Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

NCT Number: NCT03101241

Date: 6 April 2017

Clinical Study Protocol

Main Title:

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

Protocol Number: CX-8998-CLN2-001

Original Version Number: 1.2 **Date:** 06 April 2017

Official Short Title:

CX-8998 for Essential Tremor

Confidentiality Statement:

SIGNATURE PAGE FOR SPONSOR

Study No.

Protocol Title: A Phase 2 Randomized Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

Approved by the following:

[redacted]

Cavion, Inc.
600 East Water Street, Suite E
Charlottesville, VA 22902

[redacted]

Cavion, Inc.
600 East Water Street, Suite E
Charlottesville, VA 22902

[redacted]

Cavion, Inc.
600 East Water Street, Suite E
Charlottesville, VA 22902

SIGNATURE PAGE FOR INVESTIGATOR

Study No.

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

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

_____	_____	_____
Investigator Name	Signature	Date

STUDY ORGANIZATIONAL STRUCTURE

Sponsor:	Cavion, Inc. 600 East Water Street Suite E Charlottesville, VA 22902 434.200.8442
24-Hour Medical Monitor Coverage:	[redacted]

COMPLIANCE STATEMENT

This study will be conducted in full accordance all applicable Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the HIPAA Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unexpected problems in accordance with Institutional Review Board (IRB) procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

PROTOCOL SYNOPSIS

Study Title: A Randomized Phase 2, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor	
Name of Finished Product: CX-8998	**Name of Active Ingredient:**
Protocol Number: CX-8998-CLN2-001	**Study Phase:** 2
Clinical Sites: Multiple sites in the United States	
Primary Objective: To assess the efficacy of CX-8998, in doses up to 16 mg per day (8 mg BID), in reducing essential tremor	
Secondary Objectives: 1. To assess changes in tremor-affected activities of daily living 2. To assess the safety and tolerability of CX-8998 in doses up to 16 mg per day (8 mg BID) 3. To measure the concentration of CX-8998 and its metabolites (M01 and M02) in plasma **Exploratory Objectives:** 1. To assess changes in quality of life 2. To assess study drug effects on electrophysiological patterns associated with thalamo-cortical dysrhythmias (in a subset of subjects) 3. To use the concentrations of CX-8998 and its 2 primary metabolites in plasma in population pharmacokinetic, exposure-response and exposure-safety analyses (to be reported separately from the Clinical Study Report)	
Study Design: This is a double-blind, placebo-controlled, parallel-group study. Subjects will be randomized to one of two treatment groups. Group A will receive CX-8998 and Group B will receive placebo. Subject randomization will be stratified by concomitant primidone use and site type (sub-study vs non sub-study). Tremor will be assessed via The Essential Tremor Rating Assessment Scale (TETRAS) and accelerometry. In order to reduce rater bias, all subjects will be videotaped during the TETRAS performance scale testing according to a consistent script. The videotapes will be rated in a blinded manner. A subset of subjects will participate in an electroencephalography (EEG) and magnetoencephalography (MEG) sub-study to record power-spectral brain activity in specific neuro-anatomical locations and coherence with movement measures. Subjects will be screened up to one month prior to initiation of dosing. At Baseline, subjects will undergo safety and tremor assessments prior to dosing, will receive their first dose of study drug and will be monitored for safety for one hour following dosing. For one week subjects will receive 4 mg (or matching placebo) twice daily. Subjects will return to the clinic on Day 8 for safety monitoring and dose up-titration to 6 mg (or matching placebo) twice daily. At Day 15 (Week 3) subjects will return to clinic for safety and efficacy assessments and final dose up-titration to 8 mg (or matching placebo) twice daily. The final efficacy visit will occur at Day 28 (Week 4). A final safety visit will occur at Day 35 (Week 5). Should subjects experience intolerable adverse events (AEs) at 4 mg BID, 6 mg BID or 8 mg BID, the dose may be decreased at Day 8 or Day 15 to the next lowest dose one time (or 2 mg BID in the case of the	

4 mg BID dose). A dose reduction may be made if necessary prior to scheduled visits at Day 8 or Day 15. A re-up-titration is not allowed. Subjects not tolerating the next lowest dose or not tolerating 2 mg BID will be withdrawn from treatment. The Medical Monitor should be notified as soon as is feasible when a dose reduction is made.

Study Population:

Inclusion Criteria

1. Signed informed consent form (ICF) indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
2. Men or non-pregnant, non-breastfeeding women 18 years-of-age or older who are able to read and understand English.
3. Diagnosis of definite or probable essential tremor (ET) as defined by the Tremor Investigational Group with involvement of the hands and arms without present causes of enhanced physiologic tremor (Deuschl et al., 1998)
4. Diagnosis of ET before the age of 65
5. Tremor severity score of at least 2 in at least one upper extremity on the TETRAS scale
6. Total TETRAS performance score of at least 15. Note: Thresholds for items 5 & 6 should not be shared with study subjects or caregivers to limit Baseline inflation.
7. Has, in the opinion of the investigator, had an inadequate response to at least one anti-tremor medication or cannot tolerate available anti-tremor medication(s) due to side effects. Subjects must have been on a stable dose for 1 month prior to screening and must have no change in dose in concurrent anti-tremor medication for the duration of the study.
8. Subjects with reproductive capability including all males and women of child-bearing potential (WOCBP) must agree to practice continuous abstinence or adequate contraception methods (appropriate double barrier method or oral, patch, implant, or injectable contraception) from as soon as feasible during screening period until at least 30 days after the last dose (i.e., intermittent abstinence based on “rhythm”, temperature monitoring, or other means of timing is not acceptable). WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy) or is not post-menopausal. Post-menopausal is defined as:
    a. Amenorrhea ≥ 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL;
    b. Amenorrhea ≥ 12 consecutive months in women ≥ 62 years old (FSH testing is not required).

   Male subjects with a partner of child-bearing potential must be surgically sterilized or be willing to use condoms with spermicide from as soon as feasible during screening period until at least 30 days after the last dose.

Exclusion Criteria

1. Exposure to tremorigenic drugs or drug withdrawal states within the 30 days prior to the first planned dose of study drug
2. Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor
3. History or clinical evidence of psychogenic tremor origin
4. Known history of other medical or neurological conditions that may cause or explain subject’s tremor, including, but not limited to:

a. Parkinson's disease
b. Hyperthyroidism
c. Pheochromocytoma
d. head trauma or cerebrovascular disease within 3 months prior to the onset of essential tremor
e. multiple sclerosis
f. polyneuropathy
g. family history of Fragile X syndrome

5. Prior MR-guided Focused Ultrasound or surgical intervention (e.g., deep brain stimulation, ablative thalamotomy or gamma knife thalamotomy) for treatment of tremor
6. Botulinum toxin injection in the 6 months prior to screening
7. Currently using more than one anti-tremor medication. Subjects must have been on a stable dose for 1 month prior to screening and must have no change in dose in concurrent anti-tremor medication for the duration of the study.
8. Use of medication(s) in the past month that might produce tremor or interfere with the evaluation of tremor, such as, but not limited to: CNS-stimulants, lithium, amiodarone, metoclopramide, theophylline, and valproate
9. Inability to refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor on study visit days, such as but not limited to stimulant decongestants, beta-agonist bronchodilators, caffeine, alcohol and tobacco.
10. Regular use of more than two units of alcohol per day
11. Sporadic use of a benzodiazepine, sleep medication or anxiolytic to improve sleep performance. Stable use at a consistent dose is allowed as long as tremor persists against the background of regular medication use.
12. Use of prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be strong inhibitors or inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study
13. Concurrent illnesses that would be a contraindication to trial participation, including, but not limited to:
    a. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before screening
    b. NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
    c. Clinically significant ECG abnormality per the Investigator assessment or any of the following:
        (1) QTcF >450 msec (males) or >470 msec (females)
        (2) PR interval >250 msec
        (3) Atrioventricular block of second degree or higher, including Mobitz I
        (4) Persistent sinus bradycardia < 50 beats per minute; persistent means the bradycardia is present on the first ECG and on one repeat ECG performed on another day
        (5) For other ECG findings (e.g., including, but not necessarily limited to, tachycardia, bundle branch block, frequent ectopic beats, etc.) the Investigator should send a scanned, identity-blinded copy of the ECG tracing to the Medical Monitor for review
        (6) For subjects not in the EEG/MEG neurophysiology sub-study, the presence of a cardiac pacemaker does not automatically exclude eligibility. The specifics must be discussed with the Medical Monitor to make a determination of eligibility.

d. Known infection with HIV, hepatitis B, or hepatitis C, unless curative therapy completed for hepatitis C with negative PCR for HCV RNA
e. Significant hepatic (AST/ALT > 2X upper limit of normal) or renal disease (creatinine clearance <39 mL/min)
f. Significant psychiatric history including mood disorders and alcohol or substance abuse within the last year
g. History of attempted suicide in the last 5 years or a C-SSRS score of 4 or 5 at screening or at any time during the past year
h. Clinically significant impaired balance or is considered at increased risk for falls
i. Symptomatic orthostatic hypotension

14. Psychological, social, familial, or geographical reasons that would hinder or prevent compliance with the requirements of the protocol or compromise the informed consent process
15. Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (e.g., due to expected study medication non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study–related procedures)
16. Treatment with an investigational agent within 30 days prior to the first dose of CX-8998 or planning to receive an investigational agent during the study
17. For patients in the EEG/MEG sub-study only:
    a. A history of gross brain abnormalities including history of stroke, history of TIA, severe ventriculomegaly or severe periventricular white matter abnormalities
    b. a history of serious psychiatric, psychological or neurological disorders, including psychosis or major depression, bipolar disorder, alcohol or drug abuse, brain injury, seizure disorder, brain tumor, chronic pain, Parkinson's, tinnitus, generalized anxiety disorder, or schizophrenia
    c. taking psychoactive medications, including antipsychotics, anxiolytics and antidepressants, or cognitive enhancers such as cholinesterase inhibitors
    d. presence of contraindications for MEG or MRI recording, including any of the following: cardiac pacemaker, intracranial clips, metal implants, or external clips within 10 mm of the head, metal in eyes, claustrophobia, obesity and/or any other reason leading to difficulty staying in the MEG or MRI for up to one hour.

Planned Number of Patients:

Up to 92 subjects will be randomized

Test Product, Dose, and Mode of Administration:

CX-8998, 2 mg capsule, oral

Reference Product, Dose, and Mode of Administration:

placebo capsule to match CX-8998, oral

Duration of Treatment:

28 days

Administration:

CX-8998 will be administered as 4 mg twice daily (8 mg/d) in the first week; increasing to 6 mg BID (12 mg/d) in week 2, to a target of 8 mg BID (16 mg/d) in weeks 3 and 4. Study drug should be administered with food in the morning and evening.

Duration of Subject Study Participation:

Up to 12 weeks including screening, treatment and safety follow-up

Endpoints:

Primary Endpoint:

1. Change from Baseline to Day 28 on the TETRAS Performance subscale

Secondary Endpoints:

2. The proportion of Responders (subjects experiencing a decrease of at least 5.5 points on the TETRAS Performance Subscale)
   a. from Baseline to Day 15
   b. from Baseline to Day 28
3. Changes in subject response as measured by accelerometer (transducer measurement of tremor amplitude)
   a. percent changes from Baseline to Days 15 and 28 in maximum and average amplitude over 1 hour after start of TETRAS assessment
   b. changes from Baseline to Days 15 and 28 in 48 hour AUC of amplitude.
4. Change from Baseline to Day 15 on the TETRAS Performance subscale
5. Change from Baseline on the TETRAS Activity of Daily Living subscale to Days 15 and 28
6. Safety: as assessed by physical examination, neurological examination, vital signs assessment, Epworth Sleepiness Scale (ESS), clinical laboratory testing, electrocardiography, incidence of adverse events, and the Columbia Suicide Severity Rating Scale (C-SSRS)
7. Plasma levels of CX-8998 and its metabolites (M01 and M02)

Exploratory Endpoints:

1. Changes in electrophysiological patterns associated with thalamo-cortical dysrhythmias (in a subset of subjects):
   a. Electroencephalography (EEG) in a sub-study of up to 24 subjects to correlate with target engagement
   b. Magnetoencephalography (MEG) in sub-study of up to 24 subjects to record power-spectral brain activity in specific neuro-anatomical locations and coherence with movement measures
2. Change from Baseline in quality of life:
   a. Quality of Life in Essential Tremor Questionnaire (QUEST)

Efficacy Assessments:

∞ TETRAS Performance subscale: evaluates tremor of various body parts during postures, kinesis and tasks. Items are scored from 0 to 4, with 4 representing the highest degree of severity. The maximum score is 64. The tasks will be videotaped and tremor rated in a blinded manner.

∞ TETRAS ADL subscale: A 12-item questionnaire in which the subject rates to what extent tremor affects activities including eating and drinking, dressing and personal hygiene, carrying items and finer motor skills. 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.

- Accelerometry: A quantitative measure of tremor amplitude
- QUEST: a 30-item questionnaire that contributes to 5 sub-scales (physical, psychosocial, communication, hobbies/leisure and work/finance) and a total score, plus 3 additional items relating to sexual function and satisfaction with tremor control and medication side effects.

Safety Assessments:

- Adverse events: collected from the time the informed consent is signed through the follow-up telephone call.
- Clinical laboratory testing:
  - Hematology will include complete blood count (CBC) with differential and platelet count.
  - Clinical chemistry will include metabolic panel (electrolytes, glucose, creatinine, calcium, magnesium, phosphate), renal panel, and hepatic panel.
  - Urinalysis
  - Pregnancy testing for women of child-bearing potential
- Physical examination: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities
- Neurological examination: assessment of mental status, and examination of cranial nerves II-XII, motor and sensory exam, reflexes, coordination, stance, gait and balance
- Vital sign measurements: orthostatic blood pressure, pulse rate, respiratory rate, and temperature
- 12-lead electrocardiogram
- Epworth Sleepiness Scale
- Columbia Suicide Severity Rating Scale (C-SSRS)

Statistical Methods:

Primary efficacy analysis:

The primary efficacy analysis of the TETRAS performance subscale will be conducted using an analysis of covariance (ANCOVA) model with fixed effects for treatment, concomitant primidone use, site type and Baseline value of the TETRAS performance subscale. The primary hypothesis to be tested will be if the mean change from Baseline in TETRAS performance scale indicates at least a 5.5 point decrease from Baseline in the CX-8998 arm. The secondary comparison will assess whether the CX-8998 arm is different from placebo. All testing will be performed using the LSMeans from the ANCOVA model and a two-sided test at the alpha=0.05 level of significance. If the data indicate a departure from the normal distribution, a corresponding rank test will be performed.

Secondary efficacy analyses:

The proportion of subjects experiencing at least a 5.5 point decrease in the TETRAS performance scale will be summarized by treatment group. Differences between the treatment groups will be assessed with Cochran-Mantel-Haenszel General Association test stratified by concomitant primidone use and site type.

The secondary endpoints of percent change from Baseline to Day 28 in subject response as

measured by accelerometer, change from Baseline on the TETRAS Activity of Daily Living subscale, change from Baseline in the ESS, and change from Baseline on the QUEST scale will be analyzed using the same type of ANCOVA model as described for the primary endpoint. All secondary and exploratory analyses will be conducted using two-sided tests at the alpha=0.05 level of significance.

Sample size justification:

Up to 92 subjects will be randomized to one of two treatment groups: Placebo and CX-8998. Based on similarly designed studies, this sample size should be sufficient to provide preliminary safety and efficacy information on CX-8998 when administered according to this protocol.

A sample size of 43 subjects has at least 90% power to detect at least a 5.5 point change from Baseline to end of treatment in the TETRA performance subscale for CX-8998 when the standard deviation is 10.6, alpha=0.05 (PASS 2008: One sample t-test – Normal Non-Parametric Adjustment). Similarly, 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 end of treatment in the TETRA performance subscale when the standard deviation is 7.5 and alpha=0.05 (PASS 2008: Two sample t-test – Normal Non-Parametric Adjustment). Up to 92 subjects will be enrolled in order to ensure that 86 subjects are available for inclusion in the efficacy analyses.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

GLOSSARY OF TERMS AND ABBREVIATIONS

Abbreviation	Description
ADL	activity(ies) of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	Area under the concentration-time curve
β-HCG	beta human chorionic gonadotropin
BMI	body mass index (kg/m^2)
BP	Sitting systolic and diastolic blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CI	confidence interval
CNS	central nervous system
C_{max}	maximum concentration
C_{min}	minimum concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
dL	deciliter
ECG	electrocardiogram
EEG	electroencephalogram
ESS	Epworth Sleepiness Scale
ET	essential tremor
F	Fahrenheit
GCP	Good Clinical Practice
h	hour(s)
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IO	inferior olive
IRB	Institutional Review Board
ITT	intent-to-treat population

IV	intravenous
IWRS	interactive web response system
kg	kilogram
LDH	lactic dehydrogenase
MEG	magnetoencephalography
µg	microgram
mg	milligram
mL	milliliter
mM	millimolar
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHV	normal healthy volunteers
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
RNA	ribonucleic acid
QOL	quality of life
QUEST	Quality of Life in Essential Tremor Questionnaire
SAE	serious adverse event
SD	standard deviation
SWA	slow wave activity
Vd	Volume of distribution
$t_{1/2}$	terminal half life
TCD	thalamocortical dysrhythmia
TEAE	treatment emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
T_{max}	time to maximum concentration

1 Background Information and Rationale

1.1 Background Information on Essential Tremor

1.1.1 Defining Essential Tremor

Once known as familial tremor, benign tremor or hereditary tremor, essential tremor (ET) is a neurological condition that causes a rhythmic trembling of the hands, head, voice, legs or trunk.

The consensus statement of the Movement Disorder Society on tremor (Deuschl et al., 1998) includes the following clinical criteria for the diagnosis of ET: bilateral postural tremor with or without kinetic tremor, involving hands and forearms, that is both visible and persistent without:

1. Other abnormal neurological signs (except Froment's sign);
2. Known causes of increased physiological tremor;
3. Concurrent or recent exposure to tremorigenic drugs or the presence of a drug withdrawal state;
4. Direct or indirect trauma to the nervous system within 3 months before the onset of tremor;
5. Historical or clinical evidence of psychogenic origins, and
6. Convincing evidence of sudden onset or evidence of stepwise deterioration.

1.1.2 The Impact of Essential Tremor

Essential Tremor is among the most prevalent of all movement disorders in adults. In a 2010 meta-analysis, Louis et al. (1998) estimated the pooled prevalence (all ages) to be 0.9%, with statistically significant heterogeneity across studies ($I2 = 99\%$, $p<0.001$). The prevalence in adults ≥65 years old was estimated to be 4.6%. In one study of those age ≥95 years, crude prevalence equaled 21.7% (Louis and Ferreira, 2010).

While ET does not shorten life expectancy, its impact on the patient's ability to perform activities of daily living (ADLs) at home and in the work place negatively affects quality of life, social interactions, and mental status (Lorenz et al., 2006; Louis & Machado, 2015; George and Lydiard, 1994). It is increasingly recognized that ET is not a monosymptomatic disorder (Bermejo-Pareja, 2011). Effects include everyday activities such as writing and eating (Zesiewicz et al., 2011). Effects on cognitive functions are heterogeneous and include impairments in attention, executive function, verbal fluency, visuospatial functioning, memory, and working memory (Bermejo-Pareja & Puertas-Martin, 2012). Sleep disturbances and fatigue are also more common in patients with ET than in their age-matched controls (Chandran et al., 2012).

1.1.3 Treatment of Essential Tremor

Propranolol is the only medication approved for the treatment of ET. None of the other medications currently used as ET therapy were developed specifically for this purpose. In 2011, the American Academy of Neurology (AAN) conducted an evidence-based update of

the AAN 2005 practice parameters regarding the treatment of ET (Zesiewicz et al., 2011). The following conclusions and recommendations were unchanged from the 2005 guideline:

- Propranolol, primidone (Level A, established as effective);
- Alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate (Level B, probably effective);
- Nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation (DBS), thalamotomy (Level C, possibly effective), and
- Gamma knife thalamotomy (Level U, insufficient evidence).

Changes to conclusions and recommendations from the previous guideline include the following:

- Levetiracetam and 3,4-diaminopyridine probably do not reduce limb tremor in ET and should not be considered (Level B);
- Flunarizine possibly has no effect in treating limb tremor in ET and may not be considered (Level C), and
- There is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozapine as treatment for ET (Level U).

Alternatives to medications include invasive surgical treatments (DBS and gamma-knife thalamotomy), non-invasive MR-guided Focused Ultrasound, botulinum toxin, and alcohol (alcohol is associated with habituation and rebound effects).

The lack of any new positive recommendations by the 2011 Academy of Neurology evidence-based guideline update on the treatment of ET (as compared to the 2005 guidelines) attests to the poor yield of present approaches to drug discovery (Zesiewicz et al., 2011). Given that half of the patients with ET ≥65 years of age take medication for tremor (Louis et al., 2000) and the 2012 demographic data showed that of the 1,006.9 million persons living in the European Union, the United States, Japan, Canada, Australia, and New Zealand, 163.7 million persons are ≥65 years of age, it can be estimated that 3.8 million persons in this age group in these countries are potential candidates for treatment of ET.

A survey of 223 patients (52.7% male, mean age of 63.4 (±17.9) years of age at last visit) in a clinical database revealed that 70.9% had taken primidone or propranolol, and 56.3% had discontinued one or both medications (Diaz & Louis, 2010). Reasons for discontinuing primidone included side effects (51.9%), lack of efficacy (19.0%), or both (20.3%). Reasons for discontinuing propranolol included lack of efficacy (44.6%), side effects (24.6%), or both (13.9%). Because approximately 30%-50% of patients with ET will not respond adequately to currently available medications (Koller & Vetere-Overfield, 1989), new therapies for ET are warranted.

1.2 Rationale for Evaluating CX-8998 in Essential Tremor

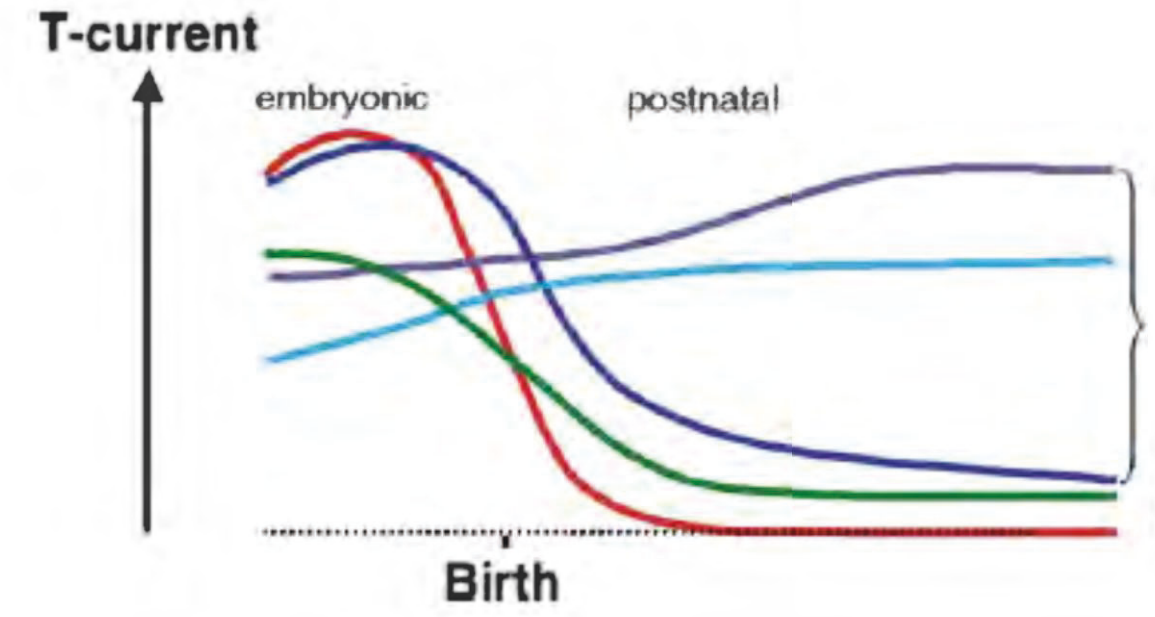
1.2.1 Cav3 and its Role in Neurological Disorders with Excessive or Abnormal Rhythmicity

Multiple calcium ion channels regulate calcium influx in response to membrane depolarization, voltage changes, or substrate, which include the pore-forming alpha1 subunit Cav3 channel (Catterall, 2005; Adams & Snutch, 2007). The T-type calcium channel, Cav3, its three (3) isoforms (3.1, 3.2 and 3.3), and their genes *CACNA1G, CACNA1H, and CACNA1I* were discovered and cloned in the early 1990s, where their function as low-threshold, voltage-gated calcium channel was elucidated (Cribbs et al., 1998).

Cav3 channels have the unique property of activating upon small depolarizations of the membrane, contributing to the setting of the resting membrane potential and transition to action potentials (AP) (Rossier, 2016). Cav3's isoforms are expressed throughout the central nervous system (CNS) and the peripheral nervous system (PNS), including the thalamocortical pathway[1] (Ertel et al., 2000).

Cav3 is highly expressed during embryogenesis then downregulated at parturition (Lory et al., 2006). Post-parturition, normal hosts demonstrate low levels of expression in the thalamus, sensory neurons, and cortex (Lory et al., 2006). In pathologic states, Cav3 is either upregulated or found to have increased activity, becoming a selective target for specific neurologic diseases (Tai et al., 2011; Park et al., 2010; Bourinet et al., 2005).

Figure 1 Cav3 Expression in Organisms over Time

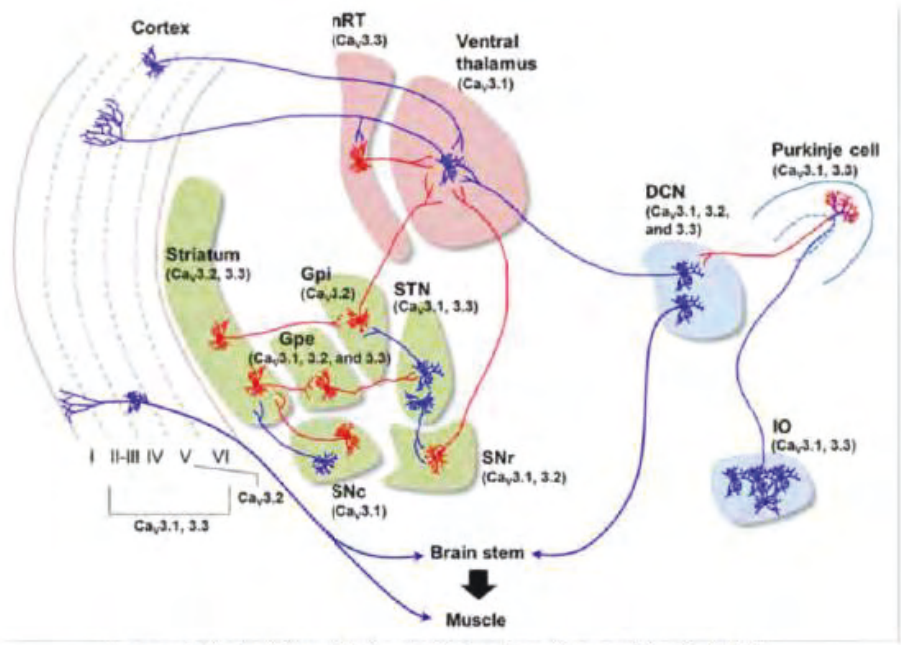


Cav3 is widely expressed in embryonic tissues; however, upon parturition, postnatal expression is down regulated with expression almost entirely restricted to very low-levels in normal, healthy, thalamic neurons (Lory et al., 2006).

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

Cav3 is found in the central nervous system and selective regions of the peripheral nervous system, particularly in pathologic conditions. Deep cerebellar nuclei (DCN), Substantia nigra (SNC), Globus pallidus externa (Gpe), globus pallidus interna (GPi), subthalamic nucleus (STN), have been noted to have oscillations in healthy hosts and excessive rhythmicity in animals and humans with pathologic conditions of the nervous system. It has been discovered that Cav3 is a mediator of subthreshold oscillations and excessive rhythmicity (or, thalamocortical dysrhythmia) in pathophysiologic states found in neuropathic pain, epilepsy, Parkinson's and tremor.

Figure 2 Cav3 Isoform Specific Expression Location in Nuclei



Source: Adapted from Park, et al., Frontiers Neural Circuits. 2013

Pathways: Blue = excitatory neurons, Red = inhibitory neurons, Blue Regions = olivocerebellar pathway, Green regions = basal ganglia circuits, Red regions = thalamocortical pathways. Locations: IO = Inferior Olive DCN = deep cerebellar nuclei, SNc = substantia nigra Gpe = globus pallidus externa, Gpi = globus pallidus interna, STN = subthalamic nucleus, SNr = substantia nigra reticulate. These nuclei exist in the thalamocortical pathway and include: DCN, Purkinje cell, Inferior-Olive, SNr, STN, Gpi, Gpe, Striatum, nRT, Ventral thalamus, with synapses in the cortex (Park et al., 2013).

At the macrocellular level, different regions of the brain are responsible for different cognitive and motor functions. A network of neurons between the thalamus and the cortex create corticothalamic pathways that facilitate communication and interaction between the thalamus and the cortex. Electrophysiological observation demonstrates rhythmic electrical activity in the cerebral cortex, thalamus, inferior olive and cerebellum and in their network of interconnected pathways (see Figure 2).

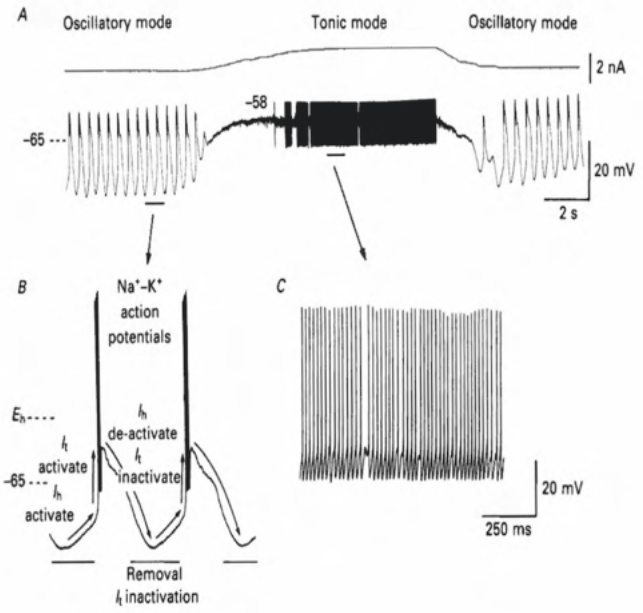
In particular pathologic states of the central nervous system electrical activity of the cortex and thalamus is found to deviate from baseline oscillations, demonstrating excessive rhythmicity (Handforth et al., 2005; Llinás et al., 1999; Llinás, 2003; Park et al., 2013). These "dysrhythmias" across thalamocortical nuclei are a common pathophysiological

mechanism of brain disorders, including neuropathic pain, epilepsy, tremor, and Parkinson's disease (Llinás, 1988) in which "excessive rhythmicity" or diminution of coherent electrical activity are observed.

Cav3 currents modulate burst firing in neurons (McCormick & Pape, 1990). Burst firing of thalamocortical relay neurons is absent when Cav3 channels are absent (Kim et al., 2001, Anderson et al., 2005, Choi et al., 2016). In baseline physiologic states, Cav3 contributes to the resting membrane potential. The transition from normal oscillatory mode (standard cross-talk between nuclei) to the burst, (tonic) firing mode is promoted by increased membrane depolarization. Cav3 mediates the increased depolarization and thus burst firing. It has been shown that the potentiation of neuronal oscillations in the inferior olive is $Ca_V3.1$ channel-dependent (Park et al., 2010).

The calcium currents produced via Cav3 activity mediate the transition between tonic and oscillatory firing (McCormick & Pape, 1990). Because Cav3 contributes to setting the resting membrane potential voltage, when Cav3 has increased activity (either via upregulation, single nucleotide polymorphisms (SNPs), gain-of-function mutations or other causes), the calcium influx lowers the resting membrane potential (mV), thus lowering the threshold for burst firing of the neuron and action potential transmission (Dreyfus et al., 2010; Kim et al., 2001).

Figure 3 T-type (Cav3) Current Contributes to Neuron Resting Membrane Potential



Burst firing is initiated by membrane depolarization. Cav3 currents play a role in the transition between tonic and oscillatory firing. (McCormick and Pape, 1990; Dreyfus et al., 2010)

1.2.2 Macro-electrophysiological Findings in Thalamocortical Pathways

Coordinated electrical activity is characterized by normal neuronal oscillation, wherein neurons discharge electrical impulses at specific frequencies, thereby causing electrical oscillation. Neuronal oscillation generally occurs within distinct frequency bands. These frequency bands include the delta (δ) band (oscillations in the < 3 Hz range), theta (θ) band

4-8 Hz), alpha (α) band (8-13 Hz), beta (β) band (>13 Hz) and gamma (γ) band (20-50 Hz) range.

Utilizing magnetoencephalography (MEG) techniques the disordered rhythmicity of patients diagnosed with neurologic diseases such as movement disorders, epilepsy, tinnitus, neurogenic pain and major depression, among others, have been characterized. During the awake state, they found a shift from normal α activity to low-frequency θ activity in the patients as compared to controls (Llinás et al., 1999). When animals and humans are administered a Cav3 antagonist, the target engagement of the Cav3 inhibitor can be observed and correlated with impact on EEG and MEG frequencies.

1.2.3 T-Type Calcium Channels, Cav3, and Electrophysiological Properties in Neurons

Calcium is a ubiquitous intracellular second messenger critical for cellular functions. The elevation of free intracellular Ca^{2+} levels triggers various responses including the activation of Ca^{2+} dependent enzymes, the secretion of neurotransmitters, and muscle contraction. T-type ("T" is for transient) calcium channels are low voltage-activated (LVA) channels predominantly found in neurons. As stated previously, a unique and discriminating property of T-type channels (Cav3) is their ability to activate upon small depolarization of the membrane, contributing to the setting of the resting membrane potential and allowing a surge of calcium entry into excitable cells at the beginning of an action potential. Cav3's rapid, voltage-dependent inactivation and their slow deactivation make their gating characteristics distinct from those of other channels (Rossier, 2016).

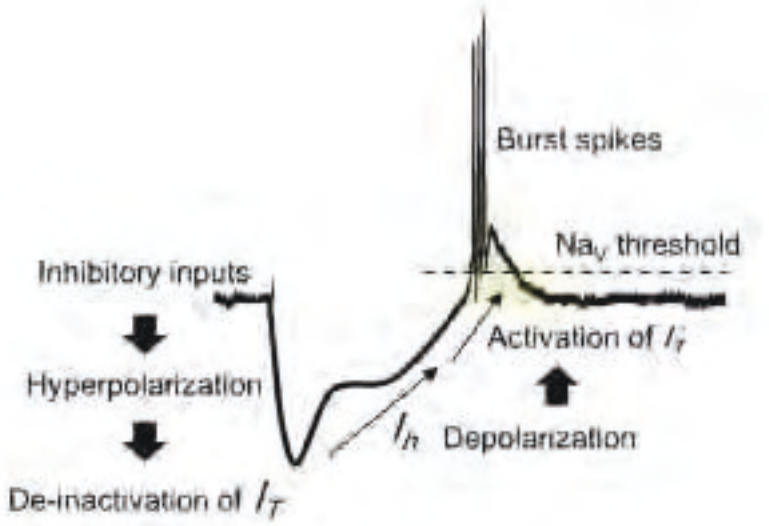
At the cellular membrane level, Cav3 open at approximately −70mV. When the membrane potential is between −80mV and −40mV, T-type calcium channels can cycle from fully closed to fully open and from fully inactivated to fully de-inactivated, such that at all times, some Cav3 channels are open, producing a "window" current through which a large amount of calcium may accumulate inside the cell (Kopecky et al., 2014). In normal crosstalk, coherent theta-activity is due to low-threshold calcium spike bursts in thalamic cells (Llinás, 2003; Park et al., 2013). In neurologic disease states, the nuclei demonstrate aberrant and asynchronous signaling, which is mediated by the low-threshold calcium influx.

The inferior olive (IO) appears to function as a tremor generator and animal models suggest the IO functions as an intrinsic pacemaker (Long et al., 2002). Essential tremor may result from excessive rhythmic synchronous firing of populations of neurons in the IO, which affects the function of the cerebellum (Elble, 1996). In the brainstem, harmaline, a plant alkaloid, which induces tremor, is found to increase Cav3 mediated calcium spikes in inferior-olive neurons. The IO neurons transition from subthreshold oscillations to rhythmic 8-12 Hz burst firing (Llinás & Yarom, 1981b; 1986).

In normal organisms the thalamus and inferior olivary (IO) neurons demonstrate subthreshold membrane oscillations at 10 Hertz (Hz) (McCormick & Pape, 1990; Dreyfus et al., 2010). These oscillations are mediated by a rhythmic cascade of channel openings involving a high-threshold calcium channel, potassium ion channels and low-threshold (Cav3) calcium channel. The neurophysiologic process of hyperpolarization triggers the Cav3 channel to open, subsequently triggering the high-threshold calcium channel to open

which cause depolarization which have the possibility of being sufficient to trigger a sodium spike and axonal firing.

Figure 4 Potentiation of Cav3 Conductance and Generation of Low-threshold Spikes



Hyperpolarization & subsequent depolarization by HCN channel mediated current (Ih) open Cav3 channels. I_T = Cav3 current. Na_v = voltage-gated sodium channel (Jasinska-Myga & Wider, 2010; Merner et al., 2012; Louis et al., 2001; Tanner et al., 2006; Handforth, 2012; Park, 2013)

Single olivary neurons typically discharge at only 1 Hz (Lang et al., 2002; Llinás & Yarom, 1981a; 1981b; 1986). IO neurons are electrically coupled to adjacent IO neurons via gap junctions. Together they form unit clusters so that each unit of IO neurons oscillate synchronously at approximately10 Hz, sending precisely timed axonal discharges to a bundle of Purkinje neurons via climbing fibers (Eckardt et al., 2004; Llinás & Yarom, 1981a; 1981b; 1986; Sasaki et al., 1989). The oscillations are a Cav3 mediated rhythmic cascade of channel openings by high-threshold Ca, K, and low-threshold Cav3 antagonists.

Cav3 is highly expressed in the inferior-olive and cerebellum. Cav3.1 is the predominate Cav3 isoform expressed in the inferior olive (IO). Within the cerebellar system it is also found on Purkinje cell bodies, DCN, stellate, basket, dendrites and Golgi cells (Molineux et al., 2006). In these locations, Ca_V3 functions as a tremor generator and ongoing rhythm pacemaker (Park et al., 2010). Park et al. reported that tremor-related oscillations in the olivocerebellar pathways are a neural signature for essential tremor and that $Ca_V3.1$ plays a critical role in the onset of tremor-related rhythms (Park et al., 2010).

Harmaline, a plant alkaloid that acts on the cerebellum and IO, induces tremor in animals. Harmaline-induced tremor in animals, like ET, involves the cerebellum. Lesions of the IO reduce harmaline tremors in rats (Simantov et al., 1976). Harmaline tremor is similar to clinical ET in a number of respects, including cerebellar hypermetabolism and a positive response to all known anti-ET agents, including alcohol, primidone, propranolol, gabapentin, zonisamide, and benzodiazepines.

Normally, IO neurons show spontaneous subthreshold membrane oscillations mediated by a rhythmic cascade of ion channel openings that include T-type calcium (Cav3) channels

and potassium channels (Llinás & Yarom 1981a; 1981b; Sasaki et al., 1989). Harmaline increases rebound calcium spikes in IO cells, so that IO neurons convert from subthreshold oscillations to rhythmic burst-firing (Llinás & Yarom, 1981b; 1986). In animals, harmaline induces rhythmic bursting selectively in accessory olivary nuclei (De Montigny & Lamarre, 1973; 1975) that is propagated to the rest of cerebellum, leading to tremor.

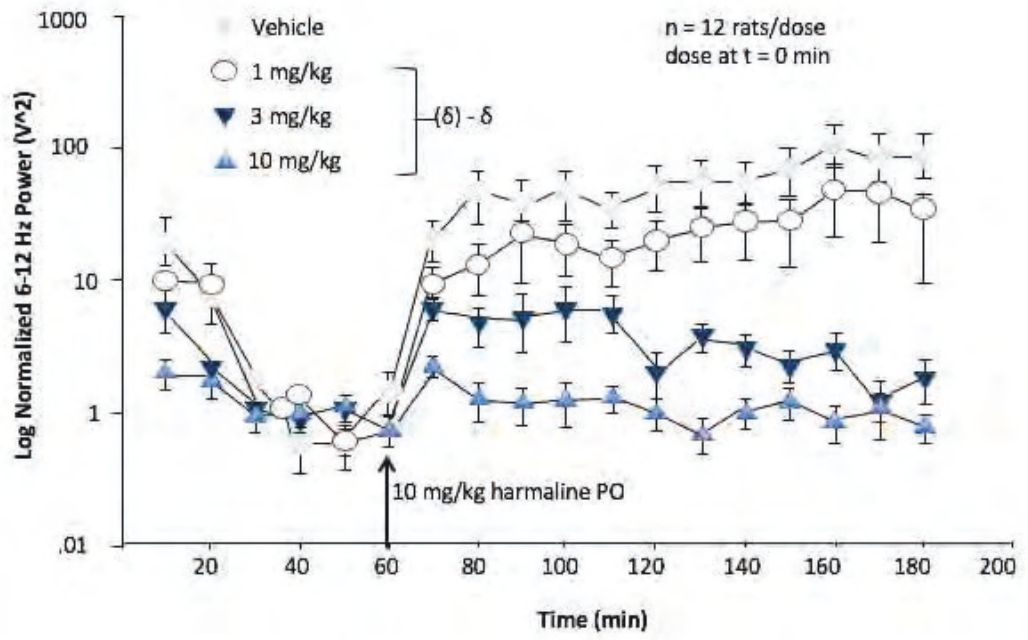
1.2.4 Cav3 antagonists in animal studies

Several investigators have evaluated multiple Cav3 compounds and their impact on tremor in animal studies. Handforth et al. tested whether both clinically available and experimental compounds that antagonize T-type calcium channel currents suppress tremor in two mouse models: harmaline-induced tremor and the GABA(A) receptor α1 subunit-null model. Mice were administered ethosuximide, zonisamide, the neuroactive steroid ECN, the 3,4-dihydroquinazoline derivative KYS05064, the mibefradil derivative NNC 55-0396, or vehicle. Tremor was measured using digitized spectral motion power analysis. In non-sedating doses, each compound reduced tremor in the harmaline-induced model by at least 50% (range of maximal suppression: 53-81%), and in the GABA(A) α1-null model by at least 70% (range 70-93%) (Handforth et al., 2010). Quesada et al. evaluated both mibefradil and NNC-55-0396 in the $GABA_{A1}$ null model and harmaline animal models of tremor and observed reductions in tremor (Quesada et al., 2011).

Tremor suppression by alcohol has been remarked on since the 19th century. Suppression of harmaline tremor by ethanol has been well replicated (Martin et al., 2005; Rappaport et al., 1984). Isomers of octanol suppress harmaline tremor in rodents (Martin & Handforth, 2006; Sinton et al., 1989); subsequently 1-octanol was found to reduce tremor in ET (Shill et al., 2004). Gamma-hydroxybutyrate also suppresses harmaline tremor and ET tremor (Frucht et al., 2005; Paterson et al., 2009). 1-octanol functions as a Cav3 antagonist (Sinton et al. 1989).

Finally, CX-8998's analogue TTA-A2 has been evaluated in the harmaline model of tremor and demonstrated significant improvement (Figure 5). Rats were placed in one of four conditions, vehicle, versus TTA-A2 1mg/kg, 3mg/kg, or 10mg/kg. TTA-A2 normalized both physiologic tremor prior to harmaline administration and harmaline-induced tremor in a dose-dependent response (Shipe et al., 2008).

Figure 5 TTA-A2 Normalization of Harmaline Tremor in Rats



Rats assigned to vehicle or one of three ascending doses of TTA-A2 demonstrated a dose-dependent response to harmaline-induced tremor following *per os* administration. Prior to administration of harmaline, rats also demonstrated dose-dependent response to a reduction in physiologic tremor (Shipe et al., 2008).

1.2.5 Brief History of Blockers of Ca_V3 as a Target for Treatment of Neurological Diseases in Humans

A number of blockers for T-type calcium channels have been developed to treat various neurologic diseases, including epilepsy, tremor and Parkinson's disease, which share a common pathophysiology.

Epilepsy: One major class of calcium channel blockers (CCBs) is the family of antiepileptic drugs that includes ethosuximide, trimethadione and zonisamide. Both ethosuximide and trimethadione are used for the treatment of absence seizures by blocking the $Ca_V3.1$ channel. A fundamental feature of absence epilepsy is the abnormal and inappropriate switching of the thalamocortical circuitry from a tonic to oscillatory mode of firing (Talley et al., 1999; Danober et al., 1998). Ca_V3, expressed in the thalamus and cortex, is crucial to this process (Pinault et al., 2005; Tsakiridou et al., 1995). While absence seizures involve a generalized cortical involvement, partial seizures affect only a small region of the brain. Zonisamide is chemically classified as a sulfonamide and is unrelated to other antiepileptic agents. Zonisamide is effective in the treatment of partial seizures and childhood epilepsy.

