STATISTICAL ANALYSIS PLAN

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
Phase:	2a
Protocol No.:	CX-8998-CLN2-002
Protocol Date:	Original Version 1.0: 23OCT2017 Amendment 1 Version 2.0: 12DEC2017 Amendment 2 Version 3.0: 30APR2018 Amendment 3 Version 4.0: 24SEP2018 Amendment 4 Version 5.0: 29APR2019 Amendment 5 Version 6.0: 30MAY2019
Analysis Plan Version and Date:	Final Version: 21APR2020
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NCT03406702

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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21-Apr-2020 | 14:09 PM EDT

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol CX-8998-CLN2-002. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection.

1.1. STUDY OVERVIEW

CX-8998-CLN2-002 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 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.

Eligible subjects will receive titrating doses of CX-8998 up to 10 mg BID as follows:

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);
6. Day 27: 10 mg (5 capsules) (10 mg/d) (once, morning dose only).

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 four hours post-dosing prior to discharge at Visit 1.

At clinic visits at which PK blood draws are scheduled in the afternoon, 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.

Subjects experiencing specified adverse events will have their dose adjusted.

A member of the study staff will contact any subject who is suspected of experiencing neuropsychiatric adverse events to determine the need for an unscheduled visit before further dose escalation may proceed.

Though amendments 4 and 5 of the protocol were executed, no subjects enrolled under these amendments. Amendment 4 changed the target population and replaced the use of ambulatory electroencephalograms (EEG) withstandard multi-lead video EEGs. Amendment 5 removed dosing

on Day 27. Since no subjects enrolled under these amendments, this schedule of assessments below and the data included in listings will be presented based on amendment 3.

1.2. 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	27	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]			
Nurse home visit					X[2]				X[2]				X[1]	
Telephone call [3]			X				X[2]							X
Informed consent [4]	X													
Demography/medical history [5]	X													
Eligibility criteria	X													
Complete physical exam[6]	X										X			
Targeted physical exam		X									X			
Neurological exam	X										X			
Vital Signs [7]	X	X			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			

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	27	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]			
Nurse home visit					X[2]				X[2]				X[1]	
Telephone call [3]			X				X[2]							X
Ambulatory EEG [15]	X										X			
Seizure-Related Disability Assessment Scale		X									X			
Daily Seizure Diary	X	X	X	X	X	X	X	X	X	X	X	X		
Epitel device (based on device availability)[16]	X				X				X		X			
Epworth Sleepiness Scale		X					X				X			
C-SSRS [17]	X	X					X				X			
UM-PDHQ [18]		As needed												
Prior / Concomitant meds	X	X			X[20]		X		X[20]		X			
AE review[19]		X			X[20]		X		X[20]		X		X	X[19]
Study drug admin. in clinic		X[21]									X[21]			
Study drug admin. outpatient		X[21]	X	X	X	X	X	X	X	X	X[21]	X[21]		
Drug compliance		X[22]			X[23]		X[22]		X[23]		X[22]	X[24]		

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; PK = pharmacokinetic; 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.
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 on Day 26. 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) and EOT, 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. PK samples will be taken at time 0 (predose) and at 2 and 4 hours after administration of study drug. The time of the last dose of study drug and the time of the blood draw will be recorded.
15. Multi-lead EEG will be recorded for 24 hours using an ambulatory system. The EEG will be centrally evaluated by a qualified rater.
16. A single lead EEG will be bipolarly recorded for 5 days using a wearable EEG patch (Epitel device). The EEG recording will be centrally evaluated by a qualified rater. Subjects will be trained in the use of the device by site personnel and will replace the EEG patch every 7 days. Subjects will receive the device at screening. On Days 8 and 20, the nurse who conducts the home visit will check positioning of the device. The device will be returned on the Day 26 clinic visit. This assessment is based on device availability.
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 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, 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. Concomitant medications and adverse events will be recorded by the visiting nurse on Days 8 and 20.

21. Study drug will be administered in the clinic on the morning of Day 1 and Day 26. Study drug will be administered on an outpatient basis on the evening of Day 1 and Day 26 and on the morning of Day 27.
22. Drug compliance will be assessed by a remote mobile technology monitoring application (AiCure).
23. Evaluation of drug compliance and dosing accuracy will be assessed by the visiting nurse.
24. Subjects will return all remaining study drug (including empty bottles) to the site via a prepaid mailer.

