# Clinical Trial Protocol

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| Clinical Trial Title | A Phase 2a, Randomized, Placebo-Controlled, Double-Blind, Crossover Study to Evaluate the Safety, Tolerability and Effects of CST-2032 and CST-107 on Cognition in Subjects with Mild Cognitive Impairment or Mild Dementia due to Parkinson's or Alzheimer's Disease. |
| Protocol Number | CST2032/CST107-CLIN-015 |
| IND Number | 158123 |
| Clinicaltrials.gov NCT | NCT05104463 |
| Investigational Products | CST-2032, CST-107 |
| Indication | Cognitive Impairment |
| Sponsor | CuraSen Therapeutics, Inc.<br>930 Brittan Avenue, #306<br>San Carlos, CA 94070, USA<br>Phone: +1 650-475-2842 |
| Sponsor's Medical Monitors | [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 / November 8, 2021<br>Amendment 1 / November 12, 2021<br>Amendment 2 / November 17, 2021<br>Amendment 3 / January 10, 2022<br>Amendment 4 / February 28, 2022<br>Amendment 5 / May 26, 2022<br>Amendment 6 / August 04, 2022<br>Amendment 7 / September 27, 2022<br>Amendment 8 / December 09, 2022<br>Amendment 9 / March 15, 2023<br>Amendment 10 / July 11, 2023 |

# SIGNATURE PAGE

**Declaration of Sponsor**

Title:

A Phase 2a, Randomized, Placebo-Controlled, Double-Blind, Crossover Study to Evaluate the Safety, Tolerability and Effects of CST-2032 and CST-107 on Cognition in Subjects with Mild Cognitive Impairment or Mild Dementia due to Parkinson's or Alzheimer's Disease.

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.

_____ _____

Name: [redacted] Date
Title: Chief Medical Officer
CuraSen Therapeutics, Inc.

## INVESTIGATOR'S AGREEMENT

Title:

A Phase 2a, Randomized, Placebo-Controlled, Double-Blind, Crossover Study to Evaluate the Safety, Tolerability and Effects of CST-2032 and CST-107 on Cognition in Subjects with Mild Cognitive Impairment or Mild Dementia due to Parkinson's or Alzheimer's Disease.

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 Medical Monitor (US) | [redacted] | [redacted] |
| CuraSen Medical Monitor (NZ) | [redacted] | [redacted] |

# PROTOCOL SYNOPSIS

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| Title | A Phase 2a, Randomized, Placebo-Controlled, Double-Blind, Crossover Study to Evaluate the Safety, Tolerability and Effects of CST-2032 and CST-107 on Cognition in Subjects with Mild Cognitive Impairment or Mild Dementia due to Parkinson's or Alzheimer's Disease. |
| Sponsor | CuraSen Therapeutics, Inc. |
| Study Medication | CST-2032 co-administered with CST-107 |
| Primary Objective | The primary objective of this study is to evaluate the safety and tolerability of CST-2032 when combined with CST-107. |
| Secondary Objectives | The secondary objectives of this study will evaluate the effects of CST-2032 when combined with CST-107 versus placebo on the following measures:<br>1. Cognition<br>2. Mood<br>3. Attention Deficit<br>4. Apathy<br>5. Overall clinical improvement<br>6. PK |
| Exploratory Objectives | The exploratory objectives are:<br>• To evaluate whether baseline disease characteristics impact response to treatment.<br>• To characterize the effects of treatment 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. |
| Primary Endpoint | The primary endpoint is safety and tolerability of CST-2032 including adverse event rates (AEs), serious adverse event rates (SAEs), study discontinuation rates, electrocardiograms (ECGs), vital signs, and laboratory safety observations. |
| Secondary Endpoints | The secondary endpoints will compare the effect of CST-2032 administered with CST-107 versus placebo on the following:<br>• Cognitive tasks in the Cambridge Neuropsychological Test Automated Battery (CANTAB) and other cognitive measures:<br>o Reaction Time (RTI) - attention<br>o Verbal Recognition Memory (VRM) – episodic memory (verbal stimuli)<br>o Adaptive Tracking Task (ATT) – visuospatial with strong attentional demand |

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| | ○ Paired Associates Learning (PAL) – episodic memory (visual stimuli)<br>○ Delayed Verbal Recall - episodic memory (verbal stimuli)<br>○ Stop Signal Task (SST) – response inhibition (impulsivity), an aspect of executive function<br>○ Phonological verbal fluency (pVFT)<br>○ Digit symbol substitution test (DSST)<br>○ Color Trails Test (select sites only)<br>• Facial expression recognition task (FERT)<br>• Geriatric Depression Scale – 30 questions (GDS-30)<br>• Conners Adult Attention Deficit Hyperactivity Disorder Scale (ADHD) Rating Scale, short form, self-report (CAARS)<br>• Starkstein Apathy scale short form (SAS-6)<br>• Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)<br>• Suicidal ideation using the Columbia Suicide Severity Rating Scale (C-SSRS).<br>• Plasma pharmacokinetics (PK) parameters of CST-2032 and CST-107 (including $C_{max}$, $t_{max}$, $AUC_t$, $t_{1/2}$). |
| Exploratory Endpoints | The following exploratory endpoints may be undertaken to evaluate:<br>• Subgroup and/or correlation analyses of effects of treatment on baseline disease characteristics including but not limited to disease activity as determined from relevant disease scales at screening, genetic variants involved in neurodegenerative disease including but not limited to apolipoprotein E4 (APOE4), leucine rich repeat kinase 2 (LRRK2), and glucocerebrosidase (GCase) protein (GBA) (optional and where applicable).<br>• 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 treatment may be evaluated.<br>• Change in average z-score for baseline-deficit cognitive tasks identified for each subject from the Cognitive tasks in the Cambridge Neuropsychological Test Automated Battery (CANTAB) and other cognitive measures. |
| Methodology | This is a Phase 2a, randomized, placebo-controlled, double-blind, crossover study to evaluate the safety, tolerability and effects |

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| | CST-2032 administered with CST-107 on cognition in subjects with MCI or mild dementia.<br><br>Approximately 60 subjects will be enrolled in a 2 period, 2-way crossover design following study eligibility confirmation during the screening period.<br><br>During each treatment period, subjects will receive 3 mg CST-107 or matching placebo on Day -1, followed by daily doses of CST-2032 (co-administered with CST-107) or matching placebo on Day 1 through Day 14. Each treatment period will be separated by a washout period of at least 7 days and up to 21 days.<br><br>All subjects will complete clinical, cognitive and pharmacodynamic assessments during each treatment period as indicated in the Schedule of Events.<br><br>PK blood samples will be collected prior to, during and after study medication administration, as indicated in the Schedule of Events. |
| Number of Subjects | Approximately 60 subjects will be enrolled in this study. |
| Number of Sites | Subjects will be enrolled at up to 20 clinical sites globally |

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| Inclusion Criteria | A subject will be considered eligible for enrollment if all of the following are met:<br><br>1. Male or female subjects ≥ 50 and ≤ 85 years of age at time of informed consent.<br>2. Diagnosis of mild cognitive impairment (per National Institute on Aging-Alzheimer's Association core clinical criteria [refer to Section 4.4]) OR mild dementia due to either:<br>a. Parkinson's disease (as defined by the United Kingdom Parkinson's 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 RBD Single-Question Screen (RBD1Q) and without hallucinations [refer to Section 4.4], OR<br>b. Alzheimer's Disease (probable Alzheimer's disease based on National Institute on Aging-Alzheimer's Association core clinical criteria [refer to Section 4.4]).<br>3. If the subject is taking medications, they have been on a stable dose for at least 30 days (90 days for anti-psychotic medications) prior to Day -1, and the dose and regimen must remain unchanged through the End of Study Visit unless required for management of adverse events (AEs).<br>4. Cognitive decline not primarily caused by vascular, traumatic, or medical problems (alternative causes of cognitive decline are ruled out).<br>5. Adequate visual and auditory abilities and motor skills to perform all aspects of the cognitive and functional assessments.<br>6. Has a partner or caregiver who can accompany the subject at specified study visits (if required based on cognitive function).<br>7. MoCA score ≥ 14 and ≤ 26.<br>8. Unless confirmed to be azoospermic (vasectomized or secondary to medical cause), males must agree to use a male condom from Day -1 until the End-of-Study visit when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.<br><br>Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse |

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| | or use a condom during each episode of penile-vaginal penetration until after the End-of-Study Visit.<br><br>9. 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:<br>a. use a highly effective method of birth control (refer to Section 5.6), or<br>b. monogamous relationship with a male partner of confirmed sterility, or<br>c. practice complete abstinence (refer to Section 5.6).<br>10. Females of non-childbearing potential may be enrolled if it is documented that they are postmenopausal (refer to Section 5.6).<br>11. Body weight greater or equal to 50 kg and body mass index (BMI) between 18 and 35 kg/$m^2$, inclusive at Screening.<br>12. Stable medical conditions for 30 days prior to Screening visit (e.g., controlled hypertension, dyslipidemia).<br>13. Willing to follow the protocol requirements and comply with protocol restrictions.<br>14. Capable of providing informed consent and complying with study procedures.<br>15. Able to speak, understand and read English. |

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| Exclusion Criteria | Subjects with any of the following will not be eligible for participation.<br><br>1. Subjects with poorly controlled hypertension despite lifestyle modifications and/or pharmacotherapy.<br>2. Subjects with pulmonary disease, including asthma, or evidence of clinically significant moderate or severe pulmonary symptoms.<br>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.<br>4. Current evidence of epilepsy, focal brain lesion, head injury with loss of consciousness or meeting DSM-V diagnostic criteria for psychotic disorders, such as schizophrenia or bipolar disorder, or have unstable concomitant psychiatric symptomatology (NOTE: Subjects with psychotic disorders may be enrolled if their condition is effectively managed (i.e., must be receiving stable doses of anti-psychotic medication(s) 90 daysprior to randomization and must remain on that dose throughout both treatment periods)<br>5. Evidence of any significant clinical disorder or laboratory finding (e.g., potassium levels below normal range) that renders the participant unsuitable for receiving an investigational drug including clinically significant or unstable hematologic, moderate and severe impairment of hepatic function (as defined by the National Cancer Institute Organ Dysfunction Working Group),cardiovascular, pulmonary, gastrointestinal, endocrine (including thyrotoxicosis, excluding managed hypo- or hyper- thyroidism), immunologic, dermatologic, neurologic, musculoskeletal, metabolic, renal, or other systemic disease or laboratory abnormality.<br>6. Participants with a history of malignant disease within 5 years, including solid tumors and hematologic malignancies (exceptions: [a] basal cell and squamous cell carcinomas of the skin or solid tumors that have been completely excised and are considered cured; [b] low-grade adenocarcinoma of the prostate, which are slow growing, and are unlikely to progress or metastasize during the clinical trial).<br>7. Any current clinically significant medical condition or disease as determined by medical history, physical |

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| | examination, 12-lead electrocardiogram (ECG) and clinical laboratory assessments that, in the view of the Principal Investigator, will interfere with participation in the study or interpretation of results.<br>8. Clinically significant abnormalities of 12-lead ECG (as determined by a central reader), including QTcF > 440 ms, for males and females, and/or HR < 50 beats per minute, or evidence of bundle branch block, as indicated on the Mean ECG Analysis Report during the screening period.<br>9. A calculated creatinine clearance of ≤ 60 mL/min according to the Cockcroft-Gault equation.<br>10. Current use of any prohibited prescription medication, over-the-counter medication, or herbal supplements including green tea products (refer to Section 5.4) during Screening or throughout study, unless approved by both the Investigator and the Sponsor Medical Monitor.<br>11. Prior and/or concurrent 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.<br>12. Prior and/or concurrent 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. Subjects may be on stable doses of serotonin-selective reuptake inhibitor (SSRI) antidepressants but are prohibited to be on serotonin-noradrenaline reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCAs), or any treatment for ADHD including noradrenaline reuptake inhibitors (NRIs), or amphetamines within the last month prior to Screening.<br>13. A history of heart failure, sinus bradycardia, second- or third-degree heart block, hypokalemia, attack of unconsciousness possibly associated with torsades de pointes (TdP) or family history of Long QT Syndrome.<br>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.<br>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.<br>16. Positive screening test for human immunodeficiency virus (HIV), hepatitis C antibody (HCV Ab) or current hepatitis B infection (defined as positive for hepatitis B |

