Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of CX8998 for Essential Tremor

NCT Number: NCT03101241

Date: 27 June 2018

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor
Phase:	2
Protocol No.:	CX-8998-CLN2-001
Protocol Date:	Version 3.0: 30MAY2018 Version 2.0: 08AUG2017 Version 1.2: 06APR2017
Analysis Plan Version and Date:	Final Version 1: 27JUN2018
Prepared By:	PI PharPoint Research, Inc. 5003 S. Miami Blvd, Ste. 100 Durham, NC 27703
Prepared For:	Cavion, Inc. 1 Broadway Cambridge, MA 02142

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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

TABLE OF CONTENTS

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-CLN2-001. 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. The reader is referred to the Pharmacokinetic Analysis Plan for details on pharmacokinetic analyses. Separate reports will be prepared for the digital substudy and for the exploratory exposure efficacy and exposure safety analyses; the statistical methods for these analyses are not described in this document.

1.1. STUDY OVERVIEW

This is a randomized, double-blind, placebo-controlled, parallel-group study of the efficacy, safety and tolerability of CX-8998 for the reduction of essential tremor.

Subjects will be screened up to 4 weeks prior to the initiation of treatment (6 weeks prior if the subject wishes to discontinue primidone in order to be eligible for the study). On Day 1, after randomization to either CX-8998 (2 mg capsules) or placebo (matching capsules) and baseline measurements, subjects will receive 2 capsules twice daily (BID) for 7 days. Subjects will return to the clinic on Day 8 for safety monitoring and up-titration of the dose to 4 capsules BID if the 2-capsule (4 mg or placebo) dose is well tolerated. Subjects will return to the clinic on Day 15 for safety monitoring, efficacy assessments, and final up-titration of the dose to 5 capsules BID if the 4-capsule (8 mg or placebo) dose is well tolerated. Subjects will be monitored for a minimum of 2 hours after dosing and prior to discharge from the clinic. The final efficacy visit will occur at Day 28. The final safety visit will occur at Day 35.

If subjects experience intolerable adverse events (AEs)—defined as Grade 3 or 4 AEs that are considered by the investigator to be related to study drug or Grade 1 or 2 AEs is that are considered related to study drug and that prompt the subject to ask to discontinue dosing—the dose may be decreased to the next lower dose (1 capsule BID in the case of the starting dose). Subjects who do not tolerate the next lower dose or who cannot tolerate 1 capsule BID will be withdrawn from treatment.

1.2. SCHEDULE OF ASSESSMENTS

	Procedure		TREATMENT PERIOD				
	Visit	Screen	Visit 1 Baseline	Visit 2	Visit 3	Visit 4	EOS
	Study Day (window) End of week	-28 to 0	1 -	8 (±2) 1	15 (±2) 2	28 (-1) 4	35 (±2) 5
1	Informed consent	X					
2	Demography/medical history	X					
3	Eligibility criteria	X					
4	Complete physical exam	X	X				X
5	Targeted physical exam			X	X	X	
6	Neurological exam	X	X	X	X	X	X
7	Vital Signs	X	X	X	X	X	X
8	Clinical laboratory tests	X	X		X	X	X
9	Electrocardiogram	X	X	X	X	X	X
10	Urine (+/- serum) pregnancy	X	X			X	
11	Serum FSH	X					
12	TETRAS performance (video)	X	X		X	X	
13	Accelerometry (Kinesia ONE)		X		X	X	
14	TETRAS ADL		X		X	X	
15	QUEST		X		X	X	
16	CGI-S, CGI-I		X		X	X	
17	PGIC				X	X	
18	Goal Attainment Scale		X		X	X	
19	Epworth Sleepiness Scale		X	X	X	X	
20	C-SSRS	X	X	X	X	X	X
21	UM-PDHQ		As needed				
22	Pharmacokinetic sampling			X	X	X	
23	Pharmacogenomic sampling		X				

24	Prior/Concomitant medications	X	X	X	X	X	X
25	AE review	X	X	X	X	X	X
26	Study drug administration in clinic		X	X	X	X	
27	Dosing		X				
28	Drug compliance			X	X	X	

ADL – activities of daily living; AE – adverse event; CGI-I – Clinical Global Impression – Improvement; CGI-S – Clinical Global Impression – Severity; C-SSRS – Columbia Suicide Severity Rating Scale; EOS – end of study; FSH – follicle stimulating hormone; FU – follow-up; PGIC – Patient Global Impression of Change; QUEST – Quality of Life in Essential Tremor Questionnaire; TETRAS – The Essential Tremor Rating Assessment Scale; UM-PDHQ - University of Miami Parkinson's Disease Hallucinations Questionnaire.

1. Informed consent must be signed prior to initiation of all other screening procedures (Section 12.2.3).
2. Conditions recorded in medical history will not be reported as adverse events unless the pre-existing condition worsens in severity or frequency. Medical history will include handedness, the age at onset of tremor and whether tremor is responsive to alcohol.
3. Subjects must meet all criteria specified in Sections 6.2 and 6.3. Eligibility will be confirmed by a central reviewer. Subjects taking primidone at screening who are deemed eligible for participation and are willing to discontinue primidone will be allowed an additional 2 weeks of screening (a total of 6 weeks/42 days) to ensure safe primidone discontinuation.
4. A complete physical exam will include 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 (Section 10.1.2). Complete physical examination need not be repeated at Visit 1 (Day 1) if Day 1 is ≤ 7 days from the screening visit.
5. A targeted physical exam will be based on subject reports of signs and symptoms and investigator's observations (Section 10.1.2).
6. A neurological examination will include assessment of mental status (which should include assessment of orientation to person, place, time, and situation) and examination of cranial nerves II-XII, motor and sensory exam, reflexes, coordination, stance, gait and balance (Section 10.1.3). The details of the examination are left to the discretion of the investigator or the investigator's qualified designee but should be sufficiently comprehensive to enable a determination of whether the identified items are within the range of normal or are abnormal, and specific abnormalities should be described, e.g., "not oriented to time", or "left cranial nerve VII palsy", etc.
7. Vital signs include body temperature, systolic and diastolic blood pressure, 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 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. At Screening, triplicate recordings of blood pressure and pulse rate will be made. The average of the 3 measurements will be used for comparison to single recordings at Visits 1 – 4. On Visits 1, 2, 3 & 4 (dosing days) orthostatic BP and pulse rate will be measured before dosing (recumbent and standing) and approximately 1-2 hours after dosing (recumbent and standing) as convenient between other required visit procedures. During any 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 BP/pulse measurements). (Section 10.1.4)

