Statistical Analysis Plan for Interventional Studies

Sponsor Name: Promentis Pharmaceuticals, Inc.

Protocol Number: PRO-201

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

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Authors: Michael L. White, Principal Statistician

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I confirm that I have reviewed this document and agree with the content.

Approvals		
Syneos Health Approval		
Michael L. White, MS, Principal Biostatistician	Michael L White	24-JAN-2020
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
Vipul Devas, PhD, Senior Director, Biostatistics	Vipul	24 Jan 2020
Name, Title	Signature	Date (DD-Mmm-YYYY)
Promentis Pharmaceuticals Approval		
Daniel Lawton President		23-JAN-2020
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BIS	Barratt Impulsiveness Scale
BMI	Body Mass index
BP	Blood Pressure
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBT	Cognitive Behavioral Therapy
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CGT	Cambridge Gambling Task
CI	Confidence Interval
cm	centimeter
CrCl	Creatinine clearance
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ePRO	Electronic Patient Report Outcome
F	Fahrenheit
GCP	Good Clinical Practice
GSH	Glutathione
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identifier
ITT	Intent-to-Treat
kg	kilograms
lb.	pounds

Abbreviation	Description
Max	Maximum
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MGH-HPS	Massachusetts General Hospital Hairpulling Scale
Min	Minimum
MINI	Mini-International Neuropsychiatric Interview
MINI-TTM	Trichotillomania and Body Dysmorphic Disorder modules
MIST-A	Milwaukee Inventory of Subtypes of TTM - Adult Version
mmHG	millimeters mercury
MMRM	Mixed Model with Repeated Measures
MOP	Manual of Operations
NA	Not Applicable
PAL	Paired Associates Learning
PGI-S	Patient Global Impression of Severity
PGI-C	Patient Global Impression of Change
PI	Principal Investigator
PP	Per Protocol
PPS	Per Protocol Set
PT	Preferred Term
Q1	Lower quartile
Q3	Upper quartile
QC	Quality Control
QD	once per day
QTc	Corrected QT Interval
RTI	Reaction Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	serum creatinine
SD	Standard Deviation
SE	Standard Error

Abbreviation	Description
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
SSRI	Selective serotonin re-uptake inhibitors
SNRI	Serotonin-norepinephrine reuptake inhibitors
SST	Stop Signal Task
TEAE	Treatment Emergent Adverse Event
TFL	tables, figures, data listings
TSD	Trichotillomania Symptom Diary
TTM	Trichotillomania
WHO	World Health Organization
WT	Weight

2. Purpose

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 trichotillomania (TTM).

The purpose of this statistical analysis plan (SAP) is to describe the statistical analyses that will be performed and to ensure that data listings, summary tables and figures which will be produced, and the statistical methodology that will be used, are pre-specified, complete and appropriate to allow valid conclusions regarding the study objectives. This version of the SAP is based on Amendment 3 of the Protocol, dated 25 Jun 2019.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings except those tables, figures, and listings related to the Cambridge Neuropsychological Test Automated Battery (CANTAB) endpoints. The following endpoints will be analyzed by Cambridge Cognition:

- Stop Signal Task (SST)
- Cambridge Gambling Task (CGT)
- Reaction Time Index (RTI)
- Paired Associates Learning (PAL)

A separate SAP will be produced by Cambridge Cognition describing the analysis of these endpoints.

2.2. Timings of Analyses

The primary analysis of safety and tolerability of SXC-2023 in adults with TTM is planned after all subjects complete the final study visit or terminate early from the study, the database is locked, evaluability decisions are made, and the treatment identifiers unblinded.

3. Objectives

3.1. Primary Objective

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

3.2. Secondary Objective(s)

- 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.

3.3. 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 Inventory of Subtypes of TTM - Adult Version [MIST-A]).
- To test the effects of SXC-2023 on whole blood glutathione levels.

3.4. Brief Description

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 (run-in period) during the screening period. The run-in period may be repeated, if necessary.

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).

Safety will be evaluated via reports of adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, the Columbia Suicide Severity Rating Scale (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).

Table 1: Neurocognitive and other behavioral measurements (in addition to daily TSD completion) will include the following:

	Screening	Baseline (Day 1)	Week 3	Week 6	Week 8
Barratt Impulsiveness Scale (BIS)	X				
Clinical Global Impression of Change (CGI-C) [C]			X	X	
Clinical Global Impression of Severity (CGI-S) [C]		X	X	X	
CANTAB assessments (Cambridge Gambling Task (CGT), Paired Associates Learning (PAL), Stop Signal Task (SST), and Reaction Time Interval (RTI) [C]		X		X	
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X
Massachusetts General Hospital Hairpulling Scale (MGH-HPS)	X	X	X	X	
Mini-International Neuropsychiatric Interview (MINI)	X				
Mini-International Neuropsychiatric Interview Trichotillomania and Body Dysmorphic Disorder modules (MINI-TTM)	X				
Milwaukee Inventory of Subtypes of TTM - Adult Version (MIST-A)		X	X	X	
Patient Global Impression of Change (PGI-C) [C]			X	X	
Patient Global Impression of Severity (PGI-S) [C]		X	X	X	
Trichotillomania Symptom Diary (TSD)[d e]	X	X	X	X	

Note: [C] = completed using the iPad device, [d]= daily, [e]= completed using the iPhone device (ePRO)

During the screening period, all subjects will undergo evaluation for eligibility. The subjects will be randomly assigned on Day 1 to 1 of the following 4 treatment arms in a 1:1:1:1 ratio:

- 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.

3.5. Subject Selection

Inclusion and exclusion criteria are shown in the following sections:

3.5.1. Inclusion Criteria

Under Amendment 1, the following inclusion criteria were used. 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, sulfasalazine, and over the counter/herbal psychoactive drugs (e.g., melatonin, St. John's Wort), for 30 days prior to first screening visit. 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.
5. Has not used NAC for at least 90 days prior to the first screening visit.
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:
    - Hormonal contraception and non-hormone releasing intrauterine device used for at least 3 months prior to the first dosing and with either a physical (e.g., condom, diaphragm, or other) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study.
    - Double physical barrier method (e.g., condom and diaphragm) 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.

Under Amendment 2, the following were the 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.

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

5. Has not used N-acetylcysteine (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 lifestyle) 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 and non-hormone releasing intrauterine device used for at least 3 months prior to the first dosing and with either a physical (e.g., condom, diaphragm, or other) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study. Depo or implant contraception after minimum duration per current labeling.

• Double physical barrier method (e.g., condom with spermicide and diaphragm with spermicide) from 14 days prior to the first dose and throughout the study.

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

Under Amendment 3, the following were the 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.

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

5. Has not used N-acetylcysteine (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 lifestyle) 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

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.

