in the 300 mg/kg/day group was euthanized due to severe body weight loss and reduced food consumption on DG 24. Mean maternal body weight gain was lower than controls by 23% from DG 10 to 13, and by 35% from DG 16 to 20 (65% of the control). There was a mean maternal body weight loss for the interval DG 14 to 15 of -9.07g. During the post dose period, mean body weight gains in this group were higher than the control (131% of the control from DG 20 to 29) such that overall mean body weights on DG 29 were comparable across all groups (including control).

There were no SXC-2023-related changes in ovarian, uterine, or litter parameters, including embryo-fetal survival and mean fetal body weights up to 300 mg/kg/day. Mean male, female, and combined fetal weights were lower in the 300 mg/kg/day dose group compared to the control values (95%, 93%, and 94% of the control, respectively). Each of the mean the values was within the Testing Facility Historical Control Data range. Although these values were within the Testing Facility Historical Control Data, they were lower than the concurrent control. There were no SXC-2023-related fetal external or visceral malformations or variations observed up to 300 mg/kg/day. Fetal ossification site averages per fetus were comparable across all groups (including control).

Based on the lower maternal body weight gain and body weight loss, reduced food consumption, at 300 mg/kg/day, the NOAEL of SXC-2023 was determined to be 100 mg/kg/day in this study.

Based on results from a pivotal Ames mutagenicity assay, a human peripheral blood lymphocyte chromosome aberration assay, and an *in vivo* micronucleus assay in Wistar rats, SXC-2023 is considered not genotoxic.

Refer to the Investigator's Brochure, Version 5.0 (SXC-2023, November 2018) for detailed information on SXC-2023.

3.1.2 Effects of SXC-2023 in Humans

As described below, SXC-2023 has been investigated in a randomized, double-blind, placebo-controlled, single ascending dose (SAD) and food effect (FE) study in healthy subjects (PRO-101) and a randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study in healthy subjects (PRO-104). In both studies, SXC-2023 was administered as enteric capsule(s) in 50-mg or 200-mg unit dose strengths as single doses (up to 1600 mg) or multiple doses (up to 800 mg once per day [QD] for 14 days). Additionally, an open label oral contraceptive/drug-drug interaction (OC/DDI) study (PRO-103) to evaluate the pharmacokinetic (PK) effects of a single dose of SXC-2023 (800 mg) and oral contraceptives (norethindrone [NET]/ethinyl estradiol [EE2]) was completed.

Safety and PK findings are briefly summarized herein. Refer to the Investigator's Brochure, Version 5.0 (SXC-2023, 2018) for further information about the safety and PK data of SXC-2023.

3.1.2.1 Safety

As of 26 November 2018, a total of 96 subjects have been exposed to SXC-2023. Overall, SXC-2023 has been generally safe and well-tolerated in doses ranging from 50 mg to 1600 mg in the single ascending dose (SAD) and food effect (FE) study, 800 mg in combination with oral contraceptives and 200 mg to 800 mg multiple ascending dose study for 14 days. The most common adverse events in subjects randomized to SXC-2023 in all Phase 1 studies include headache (frontal, generalized, occipital, or temporal) in 11% of subjects, dizziness in 5%, and constipation, myalgia and somnolence in 3% each.

In all studies, changes from baseline in vital sign measurements and electrocardiogram (ECG) findings were also assessed. Vital signs were normal and no evidence of ECG abnormalities such as corrected QT (QTc) prolongation, was seen. In addition, no abnormal laboratory findings reported were considered clinically significant by the Investigator.

In the PRO-103 and PRO-104 studies, safety laboratory results indicated that several subjects exhibited notable shifts in urinalysis measures of occult blood or red blood cells postdose. These were most likely due to several subjects with menses during the studies.

PRO-101: SAD/FE Study

The SAD/FE study examined the safety and tolerability of single oral doses of SXC-2023 ranging from 50 mg to 1600 mg. A total of 48 healthy, adult male and female subjects were enrolled in 6 cohorts of 8 subjects each (6 active and 2 placebo).

SXC-2023 was safe and well-tolerated. A total of 36 subjects were dosed with SXC-2023 on Study PRO-101 in six cohorts (50 mg, 100 mg, 200 mg, 400 mg, 800 mg and 1600 mg). Overall, adverse events across body systems were mild or moderate. In subjects who received SXC-2023, the most common AEs were headache (in 5 subjects), followed by constipation, nausea, vomiting, and presyncope (in 2 subjects each). There were no serious adverse events (SAEs) reported or subject discontinuations related to AEs, or deaths in this study. Additionally, there was no evidence of impact on safety parameters for SXC-2023 in the presence of food.

Safety was also assessed by the incidence of changes from baseline in clinical laboratory, vital sign measures, and ECG findings. Safety laboratory results and vital signs were normal and no evidence of ECG abnormalities, such as corrected QT (QTc) prolongation, was seen.

PRO-103: OC/DDI Study

This open label OC/DDI study evaluated the effect of a single dose of SXC-2023 800 mg on the PK of single doses of 1 mg NET/0.035 mg EE2 (Ortho-Novum 1/35), in 28 healthy oral contraceptive-naïve females.

Overall, AEs were reported by 36% of subjects, with 21% following EE2/NET alone and 18% following EE2/NET + SXC-2023. The most common AEs were dizziness and headache, reported by 11% of subjects each. The majority of AEs were mild in severity, with 6 considered moderate in severity. All AEs resolved by end of study and there were no clinically

important trends in AEs, clinical laboratory, vital signs, ECG, or physical examination assessments. There were no deaths, SAEs, or subject discontinuations in this study.

PRO-104: MAD Study

The MAD study examined the safety, tolerability and PK of multiple oral doses (14 days) of SXC-2023 in four cohorts (200 mg QD, 400 mg QD, 400 mg twice daily and 800 mg QD) of 10 subjects each (8 active and 2 placebo per cohort). Forty total subjects have been dosed with SXC-2023 or placebo.

The MAD study examined the safety, tolerability and PK of multiple oral doses (14 days) of SXC-2023 in four cohorts (200 mg QD, 400 mg QD, 400 mg twice daily [BID] and 800 mg QD) of 10 subjects each (8 active and 2 placebo).

Overall, SXC-2023 was well tolerated across all doses without any SAEs. Additionally, there were no subject discontinuations or deaths reported in this study. Adverse events were reported by 45% of SXC-2023-treated subjects regardless of attribution. The most common in subjects who received SXC-2023 was headache, reported by 12.5% (4/32) of subjects. All AEs were mild (Grade 1) to moderate (Grade 2) in severity in all dose groups; of those considered possibly related to study treatment, the majority of Grade 2 events were reported in the placebo group.

All AEs resolved by the end of study and there were no clinically important trends in AEs, physical examination or clinical laboratory assessments. However, two subjects treated with SXC-2023 with treatment emergent adverse events (TEAEs) of urinary tract infection or asymptomatic bacteriuria recorded notable post-baseline laboratory results, including positive shifts in urinalysis measures of occult blood, leukocyte esterase, and red and white blood cells, as well as positive urine nitrites and urine culture growth.

There was no observed impact on neurocognitive assessments or suicidality via the Columbia-Suicide Severity Rating Scale (C-SSRS).

3.1.2.2 Pharmacokinetics and Product Metabolism

PRO-101: SAD/FE Study

The PK of SADs of SXC-2023 was evaluated in Study PRO-101. Six cohorts of subjects received SADs of SXC-2023 (50 mg, 100 mg, 200 mg, 400 mg, 800 mg fasted, 800 mg fed, and 1600 mg). SXC-2023 concentrations were measurable in all subjects; NAC and *p*-toluic acid were measurable in a few sporadic samples across the dose levels tested. Plasma SXC-2023 concentrations increased with increasing dose and were dose-proportional to 1600 mg. On average, maximum observed concentration (C_{max}) ranged from 1,094 ng/mL for the 50 mg dose to 35,217 ng/mL for the 1600 mg dose. Time to reach maximum observed concentration (t_{max}) was consistent across doses and was approximately 3.0 to 3.5 hours. The elimination half-life for SXC-2023 was approximately 3 to 6 hours over the 50 to 1600 mg dose range tested. Co-administration of SXC-2023 800 mg with a high-fat meal resulted in lower C_{max} and

a delay in t_{max}. Exposure, as assessed by area under the concentration-time curve (AUC), was slightly increased following administration of SXC-2023 with a high-fat meal.

PRO-103: OC/DDI Study

Concomitant SXC-2023 administration does not have an impact on the PK of NET or EE2. Changes in EE2 drug exposure were not seen with concomitant SXC-2023 and the 90% confidence intervals for EE2 were within the 80-125% confidence limits demonstrating bioequivalence. For NET, the confidence intervals suggest that NET levels are slightly higher with concomitant SXC-2023; the test/reference ratios were 116% for C_{max} and approximately 124% for the AUC parameters and the upper bounds for the confidence intervals were just outside the 125% upper range. These changes, however, were not considered clinically relevant.

PRO-104: MAD Study

Based on preliminary quality-controlled data, following single dose administration, the mean C_{max} of SXC-2023 under fasted conditions ranged from 6305 ng/mL for the 200 mg QD dose to 30, 540 ng/mL for the 800 mg dose. On Day 14, the mean C_{max} of SXC-2023 under fasted conditions ranged from 7990 ng/mL for the 200 mg QD dose to 30,540 ng/mL for the 800 mg dose. Median t_{max} was consistent across doses and dosing days and ranged from 2 to 6 hours. The elimination half-life for SXC-2023 was approximately 3.4 to 6.2 hours over the 200 mg to 800 mg dose range on Day 1 and 9.4 to 11.7 hours over the 200 mg to 800 mg dose range on Day 14. Minimal accumulation was evident for SXC-2023 following repeated QD and BID dosing and mean accumulation ratios were 1.08 to 1.58 over the 200 mg to 800 mg dose ranged tested and the PK of SXC-2023 was dose proportional with respect to C_{max} and AUC on Day 1 and Day 14.

The urinary excretion data demonstrated that very little of the administered dose of SXC-2023, <0.2%, was excreted in urine over the 200 mg to 800 mg dose range.

Following administration of single and multiple oral doses of SXC-2023 200 mg to 800 mg under fasted conditions, plasma and urine NAC levels were not quantifiable using the validated free NAC method in any subject throughout the sampling interval.

Following administration of SXC-2023 under fasted conditions, *p*-toluic acid was generally measurable in all subjects on Day 1 and Day 14. Mean maximum concentrations for *p*-toluic acid ranged from 31.98 ng/mL for the 200 mg dose group to 140.1 ng/mL for the 800 mg dose group on Day 1. On Day 14, mean maximum concentrations ranged from 44.09 ng/mL to 84.11 ng/mL over the 200 mg to 800 mg dose range tested.

Many subjects also had no measurable concentrations of urine *p*-toluic acid following dosing with SXC-2023; no clear pattern or trends in urinary excretion could be established.

