Clinical Study Protocol

Main Title:

A Phase 2a, Safety, Tolerability, Pharmacokinetics, and Quantitative EEG Study of CX-8998 in Adolescents and Adults with Idiopathic Generalized Epilepsy with Absence Seizures

Protocol Number: CX-8998-CLN2-002

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Official Short Title:

CX-8998 for Absence Seizures

Confidentiality Statement:

NCT03406702

SIGNATURE PAGE FOR SPONSOR

Study No. CX-8998-CLN2-002

Protocol Title: A Phase 2a, Safety, Tolerability, Pharmacokinetics, and Quantitative EEG Study of CX-8998 in Adolescents and Adults with Idiopathic Generalized Epilepsy with Absence Seizures

Approved by the following:

PI

31MAY2019

Date

Cavion, Inc.
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Cambridge, MA 02142

SIGNATURE PAGE FOR INVESTIGATOR

Study No. CX-8998-CLN2-002

Protocol Title: A Phase 2a, Safety, Tolerability, Pharmacokinetics, and Quantitative EEG Study of CX-8998 in Adolescents and Adults with Idiopathic Generalized Epilepsy with Absence Seizures

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with all applicable regulations, ICH and the Declaration of Helsinki.

_____	_____	_____
Investigator Name	Signature	Date

STUDY ORGANIZATIONAL STRUCTURE

Sponsor:	Cavion, Inc. One Broadway Cambridge, MA 02461 +1.434.200.8442
Study Safety Representative:	24-Hour Serious Adverse Event (SAE) Reporting Primary contact: Premier Research Pharmacovigilance Reporting email: GlobalPV-US@premier-research.com Backup reporting fax number: +1.215.972.8765

COMPLIANCE STATEMENT

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Directive 20/EC and 28/EC). Any episode of noncompliance will be documented.

The investigators are responsible for performing the study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of each investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities.

Each investigator is responsible for ensuring the privacy, health, and welfare of the subjects during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. Each investigator and the applicable study staff must be familiar with the background to, and requirements of, the study and with the properties of the study drug(s) as described in the Investigator's Brochure or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with local authorities.

PROTOCOL SYNOPSIS

Study Title: A Phase 2a, Safety, Tolerability, Pharmacokinetics, and Quantitative EEG Study of CX-8998 in Adolescents and Adults with Idiopathic Generalized Epilepsy with Absence Seizures

Name of Finished Product: CX-8998

Protocol Number: CX-8998-CLN2-002	**Study Phase:** 2a

Clinical Sites:
Multiple sites in the United States

Primary Objective

- To assess the safety and tolerability of CX-8998 in adolescents and adults with idiopathic generalized epilepsy (IGE) with absence seizures.

Secondary Objectives

- To evaluate the pharmacokinetics (PK) of CX-8998 and its metabolites (including, but not limited to, M01 and M02) in the plasma of subjects with IGE with absence seizures.

Exploratory Objectives

- To assess the exposure-response and exposure-safety relationships for plasma CX-8998 and its metabolites (including, but not limited to, M01 and M02); results to be reported separately from the clinical study report.
- To evaluate the pharmacodynamic effects of CX-8998 as measured by electroencephalogram (EEG)

Study Design:
This is a Phase 2a, open-label study consisting of a screening period of up to 4 weeks and a 4-dose-titration treatment period to a dose of up to 10 mg twice daily (BID) of CX-8998, followed by a 1-week safety follow-up period after the last dose of study medication.

Study Population:
Inclusion Criteria

1. Signed informed consent form (ICF) indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
2. Men or nonpregnant, non-breastfeeding women 16 to 55 years of age who are able to read and understand written and spoken local language.
3. Clinical diagnosis of IGE (including, but not limited to, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, or Jeavons syndrome) with absence seizures consistent with the International League against Epilepsy Revised Classification of Seizures (2017).
4. Absence seizures, by history on average once per hour, persisting despite standard of care (SOC) treatment, defined as treatment with at least 2 antiepileptic drugs (AEDs) appropriate for the patient's epilepsy syndrome. SOC failure, per investigator discretion, will be defined as insufficient clinical response or intolerable side effects, which precludes the use of the appropriate AED.
5. Observation of at least 1 provoked absence seizure during at least 1 of the hyperventilation (HV) periods and at least 3 absence seizures during the 6.5-hour video-EEG. Absence seizures

are defined on EEG as typical generalized 3-Hz spike and wave lasting ≥3 seconds during wakefulness. Hyperventilation should be carried out in the following manner: 5 minutes of HV (HV period 1), followed by 5 minutes of relaxation, followed by a second 5 minutes of HV (HV period 2). Subjects who have an induced seizure during HV period 1 do not need to undergo HV period 2. At least 75% of the background should be normal.

6. On stable doses of one or more antiepileptic medication(s) for at least 30 days. If a subject is not on medication, adequate documentation justifying lack of therapy may be acceptable for the subject after sponsor review. Ketogenic, modified Atkins diet (MAD), or low glycemic diet with stable carbohydrate ratio for at least 30 days before screening is an acceptable antiepileptic therapy. Vagal nerve stimulation at stable settings (for at least 30 days before screening), without use of the magnet, is also acceptable.
7. Body weight ≥45 kg at screening.
8. Subjects with reproductive capability, including all males and women of childbearing potential (WOCBP), must agree to practice continuous abstinence or adequate contraception methods (appropriate double barrier method or oral, patch, implant, or injectable contraception) from as soon as feasible during screening period until at least 30 days after the last dose (i.e., intermittent abstinence based on "rhythm," temperature monitoring, or other means of timing is not acceptable). WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as amenorrhea for ≥12 consecutive months without another cause, and a documented serum follicle-stimulating hormone (FSH) level ≥35 mIU/mL.
9. Male subjects with a partner of childbearing potential must be surgically sterilized or be willing to use condoms with spermicide from as soon as feasible during screening period until at least 30 days after the last dose.
10. Able and willing to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
11. Approval by the sponsor medical personnel or delegate as to final eligibility for the study.

Exclusion Criteria

1. History of surgical intervention for treatment of epilepsy.
2. Additional seizure (clinical and electrographic) types, including, but not limited to, epileptic spasms, generalized tonic seizures, atonic seizures, or focal seizures. Subjects with generalized tonic-clonic seizure (GTCS) or myoclonic seizures are eligible for the study.
3. Inadequately treated psychotic or mood disorder (e.g., schizophrenia, major depression, bipolar disorder).
4. Presence of severe intellectual disability, severe autism spectrum disorder, or severe developmental disorder such that the subject cannot sign the ICF or cannot cooperate with the study procedures.
5. Presence of positive urine drug screen for drugs of abuse, except if this is explained by use of an allowed prescription medicine.
6. Regular use of more than 2 standard drinks of alcohol per day (28 grams of pure alcohol).
7. Hypersensitivity/allergic reaction to other T-type calcium agents, such as (but not limited to) ethosuximide and zonisamide.
8. Use of strong CYP3A4 inhibitors, including prescription or nonprescription drugs or other products (e.g., grapefruit juice), which cannot be discontinued at least 2 weeks prior to Day 1 of

dosing and throughout the study (Appendix B).

9. Concurrent illnesses that would be a contraindication to trial participation, including, but not limited to:
   a) Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before screening.
   b) New York Heart Association (NYHA) Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled hypertension.
   c) Clinically significant electrocardiographic (ECG) abnormality per the investigator assessment or any of the following:
      i) QTcF ≥450 msec (males) or ≥470 msec (females).
      ii) PR interval ≥250 msec.
      iii) Atrioventricular block of second degree or higher, including Mobitz I.
      iv) Persistent sinus bradycardia of ≤50 beats per minute; persistent means the bradycardia is present on the first ECG and on one repeat ECG performed on another day.
      v) For other ECG findings (including, but not necessarily limited to, tachycardia, bundle branch block, frequent ectopic beats, etc) the investigator should send a scanned, identity-blinded copy of the ECG tracing to the Study Safety Representative for review.
10. Positive result for human immunodeficiency virus (HIV), hepatitis B [indicating ongoing infection], or hepatitis C at screening or otherwise known ongoing infection with HIV, hepatitis B, or hepatitis C, unless curative therapy completed; for hepatitis C curative therapy is defined as negative polymerase chain reaction (PCR) for hepatitis C virus (HCV) RNA.
11. Significant hepatic (aspartate aminotransferase [AST]/alanine aminotransferase [ALT] or bilirubin ≥2 times the upper limit of normal) or renal disease (creatinine clearance ≤39 mL/min) at screening.
12. History of alcohol or substance abuse within the last year.
13. A current Columbia-Suicide Severity Rating (C-SSRS) score of 4 or 5 at screening or history of suicide attempt.
14. Psychological, social, familial, or geographical reasons that would hinder or prevent compliance with the requirements of the protocol or compromise the informed consent process.
15. Any other condition and/or situation that causes the investigator or Study Safety Representative to deem a subject unsuitable for the study (including, but not limited to, expected study medication noncompliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study–related procedures).
16. Treatment with an investigational agent within 30 days prior to the first dose of CX-8998 or planning to receive an investigational agent during the study.
17. Subjects who do not experience a provoked absence seizure during either HV period and who have fewer than 3 typical absence seizures during the baseline video-EEG (considered to be screen failures).

Planned Number of Patients:

Up to approximately 15

Test Product, Dose, and Mode of Administration:

CX-8998, 2 mg capsule, oral

Reference Product, Dose, and Mode of Administration:

None

Duration of Treatment:

26 days

Administration:

CX-8998 will be administered as:

1. Days 1 – 2: 2 mg (1 capsule) BID (4 mg/d);
2. Days 3 – 8: 4 mg (2 capsules) BID (8 mg/d);
3. Days 9 – 14: 6 mg (3 capsules) BID (12 mg/d);
4. Days 15 – 20: 8 mg (4 capsules) BID (16 mg/d);
5. Days 21 – 26: 10 mg (5 capsules) BID (20 mg/d).

Study drug should be administered with food. Subjects should be instructed to take their daily dose at approximately the same times each day. Consecutive doses should be taken no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours). Subjects will remain under observation for at least 4 hours post-dosing prior to discharge at Visit 1.

At the Day 26 clinic visit at which 2 postdose PK blood draws, >2 hours apart, are scheduled to be obtained, subjects will take the morning dose at the appropriate time. Both the time of the morning dose and the time of the PK blood draw will be recorded.

A missed dose (>14 hours since the prior dose) should be skipped and should not be "doubled-up" or "made up"; the next dose should be taken 24 hours from the last administered dose. If the subject experiences emesis following the dose, that dose should not be retaken; instead the next dose should be taken 24 hours from the last administered dose without emesis. If emesis occurs, the subject should contact the investigator or qualified designee at the study site for guidance on management of the emesis.

Subjects who experience specified adverse events (AEs) will have their dose adjusted. Subjects suspected of experiencing neuropsychiatric AEs may be asked to return to the clinic for an unscheduled visit prior to further dose escalation.

Duration of Subject Study Participation:

Subjects will participate for a total of up to 9 weeks, including screening, the 4-week treatment period and follow-up.

Endpoints:

Primary Endpoint:

Safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAE),
- Changes from baseline in QTcF and other ECG parameters,
- Changes from baseline in clinical safety laboratory assessments (clinical chemistry, hematology, and urinalysis),
- Changes from baseline in vital signs,
- Number (%) of subjects who did not complete the study due to TEAEs
- Number (%) of subjects with serious adverse events (SAEs)

- Number (%) of subjects with adverse events of special interest (AESI):
  - Increased seizure frequency
  - New seizure types
  - Status epilepticus
- C-SSRS
- University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-PDHQ)

Secondary Endpoints:

- Plasma PK parameters: C_{max}, T_{max}, C_{min}, and partial AUC_{0-4h} for CX-8998 and metabolites (including, but not limited to, M01 and M02)
- Additional CX-8998 PK parameters (CL/F, V_z/F, $t_{1/2}$) may be estimated, pending performance of a population PK analysis with data pooled from several studies (to be reported separately from the clinical study report)

Exploratory Endpoints:

- Change in frequency (number of seizures per hour) of absence seizures as defined by a 3-Hz spike and wave lasting ≥3 seconds as determined by HV (HV period 1 + HV period 2)
- Change in frequency (number of seizures per hour) of absence seizures as defined by 3-Hz spike and wave lasting ≥3 seconds during wakefulness as determined by 6.5-hour video-EEG
- Time to absence seizure occurrence during HV (HV period 1 + HV period 2)
- Percent of subjects with a shift in occurrence of absence seizure during HV (e.g., shift for seizure occurring in HV period 1 or HV period 2 to no seizures occurring during either HV period; shift from absence seizure occurring to HV period 1 to HV period 2)
- Change from baseline to end of treatment in absence seizure-free days based on seizure diary
- Absence of photic response in subjects who had photic response during the baseline video-EEG
- Change in the Seizure-related Disability Assessment Scale (SERDAS)
- Relationship between the EEG parameters and the PK of CX-8998
- Exposure-response and exposure-safety relationships using plasma concentrations of CX-8998 and its 2 primary metabolites (M01 and M02) in population pharmacokinetic/pharmacodynamic (PK/PD) analyses (to be reported separately from the clinical study report)

Pharmacokinetic Variables and Endpoints:

Plasma concentrations of CX-8998 and its metabolites (including, but not limited to, M01 and M02) will be determined at various visits and doses of CX-8998. Concentrations will also be incorporated into a population PK/PD model that will estimate peak exposure (C_{max}) and overall exposure (AUC) of CX-8998.

Statistical Methods:

Sample size justification:

The sample size was not based on statistical considerations, but rather chosen to provide safety and efficacy information on CX-8998 when administered according to this protocol

Safety analyses:

Adverse events will be mapped to a MedDRA (Medical Dictionary for Regulatory Activities) preferred term and system organ classification. Severity will be assessed by investigator. The occurrence of TEAEs will be summarized using MedDRA preferred terms, system organ classifications, and severity. All AEs will be listed for individual subjects; both verbatim and preferred terms will be listed. Separate summaries of treatment-emergent SAEs, AESIs, and AEs leading to discontinuation of study or study drug will be generated.