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<tr><td></td><td>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.<br>17. Current infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<br>18. Females who are breastfeeding.<br>19. Any other reason for which the PI considers it is not in the best interest of the participant to undertake the study.</td></tr>
<tr><td>Description of Study Medications</td><td>In this study, subjects will be randomly assigned to one of 2 treatment regimens:<table><tr><th></th><th>Treatment Period 1</th><th>Treatment Period 2</th></tr><tr><td>1</td><td>3 mg CST-2032 + 3 mg CST-107</td><td>Placebo (2032) + placebo (107)</td></tr><tr><td>2</td><td>Placebo (2032) + placebo (107)</td><td>3 mg CST-2032 + 3 mg CST-107</td></tr></table>On Day -1 of each treatment period, CST-107 or matching placebo will be administered after completion of all scheduled study assessments. On all other dosing days, CST-107 or placebo will be co-administered with CST-2032 or placebo.<br><br>The study medications will be provided as oral tablets for CST-2032, CST-107, and corresponding matching placebos. All subjects will be administered the same number of tablets regardless of treatment regimen.<br><br>During Treatment Periods 1 and 2, subjects will receive once daily oral doses of 3 mg CST-2032 or matching placebo and 3 mg CST-107 or matching placebo on Days 1–14.<br><br>Subjects will be given blister cards for CST-2032 or matching placebo and blister cards or bottles for CST-107 or matching placebo containing 10 repeat doses for a 1-week supply at study visits during each treatment period and will be instructed to self-administer daily in the morning.</td></tr>
<tr><td>Study Duration</td><td>The study duration will be approximately 12 weeks, which includes a Screening period of up to 28 days, the treatment/study period of 7 weeks (two 2-week treatment periods separated by a washout period of at least 7 and up to 21 Days), and the End-of-Study Visit of up to 12 Days after the last study drug dose.</td></tr>
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| 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 -2. Subjects who meet eligibility criteria based on screening assessments may be enrolled in the study. |
| Study Procedures (continued) | 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), blood draw for evaluation of genetic variants including but not limited to APOE4, and neurodegeneration biomarkers, creatinine clearance calculation, drug and alcohol breath tests, SARS-CoV-2 test, serum HIV, 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.<br><br>Subjects with a positive drug screen (including alcohol) at Screening will be rechecked and if positive will be excluded from participation in the study.<br><br>During the Screening Visit, the following disease and cognitive assessments and measures will be completed as required to evaluate eligibility: RBD1Q (administered to all subjects but used for eligibility only in PD subjects), and MoCA. In addition, the modified Hoehn and Yahr Scale (MHYS) will be evaluated in subjects with PD for purposes of patient phenotyping. ADCS-CGIC will also be completed.<br><br>Once all screening visit procedures are completed and the subject meets all eligibility criteria, the subject will return to the site to be trained on and practice the CANTAB. Subjects will be randomly assigned to one of the two treatment regimens on Day -1.<br><br>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.<br><br>Permitted and prohibited medications are listed in Section 5.4. |

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| Sample Size Justification | The sample size estimation is based on a crossover design with the assumption that carryover effects are equal.<br><br>A total of approximately 60 subjects is planned. The sample size is based on practical considerations and is typical of studies whose objectives are to evaluate the safety and cognitive effects of a therapeutic intervention. The study is only powered for very large effect sizes. Lack of statistical significance will not be indicative of lack of a potentially meaningful treatment effect. |
| Statistical Analysis | Details of statistical parameters and methods to be used will be described in a Statistical Analysis Plan (SAP).<br><br>Analysis of effects on baseline-deficit cognitive tasks will be based on an analysis of variance of the change from baseline, where baseline is the average of the two latest pre-treatment assessments in each treatment period with each patient used as their own control. This analysis will be described in more detail in the SAP.<br><br>Continuous data will display number of subjects, means, standard deviations, median, minimum, and maximum. Categorical data will display frequency counts and percentages. Unless specified otherwise, confidence intervals will be displayed at the two-sided 95% confidence level.<br><br>Disposition and baseline data will be summarized by disease criteria (MCI and mild dementia combined and separately), treatment sequence and overall. Summaries of safety, pharmacodynamics and PK will be presented by disease criteria, treatment (active versus placebo), drug (CST-2032/ CST-107) and overall. A limited subset of summaries may be presented by treatment sequence and/or period and overall.<br><br>For primary and secondary endpoints, observed values and changes from baseline, as well as the difference between change from baseline within subject, will be summarized. For continuous endpoints, the difference is defined as change from baseline on drug minus change from baseline on 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. |

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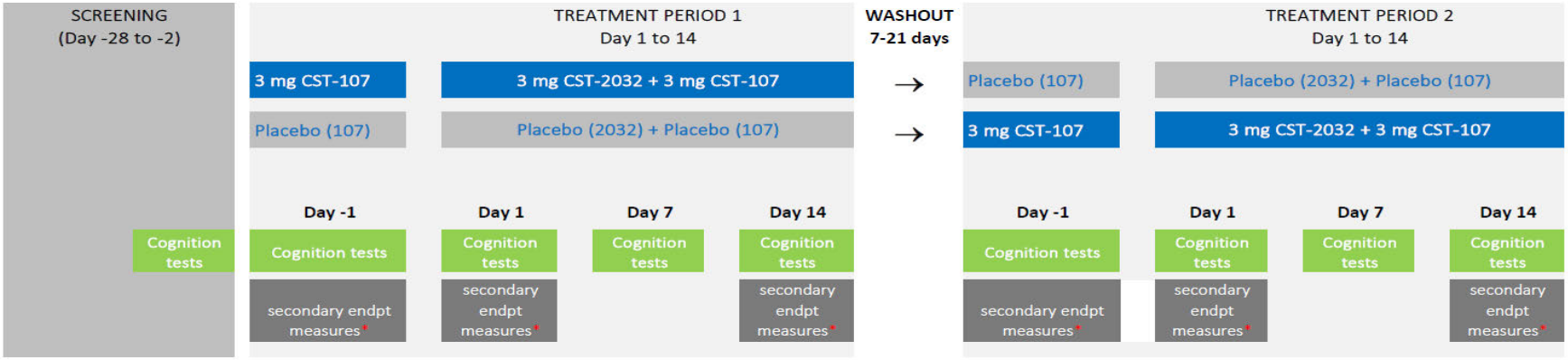
| Statistical Analysis (continued) | All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class and preferred term.<br><br>Subgroup analyses may be conducted after study completion to evaluate whether effects of treatment are influenced by baseline disease characteristics including but not limited to disease activity as determined from relevant disease scales at screening, neurodegenerative biomarkers in plasma, and genetic variants including but not limited to APOE4, LRRK2, and GBA. All data will be listed. |

# STUDY SCHEMA




Cognition tests to include (CANTAB), phonological verbal fluency test (pVFT), digit symbol substitution test (DSST).

*Secondary endpoint measures include facial expression recognition task (FERT); Geriatric Depression Scale – 30 questions (GDS-30); Conners Adult Attention Deficit Hyperactivity Disorder Scale (ADHD) Rating Scale, short form, self-report (CAARS); Starkstein Apathy scale short form (SAS-6); and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). ADCS-CGIC is not done on Day -1 or Day 1.

## SCHEDULE OF EVENTS

| | Screening | Treatment Periods 1 & 2[1] | | | | End of Study |
|---|---|---|---|---|---|---|
| | **Days -28 to -2** | **Day -1** | **Day 1** | **Day 7±1[2]** | **Day 14±1 or Early Withdrawal[2,3]** | **7-12 Days after Last Dose of Study Drug or EW Visit[2]** |
| Outpatient visit | X | X | X | X | X | X |
| Informed consent | X | | | | | |
| Randomization | | X | | | | |
| Assess Inclusion/Exclusion criteria | X | X[21] | | | | |
| Demographics | X | | | | | |
| Medical history | X | | | | | |
| Height, weight, BMI calculation | X | | | | | |
| Vital signs[5] | X | X | X | X | X[3] | X |
| ECG[6] | X | X | X | X | X[3] | X |
| Physical exam[7] | X | | | | | X |
| Safety labs[8] | X | | X[19] | X[20] | X[3, 20] | X |
| Urine drug screen | X | | | | | |
| Alcohol breath test | X | X | | | | |
| HIV and Hepatitis serologies | X | | | | | |
| Serum FSH[9] | X | | | | | |
| β-hCG pregnancy test[9] | X | | | | | |
| Serum or urine pregnancy test[9] | | X | | | X[3] | X |
| SARS-CoV-2 assessment[10] | X | | | | | |
| Genetic variants including but not limited to APOE4, LRRK2, GBA (optional and where applicable) | X | | | | | |
| Neurodegeneration biomarkers | X | | | | X | |
| PK sample[11] | | | | X | | |
| RBD1Q, MHYS[12] | X | | | | | |
| MoCA[12] | X | | | | X | |

| | Screening | Treatment Periods 1 & 2[1] | | | | End of Study |
|---|---|---|---|---|---|---|
| | **Days -28 to -2** | **Day -1** | **Day 1** | **Day 7±1[2]** | **Day 14±1 or Early Withdrawal[2,3]** | **7-12 Days after Last Dose of Study Drug or EW Visit[2]** |
| DSST[12] | X | X | X | X | X | |
| FERT[13] | | X | X | | X | |
| CANTAB, pVFT[14] | X | X | X | X | X | |
| Color Trails Test[4] | | X | | X | X | |
| SAS-6, CAARS, GDS-30[15] | | X | X | | X | |
| C-SSRS[12] | X | X[16] | | X | X[3] | X |
| ADCS-CGIC[12,17] | X | | | | X | |
| Study drug administration[18] | | → | → | → | → | |
| Provide subject dosing instructions and dispense dosing diary | | | X | | | |
| Review dosing diary | | | | X | X[3] | |
| Assessment of AEs | | X | X | X | X[3] | X |
| Concomitant medications | X | X | X | X | X[3] | X |

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

Disease assessments should be conducted after the subjects have been provided with a light meal or snack without caffeinated beverages or high sugar content in the following order if possible: **FERT before pVFT, then DSST and then CANTAB and Color Trails Test. ADCS-CGIC should be conducted last.**

1 Washout period between Treatment Periods 1 & 2 is 7 to 21 days. The washout period may be extended with prior approval by the CuraSen Medical Monitor,

2 Visit to be conducted in the clinic, or other off-site location or at the subject's home according to site preference and capabilities. In addition, 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. The End of Study visit is to occur 7-12 days after last dose of study drug.

3 Subjects who withdraw from the study prior to completion of dosing should complete these Day 14 safety assessments at the time of early withdrawal (EW).

4 The Color Trails Test should be completed after the CANTAB assessments (select sites only).

5 Vital signs to include orthostatic changes in BP and HR, respiratory rate, and oral/tympanic temperature. For assessments of orthostatic changes, BP and HR are obtained: a) after rest in a supine position for at least 5 minutes, and b) 1 minute after standing. Vital signs will be obtained at every study visit as follows:

- Screening
- Day -1 prior to administration of CST-107 or matching placebo in each treatment period
- Days 1, 7, and 14 of each treatment period:
  - Within 30 minutes prior to dosing of study drug (CST-2032+CST-107 or matching placebos),
  - Approximately 4 hours (± 30 minutes) after administration of study drug,

- End-of-Study Visit.