3.2 Rationale

3.2.1 Rationale for this Study and Study Design

Impaired cortical control over impulses, mood, urges, and other behaviors is a hallmark feature of several disorders of the CNS, specifically, ICDs such as TTM. Several clinical studies (e.g., LaRowe et al., 2007; Amen et al., 2011; Froeliger et al., 2015) in non-treatment-seeking tobacco or cocaine addicts have shown that following a brief abstinence period, subjects in acute withdrawal exhibit deficits in inhibitory control, measurements of executive function (e.g., impulsiveness) and mood. Therefore, short periods of tobacco abstinence in otherwise healthy volunteers represent a consistent approach to evaluate and further characterize the ability of novel therapeutic agents designed to restore cortical function and overall behavioral control by reversing deficits in impulsive behavior.

SXC-2023 is currently under investigation for the treatment of TTM in adults (IND No. 133689). This study is being performed to evaluate and assess the dose range of SXC-2023 that can modify measurements designed to assess impulsivity and inhibitory control, urge for cigarettes, and mood for 5 days in smokers who have abstained from smoking.

3.2.2 Rationale for Dose Selection

The proposed doses of SXC-2023 in this study are 200 mg QD and 800 mg QD. These doses were selected based on nonclinical activity of SXC-2023 in various rat models showing behavioral activity at a dose range of 10 to 30 mg/kg, which, based on allometric scaling, is equivalent to approximately 100 to 300 mg in human equivalent dosing. These data support the starting dose of 200 mg in the current study.

The safety and tolerability profile in the SAD/FE study performed in healthy male and female volunteers, where subjects received single doses up to 1600 mg, support the higher dose of 800 mg proposed in the current study. Additionally, support for these doses comes from recent safety and tolerability profiles captured in a MAD study performed in healthy volunteers, showing that 14-day oral administration of SXC-2023 at 200 mg QD, 400 mg QD and BID and 800 mg QD was generally safe and well tolerated.

3.3 Risks and/or Benefits to Subjects

As mentioned in Section 3.1.2.1, SXC-2023 was studied in a Phase 1, double-blind, placebo-controlled, SAD/FE study (Study PRO-101) in healthy volunteers. SXC-2023 was safe and well tolerated at doses of 50 mg to 1600 mg. The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, 12-lead ECGs, clinical laboratory tests, and AEs) were adequate to protect the subjects' safety and detected all expected treatment-emergent AEs (TEAEs).

In the MAD study, SXC-2023 was generally safe and well tolerated at doses of 200 mg to 800 mg QD and 400 mg BID. The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, 12-lead ECG, neurocognitive testing, clinical laboratory tests, and AEs) are adequate to protect the subjects' safety and detected all expected TEAEs.

Additionally, cognitive tests were included as part of a broader cognitive safety assessment along with the C-SSRS to ensure that there were no CNS side effects.

In the current study, subjects will be monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs. Further, clinical laboratory tests, physical examination, vital signs, and ECGs will be used to evaluate safety.

The approximate volume of blood planned for collection from each subject over the course of the study presents no undue risk to the subjects.

There will be no direct health benefit for study participants from receipt of the study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study, as well as brief periods of abstinence from tobacco use.

4 STUDY OBJECTIVES

4.1 Primary Objectives

- To explore the safety and tolerability of SXC-2023 when dosed for 5 days in adults diagnosed with tobacco use disorder (i.e., cigarette smokers) who voluntarily abstain from the use of cigarettes.

- To test the activity of SXC-2023 when dosed for 5 days on measures of abstinence-induced impulsivity and inhibitory control, urge for cigarettes, and mood.

4.2 Exploratory Objectives

- To explore the effects of 5 days of tobacco abstinence on levels of total and/or reduced glutathione (GSH) in blood/plasma.
- To test the possible effects of SXC-2023 on levels of total and/or reduced GSH deficits via assay of blood/plasma GSH levels.

INVESTIGATIONAL PLAN

4.3 Overall Study Design and Plan

This randomized, double-blinded, placebo-controlled, crossover study will evaluate the effect of two doses of SXC-2023 on measures of impulsivity and inhibitory control, urge for cigarettes, and mood in non-treatment seeking smokers who are abstaining from smoking. To be eligible, subjects must meet the protocol-specified eligibility criteria which include a score of ≥4 on the Fagerstrom Test of Nicotine Dependence (FTND) at screening and an expelled carbon monoxide (CO) level of ≥10 ppm at screening and on Day 1 of Period 1, prior to dosing. On Day 1 of Period 2, subjects who have a score of < 4 on the FTND and have a CO level of <10 ppm can continue on study.

To date, four (4) total subjects have been dosed at Baylor. At Celerion, two groups of 14 subjects, a total of 28 subjects, will be assigned to receive two treatment regimens: SXC-2023

200 mg QD vs. matching placebo or SXC-2023 800 mg QD and matching placebo, in a 2-treatment crossover design. Subjects will receive one treatment regimen per 5-day treatment period of the crossover with a 9-day washout between treatment periods where subjects will be able to smoke as usual. Subjects will be randomized to treatment pair comparison (SXC-2023 200 mg QD vs. matching placebo, SXC-2023 800 mg QD vs. matching placebo) and to treatment sequence within each pair. Twenty eight total subjects are planned. Seven (7) subjects will be randomized to each of the 4-treatment pair sequence combinations. However, subjects who complete Period 1 in Group 1 but do not return on Day 1 of Period 2 of the crossover will be replaced in Group 2. A total of 4 subject replacements may be enrolled in Group 2.

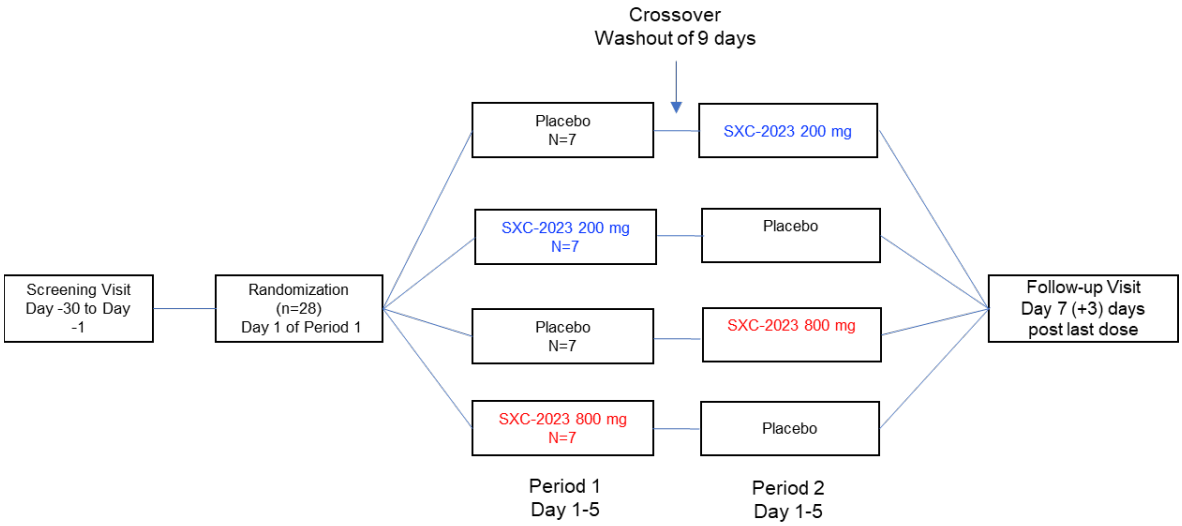
Subjects can smoke as usual up until they enter the Celerion facility for start of the study on Period 1, Day 1. Subjects will abstain from ingesting all forms of nicotine during both Periods of the crossover. Subjects participating at Celerion will be confined with no access to cigarettes/nicotine throughout the duration of Period 1 and Period 2 of the study. Subjects who relapse during Period 1 or Period 2 of the study will be terminated from the study and not permitted to re-screen.

Measurements of neurocognitive control will be performed on Day 1 prior to study drug administration and approximately 4-5 hours post dose on Day 5 to assess the effect of SXC-2023 on abstinence-induced measures of impulsivity and inhibitory control. Additional assessments will include measures of urge for cigarettes and mood. Neurocognitive testing will include the Stop Signal Task (SST), Cambridge Gambling Task (CGT), Paired Associates Learning (PAL), Reaction Time (RTI), Questionnaire on Smoking Urges (QSU), Positive and Negative Affect Schedule (PANAS), and the Cigarette Evaluation Questionnaire (CEQ). Cue reactivity will be evaluated using the International Affective Picture System (IAPS) images (for neutral and positive images) and those validated in the TRAIN lab at MUSC (PI Froeliger) and smoking images on Day 2 (following 24 hours of abstinence) and on Day 5, and two Likert scale assessments will be performed on Days 2 and 5. Levels of GSH in whole blood will be collected at baseline (prior to dosing on Day 1) and after 5 days of tobacco abstinence (after dosing on Day 5). Following the completion of the first 5 days of treatment with SXC-2023 200 mg QD, SXC-2023 800 mg QD, or placebo, subjects will be allowed to go home and smoke *ad lib* during a 9-day washout period. Following the washout period, subjects will crossover into Period 2 of this study and will receive a different study drug and will repeat the study procedures and assessments employed in Period 1, unless noted otherwise in Section 6.4.

A follow-up visit will be scheduled to occur approximately 7-10 days after the last dose of study drug (SXC-2023 200 mg, SXC-2023 800 mg, or placebo) is administered.

The study design in outlined in Figure 1. The Schedule of Events is provided in Appendix A, and list and description of the assessments performed at each study day are presented in Section 6.

Figure 1 Diagram of Study Design



As discussed in Section 5.1, subjects will be enrolled in 2 groups.

4.4 All Parts

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Subjects who do not return prior to start of Period 2 in Group 1, may be replaced in Group 2. A total of 4 subject replacements may be enrolled in Group 2.

4.5 Confinement, Return Visits and Follow Up

Twenty-eight (28) subjects will be housed on Day 1, at the time indicated by the CRU, until the end of Period 1 procedures on Day 5. A subject may be required to remain at the CRU for longer at the discretion of the PI or designee. The subjects will leave the site and will be instructed to smoke if they like, prior to their return to site on Day 1 of Period 2. All subjects will be released after all procedures are performed on Day 5 of Period 2. All subjects who receive a dose of study drug/placebo (including subjects who terminate the study early) will return to the CRU approximately 7 days after the last study drug/placebo administration for follow up procedures, and to determine if any AEs have occurred since the last study visit.

4.6 Study Duration

Subjects will be dosed for 5 consecutive days in each treatment period. The maximum anticipated subject participation will be approximately 59 days (30 days for screening period, 5 days for Period 1 of the crossover, 9 days for the washout, 5 days for Period 2 of the crossover, and maximum of 10 days until the follow-up visit).

4.7 Study Conduct

Please see the Schedule of Events (Appendix A) for a summary of the study assessments and procedures. Please see Section 6 for a listing and description of study procedures.

5 STUDY POPULATION

5.1 Number of Subjects

A total of 36 subjects may be enrolled on this study. To date, four (4) subjects were enrolled at Baylor College of Medicine.

At Celerion, subjects will be enrolled in two (2) groups. Up to 32 subjects are planned to enter this study (a total of 28 subjects will be enrolled with an additional 4 subjects to be used as replacements). With a crossover design illustrated in Figure 1, 14 subjects will be exposed to SXC-2023 200 mg and placebo, and 14 subjects to SXC-2023 800 mg and placebo. Four subjects can be used as replacements. Subjects who do not return prior to start of Period 2 in Group 1, may be replaced in Group 2.