8. Clinical chemistry, hematology, urinalysis and coagulation panel. See Section 10.1.5 for complete details. Screening labs need not be repeated at Visit 1 (Day 1) if Day 1 is ≤7 days from the screening visit. A positive drug screen will result in exclusion from the study unless it is explained by use of an allowed prescription medication (Section 10.1.6).
9. A triplicate 12-lead ECG will be performed at Screening and End of Study. At Visits 1, 2, 3 and 4 triplicate 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. (Section 10.1.8)
10. Women of childbearing potential only. A positive urine pregnancy test will be confirmed via serum testing. (Section 10.1.6)
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. Execution of the TETRAS Performance subscale will be video recorded for assessment by the central reader. Assessment by the site rater should be performed during the videotaping session. At Visit 1, the TETRAS Performance subscale should be performed prior to administration of study drug in the clinic. At Visits 3 and 4, the TETRAS Performance subscale should be performed during a window of 1 to 3 hours after administration of study drug in the clinic. (Section 8.1.1)
13. The Kinesia ONE device will be worn in the clinic after execution of the TETRAS Performance subscale assessment and, at Visit 1, prior to administration of study drug in the clinic. (Section 8.2.1)
14. TETRAS ADL: A 12 item scale where each item is rated on a 0 to 4 scale, with 0 representing normal activity and 4 representing severe abnormality. The sum of the individual scores provides the overall score, ranging from 0 to 48. At Visit 1, the TETRAS ADL subscale should be performed after the TETRAS Performance subscale (performed during a window of 1 to 3 hours after administration of study drug in the clinic) and Kinesia ONE accelerometry and prior to administration of study drug in the clinic. At Visits 3 and 4, the TETRAS ADL should be performed after the TETRAS Performance subscale and Kinesia ONE accelerometry. (Section 8.1.2)
15. QUEST: a 30-item quality of life questionnaire (Section 8.3.1)
16. The Clinical Global Impression Severity (CGI-S) will be administered at Visit 1. The Global Clinical Impression Improvement (CGI-I) will be administered at Visits 3 and 4. (Section 8.3.2)
17. The Patient Global Impression of Change (PGIC) will be administered at Visits 3 and 4. (Section 8.3.3)
18. Subjects will identify 3 specific, personal goals at Visit 1. Progress towards the goals will be assessed via Goal Attainment Scaling (GAS) at Visit 4. (Section 8.3.4)
19. The Epworth Sleepiness Scale is intended to measure daytime sleepiness. (Section 10.1.10).
20. C-SSRS identifies behaviors that may be indicative of an individual's intent to commit suicide. Subjects answering “yes” to Suicidal Ideation item 4 or 5 on the C-SSRS during the study must be withdrawn from the study treatment. (Section 10.1.9)
21. 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. (Section 10.1.11)

22. Collection of samples will occur pre-dose on Visits 2, 3, and 4. Additionally, at Visit 4, a post-dose sample will be collected as close to 4 hours post-dose as possible, but within the window of 4-6 hours post-dose (i.e., a total of two PK samples are collected at Visit 4. (Section 9.1)
23. A sample for pharmacogenomic testing will be collected in all subjects except where prohibited by local regulation. (Section 9.3)
24. Concomitant medications will be recorded from the time of informed consent through the End of Study. See Section 7.3 for a list of prohibited and restricted medications. At each visit, the study site staff will re-confirm the dose and schedule of other anti-ET drugs the subject is taking.
25. AEs will be collected from signature of the ICF through 30 days after the last dose of study drug (Section 10.2.2). Adverse events will be followed for resolution in accordance with Section 10.2.3.
26. The first dose of study drug at each dose level will be administered in the clinic. Subjects will be instructed to eat breakfast. At Visits 2, 3, and 4 subjects should hold their morning dose, as their dose will be administered in the clinic after the subject has undergone the first set of orthostatic VS and required pre-dose PK sampling, and/or has been evaluated by the investigator for suitability to undergo specified dose increase. Subjects will remain under observation for a minimum of 2 hours post dosing prior to discharge at Visits 1, 2 and 3, or the time that is required to complete all of the required procedures for the visit (Section 4.3.)
27. Subjects will initiate dosing at 4 mg (2 capsules) administered twice daily with food. After 7 days dosing, the dose will be increased to 8 mg (4 capsules) twice daily, per subject tolerance. After 7 days at 8 mg BID, the dose will be increased to 10 mg (5 capsules) twice daily, per subject tolerance (Section 4.3).
28. Compliance will be assessed via pill counts. (Section 4.4.)

1.3. GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
ANCOVA	Analysis of covariance
BID	Twice daily
BLQ	Below limit of quantification
CAS	Completers Analysis Set
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CSR	Clinical study report
eCRF	Electronic case report form
EOS	End of study
ESS	Epworth Sleepiness Scale
FAS	Full analysis set
GAS	Goal Attainment Scale
ITT	Intent to treat
IWRS	Interactive web response system
LLOQ	Lower limit of quantification
LSMean	Least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
PD	Pharmacodynamic
PK	Pharmacokinetic
PPAS	Per Protocol Analysis Set
PGIC	Patient Global Impression of Change
QUEST	Quality of Life in Essential Tremor Questionnaire
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale

Abbreviation	Definition
WHO	World Health Organization

2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this study is to assess the efficacy of CX-8998, in doses up to 10 mg twice daily (BID), in reducing the severity of essential tremor.

2.2. SECONDARY OBJECTIVES

The secondary objectives are as follows:

1. To assess the effects of CX-8998 on tremor-affected activities of daily living (ADL)
2. To objectively quantify changes in essential tremor severity using accelerometry
3. To assess the safety and tolerability of CX-8998 in doses up to 20 mg per day (10 mg BID)
4. To measure the concentration of CX-8998 and its 2 primary metabolites (M01 and M02) in plasma (to be reported separately from the Clinical Study Report [CSR])

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

1. To assess changes in quality of life in subjects with essential tremor
2. To assess the efficacy of CX-8998 in doses up to 8 mg BID in reducing the severity of essential tremor.
3. To assess study drug effects on digital biomarker patterns associated with essential tremor (in a subset of subjects). Substudy analyses will be reported in an addendum to the study report.
4. To use the plasma concentrations of CX-8998 and its 2 primary metabolites in plasma in population pharmacokinetic (PK)/pharmacodynamic (PD) analyses to evaluate the exposure-efficacy and exposure-safety relationships (to be reported separately from the CSR)

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

Approximately 106 subjects will be randomized to one of two treatment groups: Placebo or CX-8998. Based on similarly designed studies, this sample size should be sufficient to provide preliminary safety and efficacy information on CX-8998.