3.5.2. Exclusion Criteria

The following were the exclusion criteria for **Amendment 1**.

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 30 days prior to first screening visit. For other psychotherapies, subject must have been engaged in that psychotherapy for a minimum of 4 weeks at time of first screening visit and must be willing to maintain the same frequency and type of therapy for the duration of the study period.
3. Subjects engaged in any other behavioral interventions (e.g., wearable devices, behavioral self-help strategies) within 60 days of the first screening visit.
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 primary 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. 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.
11. 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.
12. Subjects with any of the following:
    - Any psychiatric hospitalizations in the past year,
    - Imminent risk of suicide based on PI's or designee's clinical judgment or psychiatric examination,
    - Active suicidal ideation in the past 6 months as evidenced by positive endorsement to Item 4 or 5 on the C-SSRS, OR
    - 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.
13. Has previously participated in any Promentis Phase 1 study.
14. 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.

The following are the exclusion criteria under **Amendment 2**.

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 engaged in 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 primary 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 creatine 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.

The following are the exclusion criteria under **Amendment 3**.

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 engaged in 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 primary 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 creatine 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.

3.6. Determination of Sample Size

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. 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. An effect size of 0.7 is in the range of 0.5 (medium) to 0.8 (large) effects.

3.7. Treatment Assignment & 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.

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.

3.8. Administration of Study Medication

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.

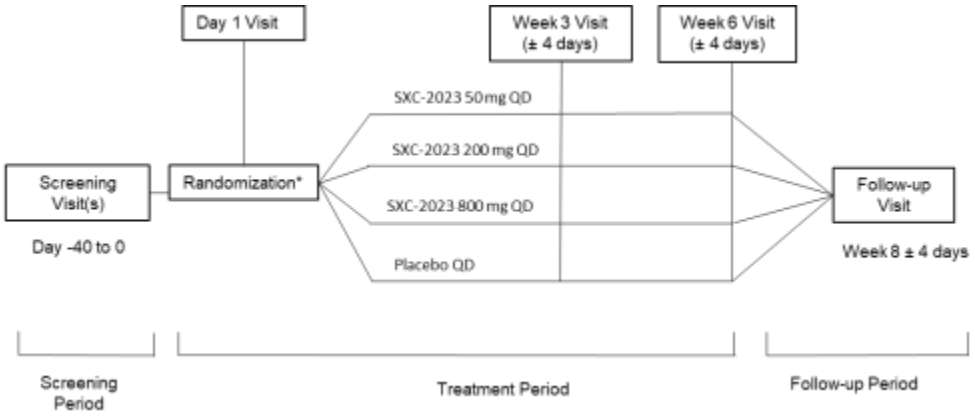
Subjects will be administered study drug at the clinical site at the Day 1 visit. The SXC-2023 or placebo dose will be administered with water. Qualified personnel will administer study drug. After dosing, unit personnel will perform a hand and mouth check to ensure the subjects have swallowed the dose administered. The remaining doses will be self-administered by the subject every day for approximately 6 weeks outside the clinic.

Subjects will be 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.

3.9. Study Procedures and Flowchart

The following diagram of the study design is copied from Figure 1 of the protocol.

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.

The schedule of procedures is copied from Appendix A of the protocol.

APPENDIX A SCHEDULE OF EVENTS

	Screening[1]	Treatment			Follow-up/ET
		Baseline	Week 3	Week 6	Week 8
Procedures	**Day -40 to Day 0**	**Day 1**	**Day 21 +/- 4 days**	**Day 42 +/- 4 days**	**Day 56 +/- 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)	X	X (pre)			X
MINI-TTM	X				
Columbia-Suicide Severity Rating Scale	X	X (pre)	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 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 the baseline TSD assessments and 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 complete the TSD at home every 24 hours (in the evening) for a 7-day run-in period within the screening period

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.

4. Endpoints

4.1. TSD-Related Efficacy Endpoints

The TSD-Related efficacy endpoints are:

- Average frequency of hairpulling episodes (episodes/day)
- Maximum number of hairpulling episodes per day
- Average minutes per day spent pulling hair
- Maximum minutes per day spent pulling hair
- Average number of episodes per day where subject felt the urge to pull hair
- Maximum number of episodes per day where subject felt the urge to pull hair
- Average number of episodes per day where subject resisted the urge to pull hair
- Maximum number of episodes per day where subject resisted the urge to pull hair

4.2. Other Efficacy Endpoints

- Change from baseline in MGH-HPS
- CGI-S
- CGI-C
- PGI-S
- PGI-C

4.3. Exploratory Endpoints

- Change from baseline in SST
- Change from baseline in CGT
- Change from baseline in RTI
- Change from baseline in PAL
- Change from baseline in MIST-A
- Change from baseline in blood glutathione (GSH) levels

Cambridge Cognition will be responsible for the analysis of the SST, CGT, RTI, and PAL CANTAB neurocognitive assessments.

4.4. Safety Endpoints

Outcome measures that have been established as clinically relevant for assessing the safety and tolerability of SXC-2023 in adults with TTM:

- Incidence of adverse events (AEs)
- Incidence of serious adverse events (SAEs) and AEs leading to withdrawal

- Changes in vital signs (blood pressure [BP], temperature, respiration rate, and heart rate [HR])
- Change from baseline in clinical laboratory tests (hematology, chemistry, coagulation, and urinalysis)
- Change from baseline in electrocardiogram (ECG) parameters
- C-SSRS

5. Analysis Sets

5.1. Enrolled Set

The Enrolled Set will include all subjects screened and assigned a user subject number. Unless specified otherwise, this set will be used for subject listings and for summaries of subject disposition.

5.2. Randomized Set

The Randomized Set will include all subjects randomized to a treatment group.

5.3. Safety Set

The Safety Set (SS) will include all subjects who were administered at least one dose of study medication. Subjects will be analyzed according to treatment received. The SS will be used for all analyses of safety endpoints.

5.4. Intent-to-Treat (Full Analysis Set)

The Intent-to-Treat (ITT) Set will include all randomized subjects. The ITT Set will be used for all analyses of efficacy endpoints.

5.5. Per Protocol or Evaluable Sets

Two different Per Protocol sets will be defined for the study. The first population will be called Per Protocol Set One (PPS One). It will include randomized subjects who have completed the Week 6 visit of the study and have no important protocol deviations. Subjects who have missed a total of 6 days of study drug administration at the Week 3 visit will be dropped from the Per Protocol (PP) Population analyses and replaced. Subjects who have missed a total of 6 days of study drug administration between the Week 3 and Week 6 visits will be dropped from the Per Protocol (PP) Population analyses. Subjects will be analyzed according to randomized treatment. This population will be used for all efficacy endpoints, except those associated with the TSD-related endpoints. Correlation summaries that involve efficacy endpoints not associated with the TSD-related endpoints will also use this population.

