PROMENTIS
PHARMACEUTICALS, INC.

CLINICAL PROTOCOL

A Phase 2, Double Blind, Placebo-Controlled Study to Explore the Safety, Tolerability, and Activity of SXC-2023 in Adults with Moderate to Severe Trichotillomania (TTM) When Dosed for 6 Weeks

Protocol No.:	PRO-201
US IND No.:	133689
Amendment 3:	25 June 2019

Previous versions

Amendment 2:	01 May 2019
Amendment 1:	02 November 2018
Original Protocol Date:	16 August 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
17 June 2019/ Amendment 3	• Study procedures were updated with administration of the C-SSRS since last visit version at subject's Day 1 and Week 8 visits. • Inclusion criteria #8 was updated to clarify contraceptive requirements. • First page: Administrative change, protocol amendment 2 date of finalization changed from 16 April to 01 May • Study procedures updated to clarify that pregnancy tests will only be performed for female subjects without confirmation of sterility. • Updates to MAD (PRO-104) study information (safety and PK).
01 May 2019/ Amendment 2	• The screening period for subjects was expanded from up to 30 days to up to 40 days. • Inclusion criterion 4 was updated to clarify that stimulants are not allowed and that certain over-the-counter/herbal psychoactive drugs are allowable with medical monitor approval. The requirement for subjects to not use any of the listed medications has been changed from 30 days prior to screening, to 30 days prior to first dose. • Inclusion criterion 5 timeline for N-Acetylcysteine changed from at least 90 days prior to first screening to at least 90 days prior to first dose. • Inclusion criterion 8 was updated to elaborate on requirements for contraception for females of childbearing potential. • Exclusion criterion 2 was updated to prohibit CBT for TTM, or other body-focused repetitive behavior or any obsessive compulsive related or impulse control disorder any time from within 30 days prior to first screening to within 60 days prior to first dose. For other psychotherapies, changed from a minimum of 4 weeks at time of first screening to a minimum of 60 days at time of first dose. • Exclusion criterion 3 was updated to prohibit other behavioral interventions for TTM for 60 days prior to first dosing. • An exclusionary criterion was added for laboratory evidence of renal impairment. • Section 6.2.3.3 was updated to add melatonin as a disallowed treatment within 24 hours prior to any study visits. • The Safety and PK sections for the 104 MAD study were updated with final data. • Change in Figure 1 (Diagram of study design) and Appendix A, Schedule of Assessments to reflect integration of 7 day run-in as part of screening. Screening period reflects now reflects Day -40 to Day 0. • Added Section 9.8 Medication errors requirements. • Clarification made in overdose section. • Protocol Violation changed to Protocol Deviation. • Minimal administrative changes throughout.

02 November 2018/Amendment 1	• The protocol has been revised to provide additional information on the nonclinical studies (e.g., 90-day toxicity data were added) as well as additional information on the safety and pharmacokinetic findings in the multiple ascending dose study and the single ascending dose study. • The title of the protocol has been updated and the Phase has been modified from Phase 2A to Phase 2. • The fax number and email address for the pharmacovigilance team were added for purposes of safety reporting. • The protocol was modified to indicate that the 7-day Trichotillomania Symptom Diary baseline period could be performed at any time during the screening window. • The protocol was modified to indicate that the CGI-S/C will be performed using the iPad device and training for the PGI-S/C and CGI-S/C software was added. • An electrocardiogram assessment was added at the end of the treatment period. • Clarifications were made to the eligibility criteria, including the exclusion of subjects using wearable devices or other behavioral self- help strategies. • Restrictions on alcohol and cannabinoid use were added. • Instructions indicating that the screening assessments may occur over multiple visits were added and instructions regarding a 10-day extension of the screening window were added. • Clarification was added regarding the criteria for repeating the baseline 7-day Trichotillomania Symptom Diary period. • Details regarding the study drug supplies and study drug administration were added. • The statistical section was updated to provide additional details on the sample size estimation and the planned analyses. • Additional details were added regarding the number of missed doses and diary non-compliance that are permitted before a subject would be removed from the Per Protocol Population. Missed doses and diary non-compliance were added as separate reasons for discontinuation. • Additional instructions were added regarding dose suspensions. • Clarification was added regarding the recording of adverse events during screening (pre-dose Day 1). • Clarification was made that a urine drug test is not required at Week 3 and Week 6 and the components of the test were modified. • The protocol was modified to indicate that re-confirmation of eligibility through assessment of changes in medical and psychiatric history and concomitant medications would be performed at Day 1. • Clarification was added that the subject does not have be

	in the supine position for at least 5 minutes prior to respiratory rate and temperature assessments. • Instructions for the early termination visit were updated. • Uric acid was added as a clinical laboratory assessment.

PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase 2, Double Blind, Placebo-Controlled Study to Explore the Safety, Tolerability, and Activity of SXC-2023 in Adults with Moderate to Severe Trichotillomania (TTM) When Dosed for 6 Weeks

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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

A Phase 2, Double Blind, Placebo-Controlled Study to Explore the Safety, Tolerability, and Activity of SXC-2023 in Adults with Moderate to Severe Trichotillomania (TTM) When Dosed for 6 Weeks

Sites

Up to 15 sites in the United States

Phase of Development

Phase 2

Dosage and Administration

Double-blinded study drug:

- SXC-2023 50 mg once daily (QD)
- SXC-2023 200 mg QD
- SXC-2023 800 mg QD
- Placebo QD

SXC-2023 supplied as 50 mg and 200 mg capsules. Matching placebo capsules will be used for blinding.

Primary Objective

- To explore the safety and tolerability of SXC-2023 in adults with TTM when dosed for a period of 6 weeks.

Secondary Objectives

- To explore the activity of SXC-2023 in subjects with moderate to severe TTM when dosed for a period of 6 weeks using assessments of TTM disease activity (e.g., Trichotillomania Symptom Diary [TSD], Massachusetts General Hospital Hairpulling Scale [MGH-HPS], Clinical Global Impression of Severity and Change [CGI-S/CGI-C], and Patient Global Impression of Status and Change [PGI-S/PGI-C]).
- To provide preliminary psychometric evidence of the reliability, validity, and responsiveness of the newly developed TSD assessment.

Exploratory Objectives

- To test the activity of SXC-2023 on neurocognitive assessments (e.g., Stop Signal Task [SST], Cambridge Gambling Task [CGT] and other behavioral measures including Reaction Time [RTI], Paired Associates Learning [PAL], and Milwaukee Inventory of Subtypes of TTM - Adult Version [MIST-A]).
- To test the effects of SXC-2023 on whole blood glutathione levels.

Study Design

This study is a randomized, double blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, and activity of SXC-2023 (50 mg, 200 mg, or 800 mg QD) when dosed for 6 weeks compared to placebo in adult subjects diagnosed with moderate to severe TTM. Subjects will be screened and will perform required assessments for eligibility during a 40-day screening period. During the screening period, subjects will be trained on site on how to use an electronic Patient Report Outcome (ePRO) handheld device to complete the TSD. After all screening assessments are complete, the subjects will complete the TSD at home every evening for 7 consecutive days during the screening period.

On Study Day 1, eligible subjects will complete protocol-specified assessments and study procedures, including neurocognitive and other assessments, and will be assigned to receive one of three doses of SXC-2023 or matching placebo. Subjects will be assigned to treatment groups using a randomization scheme including a stratification factor for whether subjects are currently taking concomitant selective serotonin re-uptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs). Subjects will be instructed to complete the TSD on their ePRO handheld device every 24 hours (just prior to bedtime) during the 6-week treatment period. Subjects will be instructed to take their study medication at approximately the same time each day (preferably in the morning at least 1 hour prior to or 2 hours after a meal). Subjects will return to the site to complete assessments at Week 3 (±4 days) and Week 6 (±4 days). Subjects will then return for follow-up at Week 8 (±4 days).

Neurocognitive and other behavioral measurements (in addition to daily TSD completion) will include the following:

Screening (neurocognitive and other behavioral measurements must be performed at one visit):

- Mini-International Neuropsychiatric Interview (MINI) version 7.0.2 with Trichotillomania and Body Dysmorphic Disorder modules (MINI-TTM)
- Training on the Cambridge Neuropsychological Test Automated Battery (CANTAB) iPad device which will be used for the SST, CGT, RTI, and PAL
- Training on the TSD on the ePRO handheld device. Once trained, subject to complete the TSD on their ePRO handheld device every 24 hours for 7 days at home.
- Training on the PGI-S, PGI-C, CGI-S, and CGI-C software using the iPad device
- Barratt Impulsiveness Scale (BIS)
- MGH-HPS
- Columbia Suicide Severity Rating Scale (C-SSRS)

Day 1 (Baseline):

- SST, CGT, RTI, and PAL (completed using the CANTAB iPad device)
- MGH-HPS
- PGI-S (completed using an iPad device)
- CGI-S (completed using an iPad device)
- C-SSRS
- MIST-A

Week 3 (±4 days):

- MGH-HPS
- PGI-S and PGI-C (completed using an iPad device)

- CGI-S and CGI-C (completed using an iPad device)
- MIST-A
- C-SSRS

Week 6 (±4 days):

- SST, CGT, RTI, and PAL (completed using the CANTAB iPad device)
- MGH-HPS
- PGI-S and PGI-C (completed using an iPad device))
- CGI-S and CGI-C (completed using an iPad device)
- MIST-A
- C-SSRS

Follow up/ET, Week 8 (±4 days):

- C-SSRS

Safety will be evaluated via reports of adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, the C-SSRS, electrocardiograms (ECGs), and concomitant treatments. Evaluation of AEs will include assessment of changes in psychiatric symptoms, including changes in emotions, cognition, or behavior, to determine whether changes are clinically significant (e.g., onset or exacerbation of depressed mood) and possibly related to study drug.

Whole blood samples for glutathione measurements will be taken at baseline (prior to dosing) and at Week 6 (±4 days).

Study Duration

Subjects will be dosed for 38 to 46 consecutive days. The maximum anticipated subject participation will be approximately 100 days (40 days for the screening period, 6 weeks of treatment, and a follow-up visit on Day 60 at the latest). One 10-day extension of the screening period may be permitted on a case-by-case basis with medical monitor or designee approval (e.g., if needed for adequate drug washout or additional ePRO training).

Number of Subjects (Planned)

Approximately 120 subjects are planned to be enrolled so that 100 subjects complete the study. In the event that a subject leaves the study (e.g., voluntarily withdraws, discontinues due to an AE, is lost to follow-up) prior to completing study procedures and assessments at the Week 3 visit, an additional subject may be randomized. Subjects who leave the study after the Week 3 visit but before study completion will be considered as part of the final enrollment sample of 120 subjects.

Inclusion Criteria

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

1. Adult, female or male, 18-45 years of age, inclusive at screening.
2. Has provided signed written informed consent with willingness and ability to comply with all aspects of the protocol.
3. Diagnosis of current TTM based on Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria and confirmed using the clinician-administered MINI-TTM. In addition, subjects should:
    a. Have a history of TTM for at least one year
    b. Have a history of daily hair pulling for at least 6 months prior to the first dose

4. Except for SSRIs and SNRIs, has not used any psychoactive medications including, but not limited to, other antidepressants, anxiolytics, mood stabilizers, anti-psychotics, benzodiazepines, stimulants, sulfasalazine, and St. John's Wort 30 days prior to first dose. Subjects will be allowed to maintain background therapy with SSRIs or SNRIs if on stable regimen for a minimum of 90 days prior to first dose and there are no anticipated changes to the SSRI/SNRI during course of trial. Please refer to Section 6.2.3.2.
    a. Certain over-the-counter/herbal psychoactive drugs may be allowable with medical monitor approval (e.g., melatonin).
5. Has not used N-acetylcysteine for at least 90 days prior to the first dose.
6. Has not used gemfibrozil or repaglinide for 1 week prior to the first screening visit.
7. Medically healthy with no clinically significant findings in medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the Principal Investigator (PI) or designee.
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 one of the following acceptable birth control options:
    - Oral contraception for at least 3 months prior to the first dosing along with either a physical (e.g., condom, diaphragm) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study
    - IUD (either hormone-releasing or non-hormone releasing) for at least minimum duration per current labeling along with either a physical (e.g., condom, diaphragm) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study
    - Depo contraception for at least minimum duration per current labeling prior to the first dosing along with either a physical (e.g., condom, diaphragm) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study
    - Double physical barrier method (e.g., condom and diaphragm) from 14 days prior to the first dose and throughout the study
    - Physical plus chemical barrier method (e.g., condom 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 30 days following the last dose.