A sample size of 43 subjects per group has at least 90% power to detect at least a 5.5-point difference between CX-8998 and placebo in change from Baseline to Day 28 (end of treatment) in the TETRAS performance subscale total score when the standard deviation is 7.5 and alpha=0.05 (calculations based on a Wilcoxon-Mann-Whitney test for two independent means, assuming normal distributions for each treatment group with a common, but unconfirmed, standard deviation. PASS 2008). Approximately 106 subjects will be enrolled to ensure that 86 subjects are available for inclusion in the efficacy analyses.

3.2. RANDOMIZATION AND BLINDING

This is a multicenter, randomized, double-blind, parallel-group study. Subjects will be centrally randomized via an interactive web response system (IWRS) in a 1:1 ratio to 1 of 2 groups:

Group A	Titrating doses of CX-8998 up to 10 mg BID
Group B	Placebo

Subject randomization will be stratified by concomitant use of an anti-tremor medication and by site type (substudy vs non-substudy). The randomization schedule will be prepared by a non-study statistician using PharPoint standard operating procedure BIO002. An IWRS will facilitate randomization and treatment shipments to each site.

During the study, if both types of drug are not available at a study site, subjects may be randomized manually by the unblinded study team (unblinded statistician and IWRS team). In these cases, the subject will be assigned to an available treatment kit at the study site and recorded in the IWRS. However, the randomization number assigned to the subject may not match the treatment as assigned on the pre-specified IWRS randomization schedule. These subjects will be considered to be assigned the treatment to which they were assigned by the manual randomization process.

This is a double-blind study. The treatment assignment and drug contents are not known to the sponsor, the subject, the investigator, or other study personnel. Every effort will be made to maintain the blind. However, in the event of a medical emergency or pregnancy (including pregnancy in the sexual partner of a male subject) in which knowledge of the investigational product is critical to the subject's management, the blind may be broken for that subject by the treating investigator. See Protocol Section 4.8 for further detail.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

All efficacy analyses will be adjusted for the stratification variables: anti-tremor medication use (yes or no) and site type (substudy vs. non-substudy).

3.3.2. Examination of Subject Subsets

A digital biomarker substudy, which will include up to 30 total subjects, will be performed at certain sites. The analysis of Exploratory Objective 3 will be conducted using data from subjects who are enrolled in the substudy. This SAP does not describe analyses for these data.

Exploratory subgroup analyses of the primary and secondary efficacy endpoints will include the following subgroups formed from baseline parameters:

1. Sex: male and female
2. Age at the time of informed consent as defined by: subjects up to 65 years of age and subjects >65 years of age
3. Baseline severity as assessed by centrally rated TETRAS performance score baseline values: greater than and less than the median value.
4. Baseline tremor asymmetry defined as a >1 point difference between the right and left side on any one of the TETRAS performance subscale items 4A (postural tremor), 4B (wing-beating tremor) or 4C (kinetic tremor): asymmetry present and asymmetry absent
5. Baseline ratio of TETRAS performance postural tremor (subscale item 4A) versus kinetic tremor (subscale item 4C) as defined by the ratio of total postural tremor (sum of left and right hand) divided by total kinetic tremor (sum of left and right hand): greater than and less than the median ratio
6. Baseline ratio of Kinesia ONE postural tremor versus kinetic tremor defined and grouped similarly to the ratio above
7. Baseline rest tremor as defined as total rest score (sum of rest for left and right hand) measured by Kinesia ONE at baseline of greater than (presence) or less than (absence) the median total rest tremor score: presence of rest tremor and absence of rest tremor
8. Concurrent essential tremor medication at Day 1: yes and no, also a subgroup on subjects taking beta-blockers will be examined
9. Primidone use at study start as defined as subjects who discontinued primidone use within two weeks prior to or during the screening period: taking primidone and not taking primidone

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 randomized subjects. However, for subjects who are missing data for the primary endpoint (The Essential Tremor Rating Assessment Scale [TETRAS] performance subscale total score at Day 28), multiple imputation will be used to estimate the response for each missing component of the subscale, prior to the calculation of the total score (see Section 3.3.7). Sensitivity analyses will be performed to determine the effect of multiple imputation on inference. Analyses are described in more detail in Section 5.4.2. Multiple imputation and sensitivity analyses will only be used for analysis of the primary hypothesis.

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

Results from assessments of clinical laboratory tests, physical examinations, neurological examinations, vital signs, electrocardiograms (ECGs), TETRAS Performance and ADL subscales, Quality of Life in Essential Tremor Questionnaire (QUEST), Clinical Global Impression – Improvement (CGI-I), Patient Global Impression of Change (PGIC), Goal Attainment Scale (GAS), and the Epworth Sleepiness Scale (ESS) will be summarized by study visit and treatment group. If assessments are collected multiple times within a given study visit date, the result closest to the scheduled visit date will be used for summary presentations. If two measurements have the same distance to the expected date, the most recent assessment will be used. If a subject has multiple non-missing scheduled values on the same date, the most recent assessment will be used. If a scheduled assessment and an unscheduled or early termination assessment are collected within a given visit, the scheduled assessment will be chosen. Unscheduled and early termination visits will be assigned to a study visit using the analysis windows described in Table 1 in case the scheduled visit was not performed. All assessments will be presented in the listings.

Table 1: Visit Windows

Visit	Target Day	Clinical Laboratory Window	Physical Exam, Neurological Exam, Vital Signs, and ECG Window	TETRAS Performance Subscale Window	ESS Window	TETRAS ADL Subscale, Accelero-metry QUEST, CGI-I, and GAS Window	PGIC Window
Screening	-28 to 0	-28 – 0	-28 – 0	-28 – 0	n/a	n/a	n/a
Visit 1	1	1	1	1	1	1	n/a
Visit 2	8	n/a	2 – 11	n/a	2 – 11	n/a	n/a
Visit 3	15	2 – 22	12 – 22	2 – 22	12 – 22	2 – 22	2 – 22
Visit 4	28	23 – 30	23 – 30	23+	23 – 30	23+	23+
EOS	35	31+	31+	n/a	n/a	n/a	n/a

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.