The second population will be called the Per Protocol Diary Set (PPS Diary). It will be a subset of the subjects in the PPS One Set. Subjects in the PPS Diary Set will include those subjects with at least 4 valid diary collections in each of 5 weeks (not necessarily consecutive) from Week 1 through Week 6. A valid diary day will be a diary where the actual collection time is collected from 6 hours prior to expected collection time to 24 hours after the expected collection time. The expected collection date/time will be based on the date of randomization with expected time on each day as 9:00 pm (i.e. 21:00 hours). Section 6.2.4 contains the formula used to determine the expected diary collection date/time.

The PPS Diary set will be used for the analysis of TSD-related efficacy endpoints.

5.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization (ICH) Good Clinical Practices (GCP), or MOP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. Protocol deviations will be categorized as major or minor by the sponsor. Categorization will be finalized at a blinded data review meeting prior to database lock and unblinding. 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 PPS.

In addition to site level deviations, individual subject level protocol deviations may include (but are not limited to) the following:

- Deviations from inclusion/exclusion criteria
- Deviations from randomization criteria or procedures
- Devotions involving administration of study medication
- Noncompliance with other study procedures
- Use of prohibited concomitant medications
- Subject not discontinued in accordance with protocol requirements
- Missing essential data
- Deviations from assessment windows
- Other noncompliance

Multiple deviations can occur in the same subject and thus a subject can be counted in more than 1 deviation category.

Major protocol deviations that are thought to affect the evaluation of efficacy and/or safety (important deviations) will lead to exclusion of subjects from the PPS One.

6. General Aspects for Statistical Analysis

6.1. General Methods

The following conventions will be utilized in the analyses:

- The final statistical analysis will not be performed until all the reportable data have been collected, queries answered, and the database locked.
- As the study is early phase and the objectives are exploratory, additional analyses of outcomes, including correlations between endpoints, additional versions of outcomes determined from the TSD, and subset analyses may be performed.
- All relevant individual subject data will be provided in data listings sorted by treatment arm and subject number. Summaries will be presented by treatment group and overall. Treatment group labels will be displayed as follows;

Placebo QD	SXC-2023 QD 50 mg	SXC-2023 QD 200 mg	SXC-2023 QD 800 mg

Overall columns are to be included within the table shells as follows:

Disposition	Treatment and overall
Demography	Treatment and overall
Baseline	Treatment and overall
Efficacy	Treatment
AEs	Treatment
Other safety	Treatment

Where subjects who were not randomized are included in listings, the treatment arm will be indicated as "Not Randomized".

- Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. All tabular summaries will be presented by treatment arm as indicated above. A total column may be included under "All Subjects" where necessary or appropriate.
- In general, continuous variables will be summarized by descriptive statistics including the number of observations (n), mean, standard deviation (SD) or standard error (SE), median, minimum (min), and maximum (max); the lower (Q1) and upper quartile (Q3) may be included in some summaries if deemed necessary or important. The same number of decimal places as the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean, median, lower and upper quartiles, and 2 more decimal places than in the raw data will be presented when reporting SD or SE.
- Categorical data will be summarized using the number of observations (n), frequency, and percentage of subjects in the relevant analysis set and treatment group falling within each category.

- For numerical variables, change from baseline will be calculated as the value of interest at the time of measurement minus the corresponding baseline value.
- Confidence intervals (CI) will be 2-sided and have 95% confidence level. They will be considered exploratory.
- P-values will not be presented, as the study is considered exploratory.
- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.
- Data analyses will be conducted using validated computer software (e.g. SAS® Version 9.4 or higher).
- Adverse events and medical history terms will be coded using the most recent MedDRA Version 21.1.
- Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) Global March 2018 version.

6.2. Key Definitions

6.2.1. Baseline

Unless otherwise specified, baseline is defined as the last observed value of the parameter of interest prior to the first intake of study medication (this includes unscheduled visits). Definitions of baseline for specific efficacy and/or safety parameters are provided in relevant sections where those parameters are defined and their analysis methods described.

Unless otherwise specified, where there are multiple measurements at a post-baseline visit or time of assessment, the value closest to the target date within the specified window for the assessment visit will be used for analysis.

For numerical variables, change from baseline will be calculated as the value of interest at the time of measurement minus the corresponding baseline value.

6.2.2. Study Day

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. Study days used in the subject listings are calculated from Study Day 1.

For Study days on or after the date of treatment start, Study Day will be calculated as:

Study day = Assessment date – First dose date + 1

For study days prior to dosing, Study Day will be calculated as:

Study day = Assessment date – First dose date

There is no Study Day 0.

6.2.3. Extent of exposure

Extent of exposure is defined as the last dose date of the study drug – First dose date + 1

Extent of exposure will be categorized at weekly levels as:

- 1 -7 days

- 8-14 days
- 15-21 days
- 22-28 days
- 29-35 days
- 36-42 days
- 43-49 days
- 50-57 days
- > 57 days

6.2.4. Expected Diary Collection Date/Time

For the TSD Diary data, the post-baseline diaries are recorded with a visit label as: "Diary Day X", where the X is ≥ 1. Included in each diary collection is the actual date / time the subject recorded the data.

The SAS formula for expected collection date/time for Diary Day X is:

ADTM = DHMS (RANDDT + (X-1), 21, 0, 0). This is 09:00 pm on the diary day. As an example, the expected diary collection date/time on Diary Day 1 is 09:00 pm on the date of randomization.

The elapsed time difference will be calculated using the actual collection date/time and the expected date/time of collection.

6.2.5. Study Period

This study has 3 periods: a 4-week screening period (maximum days 40 days), with a Daily ePRO TSD assessment for a 7-day period and possible 7-day repeat run-in period prior to the administration of study medication on Day 1; a 6-week treatment period (Day 1 to Week 6); and a 2 weeks follow-up period.

Table 2: Treatment periods

Period	Start	End	Maximum Duration
Screening	Visit 1 date	Day 1 (Baseline) date - 1	40 days
Double-blind Treatment	Day 1 (Baseline)	Day 43/EOT date - 1	50 days
Follow-up	Day 43/EOT date	Week 8 Visit	18 days

6.3. Missing Data

6.3.1. Medical History Diagnosis Dates

If the onset date of the diagnosis is only partially available, the first of the month will be imputed for any missing days and January will be imputed for any missing months. Imputed dates will not be presented in the data listings.

6.3.2. Medication Dates

For prior and concomitant medications with incomplete dates, the following rules will be used to impute start and/or stop dates for the purposes of determining if a medication is prior or concomitant only. Imputed dates will not be presented in the data listings.

