Clinical Trial Protocol

Clinical Trial Title	A Phase II, Randomized, Placebo-Controlled, Double-Blind, Crossover, Study of the Pharmacodynamic Effects of CST-103 co-administered with CST-107 on the Central Nervous System in Subjects with Neurodegenerative Disorders
Protocol Number	CST103/CST107-CLIN-011
EudraCT Number	2020-006067-28
Investigational Products	CST-103, CST-107
Indication	Neurodegenerative disease
Sponsor	CuraSen Therapeutics, Inc. 930 Brittan Avenue, #306 San Carlos, CA 94070 USA Phone: +1 650-475-2842
Sponsor's Medical Monitor (AUS/NZ)	[redacted]
Clinical Trial Compliance	This clinical trial will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation (ICH) and all applicable federal and local regulations.
Version/Date	Version 1.0 / 08 JAN 2021 Version 1.1 / 27 JAN 2021, Amendment 1 Version 2.0 / 14 MAY 2021, Amendment 2 AUS-NZ Version 3.0 / 18 JUL 2021, Amendment 3 AUS-NZ Version 4.0 / 23 AUG 2021, Amendment 4 AUS-NZ Version 5.0 / 19 OCT 2021, Amendment 5 AUS-NZ Version 6.0 / 18 FEB 2022, Amendment 6 AUS-NZ

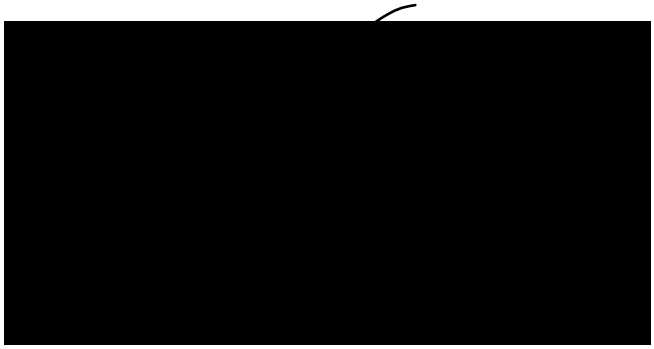
SIGNATURE PAGE

Declaration of Sponsor

Title:

A Phase II, Randomized, Placebo-Controlled, Double-Blind, Crossover, Study of the Pharmacodynamic Effects of CST-103 co-administered with CST-107 on the Central Nervous System in Subjects with Neurodegenerative Disorders

This clinical trial protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the Investigational Products, with moral, ethical, and scientific principles governing clinical research and in accordance with Good Clinical Practice and applicable federal and local regulations.



21 February 2022

Date

INVESTIGATOR'S AGREEMENT

Title:

A Phase II, Randomized, Placebo-Controlled, Double-Blind, Crossover, Study of the Pharmacodynamic Effects of CST-103 co-administered with CST-107 on the Central Nervous System in Subjects with Neurodegenerative Disorders

I have read all pages of this clinical study protocol and any amendments for which CuraSen is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with Good Clinical Practice (cGCP) guidelines. I will also ensure that sub-investigator(s) and other relevant staff members have access to copies of this protocol and all other relevant information provided by Sponsor and the ICH cGCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator

_____ _____

Name Date
Title
Institution

CONTACTS IN CASE OF EMERGENCY

Role in Study	Name	Telephone and Email
CuraSen's Medical Monitor (AUS/[redacted]	[redacted]	Phone: [redacted] Email: [redacted]

PROTOCOL SYNOPSIS

Title	A Phase II, Randomized, Placebo-Controlled, Double-Blind, Crossover, Study of the Pharmacodynamic Effects of CST-103 co-administered with CST-107 on the Central Nervous System in Subjects with Neurodegenerative Disorders
Sponsor	CuraSen Therapeutics, Inc.
Study Medication	CST-103 and CST-107
Primary Objectives	The primary objective of this study is to identify a CNS signal in one of the planned pharmacodynamic measurements after multiple oral doses of CST-103 in the presence of CST-107 in four populations of subjects with Neurodegenerative Disorders (NDD): Cohort A 1. Parkinson's Disease (PD) with REM Sleep Behavior Disorder (RBD) and Depressive Symptoms 2. Mild Cognitive Impairment (MCI) with Depressive Symptoms Cohort B 1. Dementia with Lewy Bodies (DLB) with Cognitive Fluctuations 2. Parkinson's Disease Dementia (PDD) with Cognitive Fluctuations These pharmacodynamic assessments will compare the effect of CST-103 co-administered with CST-107 with that of placebo on the following: Cohort A: • Emotional Facial Processing Cohort B: • Cognitive fluctuations

Secondary Objectives	The secondary objectives for all subjects include the comparison of the effect of CST-103 co-administered with CST-107 with that of placebo on the following: 1. Cognition 2. Movement and time spent sitting, standing and sleeping 3. Sleep 4. Pupillary reactivity 5. Mood Assessment 6. Safety and tolerability of CST-103 co-administered with CST-107 7. The pharmacokinetic (PK) profiles of CST-103 and CST-107
Exploratory Objective	The exploratory objectives are: 1. To characterize the effect of CST-103 co-administered with CST-107 on inflammatory biomarkers in blood, such as C-reactive protein and cytokine levels. 2. To characterize the effect of CST-103 co-administered with CST-107 on Neurodegenerative biomarkers in the blood such as neurofilament light chain, total and phosphorylated tau protein, and amyloid-β (Aβ) peptides may also be measured. 3. To characterize the effect of CST-103 co-administered with CST-107 on performance on a sustained attention task in subjects in Cohort B. 4. To characterize the effect of CST-103 co-administered with CST-107 on Freezing of Gait (FOG) (for subjects with RBD+PD, PDD and DLB). 5. To characterize the locus coeruleus volume and contrast ratio; this is an optional procedure based on imaging capabilities
Primary Endpoints	The primary endpoints include: Cohort A: Change in Negative Emotional Bias in the Facial Expression Recognition Task Cohort B: Cognitive Fluctuations as measured by: 1. Spectral analysis of waking EEG 2. Activity Tracking 3. Pupillometry 4. Dementia Cognitive Fluctuation Scale (DCFS)

Secondary Endpoints	The secondary endpoints will compare the effect of CST-103 co-administered with CST-107 with that of placebo on the following: 1. Verbal fluency test (alphabet & category) and CANTAB cognitive assessments, which include the following: • Reaction Time (RTI) • Rapid Visual Information Processing (RVP) • Verbal Recognition Memory (VRM) Phase I • Adaptive Tracking Task (ATT) • Paired Associates Learning Task (PAL) • Stop Signal Task (SST) • Delayed Verbal Recall 2. Digital wearable device (BioStamp) data, which includes four key measures of interest: a. Activity and posture classifications, durations, and temporal patterns b. Sleep (duration, posture transitions, and activity counts) c. Autonomic function – heart rate variability (HRV) d. Temporal pedometry (daily step count, and gait cadence) 3. Assessment of sleep using digital device and Epworth Sleepiness Scale (ESS) 4. Change in pupillary diameter as measured using the pupillary light reflex test 5. Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS) 6. Adverse events (AE), electrocardiograms (ECGs), vital signs, laboratory safety tests (hematology, chemistry and urinalysis). 7. Plasma PK parameters of CST-103 and CST-107 (including C_{max}, t_{max}, $AUC_{t,}$ AUC_{inf}, $t_{1/2}$)

Exploratory Endpoints	The exploratory endpoints are: 1. Changes in inflammatory biomarkers, such as C-reactive protein and cytokine levels, as measured prior to and after CST-103 co-administered with CST-107 may be determined. 2. Changes in neurodegenerative biomarkers, such as neurofilament light chain, total and phosphorylated tau protein, and amyloid-β (Aβ) peptides, as measured prior to and after CST-103 co-administered with CST-107 may be evaluated. 3. Performance on the SART as measured prior to and after CST-103 co-administered with CST-107. 4. Assessment of FOG using the FOG-Q (for subjects with RBD+PD, PDD and DLB). 5. The characterization of the brain imaging signal in the locus coeruleus complex using neuromelanin-sensitive MRI sequence. This is an optional endpoint based on imaging capabilities.
Methodology	**Study Design** This is a Phase II, randomized, placebo-controlled, double-blind, crossover study on the CNS and pharmacodynamic effects of CST-103 co-administered with CST-107 in 4 subject populations with Neurodegenerative Disorders. Approximately 40 subjects (approximately 20 subjects in Cohort A with RBD+PD or MCI and approximately 20 subjects in Cohort B with PDD or DLB) will be enrolled in a 2 period, 2-way crossover design following study eligibility confirmation during the screening period. The number of subjects enrolled in each cohort may change as emerging data are reviewed from this and other studies. During each treatment period, subjects will receive daily doses of CST-103 co-administered with CST-107 or matching placebo for 14 days. Each treatment period will be separated by a washout period of 14 days (+5-day window). All subjects will complete clinical and pharmacodynamic assessments during each treatment period as indicated in the Schedule of Events. PK blood samples will be collected prior to, during and after study medication administration, as indicated in the Schedule of Events.

	Subjects will complete scheduled study assessments throughout the study duration according to the Schedule of Events. **Safety Review Meetings (SRM)** Safety Review Meetings (SRM) will be held to review blinded safety data (such as AEs, vital signs, ECGs, and safety labs), and PK (if available), when 25%, 50%, and 75% of the subjects have completed the study. The SRM members will be composed of the regional Lead Investigator(s) or delegated representative, CuraSen Chief Medical Officer, CuraSen Medical Monitor(s), and Clinical Research Study Manager(s). Additional members may be added as needed (e.g., Biostatistics, PK scientist).
Number of Subjects	Approximately 40 subjects will be enrolled in this study: approximately 20 in Cohort A (RBD+PD or MCI) and approximately 20 subjects in Cohort B (PDD or DLB). The number of subjects enrolled in each cohort may change as emerging data are reviewed from this and other studies.
Number of Sites	Subjects will be enrolled at up to 10 clinical sites.

Inclusion Criteria	A subject will be considered eligible for enrollment if all of the following are met: <u>Cohort A</u> Subjects with RBD+PD: 1. Male or female subjects ≥ 40 and ≤ 80 years of age, at time of informed consent. 2. Subject diagnosed with Parkinson's Disease, as defined by the United Kingdom Parkinson Disease Brain Bank criteria, associated with REM sleep behavior disorder (RBD+PD), diagnosed according to the International Classification of Sleep Disorders, Third Edition (ICSD-3) (albeit documentation by polysomnography is not required) and positive response to the REM Sleep Behavior Disorder Single-Question Screen (RBD1Q). 3. Subject who is Modified Hoehn & Yahr ≥ stage 1 and ≤ stage 3 during "On" period as documented in the 3 months prior to Screening or completed at Screening. 4. Montreal Cognitive Assessment (MoCA) score ≥ 18 and ≤ 28. Subjects with MCI: 6. Male or female subjects ≥ 50 and ≤ 80 years of age, at time of informed consent. 7. Subjects who meet the criteria for amnestic Mild Cognitive Impairment (MCI) as per the National Institute on Aging-Alzheimer's Association core clinical criteria. 8. Montreal Cognitive Assessment (MoCA) score ≥ 18 and ≤ 26. 9. No dementia according to the International Classifications of Diseases (ICD)-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV. 10. A memory complaint reported by the subject or his/her partner, family member or caregiver. 11. A score of greater than or equal to one standard deviation below age and educational norms in the Digit Symbol Substitution Test (DSST) during Screening. 12. Cognitive decline not primarily caused by vascular, traumatic, or medical problems (alternative causes of cognitive decline are ruled out). <u>Cohort B</u> Subjects with Dementia with Lewy Bodies (DLB) or Parkinson's Disease Dementia (PDD): 14. Male or female subjects ≥ 50 and ≤ 80 years of age, at time of informed consent.

	15. A diagnosis of dementia associated with Dementia with Lewy Bodies (McKeith 2017) or Parkinson's disease (PDD) (Emre 2007). 16. Documented cognitive fluctuations endorsed on the Dementia Cognitive Fluctuation Scale (DCFS) with a combined score of ≥8 in items 4, 11, 12 and 14 must be present. 17. Montreal Cognitive Assessment (MoCA) score ≥ 18 and ≤ 26. 18. Subject having informant or caregiver throughout the study who will submit written consent to cooperate with this study, who routinely accompanies and/or stays with subject 12 hours or more a week, assists with treatment compliance, provides assessments and is able to escort the subject on required visits to study institution. 19. Subject who is Modified Hoehn & Yahr ≥ stage 1 and ≤ stage 3 during "On" period as documented in the 3 months prior to Screening or completed at Screening. 20. Stable concomitant medical and/or psychiatric illnesses in the judgement of the PI. For ALL Subjects: 21. Unless confirmed to be azoospermic (vasectomized or secondary to medical cause), males must agree to use a male condom from Day 1 throughout the study when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a condom during each episode of penile-vaginal penetration until after the Follow-Up Visit. 22. Females of childbearing potential (i.e., not postmenopausal or surgically sterile) who have a male partner must have a negative serum pregnancy test result and must agree to one of the following from start of Screening through 30 days after the last study medication administration: a. use a reliable method of birth control (refer to section 5.6), or b. monogamous relationship with a male partner of confirmed sterility, or c. practice complete abstinence (refer to section 5.6). 23. Females of non-childbearing potential may be enrolled if it is documented that they are postmenopausal (refer to section 5.6). 24. Body weight greater or equal to 50 kg and body mass index (BMI) between 18 and 35 kg/m2, inclusive at Screening.

	25. Stable medical conditions for 3 months prior to Screening visit (e.g., controlled hypertension, dyslipidemia). 26. Willing to follow the protocol requirements and comply with protocol restrictions. 27. Capable of providing informed consent and complying with study procedures (completion of self-assessment rating scales and use of wearable devices). Subjects who are unable to provide consent may use a Legally Authorized Representative.

Exclusion Criteria	Subjects with any of the following will not be eligible for participation. 1. Subjects with poorly controlled hypertension despite lifestyle modifications and/or pharmacotherapy. 2. Subjects with pulmonary disease, including asthma if requiring the use of a β_2-Adrenergic bronchodilator, or evidence of clinically significant moderate or severe pulmonary symptoms. 3. Clinical signs indicating syndromes such as corticobasal degeneration, supranuclear gaze palsy, multiple system atrophy, chronic traumatic encephalopathy, signs of frontotemporal dementia, history of stroke, head injury or encephalitis, cerebellar signs, early severe autonomic involvement, or Babinski sign. 4. Current evidence or history in past two years of epilepsy, focal brain lesion, head injury with loss of consciousness or meeting DSM-IV diagnostic criteria for psychotic disorders, such as Schizophrenia or Bipolar Disorder, or have unstable concomitant psychiatric symptomatology that is not believed by the Investigator to be associated with PDD or DLB. 5. Evidence of any significant clinical disorder or laboratory finding (or in the case of potassium levels below normal range) that renders the participant unsuitable for receiving an investigational drug including clinically significant or unstable hematologic, hepatic, cardiovascular, pulmonary, gastrointestinal, endocrine (excluding managed hypo and hyperthyroidism), metabolic, renal, or other systemic disease or laboratory abnormality. 6. Participants with a history of malignant disease, including solid tumors and hematologic malignancies (except basal cell and squamous cell carcinomas of the skin that have been completely excised and are considered cured) within 5 years prior to Screening. 7. Any clinically significant illness or disease (apart from those typically associated with NDD) as determined by medical and surgical history, physical examination, 12-lead electrocardiogram (ECG) and clinical laboratory assessments conducted at Screening. 8. Clinically significant abnormalities of ECG, including QTcF > 450 ms, for males and QTcF > 470 ms for females, and/or HR < 50 beats per minute, or evidence of clinically significant bundle branch blocks, as indicated by 12-lead

	ECG in a supine position at Screening or during the Lead-In Period. 9. A calculated creatinine clearance of ≤60 mL/min according to the Cockcroft-Gault equation. 10. Current use of any prohibited prescription medication, over-the-counter medication, or herbal supplements/products (refer to section 5.4) during Screening or throughout study, unless approved by both the Investigator and the Sponsor Medical Monitor. 11. Known hypersensitivity to Spiropent (clenbuterol), Corgard (nadolol) or intolerance to lactose. Subjects with hereditary galactose intolerance (e.g., galactosemia, lactase deficiency or glucose galactose malabsorption) should be excluded. 12. Prior treatment with any investigational drug ≤90 days prior to dosing (Day 1), or ≤5 half-lives of the drug (whichever is longer), or current enrollment in any other study treatment or disease study, except for observational studies. 13. Prior treatment with any β-AR agonists or β-AR blockers (includes oral meds, IV or inhaled) or any meds that impact adrenergic signaling within the last month prior to Screening. 14. Known or suspected alcohol or substance abuse within the past 12 months and/or positive test for alcohol or drugs of abuse at Screening or Day 1. 15. Suicidal ideation with actual intent or plan ("Yes" answer on the C-SSRS ideation items 4 or 5) within 3 months prior to study Screening. 16. Positive screening test for hepatitis C antibody (HCV Ab) or current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] at Screening). Subjects with immunity to hepatitis B (defined as negative HBsAg and positive hepatitis B surface antibody [HBsAb]) are eligible to participate in the study. 17. Positive screening test for human immunodeficiency virus (HIV). 18. Current infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). 19. Contraindications to wearing the BioStamp digital device sensors, which include but are not limited to implanted

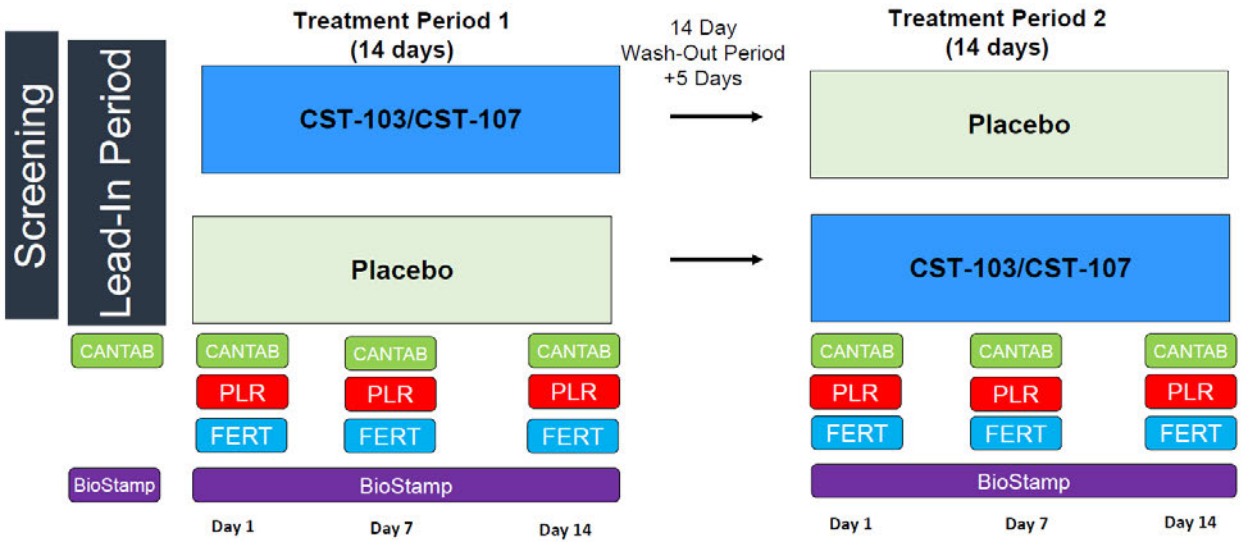
	pacemakers, defibrillators, or other active implantable devices. 20. Known allergies or hypersensitivities to adhesives or hydrogel. 21. Females who are breastfeeding. 22. Any other reason for which the PI considers it is not in the best interest of the participant to undertake the study. 23. Inability to undergo a clinical MRI of the brain due to claustrophobia, inability to lie supine for a prolonged time period, or other contraindications to undergoing an MRI of the brain including, but not limited to, pacemakers; implantable cardioverter defibrillators; cochlear implants; cerebral aneurysm clips; implanted infusion pumps; implanted nerve stimulators; metallic splinters in the eye; and, other magnetic, electronic or mechanical implants or clinical findings that in the judgment of the investigator would pose a potential hazard in combination with MRI. (NOTE: this is a procedural exclusion not a study exclusion).
Description of Study Medications	The study medications will be provided as oral capsules for CST-103, CST-107 and corresponding matching placebos. During Treatment Periods 1 and 2, subjects will receive once daily oral doses of 80 µg CST-103 or matching placebo co-administered with 1 mg CST-107 or matching placebo on Days 1 – 14. A 14-day supply of study drug will be dispensed to the subject at the beginning of each treatment period, and the subject will be instructed to self-administer daily.
Study Duration	The study duration will be approximately 12 weeks, which includes a Screening period of up to 21 days, a Lead-In Period of up to 14 days, the treatment/study period of 6 weeks (two 2-week treatment periods separated with a 2-week wash-out), and the Follow-Up Visit 2 weeks after the last study drug dose.