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. 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/placebo. (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/placebo. No restrictions are required for males with a medically documented history of biological or congenital sterility. 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).

11. If male, must agree not to donate sperm from the first dose until 30 days after the last dose administration.
12. Must be able to fluently read and write in English.
13. Understands the study procedures in the informed consent form (ICF) and is willing and able to comply with the protocol.

Exclusion Criteria

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

1. Females who are pregnant or breastfeeding or intend to become pregnant during the study period or within 30 days of the final dose of study drug.
2. Subjects engaged in cognitive behavioral therapy (CBT) for TTM or other body-focused repetitive behavior or any obsessive-compulsive related or impulse control disorder any time within 60 days prior to first dose. For other psychotherapies, subject must have been engaged in that psychotherapy for a minimum of 60 days at the time of first dose and must be willing to maintain the same frequency and type of therapy for the duration of the study period.
3. Subjects who have initiated any other behavioral interventions (e.g., wearable devices, behavioral self-help strategies) within 60 days prior to first dose.
4. Subject is mentally or legally incompetent.
5. Subject suffered a concussion in the past 6 months prior to screening. Any history of traumatic brain injury with loss of consciousness in the year prior to first screening visit.
6. Any lifetime history of any psychotic disorder, including schizophrenia, or any bipolar or bipolar-related disorder as determined by clinical history or confirmed at screening with the MINI, version 7.0.2.
7. Current major depressive episode confirmed at screening with the MINI, version 7.0.2.
8. Per PI judgment, the presence of any emotional problems or psychiatric disorders that may obscure evaluation of TTM or pose a risk to subject safety or stability during the study period. Other emotional problems or diagnoses may include, but are not limited to, other body-focused repetitive behaviors, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, compulsive gambling, borderline personality disorder, or antisocial personality disorder.
9. History of any injury, illness, or condition 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.
10. Laboratory evidence of renal impairment (e.g, a calculated creatinine clearance of < 80)
11. Presence of any substance use disorder or, in the opinion of the PI or designee, problematic substance use (excluding nicotine or caffeine) within the 2 years prior to screening.
12. History of seizure disorder with the exception of subjects who have been off anti-seizure medication and have not had a seizure in the past 5 years.
13. Subjects with any of the following:
    a. Any psychiatric hospitalizations in the past year,

b. Imminent risk of suicide based on PI's or designee's clinical judgment or psychiatric examination
c. Active suicidal ideation in the past 6 months as evidenced by positive endorsement to Item 4 or 5 on the C-SSRS,

OR

d. Any history of suicidal behavior in the past year as evidenced by positive endorsement to any of the suicidal behavior items on the C-SSRS.

14. Has previously participated in any Promentis Phase 1 study.
15. Participation in another interventional clinical study (including CBT or other behavioral intervention) within 30 days prior to the first screening visit. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to the date of initiation of screening in the current study.

2 ABBREVIATIONS

AE	Adverse event
AUC	Area under the concentration-time curve
BID	Twice daily
BIS	Barratt Impulsiveness Scale
BP	Blood pressure
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBT	Cognitive behavioral therapy
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CGT	Cambridge Gambling Task
C_{max}	Maximum observed concentration
CNS	Central nervous system
CRF/eCRF	Case report form/electronic case report form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DG	Days of gestation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	Electrocardiogram
EE2	Ethinyl estradiol
ePRO	electronic Patient Reported Outcome
FE	Food effect
GCP	Good Clinical Practice(s)
GLP	Good Laboratory Practice
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
IRB	Institutional/independent review board
Kg	Kilogram
m^2	Meters squared

MAD	Multiple ascending dose
MedDRA®	Medical Dictionary for Regulatory Activities®
Mg	Milligram
MGH-HPS	Massachusetts General Hospital Hairpulling Scale
MINI	Mini-International Neuropsychiatric Interview, version 7.0.2
MINI-TTM	Mini-International Neuropsychiatric Interview, version 7.0.2 with Trichotillomania and Body Dysmorphic Disorder modules
MIST-A	Milwaukee Inventory of Subtypes of TTM – Adult version
mL	Milliliter
mmHg	Millimeter of mercury
NAC	N-acetylcysteine
NET	Norethindrone
Ng	Nanogram
No.	Number
NOAEL	No observed adverse effect level
OC/DDI	Oral contraceptive/drug-drug interaction study
OTC	Over-the-counter
PAL	Paired Associates Learning
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Status
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred term
QA	Quality assurance
QD	Once daily
QTc	Corrected QT
QTcF	QT corrected by Fridericia's formula
RR	Respiratory rate
RTI	Reaction Time
SAD	Single ascending dose
SAE	Serious adverse event

SAP	Statistical Analysis Plan
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
SST	Stop Signal Task
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum observed concentration
TSD	Trichotillomania Symptom Diary
TTM	Trichotillomania
µg	Microgram
µM	Micromolar
US	United States
WHODD	World Health Organization Drug Dictionary

3 BACKGROUND AND RATIONALE

3.1 Background

Trichotillomania (TTM) is a chronic psychiatric illness characterized by the recurrent pulling out of one's hair as well as the associated distress or functional impairment caused by this condition. It was not until the late 1980s that TTM was included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) as an impulse control disorder. Recent studies have linked perturbations in glutamatergic neurotransmission and/or heightened levels of oxidative stress to the underlying pathophysiology of TTM. Imaging studies conducted in TTM patients identified alterations in areas of the brain, particularly those implicated in the regulation of urge control, rewarding behaviors, motor habits, mood, and executive function (Chamberlain et al., 2008; Chamberlain et al., 2010; Grant and Chamberlain, 2016; Roos et al., 2015), as key contributors to the pathophysiology of TTM and related impulse control disorders (e.g., excoriation disorder). Additionally, functional deficits in glutamate signaling within the cortical-striatal pathway and mesolimbic system (i.e., nucleus accumbens) have been proposed to contribute to the underlying pathology and symptoms of TTM (Grant et al., 2009).

SXC-2023 is a novel small molecule and new chemical entity designed to activate System xc- (also known as the cysteine glutamate antiporter). By increasing cyst(e)ine levels, SXC-2023 increases the activity of System xc- in the brain. System xc- is expressed on astrocytes and neurons within the central nervous system (CNS) and its primary function 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 are proposed to underlie the pathology of TTM, this mechanism of action is important because activation of System xc- is proposed to restore imbalances in oxidative stress and modulate glutamatergic neurotransmission in the brain.

SXC-2023 is currently in clinical development (Investigational New Drug [IND] No. 133689) and proposed as a strategy to treat TTM in adults.

Refer to the Investigator's Brochure, Version 6.0 (SXC-2023, 2019) for detailed background information on SXC-2023.

3.1.1 Preclinical Trials

3.1.1.1 Pharmacology

In preclinical rodent models, oral treatment with SXC-2023 was found to reduce anxiety behaviors as measured by an increase in the time spent in the open arm of the elevated plus maze (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 sensory motor behaviors 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 impulse control disorders.

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 of drug, concentrations of SXC-2023 and NAC in red blood cells appear to be minimal when taking background levels into consideration. Metabolism of SXC-2023 was evaluated using rat, monkey, dog, rabbit, and human hepatocytes. The primary metabolic pathway appears to include thioester cleavage, resulting in the formation of NAC and p-toluic acid. In rat, rabbit, monkey, and human hepatocytes, p-toluic acid undergoes subsequent glycine conjugation to form 4-methylhippuric acid. Another possible minor pathway of SXC-2023 metabolism includes deamidation followed by cysteine conjugation.

The parent drug, NAC, and p-toluic acid have relatively short plasma half-lives (<6 hours). All the metabolites are polar; therefore, extensive renal clearance and urinary excretion are expected.

Following *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 generally well tolerated in both male and female rats (please see Investigator's Brochure, Version 6.0 [SXC-2023, 2019] for detailed information and additional summary). 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.

A 90-day rat study was performed with SXC-2023 doses of 100, 300, and 1000 mg/kg/day. This study included a 28-day recovery arm to assess the reversibility, persistence, or delayed occurrence of any SXC-2023-related effects. 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 triiodothyronine and thyroxine serum levels occurred in males administered 1000 mg/kg/day and were not accompanied by any thyroid stimulating hormone 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 SXC-2023, the NOAEL was 1000 mg/kg/day.

In Beagle dogs, SXC-2023 was delivered once-daily for 28 days at 250, 500 and 1200 mg/kg/day. Based on the results of these studies (please see Investigator's Brochure, Version 6.0 [SXC-2023, 2019] for detailed information and additional summary), 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 to be 250 mg/kg/day.

A 90-day dog study was performed with SXC-2023 doses of 30, 100, and 300 mg/kg/day, and included a 28-day recovery arm to assess the reversibility, persistence, or delayed occurrence of any SXC-2023-related effects. 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 toxicity 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 studieswere 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 (QD) 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-relatedclinical observations or 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) QD 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) QD 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). 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 6.0 (SXC-2023, 2019) 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 QD). 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 6.0 (SXC-2023, 2019) for further information about the safety and PK data of SXC-2023.

3.1.2.1 Safety

To date, 96 human subjects have been exposed to SXC-2023. Overall, SXC-2023 has been safe and well tolerated in doses ranging from 50 mg to 1600 mg in the SAD/FE study, at a dose of 800 mg in combination with oral contraceptives, and at doses ranging from 200 mg to 800 mg for 14 days in the MAD study. The most common adverse events (AEs) 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, tolerability and PK 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, AEs 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).

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 QTc prolongation, was seen. There were no serious adverse events (SAEs), study discontinuations related to AEs or deaths in this study.

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. A total of 4 subjects (14%) had AEs deemed possibly related to

study drug when SXC-2023 was taken in combination with EE2/NET. Grades 1 and 2 AEs included dizziness, generalized headache, and nausea. There were no SAEs reported or subject discontinuations in this study.

PRO-104: MAD Study

The MAD study examined the safety and tolerability 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 due to AEs, or deaths reported in this study. Adverse events were reported by 45% (18/40) of subjects regardless of attribution. The most common AEs in subjects was headache, reported by 15% (6/40) 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, with the exception of constipation in one subject, 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.

Additionally, in cognitive safety outcome measures including Paired Associates Learning (PAL) to test episodic memory and Reaction Time (RTI), there were no impairments in cognitive performance. Furthermore, there were no significant trends in impulsivity scores across individuals or means as related to treatment, as measured by the Barratt Impulsiveness scale (BIS)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
The PK of MADs of SXC-2023 was evaluated in Study PRO-104. Four cohorts of subjects received MADs of SXC-2023 (200mg QD, 400mg QD, 800mg QD and 400mg BID). SXC-2023 concentrations were measurable in all subjects; NAC (measured as total NAC) and p-toluic acid were detected at low concentrations across the dose levels tested. Plasma SXC-2023 concentrations increased with increasing dose and were dose-proportional to 800 mg. On average, maximum observed concentration (Cmax) following 14 days of treatment ranged from 7,633 ng/mL for the 200 mg dose to 30,350 ng/mL for the 800 mg dose. Median time to reach maximum observed concentration (tmax) was consistent across doses and dosing days and ranged from 2-6 hours. The elimination half-life for SXC-2023 on day 1 was approximately 3.4 to 5.2 hours over the 200 to 800 mg dose range tested, and approximately 9.4 to 11.7 hours on 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.

