CLINICAL STUDY PROTOCOL

A Phase 2a Open-Label Study to Evaluate the Safety, Tolerability and Efficacy of CAD-1883 Oral Treatment in Adults with Essential Tremor (CADENCE-1)

Investigational Product: CAD-1883
Protocol Number: CAD1883-201 (CADENCE-1) / NCT03688685
IND Number: 140185
EudraCT Number: 2017-004223-70

Sponsor:
Cadent Therapeutics, Inc.

Personal Protected Data

Version Number: Amendment 3.0
Date: 09 July 2019

SIGNATURE PAGE

STUDY TITLE: **A Phase 2a Open-Label Study to Evaluate the Safety, Tolerability and Efficacy of CAD-1883 Oral Treatment in Adults with Essential Tremor (CADENCE-1)**

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

Personal Protected Data

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Cadent Therapeutics, Inc to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Cadent Therapeutics, Inc and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by Cadent Therapeutics, Inc, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration (FDA) Regulations, Institutional Review Board (IRB)/Ethic Committee Regulations and International Council for Harmonization (ICH) Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

Sponsor	Cadent Therapeutics, Inc.
Investigational Product	CAD-1883
Protocol Number	CAD1883-201
Protocol Title	A Phase 2a Open-Label Study to Evaluate the Safety, Tolerability and Efficacy of CAD-1883 Oral Treatment in Adults with Essential Tremor (CADENCE-1)
Study Phase	2a
Study Rationale	CAD-1883 is an investigational product being developed as a new treatment for Essential Tremor (ET), a movement disorder characterized by dysfunction of the cerebellum and its associated motor control circuit (Haubenberger et al, 2018). Tremor is defined as a rhythmic and oscillatory movement of a body part with a relatively constant frequency and variable amplitude. It is caused by alternating contractions of antagonistic muscles. Tremor is the most common of all movement disorders, and ET is the most common neurologic cause of tremor. The usual course of ET is one of gradual progression. Patients with persistent disability from ET need continuous symptomatic drug therapy. Available drug treatments are not effective in all patients, often provide inadequate symptomatic relief, and the symptomatic benefit of chronic administration often declines over time and is frequently associated with intolerable side effects. Therapy options for ET patients who do not benefit from pharmacologic treatment include deep brain stimulation (DBS) requiring surgery for placement of brain stimulator(s), magnetic resonance image (MRI)-guided thalamotomy via focused ultrasound (to treat persistently disabling unilateral limb tremor), or botulinum toxin injections (to treat persistently disabling hand, head, or vocal cord tremor). The efficacy of these invasive, non-pharmacologic therapies may also wane over time, and may be associated with intolerable side effects. Therefore, to address these important unmet medical needs, efforts are required to develop new treatments for ET targeting the cerebellar dysregulation responsible for the movement disorder. The cerebellum is required for coordinated motion, including movements of the hands, limbs, trunk, and eyes, and the synchrony of speech, all of which are disrupted in ET. The cerebellar cortex, together with the inferior olivary nucleus and deep cerebellar nuclei, comprises the olivocerebellar circuit. Cerebellar output critically depends on the precise timing of action potentials in the principal neurons of the olivocerebellar circuit, especially cerebellar Purkinje neurons (Llinas, 2014). Small conductance calcium-activated potassium (SK) channels are a family of potassium channels gated by intracellular calcium (Kshatri, 2018). In neurons, SK channels are gated by calcium that passes through voltage-gated calcium channels, which are activated by each action potential. SK channels

	regulate action potential timing by generating hyperpolarizing potassium currents between action potentials. In principle neurons of the olivocerebellar circuit, including cerebellar Purkinje neurons and their major afferent neurons of the inferior olivary nucleus, SK2 and SK3 channel-mediated after-hyperpolarizing currents represent a molecular pace-making mechanism centrally implicated in the coordination of movement. CAD-1883 is a small molecule positive allosteric modulator (PAM) of SK channels Commercially Confidential Information (CCI) CAD-1883 represents the first selective SK channel PAM candidate suitable for entering clinical development in patients with ET. CAD-1883 is anticipated to be used for the treatment of ET throughout the course of the patient's disease. This study offers the opportunity to understand the safety, tolerability, and efficacy of CAD-1883 in the ET patient population.
Study Population	Subjects will be aged between 18 and 75 years old, inclusive, with a history of tremor for at least 3 years.
Duration of Subject Involvement	Individual subject participation could be up to 56 days.
Study Objectives	**Primary Objectives** To evaluate the safety and tolerability of twice-daily oral dosing of CAD-1883 over 14 days of treatment in adult subjects with ET.
	Secondary Objectives To evaluate the efficacy of twice-daily oral dosing of CAD-1883 over 14 days of treatment as measured by: • The Essential Tremor Rating Assessment Scale (TETRAS)-performance subscale (PS) total score change from Baseline to Day 14 • TETRAS-PS upper limb subscale score change from Baseline to Day 14 Commercially Confidential Information • Change from Baseline to Day 14 in upper limb tremor severity, mean amplitude, and mean frequency, measured in the clinic using a wearable sensor Commercially Confidential Information

	Commercially Confidential Information
Study Design	This is an open-label study designed to evaluate the safety, tolerability, and efficacy of CAD-1883 administered twice daily orally to adult subjects with ET. Subjects will undergo a screening period of a minimum of 14 days up to a maximum of 35 days in which the subject will washout from prior Commercially Confidential Information, to allow the effects of previous medication(s) CCI to be eliminated. During the Screening period, each subject will undergo full assessment including medical and treatment history for ET, physical and neurological examination, in addition to laboratory testing, 12-lead electrocardiogram (ECG), and other screening assessments. The diagnosis of ET must be established by the Investigator at Screening based on the Movement Disorder Society (MDS) criteria (Bhatia, 2018) with a documented severity of tremor based on the clinician-administered TETRAS-PS (Elble, 2012). Commercially Confidential Information Per the Investigator's discretion, re-testing of any laboratory abnormality at the central lab or at a local lab is permissible, with prior approval from the Medical Monitor. Subjects who previously failed screening can be invited to rescreen up to two additional times, with recommendation by the Investigator and with approval by the Sponsor. The study will be open label consisting of 1 treatment group receiving 300 mg twice daily oral dosing of CAD-1883 for a treatment period of 14 days. Commercially Confidential Information The selected dose is anticipated to be well-tolerated by subjects with ET for the duration of the treatment period. A 14-day treatment period represents an adequate time period to permit the initial assessment of safety and tolerability of CAD-1883 as well as a determination of early treatment effect on reducing the magnitude and severity of tremor while limiting the potential risk associated with a novel investigational drug. Safety and tolerability will be monitored throughout the study duration including in-clinic assessments of adverse events (AEs), serious adverse events (SAEs), vital signs including orthostatic vital signs, 12-lead ECG, urinalysis, hematology, clinical chemistry, composite biomarker panel for renal tubular injury, and CAD-1883 plasma concentration level on Days 1, 7, 14, and 21. Efficacy will be evaluated as follows: • TETRAS-PS total score change from Baseline to Day 14 • TETRAS-PS upper limb subscale score change from Baseline to Day 14

	Commercially Confidential Information • Change from Baseline to Day 14 in upper limb tremor severity, mean amplitude, and mean frequency, measured in the clinic using a wearable sensor • Commercially Confidential Information The TETRAS-PS will be recorded via videography for centralized evaluation and rating by an independent blinded panel of experts. At the Baseline/Pre-dose visit (which is the last day of the Screening period), subjects will undergo all required procedures including confirmation that all eligibility criteria are met. The Day 1 visit can occur up to 3 business days following the Baseline/Pre-dose visit. Analysis of the pre-dose laboratory assessments (chemistry, hematology, urinalysis) should be conducted by the Central Laboratory, with the results available and reviewed by the Principal Investigator, or designee, prior to dosing the subject with CAD-1883 (Day 1 visit). On Day 1, subjects will be dosed in the clinic with the first dose of CAD-1883 300 mg (3 capsules of 100 mg each) and will be monitored in the clinic prior to ingesting the second dose of CAD-1883 300 mg (3 capsules of 100 mg each) in the clinic, 4 to 5 hours later. Additional safety and all efficacy assessments will be completed after the 2nd in clinic dose on Day 1 as indicated in the SOA (Appendix A, Table 2). Subjects will be dispensed study drug for continued twice-daily oral self-administration at home. After Day 1, subjects are instructed to ingest the first daily dose of CAD-1883 of 300 mg (3 capsules of 100 mg each) at home upon awakening in the morning. The second daily dose of 300 mg (3 capsules of 100 mg each) will be taken 8 hours (±2 hours) after the first daily dose. Each subject is provided with a medication diary to denote the date and time of at-home study drug dosing. The pre-dose laboratory assessments (chemistry, hematology, urinalysis) should be sent to the Central Laboratory for analysis. Under exceptional circumstances, the pre-dose laboratory assessments (chemistry, hematology, urinalysis) can be sent for expedited analysis at the local laboratory, along with duplicate samples sent to the Central Laboratory. The results of all laboratory assessments should be available and reviewed by the Principal Investigator, or designee, prior to dosing the subject. Subjects will return to the site for further assessments on Day 7 (-1 day) and Day 14 (±1 day). On these two site visit days, the subjects are instructed to ingest the first daily dose of CAD-1883 of 300 mg (3 capsules of 100 mg each) 4 to 5 hours prior to the scheduled and/or anticipated dosing of the second daily dose of CAD-1883 in the clinic. The second daily dose of CAD-1883 300 mg (3 capsules of 100 mg each) will be taken in the clinic, under the supervision of study staff, 4 to 5 hours after the first daily dose.