For partial start dates:

- If day is missing, and the month and year match the month and the year of the first dose date, the day of the first dose date will be imputed. Otherwise, the first of the month will be used.
- If month is missing and the year matches the year of the first dose date, the month and the day of the first dose date will be imputed. Otherwise, January will be used.
- If the start date is completely missing, the start date will not be imputed. If the stop date is after first dose date, the medication will be considered to be both prior and concomitant. If the stop date is prior to the first dose date, the medication will be considered to be prior only.
- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

For partial stop dates:

- For stop dates, if the day is missing, then the last day of the month will be used.
- If the month is missing, then December will be used.
- If the stop date is completely missing or there is indication that the medication is ongoing, then the date of last study visit will be used.

6.3.3. Adverse Events

The following rules will be used to impute start and/or stop dates for adverse events with incomplete dates, in order to determine whether an AE is treatment-emergent or not. Imputed dates will not appear in the data listings.

Adverse events with partial start dates:

- If AE start day is missing, and the month and year match the month and the year of the first dose date, the day of the first dose date will be imputed and the AE will be considered treatment-emergent. Otherwise, the first of the month will be used and the treatment-emergent status will be assessed relative to the dosing start date.
- If AE start month is missing, and the year matches the year of the first dose date, the month and the day of the first dose date will be imputed, and the AE will be considered treatment-emergent. Otherwise, January will be used and the treatment-emergent status will be assessed relative to the dosing start date.
- If the AE start date is completely missing, the AE will be considered treatment-emergent unless the stop date is complete or provides enough partial information to rule out a treatment-emergent status.

- If the AE stop date is complete and the imputed AE start date is after the AE actual stop date, then the AE start date will be imputed as the AE stop date.

Any missing severity assessments for AEs will be imputed as "severe" for summary purposes.

Any missing relationship to study medication will be considered "related" for summary purposes.

6.3.4. Efficacy Assessments

TSD Diary Response Imputation

On a TSD when the subject has responded to the first question, "In the past 24 hours, approximately how much time (total) did you spend pulling hair from your body?" with "Did not pull hair at all", the response to the second question "In the past 24 hours, approximately how many episodes of hair pulling did you have?" will be imputed as 0.

On a TSD when the subject has responded to the third question "In the past 24 hours, approximately how many times did you feel an urge to pull hair from your body?" as 0, the response to the 4th question "In the past 24 hours, approximately how many times were you able to resist an urge to pull hair from your body?" will be imputed as 0.

Missing data may arise due to subjects missing some assessments (intermittent missingness), or as a result of subject dropouts and not being available for subsequence assessments (monotone missingness).

Intermittent missing efficacy assessment values prior to subjects discontinuing study medication will not be imputed.

No imputation of data for missing data due to dropouts will be implemented in the efficacy analyses. The primary analysis via the general linear model with random effects (also called Mixed Model with Repeated Measures (MMRM)) uses all available data and assumes that the missing data due to dropouts are missing at random (MAR).

A descriptive analysis of percentage of days with missing DSD, and the percentage of DSD collections with categorized difference from expected collection date/time categorized, will be presented to assess the compliance with the DSD collection. The denominator for the calculation of the percentage will be the number of days between the first and last diary day. The maximum number of missed days per week along with the maximum number of consecutive missed diary days per week will be presented.

6.4. Visit Windows

All data will be summarized according to the scheduled visit and time points as outlined in the protocol and by the visit denoted on the electronic case report form (eCRF). Premature withdrawal (PW) visits will be assigned to the nearest scheduled visit based on the study day of occurrence relative to the target day of each scheduled visit according to the following Table.

Table 3: Visit Windows for Assigning Visits to an Analysis Visit for Neurocognitive and Other Behavioral Measurements

Study Period	Analysis Visit	Target Day	Window for Reassignment to Analysis Visit
Baseline	Baseline (Day 1)	1	≤1
Treatment Period	Week 3 (Day 21)	21	2-25
	Week 6/EOT	42	26-46

Table 4: Visit Windows for Assigning Visits to an Analysis Visit for Safety Labs

Study Period	Analysis Visit	Target Day	Window for Reassignment to Analysis Visit
Baseline	Baseline (Day 1)	1	≤1
Treatment Period	Week 3 (Day 21)	21	2-25
	Week 6/EOT	42	26-46
Follow-up Period	Week 8/EOS	66	47-60

6.5. Subgroups

Efficacy endpoints will be summarized using the SSRI/SNRI strata.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

Subject disposition will be summarized as follows;

- The number of subjects screened and re-screened, number and percent of screen failures and reason for screen failures will be provided for overall. The denominator for the percent of screen failures will be the number screened.
- The number of completers, and number who withdraw from the study during the Treatment Period and reasons for withdrawal from study medication be summarized by treatment group using the safety population.
- For subjects enrolled but not randomized to treatment and for the reasons for not being randomized the denominator used to calculate the percentage will be the number of enrolled subjects. For all other calculations the denominator will be the number of subjects randomized.
- The number of subjects in each analysis population (Enrolled, Safety, Randomized, ITT, and Per Protocol) will also be summarized.
- The number of subjects screened, screen failed, randomized will be provided by site
- The number of subjects present at each scheduled visit will be summarized by treatment group for the safety set.

Subject disposition will be presented overall and by treatment group.

All subject disposition data will be listed using the Safety Set and sorted by treatment assigned, subject ID, and site.

7.2. Demographic and Other Baseline Characteristics

The following demographic characteristics will be summarized for the Safety set:

- Age [years]
- Sex
- Race
- Ethnicity
- Height [cm]
- Weight [kg]
- BMI [kg/m^2]
- Childbearing potential (yes/no)
- SSRI/SNRI use (yes/no)

Age will be calculated in elapsed years from the date of birth to the date of screening visit.

Weight will be converted to kilograms (kg) when reported in pounds (lbs) as follows: Weight (in kg) = weight (in lbs) * 0.4536.

Height will be converted to centimeters (cm) when reported in inches (in) as follows: Height (in cm) = height (in inches) * 2.54/100.

The results of the Mini-International Neuropsychiatric Inventory with Trichotillomania and Body Dysmorphic Disorder Modules (MINI-TTM) will be summarized using the Safety set.

All subject demographics data and MINI-TTM, will be listed for the Enrolled set.

7.3. Medical History and Concomitant Diseases

Medical history information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1, summarized and presented overall and by treatment group for the Safety Set. Summaries will be ordered alphabetically by system organ class (SOC) and then, within a SOC, alphabetically by preferred term (PT).

The number and percentage of subjects will be displayed for each System Organ Class and Preferred Term within treatment group.