Parkinson's disease: Current trials using the CCBs isradipine and zonisamide are based on the observation that overactive calcium channels may play a role in the death of dopamine-producing cells in the brain – one of the hallmarks of Parkinson's disease. The studies were initiated after findings in two large population meta-analyses revealed that patients taking voltage-gated CCBs had a reduced incidence/progression of Parkinson's disease (Pasternak et al., 2012; Parkinson's Study Group, 2013; Lang et al., 2015).

Essential Tremor: Multiple studies of zonisamide have shown effectiveness in the treatment of tremor as measured by accelerometry and tremor rating scales, however all

were limited by poor tolerability and/or excessive premature discontinuations from treatment (Handforth et al., 2009; Zesiewicz et al., 2009; Morita et al., 2005; Bermejo et al., 2008; Ondo, 2007; Miwa, 2008). The same finding of effectiveness limited by poor tolerability was also reported for topiramate, a weak Ca_V3 inhibitor (Chang et al., 2015). So while CA_V3 is a biologically-validated target for development of ET therapeutics, the search for a safe and effective compound has, to date, been unsuccessful.

1.2.6 CX-8998 is a Potent and Selective Blocker of Ca_V3

CX-8998 is an orally active, potent and selective blocker of Cav3 and a potentially novel treatment for ET that was previously investigated for the treatment of insomnia and schizophrenia.

Electrophysiology experiments show that CX-8998 inhibits the $Ca_V3.3$ calcium channel as measured by a depolarized Fluorometric Imaging Plate Reader (FLIPR) assay with an [redacted]. Using a hyperpolarized state FLIPR assay [redacted]

In vivo pharmacology studies of CX-8998 in rodent and non-human primate sleep architecture have demonstrated dose-dependent increases in slow wave sleep early in the sleep period, followed by a significant increase of rapid eye movement (REM) late in the sleep period. There was also a significant suppression in REM early in the sleep period.

CX-8998 at doses of 1 mg/kg, 3 mg/kg and 10 mg/kg was also shown to dose-dependently inhibit both seizure duration and frequency in a single-dose rat model of absence epilepsy. Additional T-type antagonists from at least five structurally diverse series have shown similar efficacy in this model.

1.2.7 Key Point

In summary, the evidence that tremor arises from dysfunction in the inferior-olive – cerebellum network, that excessive rhythmicity or dysrhythmia are observed in the thalamocortical network, and that both share mediation via the Cav3 calcium channel, whose increased activity is a common pathophysiology, supports the animal and human evaluation results of Cav3 antagonists for tremor and suggest that CX-8998 may present a novel therapeutic option for the treatment of essential tremor.

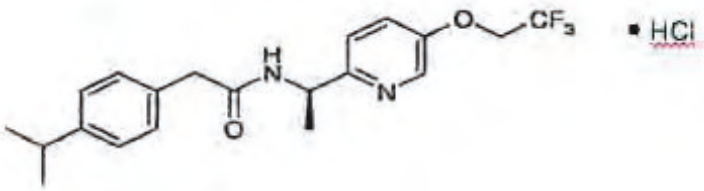
1.3 CX-8998 Non-Clinical Experience

Please refer to the current edition of the Investigator Brochure for a full discussion of prior non-clinical evaluations of CX-8998. CX-8998 is the new name applied to the Merck & Co., Inc. pharmaceutical product known as MK-8998. The name MK-8998 is used here in reference to all prior non-clinical studies conducted by Merck & Co., Inc.

1.3.1 CX-8998 is a Blocker of T-type Calcium Channels

CX-8998, as the HCl salt, is a potent, selective, and state dependent small molecule blocker of T-type calcium channels. The structure of CX-8998 is displayed in Figure 6.

Figure 6 Chemical Structure of CX-8998



Highly potent and selective T-type calcium channel blockers are of interest for the treatment of a variety of neurological conditions associated with T-type calcium channel activity in cortical, thalamic, and cerebellar circuits implicated in sleep disorders, epilepsies, psychotic disorders, and movement disorders such as essential tremor and Parkinson's disease.

In rat and non-human primate studies, MK-8998: 1) increased slow wave sleep early in the sleep period and decreased REM sleep early and increased REM sleep late in the sleep period; 2) attenuated the psychomotor activating effect of amphetamine; and 3) attenuated seizures in the WAG/rij rat model of absence epilepsy.

1.3.2 Safety Pharmacology Studies

In safety pharmacology studies, MK-8998 had no effects on cardiovascular function in conscious dogs up to doses of 2 mg/kg orall [redacted]

In conscious rats, MK-8998 produced small decreases in respiratory tidal volume/minute ventilation at all doses. Increases in an index of airway resistance were observed only at [redacted]

MK-8998 was non-genotoxic in a battery of *in vitro* and *in vivo* genotoxicity studies.

In the 5-week oral toxicology study in rats (30, 300, and 2000 mg/kg/day) the no observed adverse effect leve [redacted]

[redacted]

1.3.3 Non-clinical Pharmacokinetics

The pharmacokinetic parameters of MK-8998 in male Sprague-Dawley rats, beagle dogs and rhesus monkeys are summarized in the Investigator Brochure [redacted]

[redacted]

[redacted]

1.4 CX-8998 Clinical Experience

Please refer to the current edition of the Investigator Brochure for a full discussion of prior clinical evaluations of CX-8998. CX-8998 is the new name applied to the Merck & Co., Inc. pharmaceutical product known as MK-8998. The name MK-8998 is used here in reference to all prior clinical studies conducted by Merck & Co., Inc.

[redacted]

1.4.1 Clinical Pharmacokinetics

[redacted]

[redacted]

1.4.2 Clinical Pharmacodynamics

[redacted]

In the current study for essential tremor, a subset of subjects will undergo EEG/MEG evaluation to obtain additional pharmacodynamic data pertaining to CX-8998.

1.4.3 Clinical Safety

[redacted]

1.5 Rationale for Selected Dose

[redacted]

[redacted]

2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the efficacy of CX-8998, in doses up to 16 mg per day (8 mg BID), in reducing essential tremor.

2.2 Secondary Objectives

1. To assess changes in tremor-affected activities of daily living.
2. To assess the safety and tolerability of CX-8998 in doses up to 16 mg per day (8 mg BID).
3. To measure the concentration of CX-8998 and its metabolites (M01 and M02) in plasma.

2.3 Exploratory Objectives

1. To assess changes in quality of life.
2. To assess study drug effects on electrophysiological patterns associated with thalamocortical dysrhythmias (in a subset of subjects).
3. To use the concentrations of CX-8998 and its 2 primary metabolites in plasma in population pharmacokinetic, exposure-response and exposure-safety analyses (to be reported separately from the Clinical Study Report).

3 STUDY DESIGN AND ENDPOINTS

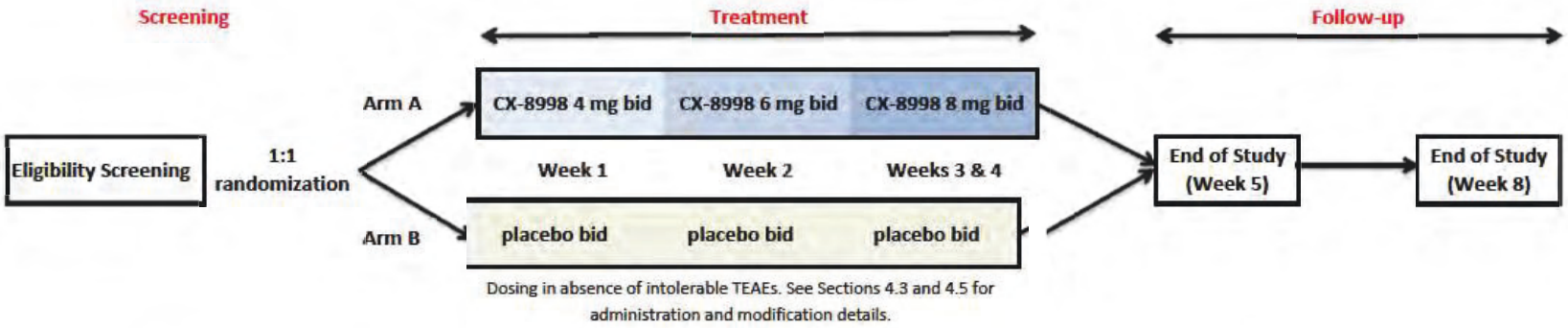
3.1 Study Type

This is a Phase 2, randomized, parallel-group, double-blind, placebo-controlled study. Subjects will be randomized in a blind-blind manner to one of two treatment groups: subjects randomized to Group A will receive CX-8998 and subjects randomized to Group B will receive placebo. Subject randomization will be stratified by concomitant use of primidone and site type (sub-study vs. non sub-study).

3.2 Schematic Study Design

The study design schematic is shown in Figure 7.

Figure 7 Schematic Study Design



3.3 Endpoints

3.3.1 Primary Endpoint

The change from Baseline to Day 28 on the TETRAS Performance subscale

3.3.2 Secondary Endpoints:

1. The proportion of Responders (subjects experiencing a decrease of at least 5.5 points on the TETRAS Performance Subscale)
    a. from Baseline to Day 15
    b. from Baseline to Day 28
2. Changes in subject response as measured by accelerometer (transducer measurement of tremor amplitude)
    a. Percent changes from Baseline to Days 15 and 28 in maximum and average amplitude over 1 hour after start of TETRAS assessment
    b. Changes from Baseline to Days 15 and 28 in 48 hour AUC of amplitude.
3. Change from Baseline to Day 15 on the TETRAS Performance subscale
4. Changes from Baseline on the TETRAS Activity of Daily Living subscale to Days 15 and 28
5. Safety: as assessed by physical examination, neurological examination, vital signs assessment, clinical laboratory testing, electrocardiography, incidence of adverse events, the Epworth Sleepiness Scale and the Columbia Suicide Severity Rating Scale
6. Plasma levels of CX-8998 and its metabolites (M01 and M02)

3.3.3 Exploratory Endpoints:

1. Changes in electrophysiological patterns associated with thalamo-cortical dysrhythmias (in a subset of subjects):
    a. Electroencephalography (EEG) in a sub-study of up to 24 subjects to correlate with target engagement
    b. Magnetoencephalography (MEG) in sub-study of up to 24 subjects to record power-spectral brain activity in specific neuro-anatomical locations and coherence with movement measures
2. Change from Baseline in quality of life:
    c. Quality of Life in Essential Tremor Questionnaire (QUEST)

4 STUDY DRUG

4.1 Supply and Storage

CX-8998 will be supplied as 2 mg capsules. Placebo capsules will be matched for CX-8998 capsules and will be indistinguishable from CX-8998 capsules. All manufacturing and packaging activities will be performed according to cGMP guidelines.

Supplies of study drug should be stored below 30° C.

4.2 Packaging and Labeling

Study medication will be supplied in 60 cc white HDPE bottles with 33 mm polypropylene, white, child-resistant closures. Each subject will receive a kit with two bottles of active drug or placebo capsules. In each kit, one bottle will contain 80 capsules (weeks 1 and 2 dosing) and a second bottle will contain 150 capsules (weeks 3 and 4 dosing). The bottles will be appropriately labeled. The affixed label will have spaces for entering the subject number, subject initials, and date dispensed. At the time of dispensing, the subject number, subject initials, and date dispensed are entered onto the appropriate lines on the label and the second panel will be removed and affixed to the CRF drug label pages provided by the sponsor.

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

- Protocol number: CX-8998-CLN2-001
- Expiration date
- Lot number
- Storage conditions
- The sentence, “Caution: New Drug – Limited by Federal Law to Investigational Use”
- Name and address of the Sponsor

4.3 Administration

CX-8998 (or placebo) will be administered as 4 mg (2 capsules) twice daily (8 mg/d) in the first week; increasing to 6 mg (3 capsules) BID (12 mg/d) in week 2, to a target of 8 mg (4 capsules) BID (16 mg/d) in weeks 3 and 4.

[redacted]

Subjects will be given a dosing diary to be used for the 28-day dosing period. They should record relevant information regarding their study drug in the diary (e.g., confirmation that each daily dose was taken, reasons for missed doses).

Treatment compliance will be assessed based on return of unused drug and the dosing diary.

Subjects experiencing specified adverse events will have their dose adjusted. See Section 4.5 for details on dose adjustments.

4.3.1 Stopping Rules

Study drug dosing for an individual subject will be permanently discontinued for intolerable AEs that do not resolve to Grade 1 or Baseline within 48 hours of suspension of dosing, and for all Grade 4 AEs. Other reasons for treatment termination are provided in Section 6.4.

4.4 Study Drug Accountability

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

Sites will keep a current log of drug accountability recording:

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

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

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

4.5 Dose Adjustments / Toxicity Management

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

Dosing will be discontinued for all Grade 4 AEs.

In all subjects with intolerable AEs (as defined in Section 10.2.1) that are considered related to study drug, treatment should be suspended for up to 48 hours or until the AE resolves to a tolerable level of severity, whichever is earlier. Dosing may then be resumed at a previously tolerated lower dose (or 2 mg BID in the case of 4 mg BID). Only a single dose-step reduction (e.g. 8 mg BID to 6 mg BID, 6 mg BID to 4 mg BID, or 4 mg BID to 2 mg BID) is permitted. Re-up-titration is NOT permitted. Dosing should be discontinued if there is recurrence of intolerable AEs after dose reduction. Subjects on the 2 mg BID dose with

intolerable AEs will be discontinued from treatment. Table 1 details dose reductions by dose level.

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

Table 1 Study Drug Dose Reduction for Intolerable AEs

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

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

The Medical Monitor should be notified of all dose reductions as soon as is feasible.

4.6 Overdose Management

To date, no overdoses of CX-8998 in humans have occurred.

Because no humans have overdosed with CX-8998, specific information regarding treatment of overdose is not currently available. In case of an acute overdose, it is recommended that the stomach be emptied and oral gavage with activated charcoal be used to help reduce absorption of CX-8998. In the event of an overdose, the medical monitor should be contacted immediately.

4.7 Randomization and Matching of Subjects

Eligible subjects will be randomized in a 1:1 ratio between CX-8998 and placebo, using an Interactive Web Response System (IWRS). Subject randomization will be stratified by concomitant use of primidone and site type (sub-study vs. non sub-study). A statistician not involved in the day-to-day study operation will create the randomization schedule. Details of the randomization process will be included in the study Operations Manual.

4.8 Study Blinding

This is a double-blind study; that is, the treatment assignment and drug contents are not revealed to the Sponsor, the subject and or investigator and other study personnel.

Maintenance of the double-blind is critical to the integrity of this clinical study. 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 for that subject may be broken by the treating Investigator.

Before breaking the blind for an individual subject, the Investigator should have determined that the information is necessary, i.e., it will alter the immediate management of the subject's care. *In the majority of cases not involving pregnancy, because there is no known specific antidote for any potential pharmacodynamic or toxic effect of CX-8998, there should rarely be a need to unblind a subject to guide immediate medical management of an emergency.*

The need to break the blind should first be discussed with the Sponsor's Medical Monitor, if at all possible. In case of an emergency, the Investigator may open the emergency unblinding envelope. Once the decision to unblind has been made, the Investigator must record the nature of the emergency that required the unblinding, along with the date and time of the unblinding, in the proper source documentation and notify the Sponsor's Medical Monitor of the unblinding. However, the Sponsor's Medical Monitor, and any other Investigators, must not be informed of the treatment assignment. The treatment assignment must not be noted in the source documentation or any other documentation submitted to the Sponsor.

Study treatment for a given subject may be unblinded for reportable safety events (e.g., suspected unexpected serious adverse reaction [SUSAR]) as required by local or other regulations, but the mere occurrence of an SAE should not routinely precipitate immediate unblinding.

In cases of accidental unblinding, the Investigator will notify the Sponsor's Medical Monitor and ensure that every attempt to preserve the blind is made. Specifically, the Investigator will not reveal the identity of the study treatment to the Sponsor's Medical Monitor or other Sponsor staff, any Contract Research Organization (CRO) staff including the clinical site staff, Clinical Research Associate (CRA), subject, or anyone else who does not already know this information.

If unblinding occurs, the study drug must be discontinued for the particular subject(s) involved.

5 INVESTIGATORS, SITES AND DURATION

5.1 Investigators and Sites

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

5.2 Duration of Study

Subjects will participate for a total of up to 12 weeks, including screening, the 4-week treatment period and follow-up.

5.3 Termination of Study

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

6 STUDY POPULATION

6.1 Number of Subjects

Up to 92 eligible subjects will be randomized to treatment. Eligibility of all subjects will be confirmed by a central reviewer.

6.2 Inclusion Criteria

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

1) Signed informed consent form (ICF) indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
2) Men or non-pregnant, non-breastfeeding women 18 years-of-age or older who are able to read and understand English.
3) Diagnosis of definite or probable essential tremor (ET) as defined by the Tremor Investigational Group with involvement of the hands and arms without present causes of enhanced physiologic tremor (Deuschl et al., 1998).
4) Diagnosis of ET before the age of 65
5) Tremor severity score of at least 2 in at least one upper extremity on the TETRAS scale.
6) Total TETRAS performance score of at least 15 (Note: Thresholds of criteria 5 & 6 shall NOT be shared with study subjects or caregiver to limit Baseline-inflation.)
7) Has, in the opinion of the investigator, had an inadequate response to at least one anti-tremor medication(s) or cannot tolerate available anti-tremor medication(s).
8) Subjects with reproductive capability including all males and women of child-bearing potential (WOCBP) must agree to practice continuous abstinence or adequate contraception methods (appropriate double barrier method or oral, patch, implant, or injectable contraception) from as soon as feasible during screening period until at least 30 days after the last dose (i.e., intermittent abstinence based on “rhythm”, temperature monitoring, or other means of timing is not acceptable). WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy) or is not post-menopausal. Post-menopausal is defined as:
    a) Amenorrhea ≥ 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL;
    b) Amenorrhea ≥ 12 consecutive months in women ≥ 62 years old (FSH testing is not required).

    Male subjects with a partner of child-bearing potential must be surgically sterilized or be willing to use condoms with spermicide from as soon as feasible during screening period until at least 30 days after the last dose.

6.3 Exclusion Criteria

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

1) Exposure to tremorigenic drugs or drug withdrawal states within the past month
2) Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor
3) History or clinical evidence of psychogenic tremor origin
4) Known history of other medical conditions that may cause or explain subject's tremor, including, but not limited to:
    a) Parkinson's disease
    b) Hyperthyroidism
    c) Pheochromocytoma
    d) head trauma or cerebrovascular disease within 3 months prior to the onset of essential tremor
    e) multiple sclerosis
    f) polyneuropathy
    g) family history of Fragile X syndrome
5) Prior MR-guided Focused Ultrasound or surgical intervention (e.g., deep brain stimulation, ablative thalamotomy or gamma knife thalamotomy) for treatment of tremor
6) Botulinum toxin injection in the 6 months prior to screening
7) Currently using more than one anti-tremor medication. Subjects must have been on a stable dose for 1 month prior to screening and must have no change in dose in concurrent anti-tremor medication for the duration of the study.
8) Use of medication(s) (in the past month) that might produce tremor or interfere with the evaluation of tremor, such as but not limited to: CNS-stimulants, lithium, amiodarone, metoclopramide, theophylline, and valproate
9) Subject is unable to refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor on study visit days, such as but not limited to stimulant decongestants, beta-agonist bronchodilators, caffeine, alcohol and tobacco.
10) Regular use of more than two units of alcohol per day. See Section 7.3.2 for definitions.
11) Sporadic use of a benzodiazepine, sleep medication or anxiolytic to improve sleep performance. Stable use at a consistent dose is allowed as long as tremor persists against the background of regular medication use.
12) Use of prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be strong inhibitors or inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study

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

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

    b) NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure

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

        i) QTcF >450 msec (males) or >470 msec (females)

        ii) PR interval >250 msec

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

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

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

        vi) For subjects not in the EEG/MEG neurophysiology sub-study, the presence of a cardiac pacemaker does not automatically exclude eligibility. The specifics must be discussed with the Medical Monitor to make a determination of eligibility.

    d) Known infection with HIV, hepatitis B, or hepatitis C, unless curative therapy completed for hepatitis C with negative PCR

    e) Significant hepatic (AST/ALT > 2X upper limit of normal) or renal disease (creatinine clearance <39 mL/min)

    f) Significant psychiatric history including mood disorders and alcohol or substance abuse within the last year

    g) History of attempted suicide within the last 5 years or a C-SSRS score of 4 or 5 at screening or at any time in the past year

    h) Clinically significant impaired balance or is considered at increased risk for falls

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

15) Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (e.g., due to expected study medication non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study–related procedures)

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

17) For patients in the EEG/MEG neurophysiology sub-study only:
    a) A history of gross brain abnormalities including history of stroke, history of TIA, severe ventriculomegaly or severe periventricular white matter abnormalities
    b) a history of serious psychiatric, psychological or neurological disorders, including psychosis or major depression, bipolar disorder, alcohol or drug abuse, brain injury, seizure disorder, brain tumor, chronic pain, Parkinson's, tinnitus, generalized anxiety disorder, or schizophrenia
    c) taking psychoactive medications, including antipsychotics, anxiolytics and antidepressants, or cognitive enhancers such as cholinesterase inhibitors
    d) presence of contraindications for MEG or MRI recording, including any of the following: cardiac pacemaker, intracranial clips, metal implants, or external clips within 10 mm of the head, metal in eyes, claustrophobia, obesity and/or any other reason leading to difficulty staying in the MEG or MRI for up to one hour.

6.4 Withdrawal of Subjects and/or Discontinuation of Treatment

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

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

A subject should be discontinued from treatment for any of the following:

1) Occurrence of defined unacceptable toxicity (Section 4.5)
2) Investigator determines that discontinuation of treatment is in the best interest of the subject.
3) Occurrence of any intercurrent condition, injury, or disease that becomes apparent during the study and necessitates the discontinuation of treatment.
4) Pregnancy
5) Subject requires use of prohibited concurrent medication.

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

If a subject withdraws from the study, attempts should be made to contact the subject to determine the reason(s) for discontinuation. If a subject does not return to the clinic for follow-up visits, attempts should be made to contact the subject via phone, email, or mail. At least 3 documented attempts (one of which should be a certified letter) should be made

to contact the subject before declaring a subject lost to follow-up. The Medical Monitor must be informed as soon as possible if a subject discontinues or withdraws early.

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

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

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

6.4.2 Procedures for Replacing Subjects Who Withdraw/Discontinue Prematurely

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

7 TREATMENT PLAN AND METHODS

7.1 Schedule of Assessments

Table 2 Schedule of Assessments

	Procedure		TREATMENT PERIOD					
	Visit	Screen	Visit 1 Baseline	Visit 2	Visit 3	Visit 4	EOS	FU (telephone)
	Study Day (window)	-28 to 0	1	8 (±2)	15 (±2)	28 (-1)	35 (±2)	58 (±2)
	End of week		-	1	2	4	5	8
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		X		X	X		
14	TETRAS ADL		X		X	X		
15	QUEST		X		X	X		
16	Epworth Sleepiness Scale		X	X	X	X		
17	C-SSRS	X	X	X	X	X	X	
18	Pharmacokinetic sampling			X	X	X		
19	Prior/Concomitant medications	X	X	X	X	X	X	
20	AE review	X	X	X	X	X	X	X
21	Study drug administration in clinic		X	X	X			
22	Dosing		X					
23	Drug compliance			X	X	X		

ADL – activities of daily living; AE – adverse event; C-SSRS – Columbia Suicide Severity Rating Scale; EOS – end of study; FSH – follicle stimulating hormone; FU – follow-up; QUEST – Quality of Life in Essential Tremor Questionnaire; TETRAS – The Essential Tremor Rating Assessment Scale

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
3. Subjects must meet all criteria specified in Sections 6.2 and 6.3. Eligibility will be confirmed by a central reviewer.
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. On Visits 1, 2 & 3 (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 anytime 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 and urinalysis. 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.
9. A single 12-lead ECG will be performed at Screening and End of Study. At Visits 1, 2 and 3 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 2 minutes of recumbency. (Section 10.1.7)
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. (Section 8.1.1)
13. At Visit 1 accelerometry will be initiated prior to performance of the TETRAS performance scale and will continue for 48 hours. For Visits 3 and 4 the device will be applied at home and worn for the 48 hours leading to the clinic visit through completion of the TETRAS Performance subscale. (Section 8.2)
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. (Section 8.1.2)
15. QUEST: a 30-item quality of life questionnaire (Section 8.3.1)
16. The Epworth Sleepiness Scale is intended to measure daytime sleepiness. (Section 10.1.9).
17. C-SSRS identifies behaviors that may be indicative of an individual's intent to commit suicide. (Section 10.1.8)
18. Collection of samples will occur pre-dose on Visits 2 and 3. At Visit 4, up to 2 samples will be collected. (Section 9.19.2)
19. 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.
20. AEs will be collected from signature of the ICF through the Follow-up telephone call on Day 58 (Section 10.2.2). Adverse events will be followed for resolution in accordance with Section 10.2.3.
21. 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 and 3, 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 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, or the time that is required to complete all of the required procedures for the visit (Section 4.3.)

22. Subjects will initiate dosing at 4 mg (2 capsules) administered twice daily with food. After 7 days dosing, the dose will be increased to 6 mg (3 capsules) twice daily, per subject tolerance. After 7 days at 6 mg BID, the dose will be increased to 8 mg (4 capsules) twice daily, per subject tolerance (Section 4.3.) the final dose of study drug will be administered at home on the morning of Visit 4.
23. Compliance will be assessed via a dosing diary and pill counts. (Section 4.4.)

7.2 Summary of Treatment Visits

7.2.1 Screening

The Screening visit must be performed within 28 days of Visit 1/Baseline. Subject informed consent must be obtained prior to initiation of any study specified procedures. A central reviewer will confirm subject eligibility prior to randomization. Details of the review will be provided in the study Operations Manual. See Table 2 for a detailed list of assessments to be performed.

7.2.2 Visit 1 (Day 1 - Baseline)

Subjects will return to the clinic within 28 days of screening. Following confirmation of continued eligibility and randomization, subjects will receive the first dose of study drug (4 mg or placebo) and undergo safety and efficacy assessments as detailed in Table 2. Subjects will be followed for adverse events, orthostatic VS, and one ECG for at least 2 hours prior to discharge. The Investigator or qualified designee will make the determination whether it is safe to release the subject from the clinic. Subjects will be instructed to take the second daily dose of study drug no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the time of their first dose, and to continue taking 4 mg (or placebo) twice daily for the following week (see Administration details in Section 4.3). Subjects will wear the accelerometry device for 48 hours from the time of initial placement (Section 8.2.)

7.2.3 Visit 2 (Day 8 – End of Week 1)

Subjects will return to the clinic for assessments as detailed in Table 2.

If the subject has been at least 80% compliant with the study drug regimen and has not experienced any intolerable adverse events (as described in Section 4.5), the dose of study drug will be increased to 6 mg (or placebo) twice daily for the following week. If compliance is determined to be less than 80%, up-titration should be discussed with the Medical Monitor.

Subjects will receive the first dose of study drug (6 mg or placebo) and undergo safety assessments. Subjects will be followed for adverse events, orthostatic VS, and one ECG for at least 2 hours prior to discharge. The Investigator or qualified designee will make the determination whether it is safe to release the subject from the clinic. Subjects will be instructed to take the second daily dose of study drug no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the time of their first dose, and to continue taking 6 mg (or placebo) twice daily for the following week (see Administration details in Section 4.3).

7.2.4 Visit 3 (Day 15 – End of Week 2)

Subjects will return to the clinic for assessments as detailed in Table 2. Subjects will have re-applied their accelerometry device 48 hours prior to the clinic visit.

If the subject has been at least 80% compliant with the study drug regimen and has not experienced any intolerable adverse events (as described in Section 4.5), the

dose of study drug will be increased to 8 mg (or placebo) twice daily for the following two weeks. If compliance is determined to be less than 80%, up-titration should be discussed with the Medical Monitor.

Subjects will receive the first dose of study drug (8 mg or placebo) and undergo safety and efficacy assessments. Subjects will be followed for adverse events, orthostatic VS, and one ECG for at least 2 hours prior to discharge. The Investigator or qualified designee will make the determination whether it is safe to release the subject from the clinic. Subjects will be instructed to take the second daily dose of study drug no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the time of their first dose, and to continue taking 8 mg (or placebo) twice daily for the following week (see Administration details in Section 4.3).

7.2.5 Visit 4 (Day 28 – End of Week 4)

Subjects will return to the clinic for assessments as detailed in Table 2. Visit 4 is the end-of-dosing visit. Subjects will have re-applied their accelerometry device 48 hours prior to the clinic visit. Subjects will take their regularly-scheduled final dose of study drug in the morning before their return to clinic. Visit must occur on or one day before Day 28 to ensure that all efficacy assessments occur while subject is still taking study drug.

7.2.6 End of Study Visit (Day 35 – End of Week 5)

Subjects will return to the clinic for the final visit assessments detailed in Table 2. Adverse events that are unresolved at the end of study visit will continue to be followed by study staff as detailed in Section 10.2.3.

7.2.7 Safety Follow-up Telephone Call (Day 58 – End of Week 8)

Twenty-eight (±2) days after Visit 4 (or after the last dose of study drug for subjects who discontinue treatment prematurely), the site will contact subjects by telephone to inquire as to the status of AEs that were ongoing at the End of Study Visit and to determine that no new AEs have occurred in the 30 days following the last dose.

7.3 Concomitant Medications and Other Restrictions

7.3.1 Concomitant Medications

Subjects may not be using more than one anti-tremor medication at the time of entry into the study. Subjects must have been on a stable dose for one month prior to screening and must have no change in dose in concurrent anti-tremor medication for the duration of the study.

Subjects may not use medications that might produce tremor or interfere with the evaluation of tremor, such as but not limited to: CNS-stimulants, lithium, amiodarone, metoclopramide, theophylline, and valproate.

On Study Visit Days, subjects must refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor, such as but not

limited to stimulant decongestants, beta-agonist bronchodilators, caffeine, alcohol and tobacco.

The stable use of a benzodiazepine, sleep medication or anxiolytic to improve sleep performance is allowed as long as tremor persists against the background of regular medication use.

The use of prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be strong inhibitors or inducers of CYP3A4 must be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study. Subjects taking primidone for treatment of their ET may continue to do so at a stable dose. Subject randomization will be stratified by primidone use and site type.

See Appendix D for a complete list of restricted inhibitors and inducers.

7.3.2 Other Restrictions

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

8 EFFICACY ASSESSMENTS

8.1 The Essential Tremor Rating Assessment Scale (TETRAS)

The Tremor Research Group first published the TRG Essential Tremor Rating Assessment Scale (TETRAS) in 2008 (Elble 2008). TETRAS consists of a 9-item performance subscale and a 12-item activities of daily living (ADL) subscale. TETRAS was developed as a rapid clinical assessment of ET that requires no equipment other than pen and paper. Administration of the performance subscale takes less than 10 minutes. The scale employs objective metrics to reduce experiential rater bias.

To evaluate the inter-rater reliability of TETRAS, Elble et al. (2012) videotaped 50 TETRAS exams, including assessments of 44 patients with ET and 6 controls. The severity of ET ranged from mild to severe. Ten specialists rated the patients in the videos 2 times with an interval of 1 to 2 months separating the ratings. Of the 10 raters, 6 had been involved in the development of TETRAS, and 4 had never used the scale.

Inter-rater reliability of the scale was calculated using a two-way random effects intraclass correlation (ICC) with an absolute agreement definition. The inter- and intra-rater ICC for head and upper limb tremor ranged from 0.86 to 0.96, and the ICC for the total score were 0.94 and 0.96. The ICC for voice, face, trunk and leg were less robust (Elble et al., 2012).

The TETRAS Performance subscale is widely used in clinical practice, and has high content validity and strong inter-rater reliability. The TETRAS ADL and

performance scores are highly correlated, and the TETRAS ratings of upper extremity function correlate strongly with transducer measures (accelerometry) of upper limb tremor (Mostile et al., 2010). TETRAS is also shown to be sensitive to change in tremor over time (Voller et al., 2014).

8.1.1 TETRAS Performance Subscale

The Performance subscale quantifies tremor in the head, face, voice, limbs and trunk. Each item is rated on a 0 to 4 rating scale, with scoring of upper limb tremor allowing for 0.5-point increments. Specific amplitude ranges (measured in centimeters) define the tremor rating (see Table 3). Raters first estimate the maximum amplitude of tremor and then assign the corresponding rating. The sum of the individual rating scores provides the overall Performance score, ranging from 0 to 64. See Appendix A1 for the complete TETRAS Performance Scale.

Table 3 TETRAS Performance Subscale Metric Amplitude Ranges

Head Tremor	Upper Limb Tremor	Lower Limb Tremor
0 = no tremor	0 = no tremor	0 = no tremor
1 = < 0.5 cm	1 = barely visible	1 = barely visible
2 = 0.5 - < 2.5 cm	1.5 = < 1 cm	2 = < 1 cm
3 – 2.5 – 5 cm	2 = 1 - < 3 cm	3 = 1 – 5 cm
4 = > 5 cm	2.5 = 3 - < 5 cm	4 = > 5 cm
	3 = 5 - < 10 cm	
	3.5 = 10 - < 20 cm	
	4 = > 20 cm	

In order to reduce rater bias, all subjects will be videotaped during the TETRAS Performance Subscale testing. The videotapes will be rated in a blinded fashion.

Full details on the recording and scoring of the TETRAS Performance scale will be provided in the study Operations Manual.

8.1.2 TETRAS Activities of Daily Living Subscale

The ADL subscale includes many of the items assessed in the scales previously developed by Fahn, Tolosa and Marin (1993), Louis et al. (2000) and Bain et al. (1993), including eating and drinking, dressing and personal hygiene, carrying items and finer motor skills. 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. See Appendix A1 for the complete TETRAS ADL Subscale.

8.2 Accelerometry

Accelerometry has long been used to obtain quantitative measurements of tremor in ET (Jankovic & Frost, 1981; Koller, 1985). Elble et al. demonstrated a logarithmic relationship between tremor amplitude, as measured via accelerometry, and changes in physician-assessed tremor rating scales (Elble, 2006). Voller et al.

reported a significant correlation (p <.001) between log-transformed accelerometer data and TETRAS scores in ET (Voller et al., 2014).

The accelerometer will be placed at the region of highest tremor intensity/amplitude. The location will be documented and placement will be kept consistent throughout the study. At Visit 1, the accelerometer will be placed prior to the TETRAS Performance assessment and will remain in place for the subsequent 48 hrs. Subjects will bring the accelerometer to the clinic at Visit 2 for downloading of data and for reinforcement of training on how to apply the device at home. For Visits 3 and 4, subjects will apply the accelerometer at home 48 hours prior to their return to clinic and will keep the device in place until TETRAS Performance assessments are complete.

Full details on the accelerometry device and use will be provided in the study Operations Manual.

8.3 Quality of Life Assessments

Health-related Quality of Life (HRQoL) is defined as a patient's perception of the effects of and illness and its treatment on his/her life and sense of will-being. In that many models suggest a strong relationship between functional status and HRQoL, ET has the potential to exert a significant and detrimental impact on HRQoL (Makedonsky et al., 2002).

8.3.1 QUEST

Until 2005, the measurement of QoL in patients with ET was performed with generic QoL indices such as the EuroQOL and Sickness Impact Profile (SIP). However, generic measures lack sensitivity in ET and may fail to address the issues most relevant to patients with ET. As such, Tröster et al. developed the Quality of Life in Essential Tremor Questionnaire (QUEST) to specifically assess the impact of ET on HRQOL (Tröster et al., 2005). The QUEST is a 30-item questionnaire that contributes to 5 sub-scales (physical, psychosocial, communication, hobbies/leisure and work/finance) and a total score, plus 3 additional items relating to sexual function and satisfaction with tremor control and medication side effects. Initial reports provide preliminary support of its reliability and validity. The internal consistency was very good to excellent for 4 scales and the total score, and moderately high for the Work/Finance scale (Tröster et al., 2005). These reliability coefficients are also supportive of the QUEST's construct validity.

The QUEST scale will be utilized as a secondary efficacy endpoint. It is proposed that successful treatment of ET, even if symptomatic rather than curative, would positively impact QoL. A sample QUEST questionnaire may be found in Appendix A2.

9 PHARMACOKINETIC ASSESSMENTS

9.1 Blood Sample Collection

All subjects will have one blood sample drawn prior to administration of CX-8998 at Visits 2 and 3. At Visit 4, up to 2 samples will be collected. In the subset of subjects participating in the neurophysiology substudy, additional blood samples will be collected. See Appendix C for substudy details.

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

9.2 Pharmacokinetic Parameters

Plasma concentrations of CX-8998 and its metabolites (M01 and M02) will be determined.

The concentrations of CX-8998 and its 2 primary metabolites in plasma will be used in population pharmacokinetic, exposure-response and exposure-safety analyses (to be reported separately from the Clinical Study Report).

10 SAFETY ASSESSMENTS

10.1 Assessment of Safety

10.1.1 Adverse Events

Adverse events (AEs) will be captured from the time the ICF is signed through the Follow-up telephone call on Day 58. Important medical events and conditions occurring prior to this period are not AEs; they will be captured within the medical chart and in the Medical History section of the Case Report Form. See Section 10.2 for definitions and instructions on the rating and collection of AEs.

10.1.2 Physical Examination

A complete physical examination includes measurement of height (screening only), weight, and examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities. Genital, rectal, and breast examination may be excluded if not clinically indicated. Weight should be measured on the same scale each time.

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

10.1.3 Neurological Examination

The neurological examination will include assessment of mental status, and examination of cranial nerves II-XII, motor and sensory exam, reflexes, coordination, gait and balance.

10.1.4 Vital Signs

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 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. On Visits 1, 2 & 3 (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 anytime 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.)

10.1.5 Clinical Laboratory Tests

Hematology testing will include hematocrit, hemoglobin, red blood cell count, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC), and platelet count.

Serum chemistry analyses will include sodium, potassium, chloride, calcium, magnesium, phosphorus, carbon dioxide (CO_2) or bicarbonate, albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, creatine kinase (CK), uric acid, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, cholesterol levels and total bilirubin.

Coagulation studies will include fibrinogen, activated partial thromboplastin time (aPTT), and international normalized ratio (INR).

Urinalysis will include color and appearance, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood by dipstick. Microscopic inspection of sediment is only to be performed as needed to clarify abnormal dipstick results at the discretion of the Investigator.

10.1.6 Pregnancy Tests

A urine pregnancy test will be performed for all women of childbearing potential. See Section 6.2, inclusion criterion # 8 for the definition of women of childbearing potential.

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

10.1.7 Electrocardiogram

A 12-lead ECG will be obtained according to the Schedules of Assessments. The ECGs will be performed using an ECG machine that reports the heart rate and PR, QRS, QT, QTcB (Bazett correction formula; may also be calculated), and QTcF (Fridericia correction formula) intervals (may also be calculated). Only QTcF (not QTcB) will be used for determination of eligibility.

The 12-lead ECGs should be obtained following 5 minutes of recumbency. ECGs will be repeated if clinically significant abnormalities are observed, if artifacts are present, or if machine/equipment errors occur. Any confirmed, clinically significant ECG changes from screening will be recorded as AEs.

10.1.8 Columbia Suicide Severity Rating Scale

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

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

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

A sample of the C-SSRS may be found in Appendix B.

10.1.9 Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a scale intended to measure daytime sleepiness that is measured by use of a very short questionnaire. It was developed by Murray Johns of Epworth Hospital in Melbourne, Australia (Johns, 1991; Johns, 2010). The questionnaire asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for 8 different situations. The scores are added together to obtain a single number.

In general, ESS scores can be interpreted as follows:

0 - 5	Lower Normal Daytime Sleepiness
6 - 10	Higher Normal Daytime Sleepiness
11 - 12	Mild Excessive Daytime Sleepiness
13 - 15	Moderate Excessive Daytime Sleepiness
16 - 24	Severe Excessive Daytime Sleepiness.

A sample of the ESS may be found in Appendix B.

10.2 Adverse Events

10.2.1 Definitions

Adverse Event

An Adverse Event (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.

Laboratory Abnormality

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 are also considered AEs.

Treatment-emergent Adverse Events

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

Treatment Period

The treatment period is the period during which a subject receives study drug (i.e., first dose through 30 days after last dose).

Intolerable Adverse Event

An intolerable AE is one that is considered by the investigator to be related to study drug (Section 10.2.2.3) AND is either a Grade 3 (severe) or 4 (life threatening) event (Section 10.2.2.2) OR is a Grade 1 or 2 event that prompts the subject to express a desire to discontinue dosing. Dose adjustments for intolerable AEs are described in Section 4.5.)

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. See Section 10.3 for more details on SAEs.

10.2.2 Collection and Rating of Adverse Events

All AEs, irrespective of the relatedness to the study drug, will be collected and reported on the Adverse Event Report Form from signature of the ICF through the

Follow-up telephone call on Day 58. In case of an SAE, a Serious Adverse Event Report Form must be completed and transmitted to the Sponsor or designee.

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

10.2.2.1 Onset Date

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

10.2.2.2 Assessment of Intensity

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

- **Grade 1 (Mild)**: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Grade 2 (Moderate)**: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) [Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc];
- **Grade 3 (Severe)**: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden]
- **Grade 4 (Life-threatening):** Life threatening consequences; urgent intervention indicated;
- **Grade 5 (Fatal)**: death related to AE.

10.2.2.3 Relationship to Study Drug

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

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

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

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

10.2.2.4 Action Taken

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

- **None:** no change in study drug dosage was made
- **Reduced:** dose of study drug was reduced, with or without a period of temporary suspension of dosing
- **Discontinued:** the study drug was permanently stopped

10.2.2.5 Outcome of Adverse Event

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

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

10.2.3 Adverse Event Follow-up

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

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

All AEs, whether serious or non-serious, will be collected beginning at the time of signing informed consent through the Follow-up Telephone Call (Day 58). All AEs should be followed until resolution or:

- 30 days from onset; or
- the Follow-up Telephone Call (Day 58); or
- the subject is lost to follow-up (as defined in Section 6.4.1); or
- the subject withdraws consent,

whichever occurs first.

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

10.3 Serious and Other Significant Adverse Events

10.3.1 Definition of a Serious Adverse Event

A serious adverse event is any adverse event that

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

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

The following are not considered SAEs:

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

10.3.2 Serious Adverse Event Reporting by the Investigator to the Sponsor

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

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

Sponsor Representative and Contact Information for SAE Reporting:

Reporting email: [redacted]

10.3.3 Handling of Follow-up Information

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

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

- The final outcome of the case is known
- The event is resolved or the medical condition of the subject is stabilized

- No further information is available
- Sponsor assessment has been finalized
- The subject has withdrawn consent for further follow-up; information obtained up to the date and time of withdrawal of consent will remain a part of the study record.

10.3.4 Reporting and Follow-up of Pregnancy

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

10.3.5 Expedited Reporting of Serious Adverse Events

10.3.5.1 Responsibilities

The Sponsor is responsible for ensuring the timely reporting of SAEs to Regulatory Authorities and all Investigators who participate in the clinical development program of the study drug. It is the responsibility of the Investigator to provide the Sponsor with the case information such that reporting timeline demands of applicable Regulatory Authorities can be met.

10.3.5.2 Expedited Reporting

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

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

10.3.5.3 Timelines

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

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

It is the responsibility of the Investigator to support Sponsor activities needed to meet the aforementioned timelines for Regulatory Authority reporting in the event of an SAE.

10.4 Safety Monitoring Plan

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

1. Subject safety and tolerability will be monitored in this study across multiple dimensions by tracking clinical adverse events; vital signs (including orthostatic pulse and blood pressure); general and neurological physical examinations; standard clinical laboratory safety panels for complete blood counts, chemistry, coagulation, and urinalysis; standard 12-lead electrocardiograms; and the Epworth Sleepiness Scale (ESS) and Columbia Suicide Severity Rating Scale (C-SSRS).
2. The specified inclusion/exclusion criteria have been carefully considered to avoid enrollment of subjects for whom exposure to the study drug might pose a hazard.
3. The anticipated subject population (with essential tremor) is acknowledged to likely be older than the healthy volunteer and schizophrenic populations that have previously undergone phase 1 and 2 study with CX-8998 (formerly MK-8998, Merck & Co., Inc.). Since older male and female subjects may experience greater CX-8998 exposures than younger males on whom most of the existing PK data are based, this study will perform a careful dose titration in which dosing of CX-8998 will be initiated at 4 mg BID for 7 days, increasing to 6 mg BID for 7 days, and finally, if tolerated, to the target dose of 8 mg BID for 14 days. Subjects will return to the clinic for each dose up-titration for safety assessment. The study is designed to allow for flexible titration; should subjects experience intolerable AEs (see section 10.2.1, Adverse Events, Definitions) at 4 mg, 6 mg or 8 mg BID, the dose may be decreased to the previous lower dose (2 mg BID in the case of 4 mg BID). Subjects experiencing intolerable AEs at 2 mg BID will be discontinued from treatment.
4. Dose up-titration (e.g., from 4 mg BID to 6 mg BID) requires that the subject be evaluated in the clinic by the PI or sub-I. PI's and sub-I's may advise a subject to reduce or suspend their dose based on telephone elicitation of adverse events. During each clinic visit involving a dose up-titration, subjects will be observed and monitored in the clinic for at least 2 hours following the first administration of the increased dose step.

