Celerion Project No.: CA22427

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A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Food Effect of SXC-2023 when Administered Orally to Healthy Adult Subjects

GCP Statement

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

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Name	Description
17Jul2017 by Ziv Machnes	Final Protocol
02Nov2017 by Tricia Cotter	Amendment 1 • Red blood cell collection and analysis • Food effect dose selection requirement
05Jan2018 by Ziv Machnes	Amendment 2 • Addition of Cohort 6 (1600 mg SXC-2023) • Minor typographical and grammatical corrections

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Food Effect of SXC-2023 when Administered Orally to Healthy Adult Subjects

SPONSOR:

Promentis Pharmaceuticals, Inc.
826 North Plankinton Avenue, Suite 400
Milwaukee, Wisconsin 53203, USA

SPONSOR'S REPRESENTATIVE:

Patricia P. Cotter
Senior Director, Head of Clinical Operations
Tel.: +1 617 300-6172
E-Mail: pcotter@promentispharma.com

Patricia Cotter
Signature

05 Jan 2018
Date

CELERION PRINCIPAL INVESTIGATOR AND CLINICAL SITE:

Terry E. O'Reilly, MD
2420 West Baseline Road
Tempe, Arizona 85283, USA
Tel.: +1 602 437-0097 ext. 67296
Fax: +1 602 437-3386
E-mail: terry.oreilly@celerion.com


Signature

05 Jan 2018
Date

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact for Serious Adverse Event Reporting	Patricia P. Cotter Senior Director, Head of Clinical Operations Tel.: +1 617 300-6172 E-mail: pcotter@promentispharma.com
Protocol Author	Ziv Machnes, PhD. Scientist II Celerion 100 Alexis-Nihon Boulevard, Suite 360 Montreal, Quebec H4M 2N8, Canada Tel.: +1 514 744-8736 Fax: +1 514 744-8700 E-mail: ziv.machnes@celerion.com
Certified Clinical Laboratory	Celerion 2420 West Baseline Road Tempe, Arizona 85283, USA Contact: Ed Gritzfeld Tel.: +1 602 437-0097 ext. 67172 Fax: +1 602 437-3386
Bioanalytical Laboratory	Covance BioAnalytic 1121 East 3900 South, Building C Salt Lake City, Utah 84124, USA Contact: Jeremy Thompson Tel: +1 801 293-2306 Fax: +1 801 313-6495
Pharmacokinetic and Statistical Analyses	Celerion 100 Alexis-Nihon Boulevard, Suite 360 Montreal, Quebec H4M 2N8, Canada Tel.: +1 514 744-9090 Fax: +1 514 744-8700 and/or Celerion 621 Rose Street Lincoln, Nebraska 68502, USA Tel.: +1 402 476-2811 Fax: +1 402 939-0428

4 TABLE OF CONTENTS

LIST OF TABLES

5 SYNOPSIS

Compound:	SXC-2023
Clinical Indication:	Treatment of trichotillomania (TTM)
Study Phase and Type:	Phase 1 – single ascending dose (SAD) and food effect (FE) first-in-human study.
Study Objectives:	**Primary:** To assess the safety and tolerability of SXC-2023 following administration of single ascending doses to healthy adult subjects. **Secondary:** Objective 1: To assess the pharmacokinetics (PK) of SXC-2023 in plasma, red blood cells (RBCs) (if applicable), and urine following administration of single ascending doses to healthy adult subjects. Objective 2: To compare the single-dose PK of SXC-2023 in plasma, RBCs (if applicable), and urine following oral administration under fed and fasting conditions. Objective 3: To assess the PK of SXC-2023 primary metabolites, N-acetylcysteine (NAC), and *p*-toluic acid, as available, in plasma, RBCs (if applicable) and urine, following administration of a single dose to healthy adult subjects.
Summary of Study Design:	This is a randomized, double-blind, placebo-controlled, SAD and FE study conducted at 1 study center in the United States (US). Subjects will participate in only one cohort. Up to 6 cohorts of 8 subjects each (6 active and 2 placebo) are planned for evaluation. Each cohort will include a sentinel group (1 active and 1 placebo) who will be dosed at least 24 hours before the remaining 6 subjects (5 active and 1 placebo). Dosing of the remaining 6 subjects will be conducted following a safety evaluation of the sentinel group by the Principal Investigator (PI), Medical Monitor, and Sponsor. In each cohort, subjects will receive a single oral dose of SXC-2023 or placebo under fasting conditions, with one cohort

	crossing over to receive the same dose of SXC-2023 or placebo for a second time under fed conditions. There will be a washout period of at least 7 days between dosing under fasting conditions and dosing under fed conditions (high-fat breakfast). Blood and urine samples will be collected predose through 72 hours following SXC-2023 administration for the PK assessment of SXC-2023, NAC, and *p*-toluic acid, as appropriate. Dose escalation to the next dose level (i.e., next cohort) will not take place until a PI, Medical Monitor, and Sponsor representative have determined that adequate safety, tolerability, and PK plasma have been demonstrated regarding the previous cohort(s) to permit proceeding to the next cohort. The dose level (i.e., cohort) to be used for the assessment of a FE will be determined based on the safety, tolerability, and PK plasma evaluations of previous cohorts. The safety and tolerability of the dose at least one dose level higher than the dose level selected for the FE cohort, may be evaluated. Safety (i.e., physical examinations, vital signs, 12-lead ECGs, clinical laboratory tests, and adverse events [AEs]) will be assessed throughout the study; serial blood samples and urine samples will be collected for these assessments. All subjects who received a dose of study drug/placebo (including subjects who terminate the study early) will return to the Clinical Research Unit (CRU) approximately 7 days after the last study drug/placebo administration for follow-up procedures, and to determine if any AEs have occurred since the last study visit.
Study Population	Subjects will be healthy male and female (women of non-childbearing potential [WONCBP]) subjects consisting of members of the community at large.
Number of Subjects:	This study is planned to enroll up to 48 subjects in 6 cohorts of 8 subjects each (6 subjects to receive active drug and 2 subjects to receive placebo per the randomization). A sentinel group (1 active and 1 placebo) in each fasted cohort will consist of 2 subjects who will be randomized to receive active drug or placebo. The remaining 6 subjects in the cohort will be randomized to receive active drug (n=5) or placebo (n=1). Attempts will be made to enroll 50% of each sex in each cohort.