6 ECGs to be obtained in triplicate (separated by approximately 1 minute) after subject is supine for 5 minutes at the following timepoints:
- Screening
- 3 sets of triplicate ECG measures (i.e., 9 ECGs) on Day -1 prior to administration of CST-107 or matching placebo in each treatment period to thoroughly establish a baseline; the time between each set of 3 ECGs should be ≤5 minutes.
- On Day 1 of each treatment period:
  - Within 30 minutes prior to dosing of study drug,
  - Approximately 1 hour after administration of study drug,
  - Approximately 2 hours after administration of study drug,
  - Approximately 4 hours after administration of study drug,
- Days 7 and 14 of each treatment period:
  - Within 30 minutes prior to dosing study drug,
  - Approximately 1 hour after administration of study drug,
  - Approximately 2 hours after administration of study drug,
  - Approximately 4 hours after administration of study drug,
- End-of-Study Visit,
- All ECGs will be evaluated by a central ECG reader.

7 A complete physical examination (PE) (excluding genital, rectal and breast exams) is required at Screening; the End-of-Study PE will be symptom-driven based on subject complaints.

8 Safety labs to include hematology, chemistries, and urinalysis. Fasting safety labs to be conducted at Screening and EOS.

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/EW and at the End-of-Study visit.

10 Subjects to be tested for current SARS-CoV-2 infection at Screening. Additional evaluations of SARS-CoV-2 infection on other visit days should be according to site standard operating procedures.

11 PK samples to be collected on Day 7 of each treatment period:
- within 15 minutes prior to dosing study drug,
- 0.5+0.25 hour after administration of study drug,
- 1+0.5 hour after administration of study drug,
- 2+0.5 hour after administration of study drug, and
- 4+0.5 hours after administration of study drug.

12 The DSST, C-SSRS, pVFT, ADCS-CGIC, MoCA and MHYS (if done within the past 3 months, MHYS does not have to be repeated) are to be administered by a qualified clinical rater. The MHYS will be recorded but not be used as an enrollment criterion.

13 Facial Recognition Task (FERT) will be conducted at the following timepoints in each treatment period:
- Day -1: Prior to administration of CST-107 or matching placebo,
- Day 1: at least 2 hours after dosing of study drug,
- Day 14: at least 2 hours after dosing of study drug.

14 First administration of CANTAB is to familiarize the subject with the tests and equipment. The CANTAB and phonological verbal fluency (pVFT) test and DSST should be administered after completion of FERT at the following timepoints in each treatment period:
- CANTAB only to be administered twice, at least 1 hour apart during the final week (Day -8 to Day -2) before Treatment Period 1 to familiarize subjects with the CANTAB
- CANTAB, pVFT and DSST to be administered on Day -1 prior to administration of CST-107 or matching placebo. These tests are to be administered in each treatment period at approximately the same time of day (±1 hour) and under approximately the same food status as planned for the tests on Days 1, 7, and 14.
- CANTAB, pVFT and DSST to be administered on Days 1, 7 and 14 of each treatment period:
    - 3±0.5 hours after administration of study drug. Tests should be conducted at approximately the same time of day (±1 hour) and under the same food status on Days -1, 1, 7 and 14.

15 SAS-6, CAARS, and GDS-30 are per subject self-report. These tests will be administered at the following timepoints in each treatment period:
- Day -1: Prior to administration of CST-107 or matching placebo
- Day 1: at least 2 hours after dosing of study drug,
- Day 14: at least 2 hours after dosing of study drug.

16 C-SSRS not completed on Day -1 during Treatment Period 1.

17 The ADCS-CGIC will be administered at the following timepoints in each treatment period:
- Screening
- Day 14: at least 3 hours after dosing of study drug.

18 On Day -1 only, CST-107 or matching placebo is to be administered upon completion of all scheduled study assessments. On all other dosing days, study drugs (CST-2032+CST-107 or matching placebos) are to be co-administered. On Days -1, 1, 7 and 14 the study drugs are administered in the clinic.

19 On Day 1, safety labs will be collected pre-dose and approximately 4 hours post-dose (chemistry only at 4 hours post-dose).

20 On Days 7 and 14, safety labs will be collected approximately 4 hours post-dose.

21 Inclusion/exclusion criteria not re-assessed on Day -1 of Treatment Period 2.

## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADCS-CGIC | Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change |
| APOE4 | Apolipoprotein E4 |
| β-AR | Beta-adrenoceptor |
| β-hCG | Beta human chorionic gonadotropin |
| AD | Alzheimer's Disease |
| AE | Adverse event |
| ADHD | Attention Deficit/Hyperactivity Disorder |
| AS | Apathy scale |
| ASL MRI | Arterial spin labelling magnetic resonance imaging |
| 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 |
| CAARS | Connors Adult Attention Deficit/Hyperactivity Disorder Scale – short form, self-report |
| cAMP | cyclic adenosine monophosphate |
| CANTAB | Cambridge Neuropsychological Test Automated Battery |
| CBF | Cerebral blood flow |
| cGCP | Current Good Clinical Practice |
| CLIN-002 | CST103/CST107/CST109-CLIN-002 |
| CLIN-007 | CST2032-CLIN-007 |
| Cmax | Maximum concentration |
| CNR | Contrast-to-noise ratio |
| CNS | Central nervous system |
| CRF | Case report form |
| CST-107 | Nadolol |
| DSMB | Data and Safety Monitoring Board |
| DSM-V | Diagnostic and Statistical Manual of Mental Disorders 5 |
| DSST | Digital Symbol Substitution Test |
| eCRF | Electronic case report form |
| EC | Ethics committee |

| Abbreviation | Definition |
|---|---|
| ECG | Electrocardiogram |
| EW | Early withdrawal |
| FERT | Facial Expression Recognition Task |
| FSH | Follicle-stimulating hormone |
| GBA | Glucocerebrosidase (GCase) protein |
| GDS-30 | Geriatric Depression Scale – 30 questions |
| HR | Heart rate |
| HbsAb | Hepatitis B surface antibody |
| HbsAg | Hepatitis B surface antigen |
| HCV Ab | Hepatitis C antibody |
| HIV | Human Immunodeficiency Virus |
| IB | Investigator Brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| ICSD-3 | International Classification of Sleep Disorders, Third Edition |
| IRB | Institutional review board |
| ISI | Interstimulus interval |
| ITT | Intent to treat |
| IV | Intravenous |
| IWRS | Interactive Web Response System |
| LC | Locus coeruleus |
| LRRK2 | Leucine rich repeat kinase 2 |
| MAOI | Monoamine oxidase inhibitor |
| MCI | Mild cognitive impairment |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHYS | Modified Hoehn & Yahr Scale |
| MoCA | Montreal Cognitive Assessment |
| PAL | Paired Associates Learning |
| PD | Parkinson's Disease |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PO | By mouth/oral administration |
| pVFT | Phonological verbal fluency test |
| QD | Once daily |
| QTcF | QT interval corrected for changes in heart rate using the Fridericia equation |
| RBD | REM Sleep Behavior Disorder |

| Abbreviation | Definition |
|---|---|
| RBD1Q | REM sleep behavior disorder (RBD) Single-Question Screen |
| RTI | Reaction Time Index |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SAS-6 | Starkstein apathy scale – short form (6 questions) |
| SIR | standard image recognition |
| SNRI | serotonin/noradrenaline reuptake inhibitors |
| SOP | Standard operating procedure |
| SSRI | Serotonin selective reuptake inhibitors |
| SST | Stop signal test |
| $t_{1/2}$ | Time to maximum observed drug concentration |
| TEAE | Treatment emergent adverse event |
| $t_{max}$ | Time of maximum concentration |
| VRM | Verbal Recognition Memory |
| WAIS-IV | Wechsler Adult Intelligence Scale, Fourth Edition |

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# 1. INTRODUCTION

The noradrenergic system, and β-Ars in particular, are promising therapeutic targets for cognitive diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). 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). Xamoterol additionally attenuates three major pathological hallmarks of AD: beta-amyloid burden, tau pathology, and neuroinflammation (Ardestani 2017). Collectively, these data suggest that targeting β-AR may have the unique potential to provide comprehensive therapeutic benefits for the treatment of AD.

Several epidemiologic studies additionally suggest that treatment with β-AR agonists may be more protective against development of PD (Aaseth 2018, Clark 2018, Gronich2018, Magistrelli 2020, Mittal 2017, Searles 2018). Additional data also suggest that the effect of β-AR agonists may generalize to other cognitive disorders such as mild cognitive impairment (MCI) and AD (Chalermpalanupap 2013, Coutellier 2014).

The locus coeruleus (LC) is a small nucleus located in the pons and is the primary source of noradrenaline (norepinephrine) in the forebrain (Brunnström 2011). LC axons project to multiple cortical and subcortical regions that underlie memory, attention, and emotional processing, including the hippocampus, frontoparietal cortex, and amygdala (Berridge 2003). Through its binding to both α and β-adrenoceptors, noradrenaline plays a key role in a variety of essential central nervous system (CNS) functions such as learning and memory, arousal, attention, and cognition, and plays an important role in maintaining brain homeostasis by regulating neuroimmune responses.

Neuroanatomical studies have identified the LC as one of the earliest sites in the brain affected in cognitive diseases including AD and PD (Braak 2011, Braak 2017). Consistent with this, profound degeneration of noradrenergic neurons is an established early finding of AD, and deficits in noradrenergic neurotransmission have been described both in human patients and mouse AD models (Adolfsson 1979, Bondareff 1987, Grudzien 2007, Hoogendijk 1999, Iversen 1983, Kalaria 1989, Tejani-Butt 1993). Importantly, the dysfunction of the noradrenergic system is tightly linked to both cognitive symptoms of AD and underlying disease progression at many levels such as neuroinflammation (Bondareff 1987, Heneka 2002, Jardanhazi-Kurutz 2010).

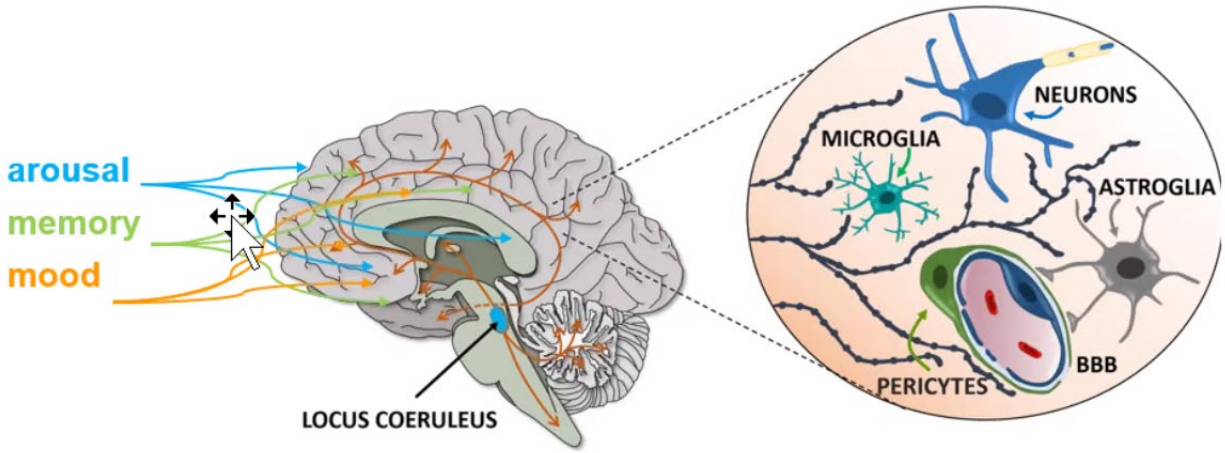
Progressive and extensive degeneration of the LC is evident early in patients with AD or PD (Kalaria 1989, Vermeiren 2017), giving rise to a hypothesis that the LC is a "ground zero" for the pathology underlying the development of cognitive impairment, and nonmotor symptoms and can further complicate the lives of PD patients (Nahimi 2018).