Study Procedures	After informed consent, all subjects will complete screening procedures and tests to establish eligibility, which will be performed between Day -28 and Day -8. Subjects who meet eligibility criteria based on screening assessments may be enrolled in the study. Screening procedures include medical history evaluation, body weight and height measurements, physical exam, vital signs (including blood pressure, heart rate, respirations, temperature), ECGs, Columbia-Suicide Severity Rating Scale (C-SSRS), safety laboratory tests (chemistry, hematology, and urinalysis), creatinine clearance calculation, drug and alcohol tests, SARS-CoV-2 status assessment, serum HIV, and Hepatitis B and C screen. A serum β-hCG pregnancy test must be completed for women of childbearing potential. Postmenopausal women will need to complete a follicle-stimulating hormone (FSH) test. Subjects with a positive drug screen (including alcohol) at Screening will be rechecked and if positive will be excluded from participation in the study. During the Screening Visit, the following disease and cognitive assessments and measures will be completed as required to evaluate eligibility for each population: DCFS, MHYS, MoCA, RBD1Q, and DSST. Once all screening visit procedures are completed and the subject meets all eligibility criteria, the subject will return to the site to begin the Lead-In Period (up to 14 days). At that time, the subject will be randomly assigned to treatment. During the Lead-In Period, the subject will be trained on and practice the CANTAB tests and verbal fluency test (alphabet & category), and complete the ESS. The Lead-In Period will also be used to establish a baseline activity profile using a digital device. The BioStamp digital device will be dispensed to the subject who will be instructed to wear it for 7 consecutive days prior to the Treatment Period 1 – Day 1 Visit. At the conclusion of the Lead-In Period, subjects will return to the clinic to begin the treatment periods. During each treatment period, subjects will receive daily doses of CST-103 co-administered with CST-107 or matching placebo for 14 days. Each treatment period will be separated by a washout period of 14 days (+5-day window). A comprehensive list of all study procedures is provided in the Schedule of Events.

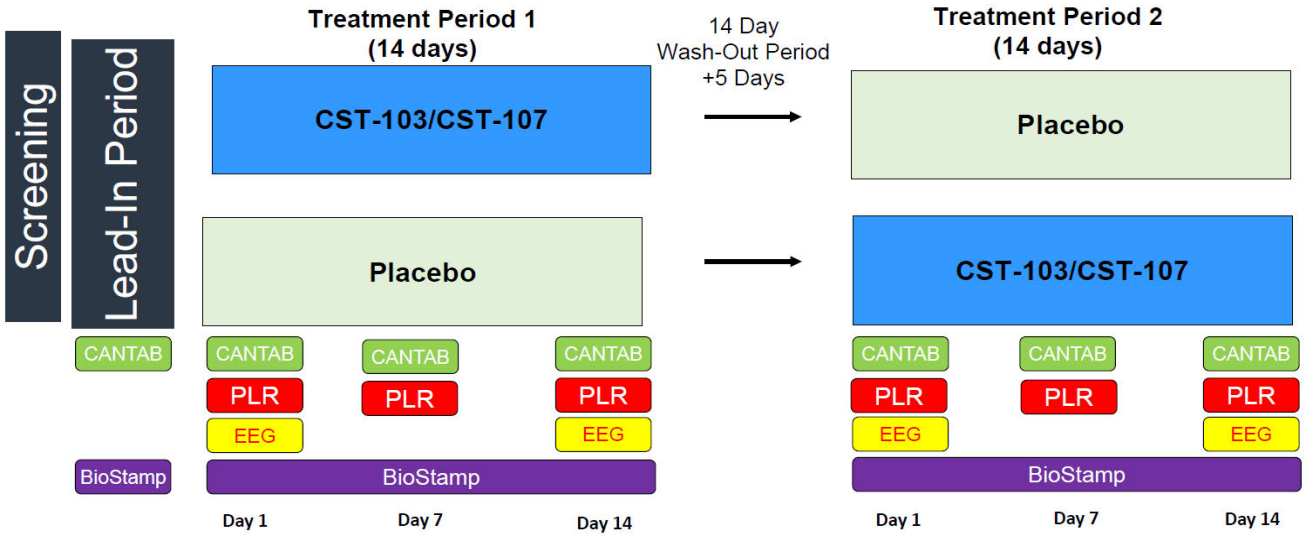
Concomitant Medications	Any concomitant therapy used from the time the subject signs the informed consent through the final visit must be recorded on the case report form (CRF) for all randomized subjects. In addition, any medication required for treatment of adverse events (AEs) or serious adverse events (SAEs) must be recorded on the CRF. Permitted and prohibited medications are listed in section 5.4.
Sample Size Justification	The sample size estimation is based on a crossover design with the assumption that carryover effects are equal. A total of approximately 40 subjects is planned, with approximately 20 subjects with RBD+PD or MCI in Cohort A, and approximately 20 subjects with DLB or PDD in Cohort B. The sample size for the study parts is based on practical considerations. No formal hypothesis testing is planned.

Statistical Analysis	Details of statistical parameters and methods to be used will be described in a Statistical Analysis Plan (SAP). Continuous data will display number of subjects, means, standard deviations, median, minimum, and maximum. Categorical data will display frequency counts and percentages. As this study is primarily descriptive in nature, no formal hypothesis testing will be performed. Unless specified otherwise, confidence intervals will be displayed at the two-sided 95% confidence level. Summaries of disposition and baseline data will be summarized by cohort (A or B), disease criteria within cohort (RBD+PD or MCI for Cohort A, and PDD or DLB for Cohort B), treatment sequence and overall. Summaries of safety, PD, and PK will be presented by disease criteria, treatment (CST-103/CST-107 versus placebo) and overall. A limited subset of summaries may be presented by treatment sequence and/or period and overall. For primary and secondary endpoints, observed values and changes from baseline will be summarized. An informal assessment of differences between CST-103/CST-107 and placebo may be performed. For continuous endpoints, the difference is defined as CST-103/CST-107 minus placebo. Comparisons may be made using a mixed model with factors for disease criteria, treatment, treatment sequence, subject nested in sequence (as a random effect), period, and baseline values as appropriate. Comparisons between treatments may also be compared using the paired t-test and/or nonparametric tests where appropriate. All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class and preferred term. All data will be listed.

STUDY SCHEMA – COHORT A IN RBD+PD OR MCI SUBJECTS



STUDY SCHEMA – COHORT B IN DLB OR PDD SUBJECTS



SCHEDULE OF EVENTS FOR EACH TREATMENT PERIOD

	Screening	**Lead-In**	**Treatment Periods 1 & 2[1]**			**Follow-Up**
	Day -28 to Day -8	**Day -14 to Day -1**	**Day 1**	**Day 7[2] (±1)**	**Day 14/[EW2,3, 4] (±1)**	**~2 Weeks after Last Dose of Study Drug or EW[2,3]**
Outpatient visit	X	X	X	X	X	X
Informed consent	X					
Randomization		X				
Inclusion / Exclusion criteria valuation	X	X	X[29]			
Medical history	X					
Height and weight, BMI calculation	X					
Vital signs[5]	X		X	X	X	X
ECG[6]	X	X	X		X	X
Physical exam, complete[7]	X					X
Safety labs[8]	X		X		X	X
Urine drug screen	X					
Alcohol test	X		X			
Hepatitis and HIV serologies	X					
TSH	X					
Serum FSH[9]	X					
β-hCG pregnancy test[9]	X					

	Screening	Lead-In	Treatment Periods 1 & 2[1]			Follow-Up
	Day -28 to Day -8	**Day -14 to Day -1**	**Day 1**	**Day 7[2] (±1)**	**Day 14/EW[2,3,4] (±1)**	**~2 Weeks after Last Dose of Study Drug or EW[2,3]**
Serum or urine pregnancy test[9]			X		X	X
SARS-CoV-2 status assessment[10]	X	X				
PK sample[11]			X		X	
APOE4 genotyping			X[28]			
Pharmacodynamic sample collection[27]			X		X	
C-SSRS[12]	X		X[25]	X	X	X
DSST[12, 13]	X					
Dementia Cognitive Fluctuation Scale (DCFS)[12, 14]	X		X		X	
Modified Hoehn & Yahr Scale (MHYS)[12, 15]	X					
HADS[16,18]	X		X		X	
Freezing of Gait Questionnaire (FOG-Q)[12, 15]			X		X	
RBD1Q[17, 18]	X					
MoCA[12]	X					
Epworth Sleepiness Scale (ESS)[18]		X	X	X	X	

	Screening	Lead-In	Treatment Periods 1 & 2[1]			Follow-Up
	Day -28 to Day -8	**Day -14 to Day -1**	**Day 1**	**Day 7[2] (±1)**	**Day 14/EW[2,3, 4] (±1)**	**~2 Weeks after Last Dose of Study Drug or EW[2,3]**
Geriatric Depression Scale (GDS)[18]			X	X	X	
CANTAB[19]		X	X	X	X	
Verbal fluency test (alphabet & category)[12,19]		X	X	X	X	
Pupillary Light Reflex (PLR) Test[20]			X	X	X	
EEG[21]			X		X	
Sustained Attention to Response Task (SART)[22]			X		X	
Facial Recognition Task (FERT) [16, 23]			X	X	X	
BioStamp digital device [24]		X	→	→	→	
CST-103+CST-107 or matching placebo administration			→	→	→	
Neuromelanin MRI scan	X[26]					X[26]
Assessment of AEs		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X

AE = adverse event; ECG = electrocardiogram; EEG = electroencephalogram; PK = pharmacokinetics

[1] Wash-out period between Treatment Periods 1 & 2 is 14 (+ 5) days. The Wash-out period may be extended further with Medical Monitor approval.
[2] Visit to be conducted in the clinic, virtually, other off-site location, or at the subject's home according to site and subject preference and capabilities.
[3] Should there be factors and/or conditions which would make a site visit unnecessarily difficult and/or potentially unsafe for a subject, some visits and/or procedures may be performed by alternate arrangement, e.g., visits in the subject's home, virtual visits.

[4] Subjects who withdraw from the study prior to completion of dosing should complete Day 14 safety assessments at the time of withdrawal.
[5] Vital signs to include BP, HR, respiration rate, and oral/tympanic temperature; triplicate BP and HR measurements (separated by approximately 1 minute) after subject is supine for 5 minutes; vital signs will be obtained at every study visit as follows:

- Screening
- Day 1 of each treatment period:
    1. Prior to dosing (within 15 minutes)
    2. 1 hour (±30 mins) after dosing
- Day 7 of each treatment period: 1 hour (±30 mins) after dosing
- Day 14 of each treatment period: 1 hour (±30 mins) after dosing
- Follow-Up Visit

[6] Subjects will be required to rest in a supine position for at least 5 minutes prior to the recording of ECG. ECGs to be obtained at the following timepoints:

- Screening
- Lead-In
- Day 1 of each treatment period:
    1. Prior to dosing (within 15 minutes)
    2. 1 hour (±30 mins) after dosing
    3. 4 hours (±30 mins) after dosing
- Day 14 of each treatment period:
    1. 1 hour (±30 mins) after dosing
    2. 4 hours (±30 mins) after dosing
- Follow-Up Visit

[7] A complete physical examination (PE) (excluding genital, rectal and breast exams) is required at Screening; the Follow-Up PE will be symptom-driven based on subject complaints.
[8] Safety labs to include hematology, chemistries, and urinalysis. Subjects should be fasting for 8 hours for the safety labs.
[9] At Screening, serum β-hCG pregnancy test for females of childbearing potential; an FSH test will be performed for postmenopausal women. Females of childbearing potential will have serum or urine pregnancy tests (per standard site practice) on Day 1, Day 14 and at the Follow-Up visit.
[10] Subjects to be assessed for current infection per local site standard procedure.
[11] PK sample timepoints (CST-103/CST-107) in each treatment period:

- Day 1:
    1. Prior to dosing
    2. 4 hours (±10 mins) post dose
- Day 14:
    1. Prior to dosing
    2. 4 hours (±10 mins) post dose

[12] The DSST, DCFS, MHYS, FOG-Q, C-SSRS, verbal fluency, and MoCA to be done by a qualified clinical rater.
[13] MCI subjects only
[14] Cohort B only; DLB and PDD subjects
[15]RBD+PD, DLB and PDD subjects only
[16] Cohort A only; MCI and RBD+PD subjects
[17] RBD+PD subjects only
[18] The RBD1Q, ESS, HADS, and GDS are per subject self-report.
[19] First administration of CANTAB and verbal fluency test is to familiarize the subject with the tests and equipment. The CANTAB and verbal fluency test should be administered after completion of FERT for Cohort A, and after completion of EEG for Cohort B at the following timepoints in each treatment period:

- Cohort A:
  - Day 1:
    1. Prior to first dose
    2. 4 hours (±30 mins) after dosing
  - Day 7: After dosing (up to 4 hours)
  - Day 14: After dosing (up to 4 hours)

- Cohort B:
  - Day 1:
    1. Prior to first dose
    2. 4 hours (±30 mins) after dosing
  - Day 7: After dosing (up to 4 hours)
  - Day 14: After dosing (up to 4 hours)

[20] The PLR test will be conducted after the CANTAB. The PLR test will be performed (twice for each eye) at the following timepoints in each treatment period:
- Day 1:
  1. Prior to first dose
  2. After post dose CANTAB
- Day 7: After post dose CANTAB
- Day 14: After post dose CANTAB

[21] Cohort B only: First assessment with EEG on Day 1 pre-dose is to obtain a baseline for each period. The EEG will be conducted on Day 14 in clinic (~1 hour). EEG will be conducted at the following timepoints in each treatment period:
- Day 1:
  1. Prior to dosing
  2. 3 hours (±15 mins) after dosing
- Day 14: After dosing (up to 3 hours)

[22]Cohort B (select sites only): First administration of Sustained Attention to Response Task (SART) is to obtain baseline for each period (it will be conducted only at a subset of sites). SART will be conducted at the following timepoints in each treatment period:
- Day 1:
  1. Prior to dosing
  2. 3 hours (±15 mins) after dosing such as to occur during the EEG collection period
- Day 14: After dosing (up to 3 hours) such as to occur during the EEG collection period

[23] Cohort A only: FERT will be conducted at the following timepoints in each treatment period:
- Day 1: Prior to dosing
- Day 7: After dosing
- Day 14: After dosing

[24] Once all screening visit procedures are completed and the subject meets all eligibility criteria, the BioStamp device will be dispensed to the subject who will be instructed to wear for 7 days prior to the Treatment Period 1 – Day 1 Visit. The BioStamp device will be re-dispensed at 2 other timepoints (at each of the Day 1 Visits in Treatment Periods 1 and 2), worn for 14 days and removed on Day 14.

[25] C-SSRS not completed on Day 1 during Treatment Period 1.

[26] The neuromelanin sensitive MRI sequence is optional depending on the imaging facility's capabilities. If not performed at Screening, it may be performed at the Follow-up visit or at any other convenient time during the study.

[27] The pharmacodynamic timepoints in each treatment period are:

- Day 1:
    1. Prior to dosing
- Day 14:
    1. 4 hours (±10 mins) post dose

[28] Treatment period 1 only. For ongoing subjects who have completed visits beyond Treatment Period 1, Day 1, the test may be done at any time during the study.
[29] Treatment period 1 only.

LIST OF ABBREVIATIONS

Abbreviation	Definition
Aβ	amyloid-β
α-syn	α-synuclein
β-AR	Beta-adrenoceptor
β-hCG	Beta human chorionic gonadotropin
AD	Alzheimer's Disease
AE	Adverse event
APOE4	Apolipoprotein E4
ATT	Adaptive tracking test
AUC_{inf}	Area under the drug concentration-time curve from time zero to infinity
AUC_t	Area under the drug concentration-time curve from time zero to time t
BMI	Body mass index
BP	Blood pressure
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBF	Cerebral blood flow
CF	Cognitive fluctuations
cGCP	Current Good Clinical Practice
CLIN-001	CST101/CST107-CLIN-001
CLIN-002	CST103/CST107/CST109-CLIN-002
CLIN-003	CST101/CST103/CST109-CLIN-003
Cmax	Maximum concentration
CNS	Central nervous system
CRF	Case report form
CK	Creatinine kinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CST-103	Clenbuterol
CST-107	Nadolol
CV	Coefficients of variation
DCFS	Dementia Cognitive Fluctuation Scale
DLB	Dementia with Lewy Bodies
DSST	Digit Symbol Substitution Test
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
EEG	Electroencephalogram

Abbreviation	Definition
ERP	Event Related Potential
ESS	Epworth Sleepiness Scale
EW	Early withdrawal
FAS	Full analysis set
FERT	Facial Expression Recognition Task
FOG	Freezing of Gait
FOG-Q	Freezing of Gait Questionnaire
FSH	Follicle-stimulating hormone
GDS	Geriatric Depression Scale
HADS	Hospital Anxiety and Depression Scale
HR	Heart rate
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C antibody
HIV	Human immunodeficiency virus
HRV	Heart rate variability
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IRT	Interactive response technology
ITT	Intent to treat
IV	Intravenous
IWRS	Interactive Web Response System
LBD	Lewy Body Dementia
MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MHYS	Modified Hoehn & Yahr Scale
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NDD	Neurodegenerative disease
PAL	Paired Associates Learning
PD	Parkinson’s Disease
PDD	Parkinson’s Disease Dementia
PI	Principal Investigator
PK	Pharmacokinetic
PKS	PK set
PLR	Pupillary Light Reflex

Abbreviation	Definition
PO	By mouth/oral administration
PPS	Per protocol set
QD	Once daily
RBD1Q	REM Sleep Behavior Disorder Single-Question Screen
RBD+PD	REM Sleep Behavior Disorder positive Parkinson's Disease
RTI	Reaction Time Index
RVP	Rapid Visual information Processing
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SART	Sustained attention response task
SOC	System organ class
SOP	Standard operating procedure
SRM	Safety review meeting
SST	Stop Signal Task
t1/2	Time to maximum observed drug concentration
TEAE	Treatment emergent adverse event
tmax	Time of maximum concentration
TP	Treatment Period
TSH	Thyroid-stimulating hormone
VRM	Verbal Recognition Memory
WAIS-IV	Wechsler Adult Intelligence Scale, Fourth Edition

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Background: Neurodegenerative Disease

1.1.1. Parkinson's Disease

Parkinson's disease (PD) was originally described by James Parkinson in the 19th century and named the "shaking palsy" (Parkinson 1817). PD affects 0.1% to 0.2% of the general population with increasing prevalence with age and up to 1% in individuals above 60 years of age, resulting in an estimated 7 to 10 million people with PD worldwide (Tysnes and Storstein 2017).