7.4. Prior and Concomitant Medication

Medications/therapies will be coded using World Health Organization Drug Dictionary (WHO-DD) Global March 2018 version. Concomitant medications are defined as medications taken on or after the date of first dose of study drug. Summaries of prior, concomitant medications, and prohibited medication use will be carried out using the Safety Set.

Medications/therapies will be summarized and sorted alphabetically separately for prior and concomitant medications/therapies by Anatomical Therapeutic Chemical (ATC) categories (Level 3: chemical or therapeutic or pharmacological subgroup) and WHO-DD preferred drug name. For each medication the number and percentage of subjects will be displayed. Subjects will be counted only once for each medication class and each preferred drug name.

Prior and concomitant medications/therapies will be listed together with a designation to identify the medications/procedure as prior and/or concomitant and sorted by start date.

The following algorithm will be used to define prior and concomitant medications. The same medication may be prior as well as concomitant if it is used before and after study medication initiation.

Medications/therapies can be prior only, concomitant only, or prior and concomitant, depending on the start and stop dates.

Any medication/therapy whose start and stop dates were before the start of study medication will be considered as prior.

Any medication/therapy initiated after commencement of study medication will be regarded as being only concomitant.

Any medication/therapy that is ongoing or has a stop date on or after the first dose date will be considered a prior and concomitant medication/therapy.

Medications/therapy that were initiated before study medication was started and ended during or after the study will be considered as prior and concomitant.

A medication/therapy will be assumed to be prior if it cannot be definitively shown that the medication/therapy did not start or continue during the treatment period.

8. Efficacy

The efficacy analyses are based on the secondary and exploratory objectives of the study. This section will describe the efficacy endpoints and how they will be analyzed and presented.

The secondary objective of this study is 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]) and to provide preliminary psychometric evidence of the reliability, validity, and responsiveness of the newly developed TSD assessment.

The primary analyses of the efficacy parameters will be performed on the PPS One or PPS Diary. The efficacy analyses will be repeated on the Full Analysis Set in order to assess the impact of protocol deviations on the inference of the efficacy parameters.

8.1. Efficacy Endpoint and Analysis

8.1.1. Trichotillomania Symptom Diary

8.1.1.1. Definition of Estimates for Weekly Hair Pulling

The ePRO device will be used by subjects to complete the TSD at home, every 24 hours during a 7-day screening period (baseline) and every day during the treatment period. Subjects will be instructed to complete the TSD assessment in evening.

On each day, the subject provides:

- The number of hours and minutes per day spent pulling hair,
- The number of episodes of hair pulling,
- The number episodes where the subject felt the urge to pull hair,
- The number of episodes where the subject resisted the urge to pull hair

For the baseline period, the diary days are labeled as: Run-in Day 1, Run-in Day 2, Run-in Day 3, Run-in Day 4, Run-in Day 5, Run-in Day 6, Run-in Day 7, or Repeat run-in Day 1, Repeat run-in Day 2, Repeat run-in Day 3, Repeat-run-in Day 4, Repeat run-in Day 5, Repeat run-in Day 6, Repeat run-in Day 7.

Post-baseline diary records will be labeled as Diary Day 1, Diary Day 2, Diary Day 3, etc.

Diary Day Validity

For the determination of weekly average diary validity, the expected collection time each evening will be 9:00 pm. See Section 6.2.4 for the calculation of the difference from expected collection date/time.

For the determination of the weekly averages, the difference from the expected collection time must be within the range from (-6:00 to 24:00 hours, inclusive of the endpoints), in order to consider the diary day to be considered valid.

For the determination of 3-week period averages, the difference from expected collection time to actual collection time must be from (-6:00 to 40:00 hours, inclusive of the endpoints), in order to consider the diary day to be considered valid.

Diary Average Periods

If a subject has to repeat run-in for 7 days, the repeat run-in days will be used to determine the baseline value. Otherwise, the diary days labeled Run-in Day 1 – Run-in Day 7 will be used for determination of the baseline values.

For the weekly averages, the following labeled diary days will be used.

Week	Starting Date*	Ending Date
Week 1	Diary Day 1	Diary Day 7
Week 2	Diary Day 8	Diary Day 14
Week 3	Diary Day 15	Diary Day 21
Week 4	Diary Day 22	Diary Day 28
Week 5	Diary Day 29	Diary Day 35
Week 6	Diary Day 36	Diary Day 42

* Diary Day 1 is collected on the date of randomization.

For the Week 1 – Week 3 averages, the diaries labeled Diary Day 1 – Diary Day 21 will be used. For the Week 3 – Week 6 averages, the diaries labeled Diary Day 22 – Diary Day 42 will be used. Diary days after Day 42 will not be used in the determination of these 3-week period averages.

For the 3-week averages, the following labeled diary days will be used.

3-Week Period	Starting Date*	Ending Date
Baseline 1 – Week 3	Diary Day 1	Diary Day 21
Week 4- Week 6	Diary Day 22	Diary Day 42

* Diary Day 1 is collected on the date of randomization.

Using the valid days in each weekly period, the number of hairpulling events experienced will be summed, then standardized by the number of valid days to get the average hairpulling events per day. The number of episodes per day result will be multiplied by 7 to get average events per week. Similarly, in each period, the maximum observed number of hairpulling events will be determined.

Using the same methodology the following TSD endpoints will be determined:

- Average minutes per day spent pulling hair
- Maximum minutes per day spent pulling hair
- Average number of episodes per day where subject felt the urge to pull hair
- Maximum number of episodes per day where subject felt the urge to pull hair
- Average number of episodes per day where subject resisted the urge to pull hair
- Maximum number of episodes per day where subject resisted the urge to pull hair

These endpoints will be completed for the baseline period, weekly periods (i.e. Week 1, Week 2, Week 3, Week 4, Week 5, and Week 6), baseline to Week 3, and Week 3 to Week 6.

Weekly summaries will be calculated if the subject has 4 or more valid diary days in the week. For the 3-week period averages, a subject must have 12 or more valid diary days in the period.

No imputation of data for missing data due to dropouts will be implemented in the analysis of efficacy endpoints.

Summary statistics at each time point will include n, mean, standard deviation, normal theory based 95% CI, median, minimum, maximum, for baseline, each time of measurement, and the change from baseline calculated as post baseline value minus the baseline value.