Descriptive summaries of vital signs and clinical laboratory results will be prepared. The number and percentage of subjects experiencing treatment-emergent laboratory abnormalities and laboratory abnormality shifts from baseline to postbaseline assessments will be summarized.

Concomitant medications will be mapped to a World Health Organization (WHO) Drug Dictionary preferred term and drug classification. The number and percent of subjects taking concomitant medications will be summarized using preferred terms and drug classifications.

Changes from baseline in ECGs during study will be evaluated. Results from the C-SSRS, UM-PDHQ, and physical examinations will be listed.

Efficacy analyses:

The change in frequency (number of seizures per hour) of absence seizures as defined by a 3-Hz spike and wave lasting for ≥3 seconds as determined by HV, the frequency (number of seizures per hour) of absence seizures (based on 6.5-hour video-EEG), the time to absence seizures during HV, the percent of subjects with a shift in the occurrence of absence seizure (e.g., from HV period 1 to HV period 2), the percent of subjects with an absence of photic response, the actual and change from baseline in SERDAS scores, and the change from baseline to end of treatment in absence seizure-free days as collected by seizure diary will be summarized. Ninety-five percent (95%) confidence intervals will be constructed.

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GLOSSARY OF TERMS AND ABBREVIATIONS

Abbreviation	Description
ABV	alcohol by volume
ADL	activity(ies) of daily living
AE	adverse event
AED	antiepileptic drug(s)
AESI	adverse events of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BUN	blood urea nitrogen
Ca_V	voltage-dependent calcium channels
CAE	childhood absence epilepsy
CNS	central nervous system
C_{max}	maximum (peak) concentration
C_{min}	minimum concentration
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CHO	Chinese hamster ovary
CK	creatine kinase
CL/F	oral clearance
CNS	central nervous system
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DNA	deoxyribonucleic acid
dnAUC	dose-normalized area under the concentration-time curve
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram

Abbreviation	Description
EOS	end of study
ET	end of treatment
FDA	Food and Drug Administration
FLIPR	Fluorometric Imaging Plate Reader
FOB	functional observation battery
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GI	gastrointestinal
GTCS	generalized tonic clonic seizure
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HV	hyperventilation
IC	inhibition concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IGE	idiopathic generalized epilepsy
IND	investigational new drug
IRB	Institutional Review Board
ITT	intent-to-treat population
JAE	juvenile absence epilepsy
LDH	lactate dehydrogenase
MAD	modified Atkins diet
MedDRA	Medical Dictionary for Regulatory Activities
NHV	normal healthy volunteer
NIH	National Institutes of Health
NOEL	no-observed-effect level
NYHA	New York Heart Association
PCP	phencyclidine
PCR	polymerase chain reaction
PD	pharmacodynamic
PGES	postictal generalized electroencephalography suppression
PK	pharmacokinetic

Abbreviation	Description
PS	photic stimulation
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SERDAS	Seizure-related Disability Scale
SOC	standard of care
$t_{1/2}$	terminal half life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal
UM-PDHQ	University of Miami Parkinson's Disease Hallucinations Questionnaire
V_z/F	volume of distribution
Vh	holding potential
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

1.1.1 Absence Epilepsy

Generalized epilepsies constitute nearly one-third of all epilepsies. Idiopathic generalized epilepsies (IGEs) manifest with absences seizures, myoclonic jerks, and generalized tonic–clonic seizures, alone or in varying combinations and severity (Panayiotopoulos, 2005). Absence seizures are the hallmark seizure type in absence epilepsy (a form of generalized epilepsy) but can also be a predominant seizure type in other generalized epileptic syndromes. Absence seizures are characterized by a transient impairment in consciousness generally not followed by a notable post-ictal state. Absence seizures are characterized clinically and electroencephalographically as typical and atypical types. Typical absence seizures show abrupt onset and resolution and are often accompanied by other features, including staring, behavioral arrest, eyelid fluttering or hand/face automatisms (Penry, 1969). Electroencephalogram (EEG) findings of a typical absence seizure show generalized spike-and-wave complexes in the 3-4.5 Hz range lasting at least 3 seconds (Holmes, 1987, Frank, 1999, Panayiotopoulos, 2008). Age of onset for typical absence seizures is bimodal with a peak at 6-7 years of age and a second peak at 12 years of age (Loiseau, 1995). Atypical absence seizures last longer than typical absences, have less abrupt onset and offset, more pronounced changes in tone and variable impairments of consciousness (Proposal for revised clinical and electroencephalographic classification of epileptic seizures, 1981). EEG findings for atypical absence seizures are more heterogeneous, often showing irregular spike-and-wave complexes that are slower (<2.5 Hz), asymmetrical, and often associated with diffuse fast activity (Holmes, 1987).

Absence epilepsy syndromes include childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), epilepsy with myoclonic absences, juvenile myoclonic epilepsy, and Jeavons syndrome. CAE is the most common pediatric epilepsy syndrome, affecting females more than males and characterized by very frequent (several to many per day) absences in school-age children, with age of onset between 4 and 10 years (Proposal for revised clinical and electroencephalographic classification of epileptic seizures, 1981; Camfield, 1996; Berg, 2000; Jallon, 2001; Fisher, 2005). CAE is self-limiting in many cases with reported remission rates ranging from 21% to 74% (Tenney, 2013) by age 12 or sooner (Posner, 2013) but with roughly 40% developing generalized tonic clonic seizures (GTCS), often 5-10 years after the initial onset of absence seizures (Loiseau 1983). JAE has a later age of onset with most cases beginning between 10 and 17 years (Loiseau, 1995). JAE is distinguished from CAE by more common incidence of GTCS which eventually occur in nearly 80% of JAE patients (Wolf, 1984) and by a higher likelihood of persistence into adulthood (Tenney, 2013). In general, later onset of absence seizures is associated with more severe, persistent and drug resistant epilepsy.

1.1.2 Treatments for Absence Seizures

Current treatments for absence seizures include ethosuximide, valproate, and the sodium channel blocker lamotrigine. Prior to 2010, a total of 6, short duration, small randomized controlled trials had examined ethosuximide, valproic acid, and lamotrigine initial monotherapy in children with

absence epilepsy. Due to multiple methodological limitations, none of these trials met the criteria for either a Class I or II study, providing insufficient evidence to inform clinical practice (Glauser et al., 2006). In 2010, a National Institutes of Health (NIH)-funded randomized controlled trial of 446 children with CAE, ethosuximide and valproate resulted in the best efficacy with 53% and 58% of patients achieving freedom-from-treatment-failure respectively, while lamotrigine showed lower efficacy with seizure free rates of 29% (Glauser et al., 2010). Other treatments less frequently used to treat absence epilepsy include clonazepam, clobazam, zonisamide, and topiramate.

Nearly a quarter of patients receiving front-line drugs experience intolerable side effects (Glauser et al., 2010). Ethosuximide is commonly associated with gastrointestinal (GI) disturbances, anorexia, weight loss, drowsiness, photophobia, headache, and behavioral and psychiatric disturbances and is rarely associated with aplastic anemia, skin reactions, and renal and hepatic impairment (Posner, 2013). Common adverse events (AEs) associated with valproate include GI disturbances, weight gain, and tremor and, rarely, behavioral and cognitive abnormalities and potentially fatal liver necrosis and pancreatitis; its use is limited clinically by weight gain and in women of childbearing potential (WOCBP) because of fetotoxicity (Posner, 2013). Lamotrigine is associated with dizziness, somnolence, nausea, vomiting and headache and can cause serious skin reactions and aseptic meningitis (Posner, 2013).

No randomized, controlled, double-blind trials have been conducted in JAE or in other generalized epilepsy syndromes with absence seizures. Separate expert opinion surveys in the US and Europe found valproic acid and lamotrigine to be the top initial treatment choice for JAE (as they treat both absences and tonic-clonic seizures) (Wheless et al., 2005; Wheless et al., 2007). Second-line (or later) treatments with evidence of modest efficacy for JAE include ethosuximide, amantadine, and the ketogenic diet (Fattore et al., 2011; Groomes et al., 2011).

While a proportion of patients diagnosed with absence seizures will respond to first-line antiepileptic drugs (AEDs) and have a generally good prognosis, a significant proportion will fail to achieve adequate seizure control with existing therapeutics or will experience intolerable side effects that limit therapy (Connock, 2006). For these patients the goal is to achieve seizure control while limiting side effects and negative impacts, especially on cognitive outcomes. Drug-resistant epilepsy has been defined as the "failure of adequate trials of 2 tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom." This operational definition, established by an International League Against Epilepsy commission, (Kwan et al., 2010) relies upon the observation that adults and children rarely achieve sustained seizure freedom once 2 agents have failed to control seizures (Mohanraj & Brodie, 2006; Kwan et al, 2010).

Despite the development of nearly a dozen new drugs for epilepsy in the 1990s and 2000s and, although many newer drugs have superior pharmacokinetic (PK) and side effect profiles than older AEDs, they possess the same degree of effectiveness (Krauss & Sperling, 2011). These AEDs rarely stop seizures once older agents have failed. Innovative pharmaceutical approaches with new antiepileptic drugs, especially those with greater potency, selectivity and a defined mechanism of action are needed to offer treatment options to these patients and yield better response rates.

1.2 Rationale for Evaluating CX-8998 in Idiopathic Generalized Epilepsy with Absence Seizures

1.2.1 Ca_V3 and its Role in Neurological Disorders with Excessive or Abnormal Rhythmicity

Calcium is a ubiquitous intracellular second messenger critical for cellular functions. The elevation of free intracellular Ca^{2+} levels triggers various responses, including the activation of Ca^{2+} dependent enzymes, the secretion of neurotransmitters, and muscle contraction. Multiple calcium ion channels regulate calcium influx in response to membrane depolarization, voltage changes, or substrate, which include the pore-forming $alpha_1$ subunit Cav3 channel (Catterall, 2005; Adams & Snutch, 2007).

The T-type calcium channel, Ca_v3, its 3 isoforms (3.1, 3.2 and 3.3), and their genes *CACNA1G, CACNA1H*, and *CACNA1I* were discovered and cloned in the early 1990s, where their function as low-threshold, voltage-gated calcium channel was elucidated (Cribbs et al., 1998). T-type ("T" is for transient) calcium channels are low voltage-activated channels predominantly found in neurons. As stated previously, a unique and discriminating property of T-type channels (Ca_V3) is their ability to activate upon small depolarization of the membrane, contributing to the setting of the resting membrane potential and allowing a surge of calcium entry into excitable cells at the beginning of an action potential. In pathologic states, Ca_V3 is either upregulated or found to have increased activity, becoming a selective target for specific neurologic diseases (Bourinet et al., 2005; Park et al., 2010; Tai et al., 2011).

Isoforms of Ca_v3 are expressed throughout the central nervous system (CNS) and the peripheral nervous system, including the thalamocortical pathway[1] (Ertel et al., 2000). Deep cerebellar nuclei, substantia nigra, globus pallidus externa, globus pallidus interna, subthalamic nucleus, have been noted to have oscillations in healthy hosts and excessive rhythmicity in animals and humans with pathologic conditions of the nervous system. It has been discovered that Ca_v3 is a mediator of subthreshold oscillations and excessive rhythmicity in pathophysiologic states found in tremor, neuropathic pain, epilepsy and Parkinson's disease (Llinás et al., 1999; Llinás, 2003; Handforth et al., 2005; Park et al., 2013).

1.2.2 Role of Cav3 in Epilepsy

It is well established that T-type calcium channels are a pharmacological target for absence seizures. Neuronal burst-firing, a key pathophysiologic contributor to epileptic seizures, is generated by low threshold calcium potentials initiated by Cav3 channel opening (Cain & Snutch, 2013). In particular, rodent models of absence epilepsy show enhanced Ca_v3 currents in thalamocortical relay neurons and enhanced burst-firing during seizures that correlate with spikes in spike-and-wave discharges. A number of single nucleotide mutations in $Ca_v3.2$ have been reported in patients with childhood absence epilepsy (Chen et al., 2004), some of which result in gains of function in channel gating and in elevated channel expression (Khosravani et al., 2004;

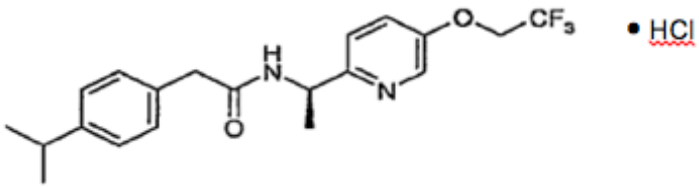
[1] Cav3.1 is the most common isoform in the thalamocortical pathway

Vikto et al., 2005; Peloquin et al., 2006; Vikto et al., 2007). In addition, overexpression of $Ca_v3.1$ results in an absence-like seizure phenotype in mice (Ernst, et al., 2009) and mice lacking $Ca_v3.1$ show reduced thalamocortical burst firing and resistance to pharmacologically induced absence seizures (Kim et al., 2001). A number of antiepileptic drugs have been reported to have nonselective Ca_v3 blocking activity, including ethosuximide, valproate, zonisamide, and phenytoin (Powell et al., 2014). These drugs are thought to act in part through suppression of Ca_v3 activity although all have substantial effects on other types of channels, including sodium, potassium, and potassium-activated calcium currents. Current treatments for absence seizures include ethosuximide, valproate, and the sodium channel blocker lamotrigine. In CAE, ethosuximide and valproate result in the best efficacy, with approximately 50% of patients achieving freedom from seizures, however, nearly a quarter of patients receiving these drugs experience intolerable side effects (Glauser et al., 2010). Thus, selective targeting Ca_v3 channels may offer a more efficacious and better-tolerated treatment option.