The role of $\beta_2$-AR extends beyond neurotransmission (Figure 1). Expression of $\beta_2$-Ars is observed across multiple cell types including neurons, nerve fibers, microglia, astrocytes, oligodendrocytes and blood vessels (Gao 2016). This diversity in cellular localization gives rise to a corresponding diversity of function. For example, $\beta_2$-Ars have been shown to promote glycogenolysis and lactate release from astrocytes which contribute to memory consolidation and long-term potentiation of synaptic strength in hippocampal neurons (Sorg 1991, Gao 2016, Suzuki 2011). Hypometabolism is an early feature of neurodegeneration in Alzheimer's and Parkinson's diseases (Cunnane 2020, Sonninen 2020),

and it is thought that glial metabolic support of neurons is neuroprotective in the context of disease (Cai 2019, Cunnane 2020). A pro-metabolic role of β-AR stimulation has been variously demonstrated: adrenergic stimulation alters the cellular metabolism of astrocytes (Dienel 2016), increased cellular cyclic adenosine monophosphate (cAMP), the second messenger produced by β-AR signaling, is associated with enhanced glycolysis (Vardjan 2018), and stimulation of β-Ars increases cellular glucose uptake (Catus 2011) and glycogenolysis (Hertz 2010).

Finally, it is hypothesized that normal noradrenergic signaling from the LC may protect against inflammation, and that neuroinflammation in degenerative diseases may result from the progressive damage to the LC. This is supported by nonclinical observations that neurotoxin-mediated lesioning of the LC induces neuroinflammation (Pugh 2007), while stimulation of $\beta_2$-AR expressed on microglia and astrocytes appears to be anti-inflammatory effect (reviewed by O'Donnell 2012).

**Figure 1 Heterocellular Role of Noradrenaline Projections from the Locus Coeruleus in Cognition**




Source: Giorgi 2019

Clinical and nonclinical studies conducted by CuraSen provide supportive evidence that CST-2032 mediates the diverse cellular functions described above. Firstly, in vitro studies confirm that CST-2032 stimulates $\beta_2$ARs endogenously expressed on neuronal cells, astrocytes, microglia, pericytes, cerebral microvascular endothelial cells and human brain vascular smooth muscle cells to produce cAMP with similar potencies. Furthermore, nonclinical studies with CST-2032 demonstrate its effects on aspects of the neuronal, metabolic, and inflammatory signaling as described above. Specifically, CST-2032 improves performance a rat model of attention and impulsivity, in the five-choice-serial reaction test. Anti-inflammatory effects of CST-2032 were demonstrated in mice in the form of a reduction in lipopolysaccharide-mediated increases in pro-inflammatory mediators including TNFα and IL-6 in plasma and brain, and a potentiation of the anti-inflammatory IL-10. Finally, in an astrocytoma cell line that endogenously expresses $\beta_2$-AR, CST-2032 shifted cellular metabolism away from mitochondrial oxidative phosphorylation and towards glycolysis, increasing the total rate of cellular ATP production.

In humans, increases in cerebral perfusion, measured as cerebral blood flow (CBF) by arterial spin labelling magnetic resonance imaging (ASL MRI) in brain regions relevant to cognition, attention and arousal, the thalamus, hippocampus and amygdala, were observed following administration of a $\beta_2$-AR agonist, clenbuterol, in a clinical study sponsored by CuraSen Therapeutics, Inc (CST103/CST107/CST-109-CLIN-002). Similarly, improvements in performance in CANTAB domains were observed following administration of CST-2032 in healthy volunteers and subjects with MCI in the phase 1 study, CST2032-CLIN-007 (Figure 2). Increases in cerebral perfusion are expected under conditions of increased neuronal activity. This phenomenon of neurovascular coupling arises from integrated responses from multiple cell types, many of which are known to express $\beta_2$ receptors, including neurons, cerebral blood vessels, microglia, oligodendrocytes, and astrocytes (Giorgi 2020).

Taken together, LC neuronal loss and the resulting widespread consequence of noradrenergic deficiency in neuronal transmission, metabolism and inflammation are believed to underpin cognitive impairment in neurodegenerative diseases. We hypothesize that this noradrenergic deficiency may be restored through exogenous adrenergic stimulation using the $\beta_2$-AR agonist, CST-2032.

The CLIN-015 study seeks to evaluate the safety and efficacy of CST-2032 when dosed with CST-107 in subjects with mild cognitive impairment or mild dementia where the disruptions in noradrenergic stimulation, metabolism and inflammation described above have been reported. In addition, secondary analyses will evaluate the effects of treatment on cognition, mood and attention, and the pharmacokinetic (PK) properties of CST-2032 when administered with CST-107. As exploratory objectives, this study may additionally evaluate whether baseline disease characteristics such as disease activity, neurodegenerative biomarkers in the plasma and Apolipoprotein E4 variant influence the effects of treatment.

Use of an agonist for stimulating β2-ARs within the CNS represents a novel approach in any neuropsychiatric indication, largely due to concerns about how such an agonist action in the brain could be selectively precipitated, while sparing likelihood of excess stimulation of the same target in the periphery. Excess stimulation of β2-ARs in the periphery has the potential to cause AEs of cardiovascular and metabolic origin. Accordingly, the concept of co-administering a β-AR antagonist ('beta blocker') that has both preference for the β2-AR subtype, and minimal CNS penetration, was developed. Examination of the large number of widely used β-AR antagonists revealed one established antagonist, nadolol (CST-107), as uniquely fitting this need, assuming that an optimal dose level could be identified that preferentially blocked only β2 AR function in the peripheral tissues, with low access to desired CNS targets. CuraSen's data from the CLIN-007 study identified the doses of nadolol that effectively minimize the peripheral effects of CST-2032. These doses are less than 10% of the lowest dose for nadolol approved for treatment of angina or hypertension (40 mg) and are likely to preferentially inhibit β2-ARs. The CLIN-007 study additionally confirmed that only 2 to 3 % of the plasma concentration of nadolol is detected in the cerebrospinal fluid, supporting the use of this combination dosing therapeutic strategy, that will eventually require formulation of a fixed dose combination drug product.

## 1.1. Rationale for Dose Selection

### 1.1.1. Rationale for CST-2032 Dose Selection

$\beta_2$-AR agonists have been used for decades as bronchodilators for treatment of bronchospasm in patients with obstructive airway disease. As such, peripherally mediated the pharmacologic effects and risks associated with this class of agent are well known, including increased heart rate, hyperglycemia, hypokalemia, muscle twitch and tremor, palpitations, and peripheral vasodilatation (see Ventolin [albuterol] HFA label).

It is understood that these peripherally mediated effects may not be ideal properties for a medication for use in long-term patient studies. Accordingly, the use of doses of CST-2032 that might produce significant changes in these peripheral measures can only be safely contemplated if simultaneously co-administered with a dose of an antagonist for these $\beta_2$-AR mediated effects, but one that fails to significantly cross the blood brain barrier, thus leaving the cerebral $\beta_2$-AR population sensitive to a CNS penetrant agonist such as CST-2032. The dose levels of CST-2032 proposed for this study therefore have been selected to be administered along with such peripherally restricted antagonist, thus attenuating any of the clinical effects listed above.

At the doses of 3 mg of CST-2032 and 3 mg of nadolol planned for the CLIN-015 study, there were no clinically significant increases in heart rate, prolongation of QTcF, or decreases in potassium levels observed in the CLIN-007 study. Furthermore, there were no instances of tremor, palpitations, dizziness, or tachycardia. Therefore, it is expected that the combination of 3 mg CST-2032 with 3 mg of nadolol will be safe and well tolerated.

In rats and dogs, the NOAELs observed with CST-2032 were determined to be 110 and 15 mg/kg/day, respectively, the highest doses tested in the GLP 28-day repeated-dose toxicity studies. Based on the CLIN-007 study, the plasma exposures observed at the dose of 3 mg CST-2032 are 588- and 193-fold below the $AUC_{0\text{-}24}$ at the no-observed adverse event levels in 28-day toxicity studies in rat and dog (Investigator Brochure [IB]).

The 3 mg dose of CST-2032 to be administered in CLIN-015 has previously been administered as single and once-daily doses for 7 days in the CLIN-007 study. Specifically, in the CLIN-007 study, CST-2032 (0.3 – 12 mg) was evaluated in healthy volunteers as monotherapy (0.3–- 6 mg, as an oral solution) or with co-administered or pre-administered CST-107 (nadolol, 1 – 40 mg, as oral capsules, or tablets). In addition, the effects on safety, PK and effects on cognition using the using measures from the CANTAB and cerebral perfusion (by ASL MRI) were evaluated in patients with MCI or PD following a single dose of 3 mg CST-2032, administered 2 hours after a single dose of 3 mg CST-107 (nadolol).

The most common AEs with CST-2032 monotherapy (other than skin reactions to ECG electrodes) were increases in heart rate, tremor, palpitations, headache, dizziness and hypokalemia as well as the observed increases in QTc and glucose and decreases in potassium and are consistent with the $\beta_2$-AR agonist drug class. Heart rate generally increased with dose when 1 – 6 mg CST-2032 was administered as monotherapy, with concomitant decreases in plasma potassium concentration. These responses, which are consistent with known effects of $\beta_2$ AR agonists, were generally transient with maximal effects at approximately 2 to 3 hours after dosing, at the approximate plasma $T_{max}$ of

CST-2032, and returned to pre-dose levels within 1 day of dosing. These effects were observed at CST-2032 exposures similar to its in vitro $\beta_2$-AR potency, and were minimized by low doses of nadolol at plasma exposures at or above the affinity constant for nadolol at $\beta_2$-AR.

Following CST-2032 monotherapy, increases in QTcF were observed, especially at time points at which decreases in potassium and increases in heart rate were most marked. The time-course of the QTc effects, generally followed the same profile as the changes in potassium and heart rate: with largest changes within the first 4 hours after administration of CST-2032 and returned to pre-dose levels within 1 day of dosing.

Breakthrough increases in QTcF were also observed when sub-optimal doses of nadolol (1 mg) were used in combination with CST-2032. Effects of CST-2032 on potassium, heart rate, and QTcF were attenuated by co-administration and pre-administration of 1 mg of the peripherally restricted $\beta_2$-AR preferring antagonist, nadolol, and essentially eliminated by pre-administration of > 1 mg nadolol. No instances of QTcF > 450 ms or $\Delta$QTcF > 30 ms were observed in subjects who received ≥3 mg nadolol with CST-2032. The observed potassium concentrations range from 3.8 to 4.3 mml/L in subjects who received 1, 3, or 10 mg CST-2032 with 3 mg nadolol.