	Additional subjects may be enrolled if it is deemed appropriate by the PI, the Sponsor, and the Medical Monitor to repeat a dose level or to study an intermediate dose level (lower than those planned).
Duration of Participation for Subjects	The total planned duration of subject participation is approximately 35 days from screening to follow-up, with CRU confinement from check-in on Day -1 to Day 4 or approximately 42 days for subjects enrolled to receive a second dose under fed conditions.
Study Products	SXC-2023 will be supplied as 50 mg and 200 mg capsules. Placebo will be provided as matching placebo capsules. An unblinded pharmacist will be responsible for providing SXC-2023 or placebo to the blinded study personnel for administration.
Dosage, Dosage Form, Route, and Dose Regimen:	Each cohort will start with a sentinel group of 2 subjects (1 active and 1 placebo) who will be dosed at least 24 hours before the remaining 6 (5 active and 1 placebo). Subjects in each cohort will receive a single oral dose of SXC-2023 or placebo on Day 1, under fasting conditions. Planned doses will be as follows: Cohort 1: 50 mg (1 x 50 mg capsule) SXC-2023 or matching placebo Cohort 2: 100 mg (2 x 50 mg capsules) SXC-2023 or matching placebo Cohort 3: 200 mg (1 x 200 mg capsule) SXC-2023 or matching placebo Cohort 4: 400 mg (2 x 200 mg capsules) SXC-2023 or matching placebo Cohort 5: 800 mg (4 x 200 mg capsules) SXC-2023 or matching placebo Cohort 6: 1600 mg (8 x 200 mg capsules) SXC-2023 or matching placebo One cohort will receive the same dose of SXC-2023 or placebo for a second time under fed conditions following a washout period of at least 7 days. The dose levels (i.e. cohort) to be used for the FE cohort will be determined based on the safety, tolerability, and PK plasma data from previous cohorts. The safety and tolerability of the dose at least one dose level higher

	than the dose level selected for the FE cohort, may be evaluated. When administered under fed conditions, SXC-2023 will be administered orally following a high-fat breakfast. All doses of study drug/placebo will be administered with approximately 240 mL of water. In Cohort 6, if the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.
Safety Assessments	Safety will be monitored through physical examinations, vital signs, 12-lead ECGs, clinical laboratory tests, and AEs.
Safety Analysis	The following analyses will be performed; however, no formal inferential statistics will be done on safety assessments. The placebo subjects from all cohorts will be pooled into a single placebo group for all summaries and presentations. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. **Adverse Events:** AEs will be coded using the most current version of MedDRA® available at Celerion. A by-subject treatment-emergent AEs (TEAEs) data listing, including verbatim term, preferred term, treatment, severity, and relationship to drug, will be provided. The number of subjects experiencing AEs and number of AEs will be summarized by cohort using frequency counts. **Medical History and Physical Examination:** Medical history will be listed by subject. **Clinical Laboratory Results, Electrocardiograms, and Vital Signs Measurements:** All clinical laboratory results, 12-lead ECGs, vital signs measurements, and their change from baseline, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

	Concomitant Medications: Concomitant medications will be coded using the most current World Health Organization (WHO) drug dictionary available at Celerion and listed by treatment.
Pharmacokinetic Sample Collection	Serial blood and urine samples will be collected prior to and through 72 hours postdose on Day 1 to determine the concentration of SXC-2023, NAC, and *p*-toluic acid in plasma and urine. For doses greater than or equal to (≥) 200 mg, RBCs will be collected to assess analytes, if applicable. The sampling schedule may be modified based on the results from previous cohorts.
Pharmacokinetic Parameters and Analysis	The following PK parameters will be calculated for SXC-2023, NAC, and *p*-toluic acid in plasma and RBCs, as appropriate, following SXC-2023 administration under fasted and fed conditions: AUC0-t, AUC0-inf, Cmax, Tmax, CL/F (parent only), Vz/F (parent only), Kel, and T½. The following PK parameters will be calculated for SXC-2023 NAC, and *p*-toluic acid in urine, as appropriate, following SXC-2023 administration under fasted and fed conditions: Aet1-t2, Ae0-72, CLr, and %Fe (parent only). Additional PK parameters may be calculated, if deemed appropriate. The effect of food on a single oral dose of SXC-2023 will be assessed by comparing appropriate plasma and RBCs (if appropriate) PK parameters (i.e., AUC0-t, AUC0-inf, and Cmax) under fed versus fasting conditions using an analysis of variance (ANOVA) approach. Dose proportionality may be assessed using the power model approach, as appropriate.

6 STUDY EVENTS FLOW CHART

Study Procedures [a]	**S** [b]	**Study Days in Each Cohort** [c]																			**FU** [d]
Days →		**-1**	**1**															**2**	**3**	**4**	
Hours →		**C-I** [e]	0	0.083	0.167	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	16 [f]	24	48	72	
Administrative Procedures																					
Informed Consent	X																				
Inclusion/Exclusion Criteria	X	X [g]																			
Medical History	X																				
Safety Evaluations																					
Full Physical Examination [h]	X																				
Height	X																				
Weight	X	X																			
12-lead ECG	X		X [i]								X							X		X [j]	
Vital Signs (HR and BP)	X		X [i]								X		X					X	X	X [j]	X
Vital Signs (RR and T)	X		X [i]								X		X					X	X	X [j]	X
Hem, Serum Chem [k], and UA	X	X																X		X [j]	
Coagulation	X																				
Serum Preg Test (♀ only)	X	X																		X [j]	
Serum Total Testosterone, LH, and FSH [l]	X [m]	X																X		X [j]	
Urine cotinine Screen	X																				
Urine Alcohol and Drug Screen	X	X																			
HIV/Hepatitis Screen	X																				
AE Monitoring		X																			X
Concomitant Medication Monitoring	X	X																			
Study Drug / Placebo Administration / PK																					
SXC-2023 / Placebo Administration			X																		
Blood for SXC-2023, NAC, and *p*-toluic acid PK [p]			X [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [j]	
Urine for SXC-2023, NAC, and *p*-toluic acid PK											X [o]										
Other Procedures																					
Confinement in the CRU		X																			
Visits	X																				X

a: For details on Procedures, refer to Section 11.

b: Within 28 days prior to first dose administration.

c: For subjects in the FE cohort, there will be a washout period of at least 7 days between doses.

d: All subjects who received a dose of study drug/placebo (including subjects who terminate the study early) will return to the CRU approximately 7 days after the last study drug/placebo administration for follow-up procedures, and to determine if any AE has occurred since the last study visit.

e: Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU.

f: The 16-hour time point following dosing on Day 1 will be either on Day 1 or Day 2, depending on the time of dosing on Day 1.

g: For subjects in the FE cohort, to be performed in the fasted treatment only.

h: Symptom-driven physical examination may be performed at other times, at the PI's or designee discretion.

i: To be performed within 24 hours prior to dosing on Day 1.

j: To be performed at the end of treatment or prior to early termination from the study. For subjects in the FE cohort to be performed at the end of each treatment period or prior to early termination from the study

k: Samples for serum chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

l: Samples for serum total testosterone, LH, and FSH will be collected at the same clock time (±1 hour) in the morning (before 10:00 AM) on each scheduled day, except for sample for FSH collected from postmenapausal women at screening.

m: At screening, only samples for FSH from postmenopausal women will be collected.

n: To be performed prior to dosing.

o: Urine collection intervals are predose, and 0-1, 1-2, 2-4, 4-8, 8-12, 12-24, 24-48, and 48-72 hours postdose.

p: Includes red blood cell collection and analysis (if applicable) in doses ≥ 200 mg.

Abbreviations: ♀ = Females, ≥ = greater than or equal to, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, CRU = Clinical research unit, ECG = Electrocardiogram, EOT/ET = End-of-Treatment or early termination, FE = Food effect, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, LH = Luteinizing hormone, PI = Principal Investigator, PK = Pharmacokinetics, Preg = Pregnancy, RR = Respiratory rate, S = Screening, T = Temperature, UA = Urinalysis.