1.3 Nonclinical Pharmacology

[redacted]

Figure 1 Chemical Structure of CX-8998



1.3.1 Primary Pharmacology Studies

[redacted]

[redacted]

[redacted]

1.3.2 Safety Pharmacology and Toxicology Studies

[redacted]

[redacted]

1.4 CX-8998 Clinical Experience

[redacted]

Table 1 Completed Clinical Studies

Study Number	Phase Population	Design; endpoints	Dose CX-8998, control
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

randomized; TETRAS = The Essential Tremor Rating Assessment Scale

1.4.1 Clinical Pharmacokinetics

[redacted]

[redacted]

1.4.2 Clinical Pharmacodynamics

[redacted]

1.4.3 Clinical Safety

[redacted]

[redacted]

1.5 Rationale for Selected Dose

[redacted]

[redacted]

[redacted]

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the safety and tolerability of CX-8998 in adolescents and adults with IGE with absence seizures

2.2 Secondary Objectives

- To evaluate the PK of CX-8998 and its metabolites (including, but not limited to, M01 and M02) in the plasma of subjects with IGE with absence seizures

2.3 Exploratory Objectives

- To assess the exposure-response and exposure-safety relationships for plasma CX-8998 and its metabolites (including, but not limited to, M01 and M02); results to be reported separately from the clinical study report
- To evaluate the PD effects of CX-8998 as measured by EEG

3 STUDY DESIGN AND ENDPOINTS

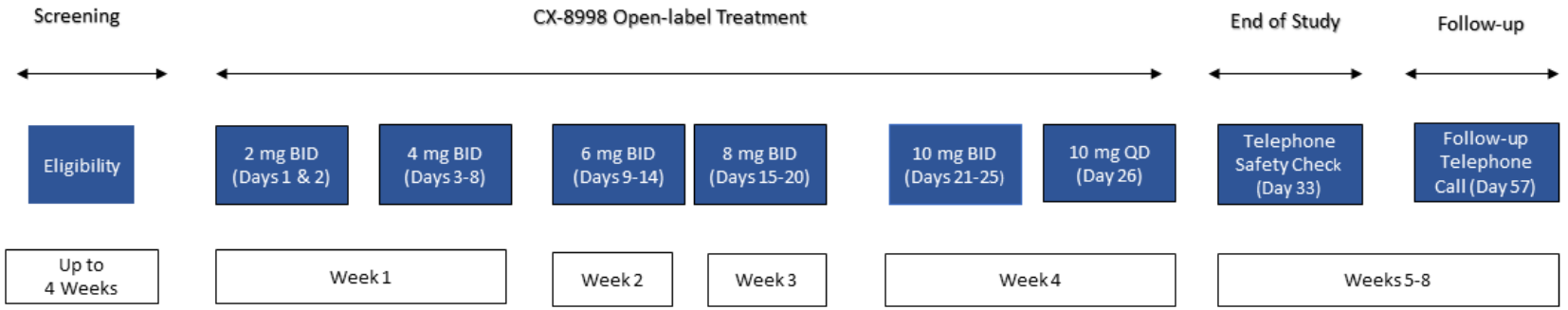
3.1 Study Type

This is a Phase 2a, multicenter, open-label study consisting of a screening period of up to 4 weeks, a 4-week dose-titration treatment period to dose of up to 10 mg BID of CX-8998, and a 1-week safety follow-up period following the last dose of study medication.

3.2 Schematic of Study Design

The study design schematic is shown in Figure 6.

Figure 6 Schematic of Study Design



3.3 Endpoints

3.3.1 Primary Endpoint

Safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAE),
- Changes from baseline in QTcF and other ECG parameters,
- Changes from baseline in clinical safety laboratory assessments (clinical chemistry, hematology, and urinalysis),
- Changes from baseline in vital signs,
- Number (%) of subjects who did not complete the study due to TEAEs
- Number (%) of subjects with SAEs
- Number (%) of subjects with adverse events of special interest (AESI):
    - Increased seizure frequency
    - New seizure types
    - Status epilepticus
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-PDHQ)

3.3.2 Secondary Endpoints

- Plasma PK parameters: C_{max}, T_{max}, C_{min}, and partial $AUC_{0\text{-}4h}$ for CX-8998 and metabolites (including, but not limited to, M01 and M02)
- Additional CX-8998 PK parameters (CL/F, V_z/F, $t_{1/2}$) may be estimated, pending performance of a population PK analysis with data pooled from several studies (to be reported separately from the clinical study report).

3.3.3 Exploratory Endpoints

- Change in frequency (number of seizures per hour) of absence seizures as defined by a 3-Hz spike and wave lasting ≥3 seconds as determined by HV (HV period 1 + HV period 2)
- Change in frequency (number of seizures per hour) of absence seizures as defined by 3-Hz spike and wave lasting ≥3 seconds during wakefulness as determined by 6.5-hour video-EEG
- Time to absence seizure occurrence during HV (HV period 1 + HV period 2)
- Percent of subjects with a shift in occurrence of absence seizure during HV (e.g., shift for seizure occurring in HV period 1 or HV period 2 to no seizures occurring during either HV period; shift from absence seizure occurring to HV period 1 to HV period 2)
- Change from baseline to end of treatment in absence seizure-free days based on seizure diary
- Absence of photic response in subjects who had photic response during the baseline video-EEG

- Change in the Seizure-related Disability Assessment Scale (SERDAS)
- Relationship between the EEG parameters and the PK of CX-8998
- Exposure-response and exposure-safety relationships using plasma concentrations of CX-8998 and its 2 primary metabolites (M01 and M02) in population PK/PD analyses (to be reported separately from the clinical study report)

4 STUDY DRUG

4.1 Supply and Storage

CX-8998 will be supplied as 2 mg capsules. All manufacturing and packaging activities will be performed according to current Good Manufacturing Practices (cGMP) guidelines.

Study drug supplies will be stored securely in a temperature-controlled storage area (a locked cupboard or pharmacy with limited access). Only authorized personnel will have access to the study drug. The study site personnel at each site will be responsible for correct storage and handling of the study drug.

Supplies of study drug should be stored at 20°C to 25°C. Temperature excursions are permitted between 15°C to 30°C.

4.2 Packaging and Labeling

Study medication will be supplied in 60-cc white HDPE bottles with 33-mm polypropylene, white, child-resistant closures. Bottles will contain 62 capsules per bottle. The bottles will be appropriately labeled. The affixed label will have spaces for entering the subject number and subject initials. At the time of dispensing, the subject number and subject initials will be entered onto the appropriate lines on the label.

The product label will contain the following information in the English language:

- Protocol number: CX-8998-CLN2-002
- Kit number (and bottle number)
- Storage conditions
- The sentence, “Caution: New Drug – Limited by Federal (or United States) law to investigational use”
- Name and address of the sponsor

4.3 Administration

CX-8998 will be administered as:

1. Days 1 – 2: 2 mg (1 capsule) BID (4 mg/d);
2. Days 3 – 8: 4 mg (2 capsules) BID (8 mg/d);
3. Days 9 - 14: 6 mg (3 capsules) BID 12 mg/d);
4. Days 15 – 20: 8 mg (4 capsules) BID (16 mg/d);
5. Days 21 - 26: 10 mg (5 capsules) BID (20 mg/d).

Study drug should be administered with food. Subjects should be instructed to take their daily dose at approximately the same times each day. Consecutive doses should be taken no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours). Subjects will remain under observation for at least 4 hours post-dosing prior to discharge at Visit 1.

At the Day 26 clinic visit at which 2 postdose PK blood draws, >2 hours apart, are scheduled to be obtained, subjects will take the morning dose at the appropriate time. Both the time of the morning dose and the time of the PK blood draw will be recorded.

A missed dose (>14 hours since the prior dose) should be skipped and should not be "doubled-up" or "made up"; the next dose should be taken 24 hours from the last administered dose. If the subject experiences emesis following the dose, that dose should not be re-taken; instead the next dose should be taken 24 hours from the last administered dose without emesis. If emesis occurs, the subject should contact the investigator or qualified designee at the study site for guidance on management of the emesis.

Treatment compliance will be assessed as described in Section 4.5.1.

Subjects experiencing specified AEs will have their dose adjusted. See Section 4.6 for details on dose adjustments.

4.4 Subject Stopping Rules

Study drug dosing for an individual subject will be permanently discontinued for intolerable AEs that do not resolve to mild in severity (as defined in Section 10.2.2.2) or baseline within 48 hours of suspension of dosing and for study drug-related SAEs.

Administration of the study treatment will be discontinued if any of the following liver chemistry stopping criteria is met:

- Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 × ULN (upper limit of normal) and total bilirubin level ≥2 × ULN
  NOTE: Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Serum ALT or AST ≥5 × ULN
- Serum ALT or AST ≥3 × ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia)

Any laboratory value that exceeds these limits should be repeated as soon as possible and, if confirmed, study treatment should be immediately discontinued. If a repeat laboratory assessment cannot be obtained within 3 days after receipt of the result showing the abnormal value, study drug should be discontinued.

A subject who meets the following ECG criteria will have study treatment discontinued:

- QTcF >500 msec or uncorrected QT >600 msec
- an increase in QTcF by ≥60 msec from Day 1 predose (baseline) with an absolute value of QTcF ≥450 msec (males) or ≥470 msec (females)

Treatment must be discontinued immediately in any subject who experiences a GTCS during the study if the subject had not had a GTCS prior to study entry. Subjects with worsening of seizures during the study should have treatment discontinued per investigator discretion. Unless consent for further follow-up is withdrawn, subjects who discontinue study drug for safety reasons should be followed in accordance with the schedule detailed in Table 3.

Other reasons for treatment termination are provided in Section 6.4.

4.5 Study Drug Accountability and Compliance

4.5.1 Study Drug Accountability

The investigator or an appointed designee is responsible for ensuring that deliveries of study drug are correctly dispensed and recorded, that the product is handled and stored safely and properly, and that it is only given to subjects in accordance with this protocol.

Sites will keep a current log of drug accountability recording:

- What drug supply was received from the sponsor
- What drug supply was dispensed to each subject
- What drug supply is current in inventory
- What drug supply was destroyed or returned to the sponsor for destruction

Note: Drug accountability is the responsibility of the investigator; a written account will be required for all discrepancies.

If the study drug supplies appear to be damaged/missing upon arrival at the investigational site, the sponsor should be contacted immediately.

The sponsor's designated monitor must verify all accountability records during periodic monitoring visits. Unused and used study drug must be stored on site until such accountability has taken place and authorization is received from the sponsor or sponsor's designee that the study drug may be returned or destroyed.

4.5.2 Subject Compliance with Study Drug

Compliance will be assessed by capsule counts. Subjects will be instructed to bring all used empty bottles and unused study drug with them to the clinic visit on Day 26.

4.6 Dose Adjustments / Toxicity Management

Adverse events will be graded for intensity by the investigator (see Section 10.2.2.2).

Dosing will be discontinued for all study drug-related SAEs.

A member of the study staff will contact any subject who is suspected of experiencing neuropsychiatric AEs to determine the need for an unscheduled visit before further dose escalation may proceed. Subjects who are experiencing any AEs may also be asked to return for an unscheduled visit. Subjects who are suspected of experiencing a neuropsychiatric event should be seen in person.

In all subjects with intolerable AEs (as defined in Section 10.2.1) that are considered related to study drug, treatment should be suspended for up to 48 hours or until the AE resolves to a tolerable level of severity, whichever is earlier. In subjects who are unable to tolerate 6 mg BID, 8 mg BID or 10 mg BID, dosing may then be resumed at a previously tolerated lower dose. Only a single dose-step reduction (i.e., 10 mg BID to 8 mg BID, 8 mg BID to 6 mg BID, or 6 mg BID to 4 mg BID) is permitted. Reescalation of the dose is NOT permitted. Dosing should be discontinued if there is recurrence of intolerable AEs after the dose reduction. Subjects who experience intolerable AEs while receiving the 2 mg BID or 4 mg BID dose will be discontinued from treatment. Table 2 details dose reductions by dose level.

Table 2 Study Drug Dose Reduction for Intolerable AEs

Dose and Schedule of Study Drug	Dose Reduction
2 mg BID	Remove from treatment [1]
4 mg BID	Remove from treatment
6 mg BID	4 mg BID
8 mg BID	6 mg BID
10 mg BID	8 mg BID

1 – Subjects who are removed from treatment for AE(s) should be followed for resolution of the AE(s) and should complete all assessments scheduled for the End-of Study (EOS)/Follow-up (FU) Visit, as well as all assessments that they are capable of completing on the scheduled visit day if the decision to remove from treatment is made on a scheduled visit day. Likewise, if the investigator plans to temporarily interrupt dosing because of an AE and the decision is made on a scheduled visit day, then the subject should complete all scheduled assessments that they are capable of completing on the visit day on which they appear.

All subjects who discontinue treatment due to AEs will be followed for AE outcome. All AEs should be followed for resolution or for 30 days from the last dose of study drug, whichever is shorter.

The Study Safety Representative should be notified of all dose reductions as soon as is feasible.

All subjects who discontinue treatment due to AEs will be followed for AE outcome. All AEs should be followed for resolution or for 30 days from the last dose of study drug, whichever is shorter.

4.7 Overdose Management

To date, no overdoses of CX-8998 in humans have occurred. Therefore, specific information regarding treatment of overdose is not currently available. In case of an acute overdose, it is recommended that the stomach be emptied and oral gavage with activated charcoal be used to help

reduce absorption of CX-8998. In the event of an overdose, the Study Safety Representative should be contacted immediately.

5 INVESTIGATORS, SITES, AND DURATION

5.1 Investigators and Sites

The study will be conducted at multiple sites in the United States.

5.2 Central Reviewers

A central reviewer and the sponsor will review eligibility criteria for all subjects. The site will submit an eligibility checklist for evaluation of each subject. No subject may be enrolled or receive study drug prior to receipt of notification that the central reviewer and review process have deemed the subject eligible.

5.3 Duration of Study

Subjects will participate for a total of up to 9 weeks, including screening, the 4-week treatment period, and follow-up.

5.4 Termination of Study

This study may be terminated at the discretion of the sponsor or the Food and Drug Administration (FDA) or in accordance with the recommendations set forth in the Safety Monitoring Plan (Section 10.4).

6 STUDY POPULATION

6.1 Number of Subjects

Up to approximately 15 eligible subjects will receive treatment.