	Subjects will return to the clinic for a Follow-up visit (Day 21 [±1 day]). On Days 1, 7, 14, and 21, subjects will undergo safety monitoring consisting of reporting of AEs or SAEs, collection of vital signs including orthostatic vital signs, undergo a 12-lead ECG, and collection of urine for urinalysis and for kidney injury biomarkers assessment, and blood for hematology, clinical chemistry, and plasma drug level. Assessment of rating scales and upper limb wearable sensor measurements will also be performed. Commercially Confidential Information subjects will have the option to complete at-home assessments of tremor using the wearable sensor. Commercially Confidential Information Upon completion of the 14-day treatment period, subjects will return to the site for the Day 21 Follow-up visit, approximately 7 days (-1 day) after the last dose of study drug was administered.
Study Endpoints	**Primary Endpoint (Safety)** **Safety:** The primary endpoint of the study is to evaluate the occurrence and severity of treatment emergent AEs. **Secondary Endpoints (Efficacy)** Secondary efficacy endpoints will be measured by: • TETRAS-PS total score change from Baseline to Day 14 • TETRAS-PS upper limb subscale score change from Baseline to Day 14 Commercially Confidential Information • Change from Baseline to Day 14 in upper limb tremor severity, mean amplitude, and mean frequency, measured in the clinic using a wearable sensor

	• Commercially Confidential Information
Efficacy Assessments: Rating Scales	The treatment effect will be evaluated by means of the TETRAS-PS, which is a validated scale that has been used in recently conducted clinical trials in subjects with ET (Elble, 2012). It provides an accurate reflection of the clinical response to treatment on the amplitude of tremor over multiple bodily locations and over time. The TETRAS assessments at Screening, Baseline/Pre-dose, Days 1, 7, 14, and Follow-up visit (Day 21) will be administered by a certified rater. TETRAS raters at each site must demonstrate expertise in the administration of the TETRAS according to criteria preset by independent central rating experts. The TETRAS raters at each site can be the Principal Investigator or a staff member delegated as a rater by the Principal Investigator. Each site must make every effort, to the extent that is possible, to ensure availability of a primary rater and a backup rater to perform all TETRAS assessments on the same subjects throughout the study duration. The TETRAS-PS assessments at the Screening visit, Baseline/Pre-dose, Day 1, Day 7, Day 14, and Day 21 clinic visits will be recorded using videography for centralized evaluation and rating by independent blinded central raters (neurologists) with expertise in the assessment of ET. Commercially Confidential Information

	Commercially Confidential Information On Day 1: the TETRAS-PS will be administered 2 to 4 hours following the second in-clinic dose. On Day 7: the TETRAS-PS, Commercially Confidential Information will be performed 2 to 4 hours following the in-clinic dose. On Day 14: the TETRAS-PS, Commercially Confidential Information will be performed 2 to 4 hours following the in-clinic dose. Commercially Confidential Information At Follow up visit (Day 21): the TETRAS-PS, CCI are performed once any time during the visit. Commercially Confidential Information
Efficacy Assessments: Wearable Sensor	In addition to the assessment of efficacy via rating scales, treatment effect will be evaluated by measuring tremor with a sensor worn on the upper limb (index finger). These assessments will be conducted during the clinic visits and optionally at-home. **In-Clinic Assessment:** The wearable sensor measurements of upper limb tremor will be completed in the clinic once at any time during the Screening visit and at two different times during the Baseline/Pre-dose site visit. During the clinic visits on Day 1, the wearable sensor measurements of upper limb tremor will be captured once, 2 to 4 hours following the second in-clinic dose. During the site visits on Days 7 and 14, the wearable sensor measurements of upper limb tremor will be captured once, 2 to 4 hours following the in-clinic dose. During the Follow-up visit (Day 21), the wearable sensor measurements of upper limb tremor will be completed once, at any time during the visit.

	In-clinic assessments will be obtained during the performance of 4 maneuvers: 1. extended arms posture, 2. wing-beating posture, 3. kinetic "finger-to-chin" movement, and 4. arm on table posture. These assessments will be performed with the sensor on the left index finger and with the sensor on the right index finger. In addition, the subject will wear the sensor on the index finger of each hand while performing 3 activities of daily living: 1. pouring from a cup, 2. drinking from a cup, and 3. eating with a spoon. Commercially Confidential Information
	Commercially Confidential Information
Sample Size	Approximately 30 subjects will be enrolled into the study.
Treatment Groups	One open-label treatment group with all subjects being assigned CAD-1883 300 mg twice daily.
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Safety Assessments	Safety will be assessed via reported AEs (including observed or volunteered problems, complaints, or symptoms), scheduled in clinic safety examinations, and changes in vital signs including orthostatic vital signs, weight, laboratory values, and ECGs. Recommendations to alter study conduct due to safety concerns will be based solely on safety risk assessment by the Medical Monitor, without regard to any effect on the final efficacy analysis.
Inclusion Criteria	1. Adult subjects between 18 and 75 years of age, inclusive, with history of tremor that fulfills the diagnostic criteria of ET according to Movement Disorder Society (MDS) Consensus Statement on the classification of tremors from the task force on tremor of the International Parkinson and Movement Disorder Society (Bhatia, 2018). 2. Duration of ET illness since the first symptoms were noticeable of at least 3 years or more prior to screening, based on the subject's self-report, with onset prior to age 65 years old, per the Principal Investigator's assessment during screening. 3. Commercially Confidential Information 4. Commercially Confidential Information 5. Commercially Confidential Information 6. Except for ET, subjects must be otherwise healthy as determined by the Investigator, based upon a medical evaluation including medical history, physical examination, laboratory tests, and 12-lead ECG. 7. Subjects are able to understand study activities required, can give written informed consent, and are willing to comply with the requirements and restrictions of the study. 8. Women of childbearing potential must undertake a pregnancy test with documented negative **serum** pregnancy test at Screening and negative **urine** pregnancy test result at Baseline/Pre-dose, Days 7 and 14 before administration of the study drug, and then at the Follow-up visit (Day 21). 9. Postmenopausal women must have had ≥365 days of spontaneous amenorrhea, with documented follicle-stimulating hormone (FSH)

	≥38 IU/mL, prior to screening. If needed, per Investigator's judgment, FSH level can be performed at Screening. 10. Surgically sterile women must have documentation of a hysterectomy, bilateral ovariectomy, or bilateral tubal ligation. 11. Female subjects with reproductive potential and male subjects with reproductive potential or who have female partners of reproductive potential, must agree to use two effective methods of contraception from signing informed consent until 90 days after the last dose of study drug. Acceptable forms of contraception include double barrier (i.e., condom with spermicide); surgically sterilized partner (180-day minimum); or abstinence. 12. Commercially Confidential Information 13. Commercially Confidential Information
Exclusion Criteria	1. Prior or ongoing medical condition or any abnormal finding on the Screening visit physical exam, ECG, laboratory testing that, in the Investigator's opinion, could adversely affect the safety of the subject or the conduct of the study assessments. 2. Any neurological abnormality other than ET upon neurological exam, including dystonia, ataxia, or any other neurodegenerative disease, including multiple sclerosis or Parkinson's disease. 3. Commercially Confidential Information 4. Significant cognitive impairment or dementia that, in the opinion of the Investigator, would interfere with participation in the study. 5. Commercially Confidential Information .

	6. Commercially Confidential Information 7. An unstable thyroid condition that, per the Investigator's judgment based on medically significant abnormality of thyroid function testing at Screening. Note: an abnormal TSH level at Screening can be followed by reflex testing of thyroid hormones (T3, T4), if needed, per the Investigator's judgment. 8. History of, or evidence of psychogenic tremor at Screening. 9. Commercially Confidential Information 10. Commercially Confidential Information 11. History of anaphylaxis or hypersensitivity reactions to any of CAD-1883 excipients 12. Alkaline phosphatase, aspartate aminotransferase (AST), and/or alanine aminotransferase (ALT) level >2.5 x upper limit of normal (ULN) at Screening and/or at Baseline/Pre-dose. 13. Serum creatinine >120 µmol/L and/or creatinine clearance <60 mL/min (according to Cockcroft-Gault formula) at Screening and/or at Baseline/Pre-dose. 14. Total bilirubin >2.0 x ULN at Screening and/or at Baseline/Pre-dose. Note: isolated bilirubin >2.0 x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%. 15. Exclusionary ECG abnormalities: 1) History of Long QT syndrome and/or QTcF (Fridericia's correction) interval >450 msec (males) or >470 msec (females) per 12-lead ECG done at Screening. Commercially Confidential Information 16. Commercially Confidential Information 17. History of Alcohol Use Disorder per Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria.