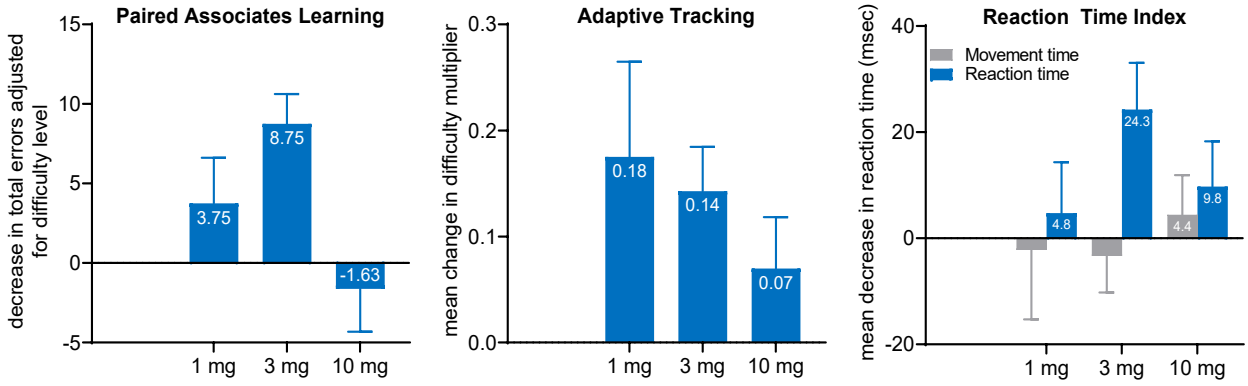
The observed increases in QTcF with CST-2032 monotherapy are suspected to be the result of concomitant decreases in potassium that were seen in some individuals. Additionally, it is possible that contribution to these increases arose from inadequate correction for associated heart rate increases using the Fridericia method. The observed increases in QTcF, whether they may be attributed to decreases in potassium or failure to adequately correct for increases in heart rate, are blocked by low doses of nadolol, and thus appear to derive from the primary pharmacological action on $\beta_2$-ARs, consistent with established class effect.

Nonclinical studies with CST-2032 are consistent with a low potential for delayed ventricular polarization. Specifically, from in vitro assessments at cardiac ion channels, a greater than 3000-fold margin was observed between the $C_{max}$ following administration of 3 mg CST-2032 to humans and the potency at the hERG potassium channel. Similarly, a greater than 300-fold margin between was observed between the $C_{max}$ and other cardiac ion channels (Nav1.5, Nav1.5 (late), KCNQ1/mink, Kv4.3/kChIP2, Kir2.1, Cav1.2).

While the data strongly suggest that the apparent QTcF prolongation seen with monotherapy is due to decreases in potassium or failure to adequately correct for increases in heart rate, in an overabundance of caution this study will exclude subjects who have a QTcF > 440 ms or have risk factors for TdP from participating.

Preliminary observations from the CLIN-007 study found that a single dose of 3 mg CST-2032 was associated with improvements in cognition (by CANTAB, Figure 2) and cerebral perfusion (by ASL MRI, see IB) in healthy volunteers and patients with MCI. Safety and tolerability assessments of CST-2032 administered at a dose of 3 mg with CST-107 has shown a good safety and tolerability profile. Based on all data, a dose of 3 mg of CST-2032 has been selected for this study and will be administered once-daily with a dose of 3 mg CST-107.

**Figure 2. Effects of 1, 3, and 10mg CST-2032 Combined with 3 mg CST-107 on CANTAB Measures of Cognition in Healthy Volunteers Aged 50–75 (N=8)**




Source: preliminary CANTAB data from CST2032-CLIN-007, Cohort D2. Scales are configured to show improvements as increases from zero. CST-107 dose = 3 mg.

### 1.1.2. Rationale for CST-107 Dose Selection

CST-107 (nadolol) is included in this study to attenuate the peripheral effects most commonly caused by CST-2032 and other $\beta_2$-AR agonists. In the phase 1 clinical trial with CST-2032, a range of doses of CST-107 was evaluated to determine the minimum dose at which the observed peripheral $\beta_2$-AR agonist clinical signs (including increased heart rate, palpitations, tremors, decreases in potassium and increases in blood glucose) were attenuated or eliminated. While the latter effects were substantially mitigated following 1 mg CST-107, more robust inhibition of the peripheral effects was observed with 3 mg CST-107. A dose level of 3 mg CST-107 (nadolol) is in marked contrast to the usual initial dose for hypertension which is 40 mg CST-107 tablets once daily. The usual maintenance dose for nadolol is 40 or 80 mg administered once daily and doses up to 240 or 320 mg administered once daily may be needed.

Separate assessments in the CLIN-007 study show that only 2-3% of the plasma concentration of CST-107 is detected in cerebrospinal fluid of healthy volunteers. Furthermore, effects of CST-2032 on measures of cognition using CANTAB and cerebral perfusion were observed in the presence of CST-107.

Taken together, these data support the use of CST-107 as a peripherally restricted $\beta_2$-AR antagonist to mitigate peripheral effects of CST-2032, e.g., on heart rate, while preserving potential central effects on cerebral perfusion, cerebral metabolism, pupillary light reflex, and cognition.

Based on the above experience, after completion of all scheduled assessments and baseline measures on Day -1, an initial dose of 3 mg CST-107 or matching placebo will be administered on Day -1 of each treatment period to provide systemic CST-107 exposure prior to the $T_{max}$ of CST-2032 on Day 1. On subsequent dosing days (Days 1 through 14) in

Treatment periods 1 and 2, 3 mg CST-107 will be co-administered with 3mg CST-2032 as, after the first dose, trough concentrations of CST-107 are predicted to be sufficient to attenuate peripheral effects of CST-2032.

## 1.2. 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 evaluate the safety and tolerability of CST-2032 when combined with CST-107.

The secondary objectives of this study will evaluate the effects of CST-2032 when combined with CST-107 versus placebo on the following measures:

- Cognition.
- Mood.
- Attention Deficit.
- Apathy.
- Overall clinical improvement.
- PK.

The exploratory objectives are:

- To evaluate whether baseline disease characteristics impact response to treatment.
- To characterize the effects of treatment 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.

## 2.2. Primary Endpoint

The primary endpoint is safety and tolerability of CST-2032 administered with CST-107 including adverse event rates (AEs), serious adverse event rates (SAEs), study discontinuation rates, electrocardiograms (ECGs), vital signs, laboratory safety observations.

## 2.3. Secondary Endpoints

The secondary endpoints will compare the effect of CST-2032 administered with CST-107 versus placebo on the following:

- Cognitive tasks in Cambridge Neuropsychological Test Automated Battery (CANTAB) and other cognitive measures:
    - Reaction Time (RTI)–- attention
    - Verbal Recognition Memory (VRM) – episodic memory (verbal stimuli)
    - Adaptive Tracking Task (ATT) – visuospatial with strong attentional demand
    - Paired Associates Learning (PAL) – episodic memory (visual stimuli)
    - Delayed Verbal Recall–- episodic memory (verbal stimuli)
    - Stop Signal Task (SST) – response inhibition (impulsivity), an aspect of executive function
    - Phonological verbal fluency (pVFT)
    - Digit symbol substitution test (DSST)
    - Color Trails Test (select sites only)
- Facial expression recognition task (FERT)
- Geriatric Depression Scale – 30 questions (GDS-30)
- Conners Adult Attention Deficit Hyperactivity Disorder Scale (ADHD) Rating Scale, short form, self-report (CAARS)
- Starkstein Apathy scale short form (SAS-6)
- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)
- Suicidal ideation using the Columbia Suicide Severity Rating Scale (C-SSRS).
- Plasma pharmacokinetics (PK) parameters of CST-2032 and CST-107 (including $C_{max}$, $t_{max}$, $AUC_t$, $t_{1/2}$).

## 2.4. Exploratory Endpoints

The following exploratory endpoints may be undertaken to evaluate:

- 
- Subgroup and/or correlation analyses of effects of treatment on baseline disease characteristics including but not limited to disease activity as determined from relevant disease scales at screening, neurodegenerative biomarkers in plasma, and genetic variants including but not limited to APOE4, LRRK2, and GBA (optional and where applicable).

- 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 treatment may be evaluated.
- Change in average z-score for baseline-deficit cognitive tasks identified for each subject from Cognitive tasks in the Cambridge Neuropsychological Test Automated Battery (CANTAB) and other cognitive measures.

# 3. STUDY DESIGN

## 3.1. Clinical Trial Design

This is a Phase 2a, randomized, placebo-controlled, double-blind, crossover study to evaluate the safety, tolerability and effects of CST-2032 administered with CST-107 on cognition in subjects with MCI or mild dementia.

Approximately 60 subjects will be enrolled in a 2 period, 2-way crossover design following study eligibility confirmation during the screening period. Subjects will be randomly assigned to receive once daily doses of (a) 3 mg CST-2032 with 3 mg CST-107 or (b) both matching placebos in a randomized sequence (see Study Schema).

During each treatment period, subjects will receive 3 mg CST-107 or matching placebo on Day -1, followed by daily doses of CST-2032 (co-administered with CST-107) or matching placebo on Day 1 through Day 14. Each treatment period will be separated by a washout period of at least 7 days and up to 21 days. The washout period may be extended with prior approval by the CuraSen Medical Monitor.

All subjects will complete clinical, cognitive 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.

## 3.2. Criteria for Termination of Study Medication

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

- Subject experiences a serious adverse event (SAE) that is deemed by the investigator to be related to study medication
- Medical or ethical reasons affecting continued participation in 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.

## 3.3. Criteria for Suspension/Termination of Trial

Administration of CST-2032 and CST-107 will be stopped if either of the following occurs:

- Two serious adverse events (SAEs) within the same system organ class (SOC) considered to be related to study drug; or
- Three severe or clinically significant adverse events (AEs) considered to be related to study drug.

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.

## 3.4. Data and Safety Monitoring Board (DSMB)

A DSMB will be established to assess participant safety at predetermined intervals (including an interim analysis – see Section 8.3.1) during the study as needed. Further details will be provided in the DSMB Charter.

# 4. SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1. Study Participation

Approximately 60 subjects with MCI or mild dementia will be randomized in this study.

All subjects must participate in the informed consent process and sign and date the informed consent before any study-related procedures are performed.

## 4.2. Inclusion Criteria

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

1. Male or female subjects ≥ 50 and ≤ 85 years of age at time of informed consent.
2. Diagnosis of mild cognitive impairment (per National Institute on Aging-Alzheimer's Association core clinical criteria [refer to Section 4.4]) OR mild dementia due to either:
    a. Parkinson's disease (as defined by the United Kingdom Parkinson's 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 for the purposes of this inclusion criteria) and positive response to the

RBD Single-Question Screen (RBD1Q) and without hallucinations [refer to Section 4.4],], OR

b. Alzheimer's Disease (probable Alzheimer's disease based on National Institute on Aging-Alzheimer's Association core clinical criteria [refer to Section 4.4]).

3. If the subject is taking medications, they have been on a stable dose and regimen for at least 30 days (90 days for anti-psychotic medications) prior to Day -1, and the dose must remain unchanged through the End of Study Visit unless required for management of adverse events (AEs).
4. Cognitive decline not primarily caused by vascular, traumatic, or medical problems (alternative causes of cognitive decline are ruled out).
5. Adequate visual and auditory abilities and motor skills to perform all aspects of the cognitive and functional assessments.
6. Has a partner or caregiver who can accompany the subject at specified study visits (if required based on cognitive function).
7. MoCA score ≥ 14 and ≤ 26.
8. Unless confirmed to be azoospermic (vasectomized or secondary to medical cause), males must agree to use a male condom from Day -1 until the End-of-Study visit 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 End-of-Study Visit.

9. 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 highly effective 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).
10. Females of non-childbearing potential may be enrolled if it is documented that they are postmenopausal (refer to Section 5.6).
11. Body weight greater or equal to 50 kg and body mass index (BMI) between 18 and 35 $kg/m^2$, inclusive at Screening.
12. Stable medical conditions for 30 days prior to Screening visit (e.g., controlled hypertension, dyslipidemia).
13. Willing to follow the protocol requirements and comply with protocol restrictions.
14. Capable of providing informed consent and complying with study procedures.
15. Able to speak, understand and read English.