1.3. GLOSSARY OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
BID	twice daily
BLQ	below limit of quantification
CRF/eCRF	case report form/electronic case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CX-8998	investigational product
d	day
ECG	electrocardiogram
EEG	electroencephalogram
EOS	end of study
EOT	end of treatment
ESS	Epworth Sleepiness Scale
FSH	follicle stimulating hormone
GSW	generalized spike and wave
HIV	human immunodeficiency virus
hr	hour
HV	hyperventilation
ITT	intent-to-treat
LLN	lower limit of normal
LLOQ	lower limit of quantification
M01	a primary metabolite of CX-8998
M02	a primary metabolite of CX-8998
M03	a metabolite of CX-8998
M04	a metabolite of CX-8998
MDMA	3,4-Methylenedioxymethamphetamine, ecstasy
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
msec	millisecond
n	number of subjects
PK	pharmacokinetic
QTcF	Fridericia corrected QT
SAE	serious adverse event
SERDAS	Seizure-related Disability Assessment Scale
s, SD	standard deviation
t*	critical value from the t distribution
TEAE	treatment emergent adverse events
ULN	upper limit of normal
UM-PDHQ	University of Miami Parkinson's Disease Hallucinations Questionnaire
WHO	World Health Organization

2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

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

2.2. SECONDARY OBJECTIVES

To evaluate the pharmacokinetics of CX-8998 and its metabolites (including, but not limited to, M01 and M02) in the plasma of subjects with idiopathic generalized epilepsy 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 pharmacodynamic effects of CX-8998 as measured by electroencephalogram (EEG).

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

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

3.2. RANDOMIZATION AND MASKING

This is an open-label study.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

There are no planned analyses by stratification factors or covariates. Should there be notable differences between the treatment groups for the exploratory efficacy parameters. Analyses may be repeated adjusting for the baseline (i.e., analysis of covariance with effects for treatment and baseline).

3.3.2. Examination of Subject Subsets

Given the relatively small sample size, there are no planned examinations of subsets.

3.3.3. Multiple Testing and Comparisons

No adjustments will be made for multiple testing.

3.3.4. Missing Data and Outliers

Every effort will be made to obtain all data at each scheduled visit from all enrolled subjects. No imputation for missing data will be implemented in this exploratory study.

3.3.5. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates may be imputed.

In particular, treatment-emergence for AEs with missing start or stop dates will be defined using the following additional criteria:

- if the start date for a particular event is after the date of first dose, then that event will be considered treatment-emergent;
- if the start date for a particular event is missing and the stop date was after the date of first dose, then that event will be considered treatment-emergent; and
- if both the start and stop dates for a particular event are missing, then that event will be considered treatment-emergent.

'Concomitant' for medications or non-drug therapies with missing start or stop dates, will be defined using the following criteria:

- if both the start and stop dates of a particular therapy are missing, then that therapy will be considered concomitant,
- if the start date of a therapy is missing and the stop date of that therapy falls on or after the date of the first dose, then that therapy will be considered concomitant,
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is missing and the therapy was listed as continuing, that therapy will be considered concomitant, and
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is completely missing and the therapy is listed as not continuing, that therapy will be considered not concomitant.

If other missing dates need to be imputed, the project statistician will impute dates in a systematic, but reasonable manner to minimize bias using the following algorithm:

- If the month/year is the same as the Day 1 month/year then the date will be set to the date of Day 1.
- In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1.

A list of incomplete and imputed dates will be prepared by the project statistician or statistical programmer(s) and will be submitted for review by the clinical project manager and sponsor prior to database lock.

3.3.6. Presentations by Study Visit

When data are collected serially over time, individual data presentations may include by-visit or by-assessment displays. For these presentations, assessments will be presented according to the nominal assessment time as obtained from the eCRF. If the planned visit from the schedule of events is present, it will be used. If it is not present, then the closest assessment to the planned visit will be used. If two assessments have the same distance to the expected study assessment, the earlier value will be used.

All assessments will be presented in the listings.

3.3.7. Definitions and Terminology

Age
The age of a subject is defined as the number of whole years between the subject's birth date and the date of informed consent.