PD is a common, progressive and debilitating neurodegenerative disease classically characterized by motor symptoms, including tremor, muscle rigidity, bradykinesia, and posture balance disorders (Kalia 2015). In addition to these classic motor symptoms, the physical burdens for PD patients include nonmotor symptoms, including cognitive dysfunction, neuropsychiatric symptoms, autonomic dysfunction, sleep disorder, and sensory dysfunction (Boland and Stacy 2012). An increasing amount of clinical and epidemiological data suggest that these nonmotor symptoms contribute throughout the entire course of PD.

PD is characterized by the progressive loss of dopaminergic neurons in the substantia nigra and by the appearance of Lewy bodies, which are intracellular inclusions of aggregated α-syn, a protein that is considered to play an important role in the pathogenesis of PD (Dehay 2015).

1.1.2. Mild Cognitive Impairment

Alzheimer's disease (AD) is a severe and life-threatening neurodegenerative disorder that affects approximately 44 million people in the world. Pathological hallmarks of AD include synaptic and neuronal loss, neuroinflammation, alterations of various neurotransmitter systems, and the accumulation of amyloid plaques and neurofibrillary tangles (Huang 2012). The approved medications that are currently available to treat AD provide transient palliative care for some patients but do not alter progression of the disease. Therefore, there is an urgent need for developing therapeutic agents capable of simultaneously addressing cognitive symptoms and pathology of AD and its precursor, amnestic mild cognitive impairment (MCI).

Evidence from both genetic at-risk cohorts and clinically normal older individuals suggests that the pathophysiological process of AD begins years, if not decades, before the diagnosis of clinical dementia during the preclinical stage of AD (Sperling 2011). Preclinical AD is the stage where subjects have amyloid deposition but do not yet have any symptoms (Buckley 2018). In contrast, patients who are at the MCI stage have cognitive deficits. Of interest is that one of the early changes seen in the preclinical stage of AD are areas of decreased cerebral perfusion that are indicative of the diagnosis (Musiek 2012) and measurement of these hypoperfusion areas have been shown to be useful as a biomarker for AD (Jack 2013).

Cerebral perfusion can be measured by arterial spin labeling perfusion magnetic resonance imaging (ASL MRI) (Fällmar 2017). ASL enables the measurement of brain perfusion non-invasively at the tissue level (Haller 2016) by utilizing magnetically labeled blood water as an endogenous tracer.

1.1.3. Lewy Body Dementias

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are Lewy body-related neurodegenerative disorders sharing common clinical and neuropathological findings (Sezgin 2019). The clinical features of both conditions include cognitive impairment, behavioral symptoms, autonomic dysfunction, sleep disorders, and parkinsonism. The cognitive profile of both disorders is characterized by particularly severe deficits in executive and visuospatial functions as well as attention. Clinical differentiation between DLB and PDD is based on an arbitrary distinction between the time of onset of parkinsonism and cognitive symptoms; extrapyramidal symptoms precede dementia in PDD, whereas it coincides with or follows dementia within 1 year in DLB. When the clinical picture is fully developed, DLB and PD-D are practically indistinguishable.

1.1.4. Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is the third most common type of dementia in the world (Heidebrink 2002) with an annual incidence of 0.1% of the general population (Zaccai 2005). Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early (Chan 2018).

DLB was first clearly defined in 1996, at the First International Workshop of the Consortium on Dementia with Lewy Bodies (McKeith 1996) and updated criteria were published in 2017 (McKeith 2017). The clinical diagnostic criteria include rapid progressive mental impairment to dementia as the central feature of DLB. A core feature of DLB is “fluctuations” which can be defined as spontaneous alterations in cognition, attention, and arousal (Sezgin 2019). There is often no consistent fluctuation pattern even within the same patient; they may occur within a day or from day to day. Other core features include persistent well-formed visual hallucinations, and one or more spontaneous cardinal features of parkinsonism such as bradykinesia, rest tremor, and rigidity. Core clinical features may precede dementia including fluctuating cognition with pronounced variations in attention and alertness, recurrent well-formed and detailed visual hallucinations, and RBD (Iranzo 2014).

1.1.5. Parkinson’s Disease Dementia

Parkinson’s disease dementia (PDD) is a late complication of Parkinson’s disease, with a cumulative prevalence of 75–90% of those with a disease duration of 10 years or more (Buter 2008; Hely., 2008; Aarsland and Kurz, 2010). It’s development negatively impacts activities of daily living (Rosenthal et al., 2010), and confers significantly increased morbidity and mortality (Reid, 1996; Levy et al., 2002). It is now widely recognized that the clinical phenotype of PD-D extends beyond the classical dysexecutive syndrome seen in early Parkinson’s disease to include additional deficits in recognition memory, attention processes and visual perception (Pagonabarraga and Kulisevsky, 2012; Kehagia 2013), as well as visual hallucinations and cognitive fluctuations (Emre, 2003, Emre 2007).

1.2. Rationale for Targeting Beta Adrenoceptors

Both nonclinical and clinical data suggest a potential role for beta adrenoceptor (β-AR) agonists in the treatment of neurodegenerative diseases (Faizi 2012, Heneka 2002, Mittal 2017). Despite decades of clinical data on β-AR agonists, however, most studies have concentrated on the pulmonary and cardiovascular effects of this drug class and have provided minimal data on central nervous system (CNS) effects.

A recent study published in Science (Mittal 2017) suggests that β_2-adrenoceptors (β_2-AR) are linked to the transcription of α-syn and increased risk of PD, therefore suggesting that they might represent novel targets for the development of therapeutics for this neurodegenerative disease. A high-throughput gene expression assay was developed for endogenous expression of human SNCA, the gene encoding α-syn. Researchers screened over a thousand compounds, including commercially available drugs. This screening led to the identification of 3 α-syn expression–lowering compounds, the β_2-AR agonists metaproterenol, salbutamol (also known as albuterol), and clenbuterol (CST-103).

Additionally, a pharmacoepidemiology study performed in Norway, using the Norwegian national prescription database of 4.6 million subjects, found that use of the β_2-AR agonist salbutamol was associated with decreased risk of PD (rate ratio of 0.66) while use of the β-AR antagonist propranolol was associated with a markedly increased risk of PD (rate ratio of 2.20) (Mittal 2017). Several additional epidemiology papers published subsequently suggest that treatment with β-AR agonists is protective against PD (Aaseth 2018, Clark and Vissel 2018, Gronich 2018, Magistrelli 2020, Searles 2018). Additional data also suggest that the effect of β-AR agonists may generalize to other neurodegenerative diseases such as mild cognitive impairment (MCI) and Alzheimer's disease (AD) (Chalermpalanupap 2013, Coutellier 2014) Research from the Shamloo laboratory at Stanford University has demonstrated that the noradrenergic system, and β-ARs in particular, are promising therapeutic targets for AD. In multiple transgenic mouse models of AD, xamoterol, a β-AR agonist, enhances cognitive function associated with the disease (Ardestani 2017, Coutellier 2014, Faizi 2011, Faizi 2012, Salehi 2009). The laboratory further discovered that in addition to the cognition-enhancing effects, xamoterol attenuates 3 major pathological hallmarks of AD: beta-amyloid burden, tau pathology, and neuroinflammation (Ardestani 2017).

1.3. Overall Risk/Benefit Assessment

While there will be no direct benefits for subjects participating in this study, the data generated will be valuable and beneficial for developing β-AR agonist therapies for neurodegenerative diseases.

The adverse events (AEs) that are expected with use of CST-103 and CST-107 for their approved indications is provided in the Investigator Brochure (IB). The medications will be administered as daily doses in this study.

Hypokalemia is a known effect of β_2-AR-agonists, but its clinical significance is unclear since it appears to be a redistribution of potassium in the body rather than total body potassium depletion (Unwin 2011, Kardalas 2018).

In CuraSen studies, CLIN-002 and CLIN-003, in which a total of 19 healthy subjects and 8 patients with PD were administered daily doses of 80 µg of CST-103 for 5-7 days only one case of mild hypokalemia was observed. It is therefore expected that hypokalemia will not be a safety concern with either β_2-AR-agonist. However, in case hypokalemia is observed during this study, the subject should be managed based on their clinical needs and presentation as appropriate as per the Investigator's discretion.

In cohort 8 from CLIN-002 when CST-103 was co-administered daily for seven days with CST-107 there were no clinically significant changes in vital signs, physical exam, ECGs, or laboratory values. Taken together with the decades of clinical safety data for CST-103 these safety results from our previous studies suggest that CST-103 will be generally well tolerated without any safety issues when co-administered with a 1 mg dose of CST-107.

Suicide ideation is always a concern for CNS-active drugs. There have been no reports of suicide due to clenbuterol, but subjects in this study will be monitored for suicide ideation.

Magnetic resonance imaging (MRI) is a painless and safe, non-invasive diagnostic procedure that uses a powerful magnet and radio waves to produce detailed images of the head or the body's organs and structures without the use of X-rays or other radiation.

There are no known harmful effects from the strong magnetic field used in MRI scans. However, the magnet is so powerful that it can affect any unsecured metal objects, which can be pulled toward the magnet. The magnet may affect pacemakers, artificial limbs, and other medical devices or implants that contain metal. The MRI will not be conducted if subjects have medical devices or implants.

1.4. Study Rationale

1.4.1. Rationale for Trial

Nonclinical data for β-AR agonists demonstrate positive effects on cognition, inflammation, and biomarkers relevant to neurodegenerative disorders. The Science publication referenced above (Mittal 2017) using pharmaco-epidemiology suggested a protective effect of the β-AR agonist salbutamol on reducing the incidence of PD. Taken together with the nonclinical data on β-AR agonists (Faizi 2012, Heneka 2002) and the neuroanatomical data showing that the locus coeruleus (LC) is one of the first areas affected in neurodegeneration, the hypothesis suggesting that β-AR agonists may have a significant role in the therapy of a variety of neurodegenerative disorders is well founded.

CuraSen's ongoing and completed signal-seeking studies demonstrate that the β_2-AR agonist CST-103 increases cerebral perfusion in healthy subjects and in patients with PD and MCI. Data using a well-established cognitive battery suggests improved cognitive performance in healthy volunteers. This trial seeks to undertake further evaluation of the effects of CST-103 administration on clinically relevant measures in patients with neurodegenerative disorders. These clinically relevant measures include effects of CST-103 on mood, arousal, cognitive performance, sleep, pupillary reactivity, and movement.

Decreased cognitive performance is a hallmark of neurodegenerative diseases and very relevant to the ability of patients to conduct their activities of daily living. Cognitive performance will be

measured through the use of the Cambridge Neuropsychological Test Automated Battery (CANTAB), which is a standardized and automated administration of cognitive testing via touch tablet.

Stimulation of the adrenergic system is well understood to have positive effects on attention, arousal and mood which maybe expected to have beneficial effects on clinical symptoms associated with these parameters such as cognition, depression and cognitive fluctuations.

Cognitive fluctuations (CF) are one of the core features of Lewy Body dementias and are a set of symptoms that describe a spontaneous and time-varying alteration of cognitive abilities, often accompanied by disturbances in alertness or arousal. While such fluctuations have been reported across several dementia syndromes, they are considered to be the most characteristic and frequent symptom of Lewy body dementias—dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD)—where they are seen in up to 90% of patients (Walker 2000). Since CF are related to arousal and the adrenergic system is intimately involved in arousal mechanisms it is our hypothesis that treatment with CST-103 will have an impact on CF. The effect of CST-103 on cognitive fluctuations will be assessed through the use of EEG, ERP, pupillometry and a digital device which measures activity.

Depressed mood is a very common feature of neurodegenerative disorders. The impact of CST-103 on mood will be measured through the use of an established facial emotional recognition task and clinical rating scales.

β-AR agonists have been postulated to have anti-inflammatory properties and have been suggested to modulate the levels of various cytokines (Bissonnette and Befus 1997, Yamaguchi 2010). Therefore, pharmacodynamic blood samples will be collected in this study to investigate the effects of CST-103 on inflammatory biomarkers.

1.4.2. Rationale for Dose Selection

1.4.2.1. Rationale for CST-103 Dose Selection

CuraSen has initiated 3 signal-seeking clinical studies – CST101/CST107-CLIN-001 (CLIN 001), CST103/CST107/CST109-CLIN-002 (CLIN-002), and CST101/CST103/CST109-CLIN-003 (CLIN-003) – to evaluate the effects of β-AR agonists on cerebral perfusion as measured by ASL MRI and cognition. Observations from those studies inform the trial design, endpoints, and doses of CST-103 planned for this study.

The 80 µg CST-103 dose was selected based on data from 2 CuraSen clinical studies:

- Study CST103/CST107/CST109-CLIN-002 (CLIN-002) evaluated single oral doses of 20, 40, 80, and 160 µg CST-103 and once-daily oral doses of 80 µg CST-103 for 7 days in healthy male subjects aged 40 to 55 years. This study (Cohort 4) is currently evaluating single oral doses of 80 µg CST-103 administered a week apart in patients with MCI or PD.
- Study CST101/CST103/CST109-CLIN-003 (CLIN-003) evaluated a single oral dose of 160 µg CST-103 and once-daily oral doses of 80 µg CST-103 administered for five days after 2 days of dose titration in healthy male and female subjects and in patients with PD.

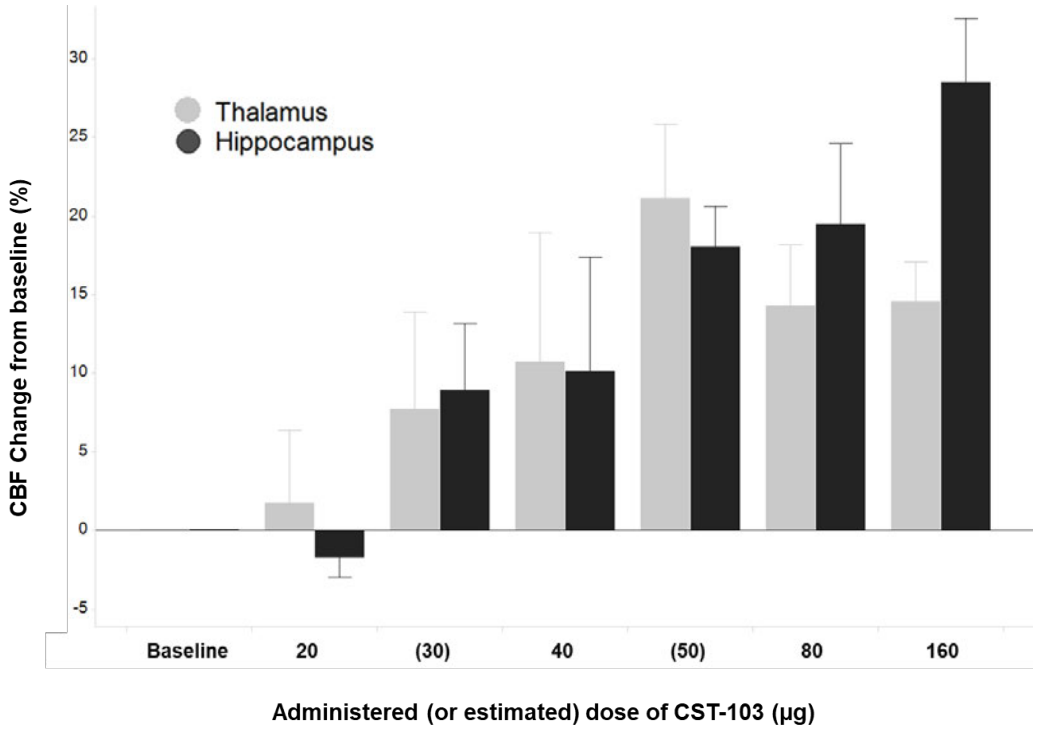
The daily 80 µg CST-103 dose is below the recommended maximum daily dose in Germany (100 µg) for the treatment of reactive airways diseases. Preliminary data from a cohort of healthy subjects (n=16) and patients with Parkinson's disease (n=8) who were administered 80 µg CST-103 daily for 5 days after a two day dose titration in CLIN-003 demonstrate that CST-103 was in general well tolerated. There were no serious AEs, and all adverse events were rated as mild with the exception of two cases of musculoskeletal pain which were labeled as moderate. No clinically significant lab values were reported.

A cohort of healthy subjects (n=4) in CLIN-002 were administered once-daily oral doses of 80 µg CST-103 for 7 days without dose titration and this regimen was tolerated. There were no SAEs, no stopping criteria were met, and no rescue medications were used. All adverse events were rated as mild with the exception of a case of increased CK labeled as moderate. There were no clinically significant changes in vital signs, physical examinations, or ECGs. Hypokalemia (3.17 mg/dl) was observed in one subject but was transient.

Data from Cohort 2 in CLIN-002, in which subjects received a single oral dose of 160 µg CST-103, demonstrated that CST-103 at this higher dose was generally well tolerated in the healthy subjects. Mild hypokalemia and hyperglycemia were observed with spontaneous recovery within the next few hours. One subject experienced mild sinus tachycardia and palpitations after dosing with CST-103. A favorable safety and tolerability profile of the planned CST-103 dose is also supported by published clinical studies, including a 52-week, double-blind, randomized, placebo-controlled study of CST-103 80 µg twice daily (Koeberl 2018).