Including an anticipated 10% dropout rate at Celerion, no more than 32 subjects will be exposed to SXC-2023.

At both sites, no more than 36 total subjects will be exposed to SXC-2023 in this study.

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

Subjects eligible for the study must meet all the following inclusion criteria:

1. Adult, female or male, 25-55 years of age, inclusive at screening.

2. BMI ≥ 16.0 and ≤ 35.0 kg/m^2 at screening.

3. Has provided signed written informed consent and has willingness and ability to comply with all aspects of the protocol, including abstaining from the use of and tobacco/nicotine products for two 5-day periods.

4. Non-treatment seeking smokers regularly using tobacco with a FTND score ≥4 at screening and self-reported use of ≥10 cigarettes/day at screening.

5. Has smoked for > 5 years at screening.

6. Meets Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria for tobacco use disorder.

7. Must have a score of ≥4 on the FTND and expired-air CO level ≥10 ppm during initial screening visit and prior to first dose.

8. For a female of childbearing potential: either be sexually inactive (abstinent as a life style) for 28 days prior to the first dosing and throughout the study or be using acceptable birth control methods as described in Section 5.2.2.4.

9. Female of non-childbearing potential: must have undergone one of the following sterilization procedures, at least 6 months prior to the first dose:
   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   Or be postmenopausal with amenorrhea for at least 1 year prior to the first dose with serum follicle stimulating hormone levels consistent with postmenopausal status or have medically documented history of biological or congenital sterility.

10. Has not used Aricept (a cholinersterase inhibitor) 30 days prior to screening.

5.2.2 Exclusion Criteria

Subjects who meet any one of the following criteria must NOT be enrolled in the study:

1. Subject is mentally or legally incapacitated or has significant emotional problems or clinically significant abnormality at the time of the screening visit or expected during the conduct of the study.

2. Subject suffered a concussion 6 months or less prior to screening.

3. Females who are pregnant or breastfeeding.

4. Positive for active hepatitis, human immunodeficiency virus, coagulopathy, or hepatic illness.

5. Use of Selective Serotonin or Norepinephrine Reuptake Inhibitors (SSRI/SNRI) for psychiatric illness (e.g. depression, anxiety, etc.), unless subject has been on a stable dose for at least 30 days prior to screening.

6. Use of antipsychotics or antiepileptics within 30 days prior to screening

7. Use of N-acetylcysteine within 30 days prior to screening.

8. Use of Chantix or related smoking cessation medications (e.g., NicoDerm path, Nicorette gum, etc) within 30 days prior to the first dose.

9. Use of sulfasalazine (Azulfidine®) within 30 days prior to the first dose.

10. DSM-5 criteria for alcohol/substance use disorder (except for tobacco use disorder).

11. History or presence of clinically significant psychiatric condition (except for tobacco use disorder) or disease in the opinion of the Principal Investigator (PI) or designee.

12. History of any illness that, in the opinion of the PI or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.

13. History of seizures.

14. Any history of psychiatric hospitalization in the past year.

15. Currently participating in a clinical study.

16. Previously participated in Phase 1 Promentis studies or dosed in this Phase 2A study.

17. FTND score <4 at screening and expelled CO levels <10 ppm at screening and prior to first dose.

18. Any clinically significant laboratory, ECG and/or vital sign abnormalities at screening.

19. Unable to read/understand/speak English.

5.2.3 Restrictions

5.2.3.1 Smoking and Other Forms of Nicotine

Subjects are to abstain from smoking cigarettes and ingesting all forms of nicotine (e.g., vape/e-cig, any form of nicotine replacement therapy including nicotine gum or patches, chewing tobacco) from Day 1 (starting on Day 1) through Day 5 in each period of the crossover. Testing for CO and urine cotinine will be performed prior to dosing on Day 1 and Day 5 of each study Period and at the discretion of the PI, on all other study days to confirm abstinence. Subjects who do not abstain from all forms of nicotine use during Period 1 and Period 2 will be released from participating in the study.

5.2.3.2 Meals

On Day 1 of each study Period, subjects must be fasted prior to first dose of study drug. Subjects will not eat for at least 1 hour after dosing. On all other days during each Period, blinded study drug (SXC-2023 or placebo) will be administered at least 2 hours after breakfast and subjects will not eat for at least 1 hour after dosing. Water is permitted at all times.

5.2.3.3 Prior/Concomitant Medications

Subjects who have used the following will NOT be permitted in the study:

- Antipsychotics or antiepileptics within 30 days prior to screening.

- SSRI/SNRI for psychiatric illness is not permitted unless subject has been on a stable dose for at least 30 days prior to screening.
- NAC within 30 days prior to screening.
- Chantix or related smoking cessation medications within 30 days prior to the first dose.
- Sulfasalazine (Azulfidine®) within 30 days prior to the first dose.
- Aricept within 30 days prior to screening.
- Positive urine screen for drugs of abuse at screening or check-in.

5.2.3.4 Contraceptive Requirements

Contraceptive requirements for **male** subjects are as follows:

1. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 30 days beyond the last dose of study drug. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dose of study drug. A male who has been vasectomized less than 4 months prior to the first dose of study drug must follow the same restrictions as a non-vasectomized male).
2. Males must also agree not to donate sperm from the first dose until 30 days after the last dose administration.

Contraceptive requirements for **female** subjects are as follows:

1. For a female of childbearing potential: either be sexually inactive (abstinent as a life style) for 28 days prior to the first dosing and throughout the study or be using one of the following acceptable birth control methods:
    - Oral contraceptives or mini pill used for at least 3 months prior to the first dose except for subjects ≥ 35 years of age.
    - Non-hormone releasing intrauterine device and progestin containing intrauterine device for at least 30 days prior to the first dose and with either a physical (e.g., condom, diaphragm, or other) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study.
    - Subdermal hormonal implant (i.e. implanon)
    - Double physical barrier method (e.g., condom and diaphragm with spermicide) from 14 days prior to the first dose and throughout the study.

In addition, female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 7 days following the last dose.

2. Female of non-childbearing potential: must have undergone one of the following sterilization procedures, at least 6 months prior to the first dose:

   - Hysteroscopic sterilization
   - Bilateral tubal ligation or bilateral salpingectomy
   - Hysterectomy
   - Bilateral oophorectomy

   Or be postmenopausal with amenorrhea for at least 1 year prior to the first dose.

6 STUDY PROCEDURES

6.1 Screening (Day −30 to Day -1)

All assigned subject numbers must be maintained in real time in the electronic database. A copy will be filed in the Investigator Binder.

The following assessments will be performed:

- Informed consent must be obtained before any other study assessments or procedures.
- Assessment of inclusion/exclusion criteria.
- Demographics, medical history, and drug use history will be recorded.
- Prior/concomitant medications will be recorded.
- A full physical examination will be performed.
- Vital signs (blood pressure and heart rate) will be recorded after the study subject has been resting supine for ≥5 minutes.
- A 12-lead ECG will be completed after the study subject has been resting supine for ≥5 minutes.
- Safety laboratory tests (hematology, chemistry, coagulation, urinalysis) and screening serology tests will be performed.
- Urine drug screen and serum pregnancy tests (in female subjects) will be performed.
- Expelled CO levels will be measured and must be ≥10 ppm.

- A urine sample will be collected for assessment of urine cotinine.
- The FTND will be completed and the score must be ≥4.
- The Barratt Impulsiveness Scale (BIS), will be performed on the iPad to capture trait impulsivity at the start of the study and to also confirm each subject's ability to read, write, and understand English.
- Subjects will be **trained** on the Cambridge Neuropsychological Test Automated Battery (CANTAB) iPad device installed with the SST, CGT, RTI, and PAL.
- Any AEs occurring after informed consent is obtained will be recorded. AEs occurring after informed consent signature but before the first dose of blinded study drug will be collected as medical history.
- Subjects will be instructed that they are allowed to smoke as usual during the screening period, prior to start of the Day 1 Period 1 and during the study washout (9 day) period.

6.2 Period 1 of Crossover

6.2.1 Day 1

Subjects will arrive at the site on Day 1 of the first period of the crossover having smoked as usual.

The following must be done **prior to dosing**:

- CO testing will be performed. Subjects with <10 ppm on the CO test will be released from participating in the study. A self-report of number of cigarettes smoked in the last 24 hours and approximate time of last cigarette smoked prior to Celerion facility entry will also be captured.
- Urine cotinine samples will be collected for all subjects (at Day 1 of each period of the crossover and at the PI or designee's discretion on other days) and subsequently assayed for cotinine to biochemically ascertain if there was any new nicotine exposure during the study.
- Serum pregnancy tests will be performed for female subjects.
- A 12-lead ECG will be completed after the study subject has been resting supine for ≥5 minutes.
- A blood sample for GSH will be taken.
- Fasting state blood sample and urine sample will be taken for clinical laboratory tests (hematology, coagulation, chemistry, and urinalysis).
- CANTAB testing (SST, CGT, RTI, PAL) will be performed on the iPad.

Additional tests on the iPad will include scales to measure craving for cigarettes (QSU), mood (PANAS), self-reported reinforcement (CEQ), FTND will be completed and the score must be ≥4.

- Vital signs (blood pressure and heart rate) will be recorded after the study subject has been resting supine for ≥5 minutes.
- Drug screen will be performed.
- Abbreviated physical examination.

Subjects will then be randomly assigned to one of two doses of SXC-2023 or matching placebo. Capsules will be administered on site by qualified personnel to confirm dosing requirements (see Section 8.2 for dosing procedures).

AEs and concomitant medications will be recorded.

Subjects will not eat for at least 1 hour after dosing.

6.2.2 Day 2, Day 3, and Day 4

The study procedures for each of these days will be identical (unless otherwise specified). Subjects are to continue to abstain from smoking and ingesting nicotine each day.

Each day (unless otherwise specified), the following will occur:

- At the discretion of the PI or designee, CO will be measured and subjects will be questioned about abstinence. Subjects with >5 ppm on CO test will be released from participating in the study.
- At the discretion of the PI or designee, urine cotinine samples may be collected and subsequently assayed to biochemically ascertain if there was any new nicotine exposure.
- **On Day 2 only**, the following assessments will be performed prior to dosing: cue reactivity with two Likert scale assessments (see Section 7.3.6).
- Subjects will be given their assigned dose of study drug (see Section 8.2 for dosing procedures) in the morning, at least 2 hours prior to breakfast or at least 1 hour post.
- Any AEs or concomitant medications will be recorded.
- Vital signs (blood pressure and heart rate) will be recorded after the study subject has been resting supine for ≥5 minutes.
- At the discretion of PI or designee, symptom-driven physical exam will be performed

6.2.3 Day 5

The following will be performed **prior to dosing** (unless otherwise stated):

- CO will be measured and subjects will be questioned about abstinence. Subjects with >5 ppm on CO test will be released from participating in the study.
- Urine cotinine samples will be collected in all subjects and subsequently assayed for cotinine to biochemically ascertain if there was any new nicotine exposure.
- Abbreviated physical examination.
- Vital signs (blood pressure and heart rate) will be recorded after the study subject has been resting supine for ≥5 minutes.
- Subjects will receive their assigned dose of blinded study drug (see Section 8.2 for dosing procedures).
- Any AEs or concomitant medications will be recorded.
- **After** dosing, ECG will be recorded after the study subject has been resting supine for ≥5 minutes.
- **After** dosing, blood will be collected to measure levels of GSH.
- Clinical laboratory testing (hematology, coagulation, chemistry, and urinalysis) will be performed **after** dosing.
- At approximately 4-5 hours post-dose, subjects will undergo the same neurocognitive testing used on Day 1, with the cue reactivity and two Likert scales being done prior to the other neurocognitive assessments.
- The CANTAB assessments should also be performed 4-5 hours post-dose. Assessments of craving (QSU), mood (PANAS), and self-reported reinforcement (CEQ) will follow the CANTAB assessments on the iPad.
- Subjects will be released from the site and will be allowed to smoke as usual.