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

Study Week
Study Week is defined relative to the study visits. Study Week 1 begins at Visit 1 through and including the days prior to Visit 2. Study Week 2 begins at Visit 2 through and including the days prior to Visit 3. Study Week 3 begins at Visit 3 through the 7 days after Visit 3. Study Week 4 is the time including 8 days after Visit 3 through Visit 4. Study Week 5 begins the day after Visit 4 through the End of Study visit.

Baseline Value
For purposes of analysis, the baseline value is generally defined as the last non-missing value obtained prior to or within 15 minutes after the initiation of study drug. For ECGs, the mean of the available triplicate pre-dose values at Visit 1 will be used as the baseline. If this value is not available, the mean of the available triplicate screening values will be used. For blood pressure and pulse rate, the mean of the triplicate recordings of blood pressure and pulse rate taken at the screening visit will be used as the baseline.

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

Baseline Severity
The baseline severity is defined as the centrally rated TETRAS performance score baseline values.

TETRAS Performance Subscale total score
The TETRAS Performance Subscale total score will be derived from the 9 items of the performance section of TETRAS (each rated 0-4). The score has a minimum value of zero and a maximum value of 64. Total scores will not be calculated if any of the items have missing values, with the exception of Item 5. If Item 5 has any available values and all other values are present, the score may be calculated.

- Items 1 (head tremor), 2 (face tremor), 3 (voice tremor), 7 (handwriting), and 9 (standing) have maximum scores of 4.

- Item 4 is the sum of 0-4 ratings of right and left upper limb tremor in three tasks in two extremities: postural tremor with upper limbs held forward and horizontally, postural tremor with upper limbs extended laterally and horizontally, with the elbows flexed and hands positioned close to each other near the chin and kinetic tremor during finger-nose (or chin)-finger movements. The sum of the three tasks and two extremities results in an item 4 score of 0-24.
- Item 5 (lower limb tremor) is scored as the maximum of the 4 maneuvers performed and produces a score with a maximum of 4,
- Items 6 (spiral drawing task) and 8 (test of upper limb tremor) are scored for the right and left upper limbs and summed to produce item scores of 0-8.

TETRAS ADL Score
The TETRAS ADL score will be derived as the sum if the 12 items (each rated 0-4) of the ADL section of TETRAS. The score has a minimum value of zero and a maximum value of 48. Total scores will not be calculated if any of the items have missing values.

TETRAS Total Score
The Total TETRAS score is defined as the sum of the TETRAS performance subscale total score and the TETRAS ADL subscale score. This score will not be calculated if either of the TETRAS performance or ADL subscale total scores are missing.

Tremor Asymmetry
Tremor asymmetry is defined as a >1 point difference between the right and left side on any one of the TETRAS performance subscale items 4A (postural tremor), 4B (wing-beating tremor) or 4C (kinetic tremor).

Ratio of Postural Tremor to Kinetic Tremor - TETRAS
The ratio of TETRAS performance postural tremor (subscale item 4A) to kinetic tremor (subscale item 4C) is defined as the ratio of the total postural tremor (sum of left and right hand) score divided by the total kinetic tremor (sum of left and right hand) score.

Ratio of Postural Tremor to Kinetic Tremor– Kinesia ONE
The ratio of postural tremor to kinetic tremor is defined as the ratio of the total postural tremor (sum of left and right hand) score divided by the total kinetic tremor (sum of left and right hand) score as provided by Kinesia ONE.

Rest Tremor
Rest tremor is defined as total rest score (sum of rest for left and right hand) measured by Kinesia ONE.

Concurrent Essential Tremor Medication Group
The concurrent essential tremor medication group is defined as subjects who are taking a medication for essential tremor at Day 1.

Beta-Blocker Group

The beta-blocker group is defined as subjects taking substances coded as beta-blockers by WHODrug.

Primidone Use
Primidone use at study start is defined as subjects who discontinued primidone use within two weeks prior to or during the screening period.

Days on Study
Days on study is defined as the number of days from the date of study drug initiation to the final clinic visit.

Days on Study Drug
Days on study drug is defined as the number of days from the date of study drug initiation to the date of the last dose on Day 28 or the date of study drug discontinuation as recorded on the End of Study (EOS) eCRF if the Day 28 dose does not occur.

Total Study Drug Received (capsules)
The total study drug received is defined as the total dispensed capsules less the total returned capsules.

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

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.

Intolerable Adverse Event
An intolerable AE is one that is considered by the investigator to be related to study drug and is either a Grade 3 (severe) or 4 (life threatening) event or is a Grade 1 (mild) or 2 (moderate) event that prompts the subject to ask to discontinue dosing.

Serious Adverse Event
A serious adverse event (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.

Treatment-emergent Adverse Event
Treatment-emergent adverse events (TEAEs) are AEs that occur after the initiation of study drug through 30 days after the last dose or a pretreatment event that worsens in intensity during the same period.

Laboratory Abnormality
For analysis purposes, a laboratory abnormality is any value that is outside of the reported normal range for a given laboratory test regardless of clinical significance.

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

Treatment Period
The treatment period is the period during which a subject receives study drug through 30 days after last dose.

Complete Dosing Period
A subject will be considered to have a complete dosing period if the subject receives study drug from Day 1 through Day 28 with ≥75% compliance.

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.

Pharmacodynamic (PD) Assessment
Any assessment performed by the Kinesia ONE instrument is considered a PD assessment.

Percent Compliance
Percent compliance will be calculated for each subject as a percentage of the total dispensed capsules minus the total returned capsules, quantity divided by the total number of capsules expected to have been taken by the subject based on their number of days on study drug, dose increase dates (Day 8/Visit 2 and Day 15/Visit 3), and dose reduction date (if applicable) multiplied by 100.

$$\text{Percent compliance} = \frac{total\ number\ of\ capsules\ dispensed - total\ number\ of\ capsules\ returned}{total\ number\ of\ capsules\ expected} * 100$$

For subjects who have discontinued or lost to follow-up, the last visit will be utilized to determine percent compliance.

3.4. TIMING OF ANALYSES

A topline analysis of efficacy will be completed after the last subject completes Day 28 and the clinical database has been cleaned and quality checked and a soft lock has been performed on the data entered.