3.2 Rationale

3.2.1 Rationale for this Study and Study Design

SXC-2023 is a novel small molecule and new chemical entity designed to activate System xc- (also known as the cysteine glutamate antiporter). By increasing cyst(e)ine levels, SXC-2023 increases the activity of System xc- in the brain. System xc- is expressed on astrocytes and neurons within the CNS and its primary function 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 are proposed to underlie the pathology of TTM, this mechanism of action is important because activation of System xc- is proposed to restore imbalances in oxidative stress and modulate glutamatergic neurotransmission in the brain.

This study is being performed to evaluate the safety, tolerability, and activity of SXC-2023 on TTM when dosed for a period of 6 weeks. A randomized, double blind, placebo-controlled design was chosen to reduce bias. Neurocognitive testing and TTM-specific assessments will be performed at baseline, Week 3, and Week 6 to assess the effect of SXC-2023 administration over the duration of the treatment period.

3.2.2 Rationale for Dose Selection

The proposed doses of SXC-2023 in this study are 50 mg, 200 mg, 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. Extrapolation to humans suggests a daily dose of 200 mg which is the mid-point dose of this study. The additional doses of 50 mg and 800 mg are included to fully explore the dose response of SXC-2023.

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 to 800 mg/day QD and 400 mg/day BID, is 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 ECG, clinical laboratory tests, and AE questioning) were adequate to protect the subjects' safety and detected all expected TEAEs.

In the MAD study, SXC-2023 was 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, ECGs, neurocognitive assessments, and the C-SSRS 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.

A potential health benefit for study participants who receive SXC-2023 as blinded study drug is improvement in TTM symptoms. An indirect health benefit to subjects enrolled in this study is the free medical tests received at screening and during the study.

4 STUDY OBJECTIVES

4.1 Primary Objective

- To explore the safety and tolerability of SXC-2023 in adults with TTM when dosed for a period of 6 weeks.

4.2 Secondary Objectives

- To explore the activity of SXC-2023 in subjects with moderate to severe TTM when dosed for a period of 6 weeks using assessments of TTM disease activity (e.g., Trichotillomania Symptom Diary [TSD], Massachusetts General Hospital Hairpulling Scale [MGH-HPS], Clinical Global Impression of Severity and Change [CGI-S/CGI-C], and Patient Global Impression of Status and Change[PGI-S/PGI-C]).

- To provide preliminary psychometric evidence of the reliability, validity, and responsiveness of the newly developed TSD assessment.

4.3 Exploratory Objectives

- To test the activity of SXC-2023 on neurocognitive assessments (e.g., Stop Signal Task [SST], Cambridge Gambling Task [CGT] and other behavioral measures including Reaction Time [RTI], Paired Associates Learning [PAL], and Milwaukee Inventoryof Subtypes of TTM - Adult Version [MIST-A]).

- To test the effects of SXC-2023 on whole blood glutathione levels.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

This study is a randomized, double blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, and activity of SXC-2023 (50 mg, 200 mg, or 800 mg QD) when dosed for 6 weeks compared to placebo in adult subjects diagnosed with moderate to severe TTM. Subjects will be screened and will perform required assessments for eligibility during a 40-day screening period. During the screening period, subjects will be trained on site on how to use an electronic Patient Report Outcome (ePRO) handheld device to complete the TSD. After all screening assessments are complete, the subjects will complete the TSD at home every evening for 7 consecutive days during the screening period.

On Study Day 1, eligible subjects will complete protocol-specified assessments and study procedures, including neurocognitive and other assessments, and will be assigned to receive one of three doses of SXC-2023 or matching placebo. Subjects will be assigned to treatment groups using a randomization scheme including a stratification factor for whether subjects are currently taking concomitant selective serotonin re-uptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs). Subjects will be instructed to complete the TSD on their ePRO handheld device every 24 hours (just prior to bedtime) during the 6-week

treatment period. Subjects will be instructed to take their study medication at approximately the same time each day (preferably in the morning at least 1 hour prior to or 2 hours after a meal). Subjects will return to the site to complete assessments at Week 3 (±4 days) and Week 6 (±4 days). Subjects will then return for follow-up at Week 8 (±4 days).

Neurocognitive and other behavioral measurements (in addition to the daily TSD) will include the following:

Screening (neurocognitive and other behavioral measurements must be performed at one visit):

- Mini-International Neuropsychiatric Interview (MINI) version 7.0.2 with Trichotillomania and Body Dysmorphic Disorder modules (MINI-TTM)
- Training on the Cambridge Neuropsychological Test Automated Battery (CANTAB) iPad device which will be used for the SST, CGT, RTI, and PAL
- Training on the TSD on the ePRO handheld device. Once trained, subject to complete the TSD on their ePRO handheld device every 24 hours for 7 days at home.
- Training on the PGI-S, PGI-C, CGI-S, and CGI-C software using the iPad device
- Barratt Impulsiveness Scale (BIS)
- MGH-HPS
- C-SSRS

Day 1 (Baseline):

- SST, CGT, RTI, and PAL (completed using the CANTAB iPad device)
- MGH-HPS
- PGI-S (completed using the iPad device)
- CGI-S (completed using the iPad device)
- C-SSRS
- MIST-A

Week 3 (±4 days):

- MGH-HPS
- PGI-S and PGI-C (completed using the iPad device)
- CGI-S and CGI-C (completed using the iPad device)

- MIST-A
- C-SSRS

Week 6 (±4 days):

- SST, CGT, RTI, and PAL (completed using the CANTAB iPad device)
- MGH-HPS
- PGI-S and PGI-C (completed using the iPad device)
- CGI-S and CGI-C (completed using the iPad device)
- MIST-A
- C-SSRS

Follow up/ET,
Week 8 (±4 days):

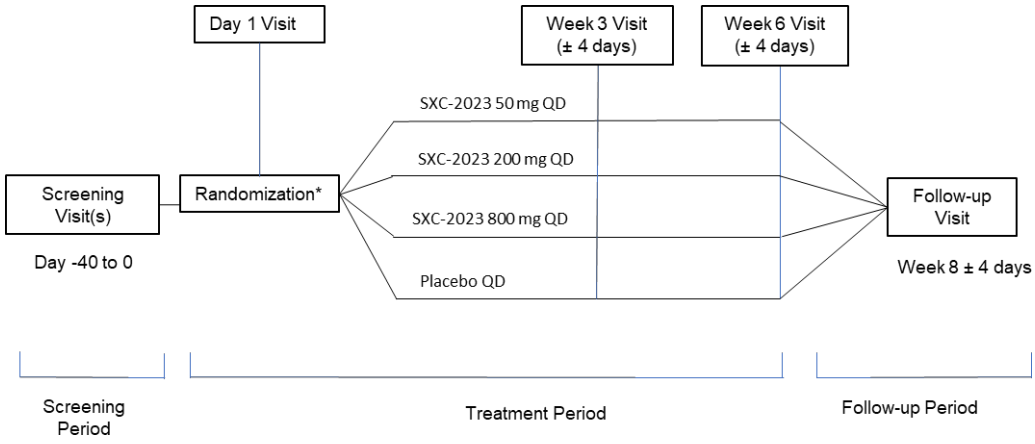
- C-SSRS

Safety will be evaluated via reports of AEs, clinical laboratory tests, physical examinations, vital signs, the C-SSRS, ECGs, and concomitant treatments. Evaluation of AEs will include assessment of changes in psychiatric symptoms, including changes in emotions, cognition, or behavior, to determine whether changes are clinically significant (e.g., onset or exacerbation of depressed mood) and possibly related to study drug.

Whole blood samples for glutathione measurements will be taken at baseline (prior to dosing) and at Week 6 (±4 days).

The study design in outlined in Figure 1. The Schedule of Events is provided in Appendix A, and a list and description of the assessments performed at each study visit are presented in Section 7.

Figure 1 Diagram of Study Design



QD=once daily; TSD=Trichotillomania Symptom Diary

*Randomization will be stratified by concomitant use of SSRIs/SNRIs and no concomitant use of SSRIs/SNRIs.
Notes: The screening period may be extended on a case-by-case basis. The screening visit may be split into multiple visits; however, the screening neurocognitive and other behavioral assessments must be performed at the same visit.

5.2 Study Duration

Subjects will be dosed for 38 to 46 consecutive days. The maximum anticipated subject participation will be approximately 100 days (40 days for the screening period, 6 weeks of treatment, and a follow-up visit on Day 60 at the latest). One 10-day extension of the screening period may be permitted on a case-by-case basis with medical monitor or designee approval (e.g., if needed for adequate drug washout or additional ePRO training).

5.3 Study Conduct

Please see the Schedule of Events (Appendix A) for a summary of the study assessments and procedures. Please see Section 7 for a listing and description of study procedures per visit.

6 STUDY POPULATION

6.1 Number of Subjects

Approximately 120 subjects are planned to be enrolled so that 100 subjects complete the study. In the event that a subject leaves the study (e.g., voluntarily withdraws, discontinues due to an AE, is lost to follow-up) prior to completing study procedures and assessments at the Week 3 visit, an additional subject may be randomized. Subjects who leave the study following Week 3 visit will be considered as part of the final enrollment sample of 120 subjects.

6.2 Eligibility Criteria

6.2.1 Inclusion Criteria

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

1. Adult, female or male, 18-45 years of age, inclusive at screening.

2. Has provided signed written informed consent with willingness and ability to comply with all aspects of the protocol.

3. Diagnosis of current TTM based on Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria and confirmed using the clinician-administered MINI-TTM. In addition, subjects should:

    a. Have a history of TTM for at least one year

    b. Have a history of daily hair pulling for at least 6 months prior to the first dose

4. Except for SSRIs or SNRIs, has not used any psychoactive medications including, but not limited to, other antidepressants, anxiolytics, mood stabilizers, anti-psychotics, benzodiazepines, stimulants, sulfasalazine, and St. John's Wort 30 days prior to first dose. Subjects will be allowed to maintain background therapy with SSRIs or SNRIs if on stable regimen for a minimum of 90 days prior to first dose and there are no anticipated changes to the SSRI/SNRI during course of trial. Please refer to Section 6.2.3.2.

    a. Certain over-the-counter/herbal psychoactive drugs may be allowable with medical monitor approval (e.g., melatonin).

5. Has not used NAC for at least 90 days prior to the first dose.

6. Has not used gemfibrozil or repaglinide for 1 week prior to the first screening visit.

7. Medically healthy with no clinically significant findings in medical history, physical examination, laboratory profiles (including coagulation), vital signs, or ECGs, as deemed by the Principal Investigator (PI) or designee.

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 one of the following acceptable birth control methods:

    - Oral contraception for at least 3 months prior to the first dosing along with either a physical (e.g., condom, diaphragm) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study
    - IUD (either hormone-releasing or non-hormone releasing) for at least minimum duration per current labeling along with either a physical (e.g., condom, diaphragm) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study
    - Depo contraception for at least minimum duration per current labeling prior to the first dosing along with either a physical (e.g., condom, diaphragm) or a chemical (e.g.,

spermicide) barrier method from the time of screening and throughout the study

- Double physical barrier method (e.g., condom and diaphragm) from 14 days prior to the first dose and throughout the studyPhysical plus chemical barrier method (e.g., condom 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 30 days following the last dose.

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. 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/placebo. (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/placebo. No restrictions are required for males with a medically documented history of biological or congenital sterility. 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).

11. If male, must agree not to donate sperm from the first dose until 30 days after the last dose administration.

12. Must be able to fluently read and write in English.

13. Understands the study procedures in the informed consent form (ICF) and is willing and able to comply with the protocol.

6.2.2 Exclusion Criteria

Subjects meeting any of the following criteria must NOT be enrolled in the study:

1. Females who are pregnant or breastfeeding or intend to become pregnant during the study period or within 30 days of the final dose of study drug.

2. Subjects engaged in cognitive behavioral therapy (CBT) for TTM or other body-focused repetitive behavior or any obsessive-compulsive related or impulse control disorder any time within 60 days prior to first dose. For other psychotherapies, subject

must have been engaged in that psychotherapy for a minimum of 60 days at the time of first dose and must be willing to maintain the same frequency and type of therapy for the duration of the study period.