Day 1 (Baseline)
Day 1 is the earliest day that study drug is initiated.

Study Day
Study Day is defined relative to Day 1 as follows: Study Day = Date of event – Date of Day 1 +1*(1 if date of event ≥ Date of Day 1, 0 otherwise).

Study Visit
Study Visit is the nominal visit as recorded on the eCRF.

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to initiation of study drug.

Change from Baseline
Change from baseline for a given endpoint is defined as the Study Day X value minus the baseline value.

Percent Change from Baseline
Percent change from baseline for a given endpoint is defined as the Study Day X value minus the baseline value, quantity divided by the baseline value, multiplied by 100.
Percent Change from Baseline = (Study Day X – Baseline)/Baseline*100

Days on Study
Days on study is defined as the number of days from the date of study drug initiation to the final study visit (includes in home or in clinic assessments).

Completer
A subject is defined as a completer if he/she completes the Day 26 EEG and Day 27 dosing regardless of completing the Day 33 visit.

Treatment Period
The treatment period is the period during which a subject receives study drug (i.e., first dose through Day 27).

Days on Study Drug
Days on study drug is defined as the number of days in the treatment period. The date of the last dose of study drug as recorded on the End of Study Visit form or from the AICure electronic data transfer.

Total Study Drug Expected (capsules)
The total study drug expected is defined as the total number of capsules expected to be taken as recorded from all sources and reported from the AICure system.

Total Study Drug Received (capsules)
The total study drug received is defined as the total number capsules of taken as recorded from all sources and reported from the AICure system.

Total Study Drug Received (mg)
The total study drug received (mg) amount will be multiplied by 2 for subjects receiving CX-8998 to calculate the amount of study drug received in mg (i.e., each capsule is 2 mg).

Treatment Compliance
Treatment compliance will be calculated for each subject as a percentage using the following formula:

total study drug received (capsules)/total study drug expected(capsules)*100

Adverse Event
An adverse event 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.

Serious Adverse Event
A serious adverse event (SAE) is any adverse event that results in death, is life-threatening, requires in-patient 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.

Treatment-emergent Adverse Event
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.

Laboratory Abnormality
Per protocol, a laboratory abnormality is any clinically significant laboratory abnormality suggesting a disease or organ toxicity and which is of a severity requiring active management (i.e., changes of dose, discontinuation of drug, more frequent follow-up, medical treatment or a diagnostic investigation). Laboratory abnormalities may also be recorded as adverse events. While laboratory values are available in the clinical database, assessment of clinical significance is not captured. As such, for analysis purposes, laboratory abnormalities are considered to be any values that are outside of the reported normal range for a given laboratory test.

Treatment-emergent Laboratory Abnormality
Treatment-emergent laboratory abnormalities are all analysis defined laboratory abnormalities occurring in the treatment period that were not within the normal range at baseline.

Concomitant Medications
Concomitant medications are those medications or non-drug therapies taken on or after the initiation of study drug. This definition includes medications started prior to the initiation of study drug that continue to be used concomitantly with study drug.

Orthostatic Blood Pressure
Orthostatic blood pressure is defined as the difference from recumbent to standing in the systolic and diastolic blood pressure measurements.

Seizure Duration
Seizure duration is calculated as the sum of the individual durations of seizures of any type (absence seizures, generalized spike and wave [GSW], focal seizures, focal epileptiform patterns, seizure [other] and electrographic seizure). This is measured in hours.

Absence Seizure Duration
Absence seizure duration is calculated as the sum of the individual durations of absence seizures. This is measured in hours.

Seizure (other) Duration
Seizure (other) duration is calculated as the sum of the individual durations of seizures of any type other than absence seizures (generalized spike and wave [GSW], focal seizures, focal epileptiform patterns, seizure [other] and electrographic seizure). This is measured in hours.

3.4. TIMING OF ANALYSES

The final analysis will be completed after the last subject completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

4. ANALYSIS POPULATIONS

The populations defined for analysis will include the intent-to-treat (ITT) population, safety population, and a pharmacokinetic (PK) population.

4.1. INTENT-TO-TREAT (ITT) POPULATION

The ITT population will include all subjects enrolled. This analysis population reflects the full analysis set for this study. The ITT population will be used for analyses of accountability, demographics, and efficacy.