7 ABBREVIATIONS

≥	greater than or equal to
µ	micro
AE	Adverse event
Aet1-t2	Amount of unchanged drug excreted in t1 to t2 urine collection interval
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
bpm	Beats per minute
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent total plasma clearance after oral (extravascular) administration
CLr	Renal clearance
Cm	Centimeter
Cmax	Maximum observed concentration
CNS	Central nervous system
CRF	Case report form
CRU	Clinical Research Unit
CYP	Cytochrome P450
DRF	Dose range finding
ECG	Electrocardiogram
%Fe	Fraction of drug excreted unchanged in urine
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
hERG	Human ether-a-go-go related gene

HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration of enzyme activity
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
Kel	Apparent terminal elimination rate constant
kg	Kilogram
LH	Luteinizing hormone
ln	Natural log
LSM	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
MRSD	Maximum recommended starting dose
msec	Millisecond
n	Sample size
NAC	N-acetylcysteine
No.	Number
NOAEL	No observed adverse effect level
OATP	Organic anion transporting polypeptide
oz	Ounce
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)

QA	Quality Assurance
QTcF	Fridericia's correction method
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum observed concentration
TTM	Trichotillomania
T½	Apparent terminal elimination half-life
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration
WHO	World Health Organization
WONCBP	Women of non-childbearing potential

8 BACKGROUND AND RATIONALE

8.1 Background

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

TTM is a chronic psychiatric illness characterized by the recurrent pulling out of one's hair as well as the associated distress or functional impairment caused by this condition. It was not until the late 1980s that TTM was included in the Diagnostic and Statistical Manual of Mental Disorders as an impulse control disorder. Recent studies have linked perturbations in glutamatergic neurotransmission and/or heightened levels of oxidative stress to the underlying pathophysiology of TTM. Imaging studies conducted in TTM patients identified alterations in areas of the brain, particularly those implicated in the regulation of urge control, rewarding behaviors, motor habits, mood, and executive function (Chamberlain et al., 2008; Chamberlain et al., 2010; Grant and Chamberlain, 2016; Roos et al., 2015), as key contributors to the pathophysiology of TTM and related impulse control disorders (e.g., excoriation disorder). Additionally, functional deficits in glutamate signaling within the cortical-striatal pathway and mesolimbic system (i.e., nucleus accumbens) have been proposed to contribute to the underlying pathology and symptoms of TTM (Grant et al, 2009). SXC-2023 is currently being assessed for the treatment of TTM in adults.

NAC, one of the primary metabolites of SXC-2023, has been approved for treating hepatic toxicity associated with acetaminophen overdose and as a mucolytic agent. In addition, NAC has also been shown to be a promising treatment for several psychiatric and neurological disorders and has been proven to be safe, even when administered at high doses. NAC has been shown to be effective in the treatment of TTM in a clinical trial. SXC-2023 has been designed to more effectively deliver NAC and cyst(e)ine to the brain.

8.1.1 Preclinical Trials

8.1.1.1 Pharmacology

In a variety of preclinical rodent models, SXC-2023 was found to increase the time spent in the open arm of the elevated plus maze, which is used to measure anxiety (a symptom of many psychiatric disorders and a clear indication of CNS penetration); ameliorated N-methyl-D-aspartate receptor antagonist (MK-801) induced deficits in pre-pulse inhibition, which tests behavior that is dependent on cortical glutamatergic transmission; and significantly lowered the number of lever presses to self-administer cocaine, an assay

measuring compulsive behavior in a model of chemical addiction. These studies, coupled with a study using rats engineered to lack a functional cystine-glutamate antiporter (specifically the *x*CT light chain protein), suggest that SXC-2023, through activation of System x_c^-, may provide a novel approach to reverse the deficits associated with glutamatergic dysfunction and heightened levels of oxidative stress implicated in the pathophysiology of TTM.

8.1.1.2 Pharmacokinetics

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

SXC-2023 has been shown to distribute into red blood cells (RBCs) and the brain of rodents, and into the RBCs and cerebral fluid of monkeys. SXC-2023 is rapidly absorbed in all species following oral administration with peak plasma concentrations occurring within 1 hour in dogs and at up to 4 hours post-dose in monkeys. In whole blood, most of the SXC-2023 and NAC are present in the plasma, with high protein binding (>96%) at a concentration of 10 μM (2.81 μg/mL). Compared to total plasma concentrations of drug, concentrations of SXC-2023 and NAC in RBCs appear to be minimal when taking background levels into consideration. Metabolism of SXC-2023 was evaluated using rat, monkey and human hepatocytes. In each species, the primary metabolites were NAC and *p*-toluic acid. Another possible minor pathway of SXC-2023 metabolism includes deamidation followed by cysteine conjugation.

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

Following *in vitro* studies to assess the potential of SXC-2023 to inhibit, induce, or be metabolized by cytochrome P450 (CYP) enzymes, it is anticipated that the likelihood of drug-drug interactions with SXC-2023 is minimal, with a possible exception for inhibition of CYP2C8 (showing half-maximal inhibitory concentration of enzyme activity [IC_{50}] of 570 μM). *In vitro* data indicates that SXC-2023 may be a substrate of organic anion-transporting polypeptide (OATP)1B1 and 1B3, but not of P-glycoproteins or breast cancer resistance protein.

8.1.1.3 Toxicity

The safety and toxicity associated with chronic treatment with SXC-2023 was evaluated in two species (rats and dogs) following chronic, 7- and 28-day dosing.

In a dose range finding (DRF) study in rats, minor, SXC-2023-related effects were observed at both 500 and 2000 mg/kg/day dose levels that included basophilic tubule and tubule dilatation findings in the kidney; however, given the magnitude of the changes and/or a lack of microscopic correlates, coupled to similar observations in the control group, none of these effects in rats were considered adverse.

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

In dogs, a 7-day DRF study demonstrated that daily oral administration of 500 mg/kg/day SXC-2023 by gavage for 7 days in dogs was well tolerated. However, the dose of 2000 mg/kg/day by gavage was not tolerated, based on the unscheduled sacrifice of 2 males and adverse findings that included emesis/vomiting, liquid feces, which correlated with decreases in body weight and food consumption. Clinical pathology findings and a decrease in thymus weights were observed only at the 2000 mg/kg/day dose group and were consistent with inflammation and/or stress. Based on this DRF study in dogs, the doses selected for the 28-day study were 250, 500 and 1200 mg/kg/day.

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

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

Also in the high dose group, lower testis weights for males administered 1200 mg/kg/day were correlated with the microscopic findings of degeneration and atrophy (slight to moderate) of the seminiferous tubules which were considered adverse. No effects on seminiferous tubules or testes weight were observed in animals administered 250 mg/kg/day or 500 mg/kg/day. Based on these findings, the Study Director of the non-clinical CRO defined the NOAEL as 500 mg/kg/day; however, based on the similar exposure levels at 500 and 1200 mg/kg/day groups, Promentis conservatively defined NOAEL to be 250 mg/kg/day.

This also takes into consideration the potential for increased exposure with the administration of enteric capsules.

Based on a pivotal Ames assay and a human peripheral blood lymphocyte chromosome aberration assay, SXC-2023 is considered not genotoxic.

Refer to the Investigator's Brochure [SXC-2023, 2017] for detailed background information on SXC-2023.

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

This clinical trial will be the first-in-human study of SXC-2023. When developing new drugs for clinical indications, it is necessary to collect data on the safety, tolerability, and PK in order to support further development of the compound as a useful clinical candidate and determine of dose levels and dose intervals in Phase 2 and subsequent studies. Subjects will be randomized to treatment to minimize assignment bias.