For the weekly values, a linear mixed model with repeated measures (MMRM) will be used, where the change from baseline in post-baseline values are the dependent variable. Independent variables in the model will include: planned treatment (Placebo, SXC-2023 50mg QD, SXC-2023 200mg QD, and SXC-2023 800mg QD), SSRI/SNRI strata, visit (categorized as Week 1, Week 2, Week 3, Week 4, Week 5, Week 6), treatment by visit interaction as fixed categorical effects, baseline value as covariate, and subject within treatment group (the repeated measures) as random effect. An unstructured covariance matrix will be used for the within-subject correlation. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. In case of a convergence failure with the unstructured covariance, the following structures will be assessed in a sequential fashion until convergence is reached: heterogeneous Toeplitz, Toeplitz, heterogeneous auto-regression, and auto-regression. Of the above 4 covariance structures, the first covariance structure yielding convergence in the MMRM model will be used for the MMRM analysis. The impact for potential covariates may be explored using this same model. Assuming treatment (TRTPN) is coded as Placebo =1, SXC-2023 50mg QD = 2, SXC-2023 200mg QD = 3, SXC-2023 800mg QD =4, SSRI/SNRI strata is coded as 0 = No and 1 = Yes, and the visit variable (WEEKN) is ordered as 1, 2, 3, 4, 5, and 6, the MMRM model of interest to be performed can be written with SAS PROC MIXED as follows:

```
PROC MIXED DATA = DATASETNAME;
    CLASS USUBJID WEEKN TRTPN SSRISTRA;
    MODEL CHG = TRTPN SSRISTRA WEEKN BASE WEEKN*TRTPN / SOLUTION DDFM=KR;
    REPEATED WEEKN / SUBJECT=USUBJID TYPE=UN;
    LSMEANS WEEKN*TRTPN / CLDIFF ALPHA=0.05;
Run;
```

Least square means of change from baseline with and their 95% confidence intervals will be presented for each visit. Estimates of treatment effect (least squares means with 95% confidence intervals of difference with placebo) will also be presented. Plots of the least square means by week for each treatment group will be presented.

A similar MMRM will be performed using the change from Baseline to Baseline to Week 3 period and change from baseline to Week 3 to Week 6 period.

A supplemental analysis of covariance (ANCOVA) will be used to analyze the change from baseline at Week 1, Week 2, Week 3, Week 4, Week 5, last post-baseline week, Week3 (using the 3 average over 3 weeks of diaries), and Week 6 (using the average over 3 weeks of diaries) value. The change from baseline will be the dependent variable. The independent variables will include planned treatment group and SNRI/SSRI strata as categorical effects, and baseline value as the baseline covariate. LS Means, standard errors of LS Means, 95% confidence intervals, LS Mean differences between active groups and placebo will be estimated. The following SAS PROC MIXED code can be used to generate the ANCOVA results.

```
PROC MIXED DATA = DATASETNAME;
    Where WEEN = x;
    CLASS TRTPN SSRISTRA;
```

```
    MODEL CHG = TRTPN SSRISTRA BASE / SOLUTION DDFM=KR;
    LSMEANS WEEKN*TRTPN / CLDIFF ALPHA=0.05;
Run;
```

Summary statistics for the observed and change from baseline in episode counts will be produced by the SSRI/SNRI strata.

8.1.2. Massachusetts General Hospital - Hairpulling Scale (MGH-HPS)

One of the efficacy outcome measures is the MGH-HPS. 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. Each item is assessed on a severity scale from 0 = no symptoms to 4 =severe symptoms. The 7 items are separated into 2 domains (Keuthen, 2007).

Domain	Question	Question Description
Severity	1	Frequency of urges
	2	Intensity of urges
	4	Frequency of hairpulling
	7	Associated distress
Resistance/Control	3	Ability to control the urges
	5	Attempts to resist hairpulling
	6	Control over hairpulling

The item scores will be summed to produce a total score which ranges from 0 to 28, with higher scores reflecting greater disease severity. The 4 questions in the severity domain will be summed to produce the severity domain score which ranges from 0 to 16. The 3 questions in the resistance/control domain will be summed to produce the resistance/control domain score which ranges from 0 to 12. In the event of a missing item response at an assessment, the MGH-HPS total score and the domain score, that the missing item is associated with, will be missing. There will be no imputation of missing item responses. The observed values and changes from baseline in the MGH-HPS total score and domain scores will be analyzed. The MGH-HPS is assessed at screening, Day 1, Week 3, and Week 6. Change from baseline in MGH-HPS total score, MGH-HPS Severity score, and MHG-HPS Resistance/Control score will be analyzed using the MMRM model and ANCOVA model described above for the TSD endpoints.

8.1.3. Change from baseline in Patient Global Impression of Status/Change

Subjects will use the iPad device to complete the PGI-S and PGI-C. PGI-S will be assessed on Day 1, Week 3, and Week 6, while PGI-C will be assessed at Week 3 and Week 6.

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 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

The PGI-S/PGI-C parameters will be analyzed using the same mixed effect model described for the TSD endpoints. For the PGI-C questions, the observed values will be used in the mixed effect model described for the TSD endpoints. There will be no baseline covariate for that model.

Listings will also be provided.

8.1.4. Change from Baseline in Clinical Global Impression of Severity/Change (CGI-S and CGI-C)

The CGI-S and CGI-C will be completed by the clinician using the iPad device on Day 1, Week 3, and Week 6.

The CGI-S 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

For CGI-S, change from baseline will be used as a response variable to fit a similar MMRM model to that described for the TSD endpoints.

The CGI-C 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

The CGI-C parameter will be analyzed using the same mixed effect model described for the TSD endpoints. The observed values will be used in the mixed effect model described for the TSD endpoints. There will be no baseline covariate for that model.

8.1.5. Change from Baseline in Milwaukee Inventory of Subtypes of Trichotillomania – Adult Version

The MIST-A will be used to assess automatic and focused pulling subtypes on Day 1, Week 3, and Week 6.

MIST-A is a 24-item self-report scale, designed to assess the degree to which individuals with symptoms of TTM engage in "automatic" and/or "focused" pulling. Each item on the MIST-A is rated from 0 ("not true of any of my hair pulling") to 9 ("true for all of my hair pulling").

The factors will be derived by summing the items associated with them;

Factor	Associated Questions
Focused	4, 5, 6, 8, 9, 10, 11, 13, 14, 15
Automatic	1, 2, 3, 7, 12
Total score	Sum of all items

Missing question responses will not be imputed. If a response for a question is not provided, then the factor score that the question is associated with and the total score will be set to missing.

The higher the score, the more the subject is engaging in hair pulling.

Each of the factors will be summarized by treatment group and visit. Change from baseline in each of the factors (focused, automatic, total score) will be analyzed using the MMRM described for MGH-HPS. A plot of the least square means and listing will be provided.

8.1.6. Barratt Impulsiveness Scale (BIS)

The Barratt Impulsiveness Scale (BIS) is used as a measure of impulsiveness. It includes 30 items that are scored to yield six impulsiveness factors (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability). The BIS is assessed at screening only. The response to each positively worded item is provided on the following scale (1 = rarely/never, 2 = occasionally, 3 = often, 4 = almost always/always). The response to each negatively worded item is provided on the following scale (4 = rarely/never, 3 = occasionally, 2 = often, 1 = almost always/always).