6.3 Washout Period (9 days)

Following Day 5 of Period 1, subjects will enter a washout period of 9 days during which they will be permitted to smoke and/or ingest nicotine.

Subjects may start smoking as soon as they are released from the site at the conclusion of Day 5 and may then smoke prior to entry in the Celerion facility on Day 1 of Period 2.

6.4 Period 2 of Crossover

In Period 2 of the crossover portion of the study, subjects will repeat Days 1 through 5. They will be treated with a different treatment than they received in Period 1 of the crossover, based on the randomized assignment. The procedures are identical for Days 1 through 5 above (Section 6.2), **except** for the following:

- FTND will be administered on Day 1. Subjects with <4 score on FTND can continue to participate in the study.
- CO testing will be performed. Subjects with <10 ppm on the CO test can continue to participate in the study.

All subjects who decide to withdraw consent or dropped from the study will not be able to re-enter the study.

6.5 Follow-up Visit/Early Termination (7-10 days after last dose)

Subjects who complete the crossover portion of the study will return for a follow-up visit approximately 7 days after the last dose. Subjects who terminate the study early will also be asked to return for the follow-up visit at the same interval as post last dose.

The following assessments will be performed:

- Abbreviated Physical examination will be performed, and an assessment of smoking status/smoking behaviors (including the number of cigarettes/packs of cigarettes smoked since the last dose) will be recorded.
- Vital signs (blood pressure and heart rate) will be assessed after the study subject has been resting supine for ≥5 minutes.
- A 12-lead ECG will be completed after the study subject has been resting supine for ≥5 minutes.
- Clinical laboratory testing (hematology, coagulation, chemistry, and urinalysis) will be performed.
- Serum pregnancy tests will be performed for female subjects.
- Any AEs or concomitant medications will be recorded.

6.6 Early Withdrawal

While subjects are encouraged to complete the study, all subjects are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice. If the subject withdraws, the reason will be carefully documented in specific language. Subjects who withdraw from the study will not be allowed to re-enter.

Reasons for premature discontinuation from the study, which will be listed on the Subject Disposition case report form (CRF), are defined as follows:

Table 1 Reasons for Discontinuation

Adverse Event	Subject is withdrawn from the study due to an AE or any clinically significant laboratory, vital signs or ECG abnormalities. Complete AE form and attempt to follow the event until it is resolved or deemed stable.
Subject Request	Subject withdraws consent. If reason is provided, explain in comments on Subject Disposition CRF.
Protocol Violation	Investigator wishes to terminate the subject from study treatment due to a protocol violation. Site monitor or Sponsor should be contacted before making decision. Explain in comments on the CRF.
Lost to Follow-Up	Subject does not return during Period 2 of the crossover. The Investigator will make reasonable efforts to contact subject and determine reason for discontinuation (phone call and if not reached by phone then follow with a registered letter). If not reached, the subject will be documented as "lost to follow-up." Subjects lost to follow up may be replaced.
Other	Any other reason for early subject withdrawal from study treatment or the study. Explain in comments.

AE=adverse event; CRF=case report form

Subjects withdrawing prematurely after taking study drug must undergo follow-up assessments at the time of termination (or as close as possible) and 7 days post last dose in case of reported AEs requiring resolution (Section 6.5). All study data from withdrawals must be retained. When an SAE or possibly or probably related AE persists at the end of the study, the PI will ensure a follow-up of the subject until the PI and Sponsor agree the event is satisfactorily resolved or stabilized.

6.7 Discontinuation of the Study

The study will be discontinued if the Sponsor judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

7 CRITERIA FOR EVALUATION

7.1 Safety Evaluation

7.1.1 Medical History, Demographic and Other Baseline Information

Medical history:

- General medical/surgical history

- Information collected includes condition/procedure, year of onset, and year ended or condition continuing

- For procedures and events such as accidents or fractures, year of occurrence should be entered for both year of onset and year ended.

Medication history:

- Information on all medications (investigational products, prescription, over-the-counter [OTC], and herbal medications) taken within the 30 days prior to the screening visit.

Drug use history:

- Information on prior and current drug and alcohol use will be recorded.

Demographics:

- Age (based on date of birth and date of screening visit)

- Ethnic origin (Hispanic/Latino or Not Hispanic/Latino)

- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black/African American)

- Height (cm), without shoes

- Body weight (kg), without shoes

- Body mass index (weight [kg]/height [m^2])

7.1.2 Physical Examination

A full physical examination at screening only will be performed as per the Schedule of Events (Appendix A). Abbreviated physical examinations will be performed on Days 1 and 5 of both Periods and follow up. Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

7.1.3 Vital Signs

The following vital signs will be measured during all subject visits and inpatient days during the study:

- Blood pressure (systolic and diastolic [mm Hg])

- Heart rate (beats per minute)

Single measurements of blood pressure and heart rate will be performed as outlined in the Schedule of Events (Appendix A). Blood pressure and heart rate measurements will be

performed after the study subject has been resting supine for ≥5 minutes. Blood pressure measurements will be taken with the appropriate cuff size using automated equipment. The same arm is preferred for all measurements.

Any clinically significant vital sign abnormality will be recorded as an AE and subject will be discontinued from the study.

7.1.4 12-Lead Electrocardiograms

Standard safety 12-lead ECGs will be performed during the study as outlined in the Schedule of Events (Appendix A). The 12-lead ECGs will be taken after the subject has been resting supine for ≥5 minutes. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QTcF interval.

All ECGs must be interpreted by a qualified physician or qualified designee for the presence of abnormalities. Any clinically significant ECG abnormality will be recorded as an AE and subject will be discontinued from the study. A subject will be withdrawn from the study by the PI or his/her designee if, in their medical judgment, ECG findings are present which make continued study participation not in the subject's best interest.

7.1.5 Clinical Laboratory Tests

Blood and urine samples will be collected for routine clinical laboratory testing (hematology, coagulation, chemistry, and urinalysis) and analysis as outlined in the Schedule of Events (Appendix A). Additional, unscheduled testing may be performed during the study if medically indicated.

Any value outside the normal range will be flagged for the attention of the PI or designee at the site. The PI or designee will indicate whether or not the value is of clinical significance.

- If the result of any test (or single repeat test, if done) from the samples taken during screening is indicated as clinically significant, the study subject will NOT be allowed into the study. Results of laboratory tests performed prior to dosing on Day 1 of each treatment period will be reviewed prior to dosing.

- If a clinically significant abnormality is found in the samples taken after treatment (e.g., on Day 5), it should be recorded as an AE, if deemed necessary by the PI and will result in subject discontinuation from the study. The study subject will be followed until the test(s) has (have) normalized or stabilized.

The following laboratory parameters will be reported:

- Hematology: hemoglobin, hematocrit, RBC count, leukocyte count with differential, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and absolute platelet count

- Coagulation: prothrombin time/International normalized ratio, activated partial thromboplastin time

- Chemistry: sodium, potassium, chloride, albumin, glucose, blood urea nitrogen, creatinine, bilirubin (total and direct), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, uric acid and creatine phosphokinase

- Serum Pregnancy Test (in female subjects)

- Serology: HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody

- Urinalysis: pH, specific gravity, glucose, ketones, nitrite, protein, bilirubin, leukocyte esterase, and blood will be performed. If urinalysis is positive for blood, protein, nitrite, and/or leukocyte esterase, microscopic urinalysis will be performed

- Urine drug screen: This test may include the following: amphetamines, cocaine, tetrahydrocannabinol, benzodiazepines, tricyclic antidepressants, barbiturates, 3,4-methylenedioxymethamphetamine, opiates, phencyclidine, oxycodone, and propoxyphene.

- Urine cotinine

An estimate of blood draw volumes over the course of the study is provided in Appendix C.

7.1.6 Adverse Events

For detailed information on collection, definition, categorization, and reporting of AEs/SAEs during the study, refer to Section 9.

AEs will be monitored and the following information recorded:

- Standard medical terminology

- Whether the event was a treatment-emergent adverse event (TEAE)

- Whether event was a serious adverse event (SAE)

- Date and time of onset

- Severity of event

- Relationship of event to study drug

- Action taken regarding study drug due to the event

- Clinical outcome of event (resolved or ongoing)

- If resolved, provide date of resolution

7.1.7 Prior and Concomitant Medications

Site personnel should document any medications (prescription and OTC, including herbal medications and vitamins) the subject received within 30 days prior to screening and throughout the study. Recorded details should include: medication name, start date and time, stop date and time, dose, route, frequency, and reason for use. The concomitant medication names will be coded according to the World Health Organization Drug Dictionary (WHODD) and classified by anatomical therapeutic chemical categories.

7.2 Glutathione Blood Collection

Blood samples will be collected at the times indicated in the Schedule of Events (Appendix A). Instructions for the sampling, processing, and storage of laboratory samples will be provided in the laboratory manual.

7.3 Neurocognitive Assessments and Scales

The following neurocognitive assessments will be assessed during the study: BIS, SST, CGT, PAL, RTI, QSU, PANAS, CEQ, FTND and cue reactivity with Likert scale assessments. Descriptions are provided herein.

7.3.1 Barratt Impulsiveness Scale

The BIS will be employed to capture trait impulsivity and to confirm each subject's ability to read, write, and understand English at screening only on the iPad device. The scale is presented in Appendix D.

7.3.2 Stop Signal Test, Cambridge Gambling Task, Paired Associates Learning, and Reaction Time

Subjects will be trained on the CANTAB iPad device with SST, CGT, PAL, and RTI at screening and the tests will be repeated as indicated in Appendix A. The SST and CGT will be used to assess impulsivity and inhibitory control at times. The PAL and RTI will be used to assess visual memory and motor/mental response speed.

These assessments are described in further detail in Appendix E.

7.3.3 Questionnaire on Smoking Urges

The QSU is a 10-question assessment of a subject's desire and urge to smoke on the iPad device. The QSU will assess cravings at the times indicated in Appendix A. The questionnaire is presented in Appendix F.

7.3.4 Positive and Negative Affect Schedule

The PANAS consists of several words that describe different feelings and emotions and will be used to assess mood at times indicated in Appendix A on the iPad device. This scale is presented in Appendix G.

7.3.5 Cigarette Evaluation Questionnaire

This assessment is a self-reported questionnaire with 12 questions to assess smoking behaviors and reinforcement and will performed at times indicated in Appendix A on the iPad device. The modified CEQ will be used and the questionnaire is provided in Appendix H.