3. Subjects who have initiated any other behavioral interventions (e.g., wearable devices, behavioral self-help strategies) within 60 days prior to first dose.

4. Subject is mentally or legally incompetent.

5. Subject suffered a concussion in the past 6 months prior to screening. Any history of traumatic brain injury with loss of consciousness in the year prior to the first screening visit.

6. Any lifetime history of any psychotic disorder, including schizophrenia, or any bipolar or bipolar-related disorder as determined by clinical history or confirmed at screening with the MINI, version 7.0.2.

7. Current major depressive episode confirmed at screening with the MINI, version 7.0.2.

8. Per PI judgment, the presence of any emotional problems or psychiatric disorders that may obscure evaluation of TTM or pose a risk to subject safety or stability during the study period. Other emotional problems or diagnoses may include, but are not limited to, other body-focused repetitive behaviors, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, compulsive gambling, borderline personality disorder, or antisocial personality disorder.

9. History of any injury, illness, or condition 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.

10. Laboratory evidence of renal impairment (e.g., a calculated creatinine clearance of < 80)

11. Presence of any substance use disorder or, in the opinion of the PI or designee, problematic substance use (excluding nicotine or caffeine) within the past 2 years prior to screening.

12. History of seizure disorder with the exception of subjects who have been off anti-seizure medication and have not had a seizure in the past 5 years.

13. Subjects with any of the following:

    a. Any psychiatric hospitalizations in the past year,

    b. Imminent risk of suicide based on PI's or designee's clinical judgment or psychiatric examination,

    c. Active suicidal ideation in the past 6 months as evidenced by positive endorsement to Item 4 or 5 on the C-SSRS,

    OR

d. Any history of suicidal behavior in the past year as evidenced by positive endorsement to any of the suicidal behavior items on the C-SSRS.

14. Has previously participated in any Promentis Phase 1 study.

15. Participation in another interventional clinical study (including CBT or other behavioral interventions) within 30 days prior to the first screening visit. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to the date of initiation of screening in the current study.

6.2.3 Restrictions

6.2.3.1 Cognitive Behavioral Therapy or Other Behavioral Interventions

Subjects engaged in CBT for TTM or other body-focused repetitive behavior or any obsessive-compulsive related or impulse control disorder any time within 60 days prior to first dose visit will not be included in the study. For other psychotherapies, subject must have been engaged in that psychotherapy for a minimum of 60 days at time of first dose and must be willing to maintain the same frequency and type of therapy for the duration of the study period.

Subjects who have initiated any other behavioral interventions (e.g., wearable devices, behavioral self- help strategies) within 60 days prior to first dose will not be included in the study.

6.2.3.2 Prior/Concomitant Medications

Except for SSRIs or SNRIs, the subject must not have used any psychoactive medications including, but not limited to, antidepressants, anxiolytics, mood stabilizers, anti-psychotics, benzodiazepines, stimulants, sulfasalazine, and St. John's Wort 30 days prior to first dose. Subjects will be allowed to maintain background therapy with SSRIs or SNRIs if on stable regimen for a minimum of 90 days prior to first dose and there are no anticipated changes to SSRI/SNRI during course of trial.

Examples include but are not limited to the following:

- SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone, and vortioxetine

- SNRIs: venlafaxine, desvenlafaxine, levomilnacipran, and duloxetine

Subjects who have used NAC within 90 days prior to the first dose will NOT be permitted in the study.

Certain over-the-counter/herbal psychoactive drugs may be allowable with medical monitor approval (e.g., melatonin).

Subjects should not have used gemfibrozil and repaglinide for 1 week prior to the first screening visit and may not use either of these medications during the course of the study.

6.2.3.3 Alcohol, Cannabinoids and Melatonin

Alcohol, cannabinoids and melatonin should not be used within 24 hours prior to all visits.

6.2.3.4 Contraceptive Requirements

Contraceptive requirements for male subjects are as follows:

- 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/placebo. (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/placebo. No restrictions are required for males with a medically documented history of biological or congenital sterility. 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).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 contraception for at least 3 months prior to the first dosing along with either a physical (e.g., condom, diaphragm) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study
    - IUD (either hormone-releasing or non-hormone releasing) for at least minimum duration per current labeling along with either a physical (e.g., condom, diaphragm) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study
    - Depo contraception for at least minimum duration per current labeling prior to the first dosing along with either a physical (e.g., condom, diaphragm) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study
    - Double physical barrier method (e.g., condom and diaphragm) from 14 days prior to the first dose and throughout the study.
    - Physical plus chemical barrier method (e.g., condom 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 30 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 with serum follicle stimulating hormone levels consistent with postmenopausal status or have medically documented history of biological or congenital sterility.

7 STUDY PROCEDURES

7.1 Screening Visit (Day −40 to Day 0)

A screening log documenting all assigned subject numbers must be maintained in real time in the electronic database and at the site. A copy will be filed in the Investigator Binder.

The following assessments/procedures will be performed at the Screening Visit. The screening assessments may be performed over multiple visits; however, all neurocognitive and other behavioral measurements must be performed at the same visit.

- Informed consent must be obtained before any other study assessments or procedures.
- Assessment of inclusion/exclusion criteria.
- Demographics and medical and psychiatric history will be recorded.
- Prior/concomitant medications taken within 90 days of the first screening visit will be recorded.
- A physical examination will be performed.
- Blood pressure and heart rate will be recorded after the study subject has been resting supine for ≥5 minutes. Respiratory rate and temperature may be taken at the same time.
- A 12-lead ECG will be completed after the study subject has been resting supine for ≥5 minutes.
- A urine sample will be collected for a urine drug screen.
- Safety laboratory tests (hematology, chemistry, coagulation, urinalysis) will be performed.
- Urine pregnancy tests will be performed in female subjects (females with confirmed sterility (e.g. oophorectomy) are excluded).
- The C-SSRS Screening version, MINI-TTM, BIS, MGH-HPS and CANTAB (training) will be completed.
- Subjects will be trained using the iPad device, which will be used for the PGI-S, PGI-C, CGI-S, and CGI-C assessments.

- Any AEs occurring after informed consent is obtained will be recorded. AEs occurring during screening and up to pre-dose Day 1 that are not procedure related will be captured and reported as medical history

- Subjects will be provided with an ePRO handheld device and will receive training on how to record TSD assessments daily. Subjects will use the ePRO device daily (evening before bedtime) to complete the TSD for a 7-day trial prior to the Day 1 Visit, and these assessments will serve as baseline assessments.

Prior to the subject's return to the site after the 7-day trial period, a review of the daily TSD assessments will be performed by site and study designee and, if not completed for all 7 days (or if not 100% compliant), site will review reasons for non-compliance to determine if further training and re-administration of the 7-day TSD assessment is needed. Medical monitor or designee approval is required if re-training and re-administration of the 7-day trial TSD period is needed.

If repeating the 7-day trial period requires an extension of the 40-day screening window, the screening window may be extended one time for an additional 10 days if the Medical monitor or designee approves.

If subjects have engaged in 5 or fewer days of hairpulling, they will not be included in the study. If the site believes that there were extenuating circumstances and the subject typically engages in daily hairpulling, a repeat of the 7-day run-in period may occur with medical monitor or designee approval.

7.1.1 Screen Failures

Subjects who sign an Informed Consent Form but are not randomized to the study must have a reason recorded as to why they were not enrolled in the study. This information will be recorded in the screening log maintained in the Investigator Binder.

7.1.2 Extension to the Screening Window

Subjects who are unable to complete required screening procedures during the 40-day screening window may be eligible for one 10-day extension of the screening period. Sites must receive approval from the medical monitor or designee for such an extension prior to the end of the initial screening period and no later than the Baseline/Day 1 visit.

7.1.3 Re-screening

Subjects may be re-screened 1 time if there is a change in the subject's medical or psychiatric status, a modification of study entry criteria, or other relevant change impacting eligibility (e.g., additional ePRO training requirement). Re-screening must be approved by the medical monitor or designee prior to the subject returning for re-entry screening visit.

7.2 Day 1

Subjects will arrive at the site on Day 1 and the following assessments/procedures will be completed:

Pre-dose

- The site will assess any changes in the subject's medical and psychiatric status or concomitant medications to confirm eligibility, prior to randomization.
- A urine sample will be collected for a urine drug screen.
- Urine pregnancy tests will be performed for female subjects (females with confirmed sterility (e.g. oophorectomy) are excluded).
- A blood sample will be collected for blood chemistry, coagulation, and hematology tests, and a urine sample will be collected for urinalysis.
- A blood sample will be taken for glutathione assessment.
- The following testing will be performed: PGI-S, CGI-S, MIST-A, and MGH-HPS. The PGI-S and CGI-S will be assessed on an iPad device at the site. In addition, the SST, CGT, RTI, and PAL will be completed on the Cambridge Neuropsychological Test Automated Battery (CANTAB) iPad device.
- C-SSRS SLV version

Treatment assignment and dosing

- After the above assessments have been completed, subjects will be randomized to receive SXC-2023 50 mg, 200 mg, or 800 mg or placebo.
- Wallet cards containing study drug (capsules) in blister packs will be distributed on site by qualified personnel to confirm dosing requirements and initial dose will be administered on site (see Section 9.2 for dosing procedures). Subjects will be provided with 3 weeks of capsules of blinded study treatment to maintain the daily dosage until the Week 3 visit, along with an extra wallet card containing one additional week of study drug to allow for the variance in the time windows throughout the remainder of the treatment period. Subjects will be instructed to bring all unused capsules when returning for the Week 3 visit for accountability.

Post-dose

- Subjects will be given instructions to continue to record the TSD assessments daily throughout the 6-week treatment period using the ePRO device. Subjects will record the first assessment in the evening of Day 1, regardless of what time of day the subject's visit took place. The assessments should be completed at the same time each day, in the evening before bedtime.
- Subjects will be instructed to take study drug daily, preferably in the morning. Subjects will also be instructed that each dose should be taken at least 1 hour prior to a meal or at least 2 hours after a meal. Subjects should take study drug with water; however, they may also take a bite of applesauce, gelatin dessert, yogurt, or other soft food to help swallow the capsules (see Section 9.2 for details).

- Any AEs will be recorded. Evaluation of AEs throughout the study should include assessment of changes in psychiatric symptoms, including changes in emotions, cognition, or behavior, to determine whether changes are clinically significant (e.g., onset or exacerbation of depressed mood) and possibly related to study drug.

7.3 Week 3 (Day 21 [±4 days])

Subjects will return to the site, and the following assessments and procedures will be done:

- An accounting of study drug doses brought in by the subject will be performed. Subjects will be provided with an additional 3 weeks of capsules of blinded study drug. They may use the extra capsules provided at Day 1 if needed to allow for the 4-day variance for the Week 6 visit. Subjects will be instructed to return all unused capsules when returning for the Week 6 visit. Subjects who have missed more than 5 consecutive doses or a total of 6 or more days of study drug administration will be dropped from the Per Protocol (PP) Population analyses and replaced. Subjects withdrawn from PP Population analyses for non-compliance will be given the option of completing the study, including continuing on study drug and completing assessments.

- If the subject used 4 or more days of medication from the additional wallet card given at Day 1, an additional wallet card will be provided to the subject.

- The TSD ePRO assessments will be reviewed prior to the completion of any Week 3 visit procedures. Five consecutive days or a total of 6 or more days of non-compliance with daily TSD completion will result in the subject being withdrawn from PP Population analyses and replaced. Subjects withdrawn from PP Population analyses for non-compliance will be given the option of completing the study, including continuing on study drug and completing assessments.

- A blood sample will be collected for blood chemistry, coagulation, and hematology tests, and a urine sample will be collected for urinalysis.

- The following scales also will be administered: C-SSRS SLV version, PGI-S/C (iPad device), CGI-S/C (iPad device), MGH-HPS, and MIST-A.

- Subjects will be reminded to continue the TSD ePRO assessments daily at approximately the same time each day (in the evening) and will be instructed to bring the device with them to the next visit.