6.2 Inclusion Criteria

Subjects may be included in the study only if they meet all of the following criteria. Subjects may undergo rescreening following consultation with and approval of the Study Safety Representative.

1) Signed informed consent form (ICF) indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
2) Men or nonpregnant, non-breastfeeding women 16 to 55 years of age who are able to read and understand the written and spoken local language.
3) Clinical diagnosis of IGE (including, but not limited to, CAE, JAE, juvenile myoclonic epilepsy, or Jeavons syndrome) with absence seizures consistent with the International League against Epilepsy Revised Classification of Seizures (2017).
4) Absence seizures, by history on average once per hour, persisting despite standard of care (SOC) treatment, defined as treatment with at least 2 AEDs appropriate for the patient's epilepsy syndrome. SOC failure, per investigator discretion, will be defined as insufficient clinical response or intolerable side effects, which precludes use of the appropriate AED.

5) Observation of at least 1 provoked absence seizure during at least 1 of the hyperventilation (HV) periods and at least 3 absence seizures during the 6.5-hour video-EEG. Absence seizures are defined on EEG as typical generalized 3-Hz spike and wave lasting ≥3 seconds during wakefulness. Hyperventilation should be carried out in the following manner: 5 minutes of HV (HV period 1), followed by 5 minutes of relaxation, followed by a second 5 minutes of HV (HV period 2). Subjects who have an induced seizure during HV period 1 do not need to undergo HV period 2. At least 75% of the background should be normal.
6) On stable doses of one or more antiepileptic medication(s) for at least 30 days. If a subject is not on medication, adequate documentation justifying lack of therapy may be acceptable for the subject after sponsor review. Ketogenic, modified Atkins diet (MAD), or low glycemic diet with stable carbohydrate ratio for at least 30 days before screening is an acceptable antiepileptic therapy. Vagal nerve stimulation at stable settings (for at least 30 days before screening), without use of the magnet, is also acceptable.
7) Body weight ≥45 kg at screening.
8) Subjects with reproductive capability, including all males and WOCBP, must agree to practice continuous abstinence or adequate contraception methods (appropriate double barrier method or oral, patch, implant, or injectable contraception) from as soon as feasible during screening period until at least 30 days after the last dose (i.e., intermittent abstinence based on "rhythm," temperature monitoring, or other means of timing is not acceptable). WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as amenorrhea for ≥12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level ≥35 mIU/mL.
9) Male subjects with a partner of childbearing potential must be surgically sterilized or be willing to use condoms with spermicide from as soon as feasible during screening period until at least 30 days after the last dose.
10) Able and willing to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
11) Approval by the sponsor medical personnel or delegate as to final eligibility for the study.

6.3 Exclusion Criteria

Subjects will be excluded from the study if any of the following conditions apply. Subjects may undergo rescreening following consultation with and approval of the Study Safety Representative.

1) History of surgical intervention for treatment of epilepsy.
2) Additional seizure (clinical and electrographic) types, including, but not limited to, epileptic spasms, generalized tonic seizures, atonic seizures, or focal seizures. Subjects with GTCS or myoclonic seizures are eligible for the study.
3) Inadequately treated psychotic or mood disorder (e.g., schizophrenia, major depression, bipolar disorder).
4) Presence of severe intellectual disability, severe autism spectrum disorder, or severe developmental disorder such that the subject cannot sign the ICF or cannot cooperate with the study procedures.

5) Presence of positive urine drug screen for drugs of abuse, except if this is explained by use of an allowed prescription medicine.

6) Regular use of more than 2 standard drinks of alcohol per day (28 grams of pure alcohol).

7) Hypersensitivity/allergic reaction to other T-type calcium agents, such as (but not limited to) ethosuximide and zonisamide.

8) Use of strong CYP3A4 inhibitors, including prescription or nonprescription drugs or other products (e.g., grapefruit juice), which cannot be discontinued at least 2 weeks prior to Day 1 of dosing and throughout the study (Appendix B).

9) Concurrent illnesses that would be a contraindication to trial participation, including, but not limited to:

   a) Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before screening.

   b) New York Heart Association (NYHA) Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure.

   c) Clinically significant ECG abnormality per the investigator assessment or any of the following:

      i. QTcF ≥450 msec (males) or ≥470 msec (females).

      ii. PR interval ≥250 msec.

      iii. Atrioventricular block of second degree or higher, including Mobitz I.

      iv. Persistent sinus bradycardia of ≤50 beats per minute; persistent means the bradycardia is present on the first ECG and on one repeat ECG performed on another day.

      v. For other ECG findings (e.g., including, but not necessarily limited to, tachycardia, bundle branch block, frequent ectopic beats) the investigator should send a scanned, identity-blinded copy of the ECG tracing to the Study Safety Representative for review.

10) Positive result for human immunodeficiency virus (HIV), hepatitis B [indicating ongoing infection], or hepatitis C at screening or otherwise known ongoing infection with HIV, hepatitis B, or hepatitis C, unless curative therapy has been completed; for hepatitis C curative therapy is defined as negative polymerase chain reaction (PCR) for hepatitis C virus (HCV) RNA.

11) Significant hepatic (AST/ALT or bilirubin ≥2 × ULN) or renal disease (creatinine clearance ≤39 mL/min).

12) History of alcohol or substance abuse within the last year.

13) A current C-SSRS score of 4 or 5 at screening or history of suicide attempt.

14) Psychological, social, familial, or geographical reasons that would hinder or prevent compliance with the requirements of the protocol or compromise the informed consent process.

15) Any other condition and/or situation that causes the investigator or Study Safety Representative to deem a subject unsuitable for the study (including, but not limited to, expected study medication noncompliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study–related procedures)

16) Treatment with an investigational agent within 30 days prior to the first dose of CX-8998 or planning to receive an investigational agent during the study.

17) Subjects who do not experience a provoked absence seizure during either HV period and who have fewer than 3 typical absence seizures during the baseline video-EEG (considered to be screen failures).

6.4 Withdrawal of Subjects and/or Discontinuation of Treatment

A subject should be withdrawn from the study for any of the following:

1) Withdrawal of subject consent.
2) Subject is lost to follow-up.
3) Investigator determines that withdrawal from the study is in the best interest of the subject.
4) Subject is noncompliant with protocol-mandated activities.
5) Occurrence of any intercurrent condition, injury, or disease that becomes apparent during the study and necessitates the termination of the subject from the study.
6) Administrative reason (e.g., termination of the clinical study by a regulatory agency or the sponsor).

A subject should be discontinued from treatment for any of the following (see also Section 4.4):

1) Occurrence of defined unacceptable toxicity (Section 4.6).
2) Investigator determines that discontinuation of treatment is in the best interest of the subject.
3) Occurrence of any intercurrent condition, injury, or disease that becomes apparent during the study and necessitates the discontinuation of treatment.
4) Pregnancy.
5) Subjects who answer "yes" to Suicidal Ideation item 4 or 5 on the C-SSRS during the study must be withdrawn from the study treatment. Investigators should also withdraw subjects from treatment if, in the judgment of the investigator, the subject develops other indicators of significant risk of suicide. In the event that suicidal ideation is observed in any study subject, the investigator will manage the situation as he/she deems medically and psychiatrically appropriate.

6.4.1 Follow-up Procedures for Subjects Who Withdraw/Discontinue Prematurely

If a subject withdraws from the study, attempts should be made to contact the subject to determine the reason(s) for discontinuation. If a subject does not return to the clinic for follow-up visits, attempts should be made to contact the subject via phone, email, or mail. At least 3 documented attempts (one of which should be a certified letter) should be made to contact the subject before declaring a subject lost to follow-up. The Study Safety Representative must be informed as soon as possible if a subject discontinues or withdraws early.

The date and the reason for study drug discontinuation or subject withdrawal from the study must be recorded on the case report form (CRF) In case of early discontinuation or withdrawal of a subject, every effort must be made to report all study-mandated observations up to the time of discontinuation/withdrawal as completely as possible.

Subjects who are removed from treatment for AE(s) should be followed for resolution of the AE(s) (see Section 10.2.3) and should complete all assessments scheduled for the End-of-Study (EOS) Visit, as well as all assessments that they are capable of completing on the scheduled visit day if the decision to remove from treatment is made on a scheduled visit day. Likewise, if the investigator plans to temporarily interrupt dosing because of an AE and the decision is made on a scheduled visit day, the subject should complete all scheduled assessments that they are capable of completing on the visit day on which they appear.

If the reason for discontinuation/withdrawal is medical and the subject has not withdrawn consent, the subject should remain under the supervision of the investigator until the medical issue is resolved or otherwise declared stable.

6.4.2 Procedures for Replacing Subjects Who Withdraw/Discontinue Prematurely

Subjects who withdraw from the study or discontinue treatment prematurely will not be replaced.

7 TREATMENT PLAN AND METHODS

7.1 Schedule of Assessments

The schedule of assessments is presented in Table 3.

Table 3 Schedule of Assessments

Visit	Screening	Dosing Period									EOT	EOS	FU
Day	-28 to -1	1	2	3-7	8	9-13	14	15-19	20	21-25	26	33	57
Visit Window		-	0		-2 d		-2 d		-2 d		±1 d	±1 d	±2 d
CX-8998 daily dose	-	4 mg		8 mg		12 mg		16 mg		20 mg			
Clinic visit	X	X									X[1]		
Telephone call[3]			X		X[2]		X[2]		X[2]			X[1]	X
Informed consent[4]	X												
Demography/medical history[5]	X												
Eligibility criteria	X	X											
Complete physical exam	X										X		
Targeted physical exam[6]		X											
Neurological exam	X										X		
Vital signs[7]	X	X									X		
Electrocardiogram[8]	X	X									X		
Clinical laboratory tests[9]	X	X									X		
Urine (+/- serum) pregnancy test[10]	X										X		
Serum FSH [11]	X												
Drug screening [12]	X										X		
Pharmacogenomics sample[13]		X											
Blood sampling for PK[14]		X									X		
Video EEG + HV and PS[15]	X										X		
Video-EEG[16]	X										X		
Seizure-related Disability Assessment Scale		X									X		

Visit	Screening	Dosing Period									EOT	EOS	FU
Day	-28 to -1	1	2	3-7	8	9-13	14	15-19	20	21-25	26	33	57
Visit Window		-	0		-2 d		-2 d		-2 d		±1 d	±1 d	±2 d
CX-8998 daily dose	-	4 mg		8 mg		12 mg		16 mg		20 mg			
Clinic visit	X	X									X[1]		
Telephone call[3]			X		X[2]		X[2]		X[2]			X[1]	X
Daily Seizure Diary	X	X	X	X	X	X	X	X	X	X	X		
C-SSRS[17]	X	X									X		
UM-PDHQ[18]		As needed											
Prior / concomitant meds	X	X			X		X		X		X		
AE review[19]		X			X		X		X		X	X	X[19]
Study drug admin. in clinic		X[20]									X[20]		
Study drug admin. outpatient		X[20]	X	X	X	X	X	X	X	X	X[20]		
Drug compliance											X[21]		

AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EEG = electroencephalogram; EOS = end of study; EOT = end of treatment; FSH = follicle-stimulating hormone; FU = follow-up; HIV = human immunodeficiency virus; HV = hyperventilation, PK = pharmacokinetic; PS = photic stimulation; UM-PDHQ – University of Miami Parkinson's Disease Hallucinations Questionnaire.

1. Visit window ± 1 day as needed for scheduling.
2. Visit window +0, -2 days as need for scheduling.
3. Before initiating dose escalation, study staff will contact the subjects by telephone and will question them about their health status, including about the occurrence of any AEs. Subjects who report AEs may be asked to return to the clinic for an unscheduled visit. Subjects who are suspected of experiencing a neuropsychiatric event should be seen in person.
4. Informed consent must be signed prior to initiation of all other screening procedures.
5. Medical history will include seizure history.
6. A targeted physical exam will be based on subject reports of signs and symptoms and investigator's observations.
7. Vital signs include body temperature, systolic and diastolic blood pressures, pulse rate and respiration rate. Vital signs will be collected predose and postdose (1-2 hours) at the Baseline (Day 1) Visit and during the Day 26 clinic visit. Blood pressure and pulse rate will be measured in the recumbent position after at least 2 minutes of recumbency, and both will be measured again after approximately no less than 1 minute of standing.
8. At baseline (Day 1), a 12-lead ECG will be performed predose and approximately 1-2 hours after the dose as convenient between other required visit procedures. All ECGs should be performed after at least 10 minutes of recumbency.

9. Clinical chemistry, and hematology. Urinalysis to be performed only as clinically indicated. Additional lab tests are obtained at the screening visit to verify eligibility (including HIV, hepatitis B and C). A positive drug screen will result in exclusion from the study unless it is explained by use of an allowed prescription medication.
10. A urine pregnancy test will be performed, and if the result is positive a serum pregnancy test should be completed.
11. Serum FSH only as needed to determine menopausal status in females <62 years old with history of ≥12 months of amenorrhea without another cause.
12. Laboratory urine testing for phencyclidine (PCP), cocaine, cannabinoids, opiates, barbiturates, benzodiazepines, amphetamines, methadone, and MDMA (Ecstasy).
13. Optional sample that requires additional informed consent.
14. On Day 1, PK samples will be taken at time 0 (predose; before subject takes first dose of study drug in the clinic) and at 1, 2, and 4 hours after administration of study drug. Two postdose PK samples, separated by >2 hours, will be obtained on Day 26. The time of the last dose of study drug and the time of the blood draw will be recorded.
15. A standard multi-lead 6.5-hour video EEG will be obtained using HV and PS. The first 30 minutes will consist of HV and PS. For HV, subjects will be hyperventilated for 5 minutes or until the subject has an absence seizure (HV period 1). If no absence seizure occurs during HV period 1, the subject will rest for 5 minutes and then perform hyperventilation for an additional 5 minutes (HV period 2). Photic stimulation will be performed as described in the EEG charter. The EEG will be centrally evaluated by a qualified rater.
16. After completion of the above 30-minute video-EEG during which HV and PS are conducted, the video-EEG will continue, and the subjects will be monitored during wakefulness for an additional 6 hours. The EEG recording will be centrally evaluated by a qualified rater.
17. The “Lifetime” version of the C-SSRS will be used at screening, and the “Since Last Visit” version will be completed at all other visits.
18. The UM-PDHQ is a 20-item clinician-administered questionnaire that quantitatively and qualitatively assesses hallucinations. The UM-PDHQ will be completed for any subject who reports hallucinations.
19. All AEs, irrespective of the relatedness to the study drug, will be captured from the time the ICF is signed through the EOS visit. All AEs should be followed until resolution, for 30 days after onset, for 30 days after the last dose of study drug, until the subject is lost to follow-up (as defined in Section 6.4.1), or the subject withdraws consent, whichever occurs first. Serious adverse events (SAEs) will be reported up to 30 days after the last dose of study drug. A follow-up phone call will be made 30 days after the last dose of study drug for evaluation of any SAEs.
20. Study drug will be administered in the clinic on the morning of Day 1. Study drug will be administered on an outpatient basis on the evening of Day 1 through the morning of Day 26. Subjects will be instructed to bring all used empty bottles and unused study drug, with them to the end-of-study visit on Day 26.
21. Drug compliance will be assessed by capsule count.