The sponsor's Study Safety Representative and a separate independent medically qualified and clinical trials-experienced Safety Monitor Physician will monitor aggregate study level safety and tolerability on a recurring basis: The first review will occur after approximately 25% of the

projected sample size of subjects have completed the EOS Visit and the second review will occur after approximately 50% of the projected sample size of subjects have completed the EOS Visit.

Upon completion of the bioanalysis of full PK sample sets from 25%, 50%, and 75% of subjects from the CX-8998 group, interim PK concentration summaries will be provided to the sponsor.

Unblinded summary efficacy tables may be provided for review by a Cavion executive committee.

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 SETS

The analysis sets covered by this analysis plan will include the intent-to-treat analysis set (ITT), the Full Analysis Set (FAS), the Per Protocol Analysis Set (PPAS), the Day 28 Completers Analysis Set (CAS) and the safety analysis set.

4.1. INTENT-TO-TREAT (ITT) ANALYSIS SET

The ITT analysis set will include all subjects who are randomized. The ITT analysis set will be used for analyses of accountability and demographics and for listings of individual subject data. Subjects will be analyzed according to the treatment as randomized.

4.2. FULL ANALYSIS SET (FAS)

The FAS will consist of all subjects who receive at least one dose of study medication and have both baseline and at least one postbaseline efficacy assessment of the same parameter for any of the efficacy parameters. The FAS will be used for the assessments of efficacy, including all primary and secondary endpoints, along with all exploratory endpoints. Subjects will be analyzed according to the treatment as randomized. The FAS will be the primary analysis set.

4.3. PER PROTOCOL ANALYSIS SET (PPAS)

The Per Protocol Analysis Set (PPAS) will consist of all subjects in the FAS with no major protocol violations, as determined before unblinding. The PPAS will be used in a secondary analysis of the primary endpoint and secondary endpoints. Subjects will be analyzed according to the treatment as randomized.

4.4. DAY 28 COMPLETERS ANALYSIS SET (CAS)

The CAS will consist of all subjects in the FAS who are considered to have a complete dosing period as defined in Section 3.3.7. This analysis set will be used in a secondary analysis of the primary endpoint. Subjects will be analyzed according to the treatment as randomized.

4.5. SAFETY ANALYSIS SET

The safety analysis set will include all subjects who are randomized and receive at least one dose of study medication. The safety analysis set will be the primary analysis set for all analyses of safety data. Subjects who receive treatment other than that intended will be analyzed according to the treatment received.

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, mean, median, standard deviation, minimum, and maximum for continuous data and frequencies and percentages for categorical data. Data will be summarized by treatment group and overall, where applicable. Additional statistical methods include analysis of covariance (ANCOVA), signed-rank testing, and Cochran-Mantel-Haenszel testing. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, then by subject number, and then by date within each subject number.

The term 'treatment group' refers to all subjects on the same study drug. There will be two treatment groups in this study:

Group A	Titrating doses of CX-8998 up to 10 mg BID
Group B	Placebo

The statistical analyses will be conducted with the SAS® System version 9.4 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be verified using independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

5.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS, AND MEDICAL HISTORY

The number of subjects in each analysis set (as defined in Section 4) will be presented by treatment group and by site. Subjects who completed the study, subjects who discontinued treatment and/or withdrew from study, and the reasons for discontinuation and withdrawal will be summarized for the ITT analysis set. Dose reductions and reasons for dose reductions, along with the days on study, will also be summarized for the ITT analysis set.

The following summaries will be presented for the ITT and safety analysis sets by treatment group and overall. Demographics will include summaries of age, sex, ethnicity, race, height (cm), and body weight (kg). Disease history, including time since onset of essential tremor, alcohol-related improvement, and handedness, will be summarized. Stable dosage of anti-tremor medication at study entry will be summarized. Baseline characteristics will be summarized including TETRAS Performance subscale, TETRAS ADL, Total TETRAS score, and the following subgroups (see section 5.5.2): age group (<=65 and > 65 years old), baseline severity group (TETRAS Performance greater than or less than the baseline median), tremor asymmetry group, postural to kinetic tremor ratio groups as measured by TETRAS performance and Kinesia ONE, rest tremor group, subjects taking beta-blockers, and primidone use at screening This information will be reviewed for baseline differences between groups, but no statistical testing will be performed.

Medical history will be listed.

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 2017. 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. EXTENT OF EXPOSURE

Extent of exposure will be summarized for the safety analysis set by treatment group using the following measures: number of patients exposed to study treatment (total and broken down by the maximum dose level received), days on study drug (total and broken down by maximum dose level received), and total study drug received (in mg), as estimated by the number of capsules dispensed and returned. Percent compliance will also be summarized. See Section 3.3.7 for definitions.

5.4. EFFICACY ANALYSIS

5.4.1. Efficacy Endpoints

5.4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Day 28 on the TETRAS Performance subscale total score, as scored by the central rater.

5.4.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

1. Change from baseline to Day 28 on the TETRAS ADL subscale
2. Change from baseline to Day 28 in accelerometry scores (sum of left and right hands), as measured by Kinesia ONE

5.4.2. Efficacy Analysis

5.4.2.1. Primary Efficacy Analysis

The primary statistical hypothesis for the study is provided below.

- H_{02}: $\mu_{Placebo} = \mu_{CX-8998}$, i.e., there is no difference between treatment groups in the mean change from baseline in TETRAS performance subscale total score at Day 28
- H_{12}: $\mu_{Placebo} \neq \mu_{CX-8998}$, i.e., there is a difference between treatment groups in mean change from baseline in TETRAS performance subscale total score at Day 28

The primary efficacy analysis of the TETRAS performance subscale will be conducted on the FAS using an ANCOVA model with fixed effects for treatment, anti-tremor medication use, site type,

and baseline value of the TETRAS performance subscale. The primary hypothesis to be tested is whether the mean change from baseline in TETRAS performance scale in the CX-8998 arm is different from placebo. All testing will be performed using the least square means (LSMeans) from the ANCOVA model and a two-sided test at the alpha=0.05 level of significance. Plots displaying the mean change from baseline over time will be provided.