The neuroimaging data from CLIN-002 using ASL MRI demonstrated that doses of CST-103 below 30 µg do not produce significant increases in cerebral perfusion and a dose of 40 µg produces a minimal increase while doses of 80 and 160 µg produce a robust global increase in cerebral perfusion, with a particularly robust increase of up to 15% in the thalamus and up to 28% in the hippocampus, which are both areas of the brain relevant to neurodegenerative diseases (Figure 1, Bartsch 2015, Leh 2016).

Figure 1: CST-103 Produces a Dose-Dependent Increase in Cerebral Perfusion (measured as cerebral blood flow [CBF]) in the Thalamus and Hippocampus as Measured by ASL-MRI



In Cohort 5 of CuraSen study CLIN-002, "estimated doses" of CST-103 were based on dose equivalents calculated from PK modeling of exposures at 24 hours (estimated dose of 50 µg) and 48 hours (estimated dose of 30 µg) after a single dose of 80 µg CST-103 administered to subjects on Day 1. On days when CST-103 was dosed ASL was conducted 3 hours post dosing.

Our hypothesis is that by improving cerebral perfusion, particularly in areas of the brain that are relevant for symptoms that are commonly found in PD and MCI, the administration of a β-AR agonist will have a positive effect on clinically relevant symptoms such as memory and cognition. In particular for cognition, preliminary data from study CLIN-003 suggest that a daily dose of 80 µg of CST-103 improves cognitive performance in healthy subjects.

Preliminary data show that once-weekly dosing of 80 µg CST-103 for 2 weeks resulted in increases of cerebral perfusion in three subjects with PD on Days 1 and 7. Furthermore, persistent increases in cerebral perfusion were noted in healthy volunteers at 24 and 48 hours after administration of 80 µg CST-103 (CLIN-002, Cohort 5). Since a single dose of 80 µg of CST-103 produces a robust increase in cerebral perfusion which lasts a few days after dosing (Figure 1), the expectation is that the positive cognitive effects seen after administration of a single dose of either 80 or 160 µg CST-103 may also be demonstrated with the 80 µg dose of CST-103 administered daily. In summary, a dose of 80 µg of CST-103 administered daily has been shown to be safe and well tolerated from previous data from the literature and in the CuraSen clinical studies CLIN-002 and CLIN-003.

1.5. Rationale for CST-107 Dose Selection

CST-107 is included in this study to attenuate the peripheral effects commonly caused by β_2-AR agonists which include increased heart rate, palpitations, tremors, decreases in potassium and increases in blood glucose. Previous CuraSen studies exploring low doses of CST-107 co-administered with 80 µg of CST-103 suggest that a 1 mg dose can attenuate these peripheral effects. This is in marked contrast to the usual initial dose for hypertension which is 40 mg CST-107 tablets once daily. The usual maintenance dose is 40 or 80 mg administered once daily and doses up to 240 or 320 mg administered once daily may be needed.

In the treatment of reactive airways disease, the use of a β-AR blocker is not normally recommended along with CST-103 in that the therapeutic effect of the agonist can be antagonized and would risk triggering a severe bronchospasm in patients with asthma. Since this study does not include patients with reactive airways disease and CST-103 is not being used for its bronchodilatory properties, this contraindication is not applicable to this study.

1.6. Compliance Statement

The clinical trial will be conducted in accordance with standards of current Good Clinical Practices (cGCP), as defined by the International Council for Harmonisation (ICH) and all applicable national and local regulations.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

The primary objective of this study is to identify a CNS signal in one of the planned pharmacodynamic measurements after multiple oral doses of CST-103 in the presence of CST-107 in four populations of subjects with Neurodegenerative Disorders (NDD):

Cohort A

1. Parkinson's Disease (PD) with REM Sleep Behavior Disorder (RBD) and Depressive Symptoms
2. Mild Cognitive Impairment (MCI) with Depressive Symptoms

Cohort B

3. Dementia with Lewy Bodies (DLB) with Cognitive Fluctuations
4. Parkinson's Disease Dementia (PDD) with Cognitive Fluctuations

These pharmacodynamic assessments will compare the effect of CST-103 co-administered with CST-107 with that of placebo on the following:

Cohort A

- Emotional Facial Processing

Cohort B

- Cognitive fluctuations

The secondary objectives for all subjects include the comparison of the effect of CST-103 co-administered with CST-107 with that of placebo on the following:

1. Cognition
2. Movement and time spent sitting, standing and sleeping
3. Sleep
4. Pupillary reactivity
5. Mood Assessment
6. Safety and tolerability of CST-103 co-administered with CST-107
7. The pharmacokinetic (PK) profiles of CST-103 and CST-107

The exploratory objectives are to characterize the effect of CST-103 co-administered with CST-107 on the following:

1. To characterize the effect of CST-103 co-administered with CST-107 on inflammatory biomarkers in blood, such as C-reactive protein and cytokine levels may be measured.
2. To characterize the effect of CST-103 co-administered with CST-107 on neurodegenerative biomarkers in the blood such as neurofilament light chain, total and phosphorylated tau protein, and amyloid-β (Aβ) peptides may also be evaluated.
3. To characterize the effect of CST-103 co-administered with CST-107 on performance of a sustained attention task in Cohort B subjects.
4. To characterize the effect of CST-103 co-administered with CST-107 on Freezing of Gait (FOG) (for subjects with RBD+PD, PDD and DLB).
5. To characterize the locus coeruleus volume and contrast ratio (this is an optional objective based on imaging capabilities).

2.2. Primary Endpoints

The primary endpoints include:

Cohort A

Comparison of the effects of CST-103 co-administered with CST-107 vs placebo on change in Negative Emotional Bias in the Facial Expression Recognition Task.

Cohort B

Comparison of the effects of CST-103 co-administered with CST-107 vs placebo on Cognitive Fluctuations as measured by:

1. Spectral analysis of waking EEG
2. Activity Tracking
3. Pupillometry
4. Dementia Cognitive Fluctuation Scale (DCFS)

2.3. Secondary Endpoints

The secondary endpoints will compare the effect of CST-103 co-administered CST-107 with that of placebo on the following:

1. Verbal fluency test (alphabet & category) CANTAB cognitive assessments, which include the following:
    - Reaction Time (RTI)
    - Rapid Visual Information Processing (RVP)
    - Verbal Recognition Memory (VRM) Phase I
    - Adaptive Tracking Task (ATT)
    - Paired Associates Learning Task (PAL)
    - Stop Signal Task (SST)
    - Delayed Verbal Recall
2. Digital wearable device (BioStamp) data, which includes four key measures of interest:
    a. Activity and posture classifications, durations, and temporal patterns
    b. Sleep (duration, posture transitions, and activity counts)
    c. Autonomic function – heart rate variability (HRV)
    d. Temporal pedometry (daily step count, and gait cadence)
3. Assessment of sleep using digital device and Epworth Sleepiness Scale (ESS)
4. Change in pupillary diameter as measured using the pupillary light reflex test
5. Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS)
6. Adverse events (AE), electrocardiograms (ECGs), vital signs, laboratory safety tests (hematology, chemistry and urinalysis).
7. Plasma PK parameters of CST-103 and CST-107 (including C_{max}, t_{max}, AUC_t, AUC_{inf}, $t_{1/2}$)

2.4. Exploratory Endpoints

Exploratory endpoints may include:

1. Changes in inflammatory biomarkers, such as C-reactive protein and cytokine levels, as measured prior to and after CST-103 co-administered with CST-107.
2. Changes in neurodegenerative biomarkers, such as neurofilament light chain, total and phosphorylated tau protein, and amyloid-β (Aβ) peptides, as measured prior to and after CST-103 co-administered with CST-107.
3. Performance on the SART as measured prior to and after CST-103 co-administered with CST-107.
4. Assessment of FOG using the FOG-Q (for subjects with RBD+PD, PDD and DLB).

5. The characterization of the brain imaging signal in the locus coeruleus complex using neuromelanin-sensitive MRI sequence. This is an optional endpoint based on imaging capabilities.

3. STUDY DESIGN

3.1. Clinical Trial Design

This is a Phase II, randomized, placebo-controlled, double-blind, crossover study on the CNS and pharmacodynamics effects of CST-103 co-administered with CST-107 in 4 subject populations with Neurodegenerative Disorders.

Approximately 40 subjects (approximately 20 subjects in Cohort A with RBD+PD or MCI and approximately 20 subjects in Cohort B with PDD or DLB) will be enrolled in a 2 period, 2-way cross over design following study eligibility confirmation during the screening period. The number of subjects enrolled in each cohort may change as emerging data are reviewed from this and other studies.

During each treatment period, subjects will receive daily doses of CST-103 co-administered with CST-107 or matching placebo for 14 days. Each treatment period will be separated by a washout period of 14 days (+5-day window).

All subjects will complete clinical and pharmacodynamic assessments during each treatment period and at the Follow-Up Visit as indicated in the Schedule of Events.

PK blood samples will be collected prior to, during and after study medication administration, as indicated in the Schedule of Events.

Pharmacodynamic blood samples will be collected as indicated in the Schedule of Events to investigate the effects of CST-103 co-administered with CST-107 on inflammatory biomarkers.

3.2. Safety Review Meetings

Safety Review Meetings (SRMs) will be held to review blinded safety data (such as AEs, vital signs, ECGs, and safety labs), and PK (if available) when 25%, 50%, and 75%, of the subjects are completed. Data to be reviewed may not necessarily be validated and cleaned (data query resolution may be pending). Data will be reviewed blinded (treatment assignment will not be revealed) unless unblinding is deemed necessary for the SRM committee.

The SRM members will include the regional Lead Investigator(s) or representative, CuraSen Chief Medical Officer, CuraSen Medical Monitor(s), and Clinical Research Study Manager. Additional members may be added as needed (e.g., statistician, PK scientist). The SRM committee will monitor subject safety and recommend whether to continue with dosing, to modify the protocol, to perform additional safety assessments and/or reviews, to delay or terminate subject enrollment, or to decrease and/or increase sample size based on emerging

safety data from this study or emerging safety, PK, and pharmacodynamics data from other ongoing and completed CuraSen studies.

3.3. Criteria for Termination of Study Medication

Dosing of the study medication will be terminated for any subject for whom the following circumstances apply:

- Any subject experiences a serious adverse event (SAE) that is assessed to be related to study medication
- Medical or ethical reasons affecting continuation of the study

Dosing of the study medication may be stopped if treatment-related AEs, changes in vital signs, ECG or clinical laboratory results are observed and these changes pose a significant health risk, in the opinion of the CuraSen Medical Monitor or Principal Investigator (PI).

A subject may be terminated at any point in time at the discretion of CuraSen Medical Monitor or PI.

3.4. Criteria for Suspension of Trial

The study will be stopped if either of the following occurs.

- One or more serious adverse events (SAEs) considered to be related to study medication; or
- Two or more severe or clinically significant adverse events (AEs) considered to be related to study medication

If following an internal safety review, it is appropriate to restart the study, a substantial amendment will be submitted to the appropriate regulatory authorities and Ethics Committee (EC). The trial will not restart in each region until the amendment has been approved by the regional regulatory authorities and ECs.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Study Participation

Approximately 40 subjects will be enrolled in this study. Approximately 20 subjects with RBD+PD or MCI will be enrolled in Cohort A. Cohort B of this study will include approximately 20 subjects with DLB or PDD. The number of subjects enrolled in each cohort may change as emerging data are reviewed from this and other studies.

All subjects must participate in the informed consent process and sign and date the informed consent before any study-related procedures are performed. Waivers for deviations from the eligibility criteria will not be granted.

4.2. Inclusion Criteria

A subject will be considered eligible for enrollment if all of the following criteria are met:

Cohort A

Subjects with RBD+PD:

1. Male or female subjects ≥ 40 and ≤ 80 years of age, at time of informed consent.
2. Subject diagnosed with Parkinson's Disease, as defined by the United Kingdom Parkinson Disease Brain Bank criteria, associated with REM sleep behavior disorder (RBD+PD), diagnosed according to the International Classification of Sleep Disorders, Third Edition (ICSD-3) (albeit documentation by polysomnography is not required) and positive response to the REM Sleep Behavior Disorder Single-Question Screen (RBD1Q).
3. Subject who is Modified Hoehn & Yahr ≥ stage 1 and ≤ stage 3 during "On" period as documented in the 3 months prior to Screening or completed at Screening.
4. Montreal Cognitive Assessment (MoCA) score ≥ 18 and ≤ 28.

Subjects with MCI:

6. Male or female subjects ≥ 50 and ≤ 80 years of age, at time of informed consent.
7. Subjects who meet the criteria for amnestic Mild Cognitive Impairment (MCI) as per the National Institute on Aging-Alzheimer's Association core clinical criteria.
8. Montreal Cognitive Assessment (MoCA) score ≥ 18 and ≤ 26.
9. No dementia according to the International Classifications of Diseases (ICD)-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV.
10. A memory complaint reported by the subject or his/her partner, family member or caregiver.
11. A score of greater than or equal to one standard deviation below age and educational norms in the Digit Symbol Substitution Test (DSST) during Screening.
12. Cognitive decline not primarily caused by vascular, traumatic, or medical problems (alternative causes of cognitive decline are ruled out).

Cohort B

Subjects with Dementia with Lewy Bodies (DLB) or Parkinson's Disease Dementia (PDD):

14. Male or female subjects ≥ 50 and ≤ 80 years of age, at time of informed consent.
15. A diagnosis of dementia associated with Dementia with Lewy Bodies (McKeith 2017) or Parkinson's disease (PDD) (Emre 2007).
16. Documented cognitive fluctuations endorsed on the Dementia Cognitive Fluctuation Scale (DCFS) with a combined score of ≥8 in items 4, 11, 12 and 14 must be present.
17. Montreal Cognitive Assessment (MoCA) score ≥ 18 and ≤ 26.
18. Subject having informant or caregiver throughout the study who will submit written consent to cooperate with this study, who routinely accompanies and/or stays with subject 12 hours or more a week, assists with treatment compliance, provides assessments and is able to escort the subject on required visits to study institution.
19. Subject who is Modified Hoehn & Yahr ≥ stage 1 and ≤ stage 3 during "On" period as documented in the 3 months prior to Screening or completed at Screening.
20. Stable concomitant medical and/or psychiatric illnesses in the judgement of the PI.

For ALL Subjects:

21. Unless confirmed to be azoospermic (vasectomized or secondary to medical cause), males must agree to use a male condom from Day 1 throughout the study when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

    Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a condom during each episode of penile-vaginal penetration until after the Follow-Up Visit.

22. Females of childbearing potential (i.e., not postmenopausal or surgically sterile) who have a male partner must have a negative serum pregnancy test result and must agree to one of the following from start of Screening through 30 days after the last study medication administration:
    a. use a reliable method of birth control (refer to section 5.6), or
    b. monogamous relationship with a male partner of confirmed sterility, or
    c. practice complete abstinence (refer to section 5.6).
23. Females of non-childbearing potential may be enrolled if it is documented that they are postmenopausal (refer to section 5.6).
24. Body weight greater or equal to 50 kg and body mass index (BMI) between 18 and 35 kg/m2, inclusive at Screening.
25. Stable medical conditions for 3 months prior to Screening visit (e.g., controlled hypertension, dyslipidemia).
26. Willing to follow the protocol requirements and comply with protocol restrictions.
27. Capable of providing informed consent and complying with study procedures (completion of self-assessment rating scales and use of wearable devices). Subjects who are unable to provide consent may use a Legally Authorized Representative.

4.3. Exclusion Criteria

A subject with any of the following criteria will not be eligible for participation:

1. Subjects with poorly controlled hypertension despite lifestyle modifications and/or pharmacotherapy.
2. Subjects with pulmonary disease, including asthma if requiring the use of a β_2-Adrenergic bronchodilator, or evidence of clinically significant moderate or severe pulmonary symptoms.
3. Clinical signs indicating syndromes such as corticobasal degeneration, supranuclear gaze palsy, multiple system atrophy, chronic traumatic encephalopathy, signs of frontotemporal dementia, history of stroke, head injury or encephalitis, cerebellar signs, early severe autonomic involvement, or Babinski sign.
4. Current evidence or history in past two years of epilepsy, focal brain lesion, head injury with loss of consciousness or meeting DSM-IV diagnostic criteria for psychotic disorders, such as Schizophrenia or Bipolar Disorder, or have unstable concomitant psychiatric symptomatology that is not believed by the Investigator to be associated with PDD or DLB.

5. Evidence of any significant clinical disorder or laboratory finding (or in the case of potassium levels below normal range) that renders the participant unsuitable for receiving an investigational drug including clinically significant or unstable hematologic, hepatic, cardiovascular, pulmonary, gastrointestinal, endocrine (excluding managed hypo and hyperthyroidism), metabolic, renal or other systemic disease or laboratory abnormality.
6. Participants with a history of malignant disease, including solid tumors and hematologic malignancies (except basal cell and squamous cell carcinomas of the skin that have been completely excised and are considered cured) within 5 years prior to Screening.
7. Any clinically significant illness or disease (apart from those typically associated with NDD) as determined by medical and surgical history, physical examination, 12-lead electrocardiogram (ECG) and clinical laboratory assessments conducted at Screening.
8. Clinically significant abnormalities of ECG, including QTcF > 450 ms, for males and QTcF > 470 ms for females, and/or HR < 50 beats per minute, or evidence of clinically significant bundle branch blocks, as indicated by 12-lead ECG in a supine position at Screening or during the Lead-In Period.
9. A calculated creatinine clearance of ≤60 mL/min according to the Cockcroft-Gault equation.
10. Current use of any prohibited prescription medication, over-the-counter medication, or herbal supplements/products (refer to section 5.4), during Screening or throughout study, unless approved by both the Investigator and the Sponsor Medical Monitor.
11. Known hypersensitivity to Spiropent (clenbuterol), Corgard (nadolol) or intolerance to lactose. Subjects with hereditary galactose intolerance (e.g., galactosemia, lactase deficiency or glucose galactose malabsorption) should be excluded.
12. Prior treatment with any investigational drug ≤90 days prior to dosing (Day 1), or ≤5 half-lives of the drug (whichever is longer), or current enrollment in any other study treatment or disease study except for observational studies.
13. Prior treatment with any β-AR agonists or β-AR blockers (includes oral medications, IV or inhaled) or any medications that impact adrenergic signaling within the last month prior to Screening.
14. Known or suspected alcohol or substance abuse within the past 12 months and/or positive test for alcohol or drugs of abuse at Screening or Day 1.
15. Suicidal ideation with acutal intent or plan ("Yes" answer on the C-SSRS ideation items 4 or 5) within 3 months prior to study Screening.
16. Positive screening test for hepatitis C antibody (HCV Ab) or current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] at Screening). Subjects with immunity to hepatitis B (defined as negative HBsAg and positive hepatitis B surface antibody [HBsAb]) are eligible to participate in the study.
17. Positive screening test for human immunodeficiency virus (HIV).
18. Current infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

19. Contraindications to wearing the BioStamp digital device sensors, which include but are not limited to implanted pacemakers, defibrillators, or other active implantable devices, and known allergies.
20. Known hypersensitivities to adhesives or hydrogel.
21. Females who are breastfeeding.
22. Any other reason for which the PI considers it is not in the best interest of the participant to undertake the study.
23. Inability to undergo a clinical MRI of the brain due to claustrophobia, inability to lie supine for a prolonged time period, or other contraindications to undergoing an MRI of the brain including, but not limited to, pacemakers; implantable cardioverter defibrillators; cochlear implants; cerebral aneurysm clips; implanted infusion pumps; implanted nerve stimulators; metallic splinters in the eye; and, other magnetic, electronic or mechanical implants or clinical findings that in the judgment of the investigator would pose a potential hazard in combination with MRI. (NOTE: this is a procedural exclusion, not a study exclusion.)