7.3.6 Cue Reactivity and Likert Assessments

Participants will be supplied with a laptop computer programmed (using E-Prime) to present images to participants. Images will include 3 categories: neutral, positive, and smoking. Neutral and positive images will be those extracted from IAPS and those validated in the TRAIN lab at MUSC (PI Froeliger), and smoking images will be from MUSC. The program will present images in sequence for 2 seconds each with a 1-second black screen between images. Each category will be presented in full (10 images over 30 seconds) and followed by a 88-point Likert scale assessing the urge for a cigarette followed by an 8-point Likert scale assessing mood. Subsequent categories will be presented and each time the same Likert scales will be completed. Subjects will use the Likert scales in Appendix I to complete the assessments.

7.3.7 Fagerstrom Test of Nicotine Dependence

A standard instrument for assessing the intensity of physical addiction to nicotine. This contains six items that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence as indicated Appendix J. This will be completed in the iPad device.

7.4 Measurement of Nicotine Ingestion

Expelled CO tests will be performed at screening, Day 1 and Day 5 of each Period, and on other treatment days, per the PI or designee's discretion. The results at screening and Day 1 of Period 1 must be ≥10 ppm in order for the subject to be eligible for the study.

Subjects should expel ≥10 ppm on Day 1 of Period 2, however, if a subject expels <10ppm, subject will be allowed to continue on study.

Urine cotinine samples will be collected on Days 1 and 5 of each treatment period, and on other treatment days, per the PI or designee's discretion. This will subsequently be assayed to biochemically ascertain if there was any nicotine exposure (tobacco, e-cig, nicotine gum/patches, etc.) in all subjects.

Those subjects with evidence that they did not abstain on Day 1(after study entry) and Days 2-5 of Period 1 or Day 1 (after study re-entry) and Days 2-5 of Period 2 will be terminated from the study and will not be allowed to re-screen.

8 TEST ARTICLE AND ADMINISTRATION

8.1 Test Article Identification, Supply, Packaging, Labeling, and Storage

SXC-2023 will be supplied as 50-mg and 200-mg capsules for use in this study. Placebo capsules will be matching SXC-2023 to maintain the blind. Subjects assigned to 200 mg QD will receive 4 x 50-mg capsules, and subjects assigned to 800 mg will receive 4 x 200-mg capsules.

SXC-2023 is stable at room temperature and requires no special protection or handling; special protection from light is not required. SXC-2023 should be stored at 20℃ to 25℃, with excursions allowed between 15℃ to 30℃.

All supplies will be packaged and labeled according to applicable local and regulatory requirements. All supplies must be stored in a locked area, accessible to authorized persons only, until needed for dispensing/dosing.

8.2 Study Drug Administration

On Day 1 of each treatment period, subjects will fast prior to first dose in the morning. Subjects may receive a meal at least one hour post dose. On other days, subjects will be administered study drug (SXC-2023 200 mg, SXC-2023 800 mg, or matching placebo) at least 2 hours after breakfast. The SXC-2023 or placebo dose will be administered with water.

Qualified personnel will administer study drug. After dosing, unit personnel will perform a hand and mouth check to ensure the subjects have swallowed the dose administered.

Subjects will fast for at least 1 hour after dosing. Water is permitted.

8.3 Study Drug Accountability and Destruction

The Sponsor will supply sufficient quantities of SXC-2023 and matching placebo to allow completion of this study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the product accountability records.

8.4 Blinding

Subjects will be randomized to treatment assignments. Treatments will be double-blinded to avoid bias by the subject, PI, and study site staff, with the exception of Pharmacy personnel. If the PI deems it is necessary to break the blind in the interest of a subject's safety, unblinding may occur. The PI must attempt to contact the Medical Monitor and must document the reason for breaking the blind. Pharmacy personnel will be unblinded.

8.5 Randomization

Up to 32 subjects (28 subjects to be enrolled with an additional 4 subjects as replacements, if necessary) will be randomized to treatment pair comparison (SXC-2023 200 mg QD vs. matching placebo, and SXC-2023 800 mg QD vs. matching placebo) and to treatment sequence within each pair. Seven (7) subjects will be randomized to each of the 4 treatment pair sequence combinations (see Figure 1).

8.6 Treatment of Overdose

Standard symptomatic support measures should be used in the case of excessive pharmacologic effects or overdose. No antidotes are available.

In the instance that a subject ingests more than 3 times the allotted dose, standard symptomatic support measures should be used. No antidotes are available. Gastrointestinal reaction would be anticipated, and the subject should be clinically followed for 48 hours.

9 ADVERSE EVENTS

Starting at the time of informed consent, subjects will be asked to spontaneously report all AEs that occur during the trial until discharge from the study. Additionally, subjects will be queried about AEs at each study visit and inpatient day. AE queries should be performed in a nonspecific manner such as “How have you felt since the last visit?”, “How do you feel?”, or “Are there any recent changes to your health?”

After the ICF is signed and before study drug is administered, AEs that are not procedure related will be captured and reported as medical history. AEs occurring after first dose of study drug will be captured in the AE page of the CRF. Non-serious AEs will be collected through the Follow-up visit. SAEs will be collected through 30 days post last dose (as reported through subject-initiated contact following the Follow-up visit).

Cases of pregnancy that occur during the study or up to 30 days following last dose of study drug should be reported, however, will not be considered an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation. Study site personnel will record the occurrence and nature of each subject’s pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Any clinically significant findings from ECGs, laboratory tests, vital sign measurements, etc. reported after the first dose of study drug (SXC-2023 or placebo) should be reported as an AE.

All AEs related to protocol procedures are reported to the Sponsor or its designee. The PI will be instructed to report to the Sponsor or its designee their assessment of the potential relatedness of each AE to protocol procedure, and study drug via CRF.

9.1 Definition

An **adverse event** (AE) can be any unfavorable and unintended sign, including an abnormal laboratory, ECG and vital sign abnormality finding, symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the study drug.

A **treatment-emergent adverse event** (TEAE) is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.

When a **serious adverse event** (SAE) or possibly or probably treatment-related AE persists at the end of the study, the PI will ensure a follow-up of the subject until the PI and Sponsor agree the event is satisfactorily resolved or stabilized.

9.2 Severity Scale for Adverse Events

The severity of an AE is to be scored according to the following scale:

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

9.3 Relationship to Study Drug

The relationship of an AE to study treatment is to be assessed according to the following definitions:

Unrelated:	Should be reserved for those events which occur prior to study treatment or for those events which cannot be even remotely related to study participation (e.g., injuries sustained in an automobile accident).
Possible:	The suspected AE may or may not follow a reasonable temporal sequence from study treatment administration but seems to be the type of reaction that cannot be dismissed as unlikely. The event could have been produced or mimicked by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.
Probable:	The suspected AE follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and cannot be reasonably explained by the known characteristics of the subject's clinical state.

9.4 Reporting Adverse Events

All clinical events, including either observed or volunteered problems, complaints or symptoms are to be recorded on the AE page(s) of the CRF. The need to capture this information is not dependent upon whether the clinical event is associated with study treatment. Adverse clinical events resulting from concurrent illnesses or reactions to

concurrent medications are also to be recorded. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words.

Each adverse clinical event is to be evaluated for duration, severity, and whether the event may be associated with the study drug or other causes. Start and stop dates, relationship to study drug, medical management, and alternative causality of event must be recorded in the AE section of the CRF. SAEs and AEs believed to be possibly or probably related to study drug must be followed until resolution or stabilization.

9.5 Serious Adverse Events

9.5.1 Definition

An SAE is any untoward medical occurrence that at any dose results in any of the following outcomes:

- Death
- Is life threatening (an event in which the subject is 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 was more severe)
- A persistent or significant disability/incapacity
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events
- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. If a subject becomes pregnant during treatment, this should be reported as if it were a SAE.

Refer to Section 9.6 in case of pregnancy.

9.5.2 Initial Reporting

Any SAE, occurring in a subject receiving treatment or if the PI becomes aware of any SAE post-treatment, must be reported by the PI to the Medical Monitor within 24 hours even if the SAE does not appear to be drug-related. This should be done by telephone or by sending a faxed copy of the SAE form plus other related information.

A Sponsor Designee will contact the PI with any follow-up questions related to the event.

The Sponsor Designee must be notified immediately of all deaths. Deaths must be reported, regardless of cause, from the time of informed consent and up to 28 days after completion of study medication administration, irrespective of the PI's opinion regarding drug relationship. Documentation of cause of death and copy of autopsy or hospital report must be provided.

Medical Monitor

Thomas Beck, MD
Chief Medical Officer
Promentis Pharmaceuticals, Inc.
Address: One Main Street, 13th floor, Cambridge MA 02142
Telephone: +1 617 231 2403
Mobile: 508-259-8446
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9.5.3 Follow-up

All additional follow-up evaluations must be reported to the Medical Monitor. Such data should be sent to the Sponsor within 10 calendar days. All SAEs will be followed until the PI and Sponsor agree the event is satisfactorily resolved. The Sponsor will be responsible for completing the safety report and for notifying the relevant authorities of any SAE as outlined in the International Conference on Harmonisation (ICH) Guidelines. The PI will also ensure that the appropriate ethics committee is notified of the SAE.

9.6 Pregnancy

If a pregnancy does occur during or 30 days after completion of study medication administration, each pregnancy must be reported by the PI to the Sponsor Designee using the Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. The PI must follow up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the clinical study.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

All outcomes of pregnancy must be reported by the PI to the Sponsor on the pregnancy outcome report form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]) and reported within 24 hours in accordance with the procedure for reporting SAEs.

For more information on pregnancy reporting, please refer to the Safety Monitoring Plan.

9.7 Stopping Criteria with Rules for Subject Replacement

Any patient who experiences an adverse experience judged to be severe (independent of attribution), an abnormal laboratory, ECG or vital signs deemed clinically significant or an SAE as defined in Section 10.5.1 of the protocol shall be immediately discontinued from the study and followed for safety, as per the protocol. Subjects who discontinue in Period 1 maywill not be replaced.

10 STUDY ADMINISTRATION

10.1 Ethics

10.1.1 Institutional Review Board

This protocol and all appropriate amendments will be reviewed by an institutional review board (IRB), and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the United States (US) Code of Federal Regulations (CFR) (21 CFR Part 56).

10.1.2 Ethical Conduct of the Study

This study will be carried out in accordance with the protocol, US 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

10.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF. The requirements of informed consent are provided in Appendix B.

10.2 Termination of the Study

Promentis reserves the right to terminate the study in the interest of subject welfare. All members of the Investigator's staff have signed confidentiality agreements. By signing this protocol, the Investigator and investigational staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential. The Investigator must guarantee the privacy of the subjects taking part in the study. Subjects will be identified throughout documentation and evaluation by a unique subject study number. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. If subject name appears on any study document, it must be redacted before the copy of the documents is supplied to the Sponsor. Any information concerning the subjects (clinical notes, identification numbers, etc.) must be kept on file by the Investigator who will ensure that it is revealed only to the Sponsor, IRB, or regulatory authorities for the purposes of trial monitoring, auditing or official inspections. As required, in the case of an event where medical expenses are the responsibility of the Sponsor, personal information, i.e., full name, social security details, etc., may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data protection laws.