If any subjects in the FAS are missing the TETRAS performance subscale total score at Day 28, multiple imputation will be used to estimate the missing parts of the subscale. Ten datasets will be generated using PROC MI in SAS to impute the missing data points. Treatment group will be used in the var statement for PROC MI to generate the value of the individual item of the TETRAS performance subscale. SAS code for this is as follows:

```
PROC MI data=midata seed=85245 nimpute=10
   out=Out1X maximum=10 minimum=0 minmaxiter=100000;
 by  xbcat xbtest xbtestcd  ;
  mcmc chain=multiple displayinit initial=em(itprint);
  var  trt01pn xbstresn ;
run;
```

Using each of the imputed datasets, the total subscale score will be calculated, and the analysis will be performed for each dataset. The results from all 10 datasets will be combined using PROC MIANALYZE to produce a single inferential result.

If the data (including imputed data) indicate a departure from the normal distribution as determined by the Shapiro-Wilk statistic and visual inspection of histograms and Q-Q plots, a corresponding rank analysis will be performed. That is, for the primary hypothesis, the change from baseline in TETRAS performance subscale scores will be ranked across treatment groups with ties given average ranks, and an ANCOVA model with fixed effects for treatment, anti-tremor medication use, site type, and baseline value of the TETRAS performance subscale total score will be used to estimate and test the difference between the treatment groups.

This analysis will be repeated for the PPAS and CAS as secondary populations.

5.4.2.2. Sensitivity Analysis

Sensitivity analyses will be performed to assess the impact of imputation on any inference on the primary efficacy endpoint:

Control-Based Pattern-Mixture Imputation (Missing = Placebo Mean)
Based on the work of Little and Yau (1996), Ratitch and O'Kelly (2011) proposed using standard SAS/STAT procedures to implement imputation via a control-based pattern-mixture model. Here, the missing observations in the experimental treatment groups (i.e., active treatments) are not constructed from the observed data in those groups but rather from the observed data in the control group (i.e., placebo), using the assessment-specific mean value of the placebo group. Similarly, any missing data from the control group is imputed from observed control group data, using the assessment-specific mean value of the placebo group. In essence, all missing postbaseline data will

be imputed using the mean of the placebo group at the corresponding time point(s) of the missing data.

Missing = Excluded
Subjects with missing values will be excluded from this sensitivity analysis.

Additionally, a sensitivity analysis evaluating the effect, if any, of the stratification factors on the primary efficacy endpoint will be evaluated: The primary analysis as specified in section 5.4.2.1 will be repeated for FAS excluding the factors for anti-tremor medication use and site type.

5.4.2.3. Secondary Efficacy Analyses

The change from baseline to Day 28 on the TETRAS ADL subscale score (Secondary Endpoint 1) and the change from baseline to Day 28 in accelerometry scores (Secondary Endpoint 2) will be summarized by treatment group using descriptive statistics. Accelerometry scores from the left and right hands will be added to create a total score prior to summarization. Comparisons between CX-8998 and placebo will be analyzed using ANCOVA models with fixed effects for treatment, anti-tremor medication use, site type, and baseline value of the assessment being examined. If the data indicate a departure from the normal distribution as determined by visual inspection of histograms and Q-Q plots, a corresponding rank analysis will be performed. Plots displaying the mean change from baseline over time will be provided.

These analyses will be performed for the FAS, PPAS, and CAS.

5.5. INTERIM ANALYSIS

5.5.1. Sample Size Re-Estimation

After at least 43 subjects in Cohort 1 have been treated and followed through Day 28 or the corresponding subjects have discontinued the study, an independent, non-study statistician will estimate the standard deviation for the mean change from baseline to the last available assessment at or prior to Day 28 in the TETRAS Performance subscale for the essential tremor cohort. This estimate will be based on the available data at the time of the interim analysis and will be calculated in a blinded manner. Two standard deviations will be estimated, one for all data available at Visit 4, and another excluding TETRAS Performance assessments done prior to 15 minutes post-dose or after 5 hours post-dose on the date of assessment. Normality will be assumed. Imputation will not be employed. This blinded estimate of the combined treatment groups will be provided to the sponsor for review and potential considerations for altering the trial size. Regardless of the results of this analysis, the sample size will not be decreased from the original planned sample size.

Based on the estimated SDs of the mean change from baseline in the TETRAS performance subscale, the blinded statistician will provide the sample sizes necessary to provide 80% power under a range of mean differences (4.0 to 5.5) at alpha=0.05.

As the sponsor will remain blinded to the treatment effect and will not have access to the randomization schedule nor the data provided to the independent statistician, no adjustment for the conduct of this blinded review is required. The sponsor will determine whether the sample size should be increased based on this analysis.

5.5.2. Blinded Safety Review

Aggregate study level safety and tolerability will be monitored on a recurring basis by the sponsor's Study Safety Representative and a separate, independent medically qualified and clinical trials-experienced Safety Monitor Physician. The first review will occur after approximately 25% of the projected sample size of subjects have completed the EOS Visit, and the second review will occur after approximately 50% of the projected sample size of subjects have completed the EOS Visit. These reviews will be based on blinded, select listings of the evolving safety and tolerability data for both treatment groups.

The Sponsor's Study Safety Representative and the independent Safety Monitor Physician will review the blinded study data to determine if there are any concerning safety signals that would warrant any of the following: 1) unblinding specific safety data; 2) eliminating one or more of the planned up-titrations in dose (e.g., not escalating from 8 to 10 mg BID); or 3) suspending new enrollment in the study until further safety review and consultation with the principal investigators and sub-investigators can be performed.

Decision-making will depend on the specifics of the safety and tolerability data reviewed. If the sponsor's Study Safety Representative and/or the independent Safety Monitor Physician decide that any data should be unblinded, then the unblinded data will be reviewed only by the independent Safety Monitor Physician. Listings of TEAEs, SAEs, abnormal laboratory values, abnormal vital signs, abnormal ECGs, concomitant medications, and protocol deviations, if available, will be provided by the data management group. Patient profiles and additional tables may also be provided at the request of the Study Safety Representative.

5.5.3. Pharmacokinetic Concentration Analysis

Upon completion of the bioanalysis of full PK sample sets from 25% of subjects in the CX-8998 group (n=11), descriptive statistics of analyte concentrations will be prepared by analyte (CX-8998, M01, M02, M03, M04), visit (2, 3, or 4), and time point (0 h or 4 h) by an unblinded statistician. Values reported as below the limit of quantification (BLQ) will be set to one-half of the lower limit of quantification (LLOQ) for summary purposes.