	18. History of human immunodeficiency virus (HIV) infection or positive screening result for: HIV 1 or 2 antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (HCVAb). Commercially Confidential Information 19. Has a diagnosis of epilepsy or any history of seizure as an adult, head trauma, stroke, transient ischemic attack within 1 year prior to Screening, unexplained loss of consciousness within 1 year prior to Screening, or any lifetime history of asymptomatic or symptomatic orthostatic hypotension (e.g., postural syncope). 20. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class 3 or 4), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year prior to screening. 21. Commercially Confidential Information 22. Commercially Confidential Information 23. Commercially Confidential Information 24. Commercially Confidential Information . 25. Any major psychiatric disorder that is uncontrolled (for the past 90 days) that, per the Investigator's judgment, can interfere with any of the study procedures. 26. Subject has cancer, except for the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin; cervical carcinoma in situ; prostatic carcinoma in situ; or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years. 27. Commercially Confidential Information

	28. Commercially Confidential Information 29. Commercially Confidential Information 30. Subjects with scheduled surgeries during the study period.
Statistical Analysis	**Statistical Analysis of Primary Safety Endpoint Data:** • Vital sign parameters outside the normal range will be listed and flagged for review. • Orthostatic vital signs parameters for blood pressure outside specified ranges will be listed and flagged for review. • Descriptive statistics of absolute and change from Baseline (pre-dose) SBP, DBP, pulse rate, respiratory rate, and oral temperature at each timepoint, will be tabulated. The mean change from Baseline data will also be plotted across time. • Twelve-lead ECG parameters will be listed with any values outside the normal range flagged. Descriptive statistics of absolute and change from Baseline (pre-dose) heart rate, PR interval, QRS interval, QT interval and QTcF interval at each timepoint, will be tabulated. The mean change from Baseline data will also be plotted across time. • In addition, frequencies of QTcF data will be calculated according to the following categories: For absolute values – QTcF >450 msec (males) and >470 msec (females) – QTcF >480 msec – QTcF >500 msec For change from Baseline – QTcF increase >30 msec – QTcF increase >60 msec **Statistical Analysis of Key Secondary Efficacy Data:** • Mean TETRAS-PS total score change from Baseline over 14 days. • Mean TETRAS-PS upper limb subscale change from Baseline over 14 days. • Mean in-clinic wearable sensor measures of upper-limb tremor change from Baseline severity, mean amplitude, and mean frequency. • Commercially Confidential Information

	• Commercially Confidential Information Analyses of additional secondary efficacy data Commercially Confidential Information will be described in further detail in the protocol and Statistical Analysis Plan.
Location of sites	The study will be conducted at up to 15 clinical research sites.

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LIST OF TABLES

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
Commercially Confidential Information	
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Commercially Confidential Information	
CFR	Code of Federal Regulations
Commercially Confidential Information	
CRO	Clinical Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DBS	Deep brain stimulation
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DSM-V	Disorder per Diagnostic Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of Study
ET	Essential Tremor
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
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HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C virus antibody
HEENT	Head, eyes, ears, nose, and throat
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IRB	Institutional Review Board
MDS	Movement Disorder Society
MRI	Magnetic resonance imaging

Abbreviation	Definition
Commercially Confidential Information	
PAM	Positive allosteric modulator
PCR	Polymerase chain reaction
PE	Physical exam
Commercially Confidential Information	
PS	Performance subscale
PV	Pharmacovigilance
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SK	Small conductance calcium-activated potassium
SOA	Schedule of Assessments
SUSAR	Suspected unexpected serious adverse reaction
TETRAS	The Essential Tremor Rating Assessment Scale
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VS	Vital Signs

1 INTRODUCTION AND BACKGROUND INFORMATION

CAD-1883 is an investigational product being developed as a new treatment for Essential Tremor (ET), a movement disorder characterized by dysfunction of the cerebellum and its associated motor control circuit (Haubenberger et al, 2018). Tremor is defined as a rhythmic and oscillatory movement of a body part with a relatively constant frequency and variable amplitude. It is caused by alternating contractions of antagonistic muscles. Tremor is the most common of all movement disorders, and ET is the most common neurologic cause of tremor. The usual course of ET is one of gradual progression. Patients with persistent disability from ET need continuous symptomatic drug therapy. Available drug treatments are not effective in all patients, often provide inadequate symptomatic relief, and the symptomatic benefit of chronic administration often declines over time and is frequently associated with intolerable side effects. Therapy options for ET patients who do not benefit from pharmacologic treatment include deep brain stimulation (DBS) requiring surgery for placement of brain stimulator(s), magnetic resonance image (MRI)-guided thalamotomy via focused ultrasound (to treat persistently disabling unilateral limb tremor), or botulinum toxin injections (to treat persistently disabling hand, head, or vocal cord tremor). The efficacy of these invasive, non-pharmacologic therapies may also wane over time, and may be associated with intolerable side effects. Therefore, to address these important unmet medical needs, efforts are required to develop new treatments for ET targeting the cerebellar dysregulation responsible for the movement disorder.

The cerebellum is required for coordinated motion, including movements of the hands, limbs, trunk, and eyes, and the synchrony of speech, all of which are disrupted in ET. The cerebellar cortex, together with the inferior olivary nucleus and deep cerebellar nuclei, comprises the olivocerebellar circuit. Cerebellar output critically depends on the precise timing of action potentials in the principal neurons of the olivocerebellar circuit, especially cerebellar Purkinje neurons (Llinas, 2014).

Small conductance calcium-activated potassium (SK) channels are a family of potassium channels gated by intracellular calcium (Kshatri, 2018) In neurons, SK channels are gated by calcium that passes through voltage-gated calcium channels, which are activated by each action potential. SK channels regulate action potential timing by generating hyperpolarizing potassium currents between action potentials. In principle neurons of the olivocerebellar circuit, including cerebellar Purkinje neurons and their major afferent neurons of the inferior olivary nucleus, SK2 and SK3 channel-mediated after-hyperpolarizing currents represent a molecular pace-making mechanism centrally implicated in the coordination of movement.

CAD-1883 is anticipated to be used for the treatment of ET throughout the course of the patient's disease. This study offers the opportunity to understand the safety, tolerability, and efficacy of CAD-1883 in the ET patient population.

1.1 Rationale and Risk Benefit

The study will be open-label consisting of 1 treatment group receiving twice-daily oral dosing of CAD-1883 for a treatment period of 14 days.

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The selected dose is anticipated to be well-tolerated by subjects with ET for the duration of the treatment period. A 14-day treatment period represents an adequate time period to permit the initial assessment of safety and tolerability of CAD-1883 as well as a determination of early treatment effect on reducing the magnitude and severity of tremor while limiting the potential risk associated with a novel investigational drug.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to evaluate the safety and tolerability of twice-daily oral dosing of CAD-1883 over 14 days of treatment in adult patients with ET.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the efficacy of twice-daily oral dosing of CAD-1883 over 14 days of treatment as measured by:

- The Essential Tremor Rating Assessment Scale (TETRAS)-performance subscale (PS) total score change from Baseline to Day 14
- TETRAS-PS upper limb subscale score change from Baseline to Day 14

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- Change from Baseline to Day 14 in upper limb tremor severity, mean amplitude, and mean frequency, measured in the clinic using a wearable sensor

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3 STUDY DESIGN

3.1 Summary of Study Design

This is an open-label study designed to evaluate the safety, tolerability, and efficacy of CAD-1883 administered twice daily orally to adult subjects with ET.

Subjects will undergo a screening period of a minimum of 14 days up to a maximum

of 35 days in which the subject will "wash-out" from prior tremorgenic and anti-tremor medications, to allow the effects of previous medication(s) on tremor to be eliminated. During the Screening period, each subject will undergo full assessment including medical and treatment history for ET, physical and neurological examination, in addition to laboratory testing, 12-lead electrocardiogram (ECG), and other screening assessments. The diagnosis of ET must be established by the Principal Investigator at Screening based on the Movement Disorder Society (MDS) criteria (Bhatia, 2018) with a documented severity of tremor based on the clinician-administered TETRAS-PS (Elble, 2012).