10.3 Data Quality Assurance

Designated personnel will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

10.4 Direct Access to Source Data/Documents

Site will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH [E6] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

10.5 Data Handling and Record Keeping

Electronic data capture (EDC) will be used for this study and electronic case report forms (eCRFs) will be developed according to the study protocol specifications. Data will be transcribed from original source by the Investigator staff into the eCRF.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Sponsor until at least 5 years after the last approval of a

marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

10.6 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

10.7 Publication Policy

All unpublished information given to site by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published or disclosed only by the Sponsor or in collaboration with participating personnel from the Sponsor or upon Sponsor's prior written consent to publish the article.

11 STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be finalized by the Sponsor prior to locking the study database. The SAP may modify the plans outlined in the protocol; however, any major modifications of endpoint definition and/or analysis will be reflected in a protocol amendment. Statistical analyses other than those described in the protocol will be documented in the SAP.

Statistical analyses will be done using SAS Version 9.4 or later, unless noted otherwise.

Unless otherwise noted, continuous variables will be summarized using number of non-missing observations, mean, standard deviation, median, minimum, and maximum; categorical variables will be summarized using the frequency count and the percentage of subjects in each category.

11.1 Determination of Sample Size

No formal sample size calculation was performed.

11.2 Analysis Populations

Safety Population: All subjects who receive a dose of blinded study drug (SXC-2023 or placebo) will be included in the safety evaluations.

Full Analysis Set (FAS)/Intent-to-Treat (ITT) Population: All subjects randomized to blinded study drug (SXC-2023 or placebo) will be included in the FAS and will be analyzed as randomized.

Per Protocol Population (PP): All subjects randomized to blinded study drug (SXC-2023 or placebo) with no major protocol violations or deviations.

11.3 Statistical Analysis

11.3.1 Subject Disposition

The number of subjects enrolled, completed, or discontinued from the study and the reason for study discontinuation will be tabulated by treatment group as appropriate. The number of discontinued subjects will be broken down by treatment period of the study. Subject count by analysis population will also be tabulated.

11.3.2 Protocol Deviations

All deviations will be listed. Protocol deviations will be categorized as major or minor. Major protocol deviations will be agreed upon by medical, clinical, and statistical staff prior to database lock. Subjects with major protocol deviations, or data points that are judged to be major protocol deviations will be excluded from the PP Population.

11.3.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be listed and summarized by treatment and overall using the Safety Population.

11.3.4 Safety Analysis

All subject data will be listed with pertinent information, e.g., demographics, treatment group.

All safety and tolerability data will be summarized using descriptive statistics. Safety data will be listed and summarized in tabular and/or graphical form. No formal statistical testing will be performed on these data. Summaries will be provided by treatment group.

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

11.3.4.1 Adverse Events

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®).

The number and percentage of subjects experiencing TEAEs, treatment-emergent SAEs, and TEAEs leading to study discontinuation will be summarized for treatment group/period by MedDRA system organ class (SOC) and/or preferred term (PT).

Summaries of TEAEs may include:

- by PT in descending order of frequency
- by SOC and PT
- by SOC, PT, and severity
- by SOC, PT, and relationship to study drug (unrelated vs. related)
    - AEs of possible or probable relationship to study drug will be combined for the "related" summaries.

11.3.4.2 Other Safety Assessments

Summary statistics for vital signs, including blood pressure and heart rate, will be presented for each scheduled time point measured and for the change from baseline to each time point.

Concomitant medications will be listed by subject and coded using the most current version of the World Health Organization (WHO) drug dictionary available at Celerion. Medical History will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion.Clinical laboratory data and change from baseline will be summarized by the scheduled time point. Subject incidences of change in classification with respect to the laboratory normal ranges will be summarized as shift tables. Baseline will be the last value obtained before the first dose of study drug. Clinically significant clinical laboratory abnormalities (as judged by the investigator) will be included in the AE tabulations.

Clinically significant physical examination abnormalities will be reported and included in the AE tabulations.

A normal-abnormal shift table will be presented for ECGs.

11.3.4.3 Concomitant Medications

Concomitant medications will be coded using the most current WHODD and listed by treatment.

11.3.5 Analysis of Neurocognitive Assessments

Within-subject contrasts for the BIS, SST, CGT, RTI, PAL, QSU, PANAS, CEQ, and Cue reactivity with Likert assessments will be analyzed using a mixed effects analysis of variance model, with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. Estimates of the treatment effect (least squares means with 95% confidence intervals) will be obtained from this model. Impact for potential covariates will be explored using this same model.

The primary analyses will use the PP Population. Subjects who have missing values for a study endpoint will not be used in the statistical analysis for that endpoint. No data will be imputed. Analyses may be repeated using the FAS.

Results of the BIS, SST, CGT, RTI, PAL, QSU, PANAS, CEQ, and Cue reactivity with Likert assessments will be summarized descriptively by treatment. Between-subject by period treatment contrasts will also be performed.

Planned analyses will follow standardized instruction manuals for neurocognitive assessments, where such manuals exist.

Results will be presented with no adjustment for multiplicity.

11.3.6 Analysis of Glutathione Concentrations

GSH concentrations will be listed and summarized descriptively.

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SXC-2023 Investigator's Brochure, Version 5.0; 2018.

APPENDIX A SCHEDULE OF EVENTS

Procedures	Screen	Period 1 of Crossover					Home	Period 2 of Crossover					Follow-up/ET
	Day -30 to Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Washout 9 days	Day 1	Day 2	Day 3	Day 4	Day 5	7-10 Days Post last dose
Confinement		X						X					
Abstain from smoking		X	X	X	X	X		X	X	X	X	X	
Informed consent	X												
Inclusion/exclusion	X												
Demographics and drug use	X												
Medical history	X												
Physical exam	X	X[a]		X[a]		X[a]		X[a]		X[a]		X[a]	X[a] (PE, smoking status)
Vital signs (BP, HR)	X	X	X	X	X	X		X	X	X	X	X	X
Safety labs (hematology, coagulation, chemistry, UA)	X	X[b] (pre)				X (post)		X[b] (pre)				X (post)	X
Serum pregnancy (females)	X	X (pre)						X (pre)					X
Screening serology	X												
Urine drug screen	X	X						X					
ECG	X	X (pre)				X		X (pre)				X	X
Breath CO/subject interview	X	X (pre)		X[c]		X (pre)		X (pre)		X[c]		X (pre)	
Urine Cotinine	X	X (pre)		X[c]		X (pre)		X (pre)		X[c]		X (pre)	
FTND	X	X						X					
BIS	X												

Procedures	Screen	Period 1 of Crossover					Home	Period 2 of Crossover					Follow-up/ET
	Day -30 to Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Washout 9 days	Day 1	Day 2	Day 3	Day 4	Day 5	7-10 Days Post last dose
QSU, PANAS, CEQ		X (pre)				X (post)		X (pre)				X (post)	
CANTAB (SST, CGT, RTI, PAL)	X (training)	X (pre)				X (post)		X (pre)				X (post)	
Cue reactivity and Likert assessments			X (pre)			X (post)			X (pre)			X (post)	
Randomization		X						X					
Study drug administration		X	X	X	X	X		X	X	X	X	X	
GSH blood sample		X (pre)				X (post)		X (pre)				X (post)	
Adverse events	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

Abbreviations: BIS= Baratt Impulsiveness Scale; BP=blood pressure; CANTAB=Cambridge Neuropsychological Test Automated Battery; CEQ= Cigarette Evaluation Questionnaire; CGT=Cambridge Gambling Task; CO=carbon monoxide; ECG=electrocardiogram; ET=early termination; FTND=Fagerstrom Test of Nicotine Dependence; GSH= glutathione; hr=hour(s); HR=heart rate; PAL=Paired Associates Learning; PANAS=Positive and Negative Affect Schedule; PE=physical examination; post=post-dose; pre=pre-dose; QSU=Questionnaire on Smoking Urges; RTI=Reaction Time; SST=Stop Signal Task; UA=urinalysis

[a] Physical exam: Day 1 and Day 5 of both Periods and FU/ET, abbreviated physical exams will be performed. Days 2-4 of both Periods, per PI or designee's discretion, symptom driven abbreviated exam may be performed.

[b] Fasting state safety labs

[c] Breath CO and Urine cotinine: Per PI or designee discretion

APPENDIX B BASIC ELEMENTS OF INFORMED CONSENT

a) Basic Elements of Informed Consent

The following information must be provided to each subject in obtaining informed consent. The subject (or subject's legal representative) should be provided with a copy of the signed written informed consent.

1. State that the study involves RESEARCH.
   a. Explain the PURPOSES of the research.
   b. State the expected DURATION of the subject's participation.
   c. Describe the PROCEDURES to be followed.
   d. Identify any EXPERIMENTAL procedures.
2. Describe any reasonably foreseeable RISKS OR DISCOMFORTS to the subject.
3. Describe any BENEFITS to the subject or to others that may reasonably be expected from the research.
4. Note appropriate ALTERNATIVE procedures or courses of treatment, if any, that might be advantageous to the subject.
5. a. Describe the extent, if any, to which CONFIDENTIALITY of records identifying the subject will be maintained.
   b. Note that the Food and Drug Administration MAY INSPECT the records.
6. For research involving more than minimal risk, explain if any COMPENSATION or medical treatments are available should injury occur. If so, explain (a) what they consist of, OR (b) where further information may be obtained.
7. State whom to contact for ANSWERS to pertinent questions about (a) the research, and (b) research subject's rights, and (c) whom to contact in the event of a research-related injury to the subject.
8. State that:
   a. participation is VOLUNTARY,
   b. refusal to participate will involve NO PENALTY or loss of benefits to which the subject is otherwise entitled, and
   c. the subject MAY DISCONTINUE participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

b). Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

c). The following statement shall be provided to each clinical trial subject in informed consent documents and processes. "A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time."

d). The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed for informed consent to be legally effective.

e). Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or Local law.

REFERENCE: 21 CFR Part 50.25 -- PROTECTION OF HUMAN Subjects, Basic elements of informed consent.

APPENDIX C SUMMARY OF BLOOD DRAW VOLUMES

Sample Type	Number of Time Points	Approximate Volume per Time Point (mL)	Approximate Sample Volume Over Course of Study (mL)
Laboratory safety tests (including hematology, coagulation, serum chemistry) and serology (at screening only)	6	16	96
Glutathione (GSH)	4	6	24
Total Blood Volume (mL)→			120

APPENDIX D BARRATT IMPULSIVENESS SCALE

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

① Rarely/Never ② Occasionally ③ Often ④ Almost Always/Always

1	I plan tasks carefully.	①	②	③	④
2	I do things without thinking.	①	②	③	④
3	I make-up my mind quickly.	①	②	③	④
4	I am happy-go-lucky.	①	②	③	④
5	I don't "pay attention."	①	②	③	④
6	I have "racing" thoughts.	①	②	③	④
7	I plan trips well ahead of time.	①	②	③	④
8	I am self controlled.	①	②	③	④
9	I concentrate easily.	①	②	③	④
10	I save regularly.	①	②	③	④
11	I "squirm" at plays or lectures.	①	②	③	④
12	I am a careful thinker.	①	②	③	④
13	I plan for job security.	①	②	③	④
14	I say things without thinking.	①	②	③	④
15	I like to think about complex problems.	①	②	③	④
16	I change jobs.	①	②	③	④
17	I act "on impulse."	①	②	③	④
18	I get easily bored when solving thought problems.	①	②	③	④
19	I act on the spur of the moment.	①	②	③	④
20	I am a steady thinker.	①	②	③	④
21	I change residences.	①	②	③	④
22	I buy things on impulse.	①	②	③	④
23	I can only think about one thing at a time.	①	②	③	④
24	I change hobbies.	①	②	③	④
25	I spend or charge more than I earn.	①	②	③	④
26	I often have extraneous thoughts when thinking.	①	②	③	④
27	I am more interested in the present than the future.	①	②	③	④
28	I am restless at the theater or lectures.	①	②	③	④
29	I like puzzles.	①	②	③	④
30	I am future oriented.	①	②	③	④

APPENDIX E CANTAB CONNECT TASK DESCRIPTIONS FOR PROMENTIS

Version 1.0 20 July 2018

Introduction

The CANTAB Connect electronic data capture (EDC) system will be used to run cognitive tests, capture subject responses and record data for transfer to Cambridge Cognition Limited.