The effect of food on the rate and extent of absorption of SXC-2023 will be investigated when the drug is administered shortly after a meal. As per the Food and Drug Administration (FDA) recommendations [FDA Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, 2002], the test meal provided will be a high-fat / high-calorie meal.

The washout period between doses in the FE cohort is expected to be sufficient to prevent carryover effects of the treatments.

This SAD and FE study is designed to meet the objectives outlined in Section 9.1.

8.2.2 Rationale for the Dose Selection

Given the findings in the 7-day DRF and 28- day studies in rats for doses of 500, 1000, and 2000 mg/kg/day and in the 7-day DRF and 28-day studies in dogs for doses of 250, 500, 1000, 1200, and 2000 mg/kg/day, a 250 mg/kg/day dose in dog was determined to be the NOAEL and therefore selected for the calculation of maximum recommended starting dose (MRSD) for the study [FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005].

The proposed clinical starting dose, 50 mg, is 193-fold lower than the human equivalent dose (HED) of 9678 mg at the rat NOAEL of 1,000 mg/kg/day and 167-fold lower than the HED of 8333 mg at the dog NOAEL of 250 mg/kg/day NOAEL. SXC-2023 was shown to have CNS activity in other relevant rodent models at a dose of 10 mg/kg in rats; the corresponding HED is about 100 mg.

The concentrations of both metabolites, NAC and p-toluic acid, following administration of 50, 100, 200, and 400 mg SXC-2023 (Cohorts 1-4) were below the levels of quantification for all subjects at all time points, with the exception of the 4.0 hours postdose time point for

NAC in a single subject, and sporadic time points for p-toluic acid, deemed not sufficient to generate PK parameters.

In the safety and tolerability assessments of Cohorts 1-4, a total of 33 AEs (15 AEs in 5 subjects in Cohort 1, 1 AE in Cohort 2, 16 AEs in 4 subjects in Cohort 3, and 1 AE in 1 subject in Cohort 4) were observed in this study to date, all of which were considered to be mild to moderate in severity. In addition, no dose dependence of AEs has been observed.

Based on the safety and tolerability profile of SXC-2023 to date, it was decided to add a dose level of 1600 mg (approximately 5-fold below the NOAEL of dog) to the study in Amendment 2.

8.3 Risks and/or Benefits to Subjects

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, 12-lead ECG, clinical laboratory tests, and AE questioning) are adequate to protect the subjects' safety, should detect all expected treatment-emergent AEs (TEAEs), and are standard for a first-in-human, SAD study.

Subjects will be admitted to the CRU, where they will be monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs. Sentinel dosing will be employed within each cohort of the study. Available blinded safety and tolerability data will be assessed after each dose level to determine if it is safe to escalate to the next dose level. PK data will also be assessed as part of the dose escalation decision for each dose level.

The approximate volume of blood planned for collection from each subject over the course of the study (see Section 11.3) presents no undue risk to the subjects nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an indwelling cannula is utilized and the possibility of collection of additional blood for recheck of safety labs if deemed necessary by the PI.

There will be no direct health benefit for study participants from receipt of study drug/placebo. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

9 STUDY OBJECTIVES AND ENDPOINTS

9.1 Study Objectives

Primary:

To assess the safety and tolerability of SXC-2023 following administration of single ascending doses to healthy adult subjects.

Secondary:

Objective 1: To assess the PK of SXC-2023 in plasma, RBCs (if applicable), and urine following administration of single ascending doses to healthy adult subjects.

Objective 2: To compare the single-dose PK of SXC-2023 in plasma, RBCs (if applicable), and urine following oral administration under fed and fasting conditions.

Objective 3: To assess the PK of SXC-2023 primary metabolites, NAC, and *p*-toluic acid, as available, in plasma, RBCs (if applicable), and urine, following administration of a single dose to healthy adult subjects.

9.2 Study Endpoints

The primary endpoints of the study will be the number and severity of TEAEs following single doses of SXC-2023 and placebo.

The secondary endpoints of the study are the PK parameters following SXC-2023 administration under fasted and fed conditions.

The PK parameters will also be computed, as appropriate:

SXC-2023:

- plasma: AUC0-t, AUC0-inf, Cmax, Tmax, CL/F, Vz/F, Kel, and T½.
- urine: Aet1-t2, Ae0-72, CLr, and %Fe.
- RBCs (if applicable): AUC0-t, AUC0-inf, Cmax, Tmax, CL/F, Vz/F, Kel, and T½.

NAC and *p*-toluic acid:

- plasma: AUC0-t, AUC0-inf, Cmax, Tmax, Kel, and T½.
- urine: Aet1-t2, Ae0-72, and CLr.
- RBCs (if applicable): AUC0-t, AUC0-inf, Cmax, Tmax, Kel, and T½.

The effect of food on a single oral dose of SXC-2023 will be assessed by comparing AUC0-t, AUC0-inf, and Cmax under fed versus fasting conditions using an ANOVA.

10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, SAD and FE study.

Up to 48 healthy, adult male and female subjects are planned to be enrolled in 6 cohorts of 8 subjects each (6 active and 2 placebo). Subjects will participate in only one cohort.

Screening of subjects will occur within 28 days prior to dosing.

Each cohort will include a sentinel group (1 active and 1 placebo) who will be dosed at least 24 hours before the remaining 6 subjects (5 active and 1 placebo). Dosing of the remaining 6 subjects will be conducted following a safety evaluation of the sentinel group by the PI, Medical Monitor, and Sponsor.

In each cohort, subjects will receive a single oral dose of SXC-2023 or placebo under fasting conditions, with one cohort crossing over to receive the same dose of SXC-2023 or placebo for a second time under fed conditions. There will be a washout period of at least 7 days between dosing under fasting conditions and dosing under fed conditions (high-fat breakfast).

Blood and urine samples will be collected predose through 72 hours postdose for the PK assessment of SXC-2023, NAC, and *p*-toluic acid, as appropriate.

Dose escalation to the next dose level (i.e., next cohort) will not take place until a PI, Medical Monitor, and Sponsor representative have determined that adequate safety, tolerability, and PK plasma have been demonstrated regarding the previous cohort(s) to permit proceeding to the next cohort.

The dose level (i.e., cohort) to be used for the assessment of a FE will be determined based on the safety, tolerability, and PK plasma evaluations of previous cohorts. The safety and tolerability of the dose at least one dose level higher than the dose level selected for the FE cohort, may be evaluated.

All Parts

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

Discontinued subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed on Day -1, at the time indicated by the CRU, until after the 72-hour blood draw and/or end of treatment procedures on Day 4. Subjects from one cohort will be confined for a second, similar, period for the FE arm of the study. A subject may be required to remain at the CRU for longer at the discretion of the PI or designee.

All subjects who received a dose of study drug/placebo (including subjects who terminate the study early) will return to the CRU approximately 7 days after the last study drug/placebo administration for follow-up procedures, and to determine if any AEs have occurred since the last study visit.

10.1.2 Study Duration

The total planned duration of subject participation is approximately 35 days from screening to follow-up, with CRU confinement from check-in on Day -1 to Day 4. The total planned duration of subject participation is approximately 42 days for subjects enrolled to receive a second dose under fed conditions.