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Safety and tolerability will be monitored throughout the study duration including in-clinic assessments of adverse events (AEs), serious adverse events (SAEs), vital signs including orthostatic vital signs, 12-lead ECG, urinalysis, hematology, clinical chemistry, and CAD-1883 plasma concentration level on Days 1, 7, 14, and 21.

Efficacy will be evaluated as follows:

- TETRAS-PS total score change from Baseline to Day 14
- TETRAS-PS upper limb subscale score change from Baseline to Day 14

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- Change from Baseline to Day 14 in upper limb tremor severity, mean amplitude, and mean frequency, measured in the clinic using a wearable sensor

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The TETRAS-PS will be recorded via videography for centralized evaluation and rating by an independent blinded panel of expert(s).

At the Baseline/Pre-dose visit, subjects will undergo all required procedures including confirmation that all eligibility criteria are met.

The Day 1 visit can occur up to 3 business days following the Baseline/Pre-dose visit. Analysis of the pre-dose laboratory assessments (chemistry, hematology, urinalysis) should be conducted by the Central Laboratory, with the results available and reviewed by the Principal Investigator, or designee, prior to dosing the subject with CAD-1883 (Day 1 visit). On Day 1, subjects will be dosed in the clinic with the first dose of CAD-1883 300 mg (3 capsules of 100 mg each) and will

be monitored in the clinic prior to ingesting the second dose of CAD-1883 300 mg (3 capsules of 100 mg each), 4 to 5 hours later. Additional safety and all efficacy assessments will be completed after the 2nd in clinic dose on Day 1 as specified in the SOA (Appendix A, Table 2).

Subjects will be dispensed study drug for continued twice-daily oral self-administration at home. After Day 1, subjects are instructed to ingest the first daily dose of CAD-1883 of 300 mg (3 capsules of 100 mg each). The second daily dose of CAD-1883 300 mg (3 capsules of 100 mg each) will be taken 8 hours (±2 hours) after the first daily dose. Each subject is provided with a medication diary to denote the date and time of at-home study drug dosing.

The pre-dose laboratory assessments (chemistry, hematology, urinalysis) should be sent to the Central Laboratory for analysis. Under exceptional circumstances, the pre-dose laboratory assessments (chemistry, hematology, urinalysis) can be sent for expedited analysis at the local laboratory, along with duplicate samples sent to the Central Laboratory. The results of laboratory assessments should be available and reviewed by the Principal Investigator, or designee, prior to dosing the subject.

Additionally, a urine sample will be collected for determination of baseline levels of composite biomarker panel for renal tubular injury, which is not part of eligibility determination.

Subjects will return to the site for further assessments on Day 7 (-1 day) and Day 14 (±1 day) and the Follow-up visit (Day 21 [±1 day]).

On Days 1, 7, 14, and 21, subjects will undergo safety monitoring consisting of reporting of AEs or SAEs, collection of vital signs including orthostatic vital signs, undergo a 12-lead ECG, and collection of urine for urinalysis and a composite biomarker panel for renal tubular injury, and blood for hematology, clinical chemistry, and plasma drug level. On Day 1, 7 and 14, all urine and blood collections should take place after the TETRAS-PS assessment. Assessment of rating scales and upper limb wearable sensor measurements will also be performed.

On Day 7 and Day 14, the subjects are instructed to ingest the first daily dose of CAD-1883 of 300 mg (3 capsules of 100 mg each) at home 4 to 5 hours prior to the scheduled and/or anticipated dosing of the second daily dose of CAD-1883. The second daily dose of CAD-1883 300 mg (3 capsules of 100 mg each) will be taken in the clinic, under the supervision of study staff, 4 to 5 hours after the first daily dose.

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subjects will have the option to complete at-home assessments of tremor using the wearable sensor.

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Upon completion of the 14-day treatment period, subjects will return to the site for the Day 21 Follow-up visit, approximately 7 days (±1 day) after the last dose of study drug was administered.

3.2 Study Indication

CAD-1883 is an investigational product being developed as a new treatment for ET, a movement disorder characterized by dysfunction of the cerebellum and its associated motor control circuit (Haubenberger et al, 2018).

3.3 Study Endpoints

3.3.1 Primary Endpoints

- The occurrence and severity of treatment emergent AEs.

3.3.2 Secondary Endpoints

- TETRAS-PS total score change from Baseline to Day 14
- TETRAS-PS upper limb subscale score change from Baseline to Day 14

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- Change from Baseline to Day 14 in upper limb tremor severity, mean amplitude, and mean frequency, measured in the clinic using a wearable sensor

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3.3.3 Exploratory Endpoints

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4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Adult subjects between 18 and 75 years of age, inclusive, with history of tremor that fulfills the diagnostic criteria of ET according to Movement Disorder Society (MDS) Consensus Statement on the classification of tremors from the task force on tremor of the International Parkinson and Movement Disorder Society (Bhatia, 2018).
2. Duration of ET illness since the first symptoms were noticeable of at least 3 years or more prior to screening, based on the subject's self-report, with onset prior to age 65 years old, per the Principal Investigator's assessment during screening.
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4. Commercially Confidential Information
5. Commercially Confidential Information
6. Except for ET, subjects must be otherwise healthy as determined by the Investigator, based upon a medical evaluation including medical history, physical examination, laboratory tests, and 12-lead ECG.
7. Subjects are able to understand study activities required, can give written informed consent, and are willing to comply with the requirements and restrictions of the study.
8. Women of childbearing potential must undertake a pregnancy test with documented negative **serum** pregnancy test at Screening and negative **urine** pregnancy test result at Baseline/Pre-dose, Days 7 and 14 before administration of the study drug, and then at the Follow-up visit (Day 21).
9. Postmenopausal women must have had ≥365 days of spontaneous amenorrhea, with documented follicle-stimulating hormone (FSH) ≥38 IU/mL, prior to screening. If needed, per Investigator's judgment, FSH level can be performed at Screening.
10. Surgically sterile women must have documentation of a hysterectomy, bilateral ovariectomy, or bilateral tubal ligation.
11. Female subjects with reproductive potential and male subjects with reproductive potential or who have female partners of reproductive potential, must agree to use two effective methods of contraception from signing informed consent until 90 days after the last dose of study drug. Acceptable forms of contraception include double barrier (i.e., condom with spermicide); surgically sterilized partner (180-day minimum); or abstinence.

12. Commercially Confidential Information

13. Commercially Confidential Information

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Prior or ongoing medical condition or any abnormal finding on the Screening visit physical exam, ECG, laboratory testing that, in the Investigator's opinion, could adversely affect the safety of the subject or the conduct of the study assessments.
2. Any neurological abnormality other than ET upon neurological exam, including dystonia, ataxia, or any other neurodegenerative disease, including multiple sclerosis or Parkinson's disease.
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4. Significant cognitive impairment or dementia that, in the opinion of the Investigator, would interfere with participation in the study.
5. Commercially Confidential Information
6. Commercially Confidential Information
7. An unstable thyroid condition that, per the Investigator's judgment based on medically significant abnormality of thyroid function testing at Screening. Note: an abnormal TSH level at Screening can be followed by reflex testing of thyroid hormones (T3, T4), if needed, per the Investigator's judgment.
8. History of, or evidence of psychogenic tremor at Screening.
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10. Commercially Confidential Information

11. History of anaphylaxis or hypersensitivity reactions to any of CAD-1883 excipients.
12. Alkaline phosphatase, aspartate aminotransferase (AST), and/or alanine aminotransferase (ALT) level >2.5 x upper limit of normal (ULN) at Screening and/or at Baseline/Pre-dose.
13. Serum creatinine >120 μmol/L and/or creatinine clearance <60 mL/min (according to Cockcroft-Gault formula) at Screening and/or at Baseline/Pre-dose.
14. Total bilirubin >2.0 x ULN at Screening and/or at Baseline/Pre-dose. Note: isolated bilirubin >2.0 x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%.
15. Exclusionary ECG abnormalities:
    a. History of Long QT syndrome and/or QTcF (Fridericia's correction) interval >450 msec (males) or >470 msec (females) per 12-lead ECG done at Screening.

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17. History of Alcohol Use Disorder per Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria.
18. History of human immunodeficiency virus (HIV) infection or positive screening result for: HIV 1 or 2 antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (HCVAb).

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19. Has a diagnosis of epilepsy or any history of seizure as an adult, head trauma, stroke, transient ischemic attack within 1 year prior to Screening, unexplained loss of consciousness within 1 year prior to Screening, or any lifetime history of asymptomatic or symptomatic orthostatic hypotension (e.g., postural syncope).
20. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class 3 or 4), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year prior to screening.

21. Commercially Confidential Information

22. Commercially Confidential Information

23. Commercially Confidential Information

24. Commercially Confidential Information

25. Any major psychiatric disorder that is uncontrolled (for the past 90 days) that, per the Investigator's judgment, can interfere with any of the study procedures.

26. Subject has cancer, except for the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin; cervical carcinoma in situ; prostatic carcinoma in situ; or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years.