The system offers a simple touch-screen interface to guide the test administrator through the process of entering required subject information e.g. subject number, any required demographic details and selecting the appropriate visit. The system then automatically administers the CANTAB tests for the subject and visit selected.

The system informs the subject how to complete each CANTAB task and each task includes practice and assessed phases. The system automatically records all subject responses. CANTAB Connect automatically synchronizes with the server at the end of each session to transfer data to the secure server.

The following CANTAB Connect tasks will be used in the clinical study.

Reaction Time (RTI)

In this reaction time task the participant must hold down a button at the bottom of the iPad screen, with the index finger of their dominant hand, until a yellow spot briefly appears in one of five circles at the top of the screen. Once the yellow spot has flashed in one of the circles

the subject must release the button and with the same finger touch inside the circle where the yellow spot appeared as quickly as they can.

The voiceover introduces the RTI test to the participant explaining how the test should be completed. There is a short practice phase prior to the assessed phase. The participant will see five circles at the top of the screen and a button at the bottom of the screen.

The voiceover prompts the participant to practice touching the button at the bottom of the screen and then informs the subject that they should hold this button down until a yellow spot flashes in one of the circles above. Once they see the yellow spot appear they should release their finger from the button as quickly as they can and using the same finger touch the circle where the yellow spot appeared. Once they have touched the circle they must return their finger to the button and hold the button until they see another yellow spot flash in one of the circles above and then once again touch the circle where the yellow spot appeared.

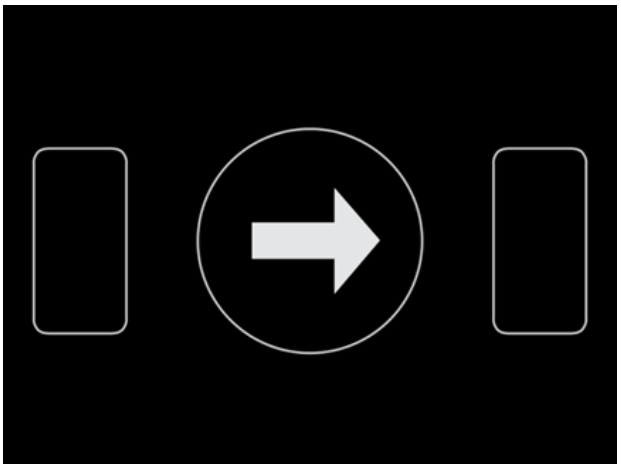
The RTI task includes a practice phase (10 trials) followed by the assessed phase. The voiceover reminds the subject that they should go as quickly as they can whilst trying to avoid making any mistakes. 30 assessed trials are then presented.

The key outcome measures for this task are median reaction and movement time.

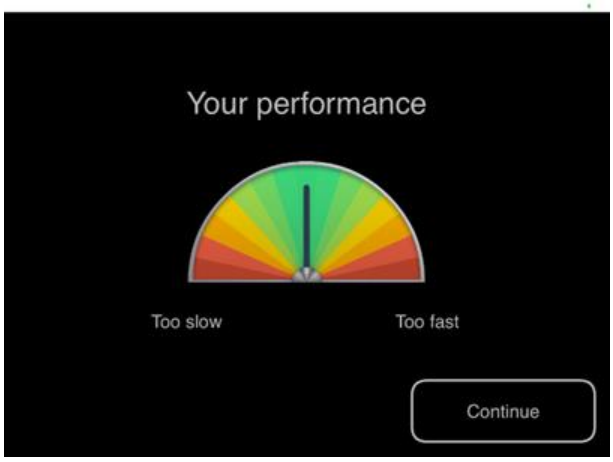
Stop Signal Task (SST)

The Stop Signal Task (SST) is a classic stop signal reaction time test that measures the participant's ability to inhibit a response. The subject is shown two buttons on the screen, one on the right side of the screen and the other on the left hand side of the screen. Arrows appear in the middle of the screen and the participant learns to press the button corresponding to the direction in which the arrow points.

The task starts with a practice phase where the subject simply responds by touching the button on the left side of the screen when the arrow points to the left and the button on the right hand side when the arrow points to the right. A stop signal (an auditory tone) is then introduced. If a stop signal is presented, the participant must inhibit their response i.e. try not to touch the on-screen button. A stop signal occurs on 25% of trials.



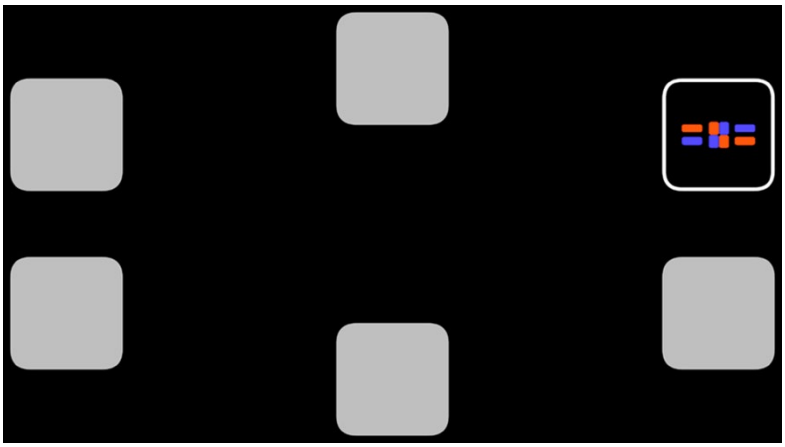
The assessed phase with the stop signal (tone) is presented in 4 blocks. At the end of each assessed block, a graphic representing the participant's performance is shown on screen. Depending on the participant's performance on the previous block the participant is encouraged to either go faster or slower on the next block, whilst trying not to touch the button whenever they hear the tone.

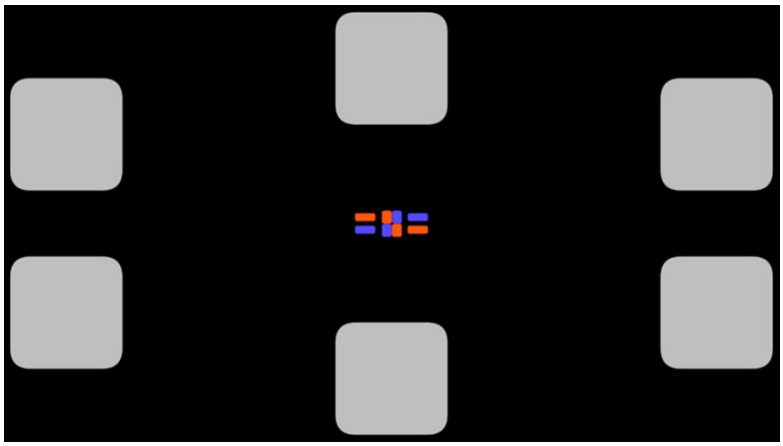


The time between the arrow being shown on screen, and the delay interval between the participant hearing the tone (Stop Signal Delay (SSD)) is varied throughout the task.

Paired Associates Learning (PAL)

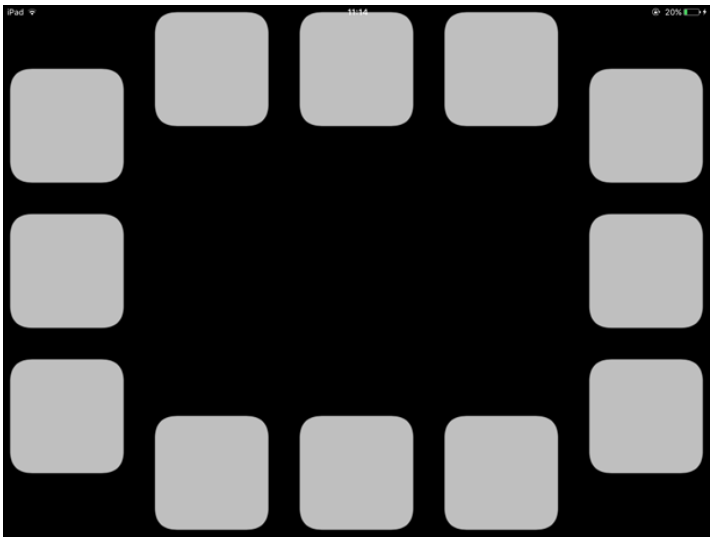
The paired Associates Learning task consists of a number of stages, which the subject must complete in order. For each stage, boxes are displayed on the screen. These boxes are opened one at a time, in a randomised order. Two or more of the boxes will contain a pattern. The patterns shown in the boxes are then displayed in the middle of the screen, one at a time, and the subject must touch the box where the pattern was originally located.





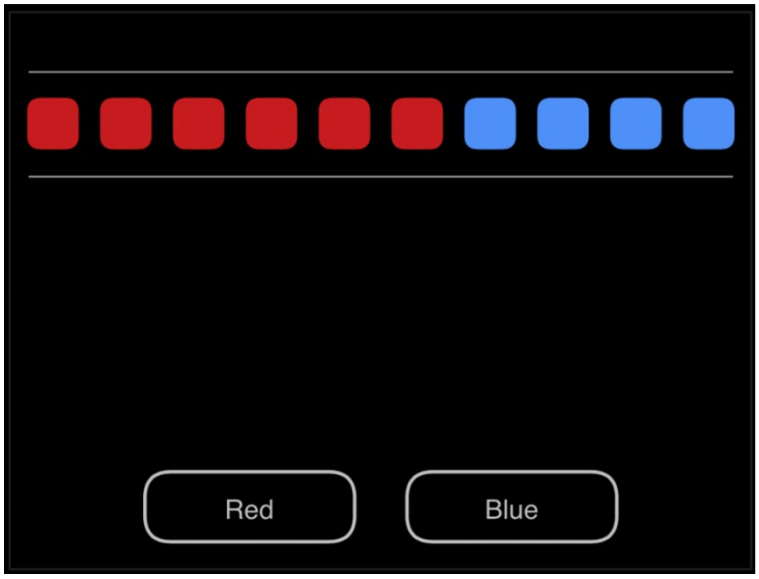
When the participant successfully identifies the correct box for all of the patterns the test moves to the next level. The PAL test gradually becomes more difficult with the number of boxes that contain a pattern increasing from 2 trials with 2 boxes that contain a pattern, 1 trial with 4 patterns, 1 trial with 6 patterns. Following successful completion of the trial with 6 boxes containing a pattern, 8 boxes are presented on the screen.