4.4. Enrollment Procedures and Randomization

4.4.1. Screening

After informed consent, all subjects will complete screening procedures and tests to establish eligibility during the Screening Period, which will be performed between Day -28 and Day -8. If a subject falls outside the Screening Period window, screening may be extended with prior approval by the CuraSen Medical Monitor. If extended beyond 21 days, some of the screening procedures and assessments may need to be repeated.

4.4.2. Subject Re-Screening

Subjects who have screen failed may be re-screened a second time if their eligibility characteristics have changed. Subjects who are re-screened must be assigned a new subject number within the Interactive Web Response System (IWRS). The screening process for such subjects must be discussed with the CuraSen Medical Monitor.

4.4.3. Randomization and Lead-In

Once all Screening tests and procedures are completed and all eligibility criteria are met, subjects will return to the clinic for randomization and begin the Lead-In Period. The IWRS will provide the randomization number. The Lead-In tests and procedures listed in the Schedule of Events will be completed within 14 days prior to Day 1 of Treatment Period 1. If subjects fall outside the Lead-In Period window, the Lead-In Period may be extended with prior approval by the CuraSen Medical Monitor.

4.5. Subject Withdrawal

At the time of early withdrawal, the subject should complete the Day 14/Early Withdrawal (EW) visit and return in 2 weeks for the Follow-Up Visit. A subject may withdraw from the clinical trial at any time without penalty and for any reason without prejudice to his or her future medical care. Subjects will be informed that the Investigator may withdraw any subject from the study without his/her consent for any reason if the Investigator thinks it is in the best interest of the subject. In such cases, the Investigator will contact the Sponsor's Medical Monitor before subject withdrawal.

4.5.1. Criteria for Withdrawal from Clinical Trial

Reasons for subject withdrawal include, but are not limited, to the following:

- Withdrawal of consent
- Adverse events
- Pregnancy
- Protocol violation/non-compliance
- Study burden
- Positive test for COVID-19
- Fear of contracting COVID-19
- Sponsor termination of the study
- Investigator's determination that it is in the best interest of the subject to discontinue
- Lost to follow-up
- Other (e.g., withdrawal of caregiver consent)

The reason for withdrawal must be recorded on the case report form (CRF). Whenever possible, the subject should continue to be followed for safety assessments (if consent has not been withdrawn). The Sponsor's Medical Monitor should be contacted before withdrawal whenever possible.

4.5.2. Follow-Up for Early Treatment Withdrawal Subjects

Subjects who discontinue the study after the Day 1 visit of either Treatment Period and who have received study drug will have Early Withdrawal and Follow-Up visits.

5. SCHEDULE OF EVENTS AND STUDY PROCEDURES

Assessments and procedures at each visit are summarized in the Schedule of Events. Certain visits (Days 7, 14, and/or Follow-up) may be conducted virtually, at another off-site location, or at the subject's home according to site and subject preference and capabilities.

5.1. Visit Assessments

5.1.1. Cohort A – RBD+PD or MCI Subjects

5.1.1.1. Screening (Day -28 to Day -8)

The following procedures will be performed, and assessments/measurements recorded:

- Consenting process and written informed consent
- Obtain a subject number from the IWRS
- Evaluation for inclusion/exclusion criteria
- Demographics (sex, age, race, ethnicity, years of education)
- Medical history including concomitant medications
- Height, body weight, BMI calculation
- Clinical and cognitive scales/assessments:
    - All subjects:
        - HADS
        - MoCA
    - MCI subjects:
        - DSST
    - RBD+PD subjects
        - RBD1Q
        - MHYS
- Vital signs (blood pressure [BP], heart rate [HR], respiration rate and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes
- 12-lead ECG, obtained after subject has rested in supine position for at least 5 minutes
- C-SSRS
- Complete physical examination, excluding genital, rectal and breast exams
- SARS-CoV-2 status assessment, per local site standard procedure
- Laboratory tests – subjects should be fasting for 8 hours prior to the safety labs
    - Hematology, chemistry (includes calculated creatinine clearance), and urinalysis
    - Urine drug screen
    - Alcohol test
    - TSH
    - Serology for HIV, hepatitis B and C
    - Serum β-hCG test for females of childbearing potential
    - FSH test for postmenopausal women

- Neuromelanin scan (optional depending on imaging capabilities). If not performed at Screening, it may be performed at the Follow-up visit or at any other convenient time during the study.

Subjects with a positive drug or alcohol screen at Screening will be rechecked once and if positive, the subject will be excluded from participation in the study. The drug and/or alcohol screen tests may be repeated per Investigator clinical judgement.

Subjects who are eligible for study participation will be scheduled to return to the clinic for Lead-In Period assessments.

5.1.1.2. **Lead-in Period (Day -14 to Day -1)**

The following procedures will be performed, and assessments/measurements recorded:

- Review of inclusion/exclusion criteria
- SARS-CoV-2 status assessment, per local site standard procedure
- Randomization
- ECG
- Verbal fluency test (alphabet & category) and CANTAB familiarization
- ESS
- BioStamp digital device dispensed – to be worn for 7 days prior to Treatment Period 1 Day 1 Visit
- Assessment of AEs
- Assessment of concomitant medications

5.1.1.3. **Day 1, Treatment Periods 1 and 2**

The following procedures will be performed, and assessments/measurements recorded:

- Review of inclusion/exclusion criteria (Treatment Period 1 only)
- Assessment of concomitant medications
- Obtain bottle numbers (for CST-103 and CST-107) from the IWRS and dispense study medication
- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes:
    1. Prior to dosing (within 15 minutes)
    2. 1 hour (±30 minutes) after dosing
- 12-lead ECG, obtained after subject has rested in supine position for at least 5 minutes:
    1. Prior to dosing (within 15 minutes)
    2. 1 hour (±30 minutes) after dosing
    3. 4 hours (±30 minutes) after dosing
- C-SSRS (not required during Treatment Period 1)
- Laboratory tests – subjects should be fasting for 8 hours prior to the safety labs
    - Hematology, chemistry, and urinalysis

    - Serum or urine pregnancy test (per standard site practice) for females of childbearing potential; positive urine pregnancy result to be confirmed by serum test
- Alcohol test
- Blood sample collection for pharmacodynamic biomarkers
- Blood sample for APOE4 genetic test (Treatment Period 1 only; for ongoing subjects who have completed visits beyond Treatment Period 1, Day 1, the test may be done at any time during the study)
- PK samples:
    1. Prior to dosing
    2. 4 hours (±10 minutes) post dose
- Pharmacodynamic sample collection prior to dosing
- FERT, administered prior to dosing
- CANTAB tests and verbal fluency test (alphabet & catgory):
    1. Prior to dosing
    2. 4 hours (±30 minutes) post dose
- Pupillary light reflex (PLR) tests (twice for each eye):
    1. Prior to dosing
    2. After the post dose CANTAB
- HADS
- GDS
- ESS
- FOG-Q (RBD+PD subjects only)
- BioStamp dispensed – to be worn daily throughout each Treatment Period and removed on Day 14
- Administer study medication
- Provision of subject dosing diary
- Assessment of AEs
- Schedule Day 7 Visit

5.1.1.4. **Day 7 (±1), Treatment Periods 1 and 2**

The following procedures will be performed, and assessments/measurements recorded:

- Assessment of concomitant medications
- Assessment of AEs
- Administer study medication and conduct a dosing compliance check
- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes:
    - 1 hour (±30 minutes) after dosing
- C-SSRS
- FERT, administered after dosing
- CANTAB and verbal fluency test alphabet & category):
    - Up to 4 hours post dose

- PLR test (twice for each eye), after the post dose CANTAB
- GDS
- ESS

5.1.1.5. **Day 14 (±1), Treatment Periods 1 and 2 / Early Withdrawal (EW)**

The following procedures will be performed, and assessments/measurements recorded:

- Assessment of concomitant medications
- Assessment of AEs
- Collection of subject dosing diary
- Administer study medication and collect bottles for accountability
- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes:
    - 1 hour (±30 minutes) after dosing
- 12-lead ECG, obtained after subject has rested in supine position for at least 5 minutes:
    - 1 hour (±30 minutes) after dosing
    - 4 hours (±30 minutes) after dosing
- C-SSRS
- Laboratory tests – subjects should be fasting for 8 hours prior to the safety labs
    - Hematology, chemistry, and urinalysis
    - Serum or urine pregnancy test (per standard site practice) for females of childbearing potential; positive urine pregnancy result to be confirmed by serum test
- PK samples:
    - Prior to dosing
    - 4 hours (±10 minutes) post dose
- Pharmacodynamic sample collection 4 hours (±10 minutes) post dose
- BioStamp collected
- FERT, administered after dosing
- CANTAB and verbal fluency (alphabet & category)
    - Up to 4 hours post dose
- PLR test (twice for each eye), after the post dose CANTAB
- HADS
- GDS
- ESS
- FOG-Q (RBD+PD subjects only)
- Schedule Follow-Up Visit

5.1.1.6. **Follow-Up – 14 (±3) Days after Treatment Period 2 Day 14 or EW Visit**

The following procedures will be performed, and assessments/measurements recorded:

- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes

- 12-lead ECG, obtained after subject has rested in supine position for at least 5 minutes
- Symptom-driven physical examination
- C-SSRS
- Laboratory tests – subjects should be fasting for 8 hours prior to the safety labs
    - Hematology, chemistry, and urinalysis
    - Serum or urine pregnancy test (per standard site practice) for females of childbearing potential; positive urine pregnancy result to be confirmed by serum test
- Assessment of concomitant medications
- Assessment of AEs
- Register visit in IWRS
- Neuromelanin scan (optional depending on imaging capabilities) if not performed at Screening or any other time during the study.

The Follow-Up Visit should be conducted in the clinic. However, should there be factors and/or conditions which would make the Follow-Up site visit unnecessarily difficult and/or potentially unsafe for a subject, this visit may be performed by alternate arrangement, e.g., visit in the subject's home, virtual visit.

5.1.2. Cohort B – DLB or PDD Subjects

5.1.2.1. Screening (Day -28 to Day -8)

The following procedures will be performed, and assessments/measurements recorded:

- Consenting process and written informed consent
- Obtain a subject number from the IWRS
- Evaluation for inclusion/exclusion criteria
- Demographics (sex, age, race, ethnicity, years of education)
- Medical history including concomitant medications
- Height, body weight, BMI calculation
- MoCA
- MHYS
- DCFS
- Vital signs (blood pressure [BP], heart rate [HR], respiration rate and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes
- 12-lead ECG, obtained after subject has rested in supine position for at least 5 minutes
- C-SSRS
- Complete physical examination, excluding genital, rectal and breast exams
- SARS-CoV-2 status assessment, per local site standard procedure
- Laboratory tests – subjects should be fasting for 8 hours prior to the safety labs
    - Hematology, chemistry (includes calculated creatinine clearance), and urinalysis
    - Urine drug screen
    - Alcohol test
    - TSH

  - Serology for HIV, hepatitis B and C
  - Serum β-hCG test for females of childbearing potential
  - FSH test for postmenopausal women
- Neuromelanin scan (optional depending on imaging capabilities). If not performed at Screening, it may be performed at the Follow-up visit or at any other convenient time during the study.

Subjects with a positive drug or alcohol test at Screening will be rechecked once and if positive, the subject will be excluded from participation in the study. The drug and/or alcohol tests may be repeated per Investigator clinical judgement.

Subjects who are eligible for study participation will be scheduled to return to the clinic for Lead-In Period assessments.

5.1.2.2. **Lead-in Period (Day -14 to Day -1)**

The following procedures will be performed, and assessments/measurements recorded:

- Review of inclusion/exclusion criteria
- SARS-CoV-2 status assessment, per local site standard procedure
- Randomization
- ECG
- Verbal fluency test (alphabet & category) and CANTAB familiarization
- ESS
- BioStamp digital device dispensed – to be worn for 7 days prior to Treatment Period 1 Day 1 Visit
- Assessment of AEs
- Assessment of concomitant medications

5.1.2.3. **Day 1, Treatment Periods 1 and 2**

The following procedures will be performed, and assessments/measurements recorded:

- Review of inclusion/exclusion criteria (Treatment Period 1 only)
- Assessment of concomitant medications
- Obtain bottle numbers (for CST-103 and CST-107) from the IWRS and dispense study medication
- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes:
  1. Prior to dosing (within 15 minutes)
  2. 1 hour (±30 minutes) after dosing
- 12-lead ECG, obtained after subject has rested in supine position for at least 5 minutes:
  1. Prior to dosing (within 15 minutes)
  2. 1 hour (±30 minutes) after dosing
  3. 4 hours (±30 minutes) after dosing
- C-SSRS (not required during Treatment Period 1)
- Laboratory tests – subjects should be fasting for 8 hours prior to the safety labs

  - Hematology, chemistry, and urinalysis
  - Serum or urine pregnancy test (per standard site practice) for females of childbearing potential; positive urine pregnancy result to be confirmed by serum test
- Alcohol test
- Blood sample collection for pharmacodynamic biomarkers
- Blood sample for APOE4 genetic test (Treatment Period 1 only; for ongoing subjects who have completed visits beyond Treatment Period 1, Day 1, the test may be done at any time during the study)
- PK samples:
  1. Prior to dosing
  2. 4 hours (±10 minutes) post dose
- Pharmacodynamic sample collection prior to dosing
- EEG (SART to be completed during EEG session at select sites):
  1. Prior to dosing
  2. 3 hours (±15 minutes) after dosing
- CANTAB tests and verbal fluency test (alphabet & category):
  1. Prior to dosing
  2. 4 hours (±30 minutes) post dose
- PLR tests (twice for each eye):
  1. Prior to dosing
  2. After the post dose CANTAB
- DCFS
- GDS
- ESS
- FOG-Q
- BioStamp dispensed – to be worn daily throughout each Treatment Period and removed on Day 14
- Administer study medication
- Provision of subject dosing diary
- Assessment of AEs
- Schedule Day 7 Visit

5.1.2.4. **Day 7 (±1), Treatment Periods 1 and 2**

The following procedures will be performed, and assessments/measurements recorded:

- Assessment of concomitant medications
- Assessment of AEs
- Administer study medication and conduct a dosing compliance check
- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes:
  - 1 hour (±30 minutes) after dosing
- C-SSRS
- CANTAB and verbal fluency test (alphabet & category):

    - Up to 4 hours after dosing
- PLR test (twice for each eye), after the post dose CANTAB
- GDS
- ESS

5.1.2.5. **Day 14 (±1), Treatment Periods 1 and 2 / Early Withdrawal (EW)**

The following procedures will be performed, and assessments/measurements recorded:

- Assessment of concomitant medications
- Assessment of AEs
- Collection of subject dosing diary
- Administer study medication and collect bottles for accountability
- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes:
    - 1 hour (±30) minutes dosing
- 12-lead ECG, obtained after subject has rested in supine position for at least 5 minutes:
    - 1 hour (±30 minutes) after dosing
    - 4 hours (±30 minutes) after dosing
- C-SSRS
- Laboratory tests – subjects should be fasting for 8 hours prior to the safety labs
    - Hematology, chemistry, and urinalysis
    - Serum or urine pregnancy test (per standard site practice) for females of childbearing potential; positive urine pregnancy result to be confirmed by serum test
- PK samples:
    - Prior to dosing
    - 4 hours (±10 minutes) post dose
- Pharmacodynamic sample collection at 4 hours (±10 minutes) post dose
- BioStamp collected
- EEG (SART to be completed during EEG session at select sites)
- CANTAB and verbal fluency test (alphabet & category)
    - Up to 4 hours after dosing
- PLR test (twice for each eye), after the post dose CANTAB
- DCFS
- GDS
- ESS
- FOG-Q
- Schedule Follow-Up Visit

5.1.2.6. **Follow-Up – 14 (±3) Days after Treatment Period 2 Day 14 or EW Visit**

The following procedures will be performed, and assessments/measurements recorded:

- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); BP and HR measurements obtained 3 times (separated by approximately 1 minute) after the subject is supine for 5 minutes

- 12-lead ECG, obtained after subject has rested in supine position for at least 5 minutes
- Symptom-driven physical examination
- C-SSRS
- Laboratory tests – subjects should be fasting for 8 hours prior to the safety labs
    - Hematology, chemistry, and urinalysis
    - Serum or urine pregnancy test (per standard site practice) for females of childbearing potential; positive urine pregnancy result to be confirmed by serum test
- Assessment of concomitant medications
- Assessment of AEs
- Register visit in IWRS
- Neuromelanin scan (optional depending on imaging capabilities) if not performed at Screening or any other time during the study.

The Follow-Up Visit should be conducted in the clinic. However, should there be factors and/or conditions which would make the Follow-Up site visit unnecessarily difficult and/or potentially unsafe for a subject, this visit may be performed by alternate arrangement, e.g., visit in the subject's home, virtual visit.

5.2. Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the Investigator and qualified healthcare professionals at the study site unless conditions prevent the subject from safely attending. In these cases, study procedures may be performed by alternate arrangement, e.g., visit to the subject's home, virtual visit. The study site will maintain contact information for each subject; if a subject fails to return for study visits, the study site will make every attempt to contact the subject, including, but not limited to, sending registered letters.

5.3. Procedures and Specifications

5.3.1. Medical History, Vital Signs, and Physical Exam

Medical history, including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history, will be collected on all subjects during Screening.

Subject height and body weight will be measured at Screening, and subject's BMI will be calculated and recorded.

Assessment of vital signs will include BP, HR, respiration rate, and oral/tympanic temperature. All routine measures of BP and HR should be made in triplicate (separated by 1 minute) while the subject rests in supine position. Vital signs will be collected as indicated in the Schedule of Events.

A complete physical exam will be performed at Screening and will include general appearance and examination of the following body systems (excludes breast, genital and rectal exams): head, neck and thyroid, eyes, ears, nose, throat, mouth, chest, respiratory, cardiovascular, lymph nodes,

abdomen, skin, nails, hair, musculoskeletal, and neurological. A symptom-driven physical exam based on subject complaints will be conducted at the Follow-Up Visit.

5.3.2. 12-Lead ECG

A 12-lead ECG will be collected as indicated in the Schedule of Events. Subjects will be required to rest in a supine position for at least 5 minutes prior to the recording of ECG. ECGs will be reviewed by the Investigator or qualified study staff.