10.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

10.2.1 Screening

Screening will begin within 28 days prior to dosing. Informed consent will be obtained at screening (see Section 13.1.3). Subjects will have to meet all eligibility criteria before being enrolled in the study (see Section 10.3). Subjects will be informed of the study restrictions (see Section 10.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), body mass index (BMI) (kg/m^2), and history of tobacco use.

Safety assessment will be conducted as listed in the Study Events Flow Chart (Section 6).

10.2.2 Check-in Procedures (Day -1)

At check-in (Day -1), subjects will return to the CRU, and those subjects who satisfy all of the inclusion criteria and none of the exclusion criteria will qualify and be eligible for randomization. A check-in questionnaire will be reviewed for each subject to ensure that subjects remain eligible for the study since screening. Questions will focus on inclusion and exclusion criteria and on study restrictions. Subjects in all cohorts will be required to satisfy all of the inclusion criteria and none of the exclusion criteria at the time of each check-in.

Safety assessment will be conducted as listed in the Study Events Flow Chart (Section 6).

10.2.3 Treatment Period (Day 1 to Day 4)

10.2.3.1 Single-dose Administration

On the morning of Day 1, predose evaluations will be obtained.

Subjects will receive a single oral dose of the assigned formulation (SXC-2023 or placebo) on the morning of Day 1 (Section 10.4.1 and Section 10.4.4).

Safety and tolerability will be monitored throughout the treatment period as listed in the Study Events Flow Chart (Section 6).

Blood samples for PK assessments (Section 11.2.1) will be collected at the time points as listed in the Study Events Flow Chart (Section 6).

Urine samples for PK assessments (Section 11.2.2) will be collected over specific intervals as listed in the Study Events Flow Chart (Section 6).

10.2.3.1.1 Food Effect Group

Following washout period of at least 7 days, subjects in one cohort will return and check-in for a second treatment period. They will receive the same treatment under fed conditions. The subjects will repeat the events outlined above (Sections 10.2.2 to 10.2.4) and as delineated in the Study Events Flow Chart (Section 6).

10.2.3.2 Meal Schedule

Water (except water provided with each dosing) will be restricted 1 hour prior to and 1 hour after each study drug/placebo administration, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

In the fasted cohorts, subjects will fast overnight for at least 10 hours prior to study drug/placebo administration. On Day 1, subjects will continue the fast for at least 4 hours postdose.

On Day 1 of the fed portion, subjects will be required to fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat breakfast which will be entirely consumed within 30 minutes. An example of high-fat breakfast would be 2 slices of buttered toast, 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, and 240 mL of whole milk [FDA Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, 2002]. Subjects will fast for at least 4 hours following dose on this day.

On Day 1, standard meals will be provided at approximately 4 and 9 hours postdose, and at appropriate times thereafter. Snacks will be provided appropriate times thereafter. When confined in the CRU, subjects will be required to fast from all food and drink except water

between meals and snacks.

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition (except for the high-fat breakfast served as part of the fed portion) and will be taken at approximately the same time in each period.

10.2.3.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours following study drug/placebo administration, except when they are supine or semi-reclined for study procedures.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Specific measures will be taken to prevent the subject from missing a urine collection by strictly controlling and providing access to designated restrooms only. Subjects will be asked to void prior to entering the shower.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

10.2.4 End-of-Treatment

Subjects will remain confined until 72 hours after Day 1 dosing. Before leaving the CRU, all subjects will have the end-of-treatment evaluation. A subject may be required to remain at the CRU longer at the discretion of the PI.

The end-of-treatment procedures are listed in the Study Events Flow Chart (Section 6).

10.2.5 Follow-up Visit / End-of-Study

All subjects who received a dose of study drug/placebo (including subjects who termination the study early) will be asked to return to the clinical facility for a follow-up visit approximately 7 days after Day 1 dosing.

For any subject enrolled in the study, the study participation will be concluded following the end-of-study evaluation (approximately 7 days after the last dose) or at early termination. Should any subjects withdraw or be withdrawn from the study, all the follow-up (end-of-study) evaluations should be performed if possible, including samples for PK assessments if applicable.

The follow-up (end-of-study) procedures are listed in the Study Events Flow Chart (Section 6).

10.2.6 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 5 cohorts or after dose-limiting clinical safety endpoints have been reached to preclude further increases of dose.

This time period may change in the event that the study is terminated early, additional cohorts are enrolled, additional time is required to review safety data between cohorts, or a decision is made to complete an unscheduled analysis between cohorts.

10.3 Selection of Study Population

10.3.1 Number of Subjects

Up to 48 healthy, adult male and female subjects will be enrolled in 6 cohorts of 8 subjects each (6 subjects to receive active drug and 2 subjects to receive placebo per the randomization)

Every attempt will be made to enroll 50% of each sex in each cohort.

A sentinel group (1 active and 1 placebo) in each fasted cohort will consist of 2 subjects who will be randomized to receive active drug or placebo. The remaining 6 subjects in the cohort will be randomized to receive active drug (n=5) or placebo (n=1).

Additional subjects may be enrolled if it is deemed appropriate by the PI, the Sponsor, and the Medical Monitor to repeat a dose level or to study an intermediate dose level (lower than those planned).

10.3.2 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study, unless otherwise specified:

1. Healthy, adult, male or female (WONCBP only), 18-55 years of age, inclusive, at screening.

2. Continuous non-smoker who has not used nicotine-containing products for at least 3 months prior to the first dose and throughout the study.

3. Body mass index (BMI) $\geq$ 18.0 and $\leq$ 32.0 kg/m^2 at screening.

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

5. 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 and FSH serum levels consistent with postmenopausal status.

6. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 90 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 dosing of study drug/placebo. A male who has been vasectomized less than 4 months prior to study dosing must follow the same restrictions as a non-vasectomized male).

7. If male, must agree not to donate sperm from the first dose until 90 days after the last dose administration.

8. For subjects in Cohorts 5 and 6, must be able to swallow multiple capsules.

9. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol.

10.3.3 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

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

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI or designee.

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

4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dose.

5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.

6. Allergy to band aids, adhesive dressing, or medical tape.

7. Female subject of childbearing potential.

8. Female subject with a positive pregnancy test or who is lactating.

9. Positive urine cotinine at screening.

10. Positive urine drug or alcohol results at screening or check-in.

11. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).

12. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.

13. QTcF interval is >460 msec (males) or >470 msec (females) or has ECG findings deemed abnormal with clinical significance by the PI or designee at screening.

14. Unable to refrain from or anticipates the use of any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to the first dose and throughout the study. After randomization/dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

15. Is lactose intolerant.

16. Has been on a diet incompatible with the on-study diet, in the opinion of the PI or designee, within the 30 days prior to the first dose and throughout the study.

17. Donation of blood or significant blood loss within 56 days prior to the first dose.

18. Plasma donation within 7 days prior to the first dose.

19. Participation in another clinical study within 30 days prior to the first dose. 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 first dose of the current study.

10.3.4 Early Termination of Subjects from the Study

Subject participation in this trial may be discontinued for any of the following reasons:

- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the PI that continued participation is not in the best interest of the subject.

- Subject's decision to withdraw.
- Requirement of prohibited concomitant medication.
- Subject failure to comply with protocol requirements or study related procedures.
- Termination of the study by the Sponsor, FDA, Celerion, or other regulatory authorities.