## 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, 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 of epilepsy, focal brain lesion, head injury with loss of consciousness or meeting DSM-V diagnostic criteria for psychotic disorders, such as schizophrenia or bipolar disorder, or have unstable concomitant psychiatric symptomatology. (NOTE: Subjects with psychotic disorders may be enrolled if their condition is effectively managed (i.e., must be receiving stable doses of anti-psychotic medication(s) 90 days prior to randomization and must remain on that dose throughout both treatment periods)
5. Evidence of any significant clinical disorder or laboratory finding (e.g., potassium levels below normal range) that renders the participant unsuitable for receiving an investigational drug including clinically significant or unstable hematologic, moderate and severe impairment of hepatic function (as defined by the National Cancer Institute Organ Dysfunction Working Group), cardiovascular, pulmonary, gastrointestinal, endocrine (including thyrotoxicosis, excluding managed hypo- or hyper- thyroidism), immunologic, dermatologic, neurologic, musculoskeletal, metabolic, renal, or other systemic disease or laboratory abnormality.
6. Participants with a history of malignant disease within 5 years, including solid tumors and hematologic malignancies (exceptions: [a] basal cell and squamous cell carcinomas of the skin or solid tumors that have been completely excised and are considered cured; [b] low-grade adenocarcinoma of the prostate, which are slow growing, and are unlikely to progress or metastasize during the clinical trial).
7. Any current clinically significant medical condition or disease as determined by medical history, physical examination, 12-lead electrocardiogram (ECG) and clinical laboratory assessments conducted that, in the view of the Principal Investigator, will interfere with participation in the study or interpretation of results.
8. Clinically significant abnormalities of 12-lead ECG (as determined by a central reader), including QTcF > 440 ms, for males and females, and/or HR < 50 beats per minute, or evidence of bundle branch blocks, as indicated on the Mean ECG Analysis Report during the screening 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 including green tea products (refer to Section 5.4) during Screening or throughout study, unless approved by both the Investigator and the Sponsor Medical Monitor.

11. Prior and/or concurrent 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.
12. Prior and/or concurrent 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. Subjects maybe on stable doses of serotonin-selective reuptake inhibitor (SSRI) antidepressants but are prohibited to be on serotonin-noradrenaline reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCAs), or any treatment for ADHD including noradrenaline reuptake inhibitors (NRIs), or amphetamines within the last month prior to Screening.
13. A history of heart failure, sinus bradycardia, second- or third-degree heart block, hypokalemia, attack of unconsciousness possibly associated with torsades de pointes (TdP) or family history of Long QT Syndrome.
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 human immunodeficiency virus (HIV), hepatitis C antibody (HCV Ab) or current hepatitis B infection (defined as positive forhepatitis 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. Current infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
18. Females who are breastfeeding.
19. Any other reason for which the PI considers it is not in the best interest of the participant to undertake the study.

## 4.4. Diagnostic criteria

The following diagnostic criteria are provided for identification of eligible subjects under inclusion criterion 2.

- The National Institute on Aging-Alzheimer's Association defines the core clinical criteria for diagnosis of MCI (Albert 2011) as follows:
  - Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time).
  - Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains).
  - Preservation of independence in functional abilities.
  - Not demented.

- The United Kingdom Parkinson's Disease Brain Bank criteria for PD (Clark 2016) are:
  - Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions).
  - And at least one of the following:
    1. muscular rigidity
    2. 4–6 Hz rest tremor
    3. postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.
- RBD diagnosis will be evaluated in subjects with PD and recorded using the International Classification of Sleep Disorders, Third Edition (ICSD-3) criteria for RBD (albeit documentation by polysomnography is not required for the purposes of this inclusion criteria) as well as the RBD1Q. The ICSD-3 criteria for RBD are:
  - repeated times of arousal during sleep where the subject talks, makes noises or performs complex motor behaviors, such as punching, kicking, or running movements that often relate to the content of the subject's dreams
  - the subject recalls dreams associated with these movements or sounds
  - if the subject awakens during the episode, they are alert and not confused or disoriented
  - the subject's sleep disturbance is not caused by another sleep disturbance, a mental health disorder, medication, or substance abuse
- The National Institute on Aging-Alzheimer's Association defines the core clinical criteria for the diagnosis of probable Alzheimer's disease (McKhann 2011) as:
  - Meets criteria for dementia, with cognitive or behavioral symptoms that:
    1. Interfere with the ability to function at work or at usual activities; and
    2. Represent a decline from previous levels of functioning and performing; and
    3. Are not explained by delirium or major psychiatric disorder;
    4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
    5. The cognitive or behavioral impairment involves a minimum of two of the following domains:

a. Impaired ability to acquire and remember new information—symptoms include repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.

b. Impaired reasoning and handling of complex tasks, poor judgment— symptoms include poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.

c. Impaired visuospatial abilities—symptoms include inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

d. Impaired language functions (speaking, reading, writing)—symptoms include difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

e. Changes in personality, behavior, or comportment—symptoms include uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

– In addition to the criteria for dementia above, probable Alzheimer's disease has the following characteristics:

1. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

2. Clear-cut history of worsening of cognition by report or observation; and

3. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

b. Nonamnestic presentations:

- Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.

- Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
- Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

## 4.5. Enrollment Procedures and Randomization

### 4.5.1. 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 -2. If a subject falls outside the Screening Period window, screening may be extended with prior approval by the CuraSen Medical Monitor. If extended beyond 28 days, some of the screening procedures and assessments may need to be repeated.

### 4.5.2. 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) and repeat all Screening procedures. The screening process for such subjects must be discussed with the CuraSen Medical Monitor.

### 4.5.3. Randomization

Once all Screening tests and procedures are completed and all eligibility criteria are met, subjects will return to the clinic for randomization and begin dosing in Treatment Period 1. The IWRS will provide the randomization number.

## 4.6. Subject Withdrawal

At the time of early withdrawal, the subject should complete the Day 14/Early Withdrawal (EW) visit and return in 7 – 12 days for the End-of-Study 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.

### 4.6.1. 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.

#### 4.6.2. End-of-Study for Early 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 End-of-Study visits.

# 5. SCHEDULE OF EVENTS AND STUDY PROCEDURES

Assessments and procedures at each visit are summarized in the Schedule of Events. For visits in which multiple disease assessments are planned, efforts should be made to conduct them after the subjects have been provided with a light meal or snack (without caffeinated beverages or high sugar content) in the following order (as relevant): FERT before pVFT, then DSST and CANTAB. The Color Trails Test should be conducted after the CANTAB assessments. ADCS-CGIC should be conducted last. SAS-6, GDS-30 and CAARS may be administered at any time before ADCS-CGIC.

## 5.1. Visit Assessments

#### 5.1.1. Screening (Day -28 to Day -2)

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
- Vital signs (blood pressure [BP], heart rate [HR], respiration rate and oral/tympanic temperature); for assessments of orthostatic changes, BP and HR are obtained: a) after rest in a supine position for at least 5 minutes, and b) 1 minute after standing
- 12-lead ECG, obtained 3 times (separated by approximately 1 minute) after the subject is supine for at least 5 minutes
- Complete physical examination, excluding genital, rectal and breast exams
- Laboratory tests
    1. Hematology, fasting chemistry (includes calculated creatinine clearance), and urinalysis
    2. Urine drug screen
    3. Alcohol breath test
    4. Serology for HIV, hepatitis B and C
    5. SARS-CoV-2 test
    6. Serum β-hCG test for females of childbearing potential
    7. FSH test for postmenopausal women
    8. Whole blood sample for determination of genetic variants including but not limited to APOE4, LRRK2, and GBA (optional and where applicable)
    9. Plasma sample for neurodegenerative biomarkers
- CANTAB administered twice, at least 1 hour apart during the final week (Day -8 to Day -2) before Treatment Period 1 to familiarize subjects with the tests.
- Other clinical and cognitive scales/assessments:
    1. MoCA
    2. ADCS-CGIC
    3. DSST
    4. RBD1Q (to be evaluated in all subjects, but to be used to assess eligibility for subjects with PD only)
    5. MHYS (only in subjects with PD; prior assessment within 3 months of Screening will suffice)
    6. C-SSRS

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 the start of Treatment Period 1.

### 5.1.2. Day -1, one day before start of dosing of Study Drug in 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
- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); for assessments of orthostatic changes, BP and HR are obtained: a) after rest in a supine position for at least 5 minutes, and b) 1 minute after standing
- 3 sets of triplicate ECG measures (i.e., 9 ECGs) prior to dosing with study drug to thoroughly establish a baseline obtained after subject has rested in supine position for at least 5 minutes; the time between each set of 3 ECGs should be ≤5 minutes
- Alcohol breath test prior to dosing CST-107 or matching placebo
- Serum or urine pregnancy test (per standard site practice) prior to dosing CST-107 or matching placebo for females of childbearing potential; positive urine pregnancy result to be confirmed by serum test

The following procedures will be administered (prior to dosing CST-107) at approximately the same time of day (±1 hour) and under approximately the same food status as planned for the tests on Days 1, 7, and 14:

- FERT
- pVFT
- DSST
- CANTAB
- Color Trails Test (select sites only), administered after CANTAB
- SAS-6
- CAARS
- GDS-30
- C-SSRS in Treatment Period 2 only

Obtain the randomization number and the Days 1-7 blister card/bottle numbers for study drug (CST-2032+CST-107 or matching placebos) from the IWRS – do not dispense blister card/bottle to the subject

Remove one CST-107 or matching placebo tablet from the bottle or the Day 10 well on the blister card and administer the dose to the subject after completion of all scheduled assessments

### 5.1.3. Day 1, Treatment Periods 1 and 2

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

- Assessment of concomitant medications
- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); for assessments of orthostatic changes, BP and HR are obtained: a) after rest in a supine position for at least 5 minutes, and b) 1 minute after standing:
    1. Within 30 minutes prior to dosing of study drug
    2. 4 hours (±30 minutes) after dosing study drug
- 12-lead ECG, obtained 3 times (separated by approximately 1 minute) after subject has rested in supine position for at least 5 minutes:
    1. Within 30 minutes prior to dosing study drug
    2. Approximately 1 hour after dosing study drug
    3. Approximately 2 hours after dosing study drug
    4. Approximately 4 hours after dosing study drug
- Laboratory tests (hematology, chemistry, and urinalysis)
    1. Pre-dose and approximately 4 hours post-dose
    2. Chemistry only at 4 hours post-dose
- Administer study medication (CST-2032 and CST-107 or matching placebos) from the blister card/bottle
- FERT administered at least 2 hours after dosing study drug and prior to administration of the cognition tests (pVFT, DSST, CANTAB)
- SAS-6, CAARS GDS-30 administered at least 2 hours after dosing study drug
- pVFT, DSST, CANTAB tests at 3 hours (± 30 minutes) after dosing study drug. Tests should be conducted at approximately the same time of day (±1 hour) and under the same food status on Days -1, 1, 7 and 14.
- Dispense study medication (Days 1-7 blister card/bottle) and provide dosing instructions to the subjects
- Dispense dosing diary
- Assessment of AEs
- Schedule Day 7 Visit. Subjects should be instructed not to administer study drug prior to the clinic visit on Day 7 as study drug will be administered on site.