5. Dose modification and stopping rules are in place for individual subjects (see section 4.5, Dose Adjustments/Toxicity Management). Near real-time safety and tolerability monitoring for individual subjects is the primary responsibility of the PI and sub-I's.
6. All serious adverse events (SAEs) meeting criteria for expedited reporting to the US FDA will be reported to the FDA and all IRBs in accordance with regulatory timelines.
7. The Sponsor's Medical and Safety Monitor *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. These reviews will be based on blinded, select listings and summary tables of the evolving safety and tolerability data for each arm of the study. The Sponsor's Medical Monitor and the independent Safety Monitor Physician will review the blinded study data to determine if there is a sufficiently clinically significant difference between the blinded treatment arms in terms of frequency, severity, and/or seriousness of adverse events to take actions such as 1) unblinding specific safety data; 2) eliminating one or more of the planned dose up-titrations (e.g., not escalating from 6 to 8 mg BID); or 3) suspending new enrollment in the study until further safety review and consultation with the PI's and sub-I's can be performed. Decision-making will depend on the specifics of the safety and tolerability data reviewed. If the Sponsor's Medical Monitor 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.
8. In the event of a treated subject's death within 30 days of the last dose of study drug and that is assessed by the treating PI/sub-I or the independent Safety Monitor Physician or the study Medical Monitor as at least possibly related to study drug, further enrollment into the study will be immediately suspended until a safety review can be conducted by the independent Safety Monitor Physician, the study Medical Monitor, the actively participating PI's and sub-I's, and the Sponsor. As required by regulation, all deaths meeting criteria for expedited reporting to the US FDA will be reported to the FDA and all IRBs within regulatory timelines. A final decision to re-open the study to new enrollment without modification(s), re-open with modification(s), or terminate the study will be made by the overall study Principal Investigator, the independent Safety Monitor Physician, and the Sponsor's Medical Monitor.

11 STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with statistical testing performed for the efficacy endpoints. All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. 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 by treatment group and overall. The term "treatment group" refers to the following: Placebo or CX-8998. All available data for enrolled subjects will be listed in by subject listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number.

All statistical analyses will be conducted with the SAS® System, version 9.2 or higher.

11.1 Statistical Analysis Plans

A SAP will be created and approved prior to the review of any data. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures.

11.2 Study Hypothesis

The primary statistical hypothesis for the study is provided below.

- H_{01}: $\propto_{\text{CX-8998}} \geq -5.5$ i.e., the mean change from Baseline in TETRAS performance scale at end of treatment for the CX-8998 is less than the published minimally important difference (5.5 points)
- H_{11}: $\propto_{\text{CX-8998}} < -5.5$, i.e., the mean change from Baseline in TETRAS performance scale at end of treatment in the CX-8998 is greater than the published minimally important difference (5.5 points)

A secondary comparison of the primary endpoint will assess the following statistical hypothesis:

- H_{02}: $\propto_{\text{Placebo}} = \propto_{\text{CX-8998}}$, i.e., there is no difference in the mean change from Baseline in TETRAS performance scale at end of treatment
- H_{12}: $\propto_{\text{Placebo}} \neq \propto_{\text{CX-8998}}$, i.e., there is a difference in mean change from Baseline in TETRAS performance scale at end of treatment

11.3 Determination of Sample Size

Up to 92 subjects will be randomized to one of two treatment groups: Placebo and CX-8998. Based on similarly designed studies, this sample size should be sufficient to provide preliminary safety and efficacy information on CX-8998 when administered according to this protocol.

A sample size of 43 subjects has at least 90% power to detect at least a 5.5 point change from Baseline to end of treatment in the TETRA performance subscale for CX-8998 when the standard deviation is 10.6, alpha=0.05 (PASS 2008: One sample t-test – Normal Non-Parametric Adjustment). Similarly, 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 end of treatment in the TETRA performance subscale when the standard deviation is 7.5 and alpha=0.05 (PASS 2008: Two sample t-test – Normal Non-Parametric Adjustment). Up to 92 subjects will be enrolled in order to ensure that 86 subjects are available for inclusion in the efficacy analyses.

11.4 Analysis Populations

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

• **Intent-To-Treat Population:** The ITT population will include all subjects who are randomized. The ITT population will be used for analyses of accountability, demographics, and efficacy. Subjects will be analyzed according to the treatment as randomized.

• **Safety Population:** The safety population will include all subjects who are randomized and receive at least one dose of randomized treatment. Subjects who receive treatment other than that intended will be analyzed according to the treatment received. The safety population will be the primary population for all analyses of safety data.

• **PK Population:** The PK population will consist of all subjects for whom PK samples were obtained, received study treatment, and for whom sufficient plasma concentrations are available.

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

11.5 Data Analysis

11.5.1 Efficacy Analyses

11.5.1.1 Primary Efficacy Analyses

The primary efficacy analysis of the TETRAS performance subscale will be conducted using an analysis of covariance (ANCOVA) model with fixed effects for treatment, concomitant primidone use, site type, and Baseline value of the TETRAS performance subscale. The primary hypothesis to be tested will be if the mean change from Baseline in TETRAS performance scale indicates at least a 5.5 point decrease from Baseline in the CX-8998 arm. The secondary comparison will assess whether the CX-8998 arm is different from placebo. All testing will be performed

using the LSMeans from the ANCOVA model and a two-sided test at the alpha=0.05 level of significance. If the data indicate a departure from the normal distribution, a corresponding rank test will be performed.

11.5.1.2 Secondary and Exploratory Efficacy Analyses

The proportion of subjects experiencing at least a 5.5 point decrease in the TETRAS performance scale will be summarized by treatment group. Differences between the treatment groups will be assessed with Cochran-Mantel-Haenszel General Association test stratified by concomitant primidone use and site type.

The secondary endpoints of change from Baseline on the TETRAS Activity of Daily Living subscale, percent change from Baseline to Day 28 in patient response as measured by accelerometer, change from Baseline in the ESS, and change from Baseline on the QUEST scale will be analyzed using the same type of ANCOVA model as described for the primary endpoint. All secondary and exploratory analyses will be conducted using two-sided tests at the alpha=0.05 level of significance.

11.5.2 Safety Analyses

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

Descriptive summaries of vital signs and clinical laboratory results will be presented by treatment group and study visit. The number and percentage of subjects experiencing treatment-emergent laboratory abnormalities will be summarized by treatment group. Laboratory abnormality shifts from Baseline to post-Baseline assessments will be summarized by treatment group.

Concomitant medications will be mapped to a WHO preferred term and drug classification. The number and percent of subjects taking concomitant medications will be summarized using preferred terms and drug classifications.

Changes from Baseline in physical examinations, neurological examinations, and ECGs during study will be evaluated.

11.5.3 Pharmacokinetic Analyses

Individual plasma concentrations and actual time of collection will be listed by treatment.

11.6 Missing, Unused and Spurious Data

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

12 STUDY MANAGEMENT

12.1 Protocol Amendment and Protocol Deviation

12.1.1 Protocol Amendment

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

12.1.2 Protocol Deviations and Waivers

No deviations from the protocol are anticipated. Requests for waivers will not be granted in advance by the Sponsor. Should a non-anticipated protocol deviation occur, the Sponsor must be informed as soon as possible. All deviations and the reasons for the deviation will be documented by the Investigator or designated staff. Reporting of protocol deviations to the IRB and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

12.2 Ethics and Regulatory Aspects

12.2.1 Ethical Conduct of the Study and Regulatory Guidelines

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

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

12.2.2 Institutional Review Board and Regulatory Approval

The study protocol and any amendments will be reviewed by an Independent Review Board. The IRB will review the written subject information sheet and the Informed Consent Form (ICF), their updates (if any), and any written materials

given to the subjects. A listing of the membership of the IRB consulted and the name of the committee chair(s) or IRB registry (accreditation) number will be documented within the Investigator File and Trial Master File of the Sponsor.

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

12.2.3 Subject Informed Consent

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

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

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

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

Each subject will be informed that a Monitor, a Quality Assurance Auditor mandated by the Sponsor, or a Health Authority Inspector, in accordance with applicable regulatory requirements, may review his or her source records and health data. Data protection will be handled in compliance with national and local regulations.

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

12.3 End of Study and Regulatory Notification

The study can be terminated in part or in whole at the discretion of the FDA, an applicable Regulatory Authority or the Sponsor.

At the end of the study, the IRBs and Regulatory Authorities will be notified by the Sponsor according to applicable Regulatory requirements.

12.4 Data Protection and Confidentiality

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

12.5 Monitoring

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

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

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

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

12.6 Quality Assurance and Quality Control

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Principal or Qualified Investigator generating the data.

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

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

The study center may also be compelled to an inspection by a Regulatory Authority.

12.7 Source Data

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

Source documents are the original data, documents, and records. Examples include hospital records, laboratory reports, clinical and office charts, laboratory notes,

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

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

13 DATA AND RECORD KEEPING

13.1 Case Report Forms

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

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

13.2 Record Keeping

The Investigator must arrange for retention of study records ("Essential Documents for the Conduct of a Trial" are listed in the ICH "Guideline for Good Clinical Practice," Section 8, E6) at the site, in a secure location, for 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or for at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The Investigator should take measures to prevent any accidental or premature destruction of these documents.

14 REFERENCES

Adams PJ, Snutch TP. Calcium channelopathies. Voltage-gated calcium channels. Subcell Biochem. 2007;45: 215-251.

Anderson MP, Mochizuki T, Xie J, et al. Thalamic Cav3.1 T-type Ca2 + channel plays a crucial role in stabilizing sleep. Proc Natl Acad Sci USA. 2005; 102: 1743–1748.

Bain PG, Findley LJ, Atchison P, et al. Assessing tremor severity. J Neurol Neurosurg Psychiatry. 1993; 56(8): 868-873.

Bermejo-Pareja F. Essential tremor—a neurodegenerative disorder associated with cognitive defects? Nature Reviews Neurology. 2011;7(5):273-282.

Bermejo-Pareja F, Puertas-Martín V. Cognitive Features of Essential Tremor: A Review of the Clinical Aspects and Possible Mechanistic Underpinnings. Louis ED, ed. *Tremor and Other Hyperkinetic Movements*. 2012;2:02-74-541-1.

Bermejo-Pareja PE, Ruiz-Huete C, Dorado R, Anciones B. Zonisamide in refractory essential tremor. Revista de Neurologia. 2008; 46(3): 139-142.

Bourinet E, Alloui A, Monteil A, et al. Silencing of the Cav3.2 t-type calcium channel gene in sensory neurons demonstrates its major role in nociception. EMBO. 2005;24(2): 315-324.

Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol Rev. 2005;57(4): 411-425.

Chandran V, Pal PK, Reddy JY, Thennarasu K, Yadav R, Shivashankar N. Non-motor features in essential tremor. Acta Neurol Scand. 2012;125:332–7.

Chang K, Wang S, Chi C. Efficacy and safety of topiramate for essential tremor: a meta analysis of randomized controlled trials. Medicine. 2015; 94(43): 1-7.

Choi S, Yu E, Hwang E, Llinás RR. Pathophysiological implication of $Ca_V3.1$ T-type Ca^{2+} channels in trigeminal neuropathic pain. Proc Natl Acad Sci USA. 2016;113: 2270–2275.

Cribbs LL, Lee JH, Yang J, et al. Cloning and characterization of alpha1H from human heart, a member of the T-type Ca2+ channel gene family. Circ. Research. 1998;83(1): 103-9.

Danober L, Deransart C, Depaulis A, Vergnes M, Marescaux C. Pathophysiological mechanisms of genetic absence epilepsy in the rat. Prog. Neurobiol. 1998;55: 27–57.

DeMontigny C, Lamarre Y. Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat. Brain Research. 1973;53(1):81-95.

DeMontigny C, Lamarre Y. Effects produced by local applications of harmaline in the inferior olive. Can J Physiol Pharmacol. 1975;53(5):845-849.

Deuschl G, Bain P, Brin M. Consensus Statement of the Movement Disorder Society on Tremor. Mov Disord. 1998;13: 2–23.

Diaz NL, Louis ED. Survey of medication usage patterns among essential tremor patients: Movement disorder specialists vs. general neurologists. Parkinsonism Relat Disorders. 2010;16(9):604-607.

Dreyfus FM, Tscherter A, Errington AC, et al. Selective T-type calcium channel block in thalamic neurons reveals channel redundancy and physiological impact of I(T)window. J Neurosci. 2010;30(1): 99-109.

Eckardt D, Theis M, Degen J, et al. Functional role of connexin43 gap junction channels in adult mouse heart assessed by inducible gene deletion. J Mol Cell Cardiol. 2004;36(1): 101-10.

Elble RJ. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. Brain. 2006;129(10):2660-2666.

Elble RJ, Brilliant M, Leffler K, Higgins C. Quantification of essential tremor in writing and drawing. Mov Disord. 1996;11:70-78.

Elble R, Comella C, Fahn S, et al. The essential tremor rating assessment scale (TETRAS). Mov Disord. 2008; 23 (Suppl 1): S1-6.

Elble R, Comella C, Fahn S, et al. Reliability of a new scale for essential tremor. Mov Disord. 2012;27(12):1567-1569.

Elble R, Lewitt P, Lyons K, et al. Inter-Rater Reliability of the Essential Tremor Rating Assessment Scale (TETRAS) (S32.004). Neurology. 2012;78 (Meeting Abstracts 1).

Ertel EA, Campbell KP, Harpold MM, et al. Nomenclature of voltage-gated calcium channels. Neuron. 2000;25:533–5.

Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, ed. *Parkinson's Disease and Movement Disorders*. Baltimore: Williams & Wilkins; 1993: 225–234.

Frucht SJ, Bordelon Y, Houghton WH. Marked amelioration of alcohol responsive posthypoxic myoclonus by gamma-hydroxybutyric acid (Xyrem). Mov Disord. 2005;20(6): 745-751.

George MS, Lydiard RB. Social Phobia Secondary to Physical Disability. Psychosomatics. 1994;35(6):520-523.

Handforth A. Harmaline Tremor: Underlying Mechanisms in a Potential Animal Model of Essential Tremor. Louis ED, ed. *Tremor and Other Hyperkinetic Movements*. 2012;2:02-92-769-1.

Handforth A, Delorey TM, Homanics GE, Olsen RW. Pharmacologic evidence for abnormal thalamocortical functioning in GABA receptor beta3 subunit-deficient mice, a model of Angelman syndrome. Epilepsia. 2005;46(12):1860-70.

Handforth A, Homanic GE, Covey DF, et al. T-type calcium channel antagonists suppress tremor in two mouse models of essential tremor. Neuropharmacology. 2010; 59(6):380-387.

Handforth A, Martin F, Kang G, Vanek Z. Zonisamide for essential tremor: an evaluator blinded study. Movement Disorders. 2009; 24(3); 437-440.

Jankovic J, Frost JD. Quantitative assessment of parkinsonian and essential tremor: Clinical application of triaxial accelerometry. Neurology. 1981;31(10):1235-1235.

Jasinska-Myga B, Wider C. Genetics of essential tremor. Parkinsonism Relat Disord. 2012;18 (Suppl 1): S138-139.

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. 1991;14(6):540-545.

Johns MW. A new perspective on sleepiness. Sleep and Biological Rhythms. 2010;8(3):170-179.

Kim D, Song I, Keum S, et al. Lack of the burst firing of thalamocortical relay neurons and resistance to absence seizures in mice lacking alpha(1G) T-type Ca(2+) channels. Neuron. 2001 Jul 19; 31(1):35-45.

Koller WC, Royse VL. Time course of a single oral dose of propranolol in essential tremor. Neurology. 1985; 35(10): 1494-1494.

Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. Neurology. 1989;39(12):1587-1587.

Kopecky BJ, Liang R, Bao J. T-type calcium channel blockers as neuroprotective agents. Pflugers Archiv : European Journal of Physiology. 2014;466(4):757-765.

Lang Y, Gong D, Fan Y. Calcium channel blocker use and risk of Parkinson's disease: a meta-analysis. Pharmacoepidemiol Drug Saf. 2015 Jun 1;24(6):559-66.

Lang, EJ. GABAergic and glutamatergic modulation of spontaneous and motor-evoked, complex spike activity. J Neurophys. 2002;87(4): 1993-2008.

Llinás R. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. Science. 1988;242(4886):1654-64.

Llinás R. Thalamo-cortical dysrhythmia syndrome: neuropsychiatric features. An R Acad National Med. 2003;120(2): 267-290.

Llinás RR, Choi S, Urbano FJ, Shin H. γ-Band deficiency and abnormal thalamocortical activity in P/Q-type channel mutant mice. Proc Natl Acad Sci. 1999; 104(45):17819-17824.

Llinás R, Yarom Y. Electrophysiology of mammalian inferior olivary neurones in vitro. Different types of voltage-dependent ionic conductances. J Physiol. 1981;315(1):549-567.

Llinás R, Yarom Y. Properties and distribution of ionic conductances generating electroresponsiveness of mammalian inferior olivary neurones in vitro. J Physiol. 1981;315(1):569-584.

Llinás R, Yarom Y. Oscillatory properties of guinea-pig inferior olivary neurones and their pharmacological modulation: an in vitro study. J Physiol. 1986;376:163-182.

Lorenz D, Schwieger D, Moises H, Deuschl G. Quality of life and personality in essential tremor patients. Mov Disord. 2006;21(8):1114-1118.

Lory P, Bidaud I, Chemin J. T-type calcium channels in differentiation and proliferation. Cell Calcium. 2006;40: 135-146.

Louis ED. Essential Tremor. Arch Neurol. 2000;57(10).

Louis ED. Medication non-adherence in essential tremor. Parkinsonism Relat Disord. 2015;21(2):138-141.

Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25(5):534-541.

Louis ED, Machado DG. Tremor-related quality of life: A comparison of essential tremor vs. Parkinson's disease patients. Parkinsonism Relat Disord. 2015;21(7):729-735.

Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder? Estimates of the prevalence of essential tremor throughout the world. Movement Disorders. 1998;13(1):5-10.

Makedonsky PV, Levin OS, Naimushina TV. The quality of life in patients with essential tremor [abstract]. Mov Disord. 2002;17:S353

Martin FC, Handforth A. Carbenoxolone and mefloquin suppress tremor in the harmaline model of essential tremor. Mov Disord. 2006;21(10):1641-1649.

McCormick D, Pape H. Properties of hyperpolarization activated cation current and its role in rhythmic oscillation in thalamic relay neurons J Phys. 1990;431: 291-318.

Merner ND, Girard SL, Catoire H, et al. Exome sequencing identifies FUS mutations as a cause of essential tremor. Am J Hum Genet. 2012;91(2): 313-319.

Miwa H, Hama K, Kajimoto Y, Kondo T. Effects of zonisamide on experimental tremor in rats. Parkinsonism Relat Disord. 2008;14:33-36.

Molineux ML, McRory JE, McKay BE, et al. Specific t-type calcium channel isoforms are associated with distinct burst phenotypes in deep cerebellar nuclear neurons. PNAS. 2006;103(41): 5555-5560.

Morita S, Miwa H, Kondo T. Effect of zonisamide on essential tremor: a pilot crossover study in comparison with arotinolol. Parkinsonism Relat Disord (2005) 11: 101–103

Mostile G, Giuffrida JP, Adam OR, Davidson A, Jankovic J. Correlation between Kinesia system assessments and clinical tremor scores in patients with essential tremor. Mov Disord. 2010;25(12):1938-1943.

Mundt JC, Greist JH, Gelenberg AJ, Katzelnick DJ, Jefferson JW, Modell JG. Feasibility and validation of a computer-automated Columbia-Suicide severity rating scale using interactive voice response technology. J Psych Res. 2010;44(16):1224-1228.

Mundt JC, Greist JH, Jefferson JW, Federico M, Mann JJ, Posner K. Prediction of Suicidal Behavior in Clinical Research by Lifetime Suicidal Ideation and Behavior Ascertained by the Electronic Columbia-Suicide Severity Rating Scale. J Clin Psych. 2013;74(09):887-893.

Ondo W. Zonisamide for essential tremor. Clin Neuropharmacol. 2007;30(6): 345-349.

Park Y, Park H, Lee CJ, et al. CaV3.1 is a tremor rhythm pacemaker in the inferior olive. PNAS. 2010;107(23):10731 – 10736.

Park Y-G, Kim J, Kim D. The potential role of T-type Ca2+ channels in motor coordination. Front Neural Circuits. 2013;7(172): 1-11.

Parkinson Study Group. Phase II safety, tolerability, and dose selection study of isradipine as a potential disease-modifying intervention in early Parkinson's disease (STEADY-PD). Mov Disord. 2013 Nov;28(13):1823-31.

Pasternak B, Svanström H, Nielsen NM, Fugger L, Melbye M, Hviid A. Use of calcium channel blockers and Parkinson's disease. Am J Epidemiol. 2012 Apr 1;175(7):627-35

Paterson NE, Malekiani SA, Foreman MM, Olivier B, Hanania T. Pharmacological characterization of harmaline induced tremor activity in mice. Eur J Pharmacol. 2009;616(1-3):73-80.

Pinault D, O'Brien TJ. Cellular and network mechanisms of genetically-determined absence seizures. Thalamus & Related Systems. 2005;3(3):181-203.

Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psych. 2011;168(12):1266-1277.

Quesada A, Bui PH, Homanics GE, Hankinson O, Handforth A. Comparison of mibefradil and derivative NNC 55-0396 effects on behavior, cytochrome P450 activity and tremor in mouse models of essential tremor. Eur J Pharmacol. 2011. 659: 30-36.

Rossier MF. T-Type calcium channel: a privileged gate for calcium entry and control of adrenal steroidogenesis. Front Endocrinol (2016) 7:43-

Sasaki K, Bower JM, Llinás R. Multiple Purkinje cell recording in rodent cerebellar cortex. Eur J Neurosci. 1989; 1:572-586.

Shill HA, Bushara KO, Mari Z, Reich M, Hallet M. Open-label dose escalation of oral 1-octanol in patients with essential tremor. Neurology. 2004;62(12): 2320-2322.

Shipe WD, Barrow JC, Yang ZQ. Design synthesis, and evaluation of a novel 4-aminomethyl-4-fluoropiperidine as a T-type Ca2+ channel antagonist. J. Med. Chem. 2008;51(3):692-3695.

Simantov R, Snyder SH, Oster-Granite M-L. Harmaline-induced tremor in the rat: Abolition by 3-acetylpyridine destruction of cerebellar climbing fibers. Brain Res. 1976;114(1):144-151.

Sinton CM, Krosser BI, Walton KD, Llinás RR. The effectiveness of different isomers of octanol as blockers of harmaline-induced tremor. Pflugers Arch. 1989;414: 31-36.

Tai C, Yang Y, Pan M, Huang C, Kuo C. Modulation of subthalamic T-type Ca2+ channels remedies locomotor deficits in a rat model of Parkinson disease. J Clin Invest. 2011;121(8): 3289-3305.

Talley EM, Cribbs LL, Lee JH, Daud A, Perez-Reyes E, Bayliss DA. Differential distribution of three members of a gene family encoding low voltage-activated (T-type) calcium channels. J. Neurosci. 1999. 19: 1895–1911 (1999).

Tanner CM, Goldman SM, Lyons KE, et al. Essential tremor in twins: an assessment of genetic vs environmental determinants of etiology. Neurology. 2001;57(8): 1389-1391.

Tsakiridou E, Bertollini L, de Curtis M, Avanzini G, Pape HC. Selective increase in T-type calcium conductance of reticular thalamic neurons in a rat model of absence epilepsy. J Neurosci. 1995;15:3110–3117.

Tröster AI, Pahwa R, Fields JA, Tanner CM, Lyons KE. Quality of life in Essential Tremor Questionnaire (QUEST): Development and initial validation. Parkinsonism Relat Disord. 2005;11(6):367-373.

Voller B, Lines E, McCrossin G, et al. Alcohol challenge and sensitivity to change of the essential tremor rating assessment scale. Mov Disord. 2014;29(4):555-558.

Zesiewicz TA, Ward CL, Hauser RA, Sanchez-Ramos J, Staffetti JF, Sullivan KL. A double blind placebo controlled trial of zonisamide (zonegran) in the treatment of essential tremor. Mov Disord. 2009;22(2): 279-282

Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: Treatment of essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2011;77(19):1752-1755.

15 APPENDICES

Appendix A – Efficacy assessments

Appendix B – Safety assessments

Appendix C – Neurophysiology Substudy

Appendix D – Cytochrome P450 Interaction Table

Appendix A1 – TETRAS Performance Scale

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor, are performed with the patient seated comfortably. For each item, score the highest amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out.

1. Head tremor: The head is rotated fully left and right and then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right with the head in mid position. The nose should be used as the landmark to assess and rate the largest amplitude excursions during the examination.

   0 = no tremor
   1 = slight tremor (< 0.5 cm)
   2 = mild tremor (0.5- < 2.5 cm)
   3 = moderate tremor (2.5-5 cm)
   4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.

   0 = no tremor
   1 = slight; barely perceptible tremor
   2 = mild: noticeable tremor
   3 = moderate: obvious tremor, present in most voluntary facial contractions
   4 = severe: gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended “aaah” sound and eee” sound for 5 seconds each. Then assess speech during normal conversation by asking patients “How do you spend your average day?”

   0 = no tremor
   1 = slight: tremor during aaah, and eee and no tremor during speech
   2 = mild: tremor in “aaah” and “eee” and minimal tremor in speech
   3 = moderate: obvious tremor in speech that is fully intelligible
   4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal reach posture is held for 5 seconds. The lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be estimated using the maximally displaced point of the hand at the point of greatest displacement along any single plane. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

   a) Forward outstretched postural tremor: Subjects should bring their arms forward, slightly lateral to midline and parallel to the ground. The wrist should also be straight and the fingers abducted so that they do not touch each other.

   b) Lateral "wing beating" postural tremor: Subjects will abduct their arms parallel to the ground and flex the elbows so that the two hands do not quite touch each other and are at the level of the nose. The fingers are abducted so that they do not touch each other. The posture should be held for 20 seconds.

   c) Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Only the position along the trajectory of greatest tremor amplitude is assessed. This will typically be either at the nose or at the point of full limb extension.

   For all three hand tremor ratings 0 = no tremor

   1 = tremor is barely visible
   1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude
   2.5 = tremor is 3- < 5 cm amplitude
   3 = tremor is 5- < 10 cm amplitude
   3.5 = tremor is 10- < 20 cm amplitude
   4 = tremor is > 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally parallel to the ground for 5 seconds each. Then perform a standard heel to shin maneuver with each leg, three times. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may exist in any part of the limb, including foot.

   0 = no tremor
   1 = slight: barely perceptible
   2 = mild, less than 1 cm at any point

3 = moderate tremor, less than 5 cm at any point
4 = severe tremor, greater than 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills 1/4 of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

   0 = normal
   1 = slight: tremor barely visible.
   2 = mild: obvious tremor
   3 = moderate: portions of figure not recognizable.
   4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand.. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

   0 = normal
   1 = slight: untidy due to tremor that is barely visible. 2 = mild: legible, but with considerable tremor.
   3 = moderate: some words illegible.
   4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X and instructs the subject to hold the tip of the pen "as close as possible to the dot (or center of an X) without touching it, (ideally approximately 1 mm) for 10 seconds ". Each hand is score separately.

   0 = no tremor
   1 = tremor is barely visible
   1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude
   2.5 = tremor is 3- < 5 cm amplitude
   3 = tremor is 5- < 10 cm amplitude
   3.5 = tremor is 10- < 20 cm amplitude
   4 = tremor is > 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20Ɣ. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk

    0 = no tremor
    1 = barely perceptible tremor
    2 = obvious but mild tremor, does not cause instability 3 = moderate tremor, impairs stability of stance
    4 = severe tremor, unable to stand without assistance

Appendix A2 – TETRAS Activities of Daily Living Scale

TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS©) V 3.1

Activities of Daily Living Subscale

Rate tremor's impact on activities of daily living (0 - 4 scoring).

1. Speaking
0 = Normal.
1 = Slight voice tremulousness, only when "nervous".
2 = Mild voice tremor. All words easily understood.
3 = Moderate voice tremor. Some words difficult to understand.
4 = Severe voice tremor. Most words difficult to understand.

2. Feeding with a spoon
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot feed with a spoon.

3. Drinking from a glass
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

4. Hygiene
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.
2 = Mildly abnormal. Some difficulty but can complete task.
3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy such as using two hands or using the less affected hand.
4 = Severely abnormal. Cannot complete hygiene activities independently.

5. Dressing
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with dressing.
2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.
3 = Moderately abnormal. Unable to do most dressing unless uses strategy such as using Velcro, buttoning shirt before putting it on or avoiding shoes with laces.
4 = Severely abnormal. Cannot dress independently.

6. Pouring
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with pouring.
2 = Mildly abnormal. Must be very careful to avoid spilling but may spill occasionally.
3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.
4 = Severely abnormal. Cannot pour.

7. Carrying food trays, plates or similar items
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.
2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.
3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.
4 = Severely abnormal. Cannot carry food trays or similar items.

8. Using Keys
0 = Normal
1 = Slightly abnormal. Tremor is present but can insert key with one hand without difficulty.
2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.
3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.
4 = Severely abnormal. Cannot put key in lock.

9. Writing
0 = Normal
1 = Slightly abnormal. Tremor present but does not interfere with writing.
2 = Mildly abnormal. Difficulty writing due to the tremor
3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.
4 = Severely abnormal. Cannot write.

10. Working. If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as it relates to housework:
0 = Normal .
1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.
2 = Mildly abnormal. Tremor interferes with work; able to do everything, but with errors. .
3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.
4 = Severely abnormal. Cannot perform any job or household work.

11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writing, etc)

Task _____

0 = Normal.
1 = Slightly abnormal. Tremor present but does not affect task.
2 = Mildly abnormal. Tremor interferes with task but is still able to perform task.
3 = Moderately abnormal. Can do task but must use strategies.
4 = Severely abnormal. Cannot do the task.

12. Social Impact

0 = None
1 = Aware of tremor, but it does not affect lifestyle or professional life.
2 = Feels embarrassed by tremor in some social situations or professional meetings.
3 = Avoids participating in some social situations or professional meetings because of tremor.
4 = Avoids participating in most social situations or professional meetings because of tremor.

Appendix A3 – QUEST

Quality of Life in Essential Tremor Questionnaire (QUEST)

Patient's Name: _____ ID: _____ Date: ____/____/____

Gender: ☐ Male ☐ Female Date of Birth: ____/____/____

Heath Status

In general, how would you rate your overall health? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Overall Quality of Life

Overall, how would you rate your quality of life? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

General Information

In the past month, has your tremor interfered with your sexual satisfaction? ☐ Y ☐ N

In the past month, have you had side effects from tremor medications? ☐ Y ☐ N

In the past month, have you been satisfied with the tremor control achieved by your medications? ☐ Y ☐ N

Which most appropriately describes your work status?

- ☐ Never worked
- ☐ Not working, retired because of tremor
- ☐ Not working, retired NOT due to tremor
- ☐ Working full time
- ☐ Working part time

TREMOR SELF ASSESSMENT

For the purposes of this questionnaire, tremor is defined as uncontrollable shaking or quivering of the body part in question.

On a typical day, how many of your waking hours do you have tremor in ANY body part?

Circle: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Put a mark in the box to rate the severity of your tremor in each of the body parts listed below.

None - no tremor at any time
Mild - mild tremor not causing difficulty in performing any activities
Moderate - tremor causes difficulty in performing **some** activities
Marked - tremor causes difficulty in performing **most** or **all** activities
Severe - tremor **prevents** performing some activities

		None	Mild	Moderate	Marked	Severe
1.	**Head**	☐	☐	☐	☐	☐
2.	Voice	☐	☐	☐	☐	☐
3.	**Right arm/hand**	☐	☐	☐	☐	☐
4.	Left arm/hand	☐	☐	☐	☐	☐
5.	**Right leg/foot**	☐	☐	☐	☐	☐
6.	Left leg/foot	☐	☐	☐	☐	☐

continued on next page

For each question below, please mark the box which best describes your current situation.

For example: N R ~~S~~ F A

N = Never/No
R = Rarely
S = Sometimes
F = Frequently
A = Always/Yes
NA = Not Applicable

1.	My tremor interferes with my ability to communicate with others.		N R S F A
2.	**My tremor interferes with my ability to maintain conversations with others.**		N R S F A
3.	It is difficult for others to understand my speech because of my tremor.		N R S F A
4.	**My tremor interferes with my job or profession.**	NA	N R S F A
5.	I have had to change jobs because of my tremor.	NA	N R S F A
6.	**I had to retire or take early retirement because of my tremor.**		N A
7.	I am only working part time because of my tremor.	NA	N A
8.	**I have had to use special aids or accommodations in order to continue my job due to my tremor.**	NA	N R S F A
9.	My tremor has led to financial problems or concerns.		N R S F A
10.	**I have lost interest in my hobbies because of my tremor.**		N R S F A
11.	I have quit some of my hobbies because of my tremor.		N A
12.	**I have had to change or develop new hobbies because of my tremor.**		N A
13.	My tremor interferes with my ability to write (for example, writing letters, completing forms).		N R S F A
14.	**My tremor interferes with my ability to use a typewriter or computer.**	NA	N R S F A
15.	My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone).		N R S F A
16.	**My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items).**		N R S F A
17.	My tremor interferes with dressing (for example, buttoning, zipping, tying shoes).		N R S F A
18.	**My tremor interferes with brushing or flossing my teeth.**		N R S F A
19.	My tremor interferes with eating (for example, bringing food to mouth, spilling).		N R S F A
20.	**My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring).**		N R S F A
21.	My tremor interferes with reading or holding reading material.		N R S F A
22.	**My tremor interferes with my relationships with others (for example, my family, friends, coworkers).**		N R S F A
23.	My tremor makes me feel negative about myself.		N R S F A
24.	**I am embarrassed about my tremor.**		N R S F A
25.	I am depressed because of my tremor.		N R S F A
26.	**I feel isolated or lonely because of my tremor.**		N R S F A
27.	I worry about the future due to my tremor.		N R S F A
28.	**I am nervous or anxious.**		N R S F A
29.	I use alcohol more frequently than I would like to because of my tremor.		N R S F A
30.	**I have difficulty concentrating because of my tremor.**		N R S F A

THANK YOU!

Appendix B1 – C-SSRS

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Lifetime Recent - Clinical

Version 1/14/09

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

Disclaimer:

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

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

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

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

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 3 months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes No** ☐ ☐ Total # of Attempts _____	**Yes No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes No** ☐ ☐	**Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted or self-interrupted _____	**Yes No** ☐ ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐ Total # of preparatory acts _____	**Yes No** ☐ ☐ Total # of preparatory acts _____

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

C-SSRS—Lifetime Recent - Clinical (Version 1/14/09)
Page 2 of 2

Appendix B2 – Epworth Sleepiness Scale Sample

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

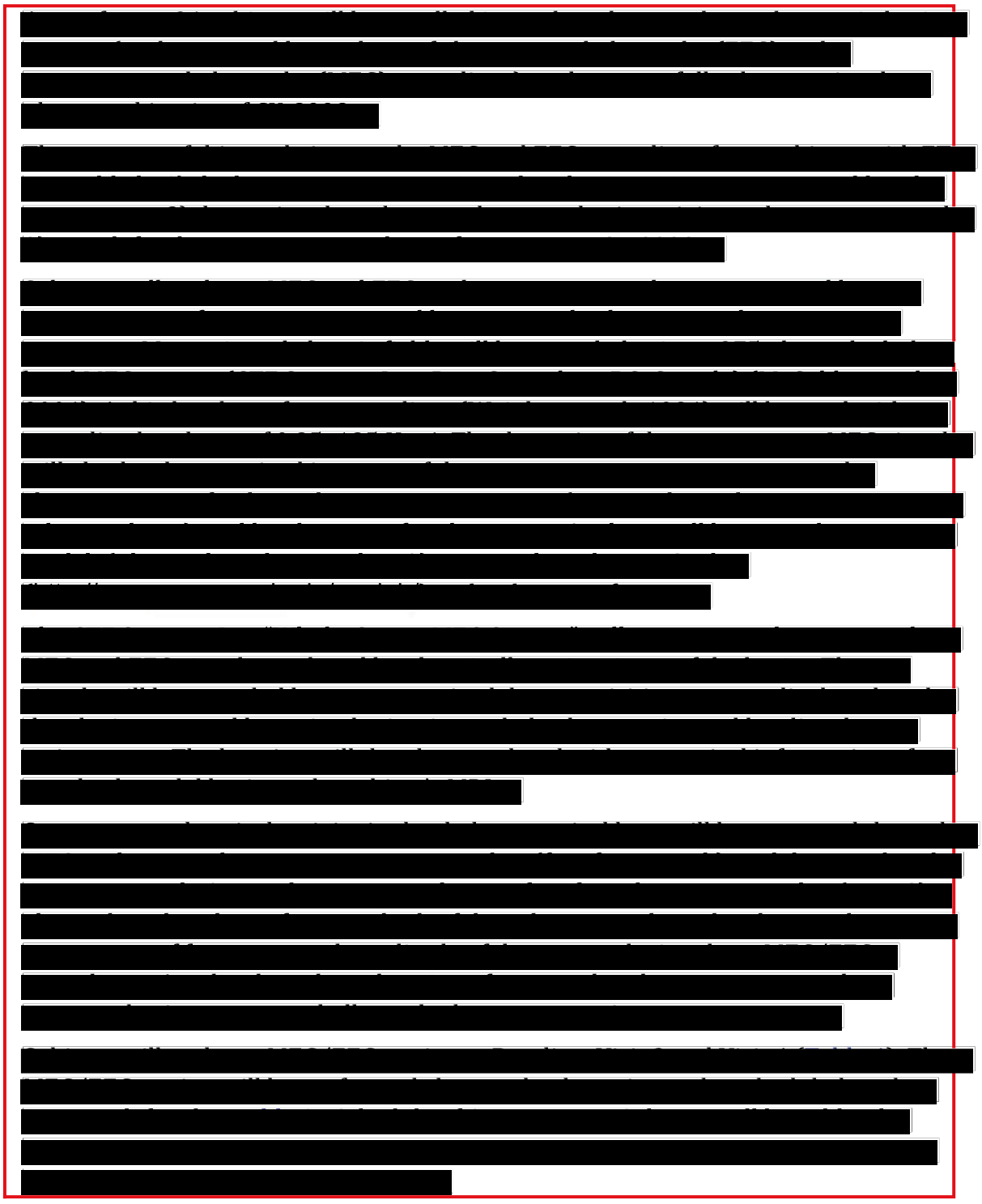
0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

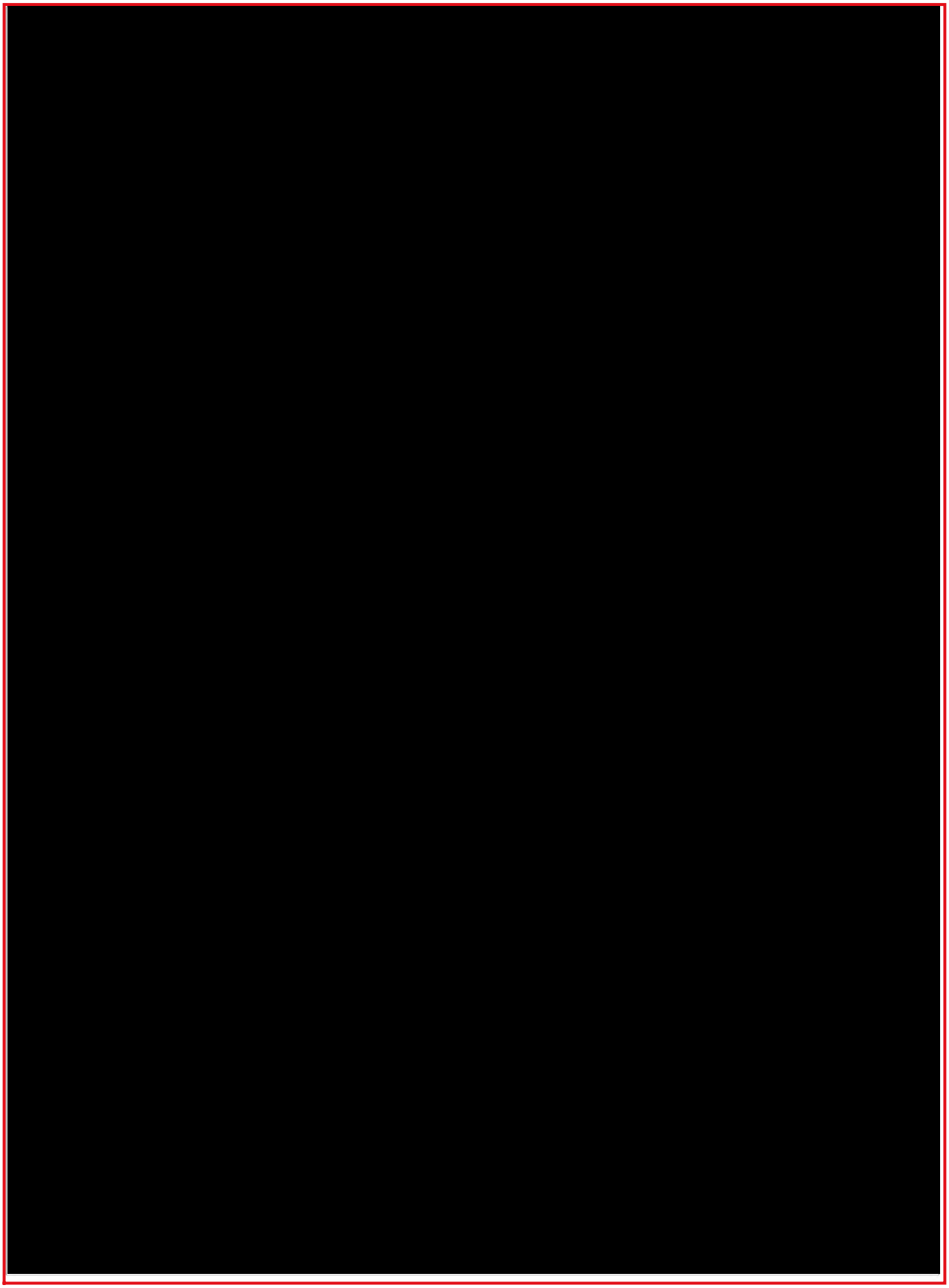
It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Appendix C – Neurophysiology Substudy





Appendix D – Cytochrome P450 Drug Interaction Table

STRONG INHIBITORS*
indinavir
nelfinavir
ritonavir clarithromycin
itraconazole
ketoconazole
nefazodone

MODERATE INHIBITORS*
erythromycin
grapefruit juice
verapamil
suboxone

* A **Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance. A **Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.

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

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

Clinical Study Protocol

Main Title:

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

Protocol Number: CX-8998-CLN2-001

Amendment 1, Version Number: 2.0 **Date:** 08 August 2017

Original Version Number: 1.2 **Date:** 06 April 2017

IND #: 130296

Official Short Title:

T-CALM: Tremor CAv3 Modulation Study

Confidentiality Statement:

SIGNATURE PAGE FOR SPONSOR

Study No.

Protocol Title: A Phase 2 Randomized Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

Approved by the following:

[redacted]

Cavion, Inc.
600 East Water Street, Suite E
Charlottesville, VA 22902

[redacted]

Cavion, Inc.
60 Thackeray Rd.
Wellesley, MA 02461

SIGNATURE PAGE FOR INVESTIGATOR

Study No.

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

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

_____	_____	_____
Investigator Name	Signature	Date

STUDY ORGANIZATIONAL STRUCTURE

Sponsor:	Cavion, Inc. 600 East Water Street Suite E Charlottesville, VA 22902 [redacted]
Study Safety Representative:	[redacted]

COMPLIANCE STATEMENT

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

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

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

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

PROTOCOL SYNOPSIS

Study Title: A Randomized Phase 2, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor	
Name of Finished Product: CX-8998	
Protocol Number: CX-8998-CLN2-001	**Study Phase:** 2
Clinical Sites: Multiple sites in the United States	

Primary Objective:

To assess the efficacy of CX-8998, in doses up to 20 mg per day (10 mg BID), in reducing the severity of essential tremor

Secondary Objectives:

1. To assess changes in tremor-affected activities of daily living
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 two primary metabolites (M01 and M02) in plasma

Exploratory Objectives:

1. To assess changes in quality of life
2. To assess study drug effects on electrophysiological and digital biomarker patterns associated with essential tremor (in a subset of subjects)
3. To use the concentrations of CX-8998 and its 2 primary metabolites in plasma in population pharmacokinetic/pharmacodynamic (PK/PD) analyses to evaluate the exposure-efficacy and exposure-safety relationships

Study Design:

This is a multicenter, double-blind, placebo-controlled, parallel-group study consisting of a screening period of up to 4 weeks (with the exception of subjects on primidone at baseline who will be allowed 6 weeks of screening to allow for safe discontinuation). Screening results from all patients meeting the eligibility requirements will be further assessed by the sponsor medical personnel for final approval of suitability for inclusion in the study. Randomized subjects will enter a 4-week double-blind dose-titration treatment period, followed by a 1-week safety follow-up period following the last dose of study medication, and a scheduled follow-up safety telephone call one week later.

Subjects will be randomized to one of two treatment groups. Group A will receive titrating doses of CX-8998 up to 10 mg BID and Group B will receive placebo. Subject randomization will be stratified by presence or absence of a single concomitant anti-tremor medication and by site-type (sub-study vs non sub-study).

Tremor will be assessed via The Essential Tremor Rating Assessment Scale (TETRAS) and accelerometry. To reduce the potential for bias in the assessments of efficacy, all subjects will be videotaped during the TETRAS performance scale testing according to a consistent script. The videotapes will be rated in a blinded manner by qualified, independent raters. A subset of subjects will participate in an electroencephalography (EEG) and digital biomarker sub-study.