5.3.3. Clinical Laboratory Analysis

The following clinical safety laboratory assessments will be performed at timepoints detailed in the Schedule of Events:

Safety Labs:

- Hematology: hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, and white blood cell (WBC) count with differential, reticulocyte count.
- Chemistry: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, calcium, bicarbonate, serum creatinine, creatine phosphokinase (CPK), glucose, lipase, phosphate, potassium, sodium, total bilirubin, total cholesterol, total protein, triglycerides, and uric acid.
- Urinalysis: Appearance, occult blood, glucose, leukocyte esterase, nitrite, pH, protein, urobilinogen by dipstick; a reflex microscopic urinalysis will be performed if dipstick protein, nitrite, leukocyte esterase, or occult blood results are positive.

Calculated creatinine clearance according to the Cockcroft-Gault equation: To be done at Screening only.

Serologies for HIV, hepatitis B, and hepatitis C: HIV Ab, HbsAg, HbsAb, and HCV Ab (Screening only). If these results are positive, the PI must refer the subject for counselling and treatment as per institution policy and procedures.

SARS-CoV-2: According to current local COVID management procedures.

Thyroid-stimulating hormone (TSH): To be done at Screening only.

Pregnancy Tests: Serum β-hCG for all female subjects of childbearing potential at Screening; serum or urine pregnancy test for women of childbearing potential on days noted in the Schedule of Events. Positive urine pregnancy tests must be confirmed by a serum test.

Urine Drug Screen: Tests for drugs of abuse.

Alcohol test: Urine or breath test per site's standard practice.

APOE4: Genetic test to be done on Day 1 of Treatment Period 1 only. For ongoing subjects who have completed visits beyond Treatment Period 1, Day 1, the test may be done at any time during the study.

CST-103 and CST-107 PK samples: Blood samples will be collected for PK analysis on Day 1 and Day 14 of each treatment period.

Pharmacodynamic samples: Blood samples will be collected on Day 1 and Day 14 of each treatment period.

Instruction on urine, blood, and plasma sample processing and shipping can be found in the Laboratory Manual.

Retesting Procedures:

Retesting of labs is only permitted if there is reason to believe that the retest value will be within acceptable parameters, such as if the initial test result was erroneous due to a sample processing error, or for bioanalytical sample analysis if in accordance with the bioanalytical test site SOPs.

5.3.4. Pregnancy Testing

A serum β-hCG pregnancy test will be performed for all female subjects of childbearing potential at the Screening visit; female subjects may not be enrolled until the result of this test is known. FSH test will be performed for postmenopausal women. Women of childbearing potential will have serum or urine pregnancy tests on days noted in the Schedule of Events. Positive urine pregnancy tests will be confirmed by a serum test.

5.3.5. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a suicidal ideation and behavior rating scale to evaluate suicide risk. It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent and behaviors." The scale identifies specific behaviors which may be indicative of an individual's intent to complete suicide. The tool is administered by a qualified rater via interview with the subject.

5.3.6. Clinical/Disease and Cognitive Scales and Assessments

Clinical/disease and cognitive scales and assessments must be administered by an appropriately qualified rater. Clinical and cognitive scales will be conducted for all subjects unless otherwise stated and will be performed as outlined on the Schedule of Events. The descriptions of these clinical/disease and cognitive scales are noted below.

5.3.6.1. Digit Symbol Substitution Test (DSST) - MCI Subjects

The DSST integrates complex neuropsychological processes and measures aspects of cognitive function, including cognitive and psychomotor speed, attention, visual scanning, and executive function.

The specific version of the DSST used in this study is the Coding subtest of the Wechsler Adult Intelligence Scale - 4th edition (WAIS-IV).

Subjects are asked to copy simple graphic symbols that are paired to the digits 1–9 within a specified time period. Using a key, the examinee is asked to draw each symbol under its corresponding number. The examinee's score is determined by the number of symbols correctly drawn within a 120-second time limit. The maximum attainable score is 135, with higher scores indicating better performance. Test scores can be benchmarked against published normative data

by age group, and education level (2008 NCS Pearson, Inc., Gaertner 2018) as a means of evaluating test performance.

5.3.6.2. Dementia Cognitive Fluctuation Scale (DCFS) – DLB and PDD Subjects

The DCFS is a 17-item informant completed questionnaire that queries confusion (3 questions), differences in functioning through the day (1 question), sleep patterns and problems (6 questions), varying levels of alertness (4 questions) and clarity of thought/communication (3 questions). Five of the items proved discriminatory between Lewy body dementias, PD and AD (items 4, 10,11,12, and 14; range of function differences during the day; REM sleep disorder; daytime sleeping; daytime lethargy/drowsiness despite adequate sleep; level of consciousness throughout the day). The reduced scale comprised of the 5 items that are sensitive and specific to the reliable identification of cognitive fluctuations in Lewy body dementias (Lee 2014).

5.3.6.3. Modified Hoehn and Yahr Scale (MHYS) – RBD+PD, DLB and PDD Subjects

The MHYS is a clinician-completed rating scale that is used to describe the symptom progression of PD. Originally described in 1967, it parsed the progression of PD into 5 stages. It has since been modified with the addition of stages 1.5 and 2.5 to account for the intermediate course of PD (Fahn 1987). As such, the MHYS is as follows:

- Stage 0: No signs of disease;
- Stage 1.0: Unilateral disease;
- Stage 1.5: Unilateral plus axial involvement;
- Stage 2: Bilateral disease, without impairment of balance;
- Stage 2.5: Mild bilateral disease, with recovery on pull test;
- Stage 3: Mild to moderate bilateral disease; some postural instability; physically independent;
- Stage 4: Severe disability; still able to walk or stand unassisted;
- Stage 5: Wheelchair bound or bedridden unless aided.

5.3.6.4. Hospital Anxiety and Depression Scale (HADS) – MCI and RBD+PD Subjects

HADS is a 14-item questionnaire with subscales for anxiety and depression. It was originally developed to screen for depression and anxiety in a hospital setting but was later validated for use in a general population. The subjects are given 14 questions in multiple-choice format, seven about depressive symptoms (HADS-D) and seven about anxiety symptoms (HADS-A) and are asked to give a score from 0 to 3 where 0 is the least depressed/anxiety option and 3 the most. A total score ≥ 12 suggests depression, whereas sub-scores of ≥ 8 suggest anxiety or depression (Bjelland 2002; Kjaergaard 2014).

5.3.6.5. REM Sleep Behavior Disorder Single-Question Screen (RBD1Q) - RBD+PD Subjects Only

The RBD1Q is a single “yes-no” question that queries the classic dream-enactment behavior of RBD (Postuma 2012).

The RBD1Q consists of a single question, answered "yes" or "no," as follows: "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?"

5.3.6.6. Montreal Cognitive Assessment (MoCA)

The MoCA (Nasreddine 2005) is a brief cognitive screening tool that is used in clinical research and practice. The scores range from 0 to 30 with scores lower than 26 suggesting cognitive disorder. The MoCA includes measures of expressive and receptive language, memory, and praxis. There are items that screen executive functions and working memory.

5.3.6.7. Epworth Sleepiness Scale (ESS)

The ESS is an 8-item, self-administered questionnaire in which subjects are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in 8 different activities. The total score is the sum of the 8 item scores, with scores ranging from 0 (no daytime sleepiness) to 24 (high sleep propensity in daily life).

5.3.6.8. Geriatric Depression Scale (GDS)

The GDS is a 30-item self-administered yes/no question test constructed for brief screening of depression in elderly persons (Yesavage 1982-1983). Scores greater than 9 are considered suspect for depression.

5.3.6.9. Sustained Attention to Response Task (SART) -- DLB and PDD Subjects at Select Sites Only

The Sustained Attention to Response Task (SART) is a computer-based go/no-go task that requires participants to withhold behavioral response to a single, infrequent target (often the digit 3) presented amongst a background of frequent non-targets. There is evidence supporting the role of the SART as a measure of working memory, sustained attention, and impulse/inhibitory control. In this task, the participant is asked to respond (e.g., button press) to the non-target and to inhibit their response to the target. To perform well, individuals must remain sufficiently attentive to their responses, such that, at the appearance of a target, they can override the dominant pre-potent motor response and substitute the directly antagonistic response (i.e., withhold button press) (Phillips 2020).

5.3.6.10. Freezing of Gait Questionnaire — RBD+PD, DLB and PDD Subjects Only

Freezing of Gait (FOG) is one of the most frequent and disabling symptoms in Parkinson's disease (PD) affecting about half of all patients, especially in the advanced stages of disease. The Freezing of Gait Questionnaire (FOG-Q) is considered a valid and reliable tool for the assessment of FOG severity. The FOG-Q consists of six items borrowed from the Gait and Falls Questionnaire (Giladi 2000).

5.3.6.11. Verbal Fluency Test

Verbal fluency tests are widely used for assessing executive function and require the generation of words from initial letters (phonological verbal fluency) or belonging to a specific category (semantic fluency), under a time constraint.

The specific versions of verbal fluency used in this study are the 'ALPHABET' and 'CATEGORY' tests from the Brief And Simple Index of Cognition (BASIC) (Harrison 2000).

For the ALPHABET task, subjects are given 1 minute to say aloud as many words they can think of that begin with the letter F, avoiding repetitions or the same words with different endings. The total score is the number of correct words generated.

For the CATEGORY task, subjects are given 1 minute to say aloud as many animals they can think of, avoiding repetitions. The total score is the number of animals generated.

5.3.7. CANTAB Assessments

The CANTAB is a standardized and automated administration of cognitive testing via touch tablet, which will include the following:

- The Reaction Time (RTI) task is a processing and psychomotor speed task. It begins with a simple stage with only one target and can be increased to 5 targets to increase demand. Once a yellow circle flashes on screen, subjects must select that circle as fast as possible.
- The Verbal Recognition Memory (VRM) Phase I and Delayed Verbal Recall recognition measures the ability to encode and subsequently retrieve verbal information. Eighteen (18) words are presented, and subjects are subsequently asked to recall them; this is repeated 2 times. Forty-five (45) minutes later free recall test and forced-choice recognition test are carried out.
- The Adaptive Tracking Task (ATT) measures visuomotor coordination and vigilance. In this test, a small circle (target) will continuously move across the screen in a semi-randomized fashion, so as to minimize the subject's ability to predict the trajectory of the target. The subject is instructed to use his/her finger upon the touch screen to move a small dot so that it is consistently within the center of the moving target on the screen. During the test, the speed of the circle is adjusted in response to the subject's ability to keep the dot in the circle, ensuring that the test is adapted to the individual subject.
- The Paired Associates Learning (PAL) task is a measure of visuo-spatial episodic memory relying on the functional integrity of the hippocampus. The task becomes gradually more difficult, benchmarking a subject's memory capacity. Subjects have to remember the location of an abstract pattern in a specific location.
- The Rapid Visual Information Processing (RVP) task is a sensitive measure of sustained attention, outputting measures of response accuracy, target sensitivity and reaction times. For the RVP task single digits appear in a pseudo-random order at a rate of 100 digits per minute in box in the center of the screen. Subjects must detect a series of 3-digit target sequences (3-5-7; 2-4-6; 4-6-8) and respond by touching the button at the bottom of the screen when they see the final number of the sequence. Nine target sequences appear every minute.
- The Stop Signal Task (SST) measures response inhibition (impulse control). The subject must respond to an arrow stimulus, by selecting one of two options, depending on the direction in which the arrow points. If an audio tone is present, the subject must withhold making that response (inhibition).

5.3.8. Pupillary Light Reflex (PLR) Test

The pupillometry measurements (PLR) will be completed in a room where ambient noise and lighting will be controlled and uniform. After resting for 5 min, and before and after receiving the study drug on Day 1 of Treatment Periods 1 and 2, the pupillometry measurements (repeated once) will be taken from each eye using a pupilometer with an opaque rubber cup covering one eye. Each pupillometry session measuring both eyes is about 1 minute. There is no need for a break between measurements.

On Day 7 and Day 14 of Treatment Periods 1 and 2, additional PLR tests will be performed, as per Schedule of Events.

Effects of treatment on pupillary light reflex include one or more of the following measures: pupil area, baseline pupil diameter (BPD), maximum constriction velocity (MCV), absolute constriction amplitude (ACA), maximum dilation velocity (MDV), time to reach 75 % of initial resting diameter during pupillary dilation (T¾), and dilation velocity at T¾ (DV¾).

5.3.9. Neuromelanin MRI Scan

Neuromelanin MRI will be measured to evaluate its suitability as a biomarker of noradrenergic regions in the brain such as the LC. The neuromelanin MRI scan will be performed once, and may be done at any time during the study. The procedure is optional since it is dependent upon on imaging center access and the capabilities of the MRI facility.

Neuromelanin is a dark insoluble complex that is synthesized as an oxidative byproduct of dopamine and noradrenaline in regions of high catecholamine activity such as the substantia nigra and LC (Wakamatsu 2015). It sequesters potentially toxic organic chemical, exogenous and endogenous metals such as iron. When bound to metals such as iron and copper, neuromelanin is highly paramagnetic, leading to T1-shortening and hyperintense signal on T1-weighted turbo spin-echo MRI sequences. As a result, neuromelanin can be detected by non-invasive MRI methodology.

The neuromelanin MRI will require the subject to lie in the MRI scanner for about 30 minutes.

5.3.10. Electroencephalogram (EEG) – DLB and PDD Subjects

EEG data will be collected in subjects at resting state with eyes open and eyes closed and during the administration of the SART (at selected site(s)) using a Stat X24 EEG system. Stat X24 offers 20 channels of high-quality EEG. Channels include sites: Fz, Fp1, Fp2, F3, F4, F7, F8, Cz, C3, C4, Pz, P3, P4, POz, T3, T4, T5, T6, O1, O2. Referencing is acquired through linked mastoids. Each EEG acquisition will be approximately 5 minutes in length for a total of 10 minutes. For eyes open data collection, the subject will be instructed to focus on a cross on the screen while seated and relaxed. For eyes closed, the subject will be instructed to sit, relaxed with eyes closed but do not fall asleep. The absolute and relative power spectral densities (PSDs) will be calculated for each 1 second epoch (1-59 Hz bins), and also grouped into the standard EEG bandwidths: delta, theta, alpha, beta, and gamma. Additionally, the PSD variables will be averaged across brain regions of interest, including frontal, central, parietal, temporal, and

occipital. Previous data suggests EEG slowing was correlated with CFs, measured by the clinician assessment of fluctuations (CAF) scale (Stylianou 2018).

5.3.11. Facial Expression Recognition Task (FERT) – MCI and RBD+PD Subjects

The Facial Expression Recognition Task assesses the recognition of facial emotions. Faces with six different basic emotions (happiness, fear, anger, disgust, sadness, surprise) are briefly displayed on the screen and participants are required to indicate the expression of the face via a button-press. Different intensity levels of each emotion are presented, which increases the ambiguity of the facial expression and the sensitivity of the task. Early change in measures of emotional bias in depressed patients treated with antidepressants has been positively correlated with the improvement in patients' symptoms of depression across a full 6–8 weeks of treatment (Tranter 2009) suggesting that such early changes detected through the use of the FERT may be predictive of antidepressant response.

5.3.12. BioStamp nPoint Data Collection

The BioStamp nPoint device is a wireless remote monitoring system intended for use by researchers and healthcare professional for continuous collection of physiological, activity and sleep data in home and professional healthcare and home settings. These data include heart rate, heart rate variability, respiration rate, activity (including step count and activity classification), and posture (body position relative to gravity). Data are transmitted wirelessly from the Sensors for storage and analysis. Four key measures of interest will be evaluated:

- Activity and posture classifications, durations, and temporal patterns
- Sleep (duration, posture transitions, and activity counts)
- Autonomic function – heart rate variability (HRV)
- Temporal pedometry (daily step count, and gait cadence)

Once all screening visit procedures are completed and the subject meets all eligibility criteria, the BioStamp nPoint device will be dispensed to the subject, who will be instructed to wear it for 7 days during the Lead-In Period. The BioStamp device will be re-dispensed at 2 other timepoints (at each of the Day 1 Visits in Treatment Periods 1 and 2), worn for 14 days and removed on Day 14 in each period.

The BioStamp nPoint device will include the BioStamp sensors, Link Hub, Link App mobile phone, adhesive stickers, and applicator guide. At the time of dispensing the BioStamp nPoint device, written instructions and training videos will be provided to the subject.

5.4. Concomitant Medications

Subjects who required routine medication to manage and treat concurrent conditions (e.g., hyperlipidemia, diabetes, hypertension) must be on stable doses 3 months prior to Screening. Any concomitant therapy taken from the time the subject signs the informed consent through the final visit must be recorded on the CRF for all enrolled subjects. The medication name, dosage, date, and indication for use must be recorded. The Medical Monitor or designee should be

notified in advance of (or as soon as possible after) any instances in which prohibited therapies are administered.

Prohibited concomitant medications include the following:

- Paracetamol >2 g per day
- PD medication changes within 3 months prior to Screening (applicable to RBD+PD, DLB and PDD subjects)
- Vitamin E >400 IU daily
- Aspirin >300 mg daily
- Cannabis and products containing THC and/or CBD
- Melatonin or hypnotics, such as Zolpidem or Zopiclone, within 48 hours prior to a study visit involving cognitive testing
- Levodopa >1.5 g daily
- Changes in clonazepam and monoamine oxidase inhibitor (MAOI) dosing within 4 weeks before Screening.
- Use of St. John's Wort or Ginkgo Biloba within 48 hours prior to study enrollment (defined as the Lead-in Period).
- Use of benzodiazepine (except clonazepam) is prohibited from Screening throughout the study.
- Use of gabapentinoids, phenylephrine and pseudoephedrine are prohibited from Screening throughout the study.
- Prior treatment with any β-AR agonists or β-AR blockers (includes oral medications, eye drops with adrenergic agents such as timolol or atenolol, IV, or inhaled), or any meds that impact adrenergic signaling within the last month prior to Screening will exclude a subject from study enrollment. Use of β-AR agonists or β-AR blockers is not allowed during the study.
- Subjects who had prior treatment with any investigational drug ≤90 days prior to dosing (Day 1), or ≤5 half-lives of the drug (whichever is longer) will be excluded.
- Subjects should not receive the influenza vaccine within 2 weeks of the Screening visit through to the Follow-Up Visit.
- Opioid use is prohibited within 1 month prior to Screening and during the study.

5.5. Escape/Rescue Medications

Since CST-103 is being co-administered with the nonselective β-AR antagonist nadolol (CST-107), the typical β-AR agonist effects such as HR increases, and hypokalemia are unlikely to occur. However, if there are intolerable HR/BP increases subjects may be administered the lowest commercially available dose of nadolol or equivalent β-AR antagonist. Nadolol has been successfully used at low doses (5 mg or less) in previous CuraSen studies to block the peripheral effects of CST-103 and other β-AR agonists. The blood pressure and heart rate increase at which treatment is given will be based on clinical judgment of the study physician and the PI. If

hypokalemia is detected, subjects should be managed based on clinical needs and presentation as appropriate per the Investigator's discretion.