The clinical report will include reason(s) for subject withdrawals as well as details relevant to the subject withdrawal. If a subject is withdrawn from the trial prior to study completion, the subject will undergo all procedures scheduled for study completion (end-of-treatment / early termination evaluations) as the situation allows (see Section 10.2.4). Any subject withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the PI or a monitoring physician and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the PI.

10.3.5 Prohibitions and Concomitant Medication

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 24 hours before dosing and throughout the study. Subjects in the FE portion will be allowed to consume xanthines/caffeine containing food and beverages from the end of sample collection in the fasted cohort and through 24 hours before the second dosing (under fed conditions);
- Alcohol: 48 hours before dosing and throughout the study. Subjects in the FE portion will be allowed to consume alcohol from the end of sample collection in the fasted cohort and through 48 hours before the second dosing (under fed conditions);
- Grapefruit/Seville orange: 14 days before dosing and throughout the study. Subjects in the FE portion will be allowed to consume Grapefruit/Seville orange from the end of sample collection in the fasted cohort and through 14 days before the second dosing (under fed conditions).

Concomitant medication will be prohibited as listed in the exclusion criteria in Section 10.3.3. After randomization/dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

If deviations occur, the PI or designee in consultation with the Sponsor will decide on a case-by-case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

10.4 Treatments

10.4.1 Treatments Administered

SXC-2023 will be supplied as 50 and 200 mg capsules.

Placebo will be provided as matching placebo capsules.

Subjects will be instructed not to crush, split or chew the study drug/placebo.

Subjects in each cohort will receive a single oral dose of SXC-2023 or placebo, under fasting conditions.

Planned doses will be as follows:

Cohort 1: 50 mg (1 x 50 mg capsule) SXC-2023 or matching placebo

Cohort 2: 100 mg (2 x 50 mg capsules) SXC-2023 or matching placebo

Cohort 3: 200 mg (1 x 200 mg capsule) SXC-2023 or matching placebo

Cohort 4: 400 mg (2 x 200 mg capsules) SXC-2023 or matching placebo

Cohort 5: 800 mg (4 x 200 mg capsules) SXC-2023 or matching placebo

Cohort 6: 1600 mg (8 x 200 mg capsules) SXC-2023 or matching placebo

One cohort will receive the same dose of SXC-2023 or placebo for a second time under fed conditions following a washout period of at least 7 days. The dose level (i.e., cohort) to be used for the FE cohort will be determined based on the safety, tolerability, and PK plasma evaluations of previous cohorts and the safety. The safety and tolerability of the dose at least one dose level higher than the dose level selected for the FE cohort, may be evaluated.

When administered under fed conditions, SXC-2023 will be administered orally following a high-fat breakfast.

A sentinel group (1 active and 1 placebo) in each fasted cohort will consist of 2 subjects who will be randomized to receive active drug or placebo. The remaining 6 subjects in the cohort will be randomized to receive active drug (n=5) or placebo (n=1).

All doses of study drug/placebo will be administered with approximately 240 mL of water. In Cohort 6, if the study drugs cannot all be swallowed at the same time, the drug administration may be divided; however, dosing should be completed within 10 minutes. Additional water, up to a maximum of 50 mL may be administered as required by the subject.

An unblinded pharmacist will be responsible for providing SXC-2023 or placebo to the blinded study personnel for administration.

The exact clock time of dosing will be recorded.

10.4.2 Repeat / Additional Dose Levels

Additional subjects may be enrolled if it is deemed appropriate by the PI, the Sponsor, and the Medical Monitor to repeat a dose level or to study an intermediate dose level (lower than those planned).

10.4.3 Dose Escalation and Stopping Rules

A decision to proceed to the next higher dose administration will be made by the safety data review team which includes but is not limited to, the following members: the PI, Medical Monitor, and Sponsor representative. The safety data review team will review all pertinent blinded safety/tolerability (e.g., physical examinations, vital signs assessments, ECGs, clinical laboratory tests, and AEs) and PK plasma data through at least 3 days following Day 1 dosing for at least 75% of subjects of the current dose level cohort and those from all previous cohorts. The safety data review team will make one of the following determinations:

- To continue with the study as planned.
- To continue with the study and add additional safety evaluations.
- To continue with the study by repeating the current dose, adjusting to an intermediate dose between the current dose and the next planned dose, or adjusting to an intermediate dose between the current dose and the previous lower dose if 1 subject at a given dose level meets any of the following criteria and the subject was determined, after unblinding, to have received active drug:
  - Has a drug-related SAE (see Section 11.1.6.4).
  - Experiences drug-related grade ≥3 severity AE (see Section 11.1.6.3).
- To terminate the study if ≥2 subjects in a cohort meet any of the following criteria and the subjects were determined, after unblinding, to have received active drug:
  - Have a drug-related SAE (see Section 11.1.6.4).
  - Experience drug-related grade ≥3 severity AE (see Section 11.1.6.3).

When applicable, a written statement fully documenting the reasons for study termination will be provided to the institutional review board (IRB).

10.4.4 Method of Assigning Subjects to Treatment Groups

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of dosing, different from the screening number, and will receive the corresponding dose of study drug/placebo, according to a randomization scheme generated at Celerion.

Subjects will participate in only one cohort (in one selected cohort, subjects will participate in the fasted portion and the fed portion).

Subjects will be randomized to receive either SXC-2023 or placebo, maintaining a 3:1 ratio in each cohort. Attempts will be made to enroll 50% of each sex in each cohort.

In each cohort, a sentinel group will consist of 2 subjects who will be randomized to receive active drug or placebo (1 active and 1 placebo). The remaining 6 subjects in the cohort will be randomized to receive active drug (n=5) or placebo (n=1).

Subjects in the first enrollment cohort will be numbered 1001 – 1008; subjects in the second enrollment cohort will be numbered 2001 – 2008, etc.

If replacement subjects are used, they will be assigned a number 100 higher than the original subject (e.g., Subject 1106 would replace Subject 1006). A second replacement for a subject will be assigned a number 100 higher than prior replacement subject (e.g., Subject 1206 would replace Subject 1106).

10.4.5 Blinding

This is a double-blind, randomized, placebo controlled study.

10.4.5.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion statistician and it shall be considered blinded (as per the following).

The randomization is available only to the clinic pharmacy staff that is preparing the drug who will not be involved in any other aspect of the study including administration of the drug. It will not be made available to the Sponsor, bioanalytical laboratory, subjects, or members of the staff responsible for the monitoring and evaluation of safety assessments.

10.4.5.2 Procedures for Breaking the Blind Prior to Study Completion

One set of sealed envelopes containing the randomization code will be supplied to the PI or designee at the start of the study.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject or in the event of an interim analysis.

In the event of a medical emergency, it is requested that the PI or designee make every effort to contact the Study Monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the PI or designee, for that subject only. In the event that the emergency is one, in which it appears that the other subjects may be at imminent risk, the blind may be broken for all subjects dosed at that dose level. The unblinding will be properly documented in the study file.

In all cases where the blind is broken, the PI or designee should record the date and reason for blind breaking.

At the end of the study, envelopes will be retained or destroyed according to site procedures unless specified otherwise by the Sponsor.

10.4.5.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, and the database is officially locked.

10.4.5.4 Interim Analysis

Safety:
All available blinded safety data will be reviewed by the PI, Medical Monitor, and Sponsor representative prior to dose escalation and to determine the dose level for the FE cohort.