- Any AEs and concomitant medications will be recorded. Evaluation of AEs should include assessment of changes in psychiatric symptoms, including changes in emotions, cognition, or behavior, to determine whether changes are clinically significant (e.g., onset or exacerbation of depressed mood) and possibly related to study drug.

7.4 Week 6 (Day 42 [±4 days])/Early Termination Visit

Subjects will return to the site, and the following assessments and procedures will be done:

- A blood sample will be taken for clinical laboratory tests (blood chemistry, coagulation,

and hematology), and a urine sample will be collected for urinalysis.

- A blood sample will be taken for glutathione assessment.
- A 12-lead ECG will be completed after the study subject has been resting supine for ≥5 minutes.
- The SST, CGT, RTI, and PAL will be completed on the CANTAB iPad device.
- The following scales also will be administered: PGI-S/C, CGI-S/C, MGH-HPS MIST-A, and C-SSRS. Note the PGI-S/C and CGI-S/C will be completed using the iPad device.
- The ePRO devices will be collected. Five consecutive days or a total of 6 or more days of non-compliance with daily TSD completion since Week 3 visit will result in the subject being withdrawn from PP Population analyses.
- Any returned study drug capsules will be collected and counted. Subjects who have missed more than 5 consecutive doses or a total of 6 or more days of study drug administration will be dropped from the PP Population analyses.
- Any AEs or concomitant medications will be recorded. Evaluation of AEs should include assessment of changes in psychiatric symptoms, including changes in emotions, cognition, or behavior, to determine whether changes are clinically significant (e.g., onset or exacerbation of depressed mood) and possibly related to study drug.

Note: If the subject terminates early, all of the assessments described above will be performed, with the following additions: physical examination, vital signs assessment, and urine pregnancy test (female subjects, subjects with confirmed sterility (e.g. oophorectomy) are excluded).

7.5 Follow-up (Day 56 [±4 days]), Week 8

Subjects will be asked to return to the site for a follow-up visit. The following assessments will be performed:

- A physical examination will be performed.
- Blood pressure and heart rate will be recorded after the study subject has been resting supine for ≥5 minutes. Respiratory rate and temperature may be taken at the same time.
- A blood sample will be taken for clinical laboratory tests (blood chemistry, coagulation, and hematology) and a urine sample will be collected for urinalysis.
- Urine pregnancy tests will be performed for female subjects (females with confirmed sterility (e.g. oophorectomy) are excluded).
- C-SSRS SLV version will be performed.

- Any AEs or concomitant medications will be recorded. Evaluation of AEs should include assessment of changes in psychiatric symptoms, including changes in emotions, cognition, or behavior, to determine whether changes are clinically significant (e.g., onset or exacerbation of depressed mood) and possibly related to study drug.

7.6 Unscheduled Visit

An unscheduled telephone contact may be performed at the discretion of the investigator at any time during the course of the trial.

An in-clinic unscheduled visit may be performed if a subject reports experiencing an AE via telephone contact or if the investigator has concerns about the subject's safety. An unscheduled visit may be performed at any time during the study at the discretion of the investigator. The assessments performed at unscheduled visits will be done at the investigator's discretion and results must be recorded in the electronic case report form (eCRF).

7.7 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.

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. Complete AE form and attempt to follow the event until it is resolved or deemed stable. Subjects withdrawn prior to the Week 3 visit may be replaced.
Subject Request	Subject withdraws consent. If reason is provided, explain in comments on Subject Disposition CRF.
Protocol Deviation	Investigator wishes to terminate the subject from study treatment due to a protocol deviation. Site monitor or Sponsor should be contacted before making decision. Comments/rationale should be documented in source documents. Subjects withdrawn prior to the Week 3 visit may be replaced.
Missed Doses	Subjects who have missed more than 5 consecutive doses or a total of 6 or more days of study drug administration will be dropped from PP Population analyses (and replaced if observed at Week 3). However, the subject would have the option of completing the study.
ePRO Non-compliance	Five consecutive days or a total of 6 or more days of non-compliance with daily TSD completion will result in the subject being withdrawn from PP Population analyses (and replaced if observed at Week 3). However, the subject would have the option of completing the study.

Lost to Follow-Up	Subject does not return for scheduled visits. 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). The site should make at least 3 attempts to contact the subject. If not reached, the subject will be documented as "lost to follow-up." Subjects lost to follow-up prior to the Week 3 visit may be replaced.
Other	Any other reason for early subject withdrawal from study treatment or the study. Explain in comments. Subjects withdrawn from study prior to the Week 3 visit may be replaced.

AE=adverse event; CRF=case report form; ePRO=electronic Patient Reported Outcome; TSD=Trichotillomania Symptom Diary

Subjects withdrawing prematurely after taking study drug must undergo the assessments described in Section 7.4. All study data from withdrawals must be retained and forwarded to the Sponsor. When an 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.

7.8 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).

8 CRITERIA FOR EVALUATION

8.1 Safety Evaluation

8.1.1 Medical History, Demographic and Other Baseline Information

Medical history:

- General medical/psychiatric/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.
- AEs that occur between time of consent and dosing that are not procedure related will be captured as past medical history.

Medication history:

- Information on all medications (investigational products, prescription, over-the-counter [OTC], and herbal medications) taken within the 90 days prior to the first

screening visit.

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])

8.1.2 Physical Examination

A full physical examination will be performed as per the Schedule of Events (Appendix A). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

8.1.3 Vital Signs

The following vital signs will be measured during the study:

- Blood pressure (systolic and diastolic [mmHg])
- Heart rate (beats per minute)
- Respiratory rate (breaths for minute)
- Temperature

Single measurements of blood pressure, heart rate, respiratory rate, and temperature 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 will be used for all measurements.

8.1.4 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 QT corrected by Fridericia's formula (QTcF) interval.

All ECGs must be interpreted by a qualified physician for the presence of abnormalities. Any clinically significant ECG abnormality will be recorded as an AE. 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.

8.1.5 Clinical Laboratory Tests

Blood and urine samples will be collected for routine clinical laboratory testing (hematology, chemistry, coagulation, 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 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.

- If a clinically significant abnormality is found in the samples taken after treatment, it should be recorded as an AE and the study subject will be followed until the test(s) has (have) normalized or stabilized.

- Subjects with evidence of renal impairment (e.g. cCrCl <80) will NOT be allowed into the study.

Blood sampling, processing, and storage instructions will be provided in a laboratory manual. Hematology, chemistry, coagulation, urinalysis, and urine drug screens will be assessed by a central laboratory. A local laboratory will be used to assess pregnancy tests.

The following laboratory parameters will be reported:

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count, leukocyte count with differential, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and absolute platelet count

- 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

- Coagulation: international normalized ratio, prothrombin time, activated partial thromboplastin time

- Urine Pregnancy Test (in female subjects): Females with confirmed sterility (e.g. oophorectomy) are excluded.

- 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 will screen for the following: amphetamines, barbiturates, benzodiazepines, cocaine (metabolite), methadone screen, opiates, phencyclidine, and propoxyphene.

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

8.1.6 Adverse Events

For detailed information on collection, definition, categorization, and reporting of AEs/SAEs during the study, refer to Section 10.

AEs will be monitored, and the following information recorded:

- Standard medical terminology
- Whether the event was a TEAE
- Whether event was an 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

8.1.7 Prior and Concomitant Medications

Site personnel should document any medications (prescription and OTC, including herbal medications and vitamins) the subject received within 90 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 and/or discontinuation (if applicable). The concomitant medication names will be coded according to the World Health Organization Drug Dictionary (WHODD) and classified by anatomical therapeutic chemical categories.

8.1.8 Columbia-Suicide Severity Rating Scale

The C-SSRS will be used to evaluate suicidal ideation/behavior at times indicated in Appendix A.

8.2 Neurocognitive and Other Behavioral Measurements

The following measures will be assessed during the study:

8.2.1 Mini-International Neuropsychiatric Interview, version 7.0.2 with Trichotillomania and Body Dysmorphic Disorder Modules

The MINI-TTM will be used at screening.

8.2.2 Barratt Impulsiveness Scale

The BIS will be employed to capture trait impulsivity at screening. The scale is presented in Appendix E.

8.2.3 Cambridge Neuropsychological Test Automated Battery

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. The PAL and RTI will be used to assess visual memory and motor/mental response speed, respectively. These assessments are described in further detail in Appendix F.

8.2.4 Massachusetts General Hospital Hairpulling Scale

The MGH-HPS will be performed to assess TTM symptoms at times indicated in Appendix A. The scale is presented in Appendix G.

8.2.5 Patient Global Impression of Status/Change

Subjects will use the iPad device to complete the PGI-S and PGI-C at the times indicated in Appendix A.

Two PGI-S items will assess TTM severity from the subject's perspective. The PGI-S items employ 5-point graded response scales and are as follows:

- How would you rate your trichotillomania symptoms now?
  0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe

- How much control do you feel you have over your trichotillomania symptoms now? 0 = Complete control, 1 = Quite a bit of control, 2 = A moderate amount of control, 3 = A little control, 4 = No control

Two PGI-C items (Lydick and Yawn, 1998; Cappelleri et al., 2014) will assess change in TTM severity from the subject's perspective and are as follows:

- Compared to the start of this study, how would you rate your trichotillomania symptoms now?

0 = Much better, 1 = Moderately better, 2 = A little better, 3 = About the same, 4 = A little worse, 5 = Moderately worse, 6 = Much worse

- Compared to the start of this study, how would you rate the strength of your urges to pull hair now?
  0 = Much weaker, 1 = Moderately weaker, 2 = A little weaker, 3 = About the same, 4 = A little stronger, 5 = Moderately stronger, 6 = Much stronger

8.2.6 Clinical Global Impression of Severity/Change

The CGI-S and CGI-C will be completed by the clinician using the iPad device at times indicated in Appendix A.

The CGI-S (Guy, 1976) is a single-item rating that asks the clinician to evaluate the severity of the subject's illness on a 7-point ordinal scale:

"Considering your total clinical experience with this particular population, how ill is the patient at this time? (1 = Normal, not at all ill; 2 = Borderline ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients)."

The CGI-C (Guy, 1976; Spearing et al., 1997) is a single-item rating that asks the clinician to evaluate the extent to which the subject's symptoms have changed since baseline on a 7-point ordinal scale:

"Compared to his/her condition at the baseline/Day 1 visit, how much have the patient's trichotillomania symptoms changed? (1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse."

8.2.7 Milwaukee Inventory of Subtypes of Trichotillomania – Adult Version

The MIST-A (Flessner et al., 2008) will be used to assess automatic and focused pulling subtypes at the times indicated in Appendix A. The scale is presented in Appendix H.

8.2.8 Trichotillomania Symptom Diary

The ePRO device will be used by subjects to complete the TSD at home, every 24 hours for the 7 days during the screening period (baseline) and every day during the treatment period. Subjects will be instructed to complete the TSD assessment in evening. At Week 3, 5 consecutive days or a total of 6 or more days of non-compliance with TSD completion will result in the subject being withdrawn from the Per Protocol Population analyses and replaced. At Week 6, 5 consecutive days or a total of 6 or more days of non-compliance with TSD completion since the Week 3 visit will also result in the subject being withdrawn from Per Protocol Population analyses.

The scale is presented in Appendix D.

8.3 Glutathione Blood Collection

Whole 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.

9 TEST ARTICLE AND ADMINISTRATION

9.1 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 will take 4 capsules of blinded study drug daily.

Capsules will be supplied in blister packs within a wallet card. 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.

9.2 Study Drug Administration

Subjects will be administered study drug at the clinical site at the Day 1 visit. 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.

The remaining doses will be self-administered by the subject every day for approximately 6 weeks outside the clinic. Subjects will be instructed to take the dose at approximately the same time each day, preferably in the morning. Subjects will be instructed that each dose should be taken at least 1 hour prior to a meal and at least 2 hours after a meal. Subjects will be instructed to take study drug with water. If needed, subjects may also take a bite of applesauce, gelatin dessert, yogurt, or other soft food to help with swallowing the capsules. However, they should not fill the stomach with soft foods, and the site should request that they try water first.