If the participant is not successful, the boxes will reopen to remind the participant where the patterns were. The participant will have up to 4 chances to correctly identify the location of the patterns at each level. If the participant fails after 4 attempts at any level the test will end. If a participant is successful at the 8 box level the final level will show 12 boxes on screen with each box containing a pattern.



Cambridge Gambling Task (CGT)

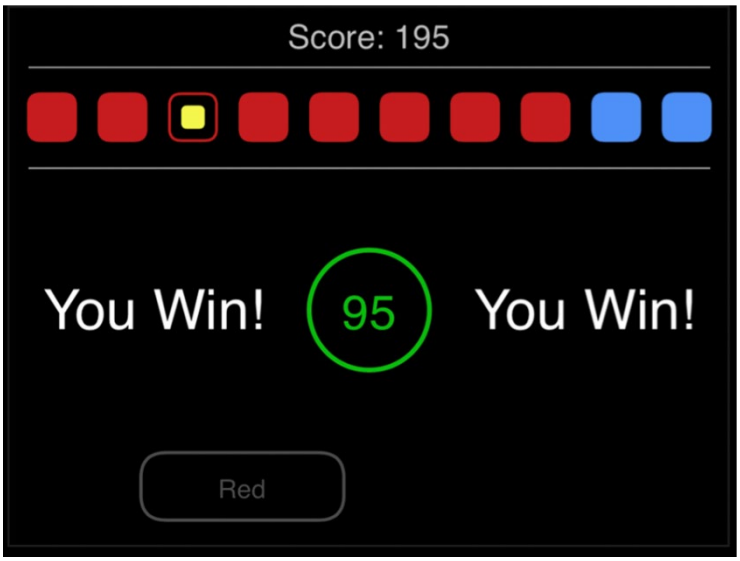
The participant is presented with a row of 10 color squares at the top of the screen. Some of the squares are blue in color others red. Beneath these colored squares are two buttons, one labelled red and the other blue. The participant is informed that a yellow token is hidden in one of the colored boxes. The participant should touch the red button at the bottom of the screen if they think it is more likely that the yellow token will be hidden in a red box or the blue button if they think it is likely to be hidden in a blue box.



If the participant is correct they see the words You Win. If incorrect the participant will see You Lose.

In the assessed phase the participant is given 100 points and can bet on their decision. The proportion of the total score that the participant wants to bet is selected as the number on the screen counts up or down from 100% by tapping the Red or Blue box to place the desired bet amount.

The participants total score increases or decreases incrementally dependent on successful or unsuccessful bet outcome. The total score is displayed at the top of the screen.



The participant must try to amass as many points as possible.

APPENDIX F QUESTIONNAIRE ON SMOKING URGES

QUESTIONNAIRE ON SMOKING URGES (QSU1)

Please indicate the degree to which you agree with each statement below.
Indicate **only one** choice.

	Strongly Disagree 1	2	3	Neutral 4	5	6	Strongly Agree 7
1. I have a desire for a cigarette right now	☐	☐	☐	☐	☐	☐	☐
2. Nothing would be better than smoking a cigarette right now	☐	☐	☐	☐	☐	☐	☐
3. If it were possible I would probably smoke now	☐	☐	☐	☐	☐	☐	☐
4. I could control things better right now if I could smoke	☐	☐	☐	☐	☐	☐	☐
5. All I want right now is a cigarette	☐	☐	☐	☐	☐	☐	☐
6. I have an urge for a cigarette	☐	☐	☐	☐	☐	☐	☐
7. A cigarette would taste good now	☐	☐	☐	☐	☐	☐	☐
8. I would do almost anything for a cigarette now	☐	☐	☐	☐	☐	☐	☐
9. Smoking would make me less depressed	☐	☐	☐	☐	☐	☐	☐
10. I am going to smoke as soon as possible	☐	☐	☐	☐	☐	☐	☐
	1 Strongly Disagree	2	3	4 Neutral	5	6	7 Strongly Agree

APPENDIX G POSITIVE AND NEGATIVE AFFECT SCHEDULE

Worksheet 3.1 The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988)

PANAS Questionnaire

This scale consists of a number of words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. **Indicate to what extent you feel this way right now, that is, at the present moment *OR* indicate the extent you have felt this way over the past week (circle the instructions you followed when taking this measure)**

1	2	3	4	5
Very Slightly or Not at All	A Little	Moderately	Quite a Bit	Extremely

_____ 1. Interested	_____ 11. Irritable
_____ 2. Distressed	_____ 12. Alert
_____ 3. Excited	_____ 13. Ashamed
_____ 4. Upset	_____ 14. Inspired
_____ 5. Strong	_____ 15. Nervous
_____ 6. Guilty	_____ 16. Determined
_____ 7. Scared	_____ 17. Attentive
_____ 8. Hostile	_____ 18. Jittery
_____ 9. Enthusiastic	_____ 19. Active
_____ 10. Proud	_____ 20. Afraid

Scoring Instructions:

Positive Affect Score: Add the scores on items 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19. Scores can range from 10 – 50, with higher scores representing higher levels of positive affect. Mean Scores: Momentary = 29.7 (*SD* = 7.9); Weekly = 33.3 (*SD = 7.2)*

Negative Affect Score: Add the scores on items 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20. Scores can range from 10 – 50, with lower scores representing lower levels of negative affect. Mean Score: Momentary = 14.8 (*SD* = 5.4); Weekly = 17.4 (*SD* = 6.2)

APPENDIX H CIGARETTE EVALUATION QUESTIONNAIRE

Study:	**SID:** _____	**Visit:** DAY _____
PI:	**MODIFIED CIGARETTE EVALUATION QUESTIONNAIRE**	**Date:** _____

I. Have you smoked since your last visit? (0) No (1) Yes

If yes, proceed with the questions, if no, do not continue with the questions.

Please mark the number that best represents how the last cigarette you smoked made you feel, based on these questions:

(1) not at all (2) very little (3) a little (4) moderately (5) a lot (6) quite a lot (7) extremely

1. Was smoking satisfying?

1 2 3 4 5 6 7

2. Did cigarettes taste good?

1 2 3 4 5 6 7

3. Did you enjoy the sensations in your throat and chest?

1 2 3 4 5 6 7

4. Did smoking calm you down?

1 2 3 4 5 6 7

5. Did smoking make you feel more awake?

1 2 3 4 5 6 7

6. Did smoking make you feel less irritable?

1 2 3 4 5 6 7

7. Did smoking help you concentrate?

1 2 3 4 5 6 7

8. Did smoking reduce your hunger for food?

1 2 3 4 5 6 7

9. Did smoking make you dizzy?

1 2 3 4 5 6 7

10. Did smoking make you nauseous?

1 2 3 4 5 6 7

11. Did smoking immediately relieve your craving for a cigarette?

1 2 3 4 5 6 7

12. Did you enjoy smoking?

1 2 3 4 5 6 7

APPENDIX I CUE REACTIVITY AND LIKERT SCALE ASSESSMENTS

Images will include 3 categories: neutral, positive, and smoking. Neutral and positive images will be those extracted from IAPS and those validated in the TRAIN lab at MUSC (PI Froeliger), and smoking images will be from MUSC.USC The program will present images in sequence for 2 seconds each with a 1-second black screen between images. Each category will be presented in full (10 images over 30 seconds) and followed by a 8-point Likert scale assessing the urge for a cigarette followed by an 8-point Likert scale assessing mood. Subsequent categories will be presented and each time the same Likert scales will be completed.

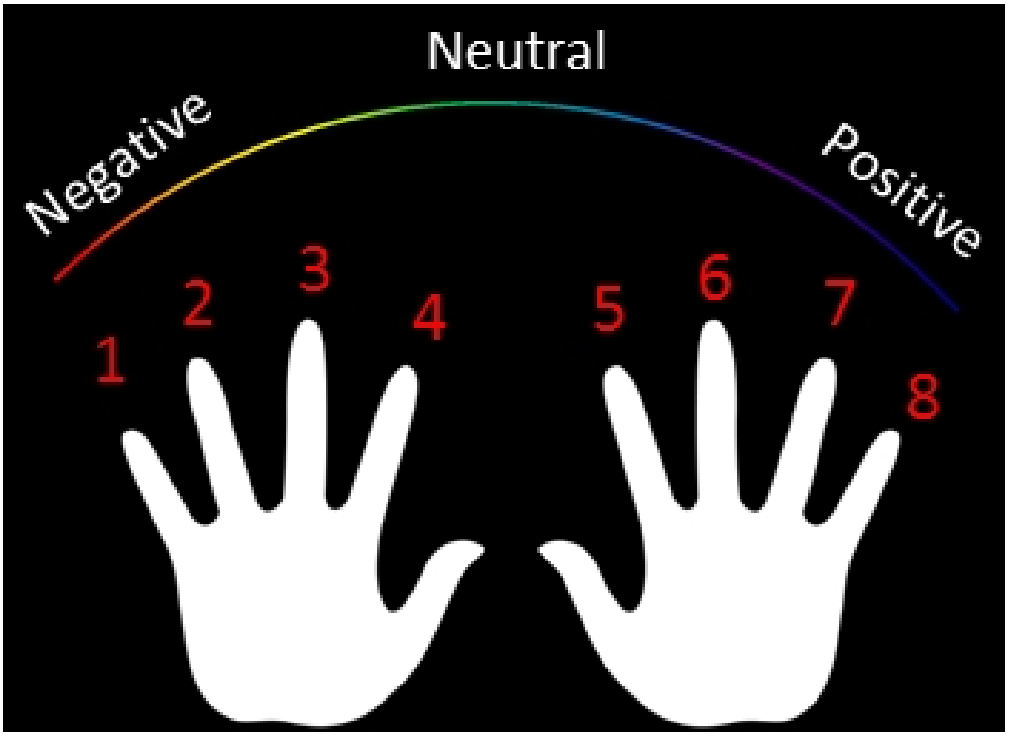
Response to the assessments will range from 1 to 8 as follows:

Urge Question – "I Have An Urge For A Cigarette"

Answer: 1 (strongly disagree) – 2 – 3 – 4 (neutral) – 5 – 6 – 7- 8 (strongly agree)

Mood Question – "Please Rate How You Feel?"

The image with the 8-point scale below will be shown with each block.



APPENDIX J FAGERSTROM TEST OF NICOTINE DEPENDENCE QUESTIONNAIRE

Fagerstrom Test for Nicotine Dependence (FTND)

	0	1	2	3
1. How soon after you wake up do you smoke your first cigarette?	After 60 Minutes	31 – 60 minutes	6-30 minutes	Within 5 minutes
2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, cinema, etc?	No	Yes		
3. Which cigarette would you hate most to give up?	All others	The first one in the morning		
4. How many cigarettes/day do you smoke?	10 or less	11-20	21-30	31 or more
5. Do you smoke more frequently during the first hours of waking than during the rest of the day?	No	Yes		
6. Do you smoke if you are so ill that you are in bed most of the day?	No	Yes		