4.2. SAFETY POPULATION

The safety population will include all subjects who are enrolled and receive at least one dose of study drug. The safety population will be the primary population for all analyses of safety data.

4.3. PK POPULATION

The PK population will consist of all subjects in Safety Population who have at least one nonmissing plasma concentration data for CX-8998 and /or its metabolites

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. 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. Presentations of data will be summarized in an overall manner. All available data for enrolled subjects will be listed in the data listings. Unless otherwise noted, the data will be sorted first by subject number and then by date within each subject number.

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

5.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS, AND EXTENT OF EXPOSURE

Subject disposition will be presented for all enrolled subjects. The number of subjects enrolled will be presented for each study population and site. The number of subjects who completed the study and discontinued from the study will be provided. The primary reasons for discontinuation from the study at any point also will be presented. Days on study will be summarized.

Demographic data and baseline characteristics including age, gender, race, ethnicity, height, weight will be summarized using descriptive statistics for the ITT population.

Extent of exposure will be summarized for the safety population using the following measures: days on study drug and total study drug received (in mg), as estimated by the number of capsules dispensed and returned. Treatment compliance also will be summarized. The number and percentage of subjects requiring a dose reduction will be summarized.

5.2. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Concomitant medications and non-drug therapies will be mapped to a World Health Organization (WHO) preferred term and drug classification (Anatomic Therapeutic Chemical Classification level 4): WHODrug March 2018. The number and percent of subjects taking concomitant medications or undergoing non-drug therapies will be summarized using preferred terms and drug classifications and sorted by descending total number of subjects. Determination of concomitant status will be determined according to the rules outlined in Section 3.3.5.

5.3. SAFETY AND TOLERABILITY

5.3.1. Safety and Tolerability Endpoints

The primary objective of this study is to assess the safety and tolerability of CX-8998. The following endpoints will be captured and evaluated:

- TEAEs
- changes from baseline in QTcF and other electrocardiogram (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 TEAE
- number (%) of subjects with SAE
- number (%) of subjects with Adverse Events of Special Interest (AESI) from the AE pages of the CRF:
    - Increased seizure frequency
    - New seizure types
    - Status epilepticus
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Epworth Sleepiness Scale (ESS)

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

5.3.2. Safety Analysis

5.3.2.1. Vital Signs and ECGs

Descriptive statistics will be presented for actual values and for the change from baseline values for systolic and diastolic blood pressure, pulse rate, respiration rate, and weight by study visit. Blood pressure summaries will include recumbent and standing measurements, as well as the change from recumbent to standing (orthostatic changes).

Incidence of vital signs outliers will be presented by visit and time point, where applicable. Outliers for recumbent and standing vital sign parameters will be determined using the criterion in Table 1.

Descriptive statistics will be presented for actual values and for the change from baseline values for the ECG parameters of heart rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec), QTc interval (msec), and QTcF interval (msec) will be summarized by treatment group and study visit.

The incidence of ECG outliers will also be summarized by visit according to the following criteria:

- QT > 500 msec
- QTcF > 450 msec for males or QTcF > 470 msec for females
- QTcF increases from baseline or pre-dose:
    - ≤ 30 msec
    - > 30 msec to ≤ 60 msec
    - > 60 msec

Table 1. Outliers for recumbent and standing vital sign parameters

Vital Sign	Criteria
Temperature	>38°C and ≥1°C increase from baseline
Pulse	>120 bpm and >30 bpm increase from baseline <50 bpm and >20 bpm decrease from baseline ≥ 20 bpm increase from baseline ≥ 40 bpm increase from baseline ≥ 20 bpm decrease from baseline ≥ 40 bpm decrease from baseline
Systolic blood pressure	>180 mmHg and with >40 mmHg increase from baseline <90 mmHg and with >30 mmHg decrease from baseline ≥ 20 mmHg increase from baseline ≥ 40 mmHg increase from baseline ≥ 20 mmHg decrease from baseline ≥ 40 mmHg decrease from baseline
Diastolic blood pressure	>105 mmHg and with >30 mmHg increase from baseline <50 mmHg and with >20 mmHg decrease from baseline ≥ 10 mmHg increase from baseline ≥ 20 mmHg increase from baseline ≥ 10 mmHg decrease from baseline ≥ 20 mmHg decrease from baseline

5.3.2.2. Clinical Laboratory Assessments

Actual values and changes from baseline in clinical laboratory assessments will be summarized by study visit.