9.3 Study Drug Accountability and Destruction

The Sponsor will supply sufficient quantities of blinded study drug 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.

Subjects will be supplied with an appropriate amount of study drug at the Day 1 and Week 3 visits to complete the planned doses and allow for variances in the study schedule. At Day 1, subjects will receive 4 weeks of study drug doses and at Week 3, subjects will receive 3 weeks

of study drug doses. The extra week of study drug provided at Day 1 will be used if needed to allow for time variances in the visit schedule throughout the treatment period. Subjects returning at the Week 3 visit who have used 4 or more days of study drug from the additional wallet card given at the Day 1 visit will be administered an additional wallet card. Subjects will be asked to bring all unused capsules at Week 3 and Week 6. Study site staff will record the number of capsules dispensed and number returned at each applicable visit.

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.

9.4 Blinding

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

9.5 Randomization

Subjects will be randomized in a 1:1:1:1 ratio to SXC-2023 50 mg, 200 mg, or 800 mg or placebo QD for approximately 6 weeks. The randomization will be stratified by whether the subject is receiving SSRI/SNRIs as the time of randomization. This stratification is to ensure balance among the treatment groups with respect to the number (%) subjects receiving these medications. There is no minimum requirement for the number of subjects with (or without) SSRIs/SNRIs in this study.

9.6 Missed Doses

Subjects who miss more than 5 consecutive doses or 6 or more total days of study drug prior to or as assessed at the Week 3 visit will be dropped from PP Population analyses and replaced after subject completes the Week 3 assessments. Subjects withdrawn from analyses for non-compliance will be given the option of completing the study, including continuing on study drug and completing assessments. Subjects who miss more than 5 consecutive doses or 6 or more total days of study drug prior to or as assessed at the Week 6 visit will be dropped from PP Population analyses but not replaced after completion of Week 6 assessments.

9.7 Dose Suspension

The PI may decide to suspend study drug in the case of an AE or concerns about the subject's safety. Dose suspensions initiated via a telephone contact should be followed by an in-clinic visit (either scheduled or unscheduled visit) as soon as possible. Subjects with dose suspensions of 5 or fewer consecutive days can resume study drug, per PI discretion; however, if more than 1 dose suspension is required during the course of the trial, medical monitor approval is required prior to resuming study drug. Subjects who require a dose suspension of longer than 5 days will also require medical monitor approval to resume study drug.

9.8 Medication Errors

Any study drug administration or usage that is not in accordance with study protocol should be reported as a protocol deviation and any comments/rationale should be documented in the subject's source documents, regardless of whether an adverse event (AE) results. Unintentional medication errors should be evaluated to provide appropriate correction and retraining as needed. Intentional medication errors (e.g., intentional misuse or abuse) should be discussed with the medical monitor to determine if subject should be withdrawn from the study.

9.9 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 consumes more IP than per protocol, the subject will be instructed to contact the site. Gastrointestinal reaction is anticipated, and the subject should be clinically followed for 48 hours.

10 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. 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?"

AEs occurring during screening and pre-dose Day 1 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).

Evaluation of AEs should include assessment of changes in psychiatric symptoms, including changes in emotions, cognition, or behavior, to determine whether changes are clinically significant (e.g., onset or exacerbation of depressed mood) and possibly related to study drug.

Cases of pregnancy that occur during the study or up to 30 days following last dose of study drug should be reported. 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. that result in a diagnosis should be reported to Promentis or its designee and included as part of the subject's medical history. After first dose of study drug, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Promentis or designee. The PI will be

instructed to report to Promentis or its designee their assessment of the potential relatedness of each AE to protocol procedure and/or study drug via CRF.

10.1 Definition

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

A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.

When an 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.

10.2 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

10.3 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 orfor 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.

10.4 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.

10.5 Serious Adverse Events

10.5.1 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 10.6 in case of pregnancy.

10.5.2 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 and to Syneos Health Safety 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 or email copy of the SAE form plus other related information.

A Sponsor Designee will contact you 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

Robert Leadbetter, MD
Medical Director
Syneos Health
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Email: robert.leadbetter@syneoshealth.com

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Fax: +1-877-464-7787
Email: safetyreporting@syneoshealth.com

10.5.3 Follow-up

All additional follow-up evaluations must be reported to the medical monitor and Syneos Health Safety. 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.

10.6 Pregnancy

If a pregnancy does occur, 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 normaldelivery 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.

11 STUDY ADMINISTRATION

11.1 Ethics

11.1.1 Institutional/Independent Review Board

This protocol and all appropriate amendments will be reviewed by an institutional/independent 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).

11.1.2 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).

11.1.3 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 informed consent form 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 informed consent form. The requirements of informed consent are provided in Appendix B.

11.2 Termination of the Study

Promentis reserves the right to terminate the study in the interest of subject welfare.

11.3 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.

11.4 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.

11.5 Data Handling and Record Keeping

Standard CRFs will be supplied. CRFs are printed off directly from the database. Each CRF is reviewed and signed by the PI.

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.

11.6 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).

11.7 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 only by the Sponsor or in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

12 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 prepared bySyneos Health and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications will be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed. These additions or changes to planned analyses will be documented in the SAP.

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.

12.1 Determination of Sample Size

The primary objective of this study is to explore the safety and tolerability of SXC-2023 in adults with TTM when dosed for a period of 6 weeks. The sample size of this study (30 per group) was determined by reviewing other studies in this disease area and early stage of drug development (Chamberlain et al., 2018; Julious, 2010; Chow et al., 2008; Machin et al.,1997; Zar et al., 1984). The planned sample size of 30 per dose group is 80% powered to detect an effect size of 0.70 (Cohen's d=0.70). This effect size for change in MGH-HPS total score corresponds to a change in the MGH-HPS of approximately 4 units (Grant et al., 2009). An effect size of 0.7 is in the range of 0.5 (medium) to 0.8 (large) effects.

12.2 Analysis Populations

ITT Population (FAS): All subjects randomized to study drug will be included in the ITT population/full analysis set (FAS).

Per Protocol (PP) Population: All subjects randomized to study drug and with no major protocol deviations will be included in the PP Population. The PP population will be used for the descriptive analyses of the neurocognitive and other behavioral tests.

Safety Population: All subjects who receive a dose of the study drug will be included in the safety population. Safety summaries will use the safety population.

12.3 Statistical Analysis

12.3.1 Subject Disposition

The number of screen failures, subjects enrolled, completed, or discontinued from the study and the reason for study discontinuation will be tabulated by treatment group. The number of discontinued subjects will be broken down by treatment period of the study. Subject count by analysis population will be tabulated. Screen failures with reason for screen failure will be summarized.

12.3.2 Protocol Deviations

Protocol deviations will be categorized as major or minor. Major deviations will be summarized by treatment group and type (reason) of deviation. Decisions regarding major/minor deviations will be determined by medical, data management and statistical review prior to database lock, as these deviations determine inclusion/exclusion in the PP population.

Protocol deviations (both major and minor) will be included in the listings.

12.3.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be listed and summarized by treatment group and overall.

12.3.4 Safety Analysis

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

Safety 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 safety 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.

12.3.4.1 Adverse Events

AEs will be collected after the first dose in the AE page of the CRF. AEs occurring during screening through pre-dose Day 1 that are not procedure related will be captured and reported as medical history. TEAEs will be defined as AEs with a start date after the first dose of the study drug. 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).

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 Medical Dictionary for Regulatory Activities® (MedDRA®) (most recent version) 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.

12.3.4.2 Other Safety Assessments

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

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 non-missing value obtained before randomization. Clinically significant clinical laboratory abnormalities will be reported and included in the AE tabulations.

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

Screening and Week 6 ECGs will be summarized descriptively.

The C-SSRS results will be summarized descriptively.

12.3.4.3 Concomitant Medications

Concomitant medications will be coded using the most current WHODD and summarized by ATC code. All reported concomitant medications will be provided by randomized treatment group.

12.3.5 Analysis of Neurocognitive and Other Behavioral Measurements

An efficacy outcome measure of focus is the MGH-HPS (Keuthen et al., 1995). The MGH-HPS is a 7-item self-report scale that rates urges to pull hair, actual amount of pulling, perceived control over the behavior, and distress associated with hair pulling in the past 7 days on severity scale from 0 to 4 for each item (total scores range from 0 to 28, with higher scores reflecting greater disease severity. Overall changes in the MGH-HPS and changes in MGH-HPS sub-factor 1 and sub-factor 2 scale scores will be analyzed. The percentage of subjects experiencing clinically significant change versus those not experiencing clinically significant changes based on CGI-S/CGI-C and the PGI-S/PGI-C will be compared using Fisher's Exact Test.

Results of the BIS, SST, CGT, RTI, PAL, MGH-HPS, PGI-S/C, CGI-S/C, MIST-A, and TSD will be summarized descriptively by treatment.

Change from baseline for MGH-HPS, PGI-S/C, CGI-S/C, MIST-A, and TSD will be analyzed using linear mixed models using treatment, SSRI/SNRI strata, visit, treatment by visit interaction as factors. 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. Multiple imputation methods may be explored to determine the impact of missing responses. Supportive analysis of covariance models for the change from baseline at Week 3, Week 6, and the last available post-baseline value will be used. Estimates of treatment effect (least squares means with 95% confidence intervals) will be obtained.

For SST, CGI, RTI, and PAL (collected only at Baseline and Week 6), analysis of covariance models for the change from baseline at Week 6 will be used. Estimates of treatment effect (least squares means with 95% confidence intervals) will be obtained.

For the neurocognitive and other behavioral measurements, the primary analyses will use the PP Population. Subjects who miss more than 5 consecutive doses or a total of 6 or more days of study drug prior to or as assessed at the Week 3 visit will be dropped from PP Population analyses and replaced. Subjects withdrawn from analyses for non-compliance will be given the option of completing the study, including continuing on study drug and completing assessments. Subjects who miss more than 5 consecutive doses or 6 or more total days of study drug prior to or as assessed at the Week 6 visit will be dropped from PP Population analyses but not replaced.

Five consecutive days or a total of 6 or more days of non-compliance with daily TSD completion at either the Week 3 or between the Week 3 and Week 6 visits will result in the subject being withdrawn from PP Population analyses (and replaced if observed at Week 3).

Analyses may be repeated using the FAS.

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

Results will be presented with no adjustment for multiplicity.

12.3.6 Analysis of Glutathione Concentrations

Glutathione levels will be summarized descriptively.

13 REFERENCES

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* 5th ed. Washington, DC: American Psychiatric Association; 2013. 251-254.

Cappelleri JC, Zou KH, Bushmakin AG, Alvir JMJ, Alemayehu D, Symonds T. Patient-reported outcomes — measurement, implementation, and interpretation. London: Chapman& Hall/CRC; 2014.

Chamberlain SR, Menzies LA, Fineberg NA, Del Campo N, Suckling J, Craig K et al. Grey matter abnormalities in trichotillomania: morphometric magnetic resonance imaging study. *Br J Psychiatry.* 2008;193(3):216-21.

Chamberlain SR, Hampshire A, Menzies LA, Garyfallidis E, Grant JE, Odlaug BL et al. Reduced brain white matter integrity in trichotillomania: a diffusion tensor imaging study. *Arch Gen Psychiatry.* 2010;67: 965–971.

Chamberlain SR, Odlaug BL, Boulougouris V, Fineberg N, Grant JE. Trichotillomania: advances in neurobiology and treatment. *Neurosci Biobehav Rev.* 2018. In press.

Chow SC, Shao J, Wang H. Sample Size Calculations in Clinical Research (Second Edition). Chapman & Hall/CRC. Boca Raton, FL: 2008.

Flessner CA, Woods DW, Franklin ME, Cashin SE, Keuthen NJ. The Milwaukee Inventory for Subtypes of Trichotillomania-Adult Version (MIST-A): development of an instrument for the assessment of "focused' and "automatic" hair pulling. *J Psychopathol Behav Assess.* 2008; 30:20-30.