5.6. Contraception

Female subjects of childbearing potential (i.e, not postmenopausal or not surgically sterile) and all male participants with sexual partners of childbearing potential must use reliable methods of birth control during their participation in the study.

Unless confirmed to be azoospermic (vasectomized or secondary to medical cause), male subjects must agree to use a male condom from Day 1 throughout the study when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant. Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a condom during each episode of penile-vaginal penetration until after the Follow-Up Visit.

Female subjects of childbearing potential who have a male partner must agree to contraception from Screening through 30 days after the last administration of study medication.

Acceptable methods of contraception for female subjects of child-bearing potential study include the following:

- Use a reliable method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, contraceptive implant, contraceptive ring, intrauterine device, intrauterine hormone-releasing system, barrier method (e.g., condoms, or diaphragm, or cervical cap when used with spermicide), or
- monogamous relationship with a male partner of confirmed sterility, or
- Practice complete abstinence, i.e., refrain from sexual intercourse.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Females of non-childbearing potential may be enrolled if it is documented that they are postmenopausal (amenorrhea for ≥12 months) and follicle-stimulating hormone (FSH) ≥ 25 IU/L, or have undergone surgical sterilization, including hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or Essure procedure. Females with FSH <25 IU/L must agree to contraception from Day 1 through 30 days after the last administration of study medication, if they have a male partner.

6. ASSESSMENT OF SAFETY

6.1. Adverse Events

6.1.1. Definitions

Adverse Event

An AE is any untoward medical occurrence associated with the use of a study drug in humans and which does not necessarily have a causal relationship with this treatment. AEs may be reported by the subject, discovered through Investigator questioning, or detected through physical examination, laboratory test, or other means.

AEs include:

- Any new undesirable medical experience or an unfavorable and unintended change of an existing condition that occurs during or after treatment, whether or not considered related to study medication.
- Abnormal laboratory findings considered by the Investigator to be clinically significant, i.e., those that are unusual for the population being studied or individual subject.
- Complications and termination of pregnancy; uncomplicated pregnancies are not considered AEs but must still be reported.

Additionally, events (including intercurrent illnesses) occurring from the time of first dose will be documented on the AE CRF. Concurrent illnesses, which existed prior to first dose into the clinical trial, will not be considered AEs unless they worsen during the treatment period.

Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (this means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe)
- Requires or prolongs subject hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that does not otherwise meet the criteria for seriousness

Medical and scientific judgment should be exercised in deciding if an event is serious if it does not meet the above definitions, such as an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or may require intervention to prevent one of the above outcomes. Specific examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

A distinction should be drawn between seriousness and severity of an AE. An AE that is assessed as severe, for example, should not be confused with an SAE. Severity is a category

utilized for rating the intensity of the event (see below); both AEs and SAEs will be assessed for severity grading. An event is defined as "serious" when it meets one of the predefined outcomes as described above.

6.1.2. Assessment of Adverse Events

Each event recorded on the AE CRF will be assessed by the Investigator with regard to the following categories.

Severity

Severity of AEs will be graded as one of:

- **Mild:** Awareness of signs or symptoms but easily tolerated. A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- **Severe:** Incapacitating the ability to do work or to do activities. A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention

Relationship to Study Medication

The Investigator or designee, using clinical judgment, will assess the causality/relationship between each AE and the most recently administered study medication (i.e., whether there is a reasonable possibility that the drug caused the event) and record that assessment in the CRF.

Unrelated: The AE is clearly not related to the study medication. The AE is clearly explained by another cause, or exposure to the study medication has not occurred.

Related: The AE may be related to the study medication. The AE and administration of the study medication are considered reasonably related in time, but the AE is more likely explained by the study medication than another cause.

AE reporting will extend from randomization until completion of the Follow-Up Visit. AEs occurring after the end of the clinical trial must be reported if the Investigator considers there is a causal relationship with the study medication.

All AEs, regardless of the relationship to study medication, will be recorded in the CRF.

All reports should contain a brief description of the event, date of onset, date of resolution, severity, treatment required, relationship to study medication, outcome, and whether the event is classified as serious. Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis into a single event term. For example, "cough, rhinitis, and sneezing" might be grouped together as "upper respiratory tract infection."

A treatment-emergent clinically significant abnormal laboratory value should be recorded as an AE.

6.1.3. Reporting Serious Adverse Events

All SAEs that occur from time of informed consent until completion of the final visit, whether considered to be associated with the study medication or not, must be reported within 24 hours by telephone, e-mail or fax to the Sponsor's Medical Monitor and/or Sponsor's designee using the appropriate contact details provided. The minimum information required for an initial report is:

- Sender of report (name, address of Investigator)
- Subject identification (subject number, NOT subject name)
- Protocol number
- Description of SAE and date of onset
- Relationship assessment
- Date of visit and study visit number
- Current status of subject

However, whenever possible, all points on the SAE form should be completed and the form faxed or scanned and emailed to the Sponsor or designee. The site should also notify the Sponsor or designee by email or voicemail if the information was sent via facsimile. In addition, the event must be documented in the CRF.

After receipt of the initial report, the Sponsor's Medical Monitor or designee will review the information and, if necessary, contact the Investigator to obtain further information for assessment of the event. The Sponsor or designee will be responsible for all information processing and reporting according to local legal requirements.

The Sponsor or designee will determine the SAEs requiring expedited reporting to regulatory agencies. The clinical trial site personnel are responsible for reporting these events to their Ethics Committee in accordance with applicable laws and regulations.

6.1.4. Follow-up of Adverse Events

All AEs and SAEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor. Any SAE that occurs after final visit but is felt to be related to the study medication by the Investigator must be reported to Sponsor or designee and any necessary regulatory agencies and must be followed by the Investigator until resolution or stabilization.

6.2. Clinical Safety Laboratory Abnormalities

Blood and urine samples for routine safety laboratory parameters will be collected at timepoints specified in the Schedule of Events. The Investigator will document review of all labs and will determine and document clinical significance. All abnormal laboratory values that are clinically

significant, treatment-emergent, and meet one of the following conditions (as determined by the Investigator) should be recorded as a single AE:

- Accompanied by clinical symptoms, or
- Requires a change in concomitant therapy

6.3. ECG Abnormalities

Any clinically significant ECG abnormality will require evaluation by the Investigator in consultation with the Sponsor's Medical Monitor to determine if the abnormality is significant and whether it is safe for the subject to continue in the study.

6.4. Pregnancy

Female subjects who become pregnant during the study period must be discontinued from the study. Pregnancy in a study subject should be reported by the Investigator within 1 business day to the Sponsor's Medical Monitor. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

Any female subject or partner of a male study subject who becomes pregnant during the trial will be asked to agree to regular reporting of the progress and outcome of her pregnancy to the Investigator (or designee) and Sponsor. Monitoring of the pregnant subject or partner should continue until the outcome (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) of the pregnancy is known and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

7. STUDY MEDICATION

7.1. Study Medication

CST-103 is provided as 40 µg capsules and matching placebo. CST-107 is provided as 1 mg capsules and matching placebo. Additional details on the study medication can be found in the Investigator Brochure.

7.2. Study Medication Dosing and Administration

Study treatments are:

- CST-103/CST-107 PO taken in the morning after the first meal of the day during each Treatment Period:
  - 80 µg CST-103, administered as two 40 µg capsules QD Day 1 – Day 14

- 1 mg CST-107, administered as one 1 mg capsule QD Day 1 – Day 14

- Matching placebo taken daily during each Treatment Period

7.2.1. Randomization

The designated Interactive Response System (IRT) will be used to randomize subjects into the study on the first day of the Lead-In Period. Eligible subjects will be randomly assigned in a 1:1 ratio to one of the following two treatment sequences (CST-103/CST-107 to placebo or placebo to CST-103/CST-107). The IWRS will provide the randomization number.

Randomization will be stratified by the following factors:

- Disease criteria:
  - Cohort A: RBD+PD or MCI
  - Cohort B: DLB or PDD
- Sex (Male vs Female)

7.2.2. Blinding

This clinical trial is a double-blinded study, with the Sponsor, subjects, and site personnel (e.g., study nurses, coordinators, investigators) blinded to treatment assignment. Limited staff will have access to treatment assignments, such as the unblinded statistical team, IRT system administration, and drug supply management team. Limited CuraSen staff or designees who are not otherwise involved in study conduct may be unblinded during study to evaluate accruing data.

A subject's treatment assignment should only be unblinded by the PI and/or by CuraSen's Medical Monitor when knowledge of the treatment is essential for the further management of the subject or may impact the safety of subjects currently enrolled. Unblinding for any other reason will be considered a protocol violation. The PI is strongly encouraged to contact the CuraSen Medical Monitor before unblinding any subject's treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject's source records.

CST-103 40 µg-matched placebo and CST-107 1 mg-matched placebo will be packaged and color-, size-, and shape-matched to be indistinguishable from CST-103 40 ug and CST-107 1 mg.

7.2.3. Packaging and Labeling

All study medication to be used in this study will be packaged in bottles of 30 capsules each. The clinical label will identify the product by name, lot number, Sponsor, storage conditions and expiration dating period. The products are limited to investigational use only.

7.2.4. Storage and Handling

Study medications will be stored in a secure, controlled-access location at the study site.

Study medications will be stored and handled at the clinical site in accordance with instructions in the Pharmacy Manual. Study medications will be stored at controlled room temperature (15-25°C) with excursions up to 30°C for not longer than 48 hours (continuous). The Sponsor must be notified immediately of any temperature excursions or damage to study medications.

Temperature monitoring is required at the storage location to ensure that the study medications are maintained within an established temperature range. The Investigator(s) is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained; the temperature should be monitored continuously by using either in house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

7.2.5. Accountability and Disposition of Study Medication

The Investigator is responsible for maintaining accurate study medication accountability records throughout the clinical trial. The site will be provided with study medication Accountability Logs on which the designated site staff, will record the receipt, dates, quantity, dispensing and return of study medication, as well as any destruction of study medication or return to the Sponsor. Where more than one secure area is being used for storage at a site, all movement of study medication through the Chain of Custody must be recorded in accountability records such that full reconciliation may be completed at the end of the study. The site may use its own study medication Accountability Logs and standard operating procedures, provided the information outlined above is collected.

After completion of the clinical trial, the Investigator is responsible for the disposal or return to the Sponsor or designee. When the Sponsor has indicated in writing that study medication is to be destroyed on site, destruction must be in accordance with local regulations for the product type and a destruction certificate must be provided to the Sponsor.

8. STATISTICAL CONSIDERATIONS

Details of statistical parameters and methods to be used will be described in a Statistical Analysis Plan (SAP). The SAP will be developed and finalized prior to database lock. The SAP will describe the statistical methodology to assess differences between treatment groups, all data handling procedures and definitions, including the methods for managing missing data.

8.1. Sample Size

A total of approximately 40 subjects is planned in this crossover study, with approximately 20 subjects with RBD+PD or MCI in Cohort A, and approximately 20 subjects with LDB or PDD in Cohort B. The sample size for the study parts are based on practical considerations. No formal hypothesis testing is planned.

The crossover design allows for an increased level of precision in estimates as compared to a parallel design with the same number of subjects. For primary and cognition related secondary endpoints, a sample size of 20 subjects in each cohort provides at least 80% power in this cross-

over design to detect a treatment difference of 0.79*SD (active versus placebo) or larger for each endpoint of interest, where SD represents the standard deviation for the endpoint of interest.

For cognition related secondary endpoints, a sample size of 40 subjects overall (both cohorts combined) provides at least 80% power in this cross-over design to detect a treatment difference of 0.54*SD (active versus placebo) or larger for each endpoint of interest. Sample size assumptions were based on a 2-sided t-test with a Type 1 error rate of 5%, equal (or no) carryover effects, and a correlation of at least 0.3 between study periods. No adjustments were made for dropouts or multiplicity.

8.2. Analysis Populations

The analysis populations are as follows:

Intent to Treat Set (ITT): All subjects who have signed informed consent and have been randomized to a treatment sequence. Subjects will be analyzed according to the treatment sequence assigned at randomization. The ITT will be the analysis set for disposition and select baseline characteristic analyses.

Safety Set: All subjects who received at least 1 dose of study drug (CST103/CST107 or placebo). Subjects will be reported based on treatment and dose received. The Safety Set will be used for reporting of safety analyses.

Full Analysis Set (FAS): All randomized subjects who have taken at least 1 dose of blinded study drug (CST-103/CST-107 or Placebo). Subjects will be analyzed according to the treatment assigned at randomization. The Full Analysis Set will be used for evaluating the pharmacodynamic endpoints, and selected secondary endpoints.

Per-Protocol Set (PPS): A subset of the Full Analysis Set who sufficiently complied with the protocol. Details of the evaluability criteria will be determined prior to study unblinding and specified in the SAP. The Per Protocol Set may be used for selected safety analyses.

Pharmacokinetic Set (PKS): All subjects in the Safety Set who have at least one valid plasma concentration assessment for CST-103 or CST-107. Subjects will be analyzed according to the treatment received. The PKS will be the analysis set for PK concentration and PK parameter analyses.

Additional analysis populations may be defined in the Statistical Analysis Plan.

8.3. Timing of Analyses

8.3.1. Safety Reviews

Cumulative, blinded safety data from the raw database will be reviewed by the SRM throughout the study when 25%, 50%, and 75% of the subjects are completed. During the review at 50% of subjects completed, primary endpoint data and selected secondary endpoint may be assessed.

8.3.2. Interim Analysis and Accruing Data Review

No formal interim analysis is planned. Accruing data will be evaluated informally on an ongoing basis.

8.3.3. Final Analysis

The final analysis will be performed after the last participant completes their follow-up visit or their last scheduled assessment per the Schedule of Events, or the sponsor terminates the study for any reason.

8.4. Multiplicity

This study is descriptive in nature and informal testing of multiple endpoints may be performed. Given the exploratory nature of the comparisons, no adjustment of Type I error is planned.

8.5. Statistical Methods

Statistical analyses will be performed using SAS 9.3 or higher. Continuous data will display number of subjects, means, standard deviations, median, minimum, and maximum. Categorical data will display frequency counts and percentages. As this study is descriptive in nature, no formal hypothesis testing will be performed. Unless specified otherwise, confidence intervals will be displayed at the two-sided 95% confidence level.

Summaries of disposition and baseline data will be summarized by cohort (A or B), disease criteria within cohort (RBD+PD or MCI for Cohort A, and PDD or DLB for Cohort B), treatment sequence and overall. Summaries of safety, pharmacodynamics, and PK will be presented by disease criteria, treatment (CST103/CST107 versus placebo) and overall. A limited subset of summaries may be presented by treatment sequence and/or period and overall.

For analysis purposes, Baseline will be defined as either the pre-dose measurement taken within each of the study periods, or as the last measurement before the first dose received. This will be detailed in the SAP for each parameter. All data will be listed.

Any changes in the planned analysis will be described and documented in the SAP and/or clinical study report.

8.5.1. Subject Disposition

Subject disposition will be summarized by cohort, disease criteria, treatment sequence and overall using the ITT. Summaries will include the number and percent of subjects: in each analysis population, entering the treatment period, completing each period, completing the study, and discontinuing study prematurely, including a description of the reason for early withdrawal. All data will be listed.

8.6. Subject Characteristics

Demographic and other baseline characteristics will be summarized by cohort, disease criteria, treatment sequence and overall using the ITT. Select summaries may also be repeated in the FAS and Safety Set, if the Safety Set differs from the FAS. All data will be listed.

8.7. Analysis of Primary Endpoints

Primary endpoint data will be summarized by cohort, disease criteria, treatment, and overall across disease criteria (i.e., Overall CST103/CST107 and Overall Placebo) using the FAS. Selected summaries may be repeated in the PPS. All data will be listed.

Informal differences between CST103/CST107 and placebo may be assessed for primary endpoints. For continuous endpoints, the difference is defined as CST107/CST107 minus placebo. Comparisons may be made using a mixed model with factors for disease criteria, treatment, treatment sequence, subject nested in sequence (as a random effect), period, and baseline values as appropriate. Comparisons between treatments may also be compared using the paired t-test and/or nonparametric tests where appropriate.

Additional analyses may be performed and will be described in the SAP.

8.7.1. Cohort A: Negative Emotional Bias

Negative Emotional Bias, measured in the Facial Expression Recognition Task (FERT) and collected before dose on Day 1 and after dose on Days 7 and 14 for Cohort A subjects, will be summarized by disease criteria and treatment. Observed values and change from baseline will be summarized.

8.7.2. Cohort B: Cognitive Fluctuations

Cognitive fluctuations among Cohort B subjects are measured by spectral analysis of waking EEG, activity tracking, pupillometry, and DCFS. The observed values and change from baseline in overall values (spectral analysis, activity tracking, and pupillometry) or scales (DCFS) will be summarized by disease criteria and treatment.

8.8. Analysis of Secondary Endpoints

Secondary endpoints related to cognition, physiological symptoms, pupillary data, mood and sleep will be summarized by disease criteria, treatment and overall using the FAS. Select summaries may be repeated in the PPS. Comparisons between treatments will be performed similar to the analysis of primary endpoints. All data will be listed.

8.8.1. Cognition, Mood, and Physiological Symptoms

The absolute values and change (when applicable) from baseline in overall scores and sub-domain scores where applicable will be summarized for Verbal Fluency (alphabet & category), CANTAB, BioStamp, GDS and HADS.

8.8.2. Pupillary-Related Endpoints

Pupillary parameters measured using the pupillary light reflex test including pupil area, baseline pupil diameter (BPD), maximum constriction velocity (MCV), absolute constriction amplitude (ACA), maximum dilation velocity (MDV), time to reach 75 % of initial resting diameter during pupillary dilation (T¾), and average dilation velocity will be summarized by disease criteria, treatment and overall using the FAS.

8.8.3. Epworth Sleepiness Scale

The absolute values and change from baseline in overall scores will be summarized for ESS.

8.8.4. Analysis of Safety

Safety endpoints will be summarized by disease criteria, treatment and overall using the Safety Set. Additional summaries may be performed by treatment sequence and/or period. A limited set of endpoints may also be summarized using other analysis populations.

8.8.5. Adverse Events

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event collection will begin during the Lead-In period and will be collected up to 14 days after the last dose of study drug. All AEs collected on/after first dose of study drug will be considered treatment emergent (TEAE). Each TEAE will further be attributed to a treatment (CST103/CST107 or placebo) based on the AE start date. If a TEAE start date is prior to the first dose in Treatment Period 2, the AE will be attributed to the treatment received in Period 1. If a TEAE start date is on/after to the first dose in Treatment Period 2, the AE will be attributed to the treatment received in Period 2.

An overall summary of the number and percentage of subjects experiencing TEAEs, serious AEs (SAEs), treatment-related AEs, AEs by maximum severity and AEs leading to treatment withdrawal will be provided. Treatment-emergent AEs, SAEs, and treatment-related AEs will be further summarized by MedDRA system organ class and preferred term and reported by treatment group.

The number and percentage of subjects with adverse events reported during the Lead-In period will also be summarized separately.

All AEs will be listed. Separate listings may be prepared for SAEs, AEs leading to study drug termination, and treatment-related AEs.