Subjects will be screened up to 4 weeks prior to initiation of dosing. Subjects taking primidone at screening who are otherwise deemed eligible for participation and are willing to discontinue

primidone will be allowed an additional 2 weeks of screening (a total of 6 weeks) to ensure safe primidone discontinuation. At Baseline, subjects will undergo safety and tremor assessments prior to dosing, will receive their first dose of study drug and will be monitored for safety for one hour following dosing. For one week subjects will receive 4 mg (or matching placebo) twice daily. Subjects will return to the clinic on Day 8 for safety monitoring and dose up-titration to 8 mg (or matching placebo) twice daily. At Day 15 (Week 3) subjects will return to clinic for safety and efficacy assessments and final dose up-titration to 10 mg (or matching placebo) twice daily. The final efficacy visit will occur at Day 28 (Week 4). A final safety visit will occur at Day 35 (Week 5). Should subjects experience intolerable adverse events (AEs) at 4 mg BID, 8 mg BID or 10 mg BID, the dose may be decreased at Day 8 or Day 15 to the next lowest dose one time (or 2 mg BID in the case of the 4 mg BID dose). A dose reduction may be made if necessary prior to scheduled visits at Day 8 or Day 15. Re-up-titration is not allowed. Subjects not tolerating the next lowest dose or not tolerating 2 mg BID will be withdrawn from treatment. The Study Safety Representative should be notified as soon as is feasible when a dose reduction is made.

Study Population:

Inclusion Criteria

1. Signed informed consent form (ICF) indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
2. Men or non-pregnant, non-breastfeeding women 18 to 75 years-of-age who are able to read and understand English.
3. Diagnosis of definite or probable bilateral essential tremor (ET) as defined by the Tremor Investigational Group with involvement of the hands and arms without present causes of enhanced physiologic tremor (Deuschl et al., 1998)
4. Diagnosis of ET before the age of 65
5. Tremor severity score of at least 2 in at least one upper extremity on at least one of the three maneuvers on the TETRAS scale
6. Total TETRAS performance score of at least 15. Note: Inclusion thresholds, including thresholds for items 5 & 6, should not be shared with study subjects or caregivers to limit Baseline inflation.
7. One concomitant anti-tremor medication (other than primidone) is allowed. Note: Primidone is NOT an allowed anti-tremor medication. Subjects must have been on a stable dose for at least one month prior to screening and must have no change in dose in the single concurrent anti-tremor medication for the duration of the study. If on primidone, subjects are allowed to extend their screening period by 2 weeks (for a total of 6 weeks) and discontinue primidone under the supervision of the investigator.
8. Able and willing to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
9. Subjects with reproductive capability including all males and women of child-bearing potential (WOCBP) must agree to practice continuous abstinence or adequate contraception methods (appropriate double barrier method or oral, patch, implant, or injectable contraception) from as soon as feasible during screening period until at least 30 days after the last dose (i.e., intermittent abstinence based on “rhythm”, temperature monitoring, or other means of timing is not acceptable). WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy) or is not post-menopausal. Post-menopausal is defined as:

a. Amenorrhea ≥ 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL;
b. Amenorrhea ≥ 12 consecutive months in women ≥ 62 years old (FSH testing is not required).

Male subjects with a partner of child-bearing potential must be surgically sterilized or be willing to use condoms with spermicide from as soon as feasible during screening period until at least 30 days after the last dose.

10. Approval by the sponsor medical personnel as to final suitability for the study

Exclusion Criteria

1. Exposure to tremorigenic drugs or drug withdrawal states within the 30 days prior to the first planned dose of study drug
2. Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor
3. History or clinical evidence of psychogenic tremor origin
4. Known history of other medical or neurological conditions that may cause or explain subject's tremor, including, but not limited to:
   a. Parkinson's disease
   b. dystonia
   c. cerebellar disease, other than essential tremor
   d. Traumatic Brain Injury
   e. alcohol abuse or withdrawal
   f. mercury poisoning
   g. hyperthyroidism
   h. pheochromocytoma
   i. head trauma or cerebrovascular disease within 3 months prior to the onset of essential tremor
   j. multiple sclerosis
   k. polyneuropathy
   l. family history of Fragile X syndrome
5. Prior MR-guided Focused Ultrasound or surgical intervention (e.g., deep brain stimulation, ablative thalamotomy or gamma knife thalamotomy) for treatment of tremor
6. Botulinum toxin injection in the 6 months prior to screening
7. Currently using more than one anti-tremor medication.
8. Experiencing clinical benefit from and/or is not willing to discontinue primidone
9. Use of medication(s) in the past month that might produce tremor or interfere with the evaluation of tremor, such as, but not limited to: CNS-stimulants, lithium, amiodarone, metoclopramide, theophylline, and valproate
10. Inability to refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor on study visit days, such as but not limited to stimulant decongestants, beta-agonist bronchodilators, caffeine, alcohol and tobacco, based on Investigator assessment at baseline
11. Positive urine drug screen (Section 10.1.6)
12. Regular use of more than two units of alcohol per day
13. Sporadic use of a benzodiazepine, sleep medication or anxiolytic to improve sleep performance. Stable use at a consistent dose is allowed as long as tremor persists against the background of regular medication use. Use on the evening prior to a study visit is prohibited.
14. Use of prescription or non-prescription drugs or other products (i.e. grapefruit juice)

known to be strong inhibitors or inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study, including primidone

15. Concurrent illnesses that would be a contraindication to trial participation, including, but not limited to:
    a. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before screening
    b. NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
    c. Clinically significant ECG abnormality per the Investigator assessment or any of the following:
        (1) QTcF >450 msec (males) or >470 msec (females)
        (2) PR interval >250 msec
        (3) Atrioventricular block of second degree or higher, including Mobitz I
        (4) Persistent sinus bradycardia < 50 beats per minute; persistent means the bradycardia is present on the first ECG and on one repeat ECG performed on another day
        (5) For other ECG findings (e.g., including, but not necessarily limited to, tachycardia, bundle branch block, frequent ectopic beats, etc.) the Investigator should send a scanned, identity-blinded copy of the ECG tracing to the Study Safety Representative for review
        (6) The presence of a cardiac pacemaker does not automatically exclude eligibility. The specifics must be discussed with the Study Safety Representative to make a determination of eligibility.
    d. Known infection with HIV, hepatitis B, or hepatitis C, unless curative therapy completed for hepatitis C with negative PCR for HCV RNA
    e. Significant hepatic (AST/ALT > 2X upper limit of normal) or renal disease (creatinine clearance <39 mL/min)
    f. Significant psychiatric history including mood disorders and alcohol or substance abuse within the last year
    g. A current C-SSRS score of 4 or 5 at screening or history of suicide attempt at any time during the past year
    h. Clinically significant impaired balance or is considered at increased risk for falls
    i. Symptomatic orthostatic hypotension
16. Psychological, social, familial, or geographical reasons that would hinder or prevent compliance with the requirements of the protocol or compromise the informed consent process
17. Any other condition and/or situation that causes the Investigator or Study Safety Representative to deem a subject unsuitable for the study (e.g., due to expected study medication non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study–related procedures)
18. Treatment with an investigational agent within 30 days prior to the first dose of CX-8998 or planning to receive an investigational agent during the study

Planned Number of Patients:

Up to 92 subjects will be randomized

Test Product, Dose, and Mode of Administration:

CX-8998, 2 mg capsule, oral

Reference Product, Dose, and Mode of Administration:

placebo capsule to match CX-8998, oral

Duration of Treatment:

28 days

Administration:

CX-8998 will be administered as 4 mg (2 capsules) twice daily (8 mg/d) in the first week; increasing to 8 mg (4 capsules) BID (16 mg/d) in week 2, to a target of 10 mg (5 capsules) BID (20 mg/d) in weeks 3 and 4. Study drug should be administered with food in the morning and evening (goal is for doses to be 12 hours apart).

Duration of Subject Study Participation:

Up to 12 weeks including screening, treatment and safety follow-up

Endpoints:

Primary Endpoint:

Change from Baseline to Day 28 on the TETRAS Performance subscale, as scored by the central rater

Secondary Endpoints:

1. Change from Baseline on the TETRAS Activity of Daily Living subscale to Day 28
2. Change from Baseline to Day 28 in accelerometry score as measured by Kinesia ONE
3. Safety and tolerability endpoints are as follows: adverse events throughout the study, changes from baseline in QTcF and other ECG parameters throughout the study, clinical safety laboratory assessments (clinical chemistry, hematology, and urinalysis) throughout the study, changes from baseline C-SSRS throughout the study, vital signs throughout the study, number (%) of subjects who did not complete the study, number (%) of subjects who did not complete the study due to adverse events and the Epworth Sleepiness Scale (ESS)

Exploratory Endpoints:

1. Change from Baseline on the Total TETRAS score to Day 15 and Day 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. The responder rate (subjects experiencing a decrease of at least 5.5 points on the TETRAS Performance Subscale, as scored by the central rater) from Baseline to Day 15 and Day 28
4. Change from Baseline to Day 15 in accelerometry score 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 Patient Global Impression of Change (PGIC)
7. Treatment success at the end of therapy as measured by Clinical Global Impression of Improvement (CGI-I)
8. Treatment success at the end of therapy as measured by Goal Attainment Scaling (GAS)
9. Change from Baseline in Quality of Life in Essential Tremor Questionnaire (QUEST)
10. Changes in electrophysiological and digital biomarker patterns associated with essential

tremor (in a subset of subjects): electroencephalography (EEG) and optional digital biomarkers (deployment of continuous remote accelerometry and tapping mobile application) in a sub-study of up to 24 subjects (details to be provided in a sub-study addendum)

Pharmacokinetic Variables and Endpoints:

PK measure will be determination of plasma concentration of CX-8998 and its metabolites (M01 and M02) associated with various visits and doses of CX-8998. Concentrations will also be incorporated into a population PK/PD model that will estimate the peak exposure (C_{max}) and overall exposure (AUC) of CX-8998.

Statistical Methods:

Sample size justification:

Up to 92 subjects will be randomized to one of two treatment groups: Placebo and CX-8998. Based on similarly designed studies, this sample size should be sufficient to provide preliminary safety and efficacy information on CX-8998 when administered according to this protocol.

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 in the TETRAS performance subscale when the standard deviation is 7.5 and alpha=0.05 (PASS 2008: Two sample t-test – Normal Non-Parametric Adjustment). Up to 92 subjects will be enrolled, in order to ensure that 86 subjects are available for inclusion in the efficacy analyses.

Primary efficacy analysis:

The primary efficacy analysis of the TETRAS performance subscale will be conducted using an analysis of covariance (ANCOVA) model with fixed effects for treatment, concomitant anti-tremor medication use, site type and Baseline value of the TETRAS performance subscale. The primary hypothesis to be tested will be if the mean change from Baseline in TETRAS performance scale indicates that the CX-8998 arm is different from placebo. All testing will be performed using the LSMeans from the ANCOVA model and a two-sided test at the alpha=0.05 level of significance. If the data indicate a departure from the normal distribution, a corresponding rank test will be performed.

Secondary efficacy analyses:

The secondary endpoints of change from Baseline to Day 28 in accelerometry score as measured by Kinesia ONE, change from Baseline on the TETRAS Activity of Daily Living subscale, and change from Baseline in the ESS will be analyzed using the same type of ANCOVA model as described for the primary endpoint. The PGIC and CGI-I will be analyzed by similar models. All secondary and exploratory analyses will be conducted using two-sided tests at the alpha=0.05 level of significance.

The proportion of subjects experiencing at least a 5.5 point decrease in the TETRAS performance scale will be summarized by treatment group. Differences between the treatment groups will be assessed with Cochran-Mantel-Haenszel General Association test stratified by concomitant anti-tremor medication use and site type.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

GLOSSARY OF TERMS AND ABBREVIATIONS

Abbreviation	Description
ADL	activity(ies) of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	Area under the concentration-time curve
β-HCG	beta human chorionic gonadotropin
BMI	body mass index (kg/m^2)
BP	Sitting systolic and diastolic blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CI	confidence interval
CNS	central nervous system
C_{max}	maximum concentration
C_{min}	minimum concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
dL	deciliter
ECG	electrocardiogram
EEG	electroencephalogram
ESS	Epworth Sleepiness Scale
ET	essential tremor
F	Fahrenheit
GAS	Goal Attainment Scale
GCP	Good Clinical Practice
GRC	Global Rating of Change (scale)
h	hour(s)
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
ICF	Informed Consent Form

ICH	International Conference on Harmonisation
IO	inferior olive
IRB	Institutional Review Board
ITT	intent-to-treat population
IV	intravenous
IWRS	interactive web response system
kg	kilogram
LDH	lactic dehydrogenase
MEG	magnetoencephalography
µg	microgram
mg	milligram
mL	milliliter
mM	millimolar
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHV	normal healthy volunteers
PCR	polymerase chain reaction
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
RNA	ribonucleic acid
QOL	quality of life
QUEST	Quality of Life in Essential Tremor Questionnaire
SAE	serious adverse event
SD	standard deviation
SWA	slow wave activity
Vd	Volume of distribution
$t_{1/2}$	terminal half life
TEAE	treatment emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
T_{max}	time to maximum concentration

1 Background Information and Rationale

1.1 Introduction

1.1.1 Essential Tremor

Essential tremor (ET) is a neurological condition that causes a rhythmic trembling of the hands, head, voice, legs or trunk.

The consensus statement of the Movement Disorder Society on tremor (Deuschl et al., 1998) includes the following clinical criteria for the diagnosis of ET: bilateral postural tremor with or without kinetic tremor, involving hands and forearms, that is both visible and persistent without:

1. Other abnormal neurological signs (except Froment's sign);
2. Known causes of increased physiological tremor;
3. Concurrent or recent exposure to tremorigenic drugs or the presence of a drug withdrawal state;
4. Direct or indirect trauma to the nervous system within 3 months before the onset of tremor;
5. Historical or clinical evidence of psychogenic origins, and
6. Convincing evidence of sudden onset or evidence of stepwise deterioration.

1.1.2 The Impact of Essential Tremor

Essential Tremor is among the most prevalent of all movement disorders in adults. In a 2010 meta-analysis, Louis et al. (1998) estimated the pooled prevalence (all ages) to be 0.9%, with statistically significant heterogeneity across studies ($I2 = 99\%$, $p<0.001$). The prevalence in adults ≥65 years old was estimated to be 4.6% (Louis and Ferreira, 2010).

While ET does not shorten life expectancy, its impact on the patient's ability to perform activities of daily living (ADLs) at home and in the work place negatively affects quality of life, social interactions, and mental status (Lorenz et al., 2006; Louis & Machado, 2015; George and Lydiard, 1994). It is increasingly recognized that ET is not a monosymptomatic disorder (Bermejo-Pareja, 2011). Effects include everyday activities such as writing and eating (Zesiewicz et al., 2011). Effects on cognitive functions are heterogeneous and include impairments in attention, executive function, verbal fluency, visuospatial functioning, memory, and working memory (Bermejo-Pareja & Puertas-Martin, 2012). Sleep disturbances and fatigue are also more common in patients with ET than in their age-matched controls (Chandran et al., 2012).

1.1.3 Treatment of Essential Tremor

Propranolol is the only medication approved for the treatment of ET. None of the other medications currently used as ET therapy were developed specifically for this purpose. In 2011, the American Academy of Neurology (AAN) conducted an evidence-based update of the AAN 2005 practice parameters regarding the treatment of ET (Zesiewicz et al., 2011). The following conclusions and recommendations were unchanged from the 2005 guideline:

- Propranolol, primidone (Level A, established as effective);
- Alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate (Level B, probably effective);
- Nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation (DBS), thalamotomy (Level C, possibly effective), and
- Gamma knife thalamotomy (Level U, insufficient evidence).

Changes to conclusions and recommendations from the previous guideline include the following:

- Levetiracetam and 3,4-diaminopyridine probably do not reduce limb tremor in ET and should not be considered (Level B);
- Flunarizine possibly has no effect in treating limb tremor in ET and may not be considered (Level C), and
- There is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozapine as treatment for ET (Level U).

Alternatives to medications include invasive surgical treatments (DBS and gamma-knife thalamotomy), non-invasive MR-guided Focused Ultrasound, botulinum toxin, and alcohol (alcohol is associated with habituation and rebound effects; in fact, patients with essential tremor demonstrate higher rates of alcoholism (Schroeder, 1982).

The lack of any new positive recommendations by the 2011 Academy of Neurology evidence-based guideline update on the treatment of ET (as compared to the 2005 guidelines) attests to the poor yield of present approaches to drug discovery (Zesiewicz et al., 2011). Given that half of the patients with ET ≥65 years of age take medication for tremor (Louis et al., 2000) and the 2012 demographic data showed that of the 1,006.9 million persons living in the European Union, the United States, Japan, Canada, Australia, and New Zealand, 163.7 million persons are ≥65 years of age, it can be estimated that 3.8 million persons in this age group in these countries are potential candidates for treatment of ET.

A survey of 223 patients (52.7% male, mean age of 63.4 (±17.9) years of age at last visit) in a clinical database revealed that 70.9% had taken primidone or propranolol, and 56.3% had discontinued one or both medications (Diaz & Louis, 2010). Reasons for discontinuing primidone included side effects (51.9%), lack of efficacy (19.0%), or both (20.3%). Because approximately 30%-50% of patients with ET will not respond adequately to currently available medications (Koller & Vetere-Overfield, 1989), new therapies for ET are warranted.

1.2 Rationale for Evaluating CX-8998 in Essential Tremor

1.2.1 Cav3 and its Role in Neurological Disorders with Excessive or Abnormal Rhythmicity

Calcium is a ubiquitous intracellular second messenger critical for cellular functions. The elevation of free intracellular Ca^{2+} levels triggers various responses including the activation of Ca^{2+} dependent enzymes, the secretion of neurotransmitters, and muscle contraction.

Multiple calcium ion channels regulate calcium influx in response to membrane depolarization, voltage changes, or substrate, which include the pore-forming alpha1 subunit Cav3 channel (Catterall, 2005; Adams & Snutch, 2007).

The T-type calcium channel, Cav3, its three (3) isoforms (3.1, 3.2 and 3.3), and their genes *CACNA1G, CACNA1H, and CACNA1I* were discovered and cloned in the early 1990s, where their function as low-threshold, voltage-gated calcium channel was elucidated (Cribbs et al., 1998). T-type ("T" is for transient) calcium channels are low voltage-activated (LVA) channels predominantly found in neurons. As stated previously, a unique and discriminating property of T-type channels (Cav3) is their ability to activate upon small depolarization of the membrane, contributing to the setting of the resting membrane potential and allowing a surge of calcium entry into excitable cells at the beginning of an action potential. In pathologic states, Cav3 is either upregulated or found to have increased activity, becoming a selective target for specific neurologic diseases (Tai et al., 2011; Park et al., 2010; Bourinet et al., 2005).

Cav3's isoforms are expressed throughout the central nervous system (CNS) and the peripheral nervous system (PNS), including the thalamocortical pathway[1] (Ertel et al., 2000). Deep cerebellar nuclei (DCN), Substantia nigra (SNC), Globus pallidus externa (Gpe), globus pallidus interna (GPi), subthalamic nucleus (STN), have been noted to have oscillations in healthy hosts and excessive rhythmicity in animals and humans with pathologic conditions of the nervous system. It has been discovered that Cav3 is a mediator of subthreshold oscillations and excessive rhythmicity in pathophysiologic states found in tremor, neuropathic pain, epilepsy and Parkinson's disease (Handforth et al., 2005; Llinás et al., 1999; Llinás, 2003; Park et al., 2013).

The inferior olive (IO) appears to function as a tremor generator and animal models suggest the IO functions as an intrinsic pacemaker (Long et al., 2002). Essential tremor may result from excessive rhythmic synchronous firing of populations of neurons in the IO, which affects the function of the cerebellum (Elble et al., 1996). Cav3 is highly expressed in the IO and the cerebellum. Cav3.1 is the predominate Cav3 isoform expressed in the inferior olive (IO). Within the cerebellar system it is also found on Purkinje cell bodies, DCN, stellate, basket, dendrites and Golgi cells (Molineux et al., 2006). In these locations, Ca_V3 functions as a tremor generator and ongoing rhythm pacemaker (Park et al., 2010). Park et al. reported that tremor-related oscillations in the olivocerebellar pathways are a neural signature for essential tremor and that $Ca_V3.1$ plays a critical role in the onset of tremor-related rhythms (Park et al., 2010).

Harmaline, a plant alkaloid that acts on the cerebellum and IO, induces tremor in animals. Harmaline-induced tremor in animals, like ET, involves the cerebellum. Lesions of the IO reduce harmaline tremors in rats (Simantov et al., 1976). Harmaline tremor is similar to clinical ET in a number of respects, including cerebellar hypermetabolism and a positive response to all known anti-ET agents, including alcohol, primidone, propranolol, gabapentin, zonisamide, and benzodiazepines.

1.2.2 Cav3 Antagonists in Animal Studies

Multiple Cav3-active compounds have been successfully evaluated for their impact on tremor in animal studies. Handforth et al. tested whether both clinically available and

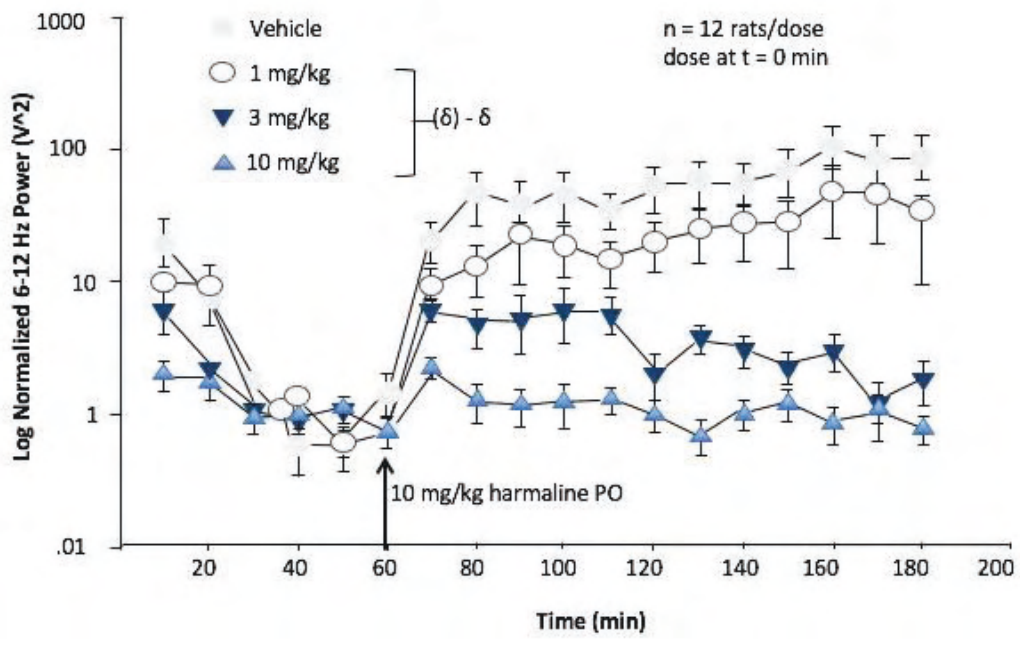
[1] Cav3.1 is the most common isoform in the thalamocortical pathway

experimental compounds that antagonize T-type calcium channel currents suppress tremor in two mouse models: harmaline-induced tremor and the GABA(A) receptor α1 subunit-null model. Mice were administered ethosuximide, zonisamide, the neuroactive steroid ECN, the 3,4-dihydroquinazoline derivative KYS05064, the mibefradil derivative NNC 55-0396, or vehicle. Tremor was measured using digitized spectral motion power analysis. In non-sedating doses, each compound reduced tremor in the harmaline-induced model by at least 50% (range of maximal suppression: 53-81%), and in the GABA(A) α1-null model by at least 70% (range 70-93%) (Handforth et al., 2010). Quesada et al. evaluated both mibefradil and NNC-55-0396 in the $GABA_{A1}$ null model and harmaline animal models of tremor and observed reductions in tremor (Quesada et al., 2011).

Tremor suppression by alcohol has been remarked on since the 19th century. Suppression of harmaline tremor by ethanol has been well replicated (Martin et al., 2005; Rappaport et al., 1984). Isomers of octanol (a fatty alcohol) suppress harmaline tremor in rodents (Martin & Handforth, 2006; Sinton et al., 1989); subsequently 1-octanol was found to reduce tremor in ET (Shill et al., 2004). Gamma-hydroxybutyrate also suppresses harmaline tremor and ET tremor (Frucht et al., 2005; Paterson et al., 2009). 1-octanol functions as a Cav3 antagonist (Sinton et al. 1989).

Finally, CX-8998's analogue TTA-A2 has been evaluated in the harmaline model of tremor and demonstrated significant improvement (Figure 1). Rats were placed in one of four conditions, vehicle, versus TTA-A2 1mg/kg, 3mg/kg, or 10mg/kg. TTA-A2 normalized both physiologic tremor prior to harmaline administration and harmaline-induced tremor in a dose-dependent response (Shipe et al., 2008).

Figure 1 TTA-A2 Normalization of Harmaline Tremor in Rats



Rats assigned to vehicle or one of three ascending doses of TTA-A2 demonstrated a dose-dependent response to harmaline-induced tremor following *per os* administration. Prior to administration of harmaline, rats also demonstrated dose-dependent response to a reduction in physiologic tremor (Shipe et al., 2008).

1.2.3 Ca_V3 as a Target for Treatment of Essential Tremor: Clinical Experience

A number of T-type calcium channel-active compounds have been developed to treat various neurologic diseases which may share a common pathophysiology.

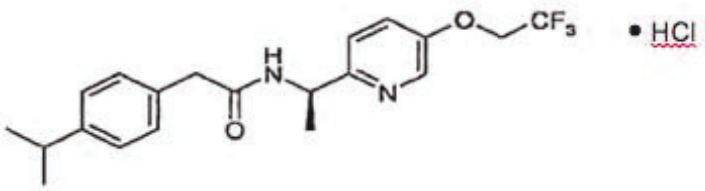
Multiple studies of zonisamide have shown effectiveness in the treatment of tremor as measured by accelerometry and tremor rating scales, however all were limited by poor tolerability and/or excessive premature discontinuations from treatment (Handforth et al., 2009; Zesiewicz et al., 2009; Morita et al., 2005; Bermejo-Pareja et al., 2008; Ondo, 2007; Miwa, 2008) [redacted]

1.3 Non-Clinical Pharmacology

Please refer to the current edition of the Investigator Brochure for a full discussion of prior non-clinical evaluations of CX-8998. CX-8998 is the new name applied to the Merck & Co., Inc. pharmaceutical product known as MK-8998. The name MK-8998 is used here in reference to all prior non-clinical studies conducted by Merck & Co., Inc. CX-8998 was previously investigated for the treatment of insomnia and schizophrenia.

[redacted]

Figure 2 Chemical Structure of CX-8998



[redacted]

In vivo pharmacology studies of CX-8998 in rodent and non-human primate sleep architecture have demonstrated dose-dependent increases in slow wave sleep early in the sleep period, followed by a significant increase of rapid eye movement (REM) late in the sleep period. There was also a significant suppression in REM early in the sleep period.

CX-8998 at doses of 1 mg/kg, 3 mg/kg and 10 mg/kg was also shown to dose-dependently inhibit both seizure duration and frequency in a single-dose rat model of absence epilepsy. Additional T-type antagonists from at least five structurally diverse series have shown similar efficacy in this model.

1.3.1 Safety Pharmacology Studies

[redacted]

1.4 CX-8998 Clinical Experience

Please refer to the current edition of the Investigator Brochure for a full discussion of prior clinical evaluations of CX-8998. CX-8998 is the new name applied to the Merck & Co., Inc. pharmaceutical product known as MK-8998. The name MK-8998 is used here in reference to all prior clinical studies conducted by Merck & Co., Inc.

[redacted]

[redacted]

1.4.1 Clinical Pharmacokinetics

[redacted]

[redacted]

1.4.2 Clinical Pharmacodynamics

[redacted]

[redacted]

In the current study for essential tremor, a subset of subjects will undergo EEG evaluation to obtain additional pharmacodynamic data pertaining to CX-8998.

1.4.3 Clinical Safety

[redacted]

1.5 Rationale for Selected Dose

[redacted]

In summary, non-clinical and clinical data from five studies in 194 subjects support the proposed study design with twice-daily doses up to 10 mg BID (20 mg total daily) with a 12 hour dosing interval at fed state with frequent safety assessments, on-site dose titration and pre-specified up- and down-titration rules.

2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the efficacy of CX-8998, in doses up to 20 mg per day (10 mg BID), in reducing the severity of essential tremor.

2.2 Secondary Objectives

1. To assess the effects of CX-8998 on tremor-affected activities of daily living.
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 two primary metabolites (M01 and M02) in plasma.

2.3 Exploratory Objectives

1. To assess changes in quality of life
2. To use the concentrations of CX-8998 and its 2 primary metabolites in plasma in population pharmacokinetic/pharmacodynamic (PK/PD) analyses to evaluate the exposure-response and exposure-safety relationships
3. To assess study drug effects on electrophysiological and digital biomarker patterns associated with essential tremor (in a subset of subjects). Sub-study analyses will be reported in an addendum to the study report.

3 STUDY DESIGN AND ENDPOINTS

3.1 Study Type

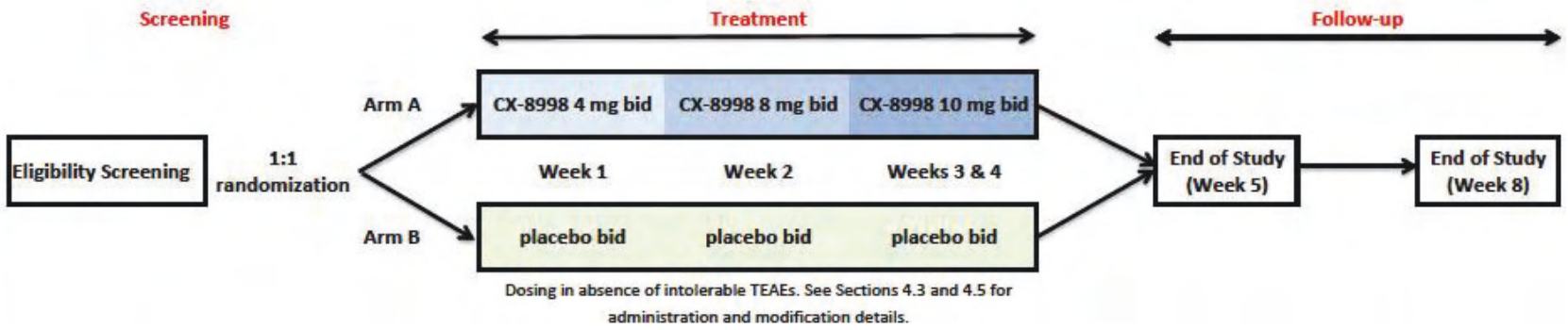
This is a Phase 2, multicenter, double-blind, placebo-controlled, parallel-group study consisting of a screening period of up to 4 weeks (with the exception of subjects on primidone at baseline who will be allowed 6 weeks of screening to allow for safe discontinuation), a 4-week randomized double-blind dose-titration treatment period, a 1-week safety follow-up period following the last dose of study medication, and a scheduled follow-up safety telephone call one week later.

Subjects will be randomized to one of two treatment groups. Group A will receive titrating doses of CX-8998 up to 10 mg BID and Group B will receive placebo. Subject randomization will be stratified by presence or absence of a single concomitant anti-tremor medication and by site-type (sub-study vs. non sub-study).

3.2 Schematic Study Design

The study design schematic is shown in Figure 5.

Figure 5 Schematic Study Design



3.3 Endpoints

3.3.1 Primary Endpoint

The change from Baseline to Day 28 on the TETRAS Performance subscale, as scored by the central rater

3.3.2 Secondary Endpoints

1. Change from Baseline on the TETRAS Activity of Daily Living subscale to Day 28
2. Change from Baseline to Day 28 in accelerometry score, as measured by Kinesia ONE
3. Safety and tolerability endpoints:
    a. adverse events,
    b. changes from baseline in QTcF and other ECG parameters,
    c. clinical safety laboratory assessments (clinical chemistry, hematology, and urinalysis),
    d. C-SSRS
    e. Epworth Sleepiness Scale (ESS),
    f. vital signs,
    g. number (%) of subjects who did not complete the study,
    h. number (%) of subjects who did not complete the study due to adverse events.

3.3.3 Exploratory Endpoints

1. Change from Baseline on the Total TETRAS score to Day 15 and Day 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. The responder rate (subjects experiencing a decrease of at least 5.5 points on the TETRAS Performance Subscale, as scored by the central rater) from Baseline to Day 15 and Day 28
4. Change from Baseline to Day 15 in accelerometry score 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 Patient Global Impression of Change (PGIC)
7. Treatment success at the end of therapy as measured by Clinical Global Impression of Improvement (CGI-I)
8. Treatment success at the end of therapy as measured by Goal Attainment Scaling (GAS)
9. Change from Baseline in Quality of Life in Essential Tremor Questionnaire (QUEST)

10. Changes in electrophysiological and digital biomarker patterns associated with essential tremor: electroencephalography (EEG) and optional digital biomarkers (deployment of continuous remote accelerometry and tapping mobile application) in a sub-study of up to 24 subjects (details to be provided in a sub-study addendum)

4 STUDY DRUG

4.1 Supply and Storage

CX-8998 will be supplied as 2 mg capsules. Placebo capsules will be matched for CX-8998 capsules and will be indistinguishable from CX-8998 capsules. All manufacturing and packaging activities will be performed according to cGMP guidelines.

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

Supplies of study drug should be stored below 30° C.

4.2 Packaging and Labeling

Study medication will be supplied in 60 cc white HDPE bottles with 33 mm polypropylene, white, child-resistant closures. Each subject will receive a kit with two bottles of active drug or placebo capsules. In each kit, one bottle will contain 80 capsules and the second bottle will contain 150 capsules. The bottles will be appropriately labeled. The affixed label will have spaces for entering the subject number, subject initials, and date dispensed. At the time of dispensing, the subject number, subject initials, and date dispensed are entered onto the appropriate lines on the label.

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

- Protocol number: CX-8998-CLN2-001
- Expiration date
- Lot number
- Storage conditions
- The sentence, “Caution: New Drug – Limited by Federal Law to Investigational Use”
- Name and address of the Sponsor

4.3 Administration

CX-8998 (or placebo) will be administered as 4 mg (2 capsules) twice daily (8 mg/d) in the first week; increasing to 8 mg (4 capsules) BID (16 mg/d) in week 2, to a target of 10 mg (5 capsules) BID (20 mg/d) in weeks 3 and 4.

[redacted]

[redacted]

Treatment compliance will be assessed based on return of unused drug.

Subjects experiencing specified adverse events will have their dose adjusted. See Section 4.5 for details on dose adjustments.

4.3.1 Stopping Rules

Study drug dosing for an individual subject will be permanently discontinued for intolerable AEs that do not resolve to Grade 1 or Baseline within 48 hours of suspension of dosing, and for all Grade 4 AEs. Other reasons for treatment termination are provided in Section 6.4.

4.4 Study Drug Accountability and Compliance

Subjects will be instructed to return all used empty bottles and unused study drug at each visit.

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

Sites will keep a current log of drug accountability recording:

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

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

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

The Sponsor's designated Monitor must verify all accountability records during periodic monitoring visits. Unused and used study drug must be stored on site until such

accountability has taken place and authorization is received from the Sponsor or Sponsor's designee that the study drug may be returned or destroyed.

To stay in the study, subjects will be required to have taken at least 75% of their study treatment doses. A subject will be considered non-compliant if they have missed more than 25% of the required doses between visits. The minimum number of required doses per 7 days is detailed below:

- Week 1: 11/14 doses (22 capsules)
- Week 2: 11/14 doses (44 capsules)
- Week 3 to 4: 21/28 doses (105 capsules)

If compliance is less than 75% or greater than 125% at any visit, the reason(s) must be noted and the subject's continued participation in the study should be discussed with the Study Safety Representative. Subjects should not make up for missed doses.

4.5 Dose Adjustments / Toxicity Management

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

Dosing will be discontinued for all Grade 4 AEs.

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

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

Table 2 Study Drug Dose Reduction for Intolerable AEs

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

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

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

4.6 Overdose Management

To date, no overdoses of CX-8998 in humans have occurred.

Because no humans have overdosed with CX-8998, specific information regarding treatment of overdose is not currently available. In case of an acute overdose, it is recommended that the stomach be emptied and oral gavage with activated charcoal be used to help reduce absorption of CX-8998. In the event of an overdose, the Study Safety Representative should be contacted immediately.

4.7 Randomization and Matching of Subjects

Eligible subjects will be randomized in a 1:1 ratio between CX-8998 and placebo, using an Interactive Web Response System (IWRS). Subject randomization will be stratified by concomitant use of an anti-tremor medication and site type (sub-study vs. non sub-study). A statistician not involved in the day-to-day study operation will create the randomization schedule. Details of the randomization process will be included in the study Operations Manual.

4.8 Study Blinding

This is a double-blind study; that is, the treatment assignment and drug contents are not revealed to the Sponsor, the subject and or investigator and other study personnel.

Maintenance of the double-blind is critical to the integrity of this clinical study. 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 for that subject may be broken by the treating Investigator.

Before breaking the blind for an individual subject, the Investigator should have determined that the information is necessary, i.e., it will alter the immediate management of the subject's care. *In the majority of cases not involving pregnancy, because there is no known specific antidote for any potential pharmacodynamic or toxic effect of CX-8998, there should rarely be a need to unblind a subject to guide immediate medical management of an emergency.*

The need to break the blind should first be discussed with the Sponsor's Study Safety Representative, if at all possible. In case of an emergency, the Investigator may use the Emergency Unblinding Function under the Randomization side menu in the IWRS. Once the decision to unblind has been made, the Investigator must record the nature of the emergency that required the unblinding, along with the date and time of the unblinding, in the proper source documentation and notify the Sponsor's Study Safety Representative of the unblinding. However, the Sponsor's Study Safety Representative, and any other Investigators, must not be informed of the treatment assignment. The treatment assignment must not be noted in the source documentation or any other documentation submitted to the Sponsor.

Study treatment for a given subject may be unblinded for reportable safety events (e.g., suspected unexpected serious adverse reaction [SUSAR]) as required by local or other regulations, but the mere occurrence of an SAE should not routinely precipitate immediate unblinding.

In cases of accidental unblinding, the Investigator will notify the Sponsor's Study Safety Representative and ensure that every attempt to preserve the blind is made. Specifically, the Investigator will not reveal the identity of the study treatment to the Sponsor's Study Safety Representative or other Sponsor staff, any Contract Research Organization (CRO) staff including the clinical site staff, Clinical Research Associate (CRA), subject, or anyone else who does not already know this information.

If unblinding occurs, the study drug must be discontinued for the particular subject(s) involved.

5 INVESTIGATORS, SITES AND DURATION

5.1 Investigators and Sites

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

5.2 Central Reviewers

A central reviewer will review eligibility criteria for all subjects. The site will submit an eligibility checklist for evaluation of each subject. A central reader will score the screening TETRAS performance video to determine if the subject meets Inclusion Criteria 5 and 6 below. No subject may be enrolled, randomized or dosed with study drug prior to receipt of notification that the central reviewer and review process has deemed the subject eligible.

5.3 Duration of Study

Subjects will participate for a total of up to 12 weeks, including screening, the 4-week treatment period and follow-up.

5.4 Termination of Study

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

6 STUDY POPULATION

6.1 Number of Subjects

Up to 92 eligible subjects will be randomized to treatment.

6.2 Inclusion Criteria

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

1) Signed informed consent form (ICF) indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
2) Men or non-pregnant, non-breastfeeding women 18 to 75 years-of-age who are able to read and understand English.
3) Diagnosis of definite or probable bilateral essential tremor (ET) as defined by the Tremor Investigational Group with involvement of the hands and arms without present causes of enhanced physiologic tremor (Deuschl et al., 1998).
4) Diagnosis of ET before the age of 65
5) Tremor severity score of at least 2 in at least one upper extremity on at least one of the three maneuvers on the TETRAS scale.
6) Total TETRAS performance score of at least 15 (Note: Inclusion thresholds, including thresholds for criteria 5 & 6 shall NOT be shared with study subjects or caregivers to limit Baseline inflation.)
7) One concomitant anti-tremor medication (other than primidone) is allowed. Subjects must have been on a stable dose for at least one month prior to screening and must have no change in dose in the single concurrent anti-tremor medication for the duration of the study. Note that primidone is NOT an allowed anti-tremor medication. If on primidone, subjects are allowed to extend their screening period by 2 weeks (for a total of 6 weeks) and discontinue primidone under the supervision of the investigator.
8) Able and willing to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
9) Subjects with reproductive capability including all males and women of child-bearing potential (WOCBP) must agree to practice continuous abstinence or adequate contraception methods (appropriate double barrier method or oral, patch, implant, or injectable contraception) from as soon as feasible during screening period until at least 30 days after the last dose (i.e., intermittent abstinence based on “rhythm”, temperature monitoring, or other means of timing is not acceptable). WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy) or is not post-menopausal. Post-menopausal is defined as:
    a) Amenorrhea ≥ 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL;
    b) Amenorrhea ≥ 12 consecutive months in women ≥ 62 years old (FSH testing is not required).

    Male subjects with a partner of child-bearing potential must be surgically sterilized or be willing to use condoms with spermicide from as soon as feasible during screening period until at least 30 days after the last dose.

10. Approval by the sponsor medical personnel as to final suitability for the study

6.3 Exclusion Criteria

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

1) Exposure to tremorigenic drugs or drug withdrawal states within the 30 days prior to the first planned dose of study drug
2) Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor
3) History or clinical evidence of psychogenic tremor origin
4) Known history of other medical conditions that may cause or explain subject's tremor, including, but not limited to:
    a) Parkinson's disease
    b) dystonia
    c) cerebellar disease, other than essential tremor
    d) Traumatic Brain Injury
    e) alcohol abuse or withdrawal
    f) mercury poisoning
    g) hyperthyroidism
    h) pheochromocytoma
    i) head trauma or cerebrovascular disease within 3 months prior to the onset of essential tremor
    j) multiple sclerosis
    k) polyneuropathy
    l) family history of Fragile X syndrome
5) Prior MR-guided Focused Ultrasound or surgical intervention (e.g., deep brain stimulation, ablative thalamotomy or gamma knife thalamotomy) for treatment of tremor
6) Botulinum toxin injection in the 6 months prior to screening
7) Currently using more than one anti-tremor medication
8) Experiencing clinical benefit from and/or is not willing to discontinue primidone
9) Use of medication(s) (in the past month) that might produce tremor or interfere with the evaluation of tremor, such as but not limited to: CNS-stimulants, lithium, amiodarone, metoclopramide, theophylline, and valproate
10) Inability to refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor on study visit days, such as but not limited

to stimulant decongestants, beta-agonist bronchodilators, caffeine, alcohol and tobacco, based on Investigator assessment at baseline

11) Positive urine drug screen (phencyclidine (PCP), cocaine, cannabinoids, opiates/barbiturates, benzodiazepines, amphetamines, methadone or MDMA (ecstasy))

12) Regular use of more than two units of alcohol per day. See Section 7.3.2 for definitions.

13) Sporadic use of a benzodiazepine, sleep medication or anxiolytic to improve sleep performance. Stable use at a consistent dose is allowed as long as tremor persists against the background of regular medication use. Use on the evening prior to a study visit is prohibited.

14) Use of prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be strong inhibitors or inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study, including primidone

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

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

    b) NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure

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

        i) QTcF >450 msec (males) or >470 msec (females)

        ii) PR interval >250 msec

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

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

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

        vi) The presence of a cardiac pacemaker does not automatically exclude eligibility. The specifics must be discussed with the Study Safety Representative to make a determination of eligibility.

    d) Known infection with HIV, hepatitis B, or hepatitis C, unless curative therapy completed for hepatitis C with negative PCR

    e) Significant hepatic (AST/ALT > 2X upper limit of normal) or renal disease (creatinine clearance <39 mL/min)

f) Significant psychiatric history including mood disorders and alcohol or substance abuse within the last year

g) A current C-SSRS score of 4 or 5 at screening, or history of suicide attempt at any time during the past year

h) Clinically significant impaired balance or is considered at increased risk for falls

i) Symptomatic orthostatic hypotension

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

17) Any other condition and/or situation that causes the Investigator to deem a subject unsuitable for the study (e.g., due to expected study medication non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study–related procedures)

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

6.4 Withdrawal of Subjects and/or Discontinuation of Treatment

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

1) Withdrawal of subject consent

2) Subject is lost to follow-up

3) Investigator determines that withdrawal from the study is in the best interest of the subject.

4) Subject is non-compliant with protocol-mandated activities.

5) Occurrence of any intercurrent condition, injury, or disease that becomes apparent during the study and necessitates the termination of the subject from the study.

6) Administrative reason (e.g., termination of the clinical study by a Regulatory Agency or the Sponsor)

A subject should be discontinued from treatment for any of the following:

1) Subject is not at least 75% compliant with study drug administration at any study visit (Section 4.4.)

2) Occurrence of defined unacceptable toxicity (Section 4.5)

3) Investigator determines that discontinuation of treatment is in the best interest of the subject.

4) Occurrence of any intercurrent condition, injury, or disease that becomes apparent during the study and necessitates the discontinuation of treatment.

5) Pregnancy

6) Subject requires use of prohibited concurrent medication

7) Subjects answering "yes" to Suicidal Ideation item 4 or 5 on the C-SSRS during the study must be withdrawn from the study treatment. Investigators should also withdraw subjects from treatment if, in the judgment of the Investigator, the subject develops other indicators of significant risk of suicide. In the event that suicidal ideation is observed in any study subject, the Investigator will manage the situation as he/she deems medically and psychiatrically appropriate.