Grant JE and Chamberlain SR. Trichotillomania. *Am J Psychiatry*. 2016;173 (9), 868-874.

Grant JE, Odlaug BL, and Kim SW. *N*-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania. *Arch Gen Psychiatry.* 2009;66(7):756-763.

Guy W. ECDEU assessment manual for psychopharmacology (United States Department of Health, Education, and Welfare Publication No. 76-338). Rockville MD: National Institute of Mental Health, 218-22; 1976.

Julious SA. Sample Sizes for Clinical Trials. Chapman & Hall/CRC. Boca Raton, FL: 2010.

Keuthen NJ, O'Sullivan RL, Ricciardi JN, Shera D, Savage CR, Borgmann AS, Jenike MA, Baer L. The Massachusetts General Hospital (MGH) Hair Pulling Scale, 1: development and factor analyses. *Psychother Psychosom*. 1995; 64(3-4):141-145.

Lydick E, Yawn BP. Clinical interpretation of health-related quality of life data. In: Staquet MJ, Hays RD, Fayers PM, eds. Quality of life assessment in clinical trials — methods and practice. New York: Oxford University Press; 1998; 299-314.

Machin D, Campbell M, Fayers P, Pinol A. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, MA: 1997.

Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin

Psychol. 1995; 5 (6):768-74.

Roos A, Grant JE, Fouche JP, Stein DJ, and Lochner C. A comparison of brain volume and cortical thickness in excoriation (skin picking) disorder and trichotillomania (hair pulling disorder) in women. *Behav Brain Res.* 2015; 279: 255-258.

Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): The CGI-BP. *Psychiatry Res.* 1997; 73(3): 159-71.

SXC-2023 Investigator's Brochure, Version 6.0; 2019.

Zar JH. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey: 1984.

APPENDIX A SCHEDULE OF EVENTS

Procedures	Screening	Treatment			Follow Up/ET
		Baseline	Week 3	Week 6	Week 8
	Day -40 to Day 0	Day 1	Day 21 ±4 days	Day 42 ±4 days	±4 days
Informed consent	X				
Inclusion/exclusion criteria	X				
Reconfirm eligibility[2]		X (pre)			
Demographics	X				
Medical and psychiatric history	X	X (pre)			
Physical exam	X				X
Vital signs (BP, HR, RR, and temperature)	X				X
Electrocardiogram	X			X	
Urine drug screen	X	X (pre)			
Safety labs (blood chemistry)	X	X (pre)	X	X	X
Safety labs (hematology)	X	X (pre)	X	X	X
Safety labs (coagulation)	X	X (pre)	X	X	X
Safety labs (urinalysis)	X	X (pre)	X	X	X
Urine pregnancy (females)[4]	X	X (pre)			X
MINI-TTM	X				
Columbia-Suicide Severity Rating Scale	X	X	X	X	X
CANTAB (SST, CGT, RTI, PAL)	X (training)	X (pre)		X	
Barratt Impulsiveness Scale	X				
MGH-HPS	X	X (pre)	X	X	
PGI-S	X (training)	X (pre)	X	X	
PGI-C			X	X	
CGI-S		X (pre)	X	X	
CGI-C			X	X	
MIST-A		X (pre)	X	X	
Glutathione blood sample		X (pre)		X	
Study drug dispensing/accountability		X	X	X	
TSD	X[3] (Training and 7 day run-in period)	Every 24 hours			
Adverse events	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X

Abbreviations: BP=blood pressure; CANTAB= Cambridge Neuropsychological Test Automated Battery; CGI-S/C=Clinical Global Impression of Severity/Change; CGT=Cambridge Gambling Task; HR=heart rate; MGH-HPS=Massachusetts General Hospital Hairpulling Scale; MINI-TTM=Mini-International Neuropsychiatric Interview, version 7.0.2 with Trichotillomania and Body Dysmorphic Disorder modules; MIST-A=Milwaukee Inventory of Subtypes of TTM-Adult Version; PAL=Paired Associates Learning: PGI-S/C=Patient Global Impression of Status/Change; pre=pre-dose; RR=respiratory rate; RTI=Reaction Time; SST=Stop Signal Task; TSD=Trichotillomania Symptom Diary.

[1] The screening period may be extended by 10 days on a case-by-case basis with medical monitor or designee approval. The screening assessments may be split across multiple visits; however, the screening neurocognitive and other behavioral assessments must be done at the same visit.
[2] On Day 1, the site will review any changes in medical/psychiatric history or concomitant medications to confirm eligibility in the study.
[3] ePRO: Training (Day 0) will be performed on site. After all of the screening assessments are complete, the subject will be instructed to complete the TSD at home every 24 hours (evening) for a 7-day run-in period within the screening window.
[4]Subjects with confirmed sterility (e.g. oophorectomy) are excluded.

Notes:
Subjects who terminate early will be asked to return for the Week 6 assessments along with the following: physical examination, vital signs assessment, and urine pregnancy test (female subjects).
Unscheduled visits may be performed at the Investigator's discretion. Assessments performed at unscheduled visits will be done at the investigator's discretion and results must be recorded in the electronic case report form.

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 thesubject.
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 thestudy.

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 anytime."

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 legallyeffective.

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, and chemistry)	5	7.2	36
Glutathione whole blood sample	2	6	12
		Total Blood Volume (mL)→	**48**

APPENDIX D TRICHOTILLOMANIA SYMPTOM DIARY

CONFIDENTIAL

ePRO: Trichotillomania Symptom Diary

The following questions listed in question #s 1-4, ask about hair pulling associated with trichotillomania. For each question, please provide a response that best describes your feelings and experiences in the PAST 24 HOURS to the best of your ability.

1. **In the past 24 hours, approximately how much time (total) did you spend pulling hair from your body?**

   ☐ Did not pull hair at all (in the last 24 hours) **[Skip to Question 3]**
   ☐ Spent less than 1 minute pulling hair
   ☐ Spent at least 1 minute but less than 1 hour pulling hair

o Please enter total amount of time:_____minute(s)

   ☐ Spent at least 1 hour pulling hair

      o Please enter total amount of time:_____hour(s) and _____ minute(s)

2. **In the past 24 hours, approximately how many episodes of hair pulling did you have? Please count only different periods of time you spent pulling hair (rather than counting individual hairs you pulled).**

   _____episodes

3. **In the past 24 hours, approximately how many times did you feel an urge to pull hair from your body? Please include every time you felt an urge to pull hair whether or not you actually pulled.**

   _____times [If never, please enter 0 here and skip question 4.]

4. **In the past 24 hours, approximately how many times were you able to resist an urge to pull hair from your body?**

   _____times [If none, please enter 0.]

APPENDIX E BARRATT IMPULSIVENESS SCALE

Note: this is a sample provided to indicate content only.

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.

	Rarely/Never	Occasionally	Often	Almost Always/Always
1 I plan tasks carefully.				
2 I do things without thinking.				
3 I make-up my mind quickly.				
4 I am happy-go-lucky.				
5 I don't "pay attention."				
6 I have "racing" thoughts.				
7 I plan trips well ahead of time.				
8 I am self controlled.				
9 I concentrate easily.				
10 I save regularly.				
11 I "squirm" at plays or lectures.				
12 I am a careful thinker.				
13 I plan for job security.				
14 I say things without thinking.				
15 I like to think about complex problems.				
16 I change jobs.				
17 I act "on impulse."				
18 I get easily bored when solving thought problems.				
19 I act on the spur of the moment.				
20 I am a steady thinker.				
21 I change residences.				
22 I buy things on impulse.				
23 I can only think about one thing at a time.				
24 I change hobbies.				
25 I spend or charge more than I earn.				
26 I often have extraneous thoughts when thinking.				
27 I am more interested in the present than the future.				
28 I am restless at the theater or lectures.				
29 I like puzzles.				
30 I am future oriented.				

Patton, Stanford, Barratt (1995). *J Clin Psy*, vol. 51, pp. 768-774

APPENDIX F CAMBRIDGE NEUROPSYCHOLOGICAL TEST AUTOMATED BATTERY

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.

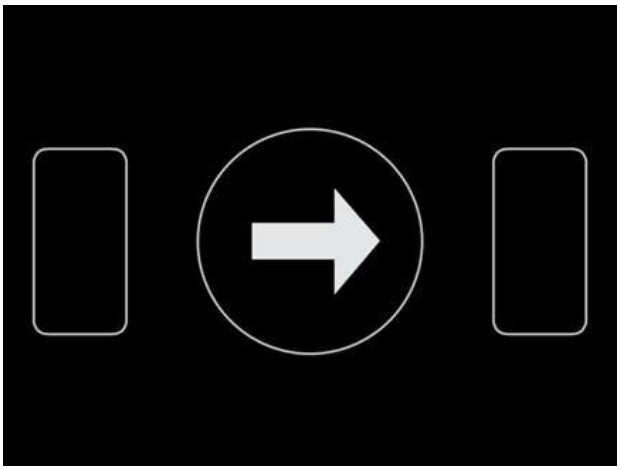
The RTI task includes a practice phase (10 trials) followed by the assessed phase. The voiceover reminds the subject that they should go as quickly as they can whilst trying to avoid making any mistakes. 30 assessed trials are then presented.

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

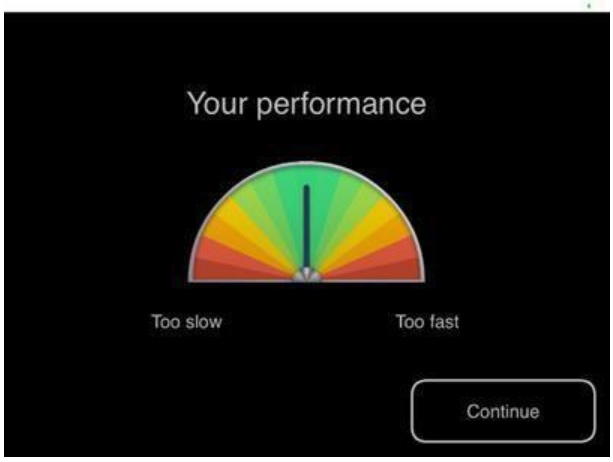
Stop Signal Task (SST)

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.



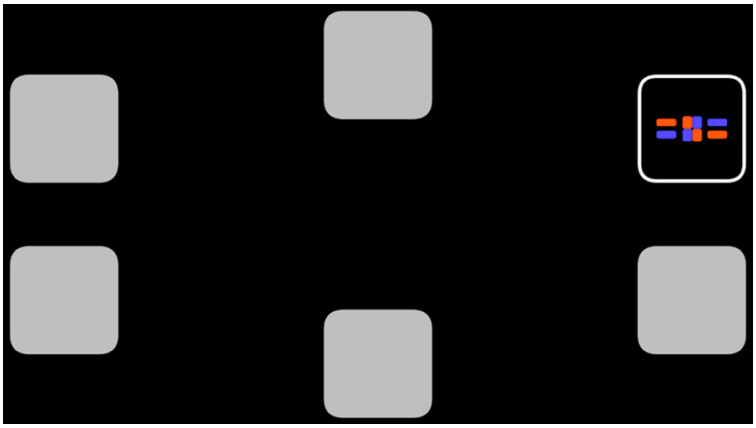
The assessed phase with the stop signal (tone) is presented in 4 blocks. At the end of each assessed block, a graphic representing the participant's performance is shown on screen. Depending on the participant's performance on the previous block the participant is encouraged to either go faster or slower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

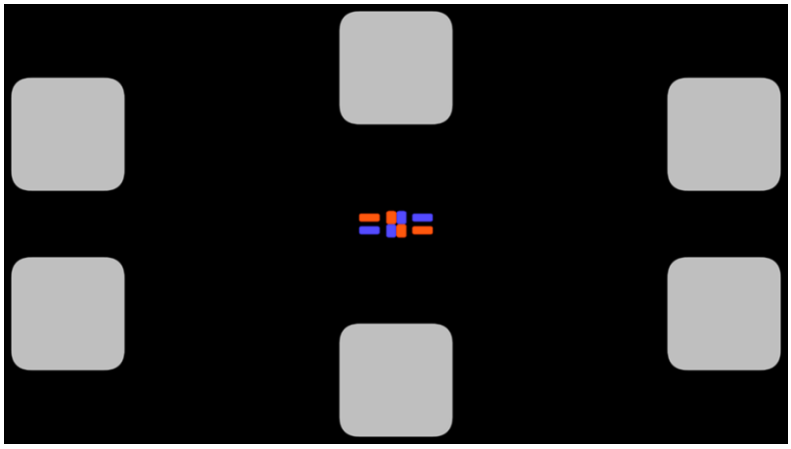


The time between the arrow being shown on screen, and the delay interval between the participant hearing the tone (Stop Signal Delay (SSD)) is varied throughout the task.