At the Sponsor's request, unblinded safety tables, figures, and data listings may be presented to the Sponsor for the purposes of planning the next clinical studies prior to database lock. These interim analyses will be performed on data that will be edit-checked and monitored.

A safety data analyst and a biostatistician at Celerion who are not involved with the present study and are not located at the Celerion's Phoenix site will be unblinded to prepare unblinded safety tables, figures, and data listings, if needed. All the personnel related to the present study will remain blinded.

Pharmacokinetics:
Preliminary PK analysis will be performed for all cohorts. PK plasma analysis data will be used to guide the dose escalation decision and may be used to evaluate the sampling time points as the study progresses. PK plasma analysis data will also be used to determine the dose level for the FE cohort.

Interim PK analysis will not use the actual subject numbers in order to avoid breaking the blind.

10.4.6 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug/placebo. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug/placebo was ingested.

11 STUDY PROCEDURES

11.1 Safety Assessments

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the primary assessment is the safety and tolerability. Safety will be determined by evaluating physical examinations, vital signs, 12-lead ECGs, clinical laboratory parameters, including but not limited to, hematology, clinical chemistry profile, urinalysis, and AEs as outlined in the Study Events Flow Chart (Section 6).

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

11.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6). BMI will be calculated.

11.1.2 Physical Examination

A full physical examination will be performed as per Study Events Flow Chart (Section 6). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

11.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 6). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g. nausea, dizziness) or if deemed necessary by the PI or designee.

Vital signs will be measured within 24 hours prior to dosing on Day 1, for the predose time point. When scheduled postdose, vital signs will be performed within approximately 10 minutes of the scheduled time point.

11.1.4 12-Lead ECG Monitoring

ECGs will be performed as outlined in the Study Events Flow Chart (Section 6).

ECGs will be measured within 24 hours prior to dosing on Day 1, for each cohort for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

ECGs will be taken following resting in the supine position in a quiet environment. Single 12-lead ECGs may be taken at any other times, if deemed necessary.

All ECGs will be interpreted on-site by the PI or designee.

A subject will be withdrawn from the study by the PI or his/her designee if, in their medical judgment, ECG findings are present which make continued study participation not in the subject's best interest.

11.1.5 Clinical Laboratory Tests

All tests listed below will be performed as per Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology
- Hemoglobin
- Hematocrit
- Mean corpuscular volume
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Total and differential leukocyte count
- RBC count
- Platelet count

Coagulation
- Prothrombin time / International normalized ratio, and activated prothrombin time

Urinalysis
- pH
- Specific gravity
- Protein***
- Glucose
- Ketones
- Bilirubin
- Blood***
- Nitrite***
- Urobilinogen
- Leukocyte esterase***

Serum Chemistry*
- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine**
- Creatine phosphokinase
- Gamma-glutamyl transferase

Additional Tests
- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opioids
  - Opiates
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Urine cotinine
- Serum pregnancy test (for females only)
- FSH ¥
- Luteinizing hormone (LH) ¥
- Total testosterone ¥

* Serum chemistry tests will be performed after at least a 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

** At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

*** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for RBCs, white blood cells, bacteria, casts, and epithelial cells) will be performed.

¥ Samples for serum total testosterone, LH, and FSH will be collected at the same clock time (±1 hour) in the morning (before 10:00 AM) on each scheduled day, except for sample for FSH collected from postmenapausal women at screening.

11.1.6 Adverse Events

11.1.6.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

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

11.1.6.2 Monitoring

Subjects will be monitored throughout confinement for adverse reactions to the study formulations and/or procedures. Prior to release, subjects will be asked how they are feeling. At the beginning of the second period of the FE cohort subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at Celerion or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

11.1.6.3 Reporting

All AEs that occurred during this clinical trial will be recorded. AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®).

The PI will review each event and assess its relationship to drug treatment (likely, probably, possibly, unlikely or unrelated). Each sign or symptom reported will be graded on the FDA (CBER) toxicity grading scale for healthy volunteers 4-point severity scale (Grade 1, 2, 3 and 4) [FDA (CBER) Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, 2007]. The date and time of onset, time relationship to drug dosing, duration, and outcome of each event will be noted.

Relationship of AE:

The relationship of each AE to the study drug will be assessed using the following definitions:

Unrelated	▪ The adverse event must clearly be caused by the participant's clinical state, or the study procedure/conditions ▪ Definitely not related to drug ▪ Temporal sequence of an adverse event onset relative to administration of drug not reasonable ▪ Another obvious cause of an adverse event
Unlikely	▪ Time sequence is unreasonable ▪ There is another more likely cause for an adverse event
Possibly	▪ Corresponds to what is known about the drug ▪ Time sequence is reasonable ▪ Could have been due to another equally, likely cause
Probably	▪ Is a known effect of the drug ▪ Time sequence from taking drug is reasonable ▪ Ceases on stopping the drug ▪ Cannot be reasonably explained by the known characteristics of the participants clinical state
Likely	▪ Is a known effect of the drug (e.g. listed in PDR, CPS, IB) ▪ Time sequence from taking drug is reasonable ▪ Event stops upon stopping drug, event returns upon restarting drug

Severity of AE:

The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious (e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.

A semi-colon indicates 'or' within the description of the grade.

Note: Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.6.4 Serious Adverse Event

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The IRB will be notified of the Alert Reports as per FDA regulations.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

If a SAE occurs to a subject on this study, contact the Sponsor personnel listed in Section 3.

11.2 Pharmacokinetic Assessments

11.2.1 Blood Sampling and Processing

As a precaution, blood samples will be collected and processed under conditions that will minimize their exposure to UV light.

For all subjects, blood samples for the determination of SXC-2023, NAC, and *p*-toluic acid will be collected in blood collection tubes at scheduled time points as delineated in the Study Events Flow Chart (Section 6). For doses ≥ 200 mg, RBCs will be collected to assess analytes, if appropriate.

Instruction for blood sampling, collection, processing, and sample shipment will be provided separately.

The allowable deviation window is as follows:

Sample time	**Allowed deviation**
≤ 8.0 hours	± 2 minutes
> 8.0 hours to ≤ 24 hours	± 5 minutes
> 24 hours to ≤ 72 hours	± 10 minutes
> 72 hours	± 15 minutes

11.2.2 Urine Sampling and Processing

As a precaution, samples will be collected and processed under conditions that will minimize their exposure to UV light.

Urine for PK assessments will be collected at the specified intervals delineated in the Study Events Flow Chart (Section 6).

Prior to the predose sample, each subject will be instructed as to urine collection methods. All urine during an interval is to be collected.

On Day 1, a spot collection will be obtained prior to dosing for the predose sample. Subjects will be asked again to empty their bladder within approximately 15 minutes prior to dosing,

and no urine will be collected at this time unless it is needed for the predose sample. Only one predose urine sample will be collected on Day 1.

Subjects will be encouraged to void at the end of each collection interval. If they do void at any time during the collection interval, the time should be documented. Should this be the case, subjects need to void again at the end of the collection period, as scheduled. However, should subjects be unable to void, this will be documented as well.

Urine will be refrigerated during the collection intervals. At the end of each interval, urine will be pooled and thoroughly mixed. Total urine volume will be weighed and recorded.

Instructions for urine sampling, collection, processing, and sample shipment will be provided separately document.