The descriptive statistics will be provided to the sponsor for review to support ongoing drug development activities. The data will not be used for making study-related decisions and, as such, no adjustment to the study assumptions are required. Neither individual subject values nor subject identification numbers will be communicated to the sponsor. This analysis will be repeated upon completion of the bioanalysis of full sample sets from 50% and 75% of subjects in the CX-8998 group (approximately n=22 and 33 subjects, respectively) or at the request of the sponsor.

5.6. EXPLORATORY ANALYSIS

5.6.1. Exploratory Endpoints

The exploratory endpoints are as follows:

1. Change from baseline in the Total TETRAS score to Days 15 and 28, as scored by the central rater
2. Change from baseline to Day 15 on the TETRAS Performance subscale, as scored by the central rater
3. Change from baseline to Day 15 in the TETRAS ADL subscale score
4. Change from baseline to Day 15 in accelerometry scores as measured by Kinesia ONE
5. Change from baseline to Day 15 and Day 28 in Kinesia ONE amplitude measures
6. Treatment success at the end of therapy as measured by PGIC
7. Treatment success at the end of therapy as measured by CGI-I
8. Treatment success at the end of therapy as measured by GAS
9. Change from Baseline in quality of life based on the QUEST
10. Digital biomarkers will be explored in tremor populations of up to 50 subjects using a battery of optional clinical outcomes and digital biomarkers (details will be provided in relevant substudy addendums).

5.6.2. Exploratory Analysis

The change from baseline in the Total TETRAS score, the change from baseline to Day 15 on the TETRAS performance and ADL subscales, the change from baseline to Day 15 in accelerometry scores (i.e., Kinesia ONE assessment), the change from baseline in Kinesia ONE amplitude measures, and the change from baseline in the QUEST score will be summarized by treatment group and study visit. Differences between treatment groups will be assessed using an ANCOVA model with fixed effects for treatment, anti-tremor medication use, site type, and the baseline score of the assessment. (Exploratory Endpoints 1, 2, 3, 4, 5, and 9)

Treatment success as measured by PGIC, CGI-I, and GAS will be summarized using descriptive statistics by treatment group and study visit. Differences between treatment groups will be assessed using an ANCOVA model with fixed effects for treatment, anti-tremor medication use, and site type. For ease of interpretation and comparison, the PGIC, Clinical Global Impression – Severity (CGI-S), and CGI-I will be mapped to the values -3 to 3, and GAS will be mapped to the values -2 to 2, from the worst outcome to the best outcome, respectively. CGI-S will be summarized using descriptive statistics only. (Exploratory Endpoints 6, 7, and 8)

Exploratory Endpoint 9 will not be examined under this SAP.

Additional exploratory subgroup analyses of the primary and secondary efficacy endpoints will include the subgroups defined in Section 3.3.2. These subgroups will have the change from baseline to Day 28 summarized using descriptive statistics, and hypothesis testing will be conducted as described for the respective efficacy endpoints. Forest plots presenting the LSMean centered at 0 and mean change from baseline may be provided for each subgroup.

5.7. SAFETY AND TOLERABILITY

5.7.1. Safety and Tolerability Endpoints

Safety and tolerability will be assessed by adverse events, clinical laboratory data, vital signs, ECGs, physical examinations, neurological examinations, the ESS, and the C-SSRS. Values for all safety variables will be listed by treatment group, subject, parameter, and visit (as applicable).

5.7.2. Safety Analysis

5.7.2.1. Adverse Events

Treatment-emergent adverse events (TEAEs) will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and system organ classes, version 20.0. 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, 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, TEAEs related to study drug, and TEAEs leading to the discontinuation of study treatment, and TEAEs by study week will be generated.

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.

5.7.2.1. Clinical Laboratory Assessments

Actual values and changes from baseline in clinical laboratory assessments will be summarized by treatment group and 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 treatment group and study visit. Shifts from baseline to normal/abnormal status for urinalysis will be presented by treatment group and study visit.

In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline value will be presented for each laboratory test by treatment group.

5.7.2.2. Vital Signs, ECGs, Physical Examinations, and Neurological Examinations

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 treatment group. 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 treatment group, visit, and time point, where applicable. Outliers for recumbent and standing vital sign parameters will be presented as follows:

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
Supine minus standing systolic blood pressure	≤-20 mmHg change
Supine minus standing diastolic blood pressure	≤-10 mmHg change

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

Shifts from baseline in physical examinations and neurological examinations will be summarized by treatment group and study visit.

5.7.2.3. Other Safety Analyses

The ESS scale is used to determine the level of daytime sleepiness. There are 8 situations listed for which patients rate their likelihood of dozing or sleeping (0=would never doze or sleep, 1=slight chance of dozing or sleeping, 2=moderate chance of dozing or sleeping, and 3=high chance of dozing or sleeping). The total score is the sum of 8 item scores and can range between 0 and 24. In case of missing item scores, the missing value will be replaced by the average of non-missing scores at the same visit from the same patient. In case all item scores are missing, the total score will be set as missing. The higher total score indicates the higher level of daytime sleepiness. A score of 10 or more is considered sleepy, and a score of 18 or more is very sleepy.

The Columbia-Suicide Severity Rating Scale(C-SSRS) Screening/Baseline Version will be measured at baseline. Any positive answer to its behavior subcomponents identifies a subject as with “Suicidal Behavior at Baseline”. Similarly, any positive answer to its ideation subcomponents identifies a subject as with “Suicidal Ideation at Baseline”. A subject identified with either “Suicidal Behavior at Baseline” or with “Suicidal Ideation at Baseline” will also be classified as with “Suicidal Behavior or Ideation at Baseline”.

The C-SSRS Since Last Visit Version will be assessed at all post-baseline visits. Any positive answer to its behavior subcomponents in any of the post-baseline visits identifies a subject as with “Suicidal Behavior During Study”. Similarly, any positive answer to its ideation subcomponents in any of the post-enrollment visits identifies a subject as with “Suicidal Ideation During Study”. A subject identified with either “Suicidal Behavior During Study” or with “Suicidal Ideation During Study” will also be classified as with “Suicidal Behavior or Ideation During Study”.

Data from the ESS and C-SSRS will be listed.

6. PROTOCOL DEVIATIONS

Protocol deviations will be documented by the investigator, assigned staff or sponsor. All deviations and reasons for deviations will be reported to the sponsor as soon as possible.