Paired Associates Learning (PAL)

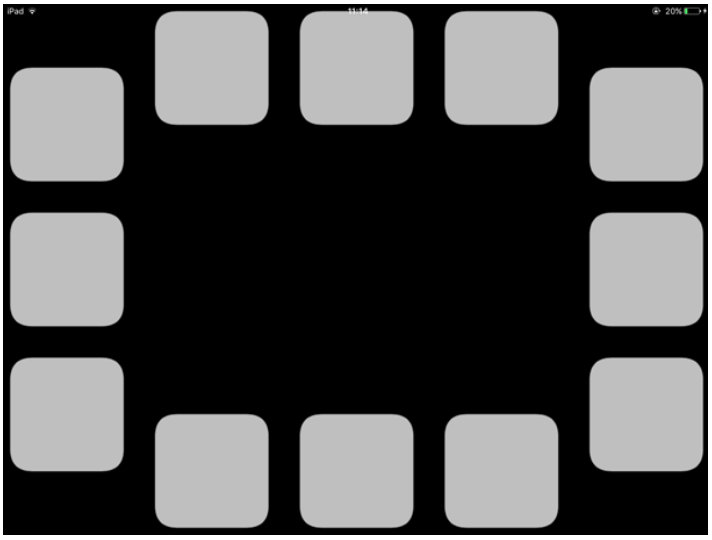
The Paired Associates Learning task consists of a number of stages, which the subject must complete in order. For each stage, boxes are displayed on the screen. These boxes are opened one at a time, in a randomised order. Two or more of the boxes will contain a pattern. The patterns shown in the boxes 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.





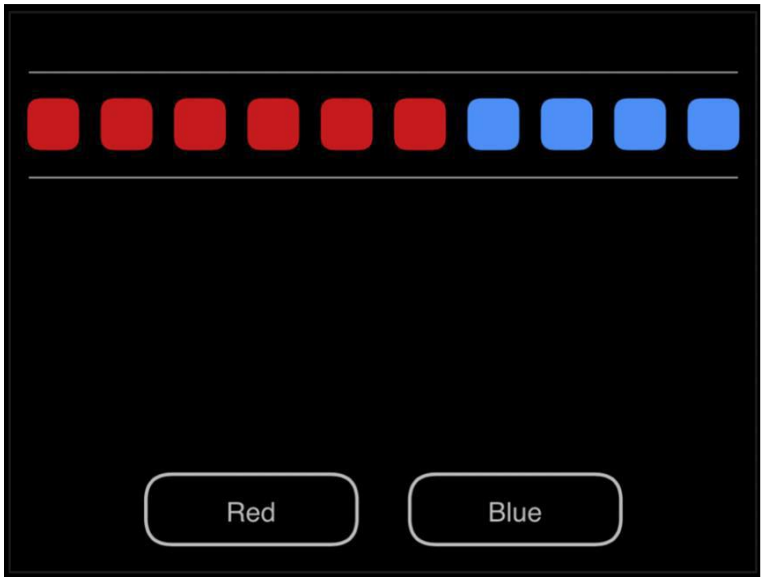
When the participant successfully identifies the correct box for all of the patterns the test moves to the next level. The PAL test gradually becomes more difficult with the number of boxes that contain a pattern increasing from 2 trials with 2 boxes that contain a pattern, 1 trial with 4 patterns, 1 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)

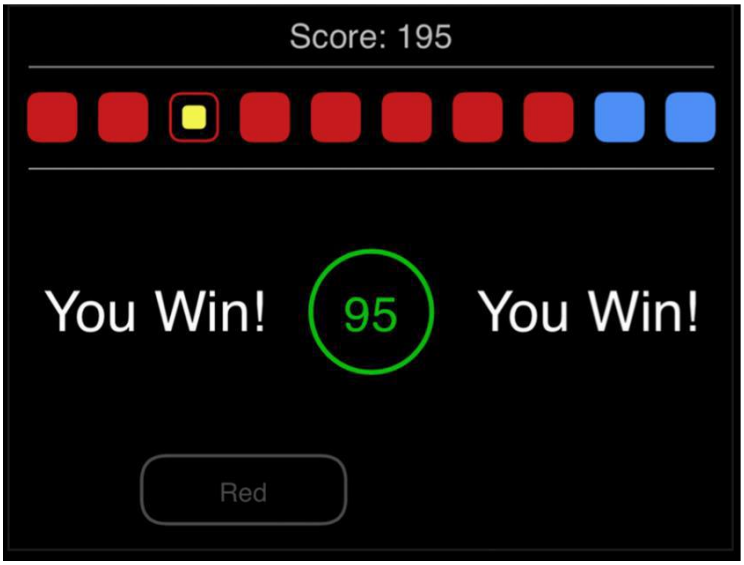
The participant is presented with a row of 10 color squares at the top of the screen. Some of the squares are blue in color others red. Beneath these colored squares are two buttons, one labelled red and the other blue. The participant is informed that a yellow token is hidden in one of the colored boxes. 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 G MASSACHUSETTS GENERAL HOSPITAL HAIRPULLING SCALE

Note: this is a sample provided to indicate content only.

Name:_____ Date:_____

Instructions: For each question, pick the one statement in that group which best describes your behaviors and/or feelings over the past week. If you have been having ups and downs, try to estimate an average for the past week. Be sure to read all the statements in each group before making your choice.

For the next three questions, rate only the urges to pull your hair.

1. **Frequency of urges.** On an average day, how often did you feel the urge to pull your hair?
   - 0 This week I felt no urges to pull my hair.
   - 1 This week I felt an **occasional** urge to pull my hair.
   - 2 This week I felt an urge to pull my hair **often.**
   - 3 This week I felt an urge to pull my hair **very often.**
   - 4 This week I felt **near constant** urges to pull my hair.

2. **Intensity of urges.** On an average day, how intense or "strong" were the urges to pull your hair?
   - 0 This week I did not feel any urges to pull my hair.
   - 1 This week I felt **mild** urges to pull my hair.
   - 2 This week I felt **moderate** urges to pull my hair.
   - 3 This week I felt **severe** urges to pull my hair.
   - 4 This week I felt **extreme** urges to pull my hair.

3. **Ability to control the urges.** On an average day, how much control do you have over the urges to pull your hair?
   - 0 This week I could **always** control the urges, or I did not feel any urges to pull my hair.
   - 1 This week I was always able to distract myself from the urges to pull my hair **most of the time.**
   - 2 This week I was able to distract myself from the urges to pull my hair **some of the time.**
   - 3 This week I was able to distract myself from the urges to pull my hair **rarely.**
   - 4 This week I was **never** able to distract myself from the urges to pull my hair.

For the next three questions, rate only the actual hairpulling.

4. **Frequency of hairpulling.** On an average day, how often did you actually pull your hair?
   - 0 This week I did not pull my hair.
   - 1 This week I pulled my hair **occasionally.**
   - 2 This week I pulled my hair **often.**
   - 3 This week I pulled my hair **very often.**
   - 4 This week I pulled my hair so often it felt like I was **always** doing it.

5. **Attempts to resist hairpulling.** On an average day, how often did you make an attempt to stop yourself from actually pulling your hair?
   - 0 This week I felt no urges to pull my hair.
   - 1 This week I tried to resist the urge to pull my hair **almost all of the time.**
   - 2 This week I tried to resist the urge to pull my hair **some of the time.**
   - 3 This week I tried to resist the urge to pull my hair **rarely.**
   - 4 This week I **never** tried to resist the urge to pull my hair.

6. **Control over hairpulling.** On an average day, H6ow often were you successful at actually stopping yourself from pulling your hair?
   - 0 This week I did not pull my hair.
   - 1 This week I was able to resist pulling my hair hair **almost all of the time.**
   - 2 This week I was able to resist pulling my hair **most of the time.**
   - 3 This week I was able to resist pulling my hair **some of the time.**
   - 4 This week I was **rarely** able to resist pulling my hair.

For the last question, rate the consequences of your hairpulling.

7. **Associated distress.** Hairpulling can make some people feel moody, "on edge," or sad. During the past week, how uncomfortable did your hairpulling make you feel?
   - 0 This week I did not feel uncomfortable about my hairpulling.
   - 1 This week I felt **vaguely uncomfortable** about my hairpulling.
   - 2 This week I felt **noticeably uncomfortable** about my hairpulling.
   - 3 This week I felt **significantly uncomfortable** about my hairpulling.
   - 4 This week I felt **intensely uncomfortable** about my hairpulling.

Scoring the Massachusetts General Hospital (MGH) Hairpulling Scale

In scoring the MGH Hairpulling Scale, each item is scored on a 5-point scale from 0 = no symptoms to 4 = severe symptoms. The item scores are summed to produce a total score (range 0 to 28).

Citation: Keuthen NJ, O'Sullivan RL, Ricciardi JN, Shera D, Savage CR, Borgmann AS, Jenike MA, Baaer L. The Massachusetts General Hospital (MGH) Hairpulling Scale: 1. Development and Factor Analyses. Psychotherapy and Psychosomatics 64:141-145, 1995.

APPENDIX H MILWAUKEE INVENTORY OF SUBTYPES OF TRICHOTILLOMANIA – ADULT VERSION

Note: this is a sample provided to indicate content only.

The Milwaukee Inventory for Styles of Trichotillomania–Adult Report

Please choose a number which best represents how the question fits your hair-pulling behavior.

0 —— 1 —— 2 —— 3 —— 4 —— 5 —— 6 —— 7 —— 8 —— 9

not true for any of my pulling — true for about half of my pulling — true for all of my pulling

1.	I pull my hair when I am concentrating on another activity.	0
2.	I pull my hair when I am thinking about something unrelated to hair pulling.	0
3.	I am in an almost "trance-like" state when I pull my hair.	0
4.	I have thoughts about wanting to pull my hair before I actually pull.	0
5.	I use tweezers or some other device other than my fingers to pull my hair.	0
6.	I pull my hair while I am looking in the mirror.	0
7.	I am usually not aware of pulling my hair during a pulling episode.	0
8.	I pull my hair when I am anxious or upset.	0
9.	I intentionally start pulling my hair.	0
10.	I pull my hair when I am experiencing a negative emotion, such as stress, anger, frustration, or sadness.	0
11.	I have a "strange" sensation just before I pull my hair.	0
12.	I don't notice that I have pulled my hair until after it's happened.	0
13.	I pull my hair because of something that has happened to me during the day.	0
14.	I pull my hair to get rid of an unpleasant urge, feeling, or thought.	0
15.	I pull my hair to control how I feel.	0

Scoring Instructions

Add your scores for questions 4–6, 8–11, and 13–15. This total represents the level of your focused pulling. Add your scores for questions 1–3, 7, and 12. This total represents the level of your automatic pulling. The higher the score, the more you are engaging in that particular type of hair pulling.

Source: Flessner, C. A., Woods, D. W., Franklin, M. E., Cashin, S. E., Keuthen, N. J., and the Trichotillomania Learning Center Scientific Advisory Board. (In press). The Milwaukee Inventory for Subtypes of Trichotillomania-Adults (MIST-A): Development, exploratory factor analysis, and psychometric properties. *Journal of Psychopathology and Behavioral Assessment.*

Douglas W. Woods, Michael P. Twohig