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28. Commercially Confidential Information

29. Commercially Confidential Information

30. Subjects with scheduled surgeries during the study period.

4.3 Diet, Activities, and Other Restrictions

4.3.1 Concomitant Medication

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Occasional use of paracetamol will be allowed up to a maximum of 4 grams per 24 hours where required, but not on a regular basis. If a concomitant medication is needed during the study, this medication must be recorded on the electronic case report form (eCRF), stating its generic name, time of administration, dose, route and duration, as well as the reason for administration.

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4.3.2 Caffeine

Consumption of caffeine- or xanthine- containing products (e.g., coffee, tea, cola drinks and chocolate) must be maintained without a change from well-established habit from 48 hours prior to the Baseline/Pre-dose visit until the Day 21 visit.

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4.3.4 Physical Activities

From Screening until the EOS examination, the subjects should refrain from excessive physical exercise and strenuous sports activities (endurance sports).

4.3.5 Dietary Aspects

No restrictions.

4.3.6 Smoking

No restrictions.

4.4 Withdrawal Criteria

Participation of a subject in this clinical study may be discontinued for any of the following reasons:

- The subject withdraws consent or requests discontinuation from the study for any reason
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject
- Pregnancy

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- Subject failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or the regulatory authority

If a subject withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination visit (Day 14). The reason for subject withdrawal must be documented in the eCRF.

Withdrawn subjects may be replaced per the Sponsor's discretion.

4.5 Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if

necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

5 STUDY TREATMENTS

5.1 Treatment Groups

There will be 1 treatment group.

5.2 Rationale for Dosing

The dose level of CAD-1883 is 300 mg (3 capsules of 100 mg each) twice daily, with the first dose for Day 1 taken in clinic, and the second daily dose taken 4 to 5 hours later on clinic visit Days 1, 7 and 14 only. The second daily dose for all other (at home) days will be taken 8 hours later (±2 hours).

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5.3 Randomization and Blinding

This will be an open label study with no blinding.

5.4 Breaking the Blind

Not applicable.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

Cadent Therapeutics, Inc. will provide CAD-1883 as capsules (Coni-Snap Gelatin, Size 4, Swedish Orange) of 100 mg dosage strength in 60-cc wide-mouth round white HDPE unit bottles with 33-mm SecuRx® Closures. Additional information on formulation and packaging can be found in the Pharmacy Manual. A detailed description of the chemistry, manufacturing, and quality controls of CAD-1883 100 mg capsules is provided in the Investigator's Brochure (IB).

5.5.2 Study Drug Preparation and Dispensing

All study drugs will be dispensed by the Investigator or a person under the Investigator's supervision.

5.5.3 Study Drug Administration

CAD-1883 is administered orally at the dose of 300 mg (3 capsules of 100 mg each) twice daily, with the first dose for Day 1 taken in clinic, and the second daily dose to be taken 4 to 5 hours later on clinic visit Days 1, 7 and 14 only. The second daily dose for all other (at home) days will be taken 8 hours later (±2 hours). Each subject is provided with a medication diary to denote the date and time of at-home study drug dosing. Dosing instructions for medication intake are provided in the pharmacy manual.

5.5.4 Treatment Compliance

The subject must return the bottle containing unused capsules (if any) to the study site for a compliance check at the visits specified in the SOA (Appendix A, Table 2).

5.5.5 Storage and Accountability

The subject kits will be stored at controlled room temperature between +15°C and +25°C in each study site pharmacy, which will be locked with restricted access. No additional procedures are required for the safe handling of the capsules.

Recommendations for subjects: the capsules should be kept in the original packaging (bottles). The bottles should be stored in the subject's home at room temperature and out of reach of children and away from direct sunlight. The study drug must not be given to other persons.

6 STUDY PROCEDURES

- Study procedures and their timing are summarized in the SOA (Appendix A, Table 2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Investigator, Medical Monitor, and Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SOA (Appendix A, Table 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. See Section 6.1.1 for information about re-screening subjects.

6.1 Study Visits

The study period consists of Screening, Baseline/Pre-dose visit, treatment period, and Follow-up visit for a total study period that could be up to 56 days. Subjects will undergo a screening period of a minimum of 14 days up to a maximum of 35 days, a 1-day Baseline/Pre-dose visit, a Day 1 visit that may occur up to 3 business days post the Baseline/Pre-dose visit, a treatment period for 14 days (including Day 1), and a Follow-up visit at Day 21. All procedures and assessments will occur as indicated in the SOA (Appendix A, Table 2).

6.1.1 Screening Period

Subjects will undergo a screening period of a minimum of 14 days up to a maximum of 35 days in which the subject will "wash-out" from prior tremorgenic and anti-tremor medications, to allow the effects of previous medication(s) on tremor to be eliminated. During the Screening period, each subject will undergo full assessment including medical and treatment history for ET, physical and neurological examination (including a focused neurological exam to include full assessment of tremor per Movement Disorder Society classification criteria (Bhatia, 2018)), in addition to laboratory testing, 12-lead ECG and other screening assessments as indicated in the SOA (Appendix A, Table 2). The diagnosis of ET must be established by the Principal Investigator at Screening based on the MDS criteria (Bhatia, 2018) with a documented severity of tremor based on the clinician-administered TETRAS-PS (Elble, 2012).

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Per the Investigator's discretion, re-testing of any laboratory abnormality at the central lab or at a local lab is permissible, with prior approval from the Medical Monitor.

Subjects who previously failed screening can be invited to re-screen up to two additional times, with recommendation by the Investigator and with approval by the Sponsor.

6.1.2 Pre-dose (Baseline) Visit

At the Baseline/Pre-dose visit, subjects will undergo all required procedures as indicated in the SOA (Appendix A, Table 2) including confirmation that all eligibility criteria are met. Analysis of the pre-dose laboratory assessments (chemistry, hematology, urinalysis) should be conducted by the Central Laboratory, with the results available and reviewed by the Principal Investigator, or designee, prior to dosing the subject with CAD-1883 (Day 1 visit).

Under exceptional circumstances, the pre-dose laboratory assessments (chemistry, hematology, urinalysis) can be sent for expedited analysis at the local laboratory, along with duplicate samples sent to the Central Laboratory. The results of the above-referenced laboratory assessments should be available and reviewed by the Principal Investigator, or designee, prior to dosing the subject.

Additionally, a urine sample will be collected for determination of baseline levels of composite biomarker panel for renal tubular injury, which is not part of eligibility determination.

6.1.3 Day 1 Visit (First In-Clinic Dosing)

The Day 1 visit may occur up to 3 business days following the Baseline/Pre-dose visit. Baseline/Pre-dose laboratory assessments should be available and reviewed by Principal Investigator, or designee prior to dosing the subject with CAD-1883.

On Day 1, subjects will be dosed in the clinic with the first dose of CAD-1883 300 mg (3 capsules of 100 mg each) and will be monitored in the clinic prior to ingesting the second dose of CAD-1883 300 mg (3 capsules of 100 mg each), 4 to 5 hours later. Additional safety and all efficacy assessments will be completed after the second in clinic dose on Day 1 as indicated in the SOA (Appendix A, Table 2).

Subjects will be dispensed study drug for continued twice-daily oral self-administration at home.

6.1.4 In-clinic Treatment Period Study Visits

Subjects will return to the site for further assessments on Day 7 (-1 day) and Day 14 (±1 day) and a Follow-up visit (Day 21 [±1 day]). On Days 7 and 14, subjects are instructed to ingest the first daily dose of CAD-1883 of 300 mg (3 capsules of 100 mg each) at home 4 to 5 hours prior to the scheduled and/or anticipated dosing of the second daily dose of CAD-1883 in the clinic. The second daily dose of CAD-1883 300 mg (3 capsules of 100 mg each) will be taken in the clinic, under the supervision of study staff, 4 to 5 hours after the first daily dose, as indicated in the SOA (Appendix A, Table 2).

6.1.5 Intervals Between Site Visits

Subjects will self-administer CAD-1883 300 mg (3 capsules of 100 mg each) twice-daily. Subjects are instructed to ingest the first daily dose of CAD-1883 at home. The second daily dose will be taken 8 hours (±2 hours) after the first daily dose. Each subject is provided with a medication diary to denote the date and time of at-home study drug dosing, as indicated in the SOA (Appendix A, Table 2).

6.1.6 Follow-up Visit

Upon completion of the 14-day treatment period, subjects will return to the site for the Day 21 Follow-up visit, approximately 7 days (±1 day) after the last dose of study drug was administered. Subjects will complete all study assessments and procedures as indicated in the SOA (Appendix A, Table 2).

6.2 Early Termination Visit and Withdrawal Procedures

The end of treatment for subjects completing the study is Follow-up Visit on Day 21 (±1 day). For subjects who are withdrawn from the study prior to completion, all Day 14 procedures will be performed at an Early Termination visit as indicated in the SOA (Appendix A, Table 2) and they will also complete the C-SSRS. Subjects withdrawing from the study early will not receive study drug on-site at the Early Termination visit.