### 5.1.4. Day 7 (±1), Treatment Periods 1 and 2

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

- Review subject dosing diary
- Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); for assessments of orthostatic changes, BP and HR are obtained: a) after rest in a supine position for at least 5 minutes, and b) 1 minute after standing:
    1. Within 30 minutes prior to dosing study drug
    2. Approximately 4 hours after dosing study drug
- 12-lead ECG, obtained 3 times (separated by approximately 1 minute) after subject has rested in supine position for at least 5 minutes:
    1. Within 30 minutes prior to dosing study drug
    2. Approximately 1 hour after dosing study drug
    3. Approximately 2 hours after dosing study drug
    4. Approximately 4 hours after dosing study drug
- C-SSRS
- Laboratory tests (hematology, chemistry, and urinalysis) at approximately 4 hours post-dose
- PK samples:
    1. Within 15 minutes prior to dosing study drug (CST-2032 and CST-107 or matching placebos)
    2. 30 minutes (+15 minutes) after administration of study drug
    3. 1 hour (+30 minutes) after dosing study drug
    4. 2 hours (+30 minutes) after dosing study drug
    5. 4 hours (+30 minutes) after dosing study drug
- Administer study drug (CST-2032 and CST-107 or matching placebos) from the Days 1-7 blister card/bottle
- Collect study drug (CST-2032 and CST-107 or matching placebos) blister cards/bottles from Days 1-7 and conduct accountability
- pVFT, DSST, CANTAB tests 3 hours (± 30 minutes) after dosing study drug. Tests should be conducted at approximately the same time of day (±1 hour) and under the same food status on Days -1, 1, 7 and 14.
- Color Trails Test (select sites only), administered after CANTAB
- Assessment of AEs
- Assessment of concomitant medications
- Obtain blister card numbers/bottle for study drug (CST-2032 and CST-107 or matching placebos) from the IWRS and dispense study medication for Days 8-14
- Schedule Day 14 Visit. Subjects should be instructed not to administer study drug prior to the clinic visit on Day 14 as study drug will be administered on site.

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

The following procedures will be performed, and assessments/measurements recorded at the Day 14 Visit of each Treatment Period. Subjects who withdraw prior to Day 14 should complete Day 14 safety assessments at the time of EW (identified with an asterisk [*]):

- *Review subject dosing diary

- *Vital signs (BP, HR, respiration rate, and oral/tympanic temperature); for assessments of orthostatic changes, BP and HR are obtained: a) after rest in a supine position for at least 5 minutes, and b) 1 minute after standing:
    1. Within 30 minutes prior to dosing study drug
    2. Approximately 4 hours after dosing study drug
- *12-lead ECG, obtained 3 times (separated by approximately 1 minute) after subject has rested in supine position for at least 5 minutes:
    1. Within 30 minutes prior to dosing study drug
    2. Approximately 1 hour after dosing study drug
    3. Approximately 2 hours after dosing study drug
    4. Approximately 4 hours after dosing study drug
- *C-SSRS
- Laboratory tests approximately 4 hours post-dose
    1. *Hematology, chemistry, and urinalysis
    2. *Serum or urine pregnancy test (per standard site practice) prior to dosing study drug for females of childbearing potential; positive urine pregnancy result to be confirmed by serum test
    3. Plasma sample for neurodegenerative biomarkers
- Administer study medication (CST-2032 and CST-107 or matching placebos) from the Days 8-14 blister cards or bottles

- *Collect study drug (CST-2032 and CST-107 or matching placebos) blister cards/bottle from Days 8-14 and conduct accountability
    - FERT administered at least 2 hours after dosing study drug and prior to administration of the cognition tests (pVRT, DSST, CANTAB)
    - pVFT, DSST, CANTAB tests 3 hours (± 30 minutes) after dosing study drug. Tests should be conducted at approximately the same time of day (±1 hour) and under the same food status on Days -1, 1, 7 and 14.
    - Color Trails Test (select sites only), administered after CANTAB
    - SAS-6, CAARS, GDS-30 administered at least 2 hours after dosing study drug
    - MoCA
    - ADCS-CGIC
    - *Assessment of AEs
    - *Assessment of concomitant medications
    - *Register visit in IWRS

- Schedule End-of-Study Visit (TP2 Day 14 or EW Visit only)

#### 5.1.6. End-of-Study – Approximately 7-12 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); for assessments of orthostatic changes, BP and HR are obtained: a) after rest in a supine position for at least 5 minutes, and b) 1 minute after standing
- 12-lead ECG, obtained 3 times (separated by approximately 1 minute) after the subject is supine for at least 5 minutes
- Symptom-driven physical examination
- Laboratory tests
    1. Hematology, fasting chemistry, and urinalysis
    2. Serum or urine pregnancy test (per standard site practice) for females of childbearing potential; positive urine pregnancy result to be confirmed by serum test
- C-SSRS
- Assessment of AEs
- Assessment of concomitant medications
- Register visit in IWRS

The End-of-Study Visit should be conducted in the clinic. However, should there be factors and/or conditions which would make the End-of-Study 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 collected (a) after rest in a supine position for at least 5 minutes, and (b) 1 minute after standing, to assess orthostatic changes. 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 End-of-Study Visit.

### 5.3.2. 12-Lead ECG

A 12-lead ECG will be collected in triplicate 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. All ECGs will be reviewed by the Investigator or qualified study staff and will be read by a central reader.

### 5.3.3. Clinical Laboratory Analysis

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

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, amylase, 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 determined at Screening only.

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

SARS-CoV-2: Conducted at Screening by central lab. After Screening, the test may be conducted according to current local COVID management procedures.

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 breath test.

CST-2032 and CST-107 PK samples: Plasma samples will be collected for PK analysis on Day 7 of each treatment period for analysis of CST-2032, CST-107 and possible metabolites. Samples may be stored for up to 2 years.

Disease Biomarkers: Whole blood will be collected for analysis of genetic variants including but not limited to APOE4, LRRK2, and GBA (optional and where applicable) during screening, and plasma will be collected during screening and on Day 14 for analysis of neurodegeneration biomarkers (may be stored for up to 5 years).

Instructions on 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.

### 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 (Posner 2011). It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent 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. Digital Symbol Substitution Test (DSST)

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 – 4$^{th}$ 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 90 or 120-second time limit. Higher scores indicate better performance; for a 120-second limit, the maximum attainable score is 135. Test scores can be benchmarked against published normative data by age group, and education level (2008 NCS Pearson, Inc.) as a means of evaluating test performance.

#### 5.3.6.2. 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.

#### 5.3.6.3. Geriatric Depression Scale-30 (GDS-30)

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

#### 5.3.6.4. Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)

The ADCS-CGIC focuses on clinicians' observations of change in the patient's cognitive, functional, and behavioral performance since the beginning of a trial (Schneider 1997). It relies on both direct examination of the patient and interview of informants. Unlike a targeted symptom scale, it takes into account a subject's overall function in the cognitive, behavioral, and functional activity domains. Scoring is based on an interview with the caregiver and examination of the patient by an independent evaluator. The MoCA will be used to provide the cognitive assessment. The ADCS-CGIC requires the assessor to consider a number of cognitive, functional, and behavioral areas prior to providing an overall "global" assessment of clinical change. It is performed by interviewing the patient to assess function and mental status and the informant, using a worksheet that comprehensively lists relevant symptoms potentially useful in judging clinically meaningful change, and allows for notes for future reference.

#### 5.3.6.5. Starkstein Apathy Scale short form (SAS-6)

The SAS-6 is a 6-item questionnaire to measure the severity of apathetic symptoms (Garofalo 2021, Starkstein 1992). In the SAS-6, each question is read by the examiner, and the patient is provided with four possible answers: "not at all," "slightly," "some," or "a lot" which are scored on a 4-point Likert scale (range: 0–3). Scores range from 0 to 18; higher scores indicate more severe apathy.

#### 5.3.6.6. Connors Adult ADHD Rating Scale – self-report short form (CAARS)

The CAARS is an 26-item scale designed to assess, diagnose, and monitor treatment of attention deficit/hyperactivity disorder (ADHD) in adults. The self-report short form contains factor-derived scales for inattention/memory, hyperactivity/restlessness,

impulsivity/emotional lability, and problems with self-concept (developed by Conners, Erhardt, and Sparrow, unpublished).

#### 5.3.6.7. REM Sleep Behavior Disorder Single-Question Screen (RBD1Q)

The RBD1Q is a single "yes-no" question that queries the classic dream-enactment behavior of RBD (Postuma 2012) and will be administered at Screening to identify subjects with REM sleep behavior disorder.

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.)?"

RBD1Q will be evaluated and recorded for all subjects, but to be used to assess eligibility for subjects with PD only.

#### 5.3.6.8. Modified Hoehn and Yahr Scale (MHYS) for subjects with PD only

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.

The MHYS will be evaluated during screening (unless completed within the past 3 months) for purposes of phenotyping of subjects with PD. It will not be used as an enrollment criterion.

#### 5.3.6.9. 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 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).

#### 5.3.6.10. Phonological Verbal Fluency Test (pVFT)

Verbal fluency tests are widely used for assessing executive function and requires the generation of words from initial letters (phonological verbal fluency) or belonging to a specific category (semantic fluency), under a time constraint (Harrison 2000). 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) (Metis Cognition, Ltd., Warminster, UK).

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.

#### 5.3.6.11. Facial Expression Recognition Task (FERT)

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.

#### 5.3.6.12. Color Trails Test (Select Sites Only)

The Color Trails Test consists of numbered circles printed with vivid pink or yellow backgrounds that are perceptible to color-blind individuals. For Part 1, the respondent uses a pencil to rapidly connect circles numbered 1-25 in sequence. For Part 2, the respondent rapidly connects numbered circles in sequence, but alternates between pink and yellow. The length of time to complete each trial is recorded.

## 5.4. Concomitant Medications

Subjects who require routine medication to manage and treat concurrent conditions (e.g., hyperlipidemia, diabetes, hypertension, Parkinson's Disease, Alzheimer's Disease) must be on stable doses 30 days prior to randomization and remain on those doses for the duration of the study. 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:

- Monoclonal antibodies for treatment of MCI or mild dementia e.g., aducanumab.
- Cannabis and products containing tetrahydro cannabinol (THC) and/or cannabidiol (CBD).
- Hypnotics, such as zolpidem or zopiclone, within 48 hours prior to a study visit involving cognitive testing.
- St. John's Wort, green tea, green tea products, or Ginkgo Biloba during Screening or throughout the study.
- Benzodiazepines from Screening throughout the study with the following exception:
    - Clonazepam is permitted when used for RBD at doses up to 1 mg at bedtime – subjects must be on a stable dose 90 days prior to randomization and remain on that dose throughout both treatment periods.
- Anti-psychotic medication(s) are permitted at stable doses 90 days prior to randomization. The doses must remain unchanged throughout both treatment periods.
- Gabapentin 900 mg per day maximum, gabapentin enacarbil 600 mg per day maximum, pregabalin 300 mg per day maximum are permitted at stable doses 90 days prior to randomization. The doses must remain unchanged throughout both treatment periods.
- Phenylephrine and pseudoephedrine are prohibited from Screening throughout the study.

- Any β-AR agonists or β-AR blockers (including oral medications, eye drops with adrenergic agents such as timolol or atenolol, IV, or inhaled), or any medications that impact adrenergic signaling within the last month prior to Screening and throughout the study, including:
    - β-AR agonists such as Ventolin (albuterol), Proventil (albuterol), Proair HFA (albuterol), Xopenex HFA (levalbuterol), Xopenex (levalbuterol), terbutaline, metaproterenol, Proair Respiclick
    - β-AR blockers such as Acebutolol, Atenolol (Tenormin), Bisoprolol (Zebeta), Metoprolol (Lopressor, Toprol XL), Nebivolol (Bystolic), Propranolol (Inderal, InnoPran XL.
- Serotonin-noradrenaline reuptake inhibitors (SNRIs) such as desvenlafaxine (Pristiq, Khedezla), duloxetine (Cymbalta, Irenka), levomilnacipran (Fetzima), milnacipran (Savella), venlafaxine (Effexor XR).
- Tricyclic antidepressants (TCAs) such as Amitriptyline, Amoxapine, Desipramine (Norpramin), Doxepin, Imipramine (Tofranil), Nortriptyline (Pamelor), Protriptyline, Trimipramine.
- Noradrenaline reuptake inhibitors (NRIs) such as atomoxetine, maprotiline, reboxetine, and viloxazine.
- Amphetamines such as dextroamphetamine, methylphenidate, dexmethylphenidate, methamphetamine, mixed amphetamine salts, amphetamine sulfate, lisdexamfetamine.
- 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 End-of-Study Visit.
- Opioid use is prohibited within 30 days prior to Screening and throughout the study.