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

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

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

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

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

6.4.2 Procedures for Replacing Subjects Who Withdraw/Discontinue Prematurely

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

7 TREATMENT PLAN AND METHODS

7.1 Schedule of Assessments

Table 3 Schedule of Assessments

	Procedure		TREATMENT PERIOD					
	Visit	Screen	Visit 1 Baseline	Visit 2	Visit 3	Visit 4	EOS	FU (telephone)
	Study Day (window)	-28 to 0	1	8 (±2)	15 (±2)	28 (-1)	35 (±2)	56 (±2)
	End of week		-	1	2	4	5	8
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	Pharmacokinetic sampling			X	X	X		
22	Pharmacogenomic sampling		X					
23	Prior/Concomitant medications	X	X	X	X	X	X	
24	AE review	X	X	X	X	X	X	X
25	Study drug administration in clinic		X	X	X	X		
26	Dosing		X					
27	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

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 (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 anytime 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.
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. (Section 8.1.1)
13. The Kinesia ONE device will be worn in the clinic after execution of the TETRAS Performance subscale assessment.. (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. (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. 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)
22. A sample for pharmacogenomic testing will be collected in all subjects except where prohibited by local regulation. (Section 9.3)
23. 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.
24. AEs will be collected from signature of the ICF through the Follow-up telephone call on Day 56 (Section 10.2.2). Adverse events will be followed for resolution in accordance with Section 10.2.3.
25. 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.)
26. 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.).
27. Compliance will be assessed via pill counts. (Section 4.4.)

7.2 Summary of Treatment Visits

7.2.1 Screening

The Screening visit must be performed within 28 days of Visit 1/Baseline. Subject informed consent must be obtained prior to initiation of any study specified procedures. Subjects who are taking primidone at screening who are otherwise deemed eligible for participation and are willing to discontinue primidone will be allowed an additional 2 weeks of screening (a total of 6 weeks) to ensure safe primidone discontinuation. A central reviewer will confirm the TETRAS-related eligibility criteria prior to randomization. Screening results from all patients meeting the eligibility requirements will be further assessed by the sponsor medical personnel for final approval of suitability for inclusion in the study. Details of the eligibility review will be provided in the study Operations Manual. See Table 3 for a detailed list of assessments to be performed.

7.2.2 Visit 1 (Day 1 - Baseline)

Subjects will return to the clinic within 28 days of screening (or 42 days in the case of those with extended screening due to discontinuation of primidone.) Following confirmation of continued eligibility and randomization, subjects will receive the first dose of study drug (4 mg or placebo) and undergo safety and efficacy assessments as detailed in Table 3. Subjects will be followed for adverse events, orthostatic VS, and one ECG for at least 2 hours prior to discharge. The Investigator or qualified designee will make the determination whether it is safe to release the subject from the clinic. Subjects will be instructed to take the second daily dose of study drug no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the time of their first dose, and to continue taking 4 mg (or placebo) twice daily for the following week (see Administration details in Section 4.3).

7.2.3 Visit 2 (Day 8 – End of Week 1)

Subjects will return to the clinic for assessments as detailed in Table 3. Subjects will have withheld their morning dose of study drug.

If the subject has been at least 75% compliant with the study drug regimen (as detailed in Section 4.4) and has not experienced any intolerable adverse events (as described in Section 4.5), the dose of study drug will be increased to 8 mg (or placebo) twice daily for the following week. If compliance is determined to be less than 75%, up-titration should be discussed with the Study Safety Representative.

Subjects will receive the first 8 mg dose of study drug (or placebo) and undergo safety assessments. Subjects will be followed for adverse events, orthostatic VS, and one ECG for at least 2 hours prior to discharge. The Investigator or qualified designee will make the determination whether it is safe to release the subject from the clinic. Subjects will be instructed to take the second daily dose of study drug no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the

time of their first dose, and to continue taking 8 mg (or placebo) twice daily for the following week (see Administration details in Section 4.3).

7.2.4 Visit 3 (Day 15 – End of Week 2)

Subjects will return to the clinic for assessments as detailed in Table 3. Subjects will have withheld their morning dose of study drug.

If the subject has been at least 75% compliant with the study drug regimen (as detailed in Section 4.4) and has not experienced any intolerable adverse events (as described in Section 4.5), the dose of study drug will be increased to 10 mg (or placebo) twice daily for the following two weeks. If compliance is determined to be less than 75%, up-titration should be discussed with the Study Safety Representative.

Subjects will receive the first 10 mg dose of study drug (or placebo) and undergo safety and efficacy assessments. Subjects will be followed for adverse events, orthostatic VS, and one ECG for at least 2 hours prior to discharge. The Investigator or qualified designee will make the determination whether it is safe to release the subject from the clinic. Subjects will be instructed to take the second daily dose of study drug no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the time of their first dose, and to continue taking 10 mg (or placebo) twice daily for the following two weeks (see Administration details in Section 4.3).

7.2.5 Visit 4 (Day 28 – End of Week 4)

Subjects will return to the clinic for assessments as detailed in Table 3. Visit 4 is the end-of-dosing visit. Subjects will have withheld their morning dose of study drug. Subjects will receive the final dose of study drug (10 mg or placebo) and undergo safety and efficacy assessments.

Visit must occur on or one day before Day 28 to ensure that all efficacy assessments occur while subject is still taking study drug.

7.2.6 End of Study Visit (Day 35 – End of Week 5)

Subjects will return to the clinic for the final visit assessments detailed in Table 3. Adverse events that are unresolved at the end of study visit will continue to be followed by study staff as detailed in Section 10.2.3.

7.2.7 Safety Follow-up Telephone Call (Day 56 – End of Week 8)

Twenty-eight (±2) days after Visit 4 (or after the last dose of study drug for subjects who discontinue treatment prematurely), the site will contact subjects by telephone to inquire as to the status of AEs that were ongoing at the End of Study Visit and to determine that no new AEs have occurred in the 30 days following the last dose.

7.3 Concomitant Medications and Other Restrictions

7.3.1 Concomitant Medications

Subjects may not be using more than one anti-tremor medication at the time of entry into the study. Subjects must have been on a stable dose for one month prior to screening and must have no change in dose in concurrent anti-tremor medication for the duration of the study. It should be noted that primidone is not a permitted anti-tremor medication.

Subjects may not use medications that might produce tremor or interfere with the evaluation of tremor, such as but not limited to: CNS-stimulants, lithium, amiodarone, metoclopramide, theophylline, and valproate.

On Study Visit Days, subjects must refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor, such as but not limited to stimulant decongestants, beta-agonist bronchodilators, caffeine, alcohol and tobacco.

The stable use of a benzodiazepine, sleep medication or anxiolytic to improve sleep performance is allowed as long as tremor persists against the background of regular medication use. Subjects should not use sleep aids on the evening prior to a study visit.

The use of prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be strong inhibitors or inducers of CYP3A4 must be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study. Subjects taking primidone for treatment of their ET may continue to do so at a stable dose. Subject randomization will be stratified by concomitant anti-tremor medication use and site type.

See Appendix C for a complete list of restricted inhibitors and inducers.

7.3.2 Other Restrictions

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

8 EFFICACY ASSESSMENTS

8.1 The Essential Tremor Rating Assessment Scale (TETRAS)

The Tremor Research Group first published the TRG Essential Tremor Rating Assessment Scale (TETRAS) in 2008 (Elble 2008). TETRAS consists of a 9-item performance subscale and a 12-item activities of daily living (ADL) subscale. TETRAS was developed as a rapid clinical assessment of ET that requires no equipment other than pen and paper. Administration of the performance subscale

takes less than 10 minutes. The scale employs objective metrics to reduce experiential rater bias.

To evaluate the inter-rater reliability of TETRAS, Elble et al. (2012) videotaped 50 TETRAS exams, including assessments of 44 patients with ET and 6 controls. The severity of ET ranged from mild to severe. Ten specialists rated the patients in the videos 2 times with an interval of 1 to 2 months separating the ratings. Of the 10 raters, 6 had been involved in the development of TETRAS, and 4 had never used the scale.

Inter-rater reliability of the scale was calculated using a two-way random effects intraclass correlation (ICC) with an absolute agreement definition. The inter- and intra-rater ICC for head and upper limb tremor ranged from 0.86 to 0.96, and the ICC for the total score were 0.94 and 0.96. The ICC for voice, face, trunk and leg were less robust (Elble et al., 2012).

The TETRAS Performance subscale is widely used in clinical practice, and has high content validity and strong inter-rater reliability. The TETRAS ADL and performance scores are highly correlated, and the TETRAS ratings of upper extremity function correlate strongly with transducer measures (accelerometry) of upper limb tremor (Mostile et al., 2010). TETRAS is also shown to be sensitive to change in tremor over time (Voller et al., 2014).

8.1.1 TETRAS Performance Subscale

The Performance subscale quantifies tremor in the head, face, voice, limbs and trunk. Each item is rated on a 0 to 4 rating scale, with scoring of upper limb tremor allowing for 0.5-point increments. Specific amplitude ranges (measured in centimeters) define the tremor rating (see Table 4). Raters first estimate the maximum amplitude of tremor and then assign the corresponding rating. The sum of the individual rating scores provides the overall Performance score, ranging from 0 to 64. See Appendix A1 for the complete TETRAS Performance Scale.

Table 4 TETRAS Performance Subscale Metric Amplitude Ranges

Head Tremor	Upper Limb Tremor	Lower Limb Tremor
0 = no tremor	0 = no tremor	0 = no tremor
1 = < 0.5 cm	1 = barely visible	1 = barely visible
2 = 0.5 - < 2.5 cm	1.5 = < 1 cm	2 = < 1 cm
3 – 2.5 – 5 cm	2 = 1 - < 3 cm	3 = 1 – 5 cm
4 = > 5 cm	2.5 = 3 - < 5 cm	4 = > 5 cm
	3 = 5 - < 10 cm	
	3.5 = 10 - < 20 cm	
	4 = > 20 cm	

To reduce the potential for bias in the assessments of efficacy, all subjects will be videotaped during the TETRAS Performance Subscale testing according to a consistent script. The videotapes will be rated in a blinded manner by qualified,

independent raters. While the Principal Investigator (or sub-Principal Investigator) will score the TETRAS performance subscale, the TETRAS Performance Subscale scores provided by the blinded central rater will be utilized in the statistical analyses of efficacy.

Full details on the recording and scoring of the TETRAS Performance scale will be provided in the study Operations Manual.

8.1.2 TETRAS Activities of Daily Living Subscale

The ADL subscale includes many of the items assessed in the scales previously developed by Fahn, Tolosa and Marin (1993), Louis et al. (2000) and Bain et al. (1993), including eating and drinking, dressing and personal hygiene, carrying items and finer motor skills. 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. See Appendix A1 for the complete TETRAS ADL Subscale.

8.2 Objective Biometric Assessments

8.2.1 Accelerometry

Accelerometry has long been used to obtain quantitative measurements of tremor in ET (Jankovic & Frost, 1981; Koller & Royse, 1985). Elble et al. demonstrated a logarithmic relationship between tremor amplitude, as measured via accelerometry, and changes in physician-assessed tremor rating scales (Elble, 2006). Voller et al. reported a significant correlation ($p < .001$) between log-transformed accelerometer data and TETRAS scores in ET (Voller et al., 2014).

8.2.1.1 Kinesia ONE Accelerometer

The Kinesia ONE device will be placed on the index finger and worn in the clinic immediately following execution of the TETRAS Performance subscale

A total of four tasks will be performed on the left side and then again on the right side to assess resting, postural, kinetic, and lateral wing beating tremor. Each task will be performed for 15 seconds.

Full details on the Kinesia ONE device and its use will be provided in the study Operations Manual.

8.3 Other Assessments

Health-related Quality of Life (HRQoL) is defined as a patient's perception of the effects of and illness and its treatment on his/her life and sense of will-being. In that many models suggest a strong relationship between functional status and HRQoL, ET has the potential to exert a significant and detrimental impact on HRQoL (Makedonsky et al., 2002).

8.3.1 QUEST

Until 2005, the measurement of QoL in patients with ET was performed with generic QoL indices such as the EuroQOL and Sickness Impact Profile (SIP). However, generic measures lack sensitivity in ET and may fail to address the issues most relevant to patients with ET. As such, Tröster et al. developed the Quality of Life in Essential Tremor Questionnaire (QUEST) to specifically assess the impact of ET on HRQOL (Tröster et al., 2005). The QUEST is a 30-item questionnaire that contributes to 5 sub-scales (physical, psychosocial, communication, hobbies/leisure and work/finance) and a total score, plus 3 additional items relating to sexual function and satisfaction with tremor control and medication side effects. Initial reports provide preliminary support of its reliability and validity. The internal consistency was very good to excellent for 4 scales and the total score, and moderately high for the Work/Finance scale (Tröster et al., 2005). These reliability coefficients are also supportive of the QUEST's construct validity.

It is proposed that successful treatment of ET, even if symptomatic rather than curative, would positively impact QoL. A sample QUEST questionnaire may be found in Appendix A2.

8.3.2 Clinical Global Impression

The Clinical Global Impressions Scale (CGI) was developed for use in NIMH-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of a patient's global functioning before and after initiating a study medication (Guy, 1976.) The CGI is a summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

The CGI has two forms—the CGI-Severity, which rates illness severity at baseline, and the CGI-Improvement, which rates change from baseline.

CGI-Severity (CGI-S). The CGI-Severity (CGI-S) consists of a single 7-point rating score of illness severity that is based on how ill the subject is relative to other subjects with whom the clinician has had experience. Raters select one response based on the following question: "Considering your total clinical experience with this particular population, how ill is the patient at this time?" Scores are: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

CGI-Improvement (CGI-I). The CGI-I consists of a single 7-point rating of total improvement or change from baseline CGI-S, regardless of whether or not the change is due entirely to drug treatment. Raters select one response based on the following question, "Compared to your subject's condition at the beginning of treatment, how much has your subject changed?" Scores are: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse.

The CGI-S/CGI-I rater may have access to all clinical information related to subject severity and change, and does not need to be independent of other assessments. However, the rater who assesses the initial CGI-S should be the clinician who rates overall change via the CGI-I during the study. The rater will be a trained member of the site investigational team (clinician).

8.3.3 Patient Global Impression of Change (PGIC)

Global rating of change (GRC) scales are designed to quantify a patient's improvement or deterioration over time, usually either to determine the effect of an intervention or to chart the clinical course of a condition. GRC scales ask a patient to assess his or her current health status, recall that status at the beginning of treatment, and then calculate the difference between the two. The simplicity of GRC scales makes them easy to administer and applicable to a wide range of patients (Kamper et al., 2009.)

The Patient Global Impression of Change (PGIC) is a 7-point GRC consisting of one question: “With respect to your essential tremor, how would you describe yourself now, as compared to when you started taking the study drug?” Subjects will choose one of the following answers: “very much worse, much worse, minimally worse, no change, minimally improved, much improved, very much improved.”

8.3.4 Goal Attainment Scaling

Goal Attainment Scaling (GAS) is a tool that involves the development of a written set of goals between a physician and patient and is used for monitoring patient progress. GAS was developed in 1968 in response to the wide variety of evaluation models regarding mental illness and treatment (Kiresuk & Sherman, 1968.) GAS has been employed in patients with physical disorders including spasticity (Ashford & Turner-Stokes, 2006) and multiple sclerosis (Kahn et al., 2008).

GAS frames the discussion in terms of individual patient-desired goals rather than universally applied health states. Goal-oriented care prompts patients to articulate which health goals are most important to them. Patients and clinicians can then monitor progress in reaching them.

Subjects will identify 3 health goals at Baseline. Examples of goals are drinking from a cup, buttoning a shirt or ability to write. Goals may be either active or passive. All goals will be specifically tailored to the individual, with each subject required to rate each goal at baseline on the level of importance, based on a 3-point scale (1 = fairly important; 2 = very important; 3 = extremely important). For the investigator, the feasibility of attaining each goal must be considered before the goals are set, and adjusted accordingly if needed. Once each goal is set, the investigator will be asked to rate the degree of difficulty in achieving each of the set goals, based on another 3-point scale (1 = probable; 2 = possible; 3 = doubtful.)

Progress towards each goal will be scored on a 5-point scale: -2 = Worse than Baseline (unfavorable outcome); -1 = No change from Baseline; 0 = Achieved the

defined goal (expected outcome); +1 = Better than expected outcome; +2 = Best anticipated outcome.

Full details on Goal Attainment Scaling will be provided in the study Operations Manual.

9 PHARMACOKINETIC AND PHARMACOGENOMIC ASSESSMENTS

9.1 Blood Sample Collection for Pharmacokinetic Assessments

All subjects will have one blood sample drawn prior to administration of CX-8998 at 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.)

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

9.2 Pharmacokinetic Parameters

Plasma concentrations of CX-8998 and its two primary metabolites (M01 and M02) will be determined.

The concentrations of CX-8998 and its 2 primary metabolites in plasma will be summarized by visit and dose using descriptive statistics. The concentration data will also be used as part of an exploratory population pharmacokinetic/pharmacodynamic (PK/PD) analysis intended to evaluate the exposure-response and exposure-safety relationships; which will be reported separately from the Clinical Study Report.

9.3 Pharmacogenomics of Drug Response

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

A 4 mL blood sample Prep D1 (K_2 EDTA whole blood collection optimized for DNA analysis) will be collected at Visit 1/Baseline to be retained for potential pharmacogenomic analyses related to drug response. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Retained Pharmacogenomic Sample(s) will be collected from all subjects *unless prohibited by local regulations.* Detailed collection, processing, storage and shipment instructions are provided in the Laboratory Manual.

10 SAFETY ASSESSMENTS

10.1 Assessment of Safety

10.1.1 Adverse Events

Adverse events (AEs) will be captured from the time the ICF is signed through the Follow-up telephone call on Day 56. Important medical events and conditions occurring prior to this period are not AEs; they will be captured within the medical chart and in the Medical History section of the Case Report Form. See Section 10.2 for definitions and instructions on the rating and collection of AEs.

10.1.2 Physical Examination

A complete physical examination includes measurement of height (screening only), weight, and examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities. Genital, rectal, and breast examination may be excluded if not clinically indicated. Weight should be measured on the same scale each time.

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

10.1.3 Neurological Examination

The neurological examination will include assessment of mental status, and examination of cranial nerves II-XII, motor and sensory exam, reflexes, coordination, stance, gait and balance.

10.1.4 Vital Signs

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 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 measurement of orthostatic blood pressure and pulse rate will be recorded. The average of these assessments will be used for comparison to single recordings at Visits 1 through 4. On Visits 1, 2 & 3 (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.)

10.1.5 Clinical Laboratory Tests

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

Hematology testing will include hematocrit, hemoglobin, red blood cell count, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC), and platelet count.

Serum chemistry analyses will include sodium, potassium, chloride, calcium, magnesium, phosphorus, carbon dioxide (CO_2) or bicarbonate, albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, creatine kinase (CK), uric acid, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, triglycerides, total cholesterol, prolactin levels and total bilirubin.

Coagulation studies will include fibrinogen, activated partial thromboplastin time (aPTT), and international normalized ratio (INR).

Urinalysis will include color and appearance, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood by dipstick. Microscopic inspection of sediment is only to be performed as needed to clarify abnormal dipstick results at the discretion of the Investigator.

10.1.6 Urine Drug Screen

Subjects will undergo urine drug screening for the presence of phencyclidine (PCP), cocaine, cannabinoids, opiates/barbiturates, benzodiazepines, amphetamines, methadone and MDMA (ecstasy) at the Screening visit.

10.1.7 Pregnancy Tests

A urine pregnancy test will be performed for all women of childbearing potential. See Section 6.2, inclusion criterion # 8 for the definition of women of childbearing potential.

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

10.1.8 Electrocardiogram

A triplicate 12-lead ECG will be obtained according to the Schedules of Assessments. Subjects must rest in the supine position for at least 10 minutes before the ECG recording is started. The ECG should be recorded during the period of rest required before blood collection and the measurements of orthostatic blood pressure, pulse and respiratory rate. A qualified physician will review the ECGs and any clinically important finding will be recorded on the appropriate CRF. The investigator is responsible for providing interpretation of all ECGs. The results will include heart

rate, PR interval, QRS interval, QT interval, and QTc interval, and assessment of rhythm and morphology. If necessary, (eg, suspected QTc prolongation) a manual reading of the ECG data will be performed.

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

10.1.9 Columbia Suicide Severity Rating Scale

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

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

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

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

A sample of the C-SSRS may be found in Appendix B.

10.1.10 Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a scale intended to measure daytime sleepiness that is measured by use of a very short questionnaire. It was developed by Murray Johns of Epworth Hospital in Melbourne, Australia (Johns, 1991; Johns, 2010). The questionnaire asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for 8 different situations. The scores are added together to obtain a single number.

In general, ESS scores can be interpreted as follows:

0 - 5	Lower Normal Daytime Sleepiness
6 - 10	Higher Normal Daytime Sleepiness
11 - 12	Mild Excessive Daytime Sleepiness
13 - 15	Moderate Excessive Daytime Sleepiness
16 - 24	Severe Excessive Daytime Sleepiness.

A sample of the ESS may be found in Appendix B.

10.2 Adverse Events

10.2.1 Definitions

Adverse Event

An Adverse Event (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.

Laboratory Abnormality

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 are also considered AEs.

Treatment-emergent Adverse Events

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

Treatment Period

The treatment period is the period during which a subject receives study drug (i.e., first dose through 30 days after last dose).

Intolerable Adverse Event

An intolerable AE is one that is considered by the investigator to be related to study drug (Section 10.2.2.3) AND is either a Grade 3 (severe) or 4 (life threatening) event (Section 10.2.2.2) OR is a Grade 1 or 2 event that prompts the subject to express a desire to discontinue dosing. Dose adjustments for intolerable AEs are described in Section 4.5.)

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. See Section 10.3 for more details on SAEs.

10.2.2 Collection and Rating of Adverse Events

All AEs, irrespective of the relatedness to the study drug, will be collected and reported on the Adverse Event Report Form from signature of the ICF through the Follow-up telephone call on Day 56. In case of an SAE, a Serious Adverse Event Report Form must be completed and transmitted to the Sponsor or designee.

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

10.2.2.1 Onset Date

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

10.2.2.2 Assessment of Intensity

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

- **Grade 1 (Mild)**: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Grade 2 (Moderate)**: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) [Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc];
- **Grade 3 (Severe)**: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden]
- **Grade 4 (Life-threatening):** Life threatening consequences; urgent intervention indicated;
- **Grade 5 (Fatal)**: death related to AE.

10.2.2.3 Relationship to Study Drug

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

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

- **Related:** the AE has at least a possible or stronger causal relationship to the study drug, i.e., there are facts in evidence to suggest a causal relationship to the study drug. The study treatment and the AE are reasonably related in time, and any alternative etiology is equally or less likely.
- **NOT Related:** Exposure to study treatment did not occur; or the occurrence of the AE is not reasonably related in time, or is due to an underlying/intercurrent illness, or to other medication or procedure; or the AE is considered unlikely to be related to the study treatment.

10.2.2.4 Action Taken

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

- **None:** no change in study drug dosage was made
- **Reduced:** dose of study drug was reduced, with or without a period of temporary suspension of dosing
- **Discontinued:** the study drug was permanently stopped

10.2.2.5 Outcome of Adverse Event

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

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

10.2.3 Adverse Event Follow-up

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

Any subject who has any AE (whether serious or non-serious) or clinically significant (in the Investigator's opinion) abnormal laboratory test values will be evaluated by the Investigator or qualified designee, and will be treated and followed

up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator and the Sponsor.

All AEs, whether serious or non-serious, will be collected beginning at the time of signing informed consent through the Follow-up Telephone Call (Day 56). All AEs should be followed until resolution or:

- 30 days from onset; or
- the Follow-up Telephone Call (Day 56); or
- the subject is lost to follow-up (as defined in Section 6.4.1); or
- the subject withdraws consent,

whichever occurs first.

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

10.3 Serious and Other Significant Adverse Events

10.3.1 Definition of a Serious Adverse Event

A serious adverse event is any adverse event that

- **Results in death.** Death is not an event per se but rather an outcome. Note that any adverse event resulting in a fatal outcome must be fully documented and reported, including deaths that occur within 30 days after treatment ends and irrespective of the causal relationship to the study drug.
- **Is life-threatening.** Life-threatening refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death, if it was more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization.** Hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an adverse event. Hospitalization describes a period of at least 24 hours. Over-night stays for observation, stays at the emergency room or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgment must always be exercised and, when in doubt, the case should be considered serious (i.e. if the case fulfills the criterion for a medically important event). Hospitalization for administrative or social purposes does not constitute an SAE. Hospital admissions and/or surgical operations planned before study inclusion are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that the condition did not deteriorate during the study.
- **Results in persistent or significant disability/incapacity.** Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. If in doubt, the decision should be left to medical judgment by the Investigator.

- **Is a congenital anomaly/birth defect.** Any congenital anomaly or birth defect observed in any offspring of the subject conceived during treatment with the study drug.
- **Is an important medical event.** Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important.

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

The following are not considered SAEs:

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

10.3.2 Serious Adverse Event Reporting by the Investigator to the Sponsor

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

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

Sponsor Representative and Contact Information for SAE Reporting:

Reporting email: [redacted]

10.3.3 Handling of Follow-up Information

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

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

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

10.3.4 Reporting and Follow-up of Pregnancy

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

10.3.5 Expedited Reporting of Serious Adverse Events

10.3.5.1 Responsibilities

The Sponsor is responsible for ensuring the timely reporting of SAEs to Regulatory Authorities and all Investigators who participate in the clinical development program of the study drug. It is the responsibility of the Investigator to provide the Sponsor with the case information such that reporting timeline demands of applicable Regulatory Authorities can be met.

10.3.5.2 Expedited Reporting

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

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

10.3.5.3 Timelines

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

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

It is the responsibility of the Investigator to support Sponsor activities needed to meet the aforementioned timelines for Regulatory Authority reporting in the event of an SAE.

10.4 Safety Monitoring and Risk Mitigation Plan

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

1. Subject safety and tolerability will be monitored in this study across multiple dimensions by tracking clinical adverse events; vital signs (including orthostatic pulse and blood pressure); general and neurological physical examinations; standard clinical laboratory safety panels for complete blood counts, chemistry, coagulation, and urinalysis; standard 12-lead electrocardiograms; and the Epworth Sleepiness Scale (ESS) and Columbia Suicide Severity Rating Scale (C-SSRS).
2. The specified inclusion/exclusion criteria have been carefully considered to avoid enrollment of subjects for whom exposure to the study drug might pose a hazard.
3. The anticipated subject population (with essential tremor) is acknowledged to likely be older than the healthy volunteer and schizophrenic populations that have previously undergone phase 1 and 2 study with CX-8998 (formerly MK-8998, Merck & Co., Inc.). Since older male and female subjects may experience greater CX-8998 exposures than younger males on whom most of the existing PK data are based, this study will perform a careful dose titration

in which dosing of CX-8998 will be initiated at 4 mg BID for 7 days, increasing to 8 mg BID for 7 days, and finally, if tolerated, to the target dose of 10 mg BID for 14 days. Subjects will return to the clinic for each dose up-titration for safety assessment. The study is designed to allow for flexible titration; should subjects experience intolerable AEs (see section 10.2.1, Adverse Events, Definitions) at 4 mg, 8 mg or 10 mg BID, the dose may be decreased to the previous lower dose (2 mg BID in the case of 4 mg BID). Subjects experiencing intolerable AEs at 2 mg BID will be discontinued from treatment.

4. Dose up-titration (e.g., from 4 mg BID to 8 mg BID) requires that the subject be evaluated in the clinic by the PI or sub-I. PI's and sub-I's may advise a subject to reduce or suspend their dose based on telephone elicitation of adverse events. During each clinic visit involving a dose up-titration, subjects will be observed and monitored in the clinic for at least 2 hours following the first administration of the increased dose step.
5. Dose modification and stopping rules are in place for individual subjects (see Section 4.5, Dose Adjustments/Toxicity Management). Near real-time safety and tolerability monitoring for individual subjects is the primary responsibility of the PI and sub-I's.
6. All serious adverse events (SAEs) meeting criteria for expedited reporting to the US FDA will be reported to the FDA and all IRBs in accordance with regulatory timelines.
7. 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. These reviews will be based on blinded, select listings and summary tables of the evolving safety and tolerability data for each arm of the study. The Sponsor's Study Safety Representative and the independent Safety Monitor Physician will review the blinded study data to determine if there is a sufficiently clinically significant difference between the blinded treatment arms in terms of frequency, severity, and/or seriousness of adverse events to take actions such as 1) unblinding specific safety data; 2) eliminating one or more of the planned dose up-titrations (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 PI's and sub-I's 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.

8. In the event of a treated subject's death within 30 days of the last dose of study drug and that is assessed by the treating PI/sub-I or the independent Safety Monitor Physician or the Study Safety Representative as at least possibly related to study drug, further enrollment into the study will be immediately suspended until a safety review can be conducted by the independent Safety Monitor Physician, the Study Safety Representative, the actively participating PI's and sub-I's, and the Sponsor. As required by regulation, all deaths meeting criteria for expedited reporting to the US FDA will be reported to the FDA and all IRBs within regulatory timelines. A final decision to re-open the study to new enrollment without modification(s), re-open with modification(s), or terminate the study will be made by the overall study Principal Investigator, the independent Safety Monitor Physician, and the Sponsor's Study Safety Representative.

11 STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with statistical testing performed for the efficacy endpoints. All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. 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 by treatment group and overall. The term "treatment group" refers to the following: Placebo or CX-8998. All available data for enrolled subjects will be listed in by subject listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number.

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

11.1 Statistical Analysis Plans

A SAP will be created and approved prior to the unblinding of the study data. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures.

11.2 Study Hypothesis

The primary statistical hypothesis for the study is provided below.

- H_{02}: $\propto_{Placebo} = \propto_{CX\text{-}8998}$, i.e., there is no difference between treatment groups in the mean change from Baseline in TETRAS performance scale at end of treatment
- H_{12}: $\propto_{Placebo} \neq \propto_{CX\text{-}8998}$, i.e., there is a difference between treatment groups in mean change from Baseline in TETRAS performance scale at end of treatment

11.3 Determination of Sample Size

Up to 92 subjects will be randomized to one of two treatment groups: Placebo and CX-8998. Based on similarly designed studies, this sample size should be sufficient to provide preliminary safety and efficacy information on CX-8998 when administered according to this protocol.

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 in the TETRAS performance subscale when the standard deviation is 7.5 and alpha=0.05 (PASS 2008: Two sample t-test – Normal Non-Parametric Adjustment). Up to 92 subjects will be enrolled in order to ensure that 86 subjects are available for inclusion in the efficacy analyses.

11.4 Analysis Populations

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

• **Intent-To-Treat Population:** The ITT population will include all subjects who are randomized. The ITT population will be used for analyses of accountability, demographics, and efficacy. Subjects will be analyzed according to the treatment as randomized.

• **Safety Population:** The safety population will include all subjects who are randomized and receive at least one dose of randomized treatment. Subjects who receive treatment other than that intended will be analyzed according to the treatment received. The safety population will be the primary population for all analyses of safety data.

• **PK Population:** The PK population will consist of all subjects for whom PK samples were obtained, received study treatment, and for whom sufficient plasma concentrations are available.

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

11.5 Data Analysis

11.5.1 Efficacy Analyses

11.5.1.1 Primary Efficacy Analyses

The primary efficacy analysis of the TETRAS performance subscale (as scored by the central rater) will be conducted using an analysis of covariance (ANCOVA) model with fixed effects for treatment, concomitant anti-tremor medication use, site type, and Baseline value of the TETRAS performance subscale. The primary hypothesis to be tested will be if the mean change from Baseline in TETRAS performance scale

indicates that the CX-8998 arm is different from placebo. All testing will be performed using the LSMeans from the ANCOVA model and a two-sided test at the alpha=0.05 level of significance. If the data indicate a departure from the normal distribution, a corresponding rank test will be performed.

11.5.1.2 Secondary and Exploratory Efficacy Analyses

The proportion of subjects experiencing at least a 5.5 point decrease in the TETRAS performance scale will be summarized by treatment group. Differences between the treatment groups will be assessed with Cochran-Mantel-Haenszel General Association test stratified by concomitant anti-tremor medication use and site type.

The change from Baseline on the TETRAS Activity of Daily Living subscale and Total TETRAS score, change from Baseline to Day 28 in accelerometry score as measured by Kinesia ONE, change from Baseline in the ESS, change from Baseline on the QUEST scale, and the PGIC, the CGI-I, and GAS will be analyzed using the same type of ANCOVA model as described for the primary endpoint, with baseline values included only as applicable. All secondary and exploratory analyses will be conducted using two-sided tests at the alpha=0.05 level of significance. Analysis of findings from the neurophysiology sub-study will be presented in a separate study report.

11.5.2 Safety Analyses

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

Descriptive summaries of vital signs and clinical laboratory results will be presented by treatment group and study visit. The number and percentage of subjects experiencing treatment-emergent laboratory abnormalities will be summarized by treatment group. Laboratory abnormality shifts from Baseline to post-Baseline assessments will be summarized by treatment group.

Concomitant medications will be mapped to a WHO preferred term and drug classification. The number and percent of subjects taking concomitant medications will be summarized using preferred terms and drug classifications.

Changes from Baseline in physical examinations, neurological examinations, and ECGs during study will be evaluated. Results from the C-SSRS will be listed by treatment.

11.5.3 Pharmacokinetic Analyses

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

11.5.4 Interim Analysis

Once at least 43 subjects have been treated and followed through Day 28 or the corresponding subjects have discontinued the study, an independent, non-study statistician will estimate the variance for the primary efficacy endpoint. This estimate will be based on the available Day 28 data at the time of the interim analysis and will be calculated in a blinded manner. This blinded estimate may be provided to the sponsor for review and potential considerations for altering the trial size.

As the sponsor will remained 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.

11.6 Missing, Unused and Spurious Data

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

12 STUDY MANAGEMENT

12.1 Protocol Amendment and Protocol Deviation

12.1.1 Protocol Amendment

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

12.1.2 Protocol Deviations and Waivers

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

12.2 Ethics and Regulatory Aspects

12.2.1 Ethical Conduct of the Study and Regulatory Guidelines

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

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

12.2.2 Institutional Review Board and Regulatory Approval

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

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

12.2.3 Subject Informed Consent

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

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

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

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

Each subject will be informed that a Monitor, a Quality Assurance Auditor mandated by the Sponsor, or a Health Authority Inspector, in accordance with applicable regulatory requirements, may review his or her source records and health data. Data protection will be handled in compliance with national and local regulations.

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

12.3 End of Study and Regulatory Notification

The study can be terminated in part or in whole at the discretion of the FDA, an applicable Regulatory Authority or the Sponsor.

At the end of the study, the IRBs and Regulatory Authorities will be notified by the Sponsor according to applicable Regulatory requirements.

12.4 Data Protection and Confidentiality

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

12.5 Monitoring

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

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

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

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

12.6 Quality Assurance and Quality Control

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and

reliability of the study data presented to the Sponsor lies with the Principal or Qualified Investigator generating the data.

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

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

The study center may also be compelled to an inspection by a Regulatory Authority.

12.7 Source Data

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

Source documents are the original data, documents, and records. Examples include hospital records, laboratory reports, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, other radiographic depictions or displays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study. All source documents must be reviewed by the PI and the sponsor (or designee) for compliance with GCP.

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

13 DATA AND RECORD KEEPING

13.1 Case Report Forms

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

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

13.2 Record Keeping

The Investigator must arrange for retention of study records ("Essential Documents for the Conduct of a Trial" are listed in the ICH "Guideline for Good Clinical Practice," Section 8, E6) at the site, in a secure location, for 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or for at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The Investigator should take measures to prevent any accidental or premature destruction of these documents.

14 REFERENCES

Adams PJ, Snutch TP. Calcium channelopathies. Voltage-gated calcium channels. Subcell Biochem. 2007;45: 215-251.

Bain PG, Findley LJ, Atchison P, et al. Assessing tremor severity. J Neurol Neurosurg Psychiatry. 1993; 56(8): 868-873.

Bermejo-Pareja F. Essential tremor—a neurodegenerative disorder associated with cognitive defects? Nature Reviews Neurology. 2011;7(5):273-282.

Bermejo-Pareja F, Puertas-Martín V. Cognitive Features of Essential Tremor: A Review of the Clinical Aspects and Possible Mechanistic Underpinnings. Louis ED, ed. *Tremor and Other Hyperkinetic Movements*. 2012;2:02-74-541-1.

Bermejo-Pareja PE, Ruiz-Huete C, Dorado R, Anciones B. Zonisamide in refractory essential tremor. Revista de Neurologia. 2008; 46(3): 139-142.

Bourinet E, Alloui A, Monteil A, et al. Silencing of the Cav3.2 t-type calcium channel gene in sensory neurons demonstrates its major role in nociception. EMBO. 2005;24(2): 315-324.

Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol Rev. 2005;57(4): 411-425.

Chandran V, Pal PK, Reddy JY, Thennarasu K, Yadav R, Shivashankar N. Non-motor features in essential tremor. Acta Neurol Scand. 2012;125:332–7.

Chang K, Wang S, Chi C. Efficacy and safety of topiramate for essential tremor: a meta analysis of randomized controlled trials. Medicine. 2015; 94(43): 1-7.

Cribbs LL, Lee JH, Yang J, et al. Cloning and characterization of alpha1H from human heart, a member of the T-type Ca2+ channel gene family. Circ. Research. 1998;83(1): 103-9.

Deuschl G, Bain P, Brin M. Consensus Statement of the Movement Disorder Society on Tremor. Mov Disord. 1998;13: 2–23.

Diaz NL, Louis ED. Survey of medication usage patterns among essential tremor patients: Movement disorder specialists vs. general neurologists. Parkinsonism Relat Disorders. 2010;16(9):604-607.

Elble RJ. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. Brain. 2006;129(10):2660-2666.

Elble RJ, Brilliant M, Leffler K, Higgins C. Quantification of essential tremor in writing and drawing. Mov Disord. 1996;11:70-78.

Elble R, Comella C, Fahn S, et al. The essential tremor rating assessment scale (TETRAS). Mov Disord. 2008; 23 (Suppl 1): S1-6.

Elble R, Comella C, Fahn S, et al. Reliability of a new scale for essential tremor. Mov Disord. 2012;27(12):1567-1569.

Elble R, Lewitt P, Lyons K, et al. Inter-Rater Reliability of the Essential Tremor Rating Assessment Scale (TETRAS) (S32.004). Neurology. 2012;78 (Meeting Abstracts 1).

Ertel EA, Campbell KP, Harpold MM, et al. Nomenclature of voltage-gated calcium channels. Neuron. 2000;25:533–5.

Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, ed. *Parkinson's Disease and Movement Disorders*. Baltimore: Williams & Wilkins; 1993: 225–234.

Frucht SJ, Bordelon Y, Houghton WH. Marked amelioration of alcohol responsive posthypoxic myoclonus by gamma-hydroxybutyric acid (Xyrem). Mov Disord. 2005;20(6): 745-751.

George MS, Lydiard RB. Social Phobia Secondary to Physical Disability. Psychosomatics. 1994;35(6):520-523.

Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.

Handforth A, Delorey TM, Homanics GE, Olsen RW. Pharmacologic evidence for abnormal thalamocortical functioning in GABA receptor beta3 subunit-deficient mice, a model of Angelman syndrome. Epilepsia. 2005;46(12):1860-70.

Handforth A, Homanic GE, Covey DF, et al. T-type calcium channel antagonists suppress tremor in two mouse models of essential tremor. Neuropharmacology. 2010; 59(6):380-387.

Handforth A, Martin F, Kang G, Vanek Z. Zonisamide for essential tremor: an evaluator blinded study. Movement Disorders. 2009; 24(3); 437-440.

Jankovic J, Frost JD. Quantitative assessment of parkinsonian and essential tremor: Clinical application of triaxial accelerometry. Neurology. 1981;31(10):1235-1235.

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. 1991;14(6):540-545.

Johns MW. A new perspective on sleepiness. Sleep and Biological Rhythms. 2010;8(3):170-179.

Kamper SJ, Maher CG, Mackay G. Global Rating of Change Scales: A Review of Strengths and Weaknesses and Considerations for Design. The Journal of Manual & Manipulative Therapy. 2009;17(3):163-170.

Kiresuk TJ, Sherman RE. Goal attainment scaling: A general method for evaluating comprehensive community mental health programs. Community Mental Health Journal. 1968;4:443–453.

Koller WC, Royse VL. Time course of a single oral dose of propranolol in essential tremor. Neurology. 1985; 35(10): 1494-1494.

Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. Neurology. 1989;39(12):1587-1587.

Llinás R. Thalamo-cortical dysrhythmia syndrome: neuropsychiatric features. An R Acad National Med. 2003;120(2): 267-290.

Llinás RR, Choi S, Urbano FJ, Shin H. γ-Band deficiency and abnormal thalamocortical activity in P/Q-type channel mutant mice. Proc Natl Acad Sci. 1999; 104(45):17819-17824.

Long MA, Deans MR, Paul DL, Connors BW. Rhythmicity without synchrony in the electrically uncoupled inferior olive. J Neurosci. 2002 Dec 15;22(24):10898-905.

Lorenz D, Schwieger D, Moises H, Deuschl G. Quality of life and personality in essential tremor patients. Mov Disord. 2006;21(8):1114-1118.

Louis ED. Essential Tremor. Arch Neurol. 2000;57(10).

Louis ED. Medication non-adherence in essential tremor. Parkinsonism Relat Disord. 2015;21(2):138-141.

Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25(5):534-541.

Louis ED, Machado DG. Tremor-related quality of life: A comparison of essential tremor vs. Parkinson's disease patients. Parkinsonism Relat Disord. 2015;21(7):729-735.

Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder? Estimates of the prevalence of essential tremor throughout the world. Movement Disorders. 1998;13(1):5-10.

Makedonsky PV, Levin OS, Naimushina TV. The quality of life in patients with essential tremor [abstract]. Mov Disord. 2002;17:S353

Martin FC, Handforth A. Carbenoxolone and mefloquin suppress tremor in the harmaline model of essential tremor. Mov Disord. 2006;21(10):1641-1649.

Martin FC, Thu Le A, Handforth A. Harmaline-induced tremor as a potential preclinical screening method for essential tremor medications. Mov Disord. 2005 Mar;20(3):298-305.

Mitsi G, Mendoza EU, Benjamin D. Wissel BD, et al. Biometric Digital Health Technology for Measuring Motor Function in Parkinson's Disease: Results from a Feasibility and Patient Satisfaction Study. Front. Neurol. 2017 Jun 13;8:273

Miwa H, Hama K, Kajimoto Y, Kondo T. Effects of zonisamide on experimental tremor in rats. Parkinsonism Relat Disord. 2008;14:33-36.

Molineux ML, McRory JE, McKay BE, et al. Specific t-type calcium channel isoforms are associated with distinct burst phenotypes in deep cerebellar nuclear neurons. PNAS. 2006;103(41): 5555-5560.

Morita S, Miwa H, Kondo T. Effect of zonisamide on essential tremor: a pilot crossover study in comparison with arotinolol. Parkinsonism Relat Disord (2005) 11: 101–103

Mostile G, Giuffrida JP, Adam OR, Davidson A, Jankovic J. Correlation between Kinesia system assessments and clinical tremor scores in patients with essential tremor. Mov Disord. 2010;25(12):1938-1943.

Mundt JC, Greist JH, Gelenberg AJ, Katzelnick DJ, Jefferson JW, Modell JG. Feasibility and validation of a computer-automated Columbia-Suicide severity rating scale using interactive voice response technology. J Psych Res. 2010;44(16):1224-1228.

Mundt JC, Greist JH, Jefferson JW, Federico M, Mann JJ, Posner K. Prediction of Suicidal Behavior in Clinical Research by Lifetime Suicidal Ideation and Behavior Ascertained by the Electronic Columbia-Suicide Severity Rating Scale. J Clin Psych. 2013;74(09):887-893.

Ondo W. Zonisamide for essential tremor. Clin Neuropharmacol. 2007;30(6): 345-349.

Park Y, Park H, Lee CJ, et al. CaV3.1 is a tremor rhythm pacemaker in the inferior olive. PNAS. 2010;107(23):10731 – 10736.

Park Y-G, Kim J, Kim D. The potential role of T-type Ca2+ channels in motor coordination. Front Neural Circuits. 2013;7(172): 1-11.

Paterson NE, Malekiani SA, Foreman MM, Olivier B, Hanania T. Pharmacological characterization of harmaline induced tremor activity in mice. Eur J Pharmacol. 2009;616(1-3):73-80.

Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psych. 2011;168(12):1266-1277.

Quesada A, Bui PH, Homanics GE, Hankinson O, Handforth A. Comparison of mibefradil and derivative NNC 55-0396 effects on behavior, cytochrome P450 activity and tremor in mouse models of essential tremor. Eur J Pharmacol. 2011. 659: 30-36.

Rappaport MS, Gentry RT, Schneider DR, Dole VP. Ethanol effects on harmaline-induced tremor and increase of cerebellar cyclic GMP. Life Sci. 1984 Jan 2;34(1):49-56.

Schroeder D, Nasrallah HA. High alcoholism Rate in Patients with Essential Tremor. Am J Psychiatry. 1982;139(11): 1471-1473.

Shill HA, Bushara KO, Mari Z, Reich M, Hallet M. Open-label dose escalation of oral 1-octanol in patients with essential tremor. Neurology. 2004;62(12): 2320-2322.

Shipe WD, Barrow JC, Yang ZQ. Design synthesis, and evaluation of a novel 4-aminomethyl-4-fluoropiperidine as a T-type Ca2+ channel antagonist. J. Med. Chem. 2008;51(3):692-3695.