6.3 Informed Consent

After adequate explanation of the aims, methods, objectives of the study and potential hazards of the study drug, a written informed consent from each individual participating in this study will be obtained.

6.4 Study Assessments and Procedures

All study assessments and procedures will be conducted as indicated in the SOA (Appendix A, Table 2) and as described in Section 7 for safety assessments, Section 8 for efficacy assessments,

7 SAFETY ASSESSMENTS

7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time the subject signs the informed consent form (ICF) until Follow-up Day 21. Subjects should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at Screening, the Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at Screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at pre-dose change in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (e.g., ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action is required to be taken with the study drug as a result of the abnormality
- Based on the clinical judgment of the Investigator

7.1.1 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of 'yes' or 'no'.

Assessment of severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality assessment:

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug-

  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

7.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations

  Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

7.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time the subject signs the informed consent until 30 days following the last administration of study drug must be reported to CRO within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to CRO or designee.

To report the SAE, complete the AE form electronically in the eCRF for the study and then the paper SAE report form. Send the paper SAE report form via email to the CRO Personal Protected Data

Personal Protected Data

within 24 hours of awareness regardless of the relationship to the study drug. The SAE report form should be completed as thoroughly as possible; however, submission of the report should not be delayed if information is not available at the time of the initial report.

Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the paper SAE report form and the AE form electronically in the eCRF and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to CRO via fax or email.

7.4 Pregnancy Reporting

If a subject becomes pregnant during the study, the Investigator is to stop dosing with study drug immediately and the subject should be withdrawn from the study. Early Termination study visit procedures as indicated in the SOA should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to the CRO within 24 hours of knowledge of the pregnancy during the study or up to 90 days after the last dose of study drug via the Pregnancy Data Collection Form. The Investigator must complete the Pregnancy Data Collection Form and fax or email it to the CRO (contact information listed in Section 7.6).

If the female partner of a male subject becomes pregnant while the subject is receiving study drug or up to 90 days after the last dose of study drug, the Investigator should notify the CRO as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Data Collection Form should be completed and faxed or emailed to the CRO (contact information listed in Section 7.6). If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

7.5 Expedited Reporting

The CRO will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSAR) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), and in any case no later than 7 days after knowledge by the CRO of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the CRO.

The CRO will also report any additional expedited safety reports required in accordance with the relevant timelines.

The CRO will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

7.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s), or the Investigator has reason to suspect that the subject has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, subject, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors. Cases of subjects missing doses of investigational product are not considered reportable as medication error.

All special situation events as described above must be reported on the Special Situations Report form and faxed or emailed to the CRO (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the paper SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

CRO Clinical Safety Contact Information:
Premier Research Pharmacovigilance (PV)

Personal Protected Data

7.7 Physical and Neurological Examinations

A complete physical examination (PE) will include general observations; head, eyes, ears, nose, and throat (HEENT); cardiovascular; respiratory; abdomen; skin; extremities; lymphatic system; and musculoskeletal. Height, weight, CCI will also be measured and

recorded. A symptom-based PE will be performed at Baseline/Pre-dose and Day 21 Follow-up visits only (includes: general, HEENT, cardiovascular, respiratory, abdomen, skin, extremities).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Neurological examinations will include assessment of mental status, cranial nerves, motor, sensory, reflexes, coordination, and gait. In addition to the complete neurological exam, a focused neurological exam is conducted during the Screening visit to include full assessment of tremor per Movement Disorder Society classification criteria (Bhatia, 2018).

Physical and neurological exams will be conducted at timepoints indicated in the SOA (Appendix A, Table 2).

7.8 Electrocardiograms

Triplicate 12-lead ECG will be obtained as indicated in the SOA (Appendix A, Table 2), using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. ECGs are to be assessed **prior** to vital signs and blood sampling for laboratory tests. Triplicate ECG recordings will be taken, after a minimum of 5 minutes of rest in supine position: 3 consecutive recordings will be made in succession, no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. These ECGs will be read by the Investigator to rule out any clinically significant findings. An ECG is to be taken at the Screening, Baseline/Pre-dose, Day 1, Day 7, Day 14 and Day 21 Follow-up visits. At the Day 1, Day 7 and Day 14 visits, ECGs are to be obtained at the following time points: 30min, 60min, and 2 hours following the first dose of the day and again 30 min, 60 min, 2 hours and 4 hours after the second dose of study drug in the clinic. On Days 7 and 14, an ECG is to be taken at 30 min, 60 min, 2 hours, and 4 hours following the dose of study drug in the clinic. There is a +/- 5-minute allowable window for these ECGs.

After a minimum of 5 minutes of rest in supine position, 3 consecutive recordings should be made in succession, no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. These ECGs will be read by the Investigator to rule out any clinically significant findings.

7.9 Vital Signs

Vital signs (VS) assessments (to be taken before blood collection for laboratory tests) will be assessed and include blood pressure (systolic and diastolic), heart rate, respiratory rate and oral temperature. Vital signs are to be taken at the Screening, Baseline/Pre-dose, Day 1, Day 7, Day 14 and Day 21 Follow-up visits. The vital signs on Day 1 are to be taken at 30min, 60min, and 2 hours following the first dose of the day and again 30 min, 60 min, 2 hours and 4 hours after the second dose of study drug in the clinic. On Days 7 and 14, the vital signs are to be taken at 30 min, 60 min, 2 hours, and 4 hours following the dose of study drug in the clinic. There is a +/- 5-minute allowable window for these vital signs.

7.10 Orthostatic Vital Signs

Orthostatic vital signs will be measured at Screening, Baseline, Day 1, Day 7, Day 14 and during the Follow-up visit.

During the Screening visit, orthostatic VS measurements will be done once, at any time during the visit.

During the Baseline/Pre-Dose visit, baseline orthostatic VS will include 3 separate measurements with each measurement of blood pressure and heart rate separated from the next by at least 15-20 minutes apart, to minimize the potential impact of biological variability of a single baseline measurement. The average of the 3 baseline orthostatic VS measurements will be used for comparison to all post-treatment measurements.

During Day 1, orthostatic VS measurements will be done twice, 2 to 4 hours following each in-clinic dose.

During Day 7 and Day 14 visits, orthostatic VS measurements will be done once, 2 to 4 hours following the in-clinic dose.

During the Follow-up visit, orthostatic VS measurements will be done once, at any time during the visit.

Orthostatic VS must be assessed using an appropriate device, and the arm position must be standardized for each subject. These measurements are to be taken in the same arm for the duration of the study. The position of the cuff on the arm should be in line with the heart with the arm lying next to the subject when semi-supine and should be in line with the heart at approximately a 45 degrees angle from horizontal for the standing measure.

In order to obtain orthostatic VS, the subjects will undergo the following procedures in sequential order:

1. The subject will rest in a supine or semi-supine position for at least 5 minutes.
2. After remaining supine or semi-supine for 5 minutes, one measurement of blood pressure and heart rate will be taken.
3. The subject will then be asked to sit on the edge of the bed/chair with feet on the floor (or with feet dangling from the bed/chair depending on the height of the bed/chair) for approximately 30 seconds.
4. The person performing the assessment will then ask the question, “Are you ready to stand?”

- If the subject responds in the affirmative, the subject will proceed to stand and then be asked to remain standing for 2 minutes. After standing for 2 minutes, blood pressure and heart rate will be recorded.

- If the subject states that he or she is not ready to stand, the subject will be allowed to sit as positioned for one additional minute and will be asked again if they are ready to stand. The subject will proceed to stand. After standing for 2 minutes, one measurement will be taken for blood pressure and heart rate.
- If the individual is still unable to stand, vital signs will be measured while the subject is in an upright seated position.

Orthostatic hypotension will be defined as a reduction in SBP of 20 mmHg or more, and/or a reduction in DBP of 10 mmHg or more, for the standing measurement compared to the supine or semi-supine measurement. If orthostatic hypotension is suspected, the measurement process may be repeated at the Investigator's discretion. Any confirmed orthostatic hypotension or clinically significant measurements that are associated with clinical symptoms will be recorded as adverse events.

If routine VS and orthostatic VS coincide at the same time points, the same values for routine VS (blood pressure and heart rate) during the supine or semi-supine position should be recorded in the CRFs as the same values of the start of orthostatic VS in the supine or semi-supine position.