7.2 Summary of Treatment Visits

7.2.1 Screening

The Screening Visit must be performed within 28 days of Visit 1/baseline. Subject informed consent must be obtained prior to initiation of any study-specified procedures. A central reviewer and the sponsor will review eligibility criteria for all subjects.

A standard multi-lead video-EEG with HV and photic stimulation (PS) will be obtained over 30 minutes and will be followed by an additional 6-hour awake video-EEG (total, 6.5 hours). Subjects will undergo HV for 5 minutes (HV period 1). If no absence seizure occurs, the subject will rest for 5 minutes and then undergo HV for an additional 5 minutes (HV period 2). Further details, including procedures for HV and PS will be elaborated in the EEG Charter.

Subjects will begin documenting absence seizure-free days in a daily diary and will continue to do so for the duration of the study. See Table 3 for a detailed list of assessments to be performed.

7.2.2 Visit 1 (Day 0 - Baseline)

Subjects will return to the clinic within 28 days of screening. Following confirmation of continued eligibility by the central reviewer and sponsor, subjects will receive the first dose of study drug (2 mg or placebo) with food and undergo assessments as detailed in Table 3. Subjects will be followed for adverse events, orthostatic vital signs, and ECG for at least 2 hours prior to discharge. The investigator or qualified designee will make the determination of whether it is safe to release the subject from the clinic. Subjects will be instructed to take the second daily dose of study drug no sooner than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the time of their first dose.

7.2.3 At Home Dose Titration (Days 1-26)

Subjects will continue twice daily dosing for 4 weeks according to the dose titration schedule detailed in Section 4.3.

7.2.4 Telephone Safety Check (Day 2)

Prior to initiating the 4 mg BID dose, study staff will contact subjects by telephone to query the subject on their health status, including the occurrence of any AEs. Subjects who are experiencing any AEs may be asked to return to the clinic for an unscheduled visit. Subjects who are experiencing nervous or psychiatric system-related AEs should return to the clinic for an unscheduled visit.

7.2.5 Telephone Safety Check (Day 8)

Prior to initiating the 6 mg BID dose, the study staff will contact the subjects by telephone to query them about their health status, including the occurrence of any AEs. Subjects who are experiencing any AEs may be asked to return for an unscheduled visit. Subjects who are

experiencing nervous or psychiatric system-related AEs should return to the clinic for an unscheduled visit. The telephone call may take place on Day 6, 7, or 8.

7.2.6 Telephone Safety Check (Day 14)

Prior to initiating the 8 mg BID dose, study staff will contact subjects by telephone to query the subject on their health status, including the occurrence of any AEs. Subjects who are experiencing any AEs may be asked to return for an unscheduled visit. Subjects who are experiencing any nervous or psychiatric system-related AEs should return to the clinic for an unscheduled visit. This call may take place on Day 12, 13, or 14.

7.2.7 Telephone Safety Check (Day 20)

Prior to initiating the 10 mg BID dose, the study staff will contact the subjects by telephone to query them about their health status, including the occurrence of any AEs. Subjects who are experiencing any AEs may be asked to return for an unscheduled visit. Subjects who are experiencing any nervous or psychiatric system-related AEs should return to the clinic for an unscheduled visit. The telephone call may take place on Day 18, 19, or 20.

7.2.8 End of Study Visit (Day 26)

Subjects will return to the clinic for the final visit assessments detailed in Table 3. This visit may take place on Day 25, 26, or 27 as needed for scheduling. Subjects will be instructed to take their dose of study drug before reporting to the clinic.

A standard multi-lead video-EEG with HV and photic stimulation (PS) will be obtained over 30 minutes and will be followed by an additional 6-hour awake video-EEG (total, 6.5 hours). During this time, safety assessments, as shown in Table 3, will be conducted, and 2 PK blood samples, separated by >2 hours, will be obtained. Subjects will undergo HV for 5 minutes (HV period 1). If no absence seizure occurs, after a 5-minute rest, subjects will undergo HV for an additional 5 minutes (HV period 2). Further details, including procedures for HV and PS will be elaborated in the EEG Charter. Adverse events that are unresolved at the visit will continue to be followed by study staff as detailed in Section 10.2.3.

7.2.9 Telephone Safety Check (Day 33)

One week after the End of Study Visit, the study staff will contact the subjects by telephone to query them about their health status, including the occurrence of any AEs. Subjects who are experiencing any AEs may be asked to return for an unscheduled visit. Subjects who are experiencing any nervous or psychiatric system-related AEs should return to the clinic for an unscheduled visit. Any AEs that remain unresolved at this visit will be noted as ongoing. This telephone call may take place on Day 32, 33, or 34.

7.2.10 Follow-up Phone Call

Study staff will contact each subject by phone 30 days after the last dose of study drug for evaluation of the occurrence of any SAEs.

7.3 Concomitant Medications and Other Restrictions

7.3.1 Concomitant Medications

The use of prescription or nonprescription drugs or other products (e.g., grapefruit juice) known to be strong inhibitors or inducers of CYP3A4 must be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study. See Appendix B for a complete list of restricted inhibitors and inducers.

7.3.2 Other Restrictions

Regular use of more than 2 standard drinks of alcohol per day is prohibited. In the United States, a standard drink contains about 14 grams of alcohol. This roughly corresponds to a 12-fluid ounce (350 mL) glass of beer (5% alcohol by volume [ABV]), a 5-fluid ounce (150 mL) glass of wine (12% ABV), or a 1.5-fluid ounce (44 mL) glass of a spirit (40% ABV).

Use of any illicit drugs is prohibited throughout the study period.

8 EFFICACY ASSESSMENTS

8.1 Electroencephalogram

A standard multi-lead video-EEG with HV and photic stimulation (PS) will be obtained over 30 minutes and will be followed by an additional 6-hour awake video-EEG (total, 6.5 hours). HV will be conducted under the protocol used in the NIH-sponsored childhood absence study (Glauser et al., 2010). The first 30 minutes will consist of HV and PS. For HV, subjects will be hyperventilated for 5 minutes or until the subject has an absence seizure (HV period 1). If no absence seizure occurs during HV period 1, the subject will rest for 5 minutes and then perform hyperventilation for an additional 5 minutes (HV period 2). Photic stimulation will be performed as described in the EEG charter. The EEG will be centrally evaluated by a qualified rater. After completion of the above 30-minute video-EEG during which HV and PS are carried out, the video-EEG will continue, and the subjects will be monitored during wakefulness for an additional 6 hours (total, 6.5 hours). The EEG recording will be centrally evaluated by a qualified rater. Procedures for VH, PS and video-EEG will be elaborated in the EEG Charter.

8.2 Seizure-related Disability Assessment Scale

The SERDAS was developed to assess functional impairment in work/school, social, and family life. The SERDAS is a 6-item self-report tool on which the patient rates the extent to which work/school, social life, and homelife or family responsibilities are impaired by his or her symptoms on a 10-point visual analog scale.

8.3 Daily Seizure Diary

Beginning at the screening visit and continuing each day until the End of Study Visit, subjects will document if they had any absence seizures on that day (absence seizure-free

day). The number of absence seizure-free days will be calculated during both the baseline period and the treatment period.

9 PHARMACOKINETIC AND PHARMACOGENOMIC ASSESSMENTS

9.1 Blood Sample Collection for Pharmacokinetic Assessments

For details on the timing, volume, handling, storage, and methods of analysis of blood samples see the Laboratory Manual.

9.2 Pharmacokinetic Parameters

Plasma concentrations of CX-8998 and its metabolites (including, but not limited to, M01 and M02) will be determined.

The concentrations of CX-8998 and its metabolites (including, but not limited to, M01 and M02) in plasma will be summarized by visit, timepoint and dose using descriptive statistics.

The concentration data will also be used as part of an exploratory population PK/PD analysis intended to evaluate the exposure-response and exposure-safety relationships, which will be reported separately from the clinical study report.

9.3 Pharmacogenomics of Drug Response

Genomic and metabolomic variation may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomics. Comparing the DNA, RNA, protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting and retaining samples for pharmacogenomic analyses makes it possible to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study.

An optional 4-mL blood sample will be collected at Visit 1/baseline and retained for potential pharmacogenomic analyses related to drug response for subjects who consent to provide sample for these potential analyses. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. Detailed collection, processing, storage and shipment instructions are provided in the Laboratory Manual.

10 SAFETY ASSESSMENTS

10.1 Assessment of Safety

10.1.1 Adverse Events

Adverse events (AEs) will be captured from the time the ICF is signed through the EOS telephone safety check on Day 33. SAEs will be reported up to 30 days after the last dose of study drug. A follow-up phone call will be made 30 days after the last dose of study drug for evaluation of any SAEs. See Section 10.2 for definitions and instructions on the rating and collection of AEs.

10.1.2 Physical and Neurological Examinations

A complete physical examination includes measurement of height (screening only), weight, and examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities. Genital, rectal, and breast examination may be excluded if not clinically indicated. Weight should be measured on the same scale each time. A neurological examination includes testing mental status, gait, cerebellar function, cranial nerves, motor functioning (including strength and reflexes), and sensation.

The targeted physical examination is at the investigator's discretion based on subject reported signs and symptoms and investigator observations.

10.1.3 Vital Signs

Vital signs include body temperature, systolic and diastolic blood pressures, pulse rate, and respiration rate.

Blood pressure and pulse rate will be measured in the recumbent position after at least 2 minutes of recumbency, and both will be measured again after approximately no less than 1 minute of standing. Subjects should be observed carefully for dizziness or unsteadiness while standing and allowed to sit if such occurs. Blood pressure and pulse rate should be recorded as soon as possible after sitting if the subject cannot stand for 1 full minute.

Recumbent and standing recordings of blood pressure and pulse rate will be made at the Screening Visit and at the Day 26 Visit. Orthostatic blood pressure and pulse rate will be measured before dosing (recumbent and standing) on Day 1. During any visit (screening, baseline, or Day 26 or an unscheduled clinic visit), blood pressure and pulse rate are to be assessed at any time subjects appear faint or complain of dizziness or other symptoms suggestive of hypotension.

Respiratory rate and temperature will be measured in the recumbent position and need only be measured one time (with the first set of blood pressure/pulse measurements)

10.1.4 Clinical Laboratory Tests

The following screening/safety laboratory tests (hematology, chemistry, and urinalysis) will be performed after 4 to 6 hours of fasting:

- Hematology testing will include hematocrit, hemoglobin, red blood cell count, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC), and platelet count.
- Serum chemistry analyses will include sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate, albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, creatine kinase (CK), uric acid, lactate dehydrogenase (LDH), ALT, AST, alkaline phosphatase, triglycerides, total cholesterol, and total bilirubin.
- Urinalysis will be performed only as clinically indicated.

10.1.5 Urine Drug Screen

Subjects will undergo urine drug screening for the presence of phencyclidine (PCP), cocaine, cannabinoids, opiates/barbiturates, benzodiazepines, amphetamines, methadone, and MDMA (Ecstasy) at the Screening Visit and at the Day 26 Visit. Subjects who have a positive urine drug screen will be excluded from the study unless the positive result is explained by the use of an approved prescription medication.

10.1.6 Pregnancy Tests

A urine pregnancy test will be performed for all WOCBP. See Section 6.2, inclusion criterion #10 for the definition of WOCBP.

Positive urine tests will be confirmed with a serum pregnancy test. Subjects may not enter the study if pregnant and must be immediately be discontinued from dosing when a positive pregnancy test is reported during study participation.

10.1.7 Electrocardiogram

A 12-lead ECG will be obtained according to the Schedule of Assessments (Table 3). Subjects must rest in the supine position for at least 10 minutes before the ECG recording is started. The ECG should be recorded during the period of rest required before blood collection and the measurements of orthostatic blood pressure, pulse rate, and respiratory rate. A qualified physician will review the ECGs and any clinically important finding will be recorded on the appropriate CRF. The investigator is responsible for providing interpretation of all ECGs. The results will include heart rate, PR interval, QRS interval, QT interval, and QTc interval, and assessment of rhythm and morphology. If necessary, (e.g., suspected QTc prolongation), a manual reading of the ECG data will be performed.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a

qualified physician's interpretation determines that the QTc values are in the acceptable range.

10.1.8 Columbia-Suicide Severity Rating Scale

The C-SSRS is a suicidal ideation rating scale created by researchers at Columbia University (Posner, 2011). It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent."

The scale identifies behaviors that may be indicative of an individual's intent to commit suicide. The C-SSRS is used extensively across primary care, clinical practice, surveillance, research, and institutional settings. It is available in more than 100 country-specific languages and is part of a national and international public health initiative involving the assessment of suicidal ideation and behavior.

The C-SSRS requires no mental health training to administer. An electronic patient-reported version of the C-SSRS is also available in tablet, interactive voice response, and web versions (Mundt 2010; Mundt 2013).