11.2.3 Analytical Method

Samples will be analyzed for SXC-2023, NAC, and *p*-toluic acid in plasma and urine using validated bioanalytical methods and samples for one or more analytes, if applicable, in RBCs will be analyzed using qualified bioanalytical methods. Samples from subjects to be assayed are specified in Section 12.2.2.

11.3 Blood Volume Drawn for Study Assessments

Table 1: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation, and serology), FSH (for postmenopausal female subjects only), and serum pregnancy (for female subjects only).	1	16	16
On-study hematology and serum chemistry (this includes serum pregnancy for female subjects only and testosterone, LH, and FSH, when scheduled at the same time)	3 (6 **)	12.5	37.5 (75 **)
Blood for SXC-2023, NAC, and *p*-toluic	18 (36 **)	4	72 (144 **)
		Total Blood Volume (mL)→	125.5 (235 **) *

* If additional safety, and/or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum and/or RBCs for analysis, additional blood may be obtained (up to a maximum of 50 mL).

** Subjects in the FE cohort.

12 DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

12.1 Pharmacokinetic Parameters

12.1.1 For Plasma and Red Blood Cells

PK parameters for plasma and RBCs (if applicable) SXC-2023, NAC, and *p*-toluic will be calculated as follows, as appropriate:

AUC0-t: The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.

AUC0-inf: The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma and RBC concentration to the elimination rate constant.

CL/F: Apparent total plasma and RBC clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf (parent only).

Cmax: Maximum observed concentration.

Tmax: Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.

Kel: Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma and RBC concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma/RBC concentrations).

T½: Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.

Vz/F: Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as Dose/(AUC0-inf x Kel) (parent only).

No value for AUC0-inf, CL/F, Vz/F, Kel, or T½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

Individual and mean plasma and RBC (if applicable) concentration time curves (both linear and log-linear) will be included in the final report.

Additional PK parameters may be calculated, if deemed appropriate.

12.1.2 For Urine

PK parameters for urine SXC-2023, NAC, and *p*-toluic will be calculated as follows:

Aet1-t2 Amount of drug excreted in the urine collection interval from t1 to t2.

Ae0-72: Total amount of drug excreted in the urine over the entire period of sample collection (0-72 h), obtained by adding the amounts excreted over each collection interval.

CLr: Renal clearance calculated as Ae(t'-t")/AUC(t'-t") where t'-t" is the longest interval of time during which Ae and AUC are both obtained.

%Fe Fraction of drug excreted unchanged in urine (parent only)

Additional PK parameters may be calculated if deemed appropriate.

12.2 Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

12.2.1 Determination of Sample Size

The sample size chosen for this study has been determined adequate to meet the study objectives.

12.2.2 Subjects to Analyze

Safety Population: All subjects who received any dose of the study drug/placebo will be included in the safety evaluations.

PK Population: Samples from all subjects will be assayed even if the subjects do not complete the study. All subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

12.2.3 Safety Evaluation

The following analyses will be performed; however, no formal inferential statistics will be performed on safety assessments.

The placebo subjects from all cohorts in each part will be pooled into a single placebo group for all summaries and presentations.

A by-subject TEAE data listing, including verbatim term, preferred term, treatment, severity, outcome, seriousness, and relationship to treatment, will be provided.

The number of subjects experiencing AEs and number of AEs will be summarized by treatment using frequency counts.

Safety data, including laboratory evaluations, vital signs assessments, and ECGs will be summarized by treatment and time point of collection.

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

A mean change-from-baseline table will be provided for vital signs, ECGs and clinical laboratory results, per treatment.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

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

AEs will be coded using the most current version of MedDRA® available at Celerion.

Concomitant medications will be listed by treatment and coded using the most current WHO drug dictionary available at Celerion and listed by treatment.

12.2.4 Pharmacokinetic Analysis

12.2.4.1 Descriptive statistics

Values will be calculated for plasma, RBCs (if appropriate) and urine SXC-2023, NAC, and *p*-toluic concentrations following SXC-2023 administration under fasted and fed conditions, and the PK parameters listed in Section 12.1 using appropriate summary statistics to be fully outlined in the SAP.

12.2.4.2 Food Effect Assessment

An ANOVA will be performed on the natural log (ln)-transformed AUC0-t, AUC0-inf, and Cmax. The ANOVA model will include dietary conditions (fast, fed) as a fixed effect and subject as a random effect. Each ANOVA will include calculation of least-squares means (LSM), the difference between regimen LSM, and the standard error associated with this difference. The above statistical analyses will be done using the appropriate statistical procedure.

Ratios of LSM will be calculated using the exponentiation of the LSM from the analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. These ratios will be expressed as a percentage relative to the fasting conditions.

Ninety percent (90%) confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between regimen LSM resulting from the analyses on the ln-transformed AUC0-t, AUC0-inf, and Cmax. The CIs will be expressed as a percentage relative to the fasting conditions.

12.2.4.3 Dose Proportionality Analysis

Dose proportionality will be evaluated for SXC-2023, NAC, and *p*-toluic AUC and Cmax parameters following administration of single doses (fasted cohorts). To evaluate dose proportionality, a regression approach will be used. A statistical linear relationship between the ln-transformed PK parameters AUC and Cmax and the ln-transformed dose will be fitted by using a regression model with ln-transformed dose as a covariate.

$Ln(Y) = \beta 0 + \beta \text{ Ln Dose} + \varepsilon$ (Model 1)

where Y represents the PK parameter, AUCs and Cmax.

This approach is usually referred to as a power model because after exponentiation:

$Y = \alpha (\text{Dose})^{\beta}$

where α only depends on β_0 and error.

Dose proportionality requires that $\beta = 1$ for dose-dependent parameters.

As a first step, the statistical linear relationship between the ln-transformed PK parameters AUC and C_{max} and the ln-transformed dose will be verified by including the $(\text{ln dose})^2$ and $(\text{ln dose})^3$ terms in model, as applicable, which corresponds to the quadratic and cubic effects. A 5% level of significance will be used to test the quadratic and/or cubic effects. The statistical linear relationship will be concluded if the quadratic and cubic terms are not statistically significant or if the effects are statistically significant, but of small magnitude (not clinically relevant). If the statistical linear relationship is established in step 1, a second step will be performed. As a second step, model will be used to calculate the 95% CIs for the slope of the ln-transformed PK parameters, AUC and Cmax.

Dose proportionality will be established if a statistical linear relationship is demonstrated and if the 95% CIs for these parameters include the value of 1 for dose-dependent parameters (AUC and Cmax). The above assessments of dose proportionality will be performed using the SAS® mixed procedure.

13 STUDY ADMINISTRATION

13.1 Ethics

13.1.1 Institutional Review Board

This protocol will be reviewed by the Chesapeake Research Review, Inc. IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant to International Council for Harmonisation (ICH) guidelines, and may be reached at:

Chesapeake IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, Maryland 21046, USA
Tel.: +1 410 884-2900

13.1.2 Ethical Conduct of the Study

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

13.1.3 Subject Information and Consent

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

Subjects will be given a copy of their signed ICF.

13.2 Termination of the Study

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

13.3 Data Quality Assurance

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

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the study report.

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

13.4 Direct Access to Source Data/Documents

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

13.5 Drug Supplies, Packaging and Labeling

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

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

13.6 Data Handling and Record Keeping

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

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Celerion until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

13.7 Report Format

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

13.8 Publication Policy

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

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

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