Laboratory values outside the normal range for each parameter will be identified using shift tables. Each subject's hematology and blood chemistry values will be flagged as "low" (below the lower limit of normal/LLN), "normal" (within the normal range), or "high" (above the upper limit of normal/ULN) relative to the normal ranges of the central laboratory. Each subject's urinalysis values will be flagged as "normal" or "abnormal."

Shifts from baseline to high/normal/low status for hematology and blood chemistry parameters will be presented by study visit. Shifts from baseline to normal/abnormal status for urinalysis will be presented by study visit.

5.3.2.3. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification, version 21.0. If a subject experiences multiple events that map to a single preferred term, the greatest severity grade and strongest assessment of relationship to study medication, as determined by the investigator, will be assigned to the preferred term for the appropriate summaries. Adverse events that have a missing severity will be classified as having the greatest severity. Adverse events that have a missing relationship will be classified as having the strongest relationship to study medication.

A summary of TEAEs will be presented to show the number and percentage of subjects with at least one AE, SAE, AESI, related AE, or Grade 3 or higher AE.

The occurrence of TEAEs will be summarized by treatment group using system organ class, preferred term, and severity. Separate summaries of treatment-emergent SAEs, AESI, TEAEs related to study drug, and TEAEs leading to the discontinuation of study treatment, and TEAEs by CX-8998 dose administered will be generated. Adverse events will be assigned to a respective CX-8998 according to the start date of the adverse event.

All TEAEs will be listed for individual subjects. The listing will show both verbatim and preferred terms, along with the system organ class and other data gathered regarding the event. All AEs that have start dates prior to the initiation of study treatment will be excluded from the tables but will be included in the listings.

Determination of treatment emergence will be determined according to the rules outlined in Section 3.3.5.

The following are considered AEs of special interest: increase in seizure frequency, new seizure type, and status epilepticus. Otherwise; seizures are not reported as AEs or SAEs.

5.3.2.4. Physical and Neurological Examinations

Data from the physical and neurological examinations will be listed.

5.3.2.5. Columbia Suicide Severity Rating Scale

Data from the C-SSRS will be listed.

5.3.2.6. Epworth Sleepiness Scale

Results from ESS will be listed.

5.3.2.7. UM-PDHQ

Data from the UM-PDHQ will be listed.

5.4. PHARMACOKINETIC ANALYSES

Descriptive statistics of analyte concentrations will be prepared by analyte (CX-8998, including, but not limited to, M01 and M02), visit, time point, and dose. Plasma concentration values reported as below the limit of quantification (BLQ) will be presented as "BQL" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and set to one-half of the lower limit of quantification (LLOQ) at post-baseline time points for summary purposes.

The following conventions will be used for the presentation of summary statistics:

- If at least 1 subject has a concentration data value of BLQ for the time point, the minimum value will be displayed as "BLQ".
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ".
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1 and median values will be displayed as "BLQ".
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median and Q3 values will be displayed as "BLQ".
- If all subjects have a concentration data values of BLQ for a given time point, all order statistics will be displayed as "BLQ" and SD will be suppressed.

Individual plasma concentrations of all measured analytes, visit, dose, nominal time point, date and time of actual collection, and actual time elapsed will be listed by subject for all subjects in PK population analysis set.

6. PROTOCOL DEVIATIONS

Protocol deviations will be documented by the investigator or assigned staff. All deviations and reasons for deviations will be reported to the Sponsor as soon as possible. Deviations will be presented in a data listing.

7. CHANGES IN THE PLANNED ANALYSES FROM THE PROTOCOL

Changes to the planned analysis from protocol:

The following endpoints will not be summarized:

- 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 hyperventilation (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.
- Change in seizure duration (determined by ambulatory EEG)
- Change in spike-wave run duration (determined by ambulatory EEG)
- Change in spike-wave density (spike-wave %) (determined by ambulatory EEG)
- Proportion of subjects with 30% and 50% reduction in seizure frequency (responder rate)and proportion of seizure-free subjects (determined by ambulatory EEG)
- Seizure-free intervals in minutes (maximum and average determined by ambulatory EEG)
- Change in the Seizure-related Disability Assessment Scale (SERDAS)
- Change in the average weekly seizure frequencyfor each type of seizure self-reported by subjects inthe daily seizure diary
- Changes in the number of seizures recorded with the Epitel device (based on device availability)
- 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

Should any additional deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

8. REFERENCES

None.

9. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for the ITT Population.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population due to missing data.
    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, will be noted.
    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted by subject number, date, and parameter, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
    - Raw measurements will be reported to the number of decimal places as captured electronically or on the eCRFs, not to exceed 4 decimal places.
    - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented, not to exceed 5 decimal places.

  - Means will be reported to the same number of decimal places as the parameter, not to exceed 4 decimal places.
  - Calculated percentages will be reported with no decimals.
- Dates will be formatted as DDMONYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HH:MM).

10. PROPOSED TABLES, LISTINGS, AND FIGURES

Summary Tables

Accountability and Baseline Characteristics

All Subjects Screened

14.1.1.1 Subject Disposition and Termination from Study

ITT Population

14.1.1.2 Protocol Deviations

14.1.2.1 Demographics and Baseline Characteristics

Safety Population

14.1.2.2 Demographics and Baseline Characteristics

14.1.3 Summary of Concomitant Medications and Non-Drug Therapies

14.1.4 Extent of Exposure and Percent Compliance

PK Population

14.1.5 Summary of Plasma Concentrations of CX-8998 and Metabolites

Safety – Safety Population

14.3.1.1 Summary of Treatment-Emergent Adverse Events

14.3.1.2 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Greatest Severity

14.3.1.3 Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class and Preferred Term

14.3.1.4 Treatment-Emergent Adverse Events by CX-8998 Dose Administered, System Organ Class, and Preferred Term

14.3.2.1 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

14.3.2.2 Treatment-Emergent Adverse Events Leading to the Discontinuation of Study Drug by System Organ Class and Preferred Term

14.3.2.3 Treatment-Emergent Adverse Events of Special Interest by System Organ Classification and Preferred Term

14.3.4.1 Summary of Hematology Assessments

14.3.4.2 Summary of Serum Chemistry Assessments

14.3.4.3 Summary of Coagulation Assessments

14.3.4.4 Summary of Urinalysis Assessments

14.3.4.5 Shift from Baseline of Laboratory Abnormalities

14.3.5.1.1 Summary of Electrocardiogram Parameters

14.3.5.1.2 Summary of Electrocardiogram Outliers

14.3.5.2.1 Summary of Respiration Rate, Temperature, and Weight

14.3.5.2.2 Summary of Blood Pressure and Pulse

14.3.5.2.3 Summary of Vital Signs Outliers

Data Listings – ITT Population

16.2.1.1 Subject Disposition

16.2.1.2 Informed Consent and Eligibility

16.2.2 Protocol Deviations
16.2.3 Reasons for Exclusion from Study Populations
16.2.4.1 Demographics and Baseline Characteristics
16.2.4.2 Medical and Surgical History
16.2.4.3 Prior and Concomitant Medications and Non-Drug Therapies
16.2.5.1 Study Drug Dose Change Log
16.2.5.2 AICure Dose Compliance
16.2.5.3 Pharmacokinetic Samples
16.2.6.1 Ambulatory EEG
16.2.6.2 Subject Diary Information
16.2.6.3 Seizure-Related Disability Assessment Scale
16.2.7 Adverse Events
16.2.8.1.1 Laboratory Tests – Hematology
16.2.8.1.2 Laboratory Tests – Serum Chemistry
16.2.8.1.3 Laboratory Tests – Coagulation
16.2.8.1.4 Laboratory Tests – Urinalysis
16.2.8.1.5 Pregnancy Test
16.2.8.1.6 Laboratory Tests – Other
16.2.8.2 Vital Signs, Height, and Weight
16.2.8.3 Physical Examination
16.2.8.4 Neurological Examination
16.2.8.5 Electrocardiogram
16.2.9.1 Epworth Sleepiness Scale
16.2.9.2 Columbia Suicide Severity Rating Scale
16.2.9.3 UM-PDHQ