Subjects with a history of attempted suicide within the past year or a C-SSRS score of 4 or 5 at screening will be excluded from the study. Subjects who answer "yes" to Suicidal Ideation item 4 or 5 on the C-SSRS during the study must be withdrawn from study treatment. Investigators should also withdraw subjects from treatment if, in the judgment of the investigator, the subject develops other indicators of significant risk of suicide. In the event that suicidal ideation is observed in any study subject, the investigator will manage the situation as he/she deems medically and psychiatrically appropriate.

The "lifetime" version of the C-SSRS will be used at screening, and the "since last visit" version will be used at all other visits.

Samples of the C-SSRS are provided in Appendix A1.

10.1.9 University of Miami Parkinson's Disease Hallucinations Questionnaire

The UM-PDHQ was specifically developed to quantitatively and qualitatively assess hallucinations in patients with Parkinson's disease (Papapetropoulos, 2008). The UM-PDHQ is a 20-item clinician-administered questionnaire that is completed during a structured interview. Questions are divided into 2 groups: a quantitative group that consists of 6 questions (modality, frequency, duration, insight, emotional burden) and a qualitative group that consists of 14 questions. The first item is a gating question to assess the presence or absence of hallucinations.

The investigator will complete the UM-PDHQ for any subject who experiences visual hallucinations during the study. The investigator should discuss the continued participation of any subject developing visual hallucinations during the study with the study safety representative.

A copy of the UM-PDHQ is provided in Appendix A2.

10.2 Adverse Events

10.2.1 Definitions

Adverse Event

An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

Seizure should not be reported as an AE or SAE unless it is a new seizure type, the frequency of seizure increases, status epilepticus occurs, or the investigator considers the seizure to be an AE or SAE.

Adverse Events of Special Interest

The following are considered AESIs: increase in seizure frequency, new seizure type, and status epilepticus.

Laboratory Abnormality

A laboratory abnormality is any clinically significant laboratory abnormality that suggests a disease or organ toxicity and that is of a severity to require active management (i.e., changes of dose, discontinuation of drug, more frequent follow-up, medical treatment, diagnostic investigation). Laboratory abnormalities are also considered AEs.

Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are all AEs occurring during the treatment period or a pretreatment event that worsens in intensity during the treatment period.

Treatment Period

The treatment period is the period during which a subject receives study drug (i.e., first dose through Day 26).

Intolerable Adverse Event

An intolerable AE is one that is considered by the investigator to be related to study drug (Section 10.2.2.3) AND is either a severe or life-threatening event (Section 10.2.2.2) OR is a mild or moderate event that prompts the subject to express a desire to discontinue dosing. Dose adjustments for intolerable AEs are described in Section 4.6.

Serious Adverse Event

An SAE is any adverse event that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the study drug, or is an important medical event. See Section 10.3 for more details on SAEs.

10.2.2 Collection and Rating of Adverse Events

All AEs, irrespective of the relatedness to the study drug, will be captured from the time the ICF is signed through the telephone safety check on Day 33. SAEs will be reported up to 30 days after the last dose of study drug. A follow-up phone call will be made 30 days after the last dose of study drug for evaluation of any SAEs. In case of an SAE, an SAE Report Form must be completed and transmitted to the sponsor or designee within 24 hours.

Overdoses and medication errors in the presence of clinical consequences should be recorded as AEs. The clinical consequence should be reported as "[enter AE] due to overdose." See Section 4.7 for overdose management.

10.2.2.1 Onset Date

The onset date is the date when the first sign(s) or symptom(s) were first noted. For example, if the AE is an abnormal laboratory test (such as "platelets low"), the onset date is the date when the sample was taken. If the subject was hospitalized for meningitis, and symptoms such as fever, headache, and nausea started the day before the hospitalization, the onset date is the day symptoms presented versus day of hospitalization.

10.2.2.2 Assessment of Intensity

Each adverse event will be graded according to the following definitions:

- **Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Moderate:** minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) [Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc];
- **Severe:** medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden]

10.2.2.3 Relationship to Study Drug

The assessment of the relationship of an AE to the administration of study drug is a clinical decision based on all available information at the time of the completion of the CRF.

The causal relationship of the study drug to an AE will be rated as follows:

- **Related:** The AE has at least a possible or stronger causal relationship to the study drug, i.e., there are facts in evidence to suggest a causal relationship to the study drug. The study treatment and the AE are reasonably related in time, and any alternative etiology is equally or less likely.

- **NOT Related:** Exposure to study treatment did not occur; or the occurrence of the AE is not reasonably related in time, or is due to an underlying/intercurrent illness, or to other medication or procedure; or the AE is considered unlikely to be related to the study treatment.

10.2.2.4 Action Taken

The action taken toward the study drug in response to an AE will be listed as one of the following:

- **None:** No change in study drug dosage was made.
- **Reduced:** Dose of study drug was reduced, with or without a period of temporary suspension of dosing.
- **Discontinued:** The study drug was permanently stopped.

10.2.2.5 Outcome of Adverse Event

The outcome of an AE will be recorded as one of the following:

- **Recovered:** fully recovered or the condition has returned to the level observed at baseline
- **Recovered with sequelae:** resulted in persistent or significant disability or incapacity; the nature of the sequelae should be specified
- **Not yet recovered**
- **Death**

10.2.3 Adverse Event Follow-up

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject.

Any subject who has any AE (whether serious or non-serious) or clinically significant (in the investigator's opinion) abnormal laboratory test values will be evaluated by the investigator or qualified designee and will be treated and followed up until the symptoms or values return to normal or acceptable levels, as judged by the investigator and the sponsor.

All AEs, whether serious or non-serious, will be collected beginning at the time the ICF is signed through the telephone safety check on Day 33. All AEs should be followed until resolution or:

1. 30 days from onset; or
2. 30 days after the last dose of study drug; or
3. the subject is lost to follow-up (as defined in Section 6.4.1); or
4. the subject withdraws consent,

whichever occurs first.

SAEs will be reported up to 30 days after the last dose of study drug. A follow-up phone call will be made 30 days after the last dose of study drug for evaluation of any SAEs.

Any follow-up information available at the time of the subject's end of study will be included in the clinical study report.

10.3 Serious and Other Significant Adverse Events

10.3.1 Definition of a Serious Adverse Event

A serious adverse event is any adverse event that

- **Results in death.** Death is not an event per se but rather an outcome. Note that any AE resulting in a fatal outcome must be fully documented and reported, including deaths that occur within 30 days after treatment ends and irrespective of the causal relationship to the study drug.
- **Is life threatening.** Life threatening refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death, if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization.** Hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an AE. Hospitalization describes a period of at least 24 hours. Over-night stays for observation, stays at the emergency room or treatment on an outpatient basis do not constitute a hospitalization. However, medical judgment must always be exercised and, when in doubt, the case should be considered serious (i.e., if the case fulfills the criterion for a medically important event). Hospitalization for administrative or social purposes does not constitute an SAE. Hospital admissions and/or surgical operations planned before study inclusion are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that the condition did not deteriorate during the study.
- **Results in persistent or significant disability/incapacity.** Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. If in doubt, the decision should be left to medical judgment by the investigator.
- **Is a congenital anomaly/birth defect.** Any congenital anomaly or birth defect observed in any offspring of the subject that was conceived during treatment with the study drug.
- **Is an important medical event.** Important medical events are events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication, or precaution; occurrence of malignancy; or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important.

An AE caused by an overdose or medical error is considered serious if a criterion listed in the definitions above is fulfilled.

The following are not considered SAEs:

- A preexisting condition that is present prior to or at the start of the study that did not worsen.
- Hospitalizations for treatment, which were elective or preplanned, for a preexisting condition unrelated to the indication under study that did not worsen.
- Admission to a hospital or other institution for general care not associated with any deterioration in condition.

10.3.2 Serious Adverse Event Reporting by the Investigator to the Sponsor

Any SAE that occurs after a subject has entered the study, whether or not related to study drug, must be reported to the sponsor or the sponsor's agent immediately (within 24 hours) via telephone or email. If initially reported via telephone, this must be followed-up by a written SAE report. The investigator must report all SAEs that occur from the time the subject signs the ICF until 30 days after last dose of the study drug.

A completed SAE Report Form with the best possible details must be transmitted to the sponsor representative within 24 hours of knowledge of the SAE according to contact details as specified below:

Sponsor Representative and Contact Information for SAE Reporting:

SAE Reporting Primary Contact:	Premier Research Pharmacovigilance
Reporting email:	GlobalPV-US@premier-research.com
Back-up reporting fax number:	+1.215.972.8765

10.3.3 Handling of Follow-up Information

Follow-up information may be required, or additional information may be requested by the sponsor (e.g., evolution of the SAE, other signs or symptoms, final diagnosis, final outcome, hospital discharge summary, autopsy report). The same procedures and timelines as for initial reporting, listed above, should be followed for any follow-up information. If necessary, the study site will be visited to collect additional information.

Follow-up information is required on all SAEs until one the following criteria is satisfied:

- The final outcome of the case is known.
- The event is resolved or the medical condition of the subject is stabilized.
- No further information is available.
- Sponsor assessment has been finalized.
- The subject has withdrawn consent for further follow-up; information obtained up to the date and time of withdrawal of consent will remain a part of the study record.

10.3.4 Reporting and Follow-up of Pregnancy

When an investigator becomes aware of the pregnancy of a female subject (or female partner of a male subject), the investigator must withdraw the subject from the study treatment and follow the pregnancy until termination or until the child is 1 month old. The pregnancy will be reported immediately by telephone and by faxing a completed Pregnancy Report to the sponsor within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator should notify the sponsor or the sponsor's agent of the outcome of the pregnancy by submitting a follow-up Pregnancy Report. Additionally, if the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly), the investigator will report the event by phone and by faxing a completed SAE Report Form to the sponsor within 24 hours of knowledge of the event.

10.3.5 Expedited Reporting of Serious Adverse Events

10.3.5.1 Responsibilities

The sponsor is responsible for ensuring the timely reporting of SAEs to regulatory authorities and to all investigators who participate in the clinical development program of the study drug. It is the responsibility of the investigator to provide the sponsor with the case information such that reporting timeline demands of applicable regulatory authorities can be met.

10.3.5.2 Expedited Reporting

All AEs that are serious, unexpected, and considered related to the study drug judged by the sponsor will undergo expedited reporting. All available information relevant to the evaluation of the SAE will be reported. Serious AEs will be considered reportable regardless of whether or not the study drug was used in accordance with the provisions in the protocol.

Adverse events that are serious, but expected, or those that are not associated with the study drug will only be subjected to expedited reporting if they are required to be reported to an authority according to national requirements.

10.3.5.3 Timelines

Fatal or life-threatening serious unexpected related cases require rapid reporting. regulatory authorities shall be notified as soon as possible but no later than 7 calendar days after first knowledge by the sponsor representative, followed by as complete a report as possible within 8 additional calendar days.

Serious unexpected related cases that are not fatal or life threatening must be submitted as soon as possible, but no later than 15 calendar days after first knowledge by the sponsor representative that the case meets the minimum criteria for expedited reporting.

It is the responsibility of the investigator to support sponsor activities needed to meet the aforementioned timelines for regulatory authority reporting in the event of an SAE.

10.4 Safety Monitoring and Risk Mitigation Plan

Measures to minimize the risks to subjects enrolled in this clinical trial have been taken with respect to the following study design elements:

- Subject safety and tolerability will be monitored in this study across multiple dimensions by tracking clinical AEs; vital signs (including orthostatic pulse and blood pressure); general and neurological physical examinations; standard clinical laboratory safety panels for complete blood counts, chemistry, coagulation, and urinalysis; standard 12-lead ECGs; the C-SSRS; and the UM-PDHQ.
- The specified inclusion/exclusion criteria have been carefully considered to avoid enrollment of subjects for whom exposure to the study drug might pose a hazard.
- This study will perform a careful dose titration in which dosing of CX-8998 will be initiated at 2 mg BID for 2 days and then increased to 4 mg BID for 6 days, to 6 mg BID for 6 days, to 8 mg BID for 6 days, and, finally, if tolerated, to the target dose of 10 mg BID for 6 days. The study is designed to allow for flexible titration. The dose should only be increased if the previous dose level is well tolerated. Should subjects experience intolerable AEs (see Section 10.2.1) at 6 mg, 8 mg, or 10 mg BID, study drug may be discontinued, or the dose may be decreased to the previous lower dose. Subjects who experience intolerable AEs at 2 mg or 4 mg BID will be discontinued from treatment.
- Dose modification and stopping rules are in place for individual subjects (see Section 4.4). Near real-time safety and tolerability monitoring for individual subjects is the primary responsibility of the principal investigators and sub-investigators.
- All SAEs meeting criteria for expedited reporting to the US FDA will be reported to the FDA and all institutional review boards (IRBs) in accordance with regulatory timelines.
- The sponsor's Study Safety Representative will monitor aggregate study level safety and tolerability after approximately 50% of the projected sample size of subjects have completed the EOS Visit. These reviews will be based on blinded, select listings and summary tables of the evolving safety and tolerability data for each arm of the study. Decision-making will depend on the specifics of the safety and tolerability data reviewed.
- In the event of a treated subject's death within 30 days of the last dose of study drug that is assessed by the treating principal investigator/sub-investigator or the Study Safety Representative as at least possibly related to study drug, further enrollment in the study will be immediately suspended until a safety review can be conducted by the Study Safety Representative, the actively participating principal investigators/sub-investigators, and the sponsor. As required by regulation, all deaths that meet the criteria for expedited reporting to the US FDA will be reported to the FDA and all IRBs within regulatory timelines. A final decision to reopen the study to new enrollment without modification(s), reopen with modification(s), or

terminate the study will be made by the overall study principal investigator, and the sponsor's Study Safety Representative.

11 STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with statistical testing performed for the efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (*n*), mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. Statistical testing, if performed, will be 2-sided and will be performed using a significance (alpha) level of 0.05. All available data for enrolled subjects will be listed by subject. Unless otherwise noted, the data will be sorted first by subject number and then by date within each subject number.

All statistical analyses will be conducted with the SAS® System, version 9.4 or higher.