The list of protocol deviations will be compiled and reviewed by the sponsor to identify major and minor deviations prior to database closure. These decisions will be documented in the study trial master file.

Deviations will be summarized by severity (major or minor), deviation category, and treatment group using counts and percentages. All deviations will be presented in a listing.

7. CHANGES IN THE PLANNED ANALYSES

The PPAS, FAS, and subgroup analyses are not included in the protocol, however, they will be incorporated into the analyses according to this SAP.

The PK analysis set has not been defined and will not be used for analyses conducted under this SAP.

The definition of laboratory abnormality has been changed from the definition described in the protocol.

No deviations in the planned analysis are anticipated. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final CSR. Any additional analyses performed after database lock and prior to the publication of the CSR will be described in the CSR.

8. REFERENCES

Little R, Yau L. “Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs,” in Biometrics, 1996, vol. 52, 1324-1333.

Ratitch B and O’Kelly, M. “Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures,” in Proceedings of PharmaSUG 2011 (Pharmaceutical Industry SAS Users Group), SP04, Nashville, 2011.

PASS 2008 Software: Hintze, J. (2008). PASS 2008. NCSS, LLC. Kaysville, Utah. www.ncss.com

PASS 2008 Software Module References:

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

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

Al-Sunduqchi, Mahdi S. 1990. Determining the Appropriate Sample Size for Inferences Based on the Wilcoxon Statistics. Ph.D. dissertation under the direction of William C. Guenther, Dept. of Statistics, University of Wyoming, Laramie, Wyoming.

9. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There will 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 will 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 set: Every summary table and figure will clearly specify the analysis set being summarized. Listings will be prepared for the ITT analysis set.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size (N) for the indicated analysis set. Of note, the header's sample size will not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis set may have missing values and thus may not be summarized. Each module will indicate the number of subjects contributing to the statistics.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules will 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 set due to missing data.
  - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size will 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 will present the total count in addition to the count in each category. Percentages will 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 treatment group, subject number, parameter, and date, 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 will be to round numbers ending in 0-4 down and numbers ending in 5-9 up.
- 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

ITT Analysis Set

14.1.1.1 Subject Disposition and Termination from Study
14.1.1.2 Protocol Deviations
14.1.2.1 Demographics and Baseline Characteristics

Safety Analysis Set

14.1.2.2 Demographics and Baseline Characteristics
14.1.3 Summary of Concomitant Medications and Non-Drug Therapy
14.1.4 Extent of Exposure and Percent Compliance

Efficacy and Subgroup Analyses

FAS, PPAS, and CAS

14.2.1.1.X Summary of TETRAS Performance Subscale
14.2.1.3.X Subgroup Analyses of TETRAS Performance Subscale
14.2.2.1.X Summary of TETRAS Activities of Daily Living Subscale
14.2.2.3.X Subgroup Analyses of TETRAS Activities of Daily Living Subscale
14.2.3.1.X Summary of Accelerometry Scores as Measured by Kinesia ONE
14.2.3.3.X Subgroup Analyses of Accelerometry Scores as Measured by Kinesia ONE

Exploratory

FAS

14.2.4 Summary of Total TETRAS Score
14.2.5 Summary of Amplitude as Measured by Kinesia ONE
14.2.6 Summary of Patient Global Impression of Change (PGIC)
14.2.7 Summary of Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I)
14.2.8 Summary of Goal Attainment Scale (GAS)
14.2.9 Summary of Quality of Life in Essential Tremor Questionnaire (QUEST)

Safety

Safety Analysis Set

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 Grade 3 or Higher by System Organ Class and Preferred Term
14.3.1.4 Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class and Preferred Term
14.3.1.5 Treatment-Emergent Adverse Events by Study Week, 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 Intolerable Adverse Events by System Organ Class 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 Summary of Physical Examinations
14.3.5.2 Summary of Neurological Examinations
14.3.5.3.1 Summary of Electrocardiogram Parameters
14.3.5.3.2 Summary of Electrocardiogram Outliers
14.3.5.4.1 Summary of Respiration Rate, Temperature, and Weight
14.3.5.4.2 Summary of Blood Pressure and Pulse
14.3.5.4.3 Summary of Vital Signs Outliers

Summary Figures

Efficacy

FAS, PPAS, and CAS

14.2.1.2.X Change from Baseline in Mean (SD) Imputed TETRAS Performance Subscale Total Score
14.2.1.4.X Forest Plots for Subgroup Analyses of TETRAS Performance Subscale
14.2.2.2.X Change from Baseline in Mean (SD) TETRAS Activities of Daily Living Subscale Total Score
14.2.2.4.X Forest Plots for Subgroup Analyses of TETRAS Activities of Daily Living Subscale Total Score
14.2.3.2.X Change from Baseline in Mean (SD) Accelerometry Scores
14.2.2.4.X Forest Plots for Subgroup Analyses of Accelerometry Scores

Data Listings

ITT Analysis Set

16.2.1.1 Subject Disposition
16.2.1.2 Informed Consent and Randomization
16.2.2.1 Protocol Deviations
16.2.2.2 Eligibility
16.2.3 Reasons for Exclusion from Analysis Sets
16.2.4.1 Demographics and Essential Tremor Information
16.2.4.2 Medical and Surgical History
16.2.4.3 Prior and Concomitant Medications
16.2.5.1 Study Drug Administration
16.2.5.2 Dose Reduction
16.2.5.3 Study Drug Accountability
16.2.5.4 Pharmacokinetic Samples

16.2.5.5 Pharmacogenomic Samples
16.2.6.1.1 TETRAS Performance Subscale
16.2.6.1.2 TETRAS Activities of Daily Living Subscale
16.2.6.1.3 Total TETRAS Score
16.2.6.2 Accelerometry
16.2.6.3 Patient Global Impression of Change (PGIC)
16.2.6.4 Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I)
16.2.6.5 Goal Attainment Scaling (GAS)
16.2.6.6 Quality of Life in Essential Tremor Questionnaire (QUEST)
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 Serum FSH Test
16.2.8.2.1 Respiration, Temperature, Height, and Weight
16.2.8.2.2 Blood Pressure and Pulse
16.2.8.3 Physical Examination
16.2.8.4 Neurological Examination
16.2.8.5 Electrocardiogram
16.2.8.6 Epworth Sleepiness Scale (ESS)
16.2.8.7 Columbia Suicide Severity Rating Scale (C-SSRS)