## 5.5. Escape/Rescue Medications

Since CST-2032 is being co-administered with the nonselective β-AR antagonist nadolol (CST-107), the typical β-AR agonist effects such as HR increases, are unlikely to occur. However, if there are intolerable HR/BP increases subjects may be administered rescue nadolol.

Nadolol has been successfully used in ongoing or previous CuraSen studies to block the peripheral effects of CST-2032 and other β-AR agonists.

## 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 End-of-Study Visit.

Female subjects of childbearing potential who have a male partner must agree to contraception from the start of 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 of highly effective birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, contraceptive implant, contraceptive ring, intrauterine device, intrauterine hormone-releasing system, dual 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

Blinded safety data, including adverse events, vitals, ECG, clinical labs, will be monitored and evaluated on an ongoing basis throughout the study.

## 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 randomization will be documented on the AE CRF. Concurrent illnesses, which existed prior to first dose in 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.

#### 6.1.2.1. 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.

#### 6.1.2.2. 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 End-of-Study 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.

It is recognized that it may be difficult to differentiate the relationship of an adverse event to CST-2032 or to CST-107 (nadolol). There is a long history of the clinical safety of nadolol and the dose of nadolol being administered in this study is less than 10% of the labeled starting dose for treatment of angina pectoris or hypertension (3 mg versus 40 mg). Therefore, unless the PI is confident in attribution of causality to CST-107 (e.g., for an AE that occurs prior to administration of CST-2032), all assessments of related AEs will be attributed to CST-2032 for expedited reporting purposes.

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

All ECGs will be evaluated by a central ECG reader and 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-2032 is provided as white tablets containing 3 mg CST-2032 that are identical in appearance to the matching placebo. CST-2032 and matching placebo will be supplied in blister cards containing 10 repeat doses for a 1-week supply.

CST-107 is provided as yellow tablets containing 3 mg nadolol that are identical in appearance to the matching placebo. CST-107 and matching placebo will be supplied in blister cards or bottles containing 10 repeat doses for a 1-week supply.

Additional details on the study medication can be found in the Investigator Brochure (IB).

## 7.2. Study Medication Dosing and Administration

The CST-2032 blister cards are designed for subjects to dispense 2 tablets on each dosing day according to the treatment the subject is randomized to receive and the treatment period in which they are participating, e.g.:

- 2 placebo tablets for administration of blinded placebo, or
- 1 tablet of 3 mg CST-2032 and 1 tablet of placebo for the blinded 3 mg dose.

The CST-107 blister cards or bottles allow subjects to dispense 1 tablet on each dosing day according to the treatment the subject is randomized to receive and the treatment period in which they are participating, e.g.:

- 1 placebo tablet for administration of blinded placebo, or
- 1 tablet of 3 mg CST-107 for the blinded 3 mg dose.

During each treatment period, subjects will receive CST-107 or matching placebo for 15 days and CST-2032 or matching placebo for 14 days:

- On Day -1, CST-107 or matching placebo will be administered in clinic after completion of all scheduled assessments.
- Study drug (CST-2032 and CST-107 or matching placebos) will be administered in clinic on Day 1 during which dispensing will be demonstrated to the subjects.

Subjects will receive a 1-week supply of study drug on Days 1 and 7 of each treatment period. CST-107 or matching placebo and CST-2032 or matching placebo are to be taken together each day during both treatment periods.

### 7.2.1. Randomization

The designated Interactive Web Response System (IWRS) will be used to randomize subjects into the study on Day -1. Eligible subjects will be randomly assigned in a 1:1 ratio to one of the following 2 treatment regimens/sequences:

| | Treatment Period 1 | Treatment Period 2 |
|---|---|---|
| 1 | 3 mg CST-2032 + 3 mg CST-107 | Placebo (2032) + placebo (107) |
| 2 | Placebo (2032) + placebo (107) | 3 mg CST-2032 + 3 mg CST-107 |

The IWRS will provide the randomization number.

### 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, IWRS system administration, and drug supply management team.

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-2032 matched placebo and CST-107 matched placebo will be packaged and color-, size-, and shape-matched to be indistinguishable from CST-2032 3 mg and CST-107 3 mg.

### 7.2.3. Packaging and Labeling

The color and labeling for tablets of CST-2032 and its matching placebo will be distinct from the packaging for color and labeling for tablets of CST-107 and its matching placebo:

- CST-2032 and matching placebo will be supplied in blister cards with a white label containing 10 repeat doses. The blister cards are designed for subjects to dispense 2 tablets on each dosing day according to the treatment the subject is randomized to receive and the treatment period in which they are participating.
- CST-107 and matching placebo will be supplied in blister cards with a blue label containing 10 repeat doses or bottles with a yellow label containing 10 doses. The blister cards are designed for subjects to dispense 1 tablet on each dosing day according to the treatment the subject is randomized to receive and the treatment period in which they are participating.

Each blister card will supply 1 week (+3 extra days) of dosing of CST-2032/placebo and 1 week (+2 extra days) of dosing for CST-107/placebo blister or bottle.

The clinical label will identify the product by name, lot number, Sponsor, and storage conditions. The blister or bottle labels will include the investigational drug caution statement: "Caution: New Drug - Limited by Federal (United States) Law 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.

CST-2032/matching placebo will be stored at refrigerated temperature 36°F–46°F (2–8°C). Minor excursions are permitted (down to 0°C and up to 25°C for up to 60 minutes) and should be recorded within the pharmacy temperature logs. Excursions longer than 15 minutes must be reported to CuraSen but the product is still suitable for use. If temperature excursions are greater than 60 minutes, CuraSen must be informed within 24 hours so that study medication can be quarantined.

CST-107/matching placebo will be stored at controlled room temperature 59°F–77°F (15–25°C) with excursions allowed up to 86°F (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.

# 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 60 subjects is planned. Although formal hypothesis testing is planned, the study is underpowered for detecting meaningful cognitive benefits and lack of significance will not be interpreted as lack of a treatment effect. The sample size is based on practical considerations and is typical of studies whose objectives are to evaluate the safety and cognitive effects of a therapeutic intervention.

## 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 (either CST-2032 or CST-107 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-2032+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 cognitive endpoints, 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-2032 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. Interim Analysis

An unblinded interim analysis may be conducted by the DSMB after approximately 40 subjects have completed Treatment Period 1.

If conducted, this will be an unblinded analysis, but patient level treatment assignments will continue to be blinded.

Details of the interim analysis will be provided in the Statistical Analysis Plan and DSMB Charter.

### 8.3.2. Final Analysis

The final analysis will be performed after the last subject completes their End-of-Study 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 9.4 or higher. Continuous data will display number of subjects, means, standard deviations, median, minimum, and maximum. Categorical data will display frequency counts and percentages. 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 treatment, disease criteria (MCI vs. mild dementia), treatment sequence and overall. Summaries of safety, and pharmacodynamic measures (e.g., effects of treatment on CANTAB, pVFT, DSST, Color

Trails Test, FERT, GDS-30, SAS-6, CAARS, ADCS-CGIC) will be presented by treatment overall. PK of CST-2032 and CST-107 will be presented by treatment and treatment sequence. A limited subset of summaries may be presented by treatment and treatment sequence and/or period and overall.

For analysis purposes, Baseline will be defined as either the pre-dose measurement(s) taken within each of the study periods, or as the last measurement(s) 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 LC integrity as determined by baseline disease characteristics, treatment, 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 disease criteria, treatment, 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 Endpoint

Primary endpoint data will be summarized by treatment using the Safety Set. Selected summaries may be repeated in the PPS. All data will be listed.

## 8.7.1. Analysis of Adverse Events

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

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event collection will begin during screening 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 (CST2032+CST-107 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 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. TEAEs, SAEs, and treatment-related AEs will be further summarized by MedDRA system organ class and preferred term and reported by treatment.

All AEs will be listed. Separate listings may be prepared for SAEs, AEs leading to study drug termination, and treatment-related AEs. Individual ECG results will be listed for each subject. Summaries of ECGs by treatment will include observed data and changes from baseline for each parameter including heart rate, QT, and QTcF. The number and percentage of subjects with abnormal ECGs will be summarized by treatment.

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

## 8.8. Analysis of Secondary Endpoints

Differences between CST-2032+CST-107 and placebo in performance in cognitive tasks will be assessed using the FAS. For continuous endpoints, the difference is defined as CST-2032+CST-107 minus placebo except as defined in the SAP (e.g., for certain CANTAB test [PAL, RTI, and SSRT]). 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 and as specified in the SAP. These analyses will be conducted for all subjects in the study and also for each disease subset (PD/AD).

Secondary endpoints related to cognition, physiological symptoms, mood and will be summarized by disease criteria, treatment, treatment sequence and overall using the FAS. Select summaries may be repeated in the PPS. Comparisons between treatments will be performed similarly for all secondary endpoints. All data will be listed.

### 8.8.1. CANTAB, pVFT, DSST, Color Trails Test

Absolute values and changes from baseline will be summarized by baseline disease characteristics, treatment and overall. In addition, comparisons of effects of CST-2032+CST-107 vs placebo may be undertaken.

Pre-dose measures of cognitive performance may be used to identify the cognitive domains for which each subject is deficient based on available population data generated outside of this protocol, as available.

A responder analysis may be performed based on whether the subject meets pre-defined criteria for one or more of the cognitive tests.

The responder criteria for will be defined after review of emerging data from ongoing CuraSen clinical trials (e.g., CST103/CST107-CLIN-010, CST103/CST107-CLIN-011, and CST2032-CLIN-007). Methods and responder criteria will be described in more detail in the SAP prior to database lock.

### 8.8.2. Mood, Apathy and Disease Activity Scales

The absolute values and change from baseline in overall scores and sub-domain scores where applicable will be summarized by baseline disease characteristics, treatment and overall for FERT, GDS-30, CAARS, SAS-6, ADCS-CGIC using the FAS.

All results will be listed.

### 8.8.3. Clinical Laboratory Results, Vital Signs, and ECGs

Absolute values and changes from baseline will be summarized by disease criteria, treatment and overall. In addition, clinical laboratory results, ECG categorical analyses, 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.

### 8.8.4. 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-2032 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-2032 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-2032 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

Subgroup analyses may be conducted after study completion to evaluate whether effects of treatment are influenced by baseline disease characteristics including but not limited to disease activity as determined from relevant disease scales at screening, neurodegenerative biomarkers (such phosphorylated tau, neurofilament light chain, total and phosphorylated tau protein, and amyloid-β (Aβ) peptides) in plasma, and genetic variants including but not limited to APOE4, LRRK2, and GBA. Additionally, change in average z-score for baseline-deficit cognitive tasks identified for each subject from Cognitive tasks in the CANTAB and other cognitive measures may be evaluated.

All exploratory endpoints will be listed.

## 8.10. Other Analyses

Medical history, physical examination, C-SSRS, protocol deviations, screening clinical & cognitive scales (e.g., MoCA, RBD1Q, MHYS), neurodegenerative biomarkers, and genetic variants including but not limited to APOE4, LRRK2, and GBA will be listed.

### 8.10.1. 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.

### 8.10.2. 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.

# 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, FDA, EC/IRB, 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 IB, copies of all clinical trial documentation, and all correspondence to and from the EC/IRB 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 informed consent forms (ICFs) 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/IRB 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/IRB 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/IRB 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 (or a locked refrigerator for CST-2032), 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.

## 9.10. 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-2032 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.

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