11.1 Statistical Analysis Plans

A statistical analysis plan (SAP) will be created and approved prior to database lock. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures.

11.2 Study Hypothesis

No formal statistical hypotheses will be tested in this exploratory study. Statistical testing may be utilized to inform hypothesis generation for subsequent studies.

11.3 Determination of Sample Size

Up to approximately 15 eligible subjects will receive CX-8998. The sample size was not based on statistical considerations but rather chosen to provide safety and efficacy information on CX-8998 when administered according to this protocol.

11.4 Analysis Populations

The populations defined for analysis will include the intent-to-treat (ITT) population, safety population, and a PK population. Additional analysis populations may be defined to evaluate study results; these populations will be defined in the SAP.

- **Intent-To-Treat Population:** The ITT population will include all subjects who are enrolled in the study. The ITT population will be used for analyses of accountability, demographics, and efficacy.
- **Safety Population:** The safety population will include all subjects who are enrolled in the study and receive at least 1 dose of CX-8998 The safety population will be the primary population for all analyses of safety data.
- **PK Population:** The PK population will consist of all subjects who received study treatment and for whom PK samples were obtained and sufficient plasma concentrations are available.

Individual data for all enrolled subjects will be presented in data listings, sorted by subject identifier.

11.5 Data Analysis

11.5.1 Efficacy Analyses

The change in frequency (number of seizures per hour) of absence seizures as defined by a 3-Hz spike and wave lasting for ≥3 seconds as determined by HV, the frequency (number of seizures per hour) of absence seizures (based on 6.5-hour video-EEG), the time to absence seizures during HV, the percent of subjects with a shift in the occurrence of absence seizure (e.g., from HV period 1 to HV period 2), the percent of subjects with an absence of photic response, the actual and change from baseline in SERDAS scores, and the change from baseline to end of treatment in absence seizure-free days as collected by seizure diary will be summarized. Ninety-five percent (95%) confidence intervals will be constructed.

11.5.2 Safety Analyses

Adverse Events will be mapped to a MedDRA preferred term and system organ classification. Severity will be assessed by investigator. The occurrence of TEAEs will be summarized using MedDRA preferred terms, system organ classifications, and severity. All AEs will be listed for individual subjects; both verbatim and preferred terms will be listed. Separate summaries of treatment-emergent SAEs, AESIs, and AEs leading to discontinuation of study or study drug will be generated.

Descriptive summaries of vital signs and clinical laboratory results will be prepared. The number and percentage of subjects experiencing treatment-emergent laboratory abnormalities and laboratory abnormality shifts from baseline to postbaseline assessments will be summarized.

Concomitant medications will be mapped to a World Health Organization (WHO) Drug Dictionary preferred term and drug classification. The number and percent of subjects taking concomitant medications will be summarized using preferred terms and drug classifications.

Changes from baseline in ECGs during study will be evaluated. Results from the C-SSRS, UM-PDHQ, and physical examinations will be listed.

11.5.3 Pharmacokinetic Analyses

Individual plasma concentrations and actual time of collection will be listed by visit and dose of CX-8998.

11.6 Missing, Unused, and Spurious Data

Every effort will be made to obtain required data at each scheduled visit from all subjects who have been randomized. In situations where it is not possible to obtain all data, it may be necessary to impute missing data. Details of imputation methods will be presented in the SAP.

12 STUDY MANAGEMENT

12.1 Protocol Amendment and Protocol Deviation

12.1.1 Protocol Amendment

Administrative amendments to the protocol will be classed as amendment of typographical errors, clarifications of confusing wording, and other minor modifications, including, but not limited to, name, address, and contact information changes that have no impact on the safety of the subject or the science of the study. Administrative amendments will be submitted to the IRB for information only. The sponsor will ensure that acknowledgement is received and filed. Otherwise, an amendment will be classed as a substantial amendment and will be submitted to the appropriate regulatory authorities and the IRB for approval.

12.1.2 Protocol Deviations and Waivers

Requests for waivers will generally not be granted in advance by the sponsor. Should a non-anticipated protocol deviation occur, the sponsor must be informed as soon as possible. All deviations and the reasons for the deviation will be documented by the investigator or designated staff. Reporting of protocol deviations to the IRB and in accordance with applicable regulatory authority mandates is an investigator responsibility.

12.2 Ethics and Regulatory Aspects

12.2.1 Ethical Conduct of the Study and Regulatory Guidelines

To ensure the ethical conduct of this clinical study, each investigator is expected to conduct the study in accordance with the protocol; the US investigational new drug (IND) regulations specified under 21 CFR 11, 50, 54, 56, and 312; the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP); and the Guidelines of the Declaration of Helsinki. The investigator will conduct all aspects of the study in accordance with all national, state and local laws of applicable regulatory authorities.

The responsibilities of the sponsor, the monitor and the investigator will be as defined in the ICH GCP consolidated guideline and applicable regulatory requirements in the country where the study takes place. The investigator is responsible for adhering to the GCP responsibilities of investigators, for dispensing the study drug in accordance with the approved protocol or a signed amendment, and for secure storage and safe handling of the study drug throughout the study.

12.2.2 Institutional Review Board and Regulatory Approval

The study protocol and any amendments will be reviewed by an IRB. The IRB will review the written subject information sheet and the ICF, their updates (if any), and any written materials given to the subjects. A listing of the membership of the IRB consulted and the name of the committee chair(s) or IRB registry (accreditation) number will be documented within the Investigator File and Trial Master File of the sponsor.

Regulatory permission to perform the study must be obtained in accordance with applicable regulatory requirements. All ethics approvals must be obtained, and all regulatory obligations must be met before a subject is exposed to any study-related procedure, including screening tests for eligibility.

12.2.3 Subject Informed Consent

Subjects will be informed about the study both verbally and in writing. Each subject will be provided with a written subject information sheet that has been approved by the IRB and will be given a reasonable time to consider the study and to ask any questions regarding the study. The written subject information sheet and ICF must be in a language that the subject can understand.

Only the investigator, a medically qualified sub-investigator, or a suitably qualified and trained authorized person may be involved in the informed consent process.

The investigator or suitable designee will obtain a freely given, written consent from each subject after an appropriate explanation of the aims, methods, potential hazards, and any other aspects of the study that are relevant to the decision of the subject to participate. The investigator will explain that the subject is completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for further care and without the need to justify.

The ICF must be signed and dated by the subject before any study-related procedure is performed, including screening tests for eligibility. The subject will receive a copy of the written subject information sheet and the ICF.

Each subject will be informed that a monitor, a quality assurance auditor mandated by the sponsor, or a health authority inspector, in accordance with applicable regulatory requirements, may review his or her source records and health data. Data protection will be handled in compliance with national and local regulations.

If new safety information becomes available and results in significant changes in the risk-to-benefit assessment, the written subject information sheet will be revised or updated where necessary. Under these circumstances, all subjects (including those already being treated) should be informed of the new information, given a copy of the revised form, and allowed to reevaluate their consent to continue in the study.

12.3 End of Study and Regulatory Notification

The study can be terminated in part or in whole at the discretion of the FDA, an applicable regulatory authority, or the sponsor.

At the end of the study, the IRBs and regulatory authorities will be notified by the sponsor according to applicable regulatory requirements.

12.4 Data Protection and Confidentiality

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirement(s).

12.5 Monitoring

The study will be monitored to ensure that the study is conducted and documented properly according to the protocol, GCPs, and all applicable regulatory requirements.

On-site visits will be made at appropriate times during the study. Monitors must have direct access to source documentation in order to check the consistency of the data recorded in the CRFs.

The investigator will make available to the monitor source documents, medical records, and source data necessary to complete CRFs. In addition, the investigator will work closely with the monitors and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

Monitoring of safety data will be conducted in accordance with the safety monitoring plan outlined in Section 10.4.

12.6 Quality Assurance and Quality Control

The sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the principal or qualified investigator generating the data.

Prior to the study initiation, the sponsor will explain the protocol, Investigator's Brochure, and CRFs to investigators. In addition, the monitor will be available to explain applicable regulations and to answer any questions regarding the conduct of the study.

At its discretion, the sponsor may conduct audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCPs, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions.

The study center may also be compelled to an inspection by a regulatory authority.

12.7 Source Data

Source data are defined as information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Source documents are the original data, documents, and records. Examples include hospital records, laboratory reports, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated

instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, other radiographic depictions or displays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study. All source documents must be reviewed by the principal investigator and the sponsor (or designee) for compliance with GCP.

The investigator will permit study-related monitoring, audit(s), IRB review(s), and regulatory inspection(s), with a direct access to all the required source documents and associated records.

13 DATA AND RECORD KEEPING

13.1 Case Report Forms

Study sites will be provided access to an electronic data capture (EDC) system that has been fully validated and conforms to 21 CFR Part 11 requirements. The sponsor or designee will train designated study site staff on the EDC system. Study site staff will not be given access to the EDC system until they have been trained. Designated study site staff will enter the data required by the protocol into the electronic CRFs (eCRFs). The investigator must certify that the data are complete and accurate prior to database lock. After database lock, the investigator will receive a CD-ROM copy of the subject data for archiving at the study site.

Designated Cavion personnel will review the data on the eCRFs entered by study site staff for completeness and accuracy. Authorized study site staff will respond to queries sent to their site and make any necessary changes to the data.

13.2 Record Keeping

The investigator must arrange for retention of study records ("Essential Documents for the Conduct of a Trial" are listed in the ICH "Guideline for Good Clinical Practice," Section 8, E6) at the site, in a secure location, for 2 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 for at least 2 years after 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 agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator should take measures to prevent any accidental or premature destruction of these documents.

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15 APPENDICES

Appendix A1 – Columbia Suicide Severity Rating Scale

Appendix A2 – University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-PDHQ)

Appendix B – Cytochrome P450 Interaction Table

Appendix C - Summary of CX-8998 Toxicology Studies

Appendix D - Summary of Previous Clinical Trial Experience with CX-8998 (MK-8998)

Appendix A1 – Columbia Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Baseline Screening - United States/English - Mapi
C-SSRS-BaselineScreening_AU5.1_eng-USori.doc

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal	Past __ Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ___ *Type # (1-5)* ___ *Description of Ideation* ___ Past X Months - ***Most Severe Ideation:*** ___ *Type # (1-5)* ___ *Description of Ideation* ___	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

C-SSRS—Baseline/Screening (Version 1/14/09)
Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage, medical attention needed (e.g., conscious but sleepy, somewhat responsive, second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact, third-degree burns less than 20% of body, extensive blood loss but can recover, major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes, third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USorl.doc

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech, first-degree burns; mild bleeding, sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns, bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix A2 – University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-PDHQ)

The University of Miami Parkinson's disease Hallucinations Questionnaire (UM-PDHQ)

Patient identifier: DATE:

	Question	A:Features/Comments	B:Score (circle appropriate)
Severity of hallucinations	1. Do you experience hallucinations? (Have you noticed anything unusual about your vision? Have you had any unusual visual experiences? Or ever see/hear/feel/smell/taste things that are not really there or that other people do not see?)	Type: (mark appropriate) 1. Visual 2. Auditory 3. Somatic/Cutaneous 4. Gustatory 5. Olfactory (assess each separately)	0. No hallucinations (skip to Annex) 1. One type only 2. Combination C: Not within the past month, but it has happened in the past
	2. How often do you experience hallucinations?		0 = Only a few times 1 = Occasionally (less than once a week, but continuously) 2 = Often (about once per week) 3 = Frequently (several times per week but < than once per day) 4 = Very frequently (≥once per day)
	3. On average, how long do the experiences last?		0 = Short Duration (< 1sec) 1 = Medium Duration (< 10secs) 2 = Prolonged Duration (> 10secs)
	4. Do you think what you are seeing/experiencing is real?		0 = Not real 1 = Sometimes real 2 = Always real
	5. How many types of images/sensations do you experience?		1 = One 2 = Few (2 or 3) 3 = Several (more than 3)
	6. How severe/emotionally distressing do you find these images/sensations or visions?		0 = No effect/Friendly 1 = Mildly – produce little distress 2 = Moderately – produce distress and are disturbing and disruptive 3 = Severely – very disturbing (medications may be required)
	Total Score (min = 0; max = 14)		

Comments:

Page 1 of 2

	Please circle the appropriate answer and provide information	
Quality of hallucinations	7. Have you been diagnosed with any eye disease? (i.e. near or far sight problems, double vision, cataract, glaucoma, retinitis, retinal detachment, diabetic or hypertensive eye disease)	Yes (please describe) No
	8. Was there a recent change in your treatment? Please describe.	Yes (please describe) No
	9. Was this change related to the appearance or change in the characteristics of hallucinations?	Yes No I cannot tell N/A
	10. Do you experience hallucinations while "on" or "off"?	On Off Anytime-not related to on-offs
	11. What do you normally see/feel/hear/smell/taste? If not visual describe here: Voices, Music, tastes, smells, skin related:	Not formed/cannot describe Whole Faces Fragmented faces □ Familiar Whole people □ Unfamiliar Animals Insects/reptiles Objects
	12. Is there anything you can do to make the images/sensations disappear?	Yes No
	13. At what time of the day or under which lighting conditions do you experience hallucinations	A. Specific time During the day/Bright During the night/Dark Dim B. Anytime
	14. When are the images most present?	When eyes are open When eyes are closed No difference N/A (for non-visual hallucinations)
	15. Do the images ever make any sound or noise (for visual hallucinations)?	Yes No N/A (for non-visual hallucinations)
	16. Do images move (for visual hallucinations)?	Yes No N/A (for non-visual hallucinations)
	17. Are the images normal size?	Yes No, smaller than normal No, larger than normal N/A (for non-visual hallucinations)
	18. Are the images transparent or solid?	Transparent Solid N/A (for non-visual hallucinations)
	19. Are the images colored?	Yes No, (black and white) N/A (for non-visual hallucinations)
	20. Is the onset of hallucinations gradual or sudden?	Gradual (appear-disappear slowly) Sudden (appear-disappear suddenly) I cannot tell

Appendix B – Cytochrome P450 Drug Interaction Table

PROHIBITED CYP3A4 INHIBITORS*

HIV antivirals (delaviridine, indinavir, nelfinavir, ritonavir)

amiodarone
cimetidine
clarithromycin
diltiazem
erythromycin
fluvoxamine
grapefruit juice
itraconazole
ketoconazole
nefazodone
suboxone

troleandomycin
verapamil

PROHIBITED CYP2C9 INHIBITORS*

amiodarone
fluconazole
izoniazid

Prohibited moderate and strong inhibitors of CYP3A4 and CYP2C9 include the lists above, but are not limited to the medications and agents listed

PROHIBITED CYP3A4 INDUCERS*

carbamazepine
efavirenz
nevirapine
phenobarbital
phenytoin
pioglitazone
primidone
rifabutin
rifampin
St. John's Wort
troglitazone

PROHIBITED CYP2C9 INDUCERS*

rifampin

secobarbital

Prohibited moderate and strong inducers of CYP3A4 and CYP2C9 include the lists above, but are not limited to the medications and agents listed

From: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "/clinpharm/ddis/clinical-table/" Accessed [6 Dec 2016].