7.11 Clinical Laboratory Evaluations

A list of clinical laboratory tests to be performed is in Appendix B. See Table 2, SOA in Appendix A for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the CRO notified.
- All protocol-required laboratory assessments, as defined in Appendix B, must be conducted in accordance with the laboratory manual and the SOA (Table 2).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in the subject's management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded as an AE in the eCRF for AEs and also the paper form if an SAE.
- On Days 1, 7, 14 all clinical laboratory samples should be collected after the TETRAS-PS assessment

7.12 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior. The C-SSRS, which uses a semi-structured interview to probe subject responses, will be administered by an individual who has received training and certification in its administration. At the Baseline/Pre-dose visit, the "baseline" version of the C-SSRS will be administered. This version assesses Suicidal Ideation and Suicidal Behavior during the subject's lifetime and during

a predefined period. At the Day 21 visit (and the Early Termination visit for subjects withdrawing early), the “since last visit” version will be administered.

8 EFFICACY ASSESSMENTS

8.1 Rating Scales

The treatment effect will be evaluated by means of the TETRAS-PS (Version 3.1), which is a validated scale that has been used in recently conducted clinical trials in subjects with ET (Elble, 2012). It provides an accurate reflection of the clinical response to treatment on the amplitude of tremor over multiple bodily locations and over time.

The TETRAS assessments at Screening, Baseline/Pre-dose, Days 1, 7, 14, and Follow-up visit (Day 21) will be administered by a certified rater. TETRAS raters at each site must demonstrate expertise in the administration of the TETRAS according to criteria preset by independent central rating experts. The TETRAS raters at each site can be the Principal Investigator or a staff member delegated as a rater by the Principal Investigator. Each site must make every effort, to the extent that is possible, to ensure availability of a primary rater and a backup rater to perform all TETRAS assessments on the same subjects throughout the study duration.

The TETRAS-PS assessments at the Screening visit, Baseline/Pre-dose, Days 1, 7, 14, and 21 clinic visits will be recorded using videography for centralized evaluation and rating by independent blinded central raters (neurologists) with expertise in the assessment of ET.

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On Screening and Baseline/Pre-dose visits: TETRAS-PS, Commercially Confidential Information are performed.

On Day 1: The TETRAS-PS will be administered 2 to 4 hours following the second in-clinic dose.

On Day 7: the TETRAS-PS, Commercially Confidential Information will be performed 2 to 4 hours following the in-clinic dose.

On Day 14: the TETRAS-PS, Commercially Confidential Information will be performed 2 to 4 hours following the in-clinic dose. Commercially Confidential Information

At Follow up visit (Day 21): the TETRAS-PS, Commercially Confidential Information are performed once any time during the visit.

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8.2 Wearable Sensor

In addition to the assessment of efficacy via rating scales, treatment effect will be evaluated by measuring tremor with a sensor worn on the upper limb (index finger). These assessments will be conducted during the clinic visits and optionally at-home.

8.2.1 In-Clinic Assessment

The wearable sensor measurements of upper limb tremor assessments will be completed in the clinic once at any time during the Screening visit and at two different times during the Baseline/Pre-dose site visit.

During the site visit on Day 1 the wearable sensor measurements of upper limb tremor will be captured once, 2 to 4 hours following the second in-clinic dose.

During the site visit on Days 7 and 14, the wearable sensor measurements of upper limb tremor will be captured once, 2 to 4 hours following the in-clinic dose.

During the Follow-up visit (Day 21), the wearable sensor measurements of upper limb tremor will be completed at any time during the visit.

In-clinic assessments will be obtained during the performance of 4 maneuvers:

1. extended arms posture,
2. wing-beating posture,
3. kinetic “finger-to-chin” movement, and
4. arm on table posture.

These assessments will be performed twice, once with the sensor on the left index finger and once with the sensor on the right index finger.

In addition, the subject will wear the sensor on the index finger of each hand while performing 3 activities of daily living:

1. pouring from a cup,
2. drinking from a cup, and
3. eating with a spoon

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11 STATISTICS

11.1 Analysis Populations

For purposes of analysis, the following populations are defined:

Safety population: All enrolled subjects who take at least 1 dose of study intervention.

- Full Analysis Set (FAS): FAS consists of subjects in the safety population who had at least 1 post-baseline assessment of both TETRAS-PS CCI . FAS will be used to summarize all efficacy data.

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- Exposed Population (EP): The exposed population includes all subjects in the Safety population who are at least 90% compliant with study treatment

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Selected efficacy analyses will be repeated in this population if this population differs from FAS.

11.2 Statistical Methods

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

11.2.1 Analysis of Primary (Safety) Endpoint Data

- Vital sign parameters outside the normal range will be listed and flagged for review.
- Orthostatic vital signs parameters for blood pressure outside the ranges specified in Section 7.10 below will be listed and flagged for review.
- Descriptive statistics of absolute and change from Baseline (pre-dose) SBP, DBP, pulse rate, respiratory rate, and oral temperature at each timepoint, will be tabulated. The mean change from Baseline data will also be plotted across time.
- Twelve-lead ECG parameters will be listed with any values outside the normal range flagged. Descriptive statistics of absolute and change from Baseline (pre-dose) heart rate, PR, QRS, QT, and QTcF intervals at each timepoint, will be tabulated. The mean change from Baseline data will also be plotted across time.
- In addition, frequencies of QTcF data will be calculated according to the following categories:

  For absolute values

- QTcF >450 msec (males) and >470 msec (females)
- QTcF >480 msec
- QTcF >500 msec

For change from Baseline

- QTcF increase >30 msec
- QTcF increase >60 msec

11.2.2 Analysis of Secondary Efficacy Endpoints

- Mean TETRAS-PS total score change from Baseline over 14 days.
- Mean TETRAS-PS upper limb subscale score change from Baseline over 14 days.
- Mean in-clinic wearable sensor measures of upper-limb tremor change from Baseline severity, mean amplitude, and mean frequency over 14 days.

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11.2.4 Sample Size Determination

Approximately 30 subjects will be enrolled. No formal statistical power analysis was conducted. Each subject will be assessed for change from their own Baseline.

12 DATA MANAGEMENT AND RECORD KEEPING

12.1 Data Management

12.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed during monitoring visits. Selected data recorded in the eCRF system will be verified with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

12.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

12.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs
- World Health Organization Drug Dictionary CCI and concomitant medications

12.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

12.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.3 End of Study

The EOS ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

13.2 Institutional Review Board/Independent Ethics Committee

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonization (ICH) Guidelines require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor or designee.

13.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator or designee will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

13.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with

the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the monitor will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

13.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

13.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator or another institution.

13.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

13.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

14 STUDY ADMINISTRATIVE INFORMATION

14.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by the Sponsor or designee. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 business days.

15 REFERENCES

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3. Haubenberger D, Hallett M. Essential Tremor. N Engl J Med. 2018 May 10;378(19):1802-10.
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APPENDIX A: SCHEDULE OF ASSESSMENTS

Table 2: Schedule of Assessments

ASSESSMENTS	SCREENING	BASELINE	TREATMENT								FOLLOW-UP
	14-35 days prior to Day 1	Pre-dose[1,2] (≤ 3 days prior to Day 1) (In-clinic)	Day 1[2] (In-clinic: Pre-Dose 1)	Day 1[2] (In-clinic: Dosing & Post-Dose 1)	Day 1[2] (In-clinic: Dosing & Post Dose 2)	Days 2-6 (At-home)	Day 7[2] (-1 day) (In-clinic)	Days 8-13 (At-home)	Day 14[2] (±1 day) / Early Termination[24] (In-clinic)	Days 15-20 (At-home)	Day 21[2] (±1 day) (In-clinic)
Eligibility Check	X	X									
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Demographics	X										
Medical History	X										
Neurological Exam	X[3]	X					X		X		X
Physical Exam	X	X[4]	X				X		X		X[4]
Height	X										
Weight CCI	X[5]								X		X
12-lead ECG[6]	X	X	X[8]	X[8] (30 min, 60 min, 2 hours post 1st dose)	X[8] (30 min, 60 min, 2 & 4 hours post 2nd dose		X[8] (30 min, 60 min, 2 & 4 hours post 2nd dose		X[8] (30 min, 60 min, 2 & 4 hours post 2nd dose		X
Vital Signs[7]	X	X	X[8]	X[8] (30 min, 60 min, 2 hours post 1st dose)	X[8] (30 min, 60 min, 2 & 4 hours post 2nd dose)		X[8] (30 min, 60 min, 2 & 4 hours post 2nd dose)		X[8] (30 min, 60 min, 2 & 4 hours post 2nd dose)		X