Simantov R, Snyder SH, Oster-Granite M-L. Harmaline-induced tremor in the rat: Abolition by 3-acetylpyridine destruction of cerebellar climbing fibers. Brain Res. 1976;114(1):144-151.

Sinton CM, Krosser BI, Walton KD, Llinás RR. The effectiveness of different isomers of octanol as blockers of harmaline-induced tremor. Pflugers Arch. 1989;414: 31-36.

Tai C, Yang Y, Pan M, Huang C, Kuo C. Modulation of subthalamic T-type Ca2+ channels remedies locomotor deficits in a rat model of Parkinson disease. J Clin Invest. 2011;121(8): 3289-3305.

Tröster AI, Pahwa R, Fields JA, Tanner CM, Lyons KE. Quality of life in Essential Tremor Questionnaire (QUEST): Development and initial validation. Parkinsonism Relat Disord. 2005;11(6):367-373.

Voller B, Lines E, McCrossin G, et al. Alcohol challenge and sensitivity to change of the essential tremor rating assessment scale. Mov Disord. 2014;29(4):555-558.

Zesiewicz TA, Ward CL, Hauser RA, Sanchez-Ramos J, Staffetti JF, Sullivan KL. A double blind placebo controlled trial of zonisamide (zonegran) in the treatment of essential tremor. Mov Disord. 2009;22(2): 279-282

Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: Treatment of essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2011;77(19):1752-1755.

15 APPENDICES

Appendix A – Efficacy assessments

Appendix B – Safety assessments

Appendix C – Cytochrome P450 Interaction Table

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

Appendix A1 – TETRAS Performance Scale

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor, are performed with the patient seated comfortably. For each item, score the highest amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out.

1. Head tremor: The head is rotated fully left and right and then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right with the head in mid position. The nose should be used as the landmark to assess and rate the largest amplitude excursions during the examination.

   0 = no tremor
   1 = slight tremor (< 0.5 cm)
   2 = mild tremor (0.5- < 2.5 cm)
   3 = moderate tremor (2.5-5 cm)
   4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.

   0 = no tremor
   1 = slight; barely perceptible tremor
   2 = mild: noticeable tremor
   3 = moderate: obvious tremor, present in most voluntary facial contractions
   4 = severe: gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended “aaah” sound and eee” sound for 5 seconds each. Then assess speech during normal conversation by asking patients “How do you spend your average day?”

   0 = no tremor
   1 = slight: tremor during aaah, and eee and no tremor during speech
   2 = mild: tremor in “aaah” and “eee” and minimal tremor in speech
   3 = moderate: obvious tremor in speech that is fully intelligible
   4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal reach posture is held for 5 seconds. The lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be estimated using the maximally displaced point of the hand at the point of greatest displacement along any single plane. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

   a) Forward outstretched postural tremor: Subjects should bring their arms forward, slightly lateral to midline and parallel to the ground. The wrist should also be straight and the fingers abducted so that they do not touch each other.

   b) Lateral "wing beating" postural tremor: Subjects will abduct their arms parallel to the ground and flex the elbows so that the two hands do not quite touch each other and are at the level of the nose. The fingers are abducted so that they do not touch each other. The posture should be held for 20 seconds.

   c) Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Only the position along the trajectory of greatest tremor amplitude is assessed. This will typically be either at the nose or at the point of full limb extension.

   For all three hand tremor ratings 0 = no tremor

   1 = tremor is barely visible
   1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude
   2.5 = tremor is 3- < 5 cm amplitude
   3 = tremor is 5- < 10 cm amplitude
   3.5 = tremor is 10- < 20 cm amplitude
   4 = tremor is > 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally parallel to the ground for 5 seconds each. Then perform a standard heel to shin maneuver with each leg, three times. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may exist in any part of the limb, including foot.

   0 = no tremor
   1 = slight: barely perceptible
   2 = mild, less than 1 cm at any point

3 = moderate tremor, less than 5 cm at any point
4 = severe tremor, greater than 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills 1/4 of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

   0 = normal
   1 = slight: tremor barely visible.
   2 = mild: obvious tremor
   3 = moderate: portions of figure not recognizable.
   4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand.. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

   0 = normal
   1 = slight: untidy due to tremor that is barely visible. 2 = mild: legible, but with considerable tremor.
   3 = moderate: some words illegible.
   4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X and instructs the subject to hold the tip of the pen "as close as possible to the dot (or center of an X) without touching it, (ideally approximately 1 mm) for 10 seconds ". Each hand is score separately.

   0 = no tremor
   1 = tremor is barely visible
   1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude
   2.5 = tremor is 3- < 5 cm amplitude
   3 = tremor is 5- < 10 cm amplitude
   3.5 = tremor is 10- < 20 cm amplitude
   4 = tremor is > 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20Ɣ. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk

   0 = no tremor
   1 = barely perceptible tremor
   2 = obvious but mild tremor, does not cause instability 3 = moderate tremor, impairs stability of stance
   4 = severe tremor, unable to stand without assistance

Appendix A2 – TETRAS Activities of Daily Living Scale

TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS©) V 3.1

Activities of Daily Living Subscale

Rate tremor's impact on activities of daily living (0 - 4 scoring).

1. Speaking
0 = Normal.
1 = Slight voice tremulousness, only when "nervous".
2 = Mild voice tremor. All words easily understood.
3 = Moderate voice tremor. Some words difficult to understand.
4 = Severe voice tremor. Most words difficult to understand.

2. Feeding with a spoon
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot feed with a spoon.

3. Drinking from a glass
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

4. Hygiene
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.
2 = Mildly abnormal. Some difficulty but can complete task.
3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy such as using two hands or using the less affected hand.
4 = Severely abnormal. Cannot complete hygiene activities independently.

5. Dressing
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with dressing.
2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.
3 = Moderately abnormal. Unable to do most dressing unless uses strategy such as using Velcro, buttoning shirt before putting it on or avoiding shoes with laces.
4 = Severely abnormal. Cannot dress independently.

6. Pouring
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with pouring.
2 = Mildly abnormal. Must be very careful to avoid spilling but may spill occasionally.
3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.
4 = Severely abnormal. Cannot pour.

7. Carrying food trays, plates or similar items
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.
2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.
3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.
4 = Severely abnormal. Cannot carry food trays or similar items.

8. Using Keys
0 = Normal
1 = Slightly abnormal. Tremor is present but can insert key with one hand without difficulty.
2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.
3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.
4 = Severely abnormal. Cannot put key in lock.

9. Writing
0 = Normal
1 = Slightly abnormal. Tremor present but does not interfere with writing.
2 = Mildly abnormal. Difficulty writing due to the tremor
3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.
4 = Severely abnormal. Cannot write.

10. Working. If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as it relates to housework:
0 = Normal .
1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.
2 = Mildly abnormal. Tremor interferes with work; able to do everything, but with errors. .
3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.
4 = Severely abnormal. Cannot perform any job or household work.

11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writing, etc)

Task _____

0 = Normal.
1 = Slightly abnormal. Tremor present but does not affect task.
2 = Mildly abnormal. Tremor interferes with task but is still able to perform task.
3 = Moderately abnormal. Can do task but must use strategies.
4 = Severely abnormal. Cannot do the task.

12. Social Impact

0 = None
1 = Aware of tremor, but it does not affect lifestyle or professional life.
2 = Feels embarrassed by tremor in some social situations or professional meetings.
3 = Avoids participating in some social situations or professional meetings because of tremor.
4 = Avoids participating in most social situations or professional meetings because of tremor.

Appendix A3 – QUEST

Quality of Life in Essential Tremor Questionnaire (QUEST)

Patient's Name: _____ ID: _____ Date: ____ / ____ / ____

Gender: ☐ Male ☐ Female Date of Birth: ____ / ____ / ____

Heath Status

In general, how would you rate your overall health? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Overall Quality of Life

Overall, how would you rate your quality of life? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

General Information

In the past month, has your tremor interfered with your sexual satisfaction?	Y	N
In the past month, have you had side effects from tremor medications?	Y	N
In the past month, have you been satisfied with the tremor control achieved by your medications?	Y	N

Which most appropriately describes your work status?

- ☐ Never worked
- ☐ Not working, retired because of tremor
- ☐ Not working, retired NOT due to tremor
- ☐ Working full time
- ☐ Working part time

TREMOR SELF ASSESSMENT

For the purposes of this questionnaire, tremor is defined as uncontrollable shaking or quivering of the body part in question.

On a typical day, how many of your waking hours do you have tremor in ANY body part?

Circle: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Put a mark in the box to rate the severity of your tremor in each of the body parts listed below.

None - no tremor at any time
Mild - mild tremor not causing difficulty in performing any activities
Moderate - tremor causes difficulty in performing **some** activities
Marked - tremor causes difficulty in performing **most** or **all** activities
Severe - tremor **prevents** performing some activities

		None	Mild	Moderate	Marked	Severe
1.	Head	☐	☐	☐	☐	☐
2.	Voice	☐	☐	☐	☐	☐
3.	Right arm/hand	☐	☐	☐	☐	☐
4.	Left arm/hand	☐	☐	☐	☐	☐
5.	Right leg/foot	☐	☐	☐	☐	☐
6.	Left leg/foot	☐	☐	☐	☐	☐

continued on next page

For each question below, please mark the box which best describes your current situation.

For example: N R **S** F A

N = **N**ever/No
R = **R**arely
S = **S**ometimes
F = **F**requently
A = **A**lways/Yes
NA = **N**ot **A**pplicable

1.	My tremor interferes with my ability to communicate with others.		N	R	S	F	A
2.	My tremor interferes with my ability to maintain conversations with others.		N	R	S	F	A
3.	It is difficult for others to understand my speech because of my tremor.		N	R	S	F	A
4.	My tremor interferes with my job or profession.	NA	N	R	S	F	A
5.	I have had to change jobs because of my tremor.	NA	N	R	S	F	A
6.	I had to retire or take early retirement because of my tremor.		N				A
7.	I am only working part time because of my tremor.	NA	N				A
8.	I have had to use special aids or accommodations in order to continue my job due to my tremor.	NA	N	R	S	F	A
9.	My tremor has led to financial problems or concerns.		N	R	S	F	A
10.	I have lost interest in my hobbies because of my tremor.		N	R	S	F	A
11.	I have quit some of my hobbies because of my tremor.		N	R	S	F	A
12.	I have had to change or develop new hobbies because of my tremor.		N	R	S	F	A
13.	My tremor interferes with my ability to write (for example, writing letters, completing forms).		N	R	S	F	A
14.	My tremor interferes with my ability to use a typewriter or computer.	NA	N	R	S	F	A
15.	My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone).		N	R	S	F	A
16.	My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items).		N	R	S	F	A
17.	My tremor interferes with dressing (for example, buttoning, zipping, tying shoes).		N	R	S	F	A
18.	My tremor interferes with brushing or flossing my teeth.		N	R	S	F	A
19.	My tremor interferes with eating (for example, bringing food to mouth, spilling).		N	R	S	F	A
20.	My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring).		N	R	S	F	A
21.	My tremor interferes with reading or holding reading material.		N	R	S	F	A
22.	My tremor interferes with my relationships with others (for example, my family, friends, coworkers).		N	R	S	F	A
23.	My tremor makes me feel negative about myself.		N	R	S	F	A
24.	I am embarrassed about my tremor.		N	R	S	F	A
25.	I am depressed because of my tremor.		N	R	S	F	A
26.	I feel isolated or lonely because of my tremor.		N	R	S	F	A
27.	I worry about the future due to my tremor.		N	R	S	F	A
28.	I am nervous or anxious.		N	R	S	F	A
29.	I use alcohol more frequently than I would like to because of my tremor.		N	R	S	F	A
30.	I have difficulty concentrating because of my tremor.		N	R	S	F	A

THANK YOU!

QUEST Scoring

Patient Name: _____ Date: _____

If a question is Not Applicable, "X" through NA and leave blank--do not assign a score of 0.

Scoring algorithm: $\frac{\text{Total } \textbf{applicable} \text{ points for each dimension}}{\text{Total possible points (\# of } \textbf{applicable} \text{ questions x 4) for each dimension}} \times 100 =$ dimension score

N=0 R=1 S=2 F=3 A=4 NA=blank Note: Questions 6, 7, 11, & 12--0 OR 4 points possible (if applicable).

Communication

1. My tremor interferes with my ability to communicate with others. _____
2. My tremor interferes with my ability to maintain conversations with others. _____
3. It is difficult for others to understand my speech because of my tremor. _____

Work and Finances

4. My tremor interferes with my job or profession. NA _____
5. I have had to change jobs because of my tremor. NA _____
6. I had to retire or take early retirement because of my tremor. _____
7. I am only working part time because of my tremor. NA _____
8. I have had to use special aids or accommodations in order to continue my job due to my tremor. NA _____
9. My tremor has led to financial problems or concerns. _____

Hobbies and Leisure

10. I have lost interest in my hobbies because of my tremor. _____
11. I have quit some of my hobbies because of my tremor. _____
12. I have had to change or develop new hobbies because of my tremor. _____

Physical

13. My tremor interferes with my ability to write (for example, writing letters, completing forms). _____
14. My tremor interferes with my ability to use a typewriter or computer. NA _____
15. My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone). _____
16. My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items). _____
17. My tremor interferes with dressing (for example, buttoning, zipping, tying shoes). _____
18. My tremor interferes with brushing or flossing my teeth. _____
19. My tremor interferes with eating (for example, bringing food to mouth, spilling). _____
20. My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring). _____
21. My tremor interferes with reading or holding reading material. _____

Psychosocial

22. My tremor interferes with my relationships with others (for example, my family, friends, coworkers). _____
23. My tremor makes me feel negative about myself. _____
24. I am embarrassed about my tremor. _____
25. I am depressed because of my tremor. _____
26. I feel isolated or lonely because of my tremor. _____
27. I worry about the future due to my tremor. _____
28. I am nervous or anxious. _____
29. I use alcohol more frequently than I would like to because of my tremor. _____
30. I have difficulty concentrating because of my tremor. _____

Appendix B1 – C-SSRS

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

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

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

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

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

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

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

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

 C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

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

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

Appendix B2 – Epworth Sleepiness Scale Sample

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (yrs): _____ Your gender (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting inactive in a public place (e.g., a theater or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car or bus, while stopped for a few minutes in traffic	___

THANK YOU FOR YOUR COOPERATION

ESS - United States/English - Version of 16 Jan 15 - Mapi.
ID037309 / ESS_AU1.0_eng-US1.doc

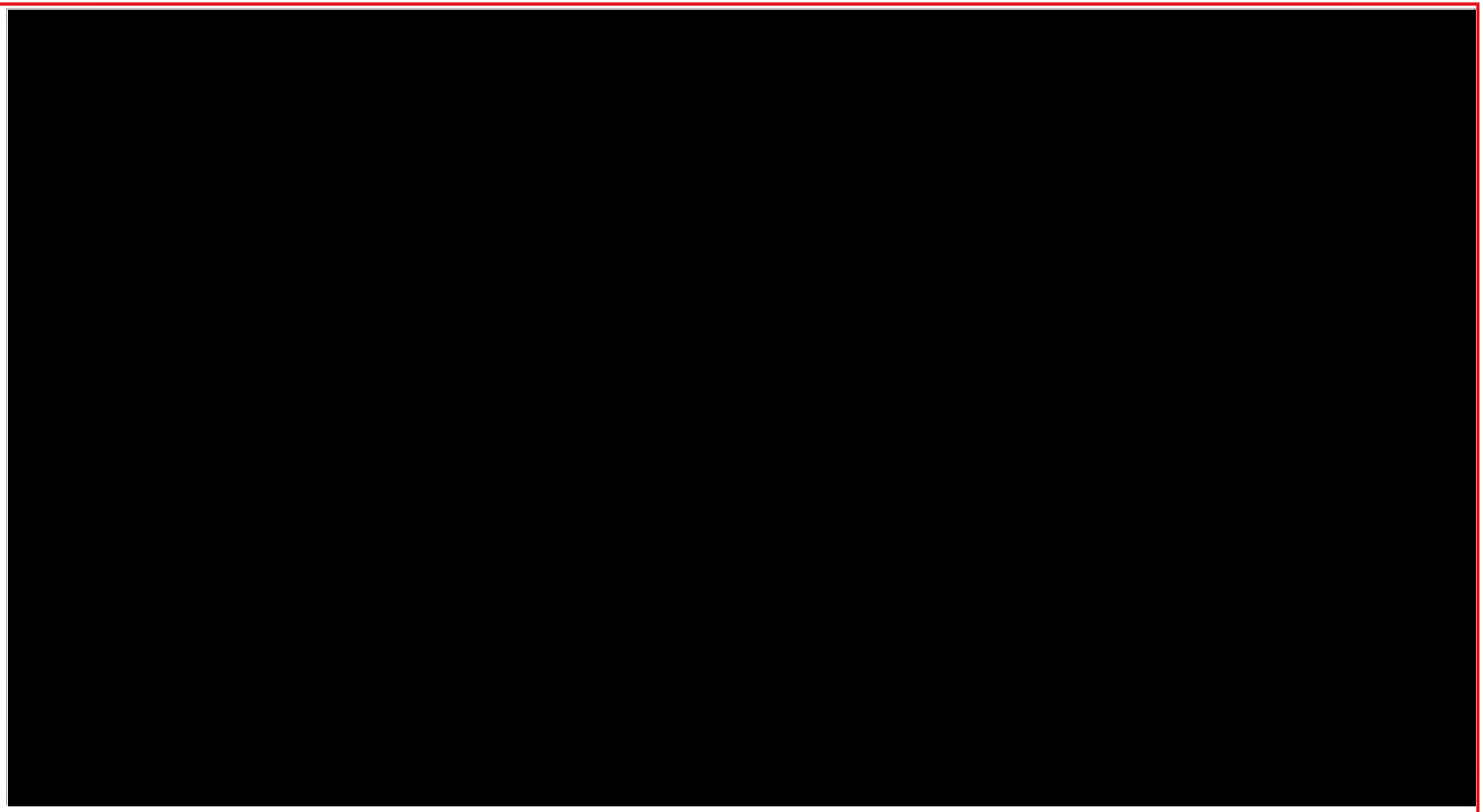
Appendix C – Cytochrome P450 Drug Interaction Table

PROHIBITED CYP3A4 INHIBITORS*	PROHIBITED CYP2C9 INHIBITORS*
HIV antivirals (delaviridine, indinavir, nelfinavir, ritonavir) amiodarone cimetidine clarithromycin diltiazem erythromycin fluvoxamine grapefruit juice itraconazole ketoconazole nefazodone suboxone troleandomycin verapamil	amiodarone fluconazole izoniazid

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

PROHIBITED CYP3A4 INDUCERS*	PROHIBITED CYP2C9 INDUCERS*
carbamazepine efavirenz nevirapine phenobarbital phenytoin pioglitazone primidone rifabutin rifampin St. John's Wort troglitazone	rifampin secobarbital
Prohibited moderate and strong inducers of CYP3A4 and CYP2C9 include the lists above, but are not limited to the medications and agents listed	

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



Clinical Study Protocol

Main Title:

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

Protocol Number: CX-8998-CLN2-001

Amendment 2, Version Number: 3.0 **Date:** 30 May 2018
Amendment 1, Version Number: 2.0 **Date:** 08 August 2017
Original Version Number: 1.2 **Date:** 06 April 2017

IND #: 130296

Official Short Title:

T-CALM: Tremor CAv3 Modulation Study

Confidentiality Statement:

SIGNATURE PAGE FOR SPONSOR

Study No. CX-8998-CLN2-001

Protocol Title: A Phase 2 Randomized Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

Approved by the following:

Cavion, Inc.
One Broadway
Cambridge, MA 02142

SIGNATURE PAGE FOR INVESTIGATOR

Study No.: CX-8998-CLN2-001

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor

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

_____	_____	_____
Investigator Name	Signature	Date

STUDY ORGANIZATIONAL STRUCTURE

Sponsor:	Cavion, Inc. 600 East Water Street Suite E Charlottesville, VA 22902 [redacted]
Study Safety Representative:	24-hour SAE Reporting: Primary Contact: Premier Research [redacted]

COMPLIANCE STATEMENT

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

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

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

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

PROTOCOL SYNOPSIS

Study Title: A Randomized Phase 2, Double-Blind, Placebo-Controlled Study of CX-8998 for Essential Tremor	
Name of Finished Product: CX-8998	
Protocol Number: CX-8998-CLN2-001	**Study Phase:** 2
Clinical Sites: Multiple sites in the United States	

Primary Objective:

To assess the efficacy of CX-8998, in doses up to 10 mg twice daily (BID), in reducing the severity of essential tremor (ET)

Secondary Objectives:

1. To assess changes in tremor-affected activities of daily living
2. To objectively quantify changes in ET 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 two primary metabolites (M01 and M02) in plasma

Exploratory Objectives:

1. To assess changes in quality of life in subjects with ET
2. To assess study drug effects on digital biomarker patterns associated with ET (in a subset of subjects)
3. To use the plasma concentrations of CX-8998 and its 2 primary metabolites in population pharmacokinetic/pharmacodynamic (PK/PD) analyses to evaluate the exposure-efficacy and exposure-safety relationships

Study Design:

This is a multicenter, double-blind, placebo-controlled, parallel-group study consisting of a screening period of up to 4 weeks (with the exception of subjects on primidone at baseline who will be allowed 6 weeks of screening to allow for safe discontinuation). Screening results from all patients meeting the eligibility requirements will be further assessed by the sponsor medical personnel for final approval of suitability for inclusion in the study. Randomized subjects will enter a 4-week, double-blind, dose-titration treatment period, followed by a 1-week safety follow-up period following the last dose of study medication.

Subjects will be randomized to one of two treatment groups. Group A will receive titrating doses of CX-8998 up to 10 mg BID and Group B will receive placebo. Subject randomization will be stratified by presence or absence of a single concomitant anti-tremor medication and by site-type (substudy vs non-substudy).

Tremor will be assessed via The Essential Tremor Rating Assessment Scale (TETRAS) and Kinesia ONE accelerometry. To reduce the potential for bias in the assessments of efficacy, all subjects will be video-recorded during the TETRAS performance scale testing according to a script. The video recordings will be rated in a blinded manner by qualified, independent raters. 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).

Subjects will be screened up to 4 weeks prior to initiation of dosing. Subjects taking primidone at screening who are otherwise deemed eligible for participation and are willing to discontinue primidone will be allowed an additional 2 weeks of screening (a total of 6 weeks) to ensure safe primidone

discontinuation. At Baseline, subjects will undergo safety and tremor assessments prior to dosing, will receive their first dose of study drug and will be monitored for safety for one hour following dosing. For one week, subjects will receive 4 mg (or matching placebo) twice daily. Subjects will return to the clinic on Day 8 for safety monitoring and dose up-titration to 8 mg (or matching placebo) twice daily. At Day 15 (Week 3) subjects will return to clinic for safety and efficacy assessments and final dose up-titration to 10 mg (or matching placebo) twice daily. The final efficacy visit will occur at Day 28 (Week 4). A final safety visit will occur at Day 35 (Week 5). Should subjects experience intolerable adverse events (AEs) at 4 mg BID, 8 mg BID or 10 mg BID, the dose may be decreased at Day 8 or Day 15 to the next lowest dose one time (or 2 mg BID in the case of the 4 mg BID dose). A dose reduction may be made if necessary prior to scheduled visits at Day 8 or Day 15. Re-up-titration is not allowed. Subjects not tolerating the next lowest dose or not tolerating 2 mg BID will be withdrawn from treatment. The study safety representative should be notified as soon as is feasible when a dose reduction is made.

Study Population:
Inclusion Criteria

1. Signed informed consent form (ICF) indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
2. Men or non-pregnant, non-breastfeeding women 18 to 75 years-of-age who are able to read and understand English.
3. Diagnosis of definite or probable bilateral essential tremor (ET) as defined by the Tremor Investigational Group with involvement of the hands and arms without present causes of enhanced physiologic tremor (Deuschl et al., 1998)
4. Diagnosis of ET before the age of 65
5. Tremor severity score of at least 2 in at least one upper extremity on at least one of the three maneuvers on the TETRAS scale
6. Total TETRAS performance score of at least 15. Note: Inclusion thresholds, including thresholds for items 5 & 6, should not be shared with study subjects or caregivers to limit Baseline inflation.
7. One concomitant anti-tremor medication (other than primidone) is allowed. Note: Primidone is NOT an allowed anti-tremor medication. Subjects must have been on a stable dose for at least one month prior to screening and must have no change in dose in the single concurrent anti-tremor medication for the duration of the study. If on primidone, subjects are allowed to extend their screening period by 2 weeks (for a total of 6 weeks) and discontinue primidone under the supervision of the investigator.
8. Able and willing to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
9. Subjects with reproductive capability including all males and women of child-bearing potential (WOCBP) must agree to practice continuous abstinence or adequate contraception methods (appropriate double barrier method or oral, patch, implant, or injectable contraception) from as soon as feasible during screening period until at least 30 days after the last dose (i.e., intermittent abstinence based on “rhythm”, temperature monitoring, or other means of timing is not acceptable). WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy) or is not post-menopausal. Post-menopausal is defined as:
    a. Amenorrhea ≥ 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL;

b. Amenorrhea ≥ 12 consecutive months in women ≥ 62 years old (FSH testing is not required).

Male subjects with a partner of child-bearing potential must be surgically sterilized or be willing to use condoms with spermicide from as soon as feasible during screening period until at least 30 days after the last dose.

10. Approval by the sponsor medical personnel as to final suitability for the study

Exclusion Criteria

1. Exposure to tremorgenic drugs or drug withdrawal states within the 30 days prior to the first planned dose of study drug
2. Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor
3. History or clinical evidence of psychogenic tremor origin
4. Known history of other medical or neurological conditions that may cause or explain subject's tremor, including, but not limited to:
   a. Parkinson's disease
   b. dystonia
   c. cerebellar disease, other than essential tremor
   d. Traumatic Brain Injury
   e. alcohol abuse or withdrawal
   f. mercury poisoning
   g. hyperthyroidism
   h. pheochromocytoma
   i. head trauma or cerebrovascular disease within 3 months prior to the onset of essential tremor
   j. multiple sclerosis
   k. polyneuropathy
   l. family history of Fragile X syndrome
5. Prior MR-guided Focused Ultrasound or surgical intervention (e.g., deep brain stimulation, ablative thalamotomy or gamma knife thalamotomy) for treatment of tremor
6. Botulinum toxin injection in the 6 months prior to screening
7. Currently using more than one anti-tremor medication.
8. Experiencing clinical benefit from and/or is not willing to discontinue primidone
9. Use of medication(s) in the past month that might produce tremor or interfere with the evaluation of tremor, such as, but not limited to: CNS-stimulants, lithium, amiodarone, metoclopramide, theophylline, and valproate
10. Inability to refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor on study visit days, such as but not limited to stimulant decongestants, beta-agonist bronchodilators, caffeine, alcohol and tobacco, based on investigator assessment at baseline
11. Positive urine drug screen unless explained by use of an allowed prescription medication (Section 10.1.6)
12. Regular use of more than two units of alcohol per day
13. Sporadic use of a benzodiazepine, sleep medication or anxiolytic to improve sleep performance. Stable use at a consistent dose is allowed as long as tremor persists against the background of regular medication use. Use on the evening prior to a study visit is prohibited.
14. Use of prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be strong inhibitors or inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study, including primidone

15. Concurrent illnesses that would be a contraindication to trial participation, including, but not limited to:
    a. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before screening
    b. NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
    c. Clinically significant ECG abnormality per the investigator assessment or any of the following:
        (1) QTcF >450 msec (males) or >470 msec (females)
        (2) PR interval >250 msec
        (3) Atrioventricular block of second degree or higher, including Mobitz I
        (4) Persistent sinus bradycardia < 50 beats per minute; persistent means the bradycardia is present on the first ECG and on one repeat ECG performed on another day
        (5) For other ECG findings (e.g., including, but not necessarily limited to, tachycardia, bundle branch block, frequent ectopic beats, etc.) the investigator should send a scanned, identity-blinded copy of the ECG tracing to the study safety representative for review
        (6) The presence of a cardiac pacemaker does not automatically exclude eligibility. The specifics must be discussed with the study safety representative to make a determination of eligibility.
    d. Known infection with HIV, hepatitis B, or hepatitis C, unless curative therapy completed for hepatitis C with negative PCR for HCV RNA
    e. Significant hepatic (AST/ALT > 2X upper limit of normal) or renal disease (creatinine clearance <39 mL/min)
    f. Significant psychiatric history including mood disorders and alcohol or substance abuse within the last year
    g. A current C-SSRS score of 4 or 5 at screening or history of suicide attempt at any time during the past year
    h. Clinically significant impaired balance or is considered at increased risk for falls
    i. Symptomatic orthostatic hypotension
16. Psychological, social, familial, or geographical reasons that would hinder or prevent compliance with the requirements of the protocol or compromise the informed consent process
17. Any other condition and/or situation that causes the investigator or study safety representative to deem a subject unsuitable for the study (e.g., due to expected study medication non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study–related procedures)
18. Treatment with an investigational agent within 30 days prior to the first dose of CX-8998 or planning to receive an investigational agent during the study

Planned Number of Patients:

Approximately 106 eligible subjects will be randomized.

Test Product, Dose, and Mode of Administration:

CX-8998, 2 mg capsule, oral

Reference Product, Dose, and Mode of Administration:

Placebo capsule to match CX-8998, oral

Duration of Treatment:

28 days

Administration:

CX-8998 will be administered as 4 mg (2 capsules) twice daily (8 mg/d) in the first week; increasing to 8 mg (4 capsules) BID (16 mg/d) in week 2, to a target of 10 mg (5 capsules) BID (20 mg/d) in weeks 3 and 4. Study drug should be administered with food in the morning and evening (goal is for doses to be 12 hours apart).

Duration of Subject Study Participation:

Up to 12 weeks including screening, treatment and safety follow-up

Endpoints:

Primary Endpoint:

Change from Baseline to Day 28 on the TETRAS Performance subscale, as scored by the central rater

Secondary Endpoints:

1. Change from Baseline to Day 28 on the TETRAS Activity of Daily Living subscale
2. Change from Baseline to Day 28 in accelerometry score as measured by Kinesia ONE
3. Safety and tolerability endpoints are as follows: adverse events throughout the study, changes from baseline in QTcF and other ECG parameters throughout the study, clinical safety laboratory assessments (clinical chemistry, hematology, and urinalysis) throughout the study, changes from baseline C-SSRS throughout the study, vital signs throughout the study, number (%) of subjects who did not complete the study, number (%) of subjects who did not complete the study due to adverse events and the Epworth Sleepiness Scale (ESS)

Exploratory Endpoints:

1. Change from Baseline on the Total TETRAS score to Day 15 and Day 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 accelerometry score as measured by Kinesia ONE
4. Change from Baseline to Day 15 and Day 28 in Kinesia ONE amplitude measures
5. Treatment success at the end of therapy as measured by Patient Global Impression of Change (PGIC)
6. Treatment success at the end of therapy as measured by Clinical Global Impression of Improvement (CGI-I)
7. Treatment success at the end of therapy as measured by Goal Attainment Scaling (GAS)
8. Change from Baseline in Quality of Life in Essential Tremor Questionnaire (QUEST)
9. 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).

Pharmacokinetic Variables and Endpoints:

PK measure will be determination of plasma concentration of CX-8998 and its metabolites (including, but not limited to, M01 and M02) associated with various visits and doses of CX-8998. Concentrations will also be incorporated into a population PK/PD model that will estimate the peak exposure (C_{max}) and overall exposure (AUC) of CX-8998.

Statistical Methods:

Sample size justification:

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

A sample size of 53 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 in the TETRAS performance subscale when the standard deviation is 7.5 and alpha=0.05 (PASS 2008: Two sample t-test – Normal Non-Parametric Adjustment) and to account for dropouts and patients who are excluded because of major protocol deviations.

A blinded interim analysis of variance will be conducted once 50% of subjects have been enrolled and followed for 28 days or discontinued from the study. Based on the results of this analysis, the sample size may be modified to achieve the desired power for the study.

Primary efficacy analysis:

The primary efficacy analysis of the TETRAS performance subscale will be conducted using an analysis of covariance (ANCOVA) model with fixed effects for treatment, concomitant anti-tremor medication use, site type and Baseline value of the TETRAS performance subscale. The primary hypothesis to be tested will be if the mean change from Baseline in TETRAS performance scale indicates that the CX-8998 arm is different from placebo. All testing will be performed using the least square (LS) means from the ANCOVA model and a two-sided test at the alpha=0.05 level of significance. If the data indicate a departure from the normal distribution, a corresponding rank test will be performed.

Secondary efficacy analyses:

Analyses of the continuous secondary and exploratory endpoints will be conducted using the same type of ANCOVA model as described for the primary endpoint, with baseline values included only as applicable. All secondary and exploratory analyses will be conducted using two-sided tests at the alpha=0.05 level of significance.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

GLOSSARY OF TERMS AND ABBREVIATIONS

Abbreviation	Description
ADL	activity(ies) of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	Area under the concentration-time curve
β-HCG	beta human chorionic gonadotropin
BMI	body mass index (kg/m^2)
BP	Sitting systolic and diastolic blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CI	confidence interval
CNS	central nervous system
C_{max}	maximum concentration
C_{min}	minimum concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
dL	deciliter
DMC	data monitoring committee
ECG	electrocardiogram
EEG	electroencephalogram
ESS	Epworth Sleepiness Scale
ET	essential tremor
F	Fahrenheit
GAS	Goal Attainment Scale
GCP	Good Clinical Practice
GRC	Global Rating of Change (scale)
h	hour(s)

Abbreviation	Description
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IO	inferior olive
IRB	Institutional Review Board
ITT	intent-to-treat population
IV	intravenous
IWRS	interactive web response system
kg	kilogram
LDH	lactic dehydrogenase
LS	least square
MEG	magnetoencephalography
µg	microgram
mg	milligram
mL	milliliter
mM	millimolar
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHV	normal healthy volunteers
PCR	polymerase chain reaction
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
RNA	ribonucleic acid
QOL	quality of life
QUEST	Quality of Life in Essential Tremor Questionnaire
SAE	serious adverse event
SD	standard deviation
SWA	slow wave activity

Abbreviation	Description
UM-PDHQ	University of Miami Parkinson's Disease Hallucinations Questionnaire
Vd	Volume of distribution
WOCBP	women of childbearing potential
$t_{1/2}$	terminal half life
TEAE	Treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
T_{max}	time to maximum concentration

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

1.1.1 Essential Tremor

Essential tremor (ET) is a neurological condition that causes a rhythmic trembling of the hands, head, voice, legs or trunk.

The consensus statement of the Movement Disorder Society on tremor (Deuschl et al., 1998) includes the following clinical criteria for the diagnosis of ET: bilateral postural tremor with or without kinetic tremor, involving hands and forearms, that is both visible and persistent without:

1. Other abnormal neurological signs (except Froment's sign);
2. Known causes of increased physiological tremor;
3. Concurrent or recent exposure to tremorgenic drugs or the presence of a drug withdrawal state;
4. Direct or indirect trauma to the nervous system within 3 months before the onset of tremor;
5. Historical or clinical evidence of psychogenic origins, and
6. Convincing evidence of sudden onset or evidence of stepwise deterioration.

1.1.2 The Impact of Essential Tremor

Essential Tremor is among the most prevalent of all movement disorders in adults. In a 2010 meta-analysis, Louis et al. (1998) estimated the pooled prevalence (all ages) to be 0.9%, with statistically significant heterogeneity across studies ($I2 = 99\%$, $p<0.001$). The prevalence in adults ≥65 years old was estimated to be 4.6% (Louis and Ferreira, 2010).

While ET does not shorten life expectancy, its impact on the patient's ability to perform activities of daily living (ADLs) at home and in the workplace negatively affects quality of life, social interactions, and mental status (Lorenz et al., 2006; Louis & Machado, 2015; George and Lydiard, 1994). It is increasingly recognized that ET is not a monosymptomatic disorder (Bermejo-Pareja, 2011). Effects include everyday activities such as writing and eating (Zesiewicz et al., 2011). Effects on cognitive functions are heterogeneous and include impairments in attention, executive function, verbal fluency, visuospatial functioning, memory, and working memory (Bermejo-Pareja & Puertas-Martin, 2012). Sleep disturbances and fatigue are also more common in patients with ET than in their age-matched controls (Chandran et al., 2012).

1.1.3 Treatment of Essential Tremor

Propranolol is the only medication approved for the treatment of ET. None of the other medications currently used as ET therapy were developed specifically for this purpose. In 2011, the American Academy of Neurology (AAN) conducted an evidence-based update of the AAN 2005 practice parameters regarding the treatment of ET (Zesiewicz et al., 2011). The following conclusions and recommendations were unchanged from the 2005 guideline:

- Propranolol, primidone (Level A, established as effective);

- Alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate (Level B, probably effective);
- Nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation (DBS), thalamotomy (Level C, possibly effective), and
- Gamma knife thalamotomy (Level U, insufficient evidence).

Changes to conclusions and recommendations from the previous guideline include the following:

- Levetiracetam and 3,4-diaminopyridine probably do not reduce limb tremor in ET and should not be considered (Level B);
- Flunarizine possibly has no effect in treating limb tremor in ET and may not be considered (Level C), and
- There is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozapine as treatment for ET (Level U).

Alternatives to medications include invasive surgical treatments (DBS and gamma-knife thalamotomy), non-invasive MR-guided Focused Ultrasound, botulinum toxin, and alcohol (alcohol is associated with habituation and rebound effects; in fact, patients with essential tremor demonstrate higher rates of alcoholism (Schroeder, 1982).

The lack of any new positive recommendations by the 2011 Academy of Neurology evidence-based guideline update on the treatment of ET (as compared to the 2005 guidelines) attests to the poor yield of present approaches to drug discovery (Zesiewicz et al., 2011). Given that half of the patients with ET ≥65 years of age take medication for tremor (Louis et al., 2000) and the 2012 demographic data showed that of the 1,006.9 million persons living in the European Union, the United States, Japan, Canada, Australia, and New Zealand, 163.7 million persons are ≥65 years of age, it can be estimated that 3.8 million persons in this age group in these countries are potential candidates for treatment of ET.

A survey of 223 patients (52.7% male, mean age of 63.4 (±17.9) years of age at last visit) in a clinical database revealed that 70.9% had taken primidone or propranolol, and 56.3% had discontinued one or both medications (Diaz & Louis, 2010). Reasons for discontinuing primidone included side effects (51.9%), lack of efficacy (19.0%), or both (20.3%). Because approximately 30%-50% of patients with ET will not respond adequately to currently available medications (Koller & Vetere-Overfield, 1989), new therapies for ET are warranted.

1.2 Rationale for Evaluating CX-8998 in Essential Tremor

1.2.1 Cav3 and its Role in Neurological Disorders with Excessive or Abnormal Rhythmicity

Calcium is a ubiquitous intracellular second messenger critical for cellular functions. The elevation of free intracellular Ca^{2+} levels triggers various responses including the activation of Ca^{2+} dependent enzymes, the secretion of neurotransmitters, and muscle contraction. Multiple calcium ion channels regulate calcium influx in response to membrane depolarization, voltage changes, or

substrate, which include the pore-forming alpha$_1$ subunit Cav3 channel (Catterall, 2005; Adams & Snutch, 2007).

The T-type calcium channel, Cav3, its three (3) isoforms (3.1, 3.2 and 3.3), and their genes *CACNA1G, CACNA1H, and CACNA1I* were discovered and cloned in the early 1990s, where their function as low-threshold, voltage-gated calcium channel was elucidated (Cribbs et al., 1998). T-type ("T" is for transient) calcium channels are low voltage-activated (LVA) channels predominantly found in neurons. As stated previously, a unique and discriminating property of T-type channels (Cav3) is their ability to activate upon small depolarization of the membrane, contributing to the setting of the resting membrane potential and allowing a surge of calcium entry into excitable cells at the beginning of an action potential. In pathologic states, Cav3 is either upregulated or found to have increased activity, becoming a selective target for specific neurologic diseases (Tai et al., 2011; Park et al., 2010; Bourinet et al., 2005).

Cav3's isoforms are expressed throughout the central nervous system (CNS) and the peripheral nervous system (PNS), including the thalamocortical pathway[1] (Ertel et al., 2000). Deep cerebellar nuclei (DCN), Substantia nigra (SNC), Globus pallidus externa (Gpe), globus pallidus interna (GPi), subthalamic nucleus (STN), have been noted to have oscillations in healthy hosts and excessive rhythmicity in animals and humans with pathologic conditions of the nervous system. It has been discovered that Cav3 is a mediator of subthreshold oscillations and excessive rhythmicity in pathophysiologic states found in tremor, neuropathic pain, epilepsy and Parkinson's disease (Handforth et al., 2005; Llinás et al., 1999; Llinás, 2003; Park et al., 2013).

The inferior olive (IO) appears to function as a tremor generator and animal models suggest the IO functions as an intrinsic pacemaker (Long et al., 2002). Essential tremor may result from excessive rhythmic synchronous firing of populations of neurons in the IO, which affects the function of the cerebellum (Elble et al., 1996). Cav3 is highly expressed in the IO and the cerebellum. Cav3.1 is the predominate Cav3 isoform expressed in the inferior olive (IO). Within the cerebellar system it is also found on Purkinje cell bodies, DCN, stellate, basket, dendrites and Golgi cells (Molineux et al., 2006). In these locations, Ca_V3 functions as a tremor generator and ongoing rhythm pacemaker (Park et al., 2010). Park et al. reported that tremor-related oscillations in the olivocerebellar pathways are a neural signature for essential tremor and that $Ca_V3.1$ plays a critical role in the onset of tremor-related rhythms (Park et al., 2010).

Harmaline, a plant alkaloid that acts on the cerebellum and IO, induces tremor in animals. Harmaline-induced tremor in animals, like ET, involves the cerebellum. Lesions of the IO reduce harmaline tremors in rats (Simantov et al., 1976). Harmaline tremor is similar to clinical ET in a number of respects, including cerebellar hypermetabolism and a positive response to all known anti-ET agents, including alcohol, primidone, propranolol, gabapentin, zonisamide, and benzodiazepines.

1.2.2 Cav3 Antagonists in Animal Studies

Multiple Cav3-active compounds have been successfully evaluated for their impact on tremor in animal studies. Handforth et al. tested whether both clinically available and experimental

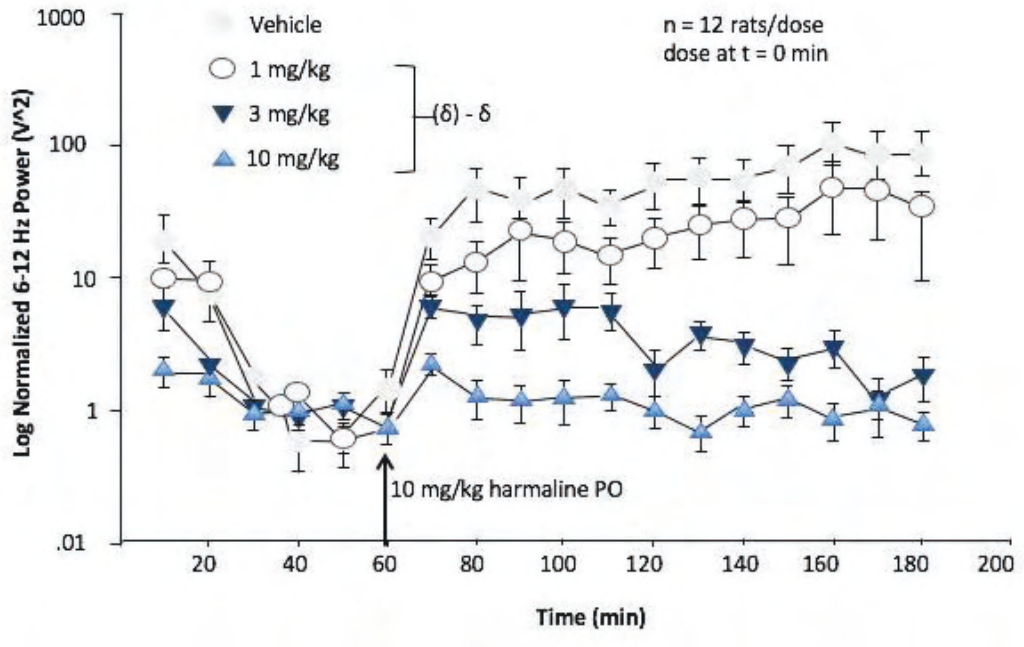
[1] Cav3.1 is the most common isoform in the thalamocortical pathway

compounds that antagonize T-type calcium channel currents suppress tremor in two mouse models: harmaline-induced tremor and the GABA(A) receptor α1 subunit-null model. Mice were administered ethosuximide, zonisamide, the neuroactive steroid ECN, the 3,4-dihydroquinazoline derivative KYS05064, the mibefradil derivative NNC 55-0396, or vehicle. Tremor was measured using digitized spectral motion power analysis. In non-sedating doses, each compound reduced tremor in the harmaline-induced model by at least 50% (range of maximal suppression: 53-81%), and in the GABA(A) α1-null model by at least 70% (range 70%-93%) (Handforth et al., 2010). Quesada et al. evaluated both mibefradil and NNC-55-0396 in the $GABA_{A1}$ null model and harmaline animal models of tremor and observed reductions in tremor (Quesada et al., 2011).

Tremor suppression by alcohol has been remarked on since the 19th century. Suppression of harmaline tremor by ethanol has been well replicated (Martin et al., 2005; Rappaport et al., 1984). Isomers of octanol (a fatty alcohol) suppress harmaline tremor in rodents (Martin & Handforth, 2006; Sinton et al., 1989); subsequently 1-octanol was found to reduce tremor in ET (Shill et al., 2004). Gamma-hydroxybutyrate also suppresses harmaline tremor and ET tremor (Frucht et al., 2005; Paterson et al., 2009). 1-octanol functions as a Cav3 antagonist (Sinton et al. 1989).