The responses to the 30-items, will be summed to yield a total score. The items that are summed to yield each of the 6 factors are shown below. Note that the questions marked with an asterisk will be negatively scored prior to creation of the total score and the factor scores.

Factor	Item
Attention	5, 9*, 11, 20*, 28
Cognitive Instability	6, 24, 26
Motor	2, 3, 4, 17, 19, 22, 25
Perseverance:	16, 21, 23, 30*
Self-Control	1*, 7*, 8*, 12*, 13*, 14

Factor	Item
Cognitive Complexity	10*, 15*, 18, 27, 29*

Each of the six factors and the total score will be summarized descriptively. The scores are scaled so that a higher score indicates more impulsiveness. A listing will be provided. A missing item response will not be imputed. In the event of a missing item response, the total score, as well as domain scores that involve the missing item will be missing.

8.1.7. Correlation of Response in Efficacy Outcomes

Correlation analyses between outcomes are described in the following table. Cross-tabulations tables will be produced separated by treatment group and then active treatment groups combined. Continuous variables will be categorized using quartiles or other appropriate clinically appropriate cut points. Scatterplots may be produced. The following table describes the variables / and time points that will be summarized using correlation tables.

Outcome / Endpoint	Time Point (s)	Correlated with Outcome / Endpoint	Time Point (s)	Proposed Analyses
CFB in Hairpulling Episodes / Week	Week 3 (weekly) Week 6 (weekly) Baseline to Week 3 Week 3 to Week 6	CFB in MGH-HPS	Week 3, Week 6	Spearman's Rank Cross-tabulation based on quartiles in both variables Scatterplots by Treatment
CFB in Hairpulling Episodes / Week	Week 3 (weekly) Week 6 (weekly) Baseline to Week 3 Week 3 to Week 6	CGI-S	Week 3, Week 6	Spearman's Rank; Cross-tabulation;
CFB in Hairpulling Episodes / Week	Week 3 (weekly) Week 6 (weekly) Baseline to Week 3 Week 3 to Week 6	CGI-C	Week 3, Week 6	Spearman's Rank; Cross-tabulation;
CFB in Hairpulling Episodes / Week	Week 3 (weekly) Week 6 (weekly)	PGI-S	Week 3, Week 6	Spearman's Rank; Cross-tabulation;

Outcome / Endpoint	Time Point (s)	Correlated with Outcome / Endpoint	Time Point (s)	Proposed Analyses
	Baseline to Week 3 Week 3 to Week 6			
CFB in Hairpulling Episodes / Week	Week 3 (weekly) Week 6 (weekly) Baseline to Week 3 Week 3 to Week 6	PGI-C	Week 3, Week 6	Spearman's Rank; Cross-tabulation;
CFB in Hairpulling Episodes / Week	Week 3 (weekly) Week 6 (weekly) Baseline to Week 3 Week 3 to Week 6	CFB in MIST-A	Week 3, Week 6	Spearman's Rank; Cross-tabulation; Scatterplots by Treatment
CFB in MGH-HPS	Week 3, Week 6	CGI-S	Week 3, Week 6	Spearman's Rank; Cross-tabulation based on quartiles for CFB in MGH-HPS;
CFB in MGH-HPS	Week 3, Week 6	CGI-C	Week 3, Week 6	Spearman's Rank; Cross-tabulation based on quartiles for CFB in MGH-HPS;
CFB in MGH-HPS	Week 3, Week 6	PGI-S	Week 3, Week 6	Spearman's Rank; Cross-tabulation based on quartiles for CFB in MGH-HPS;
CFB in MGH-HPS	Week 3, Week 6	PGI-C	Week 3, Week 6	Spearman's Rank; Cross-tabulation based on quartiles for CFB in MGH-HPS;
CGI-S	Week 3, Week 6	CGI-C	Week 3, Week 6	Spearman's Rank; Cross-tabulation
CGI-S	Week 3, Week 6	PGI-S	Week 3, Week 6	Spearman's Rank; Cross-tabulation
CGI-S	Week 3, Week 6	PGI-C	Week 3, Week 6	Spearman's Rank; Cross-tabulation
CGI-S	Week 3, Week 6	CFB in MIST-A	Week 3, Week 6	Spearman's Rank; Cross-tabulation

Outcome / Endpoint	Time Point (s)	Correlated with Outcome / Endpoint	Time Point (s)	Proposed Analyses
CGI-C	Week 3, Week 6	PGI-S	Week 3, Week 6	Spearman's Rank; Cross-tabulation
CGI-C	Week 3, Week 6	PGI-C	Week 3, Week 6	Spearman's Rank; Cross-tabulation
CGI-C	Week 3, Week 6	CFB in MIST-A	Week 3, Week 6	Spearman's Rank; Cross-tabulation
PGI-S	Week 3, Week 6	PGI-C	Week 3, Week 6	Spearman's Rank; Cross-tabulation
PGI-S	Week 3, Week 6	CFB in MIST-A	Week 3, Week 6	Spearman's Rank; Cross-tabulation
PGI-C	Week 3, Week 6	CFB in MIST-A	Week 3, Week 6	Spearman's Rank; Cross-tabulation

CFB = Change from Baseline.

8.1.8. Analysis of Cambridge Neuropsychological Test Automated Battery

Cambridge Neuropsychological Test Automated Battery parameters (SST, CGT, PAL, and RTI) will be analyzed by Cambridge Cognition.

9. Safety

The population used for safety analyses will be the Safety Set (SS). Safety will be assessed on the basis of adverse events (AE) reports, clinical laboratory data, ECG parameters, physical examinations, and vital signs.

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.

9.1. Extent of Exposure

Extent of exposure (number of days of exposure to study drug) and categorized extent of exposure will be presented by randomized treatment group for the Safety Set. Any gaps in medication dosing will not be taken into account in the calculation of treatment exposure.

9.2. Treatment Compliance

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. 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.

At Week 3 visit, 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 a total of 6 days of study drug administration at the Week 3 visit will be dropped from the Per Protocol (PP) Population analyses and replaced. Subjects who have missed a total of 6 days of study drug administration between the Week 3 and Week 6 visits will be dropped from the Per Protocol (PP) Population analyses. Subjects withdrawn from PP set analyses for non-compliance will be given the option of completing the study, including continuing on study drug and completing assessments.

Compliance will be calculated for each visit interval (Day 1 to Week 3, Week 3 to Week 6) and overall (Day 1 to Week 6).