Table 2: Schedule of Assessments

ASSESSMENTS	SCREENING	BASELINE	TREATMENT								FOLLOW-UP
	14-35 days prior to Day 1	**Pre-dose[1,2] (≤ 3 days prior to Day 1) (In-clinic)**	**Day 1[2] (In-clinic: Pre-Dose 1)**	**Day 1[2] (In-clinic: Dosing & Post-Dose 1)**	**Day 1[2] (In-clinic: Dosing & Post Dose 2)**	**Days 2-6 (At-home)**	**Day 7[2] (-1 day) (In-clinic)**	**Days 8-13 (At-home)**	**Day 14[2] (±1 day) / Early Termination[24] (In-clinic)**	**Days 15-20 (At-home)**	**Day 21[2] (±1 day) (In-clinic)**
Orthostatic VS[9]	X (3 times, 15-20 min apart)	X		X (2-4 hours post 1st dose)	X (2-4 hours post 2nd dose)		X (2-4 hours post dose)		X (2-4 hours post dose)		X
Clinical Chemistry	X	X			X[27]		X[27]		X[27]		X
Hematology	X	X			X[27]		X[27]		X[27]		X
Urinalysis[10]	X	X			X[27]		X[27]		X[27]		X
Biomarker panel for renal tubular injury		X			X[27]		X[27]		X[27]		X
Pregnancy Test	X[11]	X[12]					X[12]		X[12]		X[12]
HIV, CCI HBsAg, HCVAb	X										
TSH – FSH (optional for females only; if needed)	X										

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Table 2: Schedule of Assessments

ASSESSMENTS	SCREENING	BASELINE	TREATMENT								FOLLOW-UP
	14-35 days prior to Day 1	**Pre-dose[1,2] (≤ 3 days prior to Day 1) (In-clinic)**	**Day 1[2] (In-clinic: Pre-Dose 1)**	**Day 1[2] (In-clinic: Dosing & Post-Dose 1)**	**Day 1[2] (In-clinic: Dosing & Post Dose 2)**	**Days 2-6 (At-home)**	**Day 7[2] (-1 day) (In-clinic)**	**Days 8-13 (At-home)**	**Day 14[2] (±1 day) / Early Termination[24] (In-clinic)**	**Days 15-20 (At-home)**	**Day 21[2] (±1 day) (In-clinic)**
Administer CAD-1883 Study Drug				X[26] (in clinic)	X[26] (in clinic 4-5 hours post 1st dose)	X	X[14] (in clinic 4-5 hours post 1st dose)	X	X[14] (in clinic 4-5 hours post 1st dose)		
Dispense Study Drug					X		X				
Medication Diary						X		X			
CAD-1883 PK Sample					X[15] CCI		X[16] CCI		X[16] CCI		X[17] (Anytime during visit)
TETRAS Performance Subscale[18]	X[19]	X			X[20]		X[21]		X[21]		X
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In-clinic Wearable Sensor on Upper Limb	X[22]	X[23]			X[24]		X[24]		X[24]		X[22]
Commercially Confidential Information											

Table 2: Schedule of Assessments

ASSESSMENTS	SCREENING	BASELINE	TREATMENT								FOLLOW-UP
	14-35 days prior to Day 1	Pre-dose[1,2] (≤ 3 days prior to Day 1) (In-clinic)	Day 1[2] (In-clinic: Pre-Dose 1)	Day 1[2] (In-clinic: Dosing & Post-Dose 1)	Day 1[2] (In-clinic: Dosing & Post Dose 2)	Days 2-6 (At-home)	Day 7[2] (-1 day) (In-clinic)	Days 8-13 (At-home)	Day 14[2] (±1 day) / Early Termination[24] (In-clinic)	Days 15-20 (At-home)	Day 21[2] (±1 day) (In-clinic)
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C-SSRS[25]		X							X		X
Commercially Confidential Information											
AEs	X	Continuous reporting of adverse events									

*** Refer to list of abbreviations**

Schedule of Assessment Footnotes:

1 The Baseline/Pre-dose visit is the last day of the Screening period. The Baseline/Pre-dose visit must be conducted in the afternoon.

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3 In addition to the complete neurological exam, a focused neurological exam is conducted during the Screening visit to include full assessment of tremor per Movement Disorder Society classification criteria (Bhatia, 2018).

4 Complete PE at Screening, Days 1, 7, and 14 (includes: General; HEENT; Cardiovascular; Respiratory; Abdomen; Skin; Extremities; Lymphatic system and Musculoskeletal); symptom-based PE at Baseline/Pre-dose and Day 21 Follow-up visit (includes: General, HEENT, Cardiovascular, Respiratory, Abdomen, Skin, Extremities).

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6 Triplicate ECG recordings, after a minimum of 5 minutes of rest in supine position: 3 consecutive recordings will be made in succession, no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. These ECGs will be read by the Investigator to rule out any clinically significant findings. ECGs are to be performed prior to vital signs and blood sampling.

7 Blood pressure (systolic and diastolic), heart rate, respiratory rate and oral temperature.

8 Obtained prior to dosing and post dosing at 30min, 60min, 2 hours and 4 hours following the dose of study drug in the clinic. For Day 1, this is to be done Baseline/Pre-dose and 30min, 60min, and 2 hours after the first dose in the clinic, and again 30 min, 60 min, 2 hours, and 4 hours after the second dose in the clinic. There is a +/- 5-minute allowable time window for these assessments. ECG to be done before the corresponding vital sign measurements.

9 For details re: orthostatic vital signs measurements, refer to Section 7.10.

10 Urinalysis includes: Bilirubin, Blood, Creatinine, Glucose, Ketones, Leukocyte esterase, Microscopy, Nitrite, pH, Protein, Specific gravity, Microalbumin and Urobilinogen

[11] A serum pregnancy test is done at Screening only.
[12] A urine pregnancy test is done at Baseline/Pre-dose, Days 7, 14, and 21.
[13] Commercially Confidential Information

[14] The subject should be instructed to self-administer their first daily dose of CAD-1883 4 to 5 hours prior to the scheduled and/or anticipated dosing of the second daily dose of CAD-1883. The second daily dose of CAD-1883 should be taken in the clinic 4 to 5 hours after the first daily dose.
[15] Commercially Confidential Information
[16] Commercially Confidential Information
[17] Commercially Confidential Information
[18] TETRAS Performance Subscale assessments at Screening, Baseline/Pre-dose, Days 1, 7, 14, and 21 will be recorded via videography for central rating.
[19] Screening: Commercially Confidential Information

[20] Performed between 2-4 hours following the second dose in the clinic.
[21] Performed between 2-4 hours following the second daily dose in the clinic.
[22] Wearable sensor measurement of upper-limb tremor will be captured once at the site, at any time during Screening and Day 21.
[23] Wearable sensor measurements of upper limb tremor will be captured at two different times during the Baseline/Pre-dose visit.
[24] Wearable sensor measurements of upper limb tremor will be captured once, 2 to 4 hours following the in-clinic dose. For Day 1, this is to be done 2-4 hours after the 2nd in-clinic dose.
[25] At the Baseline/Pre-dose visit, the "baseline" version of the C-SSRS will be administered. This version assesses Suicidal Ideation and Suicidal Behavior during the subject's lifetime and during a predefined period. At the Day 21 visit (and the Early Termination visit for subjects withdrawing early), the "since last visit" version will be administered. The C-SSRS does not need to be completed at the Day 14 visit if it is not an Early Termination visit. During Early Termination visit, the subject will not receive study drug, will undergo all required procedures as well as the C-SSRS.
[26] Both doses of study drug are to be administered in the clinic with the second dose being administered 4-5 hours after the first.

[27] All laboratory collections on Days 1, 7, 14 should be performed after the TETRAS-PS assessment.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Clinical Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate
Commercially Confidential Information	Gamma-glutamyl transferase
Glucose	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Potassium	Commercially Confidential Information
Commercially Confidential Information	Sodium
	Total and direct bilirubin
Total protein	Uric acid

Biomarker panel for renal tubular injury

Endocrinology

Follicle-stimulating hormone [1]	Thyroid-stimulating hormone [2]

[1] Postmenopausal women must have had ≥365 days of spontaneous amenorrhea, with documented follicle-stimulating hormone (FSH) ≥38 IU/mL, prior to screening. If needed, per Investigator's judgment, FSH level can be performed at Screening.

[2] An abnormal TSH level at Screening can be followed by reflex testing of thyroid hormones (T3, T4), if needed, per the Investigator's judgment.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count with differentials [1]:	Red blood cell indices:
Neutrophils	MCV
Lymphocytes	MCH
Monocytes	%Reticulocytes
Eosinophils	
Basophils	

[1] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin	Blood
Creatinine	Glucose
Ketones	Leukocyte esterase
Microscopy [1]	Microalbumin
	Nitrite
pH	Protein
Specific gravity	Urobilinogen

[1] Microscopy is performed only as needed based on positive dipstick test results.

Commercially Confidential Information

Additional Laboratory Tests

HIV	Commercially Confidential Information
HBsAg	HCVAb [1]
Commercially Confidential Information	

Pregnancy (urine or serum according to SOA [Appendix A, Table 2])

[1] A positive result for HCVAb is acceptable provided that it was effectively treated as documented by negative results from Reflex Testing for HCV RNA (performed during Screening at the central lab or at a local or specialized lab) by either the quantitative (viral load) or qualitative (Real-Time polymerase chain reaction [PCR]) method.