Appendix C – Summary of CX-8998 Toxicology Studies

Summary of Preclinical Toxicology Studies

Study No. **Study Type**	**Dose (mg/kg/day) - Toxicologic Finding**	**Total/Free AUC Exposure[a] (µM·hr)**	**Total/Free Margin (Animal/ Human[b])**
06-1088 Rat 4-Week Toxicity Study 30, 300 and 2000 mg/kg/day	2000 – mortality, adverse clinical signs, nasopharyngeal inflammation, renal tubular degeneration, stomach ulcer, reduced seminal vesicle secretion ≥ 300 – adverse FOB changes; reduced prostate weight / secretion, reduced pituitary weight (M, F) ≥ 30 – reversible female reproductive organ changes indicating extended diestrus; NOAEL for FOB changes including increased number of urine pools and foot splay, decreased body temperature and number of rears, and abnormal gait	546/4.4 385/3.1 43.6[c]/0.35[d]	40.1/81.5 28.3/57.4 3.2/6.5
07-0034 Rat 4-Week Investigative Female Histology Study with 8-Week Recovery 10 and 1000 mg/kg/day	1000 – reversible female reproductive organ changes (extended diestrus); adverse clinical signs 10 – NOEL for female reproductive organ changes	751[e]/6.0[f] 13.7[g]/0.11[h]	55.2/111 1.0/2.0
08-7370 Rat Female Fertility Study 10, 30, 100, and 1000 mg/kg/day	1000 – NOEL for mating, reproductive and fertility effects; 100 – Toxicokinetic (TK) assessment	751[i]/6.0[j] 247/2.0	55.2/111 18.2/37
08-7175 Rat Embryo Fetal Development Study 10, 30, 100, 300, and 1000 mg/kg/day	1000 - Excessive maternal toxicity resulting in the early termination of this dose group ≤ 300 - Transient, dose-related maternal toxicity ≥ 100 – Reduced fetal body weight	No TK	NA
08-7185 Rabbit Embryo Fetal Developmental Study 30, 100, 300, and 1000 mg/kg/day	1000 - Excessive maternal toxicity resulting in the early termination of this dose group ≤ 300 - Transient, dose-related maternal toxicity ≤ 300 - No evidence of developmental toxicity	No TK	NA

Summary of Preclinical Toxicology Studies

Study No. **Study Type**	**Dose (mg/kg/day) - Toxicologic Finding**	**Total/Free AUC Exposure[a] (μM·hr)**	**Total/Free Margin (Animal/ Human[b])**
06-1087 Dog 4-Week Toxicity Study 2, 20 and 800 mg/kg/day	800 – mortality, adverse clinical signs, decreased testis and prostate weight, testicular seminiferous tubular degeneration and reduced spermatogenesis, immature prostate 20 - NOEL	1780/5.3 467/1.4	130.9/98.1 34.3/25.9

[a] M/F combined values unless otherwise indicated

[b] Based on anticipated human total exposure of 13.6 μM·hr (free 0.054 μM·hr) at the 10 mg BID dose; Free CX-8998 in human, rat and dog plasma is 0.4%, 0.8% and 0.3% respectively.

[c]/0.35d Female AUC value

[i]/6.0j AUC data from study 07-0034

M – male, F- female, NOEL – no effect level; NOAEL – no adverse effect level; TK – toxicokinetic

Appendix D - Summary of Previous Clinical Trial Experience with CX-8998 (MK-8998)

Study PN001

Title (population)	Part I: A Double-Blind, Randomized, Placebo-Controlled, Multiple Period, Alternating-Panel, Single-Rising-Oral- Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of MK-8998 (24 healthy males, 18-45 years old) Part II: A Double-Blind, Randomized, Placebo-Controlled Three Period Crossover Study to Assess the Effects of MK-8998 on Awake EEG in Healthy Adult Male Subjects (12 healthy males, 18-45 years old)
Design	Single oral doses of CX-8998 1-24 mg or placebo, fasted; included fasted vs. fed comparison for 1 mg po dose
Summary of findings	Safety: • Mild to moderate, transient central nervous system (CNS) AEs observed at all doses ≥3 mg, including drowsiness, relaxation, mood changes (euphoria), poor concentration, visual changes, and paresthesias • Single doses up to 16 mg generally well tolerated • 20 and 24 mg doses less well tolerated due to poor concentration, headache, mood changes, anxiety, and restlessness; and vivid dreams with night-time dosing PK: • Dose proportional increase in Cmax and $AUC_{0\text{-}inf}$ • T_{max} fasted 0.5-2 hrs; fed 4 hrs; food decreases C_{max} but AUC is similar to fasted • Biphasic elimination; terminal $T_{½}$ = 9.7-13.2 hrs • Single 8 mg dose produced C_{max} 522-580 nM PD: • Awake EEG demonstrated 25% or greater reduction in absolute power for alpha band in a dose dependent manner at CX-8998 concentrations 200-800 nM

Study PN002

Title (population)	Part I: A Double-Blind, Randomized, Placebo-Controlled, Rising-Single-Dose Study in Healthy Elderly Male Subjects (9 healthy males, 55-75 years old) Part II: A Double-Blind, Randomized, Placebo-Controlled, Serial-Panel, Rising-Multiple-Dose Study in Healthy Young Male Subjects (40 healthy males, 18-45 years old)
Design	Single oral doses 2-18 mg or placebo, fasted

Summary of findings

Safety, Part I (elderly males, single dose):

- Single doses up to 18 mg of CX-8998 were generally well tolerated
- TEAE were temporary and generally mild or moderate in intensity. The most frequent TEAE included general, nervous system, and psychiatric disorders: relaxation, fuzzy head, tiredness, headache, lightheadedness, dizziness, mood alteration
- No dose dependent, treatment related effects were observed on safety labs, ECGs, ECG telemetry monitoring or vital signs

PK (elderly males, single oral dose):

- Dose proportional increase in Cmax and AUC_{0-inf}
- T_{max} 0.5-1 hr (fasted)
- Biphasic elimination; terminal $T_{½}$ = 18.8-22.6 hrs

Safety, Part II (young males, multiple dosing once QD X 7 days):

- Multiple oral doses up to 12-mg daily X 7 days were generally well tolerated; TEAEs of mood or perceptual disturbance became more frequent and intense at the 18-mg once daily dose
- Most common TEAE's considered at least possibly drug related were headache, lightheadedness, tiredness, feeling happy or pleasant, feeling emotional, tiredness, somnolence, relaxation, abnormal or vivid dreams or day dreams, and paresthesia/hypoesthesia. No subjects treated with CX-8998 at doses < 18 mg po QD X 7 days discontinued treatment for AEs
- For subjects experiencing CNS AE's, these were generally observed at or near T_{max}; late occurrence (e.g., days after dosing) was not observed in the absence of CNS AE's near T_{max}

PK, Part II

- Dose proportional Day 1 and Day 7 C_{max} and AUC_{0-24hr}
- Terminal $T_{½}$ = 11 hrs
- Steady state trough attained after 2 days of dosing
- Day 7/Day 1 geometric mean accumulation ratios for CX-8998 were 1.31 (AUC_{0-24hr}) and 1.15 (C_{max}) for the 8 mg dose;
- Day 7 mean (±SD) C_{max} = 665 (156) nM and AUC_{0-24hr} = 4679(1495) nM•hr

- Two syncopal episodes occurred: 1) A subject fainted after standing 2 hours after the first dose of CX-8998 2 mg po; assessed as vasovagal probably not related to CX-8998, and the subject continued through the full 7 days of dosing without further events of syncope or dose related blood pressure, heart rate or orthostatic changes; and 2) A subject experienced syncope 2 hours after the first dose of CX-8998 18 mg po; the event was judged by the investigator as moderate in intensity and probably study drug related. Due to ongoing nausea and feeling weak/lethargic, this subject was discontinued from the study after the first dose
- One subject experienced a serious adverse event (SAE) of mood swings following the first dose of 18 mg CX-8998; no additional doses were given and the event was assessed as moderate in intensity and probably study drug related

Study PN003

Title (population)	A 2-Part, Adaptive Design, Randomized, Double-Blind, Placebo-Controlled Crossover Polysomnogram (PSG) Study to Evaluate the Effects of Single Doses of MK-8998 on Slow Wave Activity and Rapid Eye Movement Sleep in Healthy Middle Aged and Elderly Subjects (28 healthy males, 40-80 years old)
Design	Single oral doses of 4, 8, or 12 mg CX-8998 or placebo prior to bedtime
Summary of findings	Safety: • Single oral doses of 4, 8, or 12 mg CX-8998 were well tolerated • The most common AE's were headaches, vivid dreams, and visual and/or auditory disturbances/hallucinations. The dose of CX-8998 was administered at bedtime for this sleep study. The visual and auditory disturbances/hallucinations were typically described as seeing geometric shapes, colors, lights and/or movement, and hearing tones similar to a telephone or electronic music. These were generally not disturbing to subjects. These events had onset about 30 minutes after dosing or generally near T_{max}, and resolved within minutes or during the night. PK, PD: PK data was not yet available for this study PD, polysomnogram (PSG) study: • The hypothesis that sleep slow wave activity (SWA) would increase following dosing with CX-8998 was not supported: SWA decreased by 30% after 12 mg of CX-8998; delayed sleep onset and decreased sleep maintenance were also observed after 12 mg single doses of CX-8998 • Results of the PSG study with 4 and 8 mg of CX-8998 are not yet available

Study PN005

Title (population)	A Single Dose Clinical Trial to Test the Safety, Tolerability, and Pharmacokinetics of MK-8998 in Healthy Female Subjects of Non-Childbearing Potential (9 healthy females of non-childbearing potential, 55-75 years old)
Design	Single oral doses of 8 mg CX-8998 or placebo, fasted

Summary of findings

Safety:

- Single doses of 8 mg CX-8998 in healthy middle-aged and elderly females were generally well tolerated
- Mild laughter, nervousness, and racing thoughts were observed in 2, 1, and 1 subject administered CX-8998, respectively

One subject receiving CX-8998 had elevated serum alanine aminotransferase (ALT) deemed as possibly drug related by the investigator. This subject's pre-dose ALT was 28 IU/L and increased to 41 and 59 IU/L at one and 4 days post-dose, returning to 33 IU/L by two weeks post-dose (normal range: 6 – 40 IU/L). All serum aspartate aminotransferase, alkaline phosphatase and total bilirubin values were within the normal range for this subject

PK:

- T_{max} = 0.5 hrs
- Terminal $T_{½}$ = 30.3 hrs
- Mean C_{max} was 582 nM and $AUC_{0\text{-}inf}$ was 9420 nM•hr

Study PN004

Title (population)	A Phase IIa, Randomized, Multicenter, Double-Blind, Active Comparator- and Placebo-Controlled, Clinical Trial to Study the Safety and Efficacy of MK-8998 in Acutely Psychotic Patients with Schizophrenia (216 adult males (N=126) and females (N=90) 20-55 years old)
Design	CX-8998 (8 mg BID) was compared with olanzapine and with placebo. N=86 randomized to CX-8998, including 49M/37F, 21-55 years old (mean age 37.4 years)
Summary of findings	Safety: • The most frequent TEAEs without regard to causality classified by MedDRA System Organ Class (SOC) in the CX-8998 group were Psychiatric Disorders (19/86 [22.1%] CX-8998 vs. 10/83 [12.0%] placebo); Nervous System Disorders (10/86 [11.66%] CX-8998 vs 6/83 [7.2%] placebo); and Gastrointestinal Disorders (9/86 [10.5%] CX-8998 vs 5/83 [6.0%] placebo). Among CX-8998 treated subjects, insomnia was the only TEAE that rose to a frequency of ≥ 5% (13/86 [15.1%] vs. 7/83 [8.4%] placebo). • No treatment-emergent SAE's occurred in CX-8998 treated subjects TEAE's led to treatment discontinuation in 9/86 (10.5%) of CX-8998 treated subjects vs. 1/83 (1.2%) placebo treated subjects. Four of the CX-8998 discontinuations for AE were for worsening or exacerbation of schizophrenia, only one of which was assessed by the investigator as causally related to CX-8998. Anti-Psychotic Efficacy: • Primary endpoint measure was mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 4 • CX-8998 was not statistically significantly different from placebo in the mean change from baseline in PANSS total score at Week 4 (Mean changes from baseline: CX-8998, -13.3; olanzapine -17.0; placebo -12.7) • For one of the secondary endpoints, responders were defined as those who demonstrated ≥ 20% improvement from baseline on the PANSS total score. CX-8998 was not statistically significantly different from placebo in the responder rate after 4 weeks of treatment (responder rates were: CX-8998, 57.4%; olanzapine, 66.7%; placebo, 48.3%)

Reported safety observations in this table are limited to those that occurred in CX-8998 treated subjects more frequently than in placebo treated subjects. Serious adverse events occurring in placebo treated subjects are not included. Complete details of the safety results are contained in the latest edition of the CX-8998 Investigator's Brochure.