8.8.6. Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary. Medications taken on or after the first day of the treatment period through the end of treatment will be considered on-treatment medications and will be summarized. All medications will be listed.

8.8.7. Study Drug Administration

Subject exposure to study drug and compliance will be summarized by treatment and treatment sequence. All study medication dispensed and returned, exposure, and compliance data will be listed.

8.8.8. Clinical Laboratory Results, Vital Signs, and ECGs

Absolute values and changes from baseline will be summarized by cohort, disease criteria, treatment and overall. In addition, clinical laboratory results and ECG shift tables may be generated.

All results will be listed. Laboratory values outside of normal ranges and clinically significant ECG abnormalities will be flagged.

8.8.9. Analysis Pharmacokinetic Endpoints

PK endpoints will be summarized by disease criteria, treatment and overall using the PKS. All PK endpoints will be listed.

Individual plasma CST-103 and CST-107 concentrations will be listed for each subject and summarized by nominal sampling timepoint with descriptive statistics (sample size [N], arithmetic mean, standard deviation, median, minimum, maximum, geometric mean and coefficient of variation). Individual and mean CST-103 and CST-107 concentration-time profiles will also be presented graphically on both a linear and log-linear scale.

All PK parameters will be computed from the individual plasma CST-103 and CST-107 concentrations using an appropriate noncompartmental or compartmental approach. The actual PK sampling timepoints will be used for the PK analysis if available, and there are significant deviations from the nominal collection times.

The PK parameters that may be determined (including C_{max}, t_{max}, AUC_t, AUC_{inf}, $t_{1/2}$) will be calculated.

Additional analyses will be performed as deemed necessary upon review of the data.

8.9. Analysis of Exploratory Endpoints

Absolute values and changes from baseline in inflammatory and neurodegenerative inflammatory biomarkers will be summarized by treatment and overall using the FAS.

Brain imaging signals in the locus coeruleus complex using neuromelanin-sensitive MRI sequence will be summarized.

Correlations between clinical and biomarker data, as well as other additional analyses, may be performed and will be defined further in the SAP.

All exploratory endpoints will be listed.

8.10. Analysis of Other Endpoints

Medical history, physical examination, C-SSRS, protocol deviations, screening clinical & cognitive scales (i.e., DSST, MHYS, MoCA, HADS, FOG-Q, and RBD1Q) will be listed.

9. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

9.1. Data Quality Assurance

The Sponsor or designee will conduct either an in-person or virtual site visit to verify the qualifications of each Investigator, according to Sponsor's or designee's applicable standard operating procedure, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the clinical trial for each clinical trial subject. All information recorded on the CRFs for this clinical trial must be consistent with the subjects' source documentation (i.e., medical records).

9.2. Case Report Forms and Source Documentation

Data obtained during this clinical trial should be promptly entered in the electronic CRF (eCRF). All source documents from which eCRF entries are derived will be placed in the subject's medical records. An eCRF will be completed for every subject who was screened for participation in the clinical trial. Measurements for which source documents are available include vital signs, physical exams, laboratory assessments and ECG recordings.

A representative of the Sponsor or designee (a Site Monitor) will visit the clinical trial center periodically to monitor adherence to the protocol and to applicable regulatory regulations, and the maintenance of adequate and accurate clinical records. The eCRFs will be reviewed in detail, for which the Site Monitor will have access to subject medical records, laboratory data, and other source documentation. Remote monitoring may be utilized in some circumstances. The Site Monitor will make a decision as to their acceptability. If errors or omissions are found in the course of a data review, or if clarification of data is required, the eCRFs in question will be corrected by the Investigator or designee.

After full review by the Site Monitor and resolution of any data clarifications, the Investigator will sign and date the completed eCRF. This signature will indicate that thorough inspection of the data therein has been made and will thereby certify the contents of the form.

9.3. Access to Source Data

During the course of the clinical trial, Sponsor representatives, Site Monitors, Regulatory authorities, Ethics Committees (ECs), and/or the Sponsor's Quality Assurance Group or designee must have direct access to source data to review protocol compliance, compare CRFs and individual subject's medical records, assess drug accountability, and ensure that the clinical trial is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained. The Investigator will ensure that the Sponsor is provided with all necessary support at all times.

9.4. Data Processing

All data will be entered using an appropriate data entry system, following standard procedures.

The data review and data-handling document will include specifications for consistency and plausibility checks of data and will also include data-handling rules for obvious data errors.

9.5. Archiving Clinical Trial Records

According to ICH guidelines, essential documents will be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region.

It is the responsibility of the Investigator and clinical trial staff to maintain a comprehensive and centralized filing system of all clinical trial-related documentation. This centralized file should be available for inspection at any time by the Sponsor, Site Monitor or the Sponsor's Quality Assurance staff or designee for monitoring or auditing by the Sponsor and regulatory authorities. Elements of clinical trial documentation will include:

- Subject files containing the completed eCRF supporting source documentation and the signed informed consent form (ICF).
- Clinical trial files, containing the protocol with all amendments, the Investigator Brochure, copies of all clinical trial documentation, and all correspondence to and from the EC and the Investigator.
- Pharmacy files, containing the Study Medication Accountability Records or dispensation logs and all clinical trial agent-related correspondence.

9.6. Good Clinical Practice

The procedures set out in this clinical trial protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the cGCP guidelines of the ICH and applicable federal/national and local regulations. The clinical trial also will be carried out in keeping with local legal requirements.

9.7. Informed Consent

Before each subject is screened, written informed consent must be obtained from the subject. The consent forms must be signed and dated and retained by the Investigator as part of the clinical trial records. The Investigator will not undertake any investigation specifically required for the clinical trial until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the CRF. Each subject will receive a fully signed copy of each consent form that he/she signs for the clinical trial.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate EC and signed by all subjects subsequently enrolled in the clinical trial, as well as those currently enrolled in the clinical trial.

9.8. Protocol Approval and Amendment

Before the start of the clinical trial, the clinical trial protocol and/or other relevant documents will be approved by the EC in accordance with legal and regulatory requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is screened for the clinical trial.

The procedures outlined in the protocol and eCRFs will be reviewed by the Investigator and staff prior to clinical trial initiation to ensure appropriate interpretation and implementation. No deviations from the protocol should be made except in emergency situations in which alternative treatment is necessary for the protection, proper care, and well-being of subjects.

To alter the protocol, amendments must be written, and approvals must be received from the appropriate personnel. Amendments will originate from Sponsor and will be provided to the Investigator for submission to the EC for review and approval prior to implementation. If a protocol amendment substantially alters the clinical trial design or increases potential risk to the study subject, the ICF should be revised and, if applicable, subject's consent to continue participation should be obtained.

Administrative changes may be made without the need for a formal amendment.

9.9. Study Medication Accountability

9.9.1. Handling of Study Medications

The Investigator shall take adequate precautions, including storage of the study medications in a securely locked, substantially constructed cabinet or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substances into illegal channels of distribution.

9.9.2. Disposition of Study Medications

The Investigator is required to maintain adequate records of the disposition of the study medications, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the Investigator shall return the unused supplies to the Sponsor or designee or dispose in accordance with established site procedures. When the Sponsor has indicated in writing that study medication is to be destroyed on site, destruction must be in accordance with local regulations for the product type and a destruction certificate must be provided to the Sponsor.

9.9.3. Premature Termination of the Clinical Trial

The Sponsor reserves the right to terminate this clinical trial at any time. If the clinical trial is terminated prior to scheduled completion, the Investigator will be notified and given any necessary instructions concerning final examinations that are required. If the Investigator, the Sponsor, or the Sponsor's Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical trial continues, the clinical trial may be terminated after appropriate consultation with the relevant parties.

9.10. Confidentiality

All clinical trial findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained, and national requirements and guidelines must be followed. Subjects will be identified on eCRFs and other documents by their subject number, sex and/or birth date, not by name and subject to local requirements. Documents that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

9.11. Publication Policy

By signing the clinical trial protocol, the Investigator agrees with the use of results of the clinical trial for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

All information not previously published concerning CST-103 and/or CST-107 and the Sponsor’s operations, including, but not limited to, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor to the Investigator is considered confidential and shall remain the sole property of Sponsor. The Investigator agrees to use and maintain the confidentiality of this information in accordance with the provisions contained in the clinical trial agreement. Any use or reproduction thereof, including, but not limited to, publications or presentations by the Investigator or his/her associates, must be submitted to the Sponsor for review and approval in accordance with the provisions contained in the relevant agreement governing the conduct of this trial. All publications must acknowledge the sponsorship of Sponsor.

10. REFERENCES

Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. Brain Pathol. 2010;20(3):633-639.

Aaseth J, Dusek P, Roos PM. Prevention of progression in Parkinson's disease. Biometals. 2018 Oct;31(5):737-747.

Ardestani PM, Evans AK, Yi B, et al. Modulation of neuroinflammation and pathology in the 5XFAD mouse model of Alzheimer's disease using a biased and selective beta-1 adrenergic receptor partial agonist. Neuropharmacology. 2017;116:371-386.

Bartsch T, Wulff P. The hippocampus in aging and disease: from plasticity to vulnerability. Neuroscience. 2015 Nov 19;309:1-16.

Bissonnette EY, Befus AD. Anti-inflammatory effect of beta 2-agonists: inhibition of TNF-alpha release from human mast cells. J Allergy Clin Immunol. 1997;100(6 Pt 1):825-831.

Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002 Feb;52(2):69-77.

Boland DF, Stacy M. The economic and quality of life burden associated with Parkinson's disease: a focus on symptoms. Am J Manag Care. 2012 Sep;18(7 Suppl):S168-S175.

Buckley RF, Mormino EC, Amariglio RE, et al. Sex, amyloid, and APOE ε4 and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. Alzheimers Dement. 2018;14(9):1193-1203.

Buter TC, van den Hout A, Matthews FE, et al. Dementia and survival in Parkinson disease: a 12-year population study. Neurology. 2008;70(13):1017-1022.

Chalermpalanupap T, Kinkead B, Hu WT, et al. Targeting norepinephrine in mild cognitive impairment and Alzheimer's disease. Alzheimers Res Ther. 2013;5(2):21.

Chan PC, Lee HH, Hong CT, et al. REM sleep behavior disorder (RBD) in dementia with Lewy bodies (DLB). Behav Neurol. 2018;2018:9421098.

Clark IA, Vissel B. Therapeutic implications of how TNF links apolipoprotein E, phosphorylated tau, α-synuclein, amyloid-β and insulin resistance in neurodegenerative diseases. Br J Pharmacol. 2018 Oct;175(20):3859-3875.

Coutellier L, Ardestani PM, Shamloo M. Beta1-adrenergic receptor activation enhances memory in Alzheimer's disease model. Ann Clin Transl Neurol. 2014;1:348-360.

Dehay B, Bourdenx M, Gorry P, et al. Targeting α-synuclein for treatment of Parkinson's disease: mechanistic and therapeutic considerations. Lancet Neurol. 2015 Aug;14(8):855-866.

Emre M. Dementia associated with Parkinson's disease. Lancet Neurol. 2003;2(4):229-237.

Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord. 2007;22(12):1689-1707.

Fahn S, Elton RL. UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent Developments in Parkinson's Disease. 2nd edn Macmillan Healthcare Information; Florham Park, NJ: 1987. pp. 153–163. pp. 293–304.

Faizi M, Bader PL, Tun C, et al. Comprehensive behavioral phenotyping of Ts65Dn mouse model of Down syndrome: activation of β1-adrenergic receptor by xamoterol as a potential cognitive enhancer. Neurobiol Dis. 2011;43(2):397-413.

Fahn S, Elton RL. UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent Developments in Parkinson's Disease. 2nd edn Macmillan Healthcare Information; Florham Park, NJ: 1987. pp. 153–163. pp. 293–304

Faizi M, Bader PL, Saw N, et al. Thy1-hAPP(Lond/Swe+) mouse model of Alzheimer's disease displays broad behavioral deficits in sensorimotor, cognitive and social function. Brain Behav. 2012 Mar;2(2):142-154.

Fällmar D, Haller S, Lilja J, et al. Arterial spin labeling-based Z-maps have high specificity and positive predictive value for neurodegenerative dementia compared to FDG-PET. Eur Radiol. 2017;27(10):4237–4246.

Gaertner B, Wagner M, Luck T, et al. Normative data for the Digit Symbol Substitution Test in a population-based sample aged 65-79 years: results from the German Health Interview and Examination Survey for Adults (DEGS1). Clin Neuropsychol. 2018;32(sup1):114-132.

Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD. Construction of freezing of gait questionnaire for patients with Parkinsonism. Parkinsonism Relat Disord. 2000 Jul 1;6(3):165-170. doi: 10.1016/s1353-8020(99)00062-0. PMID: 10817956.

Gronich N, Abernethy DR, Auriel E, et al. β_2-adrenoceptor agonists and antagonists and risk of Parkinson's disease. Mov Disord. 2018 Sep;33(9):1465-1471.

Haller S, Zaharchuk G, Thomas DL, et al. Arterial spin labeling perfusion of the brain: emerging clinical applications. Radiology. 2016 Nov;281(2):337-356. Review.

Harrison, J.E., Buxton, P., Husain, M. and Wise, R. (2000), Short test of semantic and phonological fluency: Normal performance, validity and test retest reliability. British Journal of Clinical Psychology; 39:181-19.

Heidebrink JL. "Is dementia with Lewy bodies the second most common cause of dementia?" *Journal of Geriatric Psychiatry and Neurology*, vol. 15, no. 4, pp. 182–187, 2002.

Hely MA, Reid WG, Adena MA, et al. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008;23(6):837-844.

Heneka MT, Galea E, Gavriluyk V, et al. Noradrenergic depletion potentiates beta -amyloid-induced cortical inflammation: implications for Alzheimer's disease. J Neurosci. 2002;22:2434-2442.

Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell. 2012;148:1204-1222.

Iranzo A, Fernández-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One. 2014;9(2):e89741.

Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207-216.

Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;386(9996):896-912.

Kardalas E, Paschou SA, Anagnostis P, et al. Hypokalemia: a clinical update. Endocr Connect. 2018;7(4):R135-R146.

Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. Neurodegener Dis. 2013;11(2):79-92.

Kjaergaard M, Arfwedson Wang CE, Waterloo K, Jorde R. A study of the psychometric properties of the Beck Depression Inventory-II, the Montgomery and Åsberg Depression Rating Scale, and the Hospital Anxiety and Depression Scale in a sample from a healthy population. Scand J Psychol. 2014 Feb;55(1):83-9.

Koeberl DD, Case LE, Smith EC, et al. Correction of biochemical abnormalities and improved muscle function in a phase I/II clinical trial of clenbuterol in Pompe disease. Mol Ther. 2018 Sep 5;26(9):2304-2314.

Leh SE, Kälin AM, Schroeder C, et al. Volumetric and shape analysis of the thalamus and striatum in amnestic mild cognitive impairment. Alzheimers Dis. 2016;49(1):237-249.

Levy G, Schupf N, Tang MX, et al. Combined effect of age and severity on the risk of dementia in Parkinson's disease. Ann Neurol. 2002;51(6):722-729.

Magistrelli L, Comi C. Beta2-adrenoceptor agonists in Parkinson's disease and other synucleinopathies. J Neuroimmune Pharmacol. 2020;15(1):74-81.

McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88-100.

McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996;47(5):1113-1124.

Mittal S, Bjørnevik K, Im DS, et al. β_2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. Science. 2017 Sep 1;357(6354):891-898.

Musiek ES, Chen Y, Korczykowski M, et al. Direct comparison of fluorodeoxyglucose positron emission tomography and arterial spin labeling magnetic resonance imaging in Alzheimer's disease. Alzheimers Dement. 2012 Jan;8(1):51-59.

Nasreddine ZR, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-699.

Pagonabarraga J, Kulisevsky J. Cognitive impairment and dementia in Parkinson's disease. Neurobiol Dis. 2012;46(3):590-596.

Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci. 2002 Spring;14(2):223-236; discussion 222.

Phillips JR, Matar E, Martens KAE, Halliday GM, Moustafa AA, Lewis SJG. Evaluating the Sustained Attention Response Task to Quantify Cognitive Fluctuations in Dementia With Lewy Bodies. J Geriatr Psychiatry Neurol. 2020 Nov;33(6):333-339.

Postuma RB, Arnulf I, Hogl B, et al. A single-question screen for rapid eye movement sleep behavior disorder: a multicenter validation study. Mov Disord. 2012 Jun;27(7):913-916.

Reid WG, Hely MA, Morris JG, et al. A longitudinal of Parkinson's disease: clinical and neuropsychological correlates of dementia. J Clin Neurosci. 1996;3(4):327-333.

Salehi A, Faizi M, Colas D, et al. Restoration of norepinephrine-modulated contextual memory in a mouse model of Down syndrome. Sci Transl Med. 2009;1(7):7ra17.

Searles Nielsen S, Gross A, Camacho-Soto A, et al. β_2-adrenoreceptor medications and risk of Parkinson disease. Ann Neurol. 2018 Nov;84(5):683-693.

Sezgin M, Bilgic B, Tinaz S, Emre M. Parkinson's Disease Dementia and Lewy Body Disease. Semin Neurol. 2019 Apr;39(2):274-282.

Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-292.

Stylianou M, Murphy N, Peraza LR, Graziadio S, Cromarty R, Killen, O' Brien JT, Thomas AJ, LeBeau, FEN, Taylor, JP, Quantitative electroencephalography as a marker of cognitive fluctuations in dementia with Lewy bodies and an aid to differential diagnosis. Clinical Neurophysiology 129 (2018) 1209–1220

Tranter R, Bell D, Gutting P, Harmer C, Healy D, Anderson IM, The effect of serotonergic and noradrenergic antidepressants on face emotion processing in depressed patients. Journal of Affective Disorders,Volume 118, Issues 1–3,2009,Pages 87-93.

Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm (Vienna). 2017 Aug;124(8):901-905.

Unwin RJ, Luft FC, Shirley DG. Pathophysiology and management of hypokalemia: a clinical perspective. Nat Rev Nephrol. 2011 Feb;7(2):75-84.

Wakamatsu K, Tabuchi K, Ojika M, et al. Norepinephrine and its metabolites are involved in the synthesis of neuromelanin derived from the locus coeruleus. J Neurochem. 2015 Nov;135(4):768-776.

Walker MP, Ayre GA, Cummings JL, et al. Quantifying fluctuation in dementia with Lewy bodies, Alzheimer's disease, and vascular dementia. Neurology. 2000;54:1616-1625.

Yamaguchi T, Soma T, Takaku Y, et al. Salbutamol modulates the balance of Th1 and Th2 cytokines by mononuclear cells from allergic asthmatics. Int Arch Allergy Immunol. 2010;152 Suppl 1:32-40.

Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982-1983;17(1):37-49.

Zaccai J, McCracken C, and Brayne C, "A systematic review of prevalence and incidence studies of dementia with Lewy bodies," *Age and Ageing*, vol. 34, no. 6, pp. 561–566, 2005.