Compliance will be calculated as; (Number of capsules used/Number of capsules expected to be taken) x 100. For the compliance from Day 1 to Week 3, the day of the Week 3 visit will be included in the capsules used and the capsules expected to be taken. For the compliance from Week 3 to Week 6, the period will start on the day immediately after the Week 3 visit and end on the date of the Week 6 visit.

Compliance will be summarized by treatment group.

Study drug administration will be listed as well.

9.3. Adverse Events / Adverse Drug Reactions

For the purpose of this study, an adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury, or accident) that emerges or worsens following administration of the study medication and until the end of study participation. The untoward medical occurrence may not necessarily have a causal relationship to the administration of the investigational product. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory result), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose: results in death, is life-threatening, is a persistent or significant disability/incapacity, results in congenital anomaly or birth defect, requires inpatient hospitalization or leads to prolongation of existing hospitalization, or another medically important event.

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug but not more than 21 days after the last dose of study drug.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug but not more than 21 days after the last dose of study drug.

9.3.1. Relatedness of Adverse Events

A treatment-related AE is defined as an AE as being possibly or probably related to the study drug. If an AE has missing relationship it is assumed to be possibly related to the study drug for analysis purposes.

9.3.2. Severity Definition for Adverse Events

The severity of AEs will be assessed by the investigator as follows:

- **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.

An AE with missing severity will be categorized as “severe” for purposes of summarization.

The following tables will be presented for AEs:

- Overall summary showing the incidence and the number of TEAEs, Treatment related TEAES, SAEs, and Treatment related SAEs, TEAEs leading to withdrawal, Death.
- TEAE by system organ class and preferred term, incidence and number of events
- Treatment related TEAE by system organ class and preferred term, incidence and number of events
- Serious TEAE by system organ class and preferred term, incidence and number of events
- Treatment related Serious TEAE by system organ class and preferred term, incidence and number of events

- TEAE by system organ class, preferred term and maximum reported severity, incidence
- Treatment related TEAE by system organ class, preferred term and severity, incidence
- TEAEs leading to early withdrawal by system organ class and preferred term, incidence

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

All AEs will be listed. As well, listings of serious adverse events and listings of adverse events leading to treatment discontinuation will be provided.

9.4. Laboratory Evaluations

Laboratory safety parameters will be analyzed by a central laboratory using standard validated methods. Lab measurements are collected at Screening, Day 1, Week 3, Week 6, and Week 8.

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, serum chemistry, coagulation, and urinalysis parameter. In the event of multiple recorded values collected at a scheduled post-baseline assessment, the first collected value will be used in the analysis. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Categorical-valued urinalysis parameters will be classified as within normal range or abnormal. Shift tables in relation to the normal range from baseline to each post-baseline visit will be presented. Percentages will be based on the number of subjects with a value at baseline and at the visit being summarized.

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, creatinine clearance, 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)
- 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. The urine pH and specific gravity are considered the continuous value reported parameters. The others will be considered as categorical data.
- Urine drug screen: This test will screen for the following: amphetamines, barbiturates, benzodiazepines, cocaine (metabolite), methadone screen, opiates, phencyclidine, and propoxyphene.

Creatinine clearance will be calculated using the Cockcroft-Gault formula (Cockcroft and Gault, 1976). The formula is based on the observed serum creatinine, sex, age, and body weight at collection.

Cockcroft-Gault CrCl = [(140-age) x (Wt in kg) x (0.85 if female)] / (72 x sCr)

Where age is the age at collection, Wt = Weight (kg) at collection, and sCR = serum creatinine (mg/dL). For the determination of creatinine clearance, serum creatinine values reported in the unit of mmol/L will be converted to mg/dL by dividing the value reported in mmol/L by 88.42.

Results of the urine pregnancy test and urine drug screen will be only provided in listings. A listing of laboratory measurements recorded throughout the study will be presented.

9.5. Vital Signs

Vital signs are collected at screening and follow-up (Week 8). Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Respiration rate (breath/min)
- Body temperature (F)
- Body weight (kg)
- BMI (kg/m2)

9.6. Electrocardiogram (ECG)

Standard safety 12-lead ECGs will be performed during the screening visit and at Week 6. The 12-lead ECGs will be taken after the subject has been resting supine for ≥5 minutes. The following ECG parameters will be collected: Investigator's Interpretation, PR interval, QRS interval, RR interval, QT interval, and QT corrected by Fridericia's formula (QTcF) interval. The investigator's interpretation will be provided as Normal, Abnormal Not Clinically Significant (NCS), or Abnormal Clinically Significant (CS). The interpretation values and shift tables for interpretation will be provided. Percentages will be based on the number of subjects with an assessment performed at screening and at Week 6. For the other parameters, the observed and change from baseline values will be summarized. All ECG findings will be listed.

9.7. Physical Examination

Full physical examination will be performed at screening and Week 8. Symptom-driven physical examinations may be performed at other times, if deemed necessary. Results of physical exams will only be provided in listings.

9.8. Columbia-Suicide Severity Rating Scale (C-SSRS)

C-SSRS will be used to evaluate suicidal ideation/behavior. C-SSRS will be assessed at Screening, Randomization/Baseline, Week 3, Week 6, and Follow-up. Two versions will be used, one at screening which is the baseline/lifetime verison. The since last visit version will be used at the other visits.

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts

Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent
Category 6	Preparatory Acts or Behavior
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)
Category 10	Completed Suicide

Suicidal Ideation since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS

Suicidal Behavior since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal behavior questions (categories 6-10) on the C-SSRS. Listings will also be provided.

10. Interim Analyses

The is no planned interim analysis for this study

11. Changes from Analysis Planned in Protocol

In place of the single Per Protocol Set defined in the protocol, there are 2 per protocol set defined, one for the endpoints related to the non TSD-diary related endpoints (PPS One Set), and one called (PPS Diary Set), which will be used for the TSD-diary related endpoints.

Conditions related to 5 or more missed consecutive doses for inclusion in the per protocol set were removed. The collected data does not provide dates of intake of the study medication, only the counts of tablets dispensed and returned.

12. Reference List

1. SAS Institute Inc. The SAS System, Version 9.3. Cary, NC, SAS Institute Inc. 2012

2. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

3. Keuthen NJ, Flessner CA. Factor Analysis of Massachusetts General Hospital Hairpulling Scale. Journal of Psychosomatic Research 62 (2007) 707-709.

13. Programming Considerations

All tables, figures, data listings (TFLs), and statistical analyses will be generated using SAS® for Windows, Release 9.4 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format or portable document format pdf.
- Numbering of TFLs will follow ICH E3 guidance

13.2. Table, Listing, and Figure Format

13.2.1. General

- All TFLs will be produced in landscape format on American letter size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:

- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

13.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo-controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

13.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. Every p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999, then present as >0.9999
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the

number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC3 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

13.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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