Finally, CX-8998's analogue TTA-P2 has been evaluated in the harmaline model of tremor and demonstrated significant improvement (Figure 1). Rats were placed in one of four conditions, vehicle, versus TTA-P2 1, 3 or 10 mg/kg. TTA-P2 normalized both physiologic tremor prior to harmaline administration and harmaline-induced tremor in a dose-dependent response (Shipe et al., 2008).

Figure 1: TTA-P2 Normalization of Harmaline Tremor in Rats



Rats assigned to vehicle or one of three ascending doses of TTA-P2 demonstrated a dose-dependent response to harmaline-induced tremor following *per os* administration. Prior to administration of harmaline, rats also demonstrated dose-dependent response to a reduction in physiologic tremor (Shipe et al., 2008).

1.2.3 Ca_V3 as a Target for Treatment of Essential Tremor: Clinical Experience

A number of T-type calcium channel-active compounds have been developed to treat various neurologic diseases which may share a common pathophysiology.

Multiple studies of zonisamide have shown effectiveness in the treatment of tremor as measured by accelerometry and tremor rating scales, however all were limited by poor tolerability and/or excessive premature discontinuations from treatment (Handforth et al., 2009; Zesiewicz et al., 2009; Morita et al., 2005; Bermejo-Pareja et al., 2008; Ondo, 2007; Miwa, 2008). The same finding of effectiveness limited by poor tolerability was also reported for topiramate, a weak Ca_V3 inhibitor (Chang et al., 2015). So, while Ca_V3 is a biologically-validated target for development of ET therapeutics, the search for a safe and effective compound has, to date, been unsuccessful.

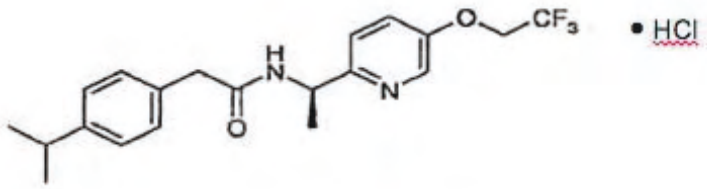
In summary, the evidence that tremor arises from dysfunction in the inferior-olive – cerebellum network, that excessive rhythmicity may be observed in the thalamocortical network, and that both share mediation via the Ca_V3 calcium channel, whose increased activity is a common pathophysiology, supports the animal and human evaluation results of Ca_V3 antagonists for tremor.

1.3 Non-Clinical Pharmacology

Please refer to the current edition of the Investigator Brochure for a full discussion of prior non-clinical evaluations of CX-8998. CX-8998 is the new name applied to the Merck & Co., Inc. pharmaceutical product known as MK-8998. The name CX-8998 is used here in reference to all prior non-clinical studies conducted by Merck & Co., Inc. CX-8998 was previously investigated for the treatment of insomnia and schizophrenia.

CX-8998, as the HCl salt, is a potent, selective, and state dependent small molecule blocker of T-type calcium channels. The structure of CX-8998 is displayed in Figure 2.

Figure 2: Chemical Structure of CX-8998



[redacted]

[redacted]

In vivo pharmacology studies of CX-8998 in rodent and non-human primate sleep architecture have demonstrated dose-dependent increases in slow wave sleep early in the sleep period, followed by a significant increase of rapid eye movement (REM) late in the sleep period. There was also a significant suppression in REM early in the sleep period.

CX-8998 at doses of 1 mg/kg, 3 mg/kg and 10 mg/kg was also shown to dose-dependently inhibit both seizure duration and frequency in a single-dose rat model of absence epilepsy. Additional T-type antagonists from at least five structurally diverse series have shown similar efficacy in this model.

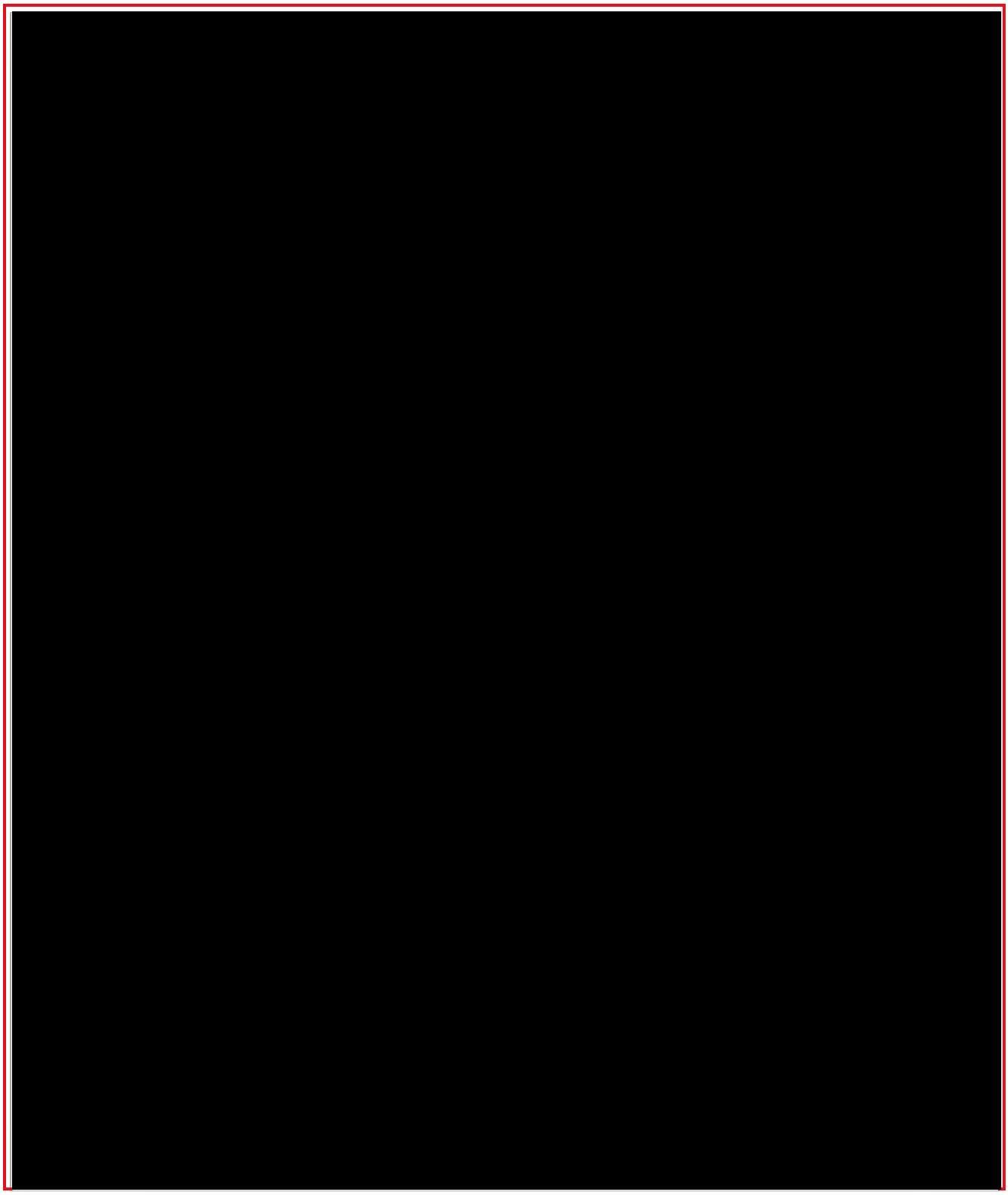
1.3.1 Safety Pharmacology Studies

[redacted]

[redacted]

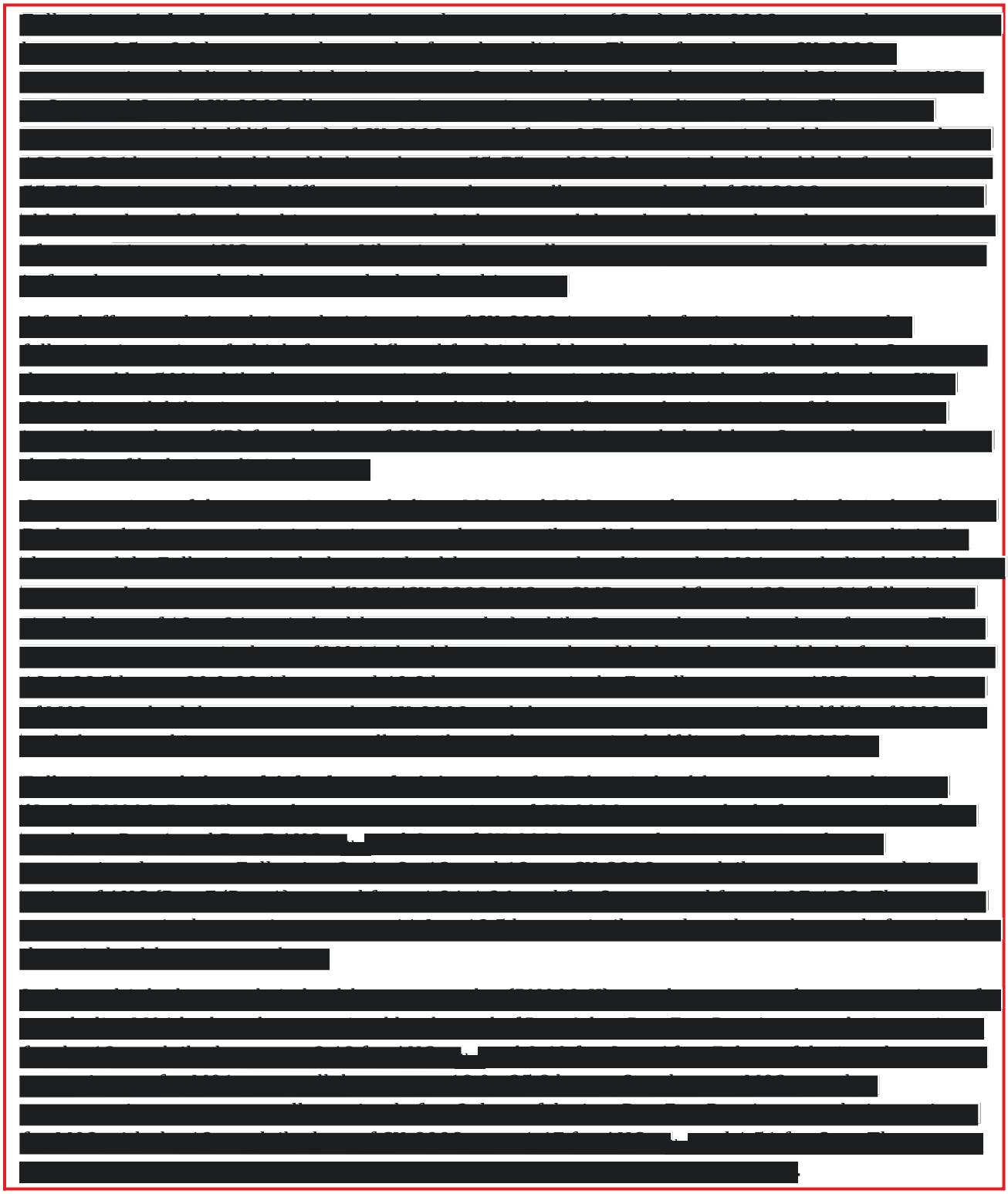
1.4 CX-8998 Clinical Experience

[redacted]



1.4.1 Clinical Pharmacokinetics

Pharmacokinetic data are available from single and multiple dose healthy subject studies (PN001, PN002 and PN005).



1.4.2 Clinical Pharmacodynamics

[redacted]

In the current study for essential tremor, a subset of subjects will undergo digital biomarker evaluation to obtain additional pharmacodynamic data pertaining to CX-8998.

1.4.3 Clinical Safety

[redacted]

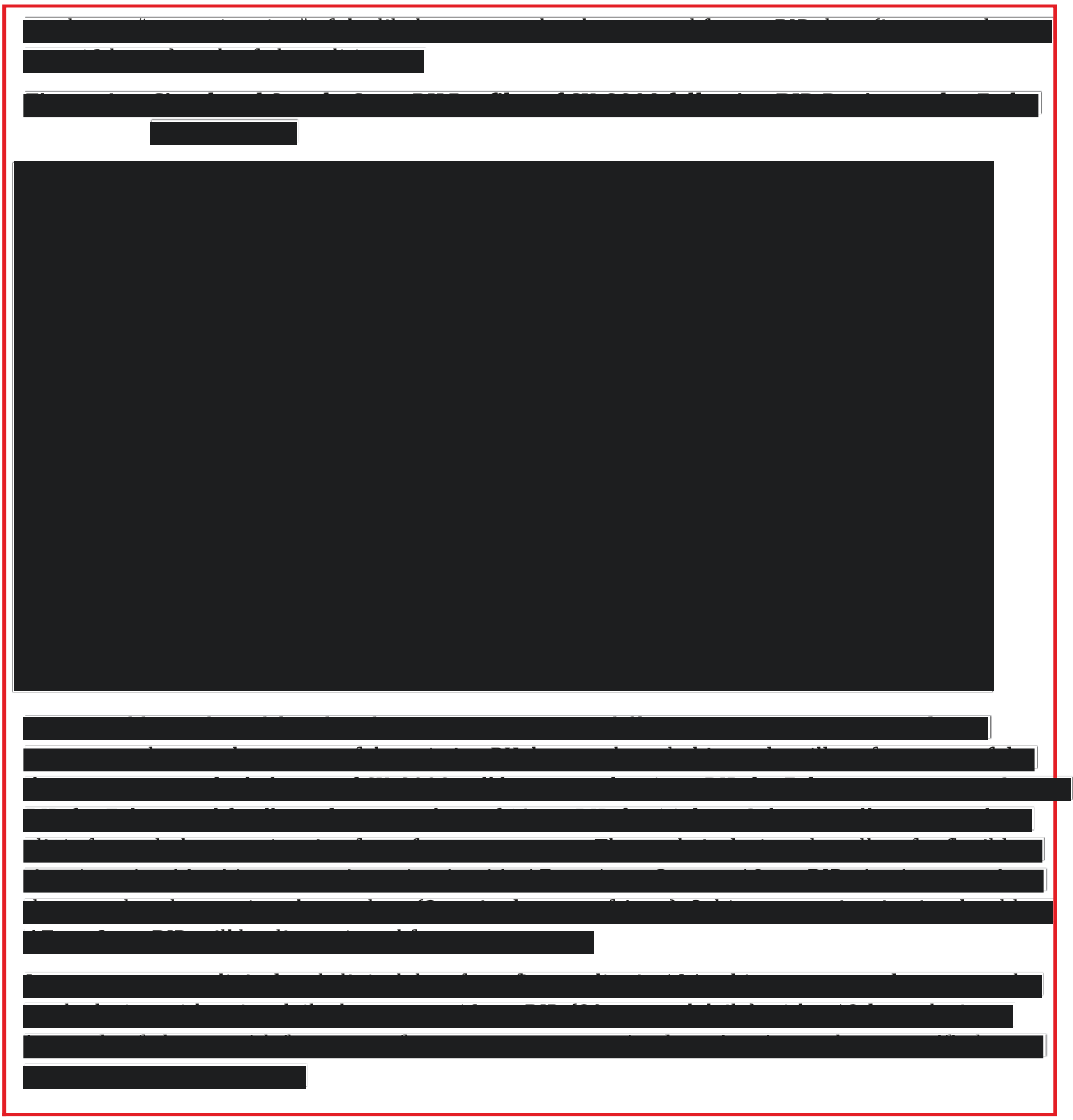
[redacted]

1.5 Rationale for Selected Dose

[redacted]

In study PN004, 8 mg twice daily for an average of 4 weeks duration (range 2-29 days) was investigated in adults with acute psychosis (N=86: 49 males and 37 female, 21-55 years old, mean age 37.4 years), and was found to be well-tolerated.

[redacted]



2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the efficacy of CX-8998, in doses up to 10 mg BID in reducing the severity of essential tremor

2.2 Secondary Objectives

1. To assess changes in tremor-affected activities of daily living.
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 two primary metabolites (M01 and M02) in plasma

2.3 Exploratory Objectives

1. To assess changes in quality of life in subjects with ET
2. To assess study drug effects on digital biomarker patterns associated with ET (in a subset of subjects).
3. To use the plasma concentrations of CX-8998 and its 2 primary metabolites in population pharmacokinetic/pharmacodynamic (PK/PD) analyses to evaluate exposure-response and exposure-safety relationships

3 STUDY DESIGN AND ENDPOINTS

3.1 Study Type

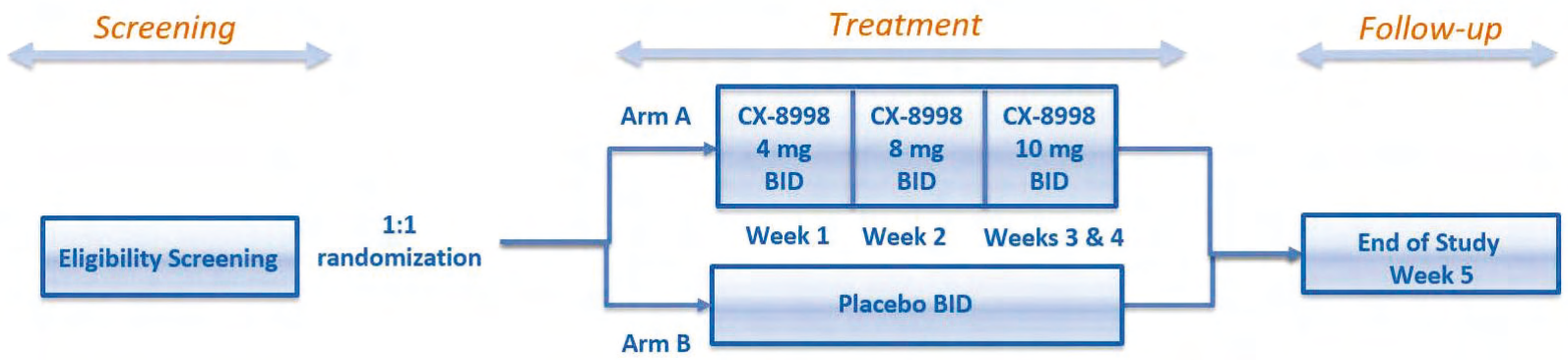
This is a Phase 2, multicenter, double-blind, placebo-controlled, parallel-group study consisting of a screening period of up to 4 weeks (with the exception of subjects on primidone at baseline who will be allowed 6 weeks of screening to allow for safe discontinuation), a 4-week, randomized, double-blind dose-titration treatment period, and a 1-week safety follow-up period following the last dose of study medication.

Subjects will be randomized to one of two treatment groups. Group A will receive titrating doses of CX-8998 up to 10 mg BID and Group B will receive placebo. Subject randomization will be stratified by presence or absence of a single concomitant anti-tremor medication and by site-type (substudy vs. non-substudy).

3.2 Schematic of Study Design

The study design schematic is shown in Figure 5.

Figure 5: Schematic of Study Design



3.3 Endpoints

3.3.1 Primary Endpoint

The change from Baseline to Day 28 on the TETRAS Performance subscale, as scored by the central rater

3.3.2 Secondary Endpoints

1. Change from Baseline to Day 28 on the TETRAS Activity of Daily Living subscale
2. Change from Baseline to Day 28 in accelerometry score, as measured by Kinesia ONE
3. Safety and tolerability endpoints:
    a. adverse events,
    b. changes from baseline in QTcF and other ECG parameters,
    c. clinical safety laboratory assessments (clinical chemistry, hematology, and urinalysis),
    d. C-SSRS
    e. Epworth Sleepiness Scale (ESS),
    f. vital signs,
    g. number (%) of subjects who did not complete the study,
    h. number (%) of subjects who did not complete the study due to adverse events.

3.3.3 Exploratory Endpoints

1. Change from Baseline on the Total TETRAS score to Day 15 and Day 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 accelerometry score as measured by Kinesia ONE
4. Change from Baseline to Day 15 and Day 28 in Kinesia ONE amplitude measures
5. Treatment success at the end of therapy as measured by Patient Global Impression of Change (PGIC)
6. Treatment success at the end of therapy as measured by Clinical Global Impression of Improvement (CGI-I)
7. Treatment success at the end of therapy as measured by Goal Attainment Scaling (GAS)

8. Change from Baseline in Quality of Life in Essential Tremor Questionnaire (QUEST)
9. 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).

4 STUDY DRUG

4.1 Supply and Storage

CX-8998 will be supplied as 2 mg capsules. Placebo capsules will be matched for CX-8998 capsules and will be indistinguishable from CX-8998 capsules. All manufacturing and packaging activities will be performed according to cGMP guidelines.

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

Supplies of study drug should be stored below 30° C.

4.2 Packaging and Labeling

Study medication will be supplied in 60 cc white HDPE bottles with 33 mm polypropylene, white, child-resistant closures. Each subject will receive a kit with two bottles of active drug or placebo capsules. In each kit, one bottle will contain 80 capsules and the second bottle will contain 150 capsules. The bottles will be appropriately labeled. The affixed label will have spaces for entering the subject number, subject initials, and date dispensed. At the time of dispensing, the subject number, subject initials, and date dispensed are entered onto the appropriate lines on the label.

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

- Protocol number: CX-8998-CLN2-001
- Expiration date
- Lot number
- Storage conditions
- The sentence, “Caution: New Drug – Limited by Federal Law to Investigational Use”
- Name and address of the sponsor

4.3 Administration

CX-8998 (or placebo) will be administered as 4 mg (2 capsules) twice daily (8 mg/d) in the first week; increasing to 8 mg (4 capsules) BID (16 mg/d) in week 2, to a target of 10 mg (5 capsules) BID (20 mg/d) in weeks 3 and 4.

[redacted]

[redacted]

Treatment compliance will be assessed based on return of unused drug.

Subjects experiencing specified adverse events will have their dose adjusted. See Section 4.5 for details on dose adjustments.

4.3.1 Stopping Rules

Study drug dosing for an individual subject will be permanently discontinued for intolerable AEs that do not resolve to Grade 1 or Baseline within 48 hours of suspension of dosing, and for all Grade 4 AEs. Other reasons for treatment termination are provided in Section 6.4.

4.4 Study Drug Accountability and Compliance

Subjects will be instructed to return all used empty bottles and unused study drug at each visit.

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

Sites will keep a current log of drug accountability recording:

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

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

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

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

To stay in the study, subjects will be required to have taken at least 75% of their study treatment doses. A subject will be considered non-compliant if they have missed more than 25% of the required doses between visits. The minimum number of required doses per 7 days is detailed below:

- Week 1: 11/14 doses (22 capsules)
- Week 2: 11/14 doses (44 capsules)
- Week 3 to 4: 21/28 doses (105 capsules)

If compliance is less than 75% or greater than 125% at any visit, the reason(s) must be noted and the subject's continued participation in the study should be discussed with the study safety representative. Subjects should not make up for missed doses.

4.5 Dose Adjustments / Toxicity Management

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

Dosing will be discontinued for all Grade 4 AEs.

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

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

Table 2: Study Drug Dose Reduction for Intolerable AEs

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

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

The study safety representative should be notified of all dose reductions as soon as is feasible.

4.6 Overdose Management

To date, no overdoses of CX-8998 in humans have occurred.

Because no humans have overdosed with CX-8998, specific information regarding treatment of overdose is not currently available. In case of an acute overdose, it is recommended that the stomach be emptied and oral gavage with activated charcoal be used to help reduce absorption of CX-8998. In the event of an overdose, the study safety representative should be contacted immediately.

4.7 Randomization and Matching of Subjects

Eligible subjects will be randomized in a 1:1 ratio between CX-8998 and placebo, using an Interactive Web Response System (IWRS). Subject randomization will be stratified by concomitant use of an anti-tremor medication and site type (substudy vs. non-substudy). A statistician not involved in the day-to-day study operation will create the randomization schedule. Details of the randomization process will be included in the study Operations Manual.

4.8 Study Blinding

This is a double-blind study; that is, the treatment assignment and drug contents are not revealed to the sponsor, the subject and or investigator and other study personnel.

Maintenance of the double-blind is critical to the integrity of this clinical study. 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 for that subject may be broken by the treating investigator.

Before breaking the blind for an individual subject, the investigator should have determined that the information is necessary, i.e., it will alter the immediate management of the subject's care. *In the majority of cases not involving pregnancy, because there is no known specific antidote for any potential pharmacodynamic or toxic effect of CX-8998, there should rarely be a need to unblind a subject to guide immediate medical management of an emergency.*

The need to break the blind should first be discussed with the sponsor’s study safety representative, if at all possible. in case of an emergency, the investigator may use the Emergency Unblinding Function under the Randomization side menu in the IWRS. Once the decision to unblind has been made, the investigator must record the nature of the emergency that required the unblinding, along with the date and time of the unblinding, in the proper source documentation and notify the sponsor’s study safety representative of the unblinding. However, the sponsor’s study safety representative, and any other investigators, must not be informed of the treatment assignment. The treatment assignment must not be noted in the source documentation or any other documentation submitted to the sponsor.

Study treatment for a given subject may be unblinded for reportable safety events (e.g., suspected unexpected serious adverse reaction [SUSAR]) as required by local or other regulations, but the mere occurrence of an SAE should not routinely precipitate immediate unblinding.

In cases of accidental unblinding, the investigator will notify the sponsor’s study safety representative and ensure that every attempt to preserve the blind is made. specifically, the

investigator will not reveal the identity of the study treatment to the sponsor's study safety representative or other sponsor staff, any contract research organization (CRO) staff, including the clinical site staff, clinical research associate (CRA), subject, or anyone else who does not already know this information.

If unblinding occurs, the study drug must be discontinued for the particular subject(s) involved.

5 INVESTIGATORS, SITES AND DURATION

5.1 Investigators and Sites

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

5.2 Central Reviewers

A central reviewer will review eligibility criteria for all subjects. The site will submit an eligibility checklist for evaluation of each subject. A central reader will score the screening TETRAS performance video to determine if the subject meets Inclusion Criteria 5 and 6 below. No subject may be enrolled, randomized or dosed with study drug prior to receipt of notification that the central reviewer and review process has deemed the subject eligible.

5.3 Duration of Study

Subjects will participate for a total of up to 12 weeks, including screening, the 4-week treatment period and follow-up.

5.4 Termination of Study

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

6 STUDY POPULATION

6.1 Number of Subjects

Approximately 106 eligible subjects will be randomized to treatment.

6.2 Inclusion Criteria

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

1) Signed informed consent form (ICF) indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
2) Men or non-pregnant, non-breastfeeding women 18 to 75 years-of-age who are able to read and understand English.

3) Diagnosis of definite or probable bilateral essential tremor (ET) as defined by the Tremor Investigational Group with involvement of the hands and arms without present causes of enhanced physiologic tremor (Deuschl et al., 1998).

4) Diagnosis of ET before the age of 65

5) Tremor severity score of at least 2 in at least one upper extremity on at least one of the three maneuvers on the TETRAS scale.

6) Total TETRAS performance score of at least 15 (Note: Inclusion thresholds, including thresholds for criteria 5 & 6 shall NOT be shared with study subjects or caregivers to limit Baseline inflation.)

7) One concomitant anti-tremor medication (other than primidone) is allowed. Subjects must have been on a stable dose for at least one month prior to screening and must have no change in dose in the single concurrent anti-tremor medication for the duration of the study. Note that primidone is NOT an allowed anti-tremor medication. If on primidone, subjects are allowed to extend their screening period by 2 weeks (for a total of 6 weeks) and discontinue primidone under the supervision of the investigator.

8) Able and willing to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

9) Subjects with reproductive capability including all males and women of childbearing potential (WOCBP) must agree to practice continuous abstinence or adequate contraception methods (appropriate double barrier method or oral, patch, implant, or injectable contraception) from as soon as feasible during screening period until at least 30 days after the last dose (i.e., intermittent abstinence based on “rhythm”, temperature monitoring, or other means of timing is not acceptable). WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy) or is not post-menopausal. Post-menopausal is defined as:

   a) Amenorrhea ≥ 12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL;

   b) Amenorrhea ≥ 12 consecutive months in women ≥ 62 years old (FSH testing is not required).

   Male subjects with a partner of childbearing potential must be surgically sterilized or be willing to use condoms with spermicide from as soon as feasible during screening period until at least 30 days after the last dose.

10. Approval by the sponsor medical personnel as to final suitability for the study

6.3 Exclusion Criteria

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

1) Exposure to tremorgenic drugs or drug withdrawal states within the 30 days prior to the first planned dose of study drug

2) Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor
3) History or clinical evidence of psychogenic tremor origin
4) Known history of other medical conditions that may cause or explain subject's tremor, including, but not limited to:
    a) Parkinson's disease
    b) dystonia
    c) cerebellar disease, other than essential tremor
    d) Traumatic Brain Injury
    e) alcohol abuse or withdrawal
    f) mercury poisoning
    g) hyperthyroidism
    h) pheochromocytoma
    i) head trauma or cerebrovascular disease within 3 months prior to the onset of essential tremor
    j) multiple sclerosis
    k) polyneuropathy
    l) family history of Fragile X syndrome
5) Prior MR-guided Focused Ultrasound or surgical intervention (e.g., deep brain stimulation, ablative thalamotomy or gamma knife thalamotomy) for treatment of tremor
6) Botulinum toxin injection in the 6 months prior to screening
7) Currently using more than one anti-tremor medication
8) Experiencing clinical benefit from and/or is not willing to discontinue primidone
9) Use of medication(s) (in the past month) that might produce tremor or interfere with the evaluation of tremor, such as but not limited to: CNS-stimulants, lithium, amiodarone, metoclopramide, theophylline, and valproate
10) Inability to refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor on study visit days, such as but not limited to stimulant decongestants, beta-agonist bronchodilators, caffeine, alcohol and tobacco, based on investigator assessment at baseline
11) Positive urine drug screen (phencyclidine (PCP), cocaine, cannabinoids, opiates/barbiturates, benzodiazepines, amphetamines, methadone or MDMA (ecstasy)) unless explained by use of an allowed prescription medication (Section 10.1.6).
12) Regular use of more than two units of alcohol per day. See Section 7.3.2 for definitions.

13) Sporadic use of a benzodiazepine, sleep medication or anxiolytic to improve sleep performance. Stable use at a consistent dose is allowed as long as tremor persists against the background of regular medication use. Use on the evening prior to a study visit is prohibited.

14) Use of prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be strong inhibitors or inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study, including primidone

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

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

    b) NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure

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

        i) QTcF >450 msec (males) or >470 msec (females)

        ii) PR interval >250 msec

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

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

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

        vi) The presence of a cardiac pacemaker does not automatically exclude eligibility. The specifics must be discussed with the study safety representative to make a determination of eligibility.

    d) Known infection with HIV, hepatitis B, or hepatitis C, unless curative therapy completed for hepatitis C with negative PCR

    e) Significant hepatic (AST/ALT > 2X upper limit of normal) or renal disease (creatinine clearance <39 mL/min)

    f) Significant psychiatric history including mood disorders and alcohol or substance abuse within the last year

    g) A current C-SSRS score of 4 or 5 at screening, or history of suicide attempt at any time during the past year

    h) Clinically significant impaired balance or is considered at increased risk for falls

    i) Symptomatic orthostatic hypotension

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

17) Any other condition and/or situation that causes the investigator to deem a subject unsuitable for the study (e.g., due to expected study medication non-compliance, inability to medically tolerate the study procedures, or a subject's unwillingness to comply with study–related procedures)

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

6.4 Withdrawal of Subjects and/or Discontinuation of Treatment

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

1) Withdrawal of subject consent

2) Subject is lost to follow-up

3) Investigator determines that withdrawal from the study is in the best interest of the subject.

4) Subject is non-compliant with protocol-mandated activities.

5) Occurrence of any intercurrent condition, injury, or disease that becomes apparent during the study and necessitates the termination of the subject from the study.

6) Administrative reason (e.g., termination of the clinical study by a regulatory agency or the sponsor)

A subject should be discontinued from treatment for any of the following:

1) Subject is not at least 75% compliant with study drug administration at any study visit (Section 4.4.)

2) Occurrence of defined unacceptable toxicity (Section 4.5)

3) Investigator determines that discontinuation of treatment is in the best interest of the subject.

4) Occurrence of any intercurrent condition, injury, or disease that becomes apparent during the study and necessitates the discontinuation of treatment.

5) Pregnancy

6) Subject requires use of prohibited concurrent medication

7) Subjects answering "yes" to Suicidal Ideation item 4 or 5 on the C-SSRS during the study must be withdrawn from the study treatment. Investigators should also withdraw subjects from treatment if, in the judgment of the investigator, the subject develops other indicators of significant risk of suicide. In the event that suicidal ideation is observed in any study subject, the investigator will manage the situation as he/she deems medically and psychiatrically appropriate.

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

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

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

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

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

6.4.2 Procedures for Replacing Subjects Who Withdraw/Discontinue Prematurely

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

7 TREATMENT PLAN AND METHODS

7.1 Schedule of Assessments

The schedule of assessments is shown in Table 3.

Table 3: 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

Table 3: Schedule of Assessments - Continued

	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
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.)

7.2 Summary of Treatment Visits

7.2.1 Screening

The Screening visit must be performed within 28 days of Visit 1/Baseline. Subject informed consent must be obtained prior to initiation of any study specified procedures. Subjects who are taking primidone at screening who are otherwise deemed eligible for participation and are willing to discontinue primidone will be allowed an additional 2 weeks of screening (a total of 6 weeks) to ensure safe primidone discontinuation. A central reviewer will confirm the TETRAS-related eligibility criteria prior to randomization. Screening results from all patients meeting the eligibility requirements will be further assessed by the sponsor medical personnel for final approval of suitability for inclusion in the study. Details of the eligibility review will be provided in the study Operations Manual. See Table 3 for a detailed list of assessments to be performed.

7.2.2 Visit 1 (Day 1 - Baseline)

Subjects will return to the clinic within 28 days of screening (or 42 days in the case of those with extended screening due to discontinuation of primidone.) Following confirmation of continued eligibility and randomization, subjects will undergo safety and efficacy assessments as detailed in Table 3 and will then receive their first dose of study drug (4 mg of CX-8998 or placebo). Subjects will be followed for adverse events for at least 2 hours after dosing. Orthostatic VS and triplicate ECGs will be obtained 1 to 2 hours after dosing. The investigator or qualified designee will make the determination whether it is safe to release the subject from the clinic. Subjects will be instructed to take the second daily dose of study drug no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the time of their first dose, and to continue taking 4 mg (or placebo) twice daily for the following week (see Administration details in Section 4.3).

7.2.3 Visit 2 (Day 8 – End of Week 1)

Subjects will return to the clinic for assessments as detailed in Table 3. Subjects will have withheld their morning dose of study drug.

If the subject has been at least 75% compliant with the study drug regimen (as detailed in Section 4.4) and has not experienced any intolerable adverse events (as described in Section 4.5), the dose of study drug will be increased to 8 mg (or placebo) twice daily for the following week. If compliance is determined to be less than 75%, up-titration should be discussed with the study safety representative.

Subjects will receive the first 8 mg dose of study drug (or placebo) and will then undergo safety assessments. Subjects will be followed for adverse events for at least 2 hours prior to discharge. Orthostatic VS and triplicate ECGs will be obtained 1 to 2 hours after dosing. The investigator or qualified designee will make the determination whether it is safe to release the subject from the clinic. Subjects will be instructed to take the second daily dose of study drug no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the time of their first dose, and to continue taking 8 mg (or placebo) twice daily for the following week (see Administration details in Section 4.3).

7.2.4 Visit 3 (Day 15 – End of Week 2)

Subjects will return to the clinic for assessments as detailed in Table 3. Subjects will have withheld their morning dose of study drug.

If the subject has been at least 75% compliant with the study drug regimen (as detailed in Section 4.4) and has not experienced any intolerable adverse events (as described in Section 4.5), the dose of study drug will be increased to 10 mg (or placebo) twice daily for the following two weeks. If compliance is determined to be less than 75%, up-titration should be discussed with the study safety representative.

Subjects will receive the first 10 mg dose of study drug (or placebo) and will then undergo efficacy assessments between 1 and 3 hours after dosing. Subjects will be followed for adverse events for at least 2 hours prior to discharge. Orthostatic VS and triplicate ECGs will be obtained 1 to 2 hours after dosing. The investigator or qualified designee will make the determination whether it is safe to release the subject from the clinic. subjects will be instructed to take the second daily dose of study drug no closer than 10 hours and no later than 14 hours (every 12 hours ± 2 hours) from the time of their first dose, and to continue taking 10 mg (or placebo) twice daily for the following two weeks (see Administration details in Section 4.3).

7.2.5 Visit 4 (Day 28 – End of Week 4)

Subjects will return to the clinic for assessments as detailed in Table 3. Visit 4 is the end-of-dosing visit. Subjects will have withheld their morning dose of study drug. Subjects will receive the final dose of study drug (10 mg or placebo) and will then undergo efficacy assessments between 1 and 3 hours after dosing. Subjects will be followed for adverse events for at least 2 hours prior to discharge. Orthostatic VS and triplicate ECGs will be obtained 1 to 2 hours after dosing.

Visit must occur on or one day before Day 28 to ensure that all efficacy assessments occur while subject is still taking study drug.

7.2.6 End of Study Visit (Day 35 – End of Week 5)

Subjects will return to the clinic for the final visit assessments detailed in Table 3. Adverse events that are unresolved at the end of study visit will continue to be followed by study staff as detailed in Section 10.2.3.

7.3 Concomitant Medications and Other Restrictions

7.3.1 Concomitant Medications

Subjects may not be using more than one anti-tremor medication at the time of entry into the study. Subjects must have been on a stable dose for one month prior to screening and must have no change in dose in concurrent anti-tremor medication for the duration of the study. It should be noted that primidone is not a permitted anti-tremor medication.

Subjects may not use medications that might produce tremor or interfere with the evaluation of tremor, such as but not limited to: CNS-stimulants, lithium, amiodarone, metoclopramide, theophylline, and valproate.

On study visit days, subjects must refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor, such as but not limited to stimulant decongestants, beta-agonist bronchodilators, caffeine, alcohol and tobacco.

The stable use of a benzodiazepine, sleep medication or anxiolytic to improve sleep performance is allowed as long as tremor persists against the background of regular medication use. Subjects should not use sleep aids on the evening prior to a study visit.

The use of prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be strong inhibitors or inducers of CYP3A4 must be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study. Subjects taking primidone for treatment of their ET may continue to do so at a stable dose. Subject randomization will be stratified by concomitant anti-tremor medication use and site type.

See Appendix C for a complete list of restricted inhibitors and inducers.

7.3.2 Other Restrictions

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

8 EFFICACY ASSESSMENTS

8.1 The Essential Tremor Rating Assessment Scale (TETRAS)

The Tremor Research Group first published the TRG Essential Tremor Rating Assessment Scale (TETRAS) in 2008 (Elble 2008). TETRAS consists of a 9-item performance subscale and a 12-item activities of daily living (ADL) subscale. TETRAS was developed as a rapid clinical assessment of ET that requires no equipment other than pen and paper. Administration of the performance subscale takes less than 10 minutes. The scale employs objective metrics to reduce experiential rater bias.

To evaluate the inter-rater reliability of TETRAS, Elble et al. (2012) videotaped 50 TETRAS exams, including assessments of 44 patients with ET and 6 controls. The severity of ET ranged from mild to severe. Ten specialists rated the patients in the videos 2 times with an interval of 1 to 2 months separating the ratings. Of the 10 raters, 6 had been involved in the development of TETRAS, and 4 had never used the scale.

Inter-rater reliability of the scale was calculated using a two-way random effects intraclass correlation (ICC) with an absolute agreement definition. The inter- and intra-rater ICC for head and upper limb tremor ranged from 0.86 to 0.96, and the ICC for the total score were 0.94 and 0.96. The ICC for voice, face, trunk and leg were less robust (Elble et al., 2012).

The TETRAS Performance subscale is widely used in clinical practice and has high content validity and strong inter-rater reliability. The TETRAS ADL and performance scores are highly correlated, and the TETRAS ratings of upper extremity function correlate strongly with transducer measures (accelerometry) of upper limb tremor (Mostile et al., 2010). TETRAS is also shown to be sensitive to change in tremor over time (Voller et al., 2014).

8.1.1 TETRAS Performance Subscale

The Performance subscale quantifies tremor in the head, face, voice, limbs and trunk. Each item is rated on a 0 to 4 rating scale, with scoring of upper limb tremor allowing for 0.5-point increments. Specific amplitude ranges (measured in centimeters) define the tremor rating (see Table 4). Raters first estimate the maximum amplitude of tremor and then assign the corresponding rating. The sum of the individual rating scores provides the overall Performance score, ranging from 0 to 64. See Appendix A1 for the complete TETRAS Performance Scale.

Table 4: TETRAS Performance Subscale Metric Amplitude Ranges

Head Tremor	Upper Limb Tremor	Lower Limb Tremor
0 = no tremor	0 = no tremor	0 = no tremor
1 = < 0.5 cm	1 = barely visible	1 = barely visible
2 = 0.5 - < 2.5 cm	1.5 = < 1 cm	2 = < 1 cm
3 – 2.5 – 5 cm	2 = 1 - < 3 cm	3 = 1 – 5 cm
4 = > 5 cm	2.5 = 3 - < 5 cm	4 = > 5 cm
	3 = 5 - < 10 cm	
	3.5 = 10 - < 20 cm	
	4 = > 20 cm	

To reduce the potential for bias in the assessments of efficacy, all subjects will be videotaped during the TETRAS Performance Subscale testing according to a consistent script. The videotapes will be rated in a blinded manner by qualified, independent raters. While the principal investigator (or sub-principal investigator) will score the TETRAS performance subscale, the TETRAS Performance Subscale scores provided by the blinded central rater will be utilized in the statistical analyses of efficacy.

Full details on the recording and scoring of the TETRAS Performance scale will be provided in the study Operations Manual.

8.1.2 TETRAS Activities of Daily Living Subscale

The ADL subscale includes many of the items assessed in the scales previously developed by Fahn, Tolosa and Marin (1993), Louis et al. (2000) and Bain et al. (1993), including eating and drinking, dressing and personal hygiene, carrying items and finer motor skills. 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. See Appendix A2 for the complete TETRAS ADL Subscale.

8.2 Objective Biometric Assessments

8.2.1 Accelerometry

Accelerometry has long been used to obtain quantitative measurements of tremor in ET (Jankovic & Frost, 1981; Koller & Royse, 1985). Elble et al. demonstrated a logarithmic relationship between tremor amplitude, as measured via accelerometry, and changes in

physician-assessed tremor rating scales (Elble, 2006). Voller et al. reported a significant correlation (p <.001) between log-transformed accelerometer data and TETRAS scores in ET (Voller et al., 2014).

8.2.1.1 Kinesia ONE Accelerometer

The Kinesia ONE device will be placed on the index finger and worn in the clinic immediately following execution of the TETRAS Performance subscale

A total of four tasks will be performed on the left side and then again on the right side to assess resting, postural, kinetic, and lateral wing beating tremor. Each task will be performed for 15 seconds.

Full details on the Kinesia ONE device and its use will be provided in the study Operations Manual.

8.3 Other Assessments

Health-related Quality of Life (HRQoL) is defined as a patient's perception of the effects of and illness and its treatment on his/her life and sense of will-being. In that many models suggest a strong relationship between functional status and HRQoL, ET has the potential to exert a significant and detrimental impact on HRQoL (Makedonsky et al., 2002).

8.3.1 QUEST

Until 2005, the measurement of QoL in patients with ET was performed with generic QoL indices such as the EuroQOL and Sickness Impact Profile (SIP). However, generic measures lack sensitivity in ET and may fail to address the issues most relevant to patients with ET. As such, Tröster et al. developed the Quality of Life in Essential Tremor Questionnaire (QUEST) to specifically assess the impact of ET on HRQOL (Tröster et al., 2005). The QUEST is a 30-item questionnaire that contributes to 5 sub-scales (physical, psychosocial, communication, hobbies/leisure and work/finance) and a total score, plus 3 additional items relating to sexual function and satisfaction with tremor control and medication side effects. Initial reports provide preliminary support of its reliability and validity. The internal consistency was very good to excellent for 4 scales and the total score, and moderately high for the Work/Finance scale (Tröster et al., 2005). These reliability coefficients are also supportive of the QUEST's construct validity.

It is proposed that successful treatment of ET, even if symptomatic rather than curative, would positively impact QoL. A sample QUEST questionnaire may be found in Appendix A3.

8.3.2 Clinical Global Impression

The Clinical Global Impressions Scale (CGI) was developed for use in NIMH-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of a patient's global functioning before and after initiating a study medication (Guy, 1976). The CGI is a summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

The CGI has two forms—the CGI-Severity, which rates illness severity at baseline, and the CGI-Improvement, which rates change from baseline.

CGI-Severity (CGI-S). The CGI-Severity (CGI-S) consists of a single 7-point rating score of illness severity that is based on how ill the subject is relative to other subjects with whom the clinician has had experience. Raters select one response based on the following question: "Considering your total clinical experience with this particular population, how ill is the patient at this time?" Scores are: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

CGI-Improvement (CGI-I). The CGI-I consists of a single 7-point rating of total improvement or change from baseline CGI-S, regardless of whether or not the change is due entirely to drug treatment. Raters select one response based on the following question, "Compared to your subject's condition at the beginning of treatment, how much has your subject changed?" Scores are: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse.

The CGI-S/CGI-I rater may have access to all clinical information related to subject severity and change and does not need to be independent of other assessments. However, the rater who assesses the initial CGI-S should be the clinician who rates overall change via the CGI-I during the study. The rater will be a trained member of the site investigational team (clinician).

8.3.3 Patient Global Impression of Change (PGIC)

Global rating of change (GRC) scales are designed to quantify a patient's improvement or deterioration over time, usually either to determine the effect of an intervention or to chart the clinical course of a condition. GRC scales ask a patient to assess his or her current health status, recall that status at the beginning of treatment, and then calculate the difference between the two. The simplicity of GRC scales makes them easy to administer and applicable to a wide range of patients (Kamper et al., 2009).

The Patient Global Impression of Change (PGIC) is a 7-point GRC consisting of one question: "With respect to your essential tremor, how would you describe yourself now, as compared to when you started taking the study drug?" Subjects will choose one of the following answers: "very much worse, much worse, minimally worse, no change, minimally improved, much improved, very much improved."

8.3.4 Goal Attainment Scaling

Goal Attainment Scaling (GAS) is a tool that involves the development of a written set of goals between a physician and patient and is used for monitoring patient progress. GAS was developed in 1968 in response to the wide variety of evaluation models regarding mental illness and treatment (Kiresuk & Sherman, 1968). GAS has been employed in patients with physical disorders including spasticity (Ashford & Turner-Stokes, 2006) and multiple sclerosis (Kahn et al., 2008).

GAS frames the discussion in terms of individual patient-desired goals rather than universally applied health states. Goal-oriented care prompts patients to articulate which

health goals are most important to them. Patients and clinicians can then monitor progress in reaching them.

Subjects will identify 3 health goals at Baseline. Examples of goals are drinking from a cup, buttoning a shirt or ability to write. Goals may be either active or passive. All goals will be specifically tailored to the individual, with each subject required to rate each goal at baseline on the level of importance, based on a 3-point scale (1 = fairly important; 2 = very important; 3 = extremely important). For the investigator, the feasibility of attaining each goal must be considered before the goals are set and adjusted accordingly if needed. Once each goal is set, the investigator will be asked to rate the degree of difficulty in achieving each of the set goals, based on another 3-point scale (1 = probable; 2 = possible; 3 = doubtful.)

Progress towards each goal will be scored on a 5-point scale: -2 = Worse than Baseline (unfavorable outcome); -1 = No change from Baseline; 0 = Achieved the defined goal (expected outcome); +1 = Better than expected outcome; +2 = Best anticipated outcome.

Full details on Goal Attainment Scaling will be provided in the study Operations Manual.

9 PHARMACOKINETIC AND PHARMACOGENOMIC ASSESSMENTS

9.1 Blood Sample Collection for Pharmacokinetic Assessments

All subjects will have one blood sample drawn prior to administration of CX-8998 at 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.)

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

9.2 Pharmacokinetic Parameters

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

The concentrations of CX-8998 and its metabolites in plasma will be summarized by visit and dose using descriptive statistics. The concentration data will also be used as part of an exploratory population pharmacokinetic/pharmacodynamic (PK/PD) analysis intended to evaluate the exposure-response and exposure-safety relationships; which will be reported separately from the Clinical Study Report.

9.3 Pharmacogenomics of Drug Response

Genomic and metabolomic variation may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomics. Comparing the DNA, RNA, protein, and metabolite variation patterns of

subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting and retaining samples for pharmacogenomic analyses makes it possible to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study.

A 4 mL blood sample Prep D1 (K_2 EDTA whole blood collection optimized for DNA analysis) will be collected at Visit 1/Baseline to be retained for potential pharmacogenomic analyses related to drug response. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Retained Pharmacogenomic Sample(s) will be collected from all subjects *unless prohibited by local regulations.* Detailed collection, processing, storage and shipment instructions are provided in the Laboratory Manual.

10 SAFETY ASSESSMENTS

10.1 Assessment of Safety

10.1.1 Adverse Events

Adverse events (AEs) will be captured from the time the ICF is signed through 30 days after the last dose of study drug. Important medical events and conditions occurring prior to this period are not AEs; they will be captured within the medical chart and in the Medical History section of the Case Report Form. See Section 10.2 for definitions and instructions on the rating and collection of AEs.

10.1.2 Physical Examination

A complete physical examination includes measurement of height (screening only), weight, and examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities. Genital, rectal, and breast examination may be excluded if not clinically indicated. Weight should be measured on the same scale each time.

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

10.1.3 Neurological Examination

The neurological examination will include assessment of mental status, and examination of cranial nerves II-XII, motor and sensory exam, reflexes, coordination, stance, gait and balance.

10.1.4 Vital Signs

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 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 measurement of orthostatic blood pressure and pulse rate will be recorded. The average of these assessments will be used for comparison to single recordings at Visits 1 through 4. On Visits 1, 2 & 3 (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.)

10.1.5 Clinical Laboratory Tests

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

Hematology testing will include hematocrit, hemoglobin, red blood cell count, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC), and platelet count.

Serum chemistry analyses will include sodium, potassium, chloride, calcium, magnesium, phosphorus, carbon dioxide (CO_2) or bicarbonate, albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, creatine kinase (CK), uric acid, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, triglycerides, total cholesterol, prolactin levels and total bilirubin.

Coagulation studies will include fibrinogen, activated partial thromboplastin time (aPTT), and international normalized ratio (INR).

Urinalysis will include color and appearance, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood by dipstick. Microscopic inspection of sediment is only to be performed as needed to clarify abnormal dipstick results at the discretion of the investigator.

10.1.6 Urine Drug Screen

Subjects will undergo urine drug screening for the presence of phencyclidine (PCP), cocaine, cannabinoids, opiates/barbiturates, benzodiazepines, amphetamines, methadone and MDMA (ecstasy) at the Screening visit. Subjects with a positive urine drug screen will be excluded, unless explained by use of an approved prescription medication.

10.1.7 Pregnancy Tests

A urine pregnancy test will be performed for all women of childbearing potential. See Section 6.2, inclusion criterion #8 for the definition of women of childbearing potential.

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

10.1.8 Electrocardiogram

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

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

10.1.9 Columbia Suicide Severity Rating Scale

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

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

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

Subjects with a history of attempted suicide within the past year or a C-SSRS score of 4 or 5 at screening will be excluded from the study. Subjects answering "yes" to Suicidal Ideation item 4 or 5 on the C-SSRS during the study must be withdrawn from the study treatment. Investigators should also withdraw subjects from treatment if, in the judgment of the investigator, the subject develops other indicators of significant risk of suicide. In the event

that suicidal ideation is observed in any study subject, the investigator will manage the situation as he/she deems medically and psychiatrically appropriate.

A sample of the C-SSRS may be found in Appendix B1.

10.1.10 Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a scale intended to measure daytime sleepiness that is measured by use of a very short questionnaire. It was developed by Murray Johns of Epworth Hospital in Melbourne, Australia (Johns, 1991; Johns, 2010). The questionnaire asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for 8 different situations. The scores are added together to obtain a single number.

In general, ESS scores can be interpreted as follows:

0 - 5	Lower Normal Daytime Sleepiness
6 - 10	Higher Normal Daytime Sleepiness
11 - 12	Mild Excessive Daytime Sleepiness
13 - 15	Moderate Excessive Daytime Sleepiness
16 - 24	Severe Excessive Daytime Sleepiness.

A sample of the ESS may be found in Appendix B2.

10.1.11 University of Miami Parkinson's Disease Hallucinations Questionnaire

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

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

A copy of the UM-PDHQ is provided in Appendix B3.

10.2 Adverse Events

10.2.1 Definitions

Adverse Event

An Adverse Event (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.

Laboratory Abnormality

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 are also considered AEs.

Treatment-emergent Adverse Events

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

Treatment Period

The treatment period is the period during which a subject receives study drug (i.e., first dose through 30 days after last dose).

Intolerable Adverse Event

An intolerable AE is one that is considered by the investigator to be related to study drug (Section 10.2.2.3) AND is either a Grade 3 (severe) or 4 (life threatening) event (Section 10.2.2.2) OR is a Grade 1 or 2 event that prompts the subject to express a desire to discontinue dosing. Dose adjustments for intolerable AEs are described in Section 4.5.)

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. See Section 10.3 for more details on SAEs.

10.2.2 Collection and Rating of Adverse Events

All AEs, irrespective of the relatedness to the study drug, will be collected and reported on the Adverse Event Report Form from signature of the ICF through 30 days after the last dose of study drug. In case of an SAE, a Serious Adverse Event Report Form must be completed and transmitted to the sponsor or designee.

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

10.2.2.1 Onset Date

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

10.2.2.2 Assessment of Intensity

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

- **Grade 1 (Mild)**: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Grade 2 (Moderate)**: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) [Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc];
- **Grade 3 (Severe)**: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden]
- **Grade 4 (Life-threatening):** Life threatening consequences; urgent intervention indicated;
- **Grade 5 (Fatal)**: death related to AE.

10.2.2.3 Relationship to Study Drug

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

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

- **Related:** the AE has at least a possible or stronger causal relationship to the study drug, i.e., there are facts in evidence to suggest a causal relationship to the study drug. The study treatment and the AE are reasonably related in time, and any alternative etiology is equally or less likely.
- **NOT Related:** Exposure to study treatment did not occur; or the occurrence of the AE is not reasonably related in time, or is due to an underlying/intercurrent illness, or to other medication or procedure; or the AE is considered unlikely to be related to the study treatment.

10.2.2.4 Action Taken

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

- **None:** no change in study drug dosage was made
- **Reduced:** dose of study drug was reduced, with or without a period of temporary suspension of dosing
- **Discontinued:** the study drug was permanently stopped

10.2.2.5 Outcome of Adverse Event

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

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

10.2.3 Adverse Event Follow-up

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

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

All AEs, whether serious or non-serious, will be collected beginning at the time of signing informed consent through 30 days after the last dose of study drug. All AEs should be followed until resolution or:

- 30 days from onset; or
- the subject is lost to follow-up (as defined in Section 6.4.1); or
- the subject withdraws consent,

whichever occurs first.

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

10.3 Serious and Other Significant Adverse Events

10.3.1 Definition of a Serious Adverse Event

A serious adverse event is any adverse event that

- **Results in death.** Death is not an event per se but rather an outcome. Note that any adverse event resulting in a fatal outcome must be fully documented and reported, including deaths that occur within 30 days after treatment ends and irrespective of the causal relationship to the study drug.
- **Is life-threatening.** Life-threatening refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death, if it was more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization.** Hospitalization means that the subject was admitted to hospital or that existing

hospitalization was extended as a result of an adverse event. Hospitalization describes a period of at least 24 hours. Over-night stays for observation, stays at the emergency room or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgment must always be exercised and, when in doubt, the case should be considered serious (i.e. if the case fulfills the criterion for a medically important event). Hospitalization for administrative or social purposes does not constitute an SAE. Hospital admissions and/or surgical operations planned before study inclusion are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that the condition did not deteriorate during the study.

- **Results in persistent or significant disability/incapacity.** Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. If in doubt, the decision should be left to medical judgment by the investigator.
- **Is a congenital anomaly/birth defect.** Any congenital anomaly or birth defect observed in any offspring of the subject conceived during treatment with the study drug.
- **Is an important medical event.** Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important.

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

The following are <u>not</u> considered SAEs:

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

10.3.2 Serious Adverse Event Reporting by the Investigator to the Sponsor

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

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

Sponsor Representative and Contact Information for SAE Reporting:

SAE Reporting Primary Contact: Premier Research Pharmacovigilance

[redacted]

10.3.3 Handling of Follow-up Information

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

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

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

10.3.4 Reporting and Follow-up of Pregnancy

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

10.3.5 Expedited Reporting of Serious Adverse Events

10.3.5.1 Responsibilities

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

10.3.5.2 Expedited Reporting

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

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

10.3.5.3 Timelines

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

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

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

10.4 Safety Monitoring and Risk Mitigation Plan

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

1. Subject safety and tolerability will be monitored in this study across multiple dimensions by tracking clinical adverse events; vital signs (including orthostatic pulse and blood pressure); general and neurological physical examinations; standard clinical laboratory safety panels for complete blood counts, chemistry, coagulation, and urinalysis; standard 12-lead electrocardiograms; and the Epworth Sleepiness Scale (ESS) and Columbia Suicide Severity Rating Scale (C-SSRS).
2. The specified inclusion/exclusion criteria have been carefully considered to avoid enrollment of subjects for whom exposure to the study drug might pose a hazard.
3. The anticipated subject population (with essential tremor) is acknowledged to likely be older than the healthy volunteer and schizophrenic populations that have previously undergone phase 1 and 2 study with CX-8998 (formerly MK-8998, Merck & Co, Inc). Since older male and female subjects may experience greater CX-8998 exposures than younger males on whom most of the existing PK data are based, this study will perform a careful dose titration in which dosing of CX-8998 will be initiated at 4 mg BID for 7 days, increasing to 8 mg BID for 7 days, and finally, if tolerated, to the target dose of 10 mg BID for 14 days. Subjects will return to the clinic for each dose up-titration for safety assessment. The study is designed to allow for flexible titration; should subjects experience intolerable AEs (see

Section 10.2.1, Adverse Events, Definitions) at 4 mg, 8 mg or 10 mg BID, the dose may be decreased to the previous lower dose (2 mg BID in the case of 4 mg BID). Subjects experiencing intolerable AEs at 2 mg BID will be discontinued from treatment.

4. Dose up-titration (e.g., from 4 mg BID to 8 mg BID) requires that the subject be evaluated in the clinic by the PI or sub-I. PI's and sub-I's may advise a subject to reduce or suspend their dose based on telephone elicitation of adverse events. During each clinic visit involving a dose up-titration, subjects will be observed and monitored in the clinic for at least 2 hours following the first administration of the increased dose step.
5. Dose modification and stopping rules are in place for individual subjects (see Section 4.5, Dose Adjustments/Toxicity Management). Near real-time safety and tolerability monitoring for individual subjects is the primary responsibility of the PI and sub-I's.
6. All serious adverse events (SAEs) meeting criteria for expedited reporting to the US FDA will be reported to the FDA and all IRBs in accordance with regulatory timelines.
7. 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. These reviews will be based on blinded, select listings and summary tables of the evolving safety and tolerability data for each arm of the study. The sponsor's study safety representative and the independent safety monitor physician will review the blinded study data to determine if there is a sufficiently clinically significant difference between the blinded treatment arms in terms of frequency, severity, and/or seriousness of adverse events to take actions such as 1) unblinding specific safety data; 2) eliminating one or more of the planned dose up-titrations (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 PI's and sub-I's 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.
8. In the event of a treated subject's death within 30 days of the last dose of study drug and that is assessed by the treating PI/sub-I or the independent safety monitor physician or the study safety representative as at least possibly related to study drug, further enrollment into the study will be immediately suspended until a safety review can be conducted by the independent safety monitor physician, the study safety representative, the actively participating PIs and sub-Is, and the sponsor. As required by regulation, all deaths meeting criteria for expedited reporting to the US

FDA will be reported to the FDA and all IRBs within regulatory timelines. A final decision to re-open the study to new enrollment without modification(s), re-open with modification(s), or terminate the study will be made by the overall study principal investigator, the independent safety monitor physician, and the sponsor's study safety representative.

11 STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with statistical testing performed for the efficacy endpoints. All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. 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 by treatment group and overall. The term "treatment group" refers to the following: Placebo or CX-8998. All available data for enrolled subjects will be listed in by subject listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number.

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

11.1 Statistical Analysis Plans

A SAP will be created and approved prior to the unblinding of the study data. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures.

11.2 Study Hypothesis

The primary statistical hypothesis for the study is provided below.

- H_{02}: $\mu_{Placebo} = \mu_{CX\text{-}8998}$, i.e., there is no difference between treatment groups in the mean change from Baseline in TETRAS performance scale at end of treatment
- H_{12}: $\mu_{Placebo} \neq \mu_{CX\text{-}8998}$, i.e., there is a difference between treatment groups in mean change from Baseline in TETRAS performance scale at end of treatment

11.3 Determination of Sample Size

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

A sample size of 53 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 in the TETRAS performance subscale when the standard deviation is 7.5 and alpha=0.05 (PASS 2008: Two sample t-test – Normal Non-Parametric Adjustment) and to account for dropouts and subjects who are excluded because of major protocol deviations.

A blinded interim analysis of variance will be conducted once 50% of subjects have been enrolled and followed for 28 days or discontinued from the study. Based on the results of this analysis, the sample size may be modified to achieve the desired power for the study.

11.4 Analysis Populations

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

• **Intent-To-Treat Population:** The ITT population will include all subjects who are randomized. The ITT population will be used for analyses of accountability, demographics, and efficacy. Subjects will be analyzed according to the treatment as randomized.

• **Safety Population:** The safety population will include all subjects who are randomized and receive at least one dose of randomized treatment. Subjects who receive treatment other than that intended will be analyzed according to the treatment received. The safety population will be the primary population for all analyses of safety data.

• **PK Population:** The PK population will consist of all subjects for whom PK samples were obtained, received study treatment, and for whom sufficient plasma concentrations are available.

11.5 Data Analysis

11.5.1 Efficacy Analyses

11.5.1.1 Primary Efficacy Analyses

The primary efficacy analysis of the TETRAS performance subscale (as scored by the central rater) will be conducted using an analysis of covariance (ANCOVA) model with fixed effects for treatment, concomitant anti-tremor medication use, site type, and Baseline value of the TETRAS performance subscale. The primary hypothesis to be tested will be if the mean change from Baseline in TETRAS performance scale indicates that the CX-8998 arm is different from placebo. All testing will be performed using the least square (LS) means from the ANCOVA model and a two-sided test at the alpha=0.05 level of significance. If the data indicate a departure from the normal distribution, a corresponding rank test will be performed.

11.5.1.2 Secondary and Exploratory Efficacy Analyses

Analyses of the continuous secondary and exploratory endpoints will be conducted using the same type of ANCOVA model as described for the primary endpoint, with baseline values included only as applicable. All secondary and exploratory analyses will be conducted using two-sided tests at the alpha=0.05 level of significance. Analysis of findings from the neurophysiology substudy will be presented in a separate study report.

11.5.2 Safety Analyses

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

Descriptive summaries of vital signs and clinical laboratory results will be presented by treatment group and study visit. The number and percentage of subjects experiencing treatment-emergent laboratory abnormalities will be summarized by treatment group. Laboratory abnormality shifts from Baseline to post-Baseline assessments will be summarized by treatment group.

Concomitant medications will be mapped to a WHO preferred term and drug classification. The number and percent of subjects taking concomitant medications will be summarized using preferred terms and drug classifications.

Changes from Baseline in physical examinations, neurological examinations, and ECGs during study will be evaluated. Results from the C-SSRS will be listed by treatment.

11.5.3 Pharmacokinetic Analyses

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

11.5.4 Interim Analysis

Once at least 50% of subjects have been treated and followed through Day 28 or the corresponding subjects have discontinued the study, an independent, non-study statistician will estimate the variance for the primary efficacy endpoint. This estimate will be based on the available Day 28 data at the time of the interim analysis and will be calculated in a blinded manner. This blinded estimate may be provided to the sponsor for review and potential considerations for altering the trial size.

As the sponsor will remained 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.

Following completion of study Visit 4 by approximately 75% of planned, the sponsor may convene an independent external data monitoring committee (DMC) to review accumulated unblinded efficacy data in collaboration with the unblinded study statistician and provide a recommendation regarding the completion, resizing, or termination of the study to the sponsor. The DMC may convene more than once per sponsor's request and/or request a meeting with the independent safety monitor to discuss safety/tolerability findings in support of its recommendation to the sponsor. Additional information pertaining to role of the DMC is provided in the DMC charter document.

11.6 Missing, Unused and Spurious Data

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

12 STUDY MANAGEMENT

12.1 Protocol Amendment and Protocol Deviation

12.1.1 Protocol Amendment

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

12.1.2 Protocol Deviations and Waivers

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

12.2 Ethics and Regulatory Aspects

12.2.1 Ethical Conduct of the Study and Regulatory Guidelines

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

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

12.2.2 Institutional Review Board and Regulatory Approval

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

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

12.2.3 Subject Informed Consent

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

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

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

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

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

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

12.3 End of Study and Regulatory Notification

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

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

12.4 Data Protection and Confidentiality

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

12.5 Monitoring

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

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

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

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

12.6 Quality Assurance and Quality Control

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

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

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

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

12.7 Source Data

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

Source documents are the original data, documents, and records. Examples include hospital records, laboratory reports, clinical and office charts, laboratory notes, memoranda,

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

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

13 DATA AND RECORD KEEPING

13.1 Case Report Forms

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

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

13.2 Record Keeping

the investigator must arrange for retention of study records (“Essential Documents for the Conduct of a Trial” are listed in the ICH “Guideline for Good Clinical Practice,” Section 8, E6) at the site, in a secure location, for 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or for at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. the investigator should take measures to prevent any accidental or premature destruction of these documents.

14 REFERENCES

Adams PJ, Snutch TP. Calcium channelopathies. Voltage-gated calcium channels. Subcell Biochem. 2007;45: 215-251.

Bain PG, Findley LJ, Atchison P, et al. Assessing tremor severity. J Neurol Neurosurg Psychiatry. 1993; 56(8): 868-873.

Bermejo-Pareja F. Essential tremor—a neurodegenerative disorder associated with cognitive defects? Nature Reviews Neurology. 2011;7(5):273-282.

Bermejo-Pareja F, Puertas-Martín V. Cognitive Features of Essential Tremor: A Review of the Clinical Aspects and Possible Mechanistic Underpinnings. Louis ED, ed. *Tremor and Other Hyperkinetic Movements*. 2012;2:02-74-541-1.

Bermejo-Pareja PE, Ruiz-Huete C, Dorado R, Anciones B. Zonisamide in refractory essential tremor. Revista de Neurologia. 2008; 46(3): 139-142.

Bourinet E, Alloui A, Monteil A, et al. Silencing of the Cav3.2 t-type calcium channel gene in sensory neurons demonstrates its major role in nociception. EMBO. 2005;24(2): 315-324.

Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol Rev. 2005;57(4): 411-425.

Chandran V, Pal PK, Reddy JY, Thennarasu K, Yadav R, Shivashankar N. Non-motor features in essential tremor. Acta Neurol Scand. 2012;125:332–7.

Chang K, Wang S, Chi C. Efficacy and safety of topiramate for essential tremor: a meta-analysis of randomized controlled trials. Medicine. 2015; 94(43): 1-7.

Cribbs LL, Lee JH, Yang J, et al. Cloning and characterization of alpha1H from human heart, a member of the T-type Ca2+ channel gene family. Circ. Research. 1998;83(1): 103-9.

Deuschl G, Bain P, Brin M. Consensus Statement of the Movement Disorder Society on Tremor. Mov Disord. 1998;13: 2–23.

Diaz NL, Louis ED. Survey of medication usage patterns among essential tremor patients: Movement disorder specialists vs. general neurologists. Parkinsonism Relat Disorders. 2010;16(9):604-607.

Elble RJ. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. Brain. 2006;129(10):2660-2666.

Elble RJ, Brilliant M, Leffler K, Higgins C. Quantification of essential tremor in writing and drawing. Mov Disord. 1996;11:70-78.

Elble R, Comella C, Fahn S, et al. The essential tremor rating assessment scale (TETRAS). Mov Disord. 2008; 23 (Suppl 1): S1-6.

Elble R, Comella C, Fahn S, et al. Reliability of a new scale for essential tremor. Mov Disord. 2012;27(12):1567-1569.

Elble R, Lewitt P, Lyons K, et al. Inter-Rater Reliability of the Essential Tremor Rating Assessment Scale (TETRAS) (S32.004). Neurology. 2012;78 (Meeting Abstracts 1).

Ertel EA, Campbell KP, Harpold MM, et al. Nomenclature of voltage-gated calcium channels. Neuron. 2000;25:533–5.

Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, ed. *Parkinson's Disease and Movement Disorders*. Baltimore: Williams & Wilkins; 1993: 225–234.

Frucht SJ, Bordelon Y, Houghton WH. Marked amelioration of alcohol responsive posthypoxic myoclonus by gamma-hydroxybutyric acid (Xyrem). Mov Disord. 2005;20(6): 745-751.

George MS, Lydiard RB. Social Phobia Secondary to Physical Disability. Psychosomatics. 1994;35(6):520-523.

Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.

Handforth A, Delorey TM, Homanics GE, Olsen RW. Pharmacologic evidence for abnormal thalamocortical functioning in GABA receptor beta3 subunit-deficient mice, a model of Angelman syndrome. Epilepsia. 2005;46(12):1860-70.

Handforth A, Homanic GE, Covey DF, et al. T-type calcium channel antagonists suppress tremor in two mouse models of essential tremor. Neuropharmacology. 2010; 59(6):380-387.

Handforth A, Martin F, Kang G, Vanek Z. Zonisamide for essential tremor: an evaluator blinded study. Movement Disorders. 2009; 24(3); 437-440.

Jankovic J, Frost JD. Quantitative assessment of parkinsonian and essential tremor: Clinical application of triaxial accelerometry. Neurology. 1981;31(10):1235-1235.

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. 1991;14(6):540-545.

Johns MW. A new perspective on sleepiness. Sleep and Biological Rhythms. 2010;8(3):170-179.

Kamper SJ, Maher CG, Mackay G. Global Rating of Change Scales: A Review of Strengths and Weaknesses and Considerations for Design. The Journal of Manual & Manipulative Therapy. 2009;17(3):163-170.

Kiresuk TJ, Sherman RE. Goal attainment scaling: A general method for evaluating comprehensive community mental health programs. Community Mental Health Journal. 1968;4:443–453.

Koller WC, Royse VL. Time course of a single oral dose of propranolol in essential tremor. Neurology. 1985; 35(10): 1494-1494.

Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. Neurology. 1989;39(12):1587-1587.

Llinás R. Thalamo-cortical dysrhythmia syndrome: neuropsychiatric features. An R Acad National Med. 2003;120(2): 267-290.

Llinás RR, Choi S, Urbano FJ, Shin H. γ-Band deficiency and abnormal thalamocortical activity in P/Q-type channel mutant mice. Proc Natl Acad Sci. 1999; 104(45):17819-17824.

Long MA, Deans MR, Paul DL, Connors BW. Rhythmicity without synchrony in the electrically uncoupled inferior olive. J Neurosci. 2002 Dec 15;22(24):10898-905.

Lorenz D, Schwieger D, Moises H, Deuschl G. Quality of life and personality in essential tremor patients. Mov Disord. 2006;21(8):1114-1118.

Louis ED. Essential Tremor. Arch Neurol. 2000;57(10).

Louis ED. Medication non-adherence in essential tremor. Parkinsonism Relat Disord. 2015;21(2):138-141.

Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25(5):534-541.

Louis ED, Machado DG. Tremor-related quality of life: A comparison of essential tremor vs. Parkinson's disease patients. Parkinsonism Relat Disord. 2015;21(7):729-735.

Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder? Estimates of the prevalence of essential tremor throughout the world. Movement Disorders. 1998;13(1):5-10.

Makedonsky PV, Levin OS, Naimushina TV. The quality of life in patients with essential tremor [abstract]. Mov Disord. 2002;17:S353

Martin FC, Handforth A. Carbenoxolone and mefloquin suppress tremor in the harmaline model of essential tremor. Mov Disord. 2006;21(10):1641-1649.

Martin FC, Thu Le A, Handforth A. Harmaline-induced tremor as a potential preclinical screening method for essential tremor medications. Mov Disord. 2005 Mar;20(3):298-305.

Mitsi G, Mendoza EU, Benjamin D. Wissel BD, et al. Biometric Digital Health Technology for Measuring Motor Function in Parkinson's Disease: Results from a Feasibility and Patient Satisfaction Study. Front. Neurol. 2017 Jun 13;8:273

Miwa H, Hama K, Kajimoto Y, Kondo T. Effects of zonisamide on experimental tremor in rats. Parkinsonism Relat Disord. 2008;14:33-36.

Molineux ML, McRory JE, McKay BE, et al. Specific t-type calcium channel isoforms are associated with distinct burst phenotypes in deep cerebellar nuclear neurons. PNAS. 2006;103(41): 5555-5560.

Morita S, Miwa H, Kondo T. Effect of zonisamide on essential tremor: a pilot crossover study in comparison with arotinolol. Parkinsonism Relat Disord (2005) 11: 101–103

Mostile G, Giuffrida JP, Adam OR, Davidson A, Jankovic J. Correlation between Kinesia system assessments and clinical tremor scores in patients with essential tremor. Mov Disord. 2010;25(12):1938-1943.

Mundt JC, Greist JH, Gelenberg AJ, Katzelnick DJ, Jefferson JW, Modell JG. Feasibility and validation of a computer-automated Columbia-Suicide severity rating scale using interactive voice response technology. J Psych Res. 2010;44(16):1224-1228.

Mundt JC, Greist JH, Jefferson JW, Federico M, Mann JJ, Posner K. Prediction of Suicidal Behavior in Clinical Research by Lifetime Suicidal Ideation and Behavior Ascertained by the Electronic Columbia-Suicide Severity Rating Scale. J Clin Psych. 2013;74(09):887-893.

Ondo W. Zonisamide for essential tremor. Clin Neuropharmacol. 2007;30(6): 345-349.

Park Y, Park H, Lee CJ, et al. CaV3.1 is a tremor rhythm pacemaker in the inferior olive. PNAS. 2010;107(23):10731 – 10736.

Park Y-G, Kim J, Kim D. The potential role of T-type Ca2+ channels in motor coordination. Front Neural Circuits. 2013;7(172): 1-11.

Paterson NE, Malekiani SA, Foreman MM, Olivier B, Hanania T. Pharmacological characterization of harmaline induced tremor activity in mice. Eur J Pharmacol. 2009;616(1-3):73-80.

Papapetropoulos S, Katzen H, Schrag A, Singer C, Scanlon BK, Nation D, Guevara A, Levin B. A questionnaire-based (UM-PDHQ) study of hallucinations in Parkinson's disease. BMC Neurol. 2008;8:21.

Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psych. 2011;168(12):1266-1277.

Quesada A, Bui PH, Homanics GE, Hankinson O, Handforth A. Comparison of mibefradil and derivative NNC 55-0396 effects on behavior, cytochrome P450 activity and tremor in mouse models of essential tremor. Eur J Pharmacol. 2011. 659: 30-36.

Rappaport MS, Gentry RT, Schneider DR, Dole VP. Ethanol effects on harmaline-induced tremor and increase of cerebellar cyclic GMP. Life Sci. 1984 Jan 2;34(1):49-56.

Schroeder D, Nasrallah HA. High alcoholism Rate in Patients with Essential Tremor. Am J Psychiatry. 1982;139(11): 1471-1473.

Shill HA, Bushara KO, Mari Z, Reich M, Hallet M. Open-label dose escalation of oral 1-octanol in patients with essential tremor. Neurology. 2004;62(12): 2320-2322.

Shipe WD, Barrow JC, Yang ZQ. Design synthesis, and evaluation of a novel 4-aminomethyl-4-fluoropiperidine as a T-type Ca2+ channel antagonist. J. Med. Chem. 2008;51(3):692-3695.

Simantov R, Snyder SH, Oster-Granite M-L. Harmaline-induced tremor in the rat: Abolition by 3-acetylpyridine destruction of cerebellar climbing fibers. Brain Res. 1976;114(1):144-151.

Sinton CM, Krosser BI, Walton KD, Llinás RR. The effectiveness of different isomers of octanol as blockers of harmaline-induced tremor. Pflugers Arch. 1989;414: 31-36.

Tai C, Yang Y, Pan M, Huang C, Kuo C. Modulation of subthalamic T-type Ca2+ channels remedies locomotor deficits in a rat model of Parkinson disease. J Clin Invest. 2011;121(8): 3289-3305.

Tröster AI, Pahwa R, Fields JA, Tanner CM, Lyons KE. Quality of life in Essential Tremor Questionnaire (QUEST): Development and initial validation. Parkinsonism Relat Disord. 2005;11(6):367-373.

Voller B, Lines E, McCrossin G, et al. Alcohol challenge and sensitivity to change of the essential tremor rating assessment scale. Mov Disord. 2014;29(4):555-558.

Zesiewicz TA, Ward CL, Hauser RA, Sanchez-Ramos J, Staffetti JF, Sullivan KL. A double blind placebo controlled trial of zonisamide (zonegran) in the treatment of essential tremor. Mov Disord. 2009;22(2): 279-282

Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: Treatment of essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2011;77(19):1752-1755.

15 APPENDICES

Appendix A – Efficacy assessments

Appendix B – Safety assessments

Appendix C – Cytochrome P450 Interaction Table

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

Appendix A1 – TETRAS Performance Scale

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor, are performed with the patient seated comfortably. For each item, score the highest amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out.

1. Head tremor: The head is rotated fully left and right and then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right with the head in mid position. The nose should be used as the landmark to assess and rate the largest amplitude excursions during the examination.

   0 = no tremor
   1 = slight tremor (< 0.5 cm)
   2 = mild tremor (0.5- < 2.5 cm)
   3 = moderate tremor (2.5-5 cm)
   4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.

   0 = no tremor
   1 = slight; barely perceptible tremor
   2 = mild: noticeable tremor
   3 = moderate: obvious tremor, present in most voluntary facial contractions
   4 = severe: gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended “aaah” sound and eee” sound for 5 seconds each. Then assess speech during normal conversation by asking patients “How do you spend your average day?”

   0 = no tremor
   1 = slight: tremor during aaah, and eee and no tremor during speech
   2 = mild: tremor in “aaah” and “eee” and minimal tremor in speech

3 = moderate: obvious tremor in speech that is fully intelligible
4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal reach posture is held for 5 seconds. The lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be estimated using the maximally displaced point of the hand at the point of greatest displacement along any single plane. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

   a) Forward outstretched postural tremor: Subjects should bring their arms forward, slightly lateral to midline and parallel to the ground. The wrist should also be straight and the fingers abducted so that they do not touch each other.
   b) Lateral "wing beating" postural tremor: Subjects will abduct their arms parallel to the ground and flex the elbows so that the two hands do not quite touch each other and are at the level of the nose. The fingers are abducted so that they do not touch each other. The posture should be held for 20 seconds.
   c) Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Only the position along the trajectory of greatest tremor amplitude is assessed. This will typically be either at the nose or at the point of full limb extension.

   For all three hand tremor ratings 0 = no tremor

   1 = tremor is barely visible
   1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude
   2.5 = tremor is 3- < 5 cm amplitude
   3 = tremor is 5- < 10 cm amplitude
   3.5 = tremor is 10- < 20 cm amplitude
   4 = tremor is > 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally parallel to the ground for 5 seconds each. Then perform a standard heel to shin maneuver with each leg, three times. The maximum tremor in either maneuver is scored, and only the

limb with the largest tremor is scored. Tremor may exist in any part of the limb, including foot.

0 = no tremor
1 = slight: barely perceptible
2 = mild, less than 1 cm at any point
3 = moderate tremor, less than 5 cm at any point
4 = severe tremor, greater than 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills 1/4 of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

   0 = normal
   1 = slight: tremor barely visible.
   2 = mild: obvious tremor
   3 = moderate: portions of figure not recognizable.
   4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand.. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

   0 = normal
   1 = slight: untidy due to tremor that is barely visible. 2 = mild: legible, but with considerable tremor.
   3 = moderate: some words illegible.
   4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X and instructs the subject to hold the tip of the pen "as close as possible to the dot (or center of an X) without touching it, (ideally approximately 1 mm) for 10 seconds ". Each hand is score separately.

0 = no tremor
1 = tremor is barely visible
1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is > 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20°. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk

0 = no tremor
1 = barely perceptible tremor
2 = obvious but mild tremor, does not cause instability 3 = moderate tremor, impairs stability of stance
4 = severe tremor, unable to stand without assistance

Appendix A2 – TETRAS Activities of Daily Living Scale

TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS©) V 3.1

Activities of Daily Living Subscale

Rate tremor's impact on activities of daily living (0 - 4 scoring).

1. Speaking
0 = Normal.
1 = Slight voice tremulousness, only when "nervous".
2 = Mild voice tremor. All words easily understood.
3 = Moderate voice tremor. Some words difficult to understand.
4 = Severe voice tremor. Most words difficult to understand.

2. Feeding with a spoon
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot feed with a spoon.

3. Drinking from a glass
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

4. Hygiene
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.
2 = Mildly abnormal. Some difficulty but can complete task.
3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy such as using two hands or using the less affected hand.
4 = Severely abnormal. Cannot complete hygiene activities independently.

5. Dressing
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with dressing.
2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.
3 = Moderately abnormal. Unable to do most dressing unless uses strategy such as using Velcro, buttoning shirt before putting it on or avoiding shoes with laces.
4 = Severely abnormal. Cannot dress independently.

6. Pouring
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with pouring.
2 = Mildly abnormal. Must be very careful to avoid spilling but may spill occasionally.
3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.
4 = Severely abnormal. Cannot pour.

7. Carrying food trays, plates or similar items
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.
2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.
3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.
4 = Severely abnormal. Cannot carry food trays or similar items.

8. Using Keys
0 = Normal
1 = Slightly abnormal. Tremor is present but can insert key with one hand without difficulty.
2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.
3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.
4 = Severely abnormal. Cannot put key in lock.

9. Writing
0 = Normal
1 = Slightly abnormal. Tremor present but does not interfere with writing.
2 = Mildly abnormal. Difficulty writing due to the tremor
3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.
4 = Severely abnormal. Cannot write.

10. Working. If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as it relates to housework:
0 = Normal .
1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.
2 = Mildly abnormal. Tremor interferes with work; able to do everything, but with errors. .
3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.
4 = Severely abnormal. Cannot perform any job or household work.

11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writing, etc)

Task _____

0 = Normal.
1 = Slightly abnormal. Tremor present but does not affect task.
2 = Mildly abnormal. Tremor interferes with task but is still able to perform task.
3 = Moderately abnormal. Can do task but must use strategies.
4 = Severely abnormal. Cannot do the task.

12. Social Impact

0 = None
1 = Aware of tremor, but it does not affect lifestyle or professional life.
2 = Feels embarrassed by tremor in some social situations or professional meetings.
3 = Avoids participating in some social situations or professional meetings because of tremor.
4 = Avoids participating in most social situations or professional meetings because of tremor.

Appendix A3 – QUEST

Quality of Life in Essential Tremor Questionnaire (QUEST)

Patient's Name: _____ ID: _____ Date: ____ / ____ / ____

Gender: ☐ Male ☐ Female Date of Birth: ____ / ____ / ____

Heath Status

In general, how would you rate your overall health? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Overall Quality of Life

Overall, how would you rate your quality of life? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

General Information

In the past month, has your tremor interfered with your sexual satisfaction?	Y	N
In the past month, have you had side effects from tremor medications?	Y	N
In the past month, have you been satisfied with the tremor control achieved by your medications?	Y	N

Which most appropriately describes your work status?

- ☐ Never worked
- ☐ Not working, retired because of tremor
- ☐ Not working, retired NOT due to tremor
- ☐ Working full time
- ☐ Working part time

TREMOR SELF ASSESSMENT

For the purposes of this questionnaire, tremor is defined as uncontrollable shaking or quivering of the body part in question.

On a typical day, how many of your waking hours do you have tremor in ANY body part?

Circle: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Put a mark in the box to rate the severity of your tremor in each of the body parts listed below.

None - no tremor at any time
Mild - mild tremor not causing difficulty in performing any activities
Moderate - tremor causes difficulty in performing **some** activities
Marked - tremor causes difficulty in performing **most** or **all** activities
Severe - tremor **prevents** performing some activities

		None	Mild	Moderate	Marked	Severe
1.	Head	☐	☐	☐	☐	☐
2.	Voice	☐	☐	☐	☐	☐
3.	Right arm/hand	☐	☐	☐	☐	☐
4.	Left arm/hand	☐	☐	☐	☐	☐
5.	Right leg/foot	☐	☐	☐	☐	☐
6.	Left leg/foot	☐	☐	☐	☐	☐

continued on next page

For each question below, please mark the box which best describes your current situation.

For example: [N] [R] [~~S~~] [F] [A]

N = Never/No
R = Rarely
S = Sometimes
F = Frequently
A = Always/Yes
NA = Not Applicable

1.	My tremor interferes with my ability to communicate with others.		N	R	S	F	A
2.	My tremor interferes with my ability to maintain conversations with others.		N	R	S	F	A
3.	It is difficult for others to understand my speech because of my tremor.		N	R	S	F	A
4.	My tremor interferes with my job or profession.	NA	N	R	S	F	A
5.	I have had to change jobs because of my tremor.	NA	N	R	S	F	A
6.	I had to retire or take early retirement because of my tremor.		N				A
7.	I am only working part time because of my tremor.	NA	N				A
8.	I have had to use special aids or accommodations in order to continue my job due to my tremor.	NA	N	R	S	F	A
9.	My tremor has led to financial problems or concerns.		N	R	S	F	A
10.	I have lost interest in my hobbies because of my tremor.		N	R	S	F	A
11.	I have quit some of my hobbies because of my tremor.		N				A
12.	I have had to change or develop new hobbies because of my tremor.		N				A
13.	My tremor interferes with my ability to write (for example, writing letters, completing forms).		N	R	S	F	A
14.	My tremor interferes with my ability to use a typewriter or computer.	NA	N	R	S	F	A
15.	My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone).		N	R	S	F	A
16.	My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items).		N	R	S	F	A
17.	My tremor interferes with dressing (for example, buttoning, zipping, tying shoes).		N	R	S	F	A
18.	My tremor interferes with brushing or flossing my teeth.		N	R	S	F	A
19.	My tremor interferes with eating (for example, bringing food to mouth, spilling).		N	R	S	F	A
20.	My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring).		N	R	S	F	A
21.	My tremor interferes with reading or holding reading material.		N	R	S	F	A
22.	My tremor interferes with my relationships with others (for example, my family, friends, coworkers).		N	R	S	F	A
23.	My tremor makes me feel negative about myself.		N	R	S	F	A
24.	I am embarrassed about my tremor.		N	R	S	F	A
25.	I am depressed because of my tremor.		N	R	S	F	A
26.	I feel isolated or lonely because of my tremor.		N	R	S	F	A
27.	I worry about the future due to my tremor.		N	R	S	F	A
28.	I am nervous or anxious.		N	R	S	F	A
29.	I use alcohol more frequently than I would like to because of my tremor.		N	R	S	F	A
30.	I have difficulty concentrating because of my tremor.		N	R	S	F	A

THANK YOU!

QUEST Scoring

Patient Name: _____ Date: _____

If a question is Not Applicable, "X" through NA and leave blank--do not assign a score of 0.

Scoring algorithm:	*Total **applicable** points for each dimension* / *Total possible points (# of **applicable** questions x 4) for each dimension*	x 100 =	dimension score

N=0 R=1 S=2 F=3 A=4 NA=blank Note: Questions 6, 7, 11, & 12--0 OR 4 points possible (if applicable).

Communication

1. My tremor interferes with my ability to communicate with others. _____
2. My tremor interferes with my ability to maintain conversations with others. _____
3. It is difficult for others to understand my speech because of my tremor. _____

Work and Finances

4. My tremor interferes with my job or profession. NA _____
5. I have had to change jobs because of my tremor. NA _____
6. I had to retire or take early retirement because of my tremor. _____
7. I am only working part time because of my tremor. NA _____
8. I have had to use special aids or accommodations in order to continue my job due to my tremor. NA _____
9. My tremor has led to financial problems or concerns. _____

Hobbies and Leisure

10. I have lost interest in my hobbies because of my tremor. _____
11. I have quit some of my hobbies because of my tremor. _____
12. I have had to change or develop new hobbies because of my tremor. _____

Physical

13. My tremor interferes with my ability to write (for example, writing letters, completing forms). _____
14. My tremor interferes with my ability to use a typewriter or computer. NA _____
15. My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone). _____
16. My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items). _____
17. My tremor interferes with dressing (for example, buttoning, zipping, tying shoes). _____
18. My tremor interferes with brushing or flossing my teeth. _____
19. My tremor interferes with eating (for example, bringing food to mouth, spilling). _____
20. My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring). _____
21. My tremor interferes with reading or holding reading material. _____

Psychosocial

22. My tremor interferes with my relationships with others (for example, my family, friends, coworkers). _____
23. My tremor makes me feel negative about myself. _____
24. I am embarrassed about my tremor. _____
25. I am depressed because of my tremor. _____
26. I feel isolated or lonely because of my tremor. _____
27. I worry about the future due to my tremor. _____
28. I am nervous or anxious. _____
29. I use alcohol more frequently than I would like to because of my tremor. _____
30. I have difficulty concentrating because of my tremor. _____

Appendix B1 – C-SSRS

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer.

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

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

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

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

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

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

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

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it....and I would never go through with it".*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

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

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

Appendix B2 – Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (yrs): _____ Your gender (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting inactive in a public place (e.g., a theater or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car or bus, while stopped for a few minutes in traffic	___

THANK YOU FOR YOUR COOPERATION

ESS - United States/English - Version of 16 Jan 15 - Mapi.
ID037309 / ESS_AU1.0_eng-US1.doc

Appendix B3 – University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-PDHQ)

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

Patient identifier:
DATE:

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

Comments:

Page 1 of 2

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

Page 2 of 2

Appendix C – Cytochrome P450 Drug Interaction Table

PROHIBITED CYP3A4 INHIBITORS*

HIV antivirals (delaviridine, indinavir, nelfinavir, ritonavir)

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

troleandomycin
verapamil

PROHIBITED CYP2C9 INHIBITORS*

amiodarone
fluconazole
izoniazid

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

PROHIBITED CYP3A4 INDUCERS*

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

PROHIBITED CYP2C9 INDUCERS*

rifampin

secobarbital

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

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