A PHASE II, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, CROSSOVER STUDY OF THE PHARMACODYNAMIC EFFECTS OF CST-103 CO-ADMINISTERED WITH CST-107 ON THE CENTRAL NERVOUS SYSTEM IN SUBJECTS WITH NEURODEGENERATIVE DISORDERS

Statistical Analysis Plan

PROTOCOL NUMBER:

CST103/CST107-CLIN-011

EUDRACT NUMBER:

2020-006067-28

VERSION / DATE OF PLAN:

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STUDY DRUG:

CST-103 and CST-107

PREPARED FOR:

CuraSen Therapeutics, Inc.

SAP Approval Signature Page

Array Biostatistics, LLC

[redacted] Date

[redacted] Date

CuraSen Therapeutics, Inc.

[redacted] Date

Contents

1. ABBREVIATIONS

Aβ	amyloid-β
α-syn	α-synuclein
β-AR	Beta-adrenoceptor
β-hCG	Beta human chorionic gonadotropin
AD	Alzheimer's Disease
AE	Adverse event
ATT	Adaptive tracking test
AUCinf	Area under the drug concentration-time curve from time zero to infinity
AUCt	Area under the drug concentration-time curve from time zero to time t
BMI	Body mass index
BP	Blood pressure
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBF	Cerebral blood flow
CF	Cognitive fluctuations
cGCP	Current Good Clinical Practice
CLIN-001	CST101/CST107-CLIN-001
CLIN-002	CST103/CST107/CST109-CLIN-002
CLIN-003	CST101/CST103/CST109-CLIN-003
Cmax	Maximum concentration
CNS	Central nervous system
CRF	Case report form
CK	Creatinine kinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CST-103	Clenbuterol HCl
CST-107	Nadolol
CV	Coefficients of variation
DCFS	Dementia Cognitive Fluctuation Scale
DLB	Dementia with Lewy Bodies
DSST	Digital Symbol Substitution Test
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
EEG	Electroencephalogram
ERP	Event Related Potential
ESS	Epworth Sleepiness Scale
EW	Early withdrawal
FAS	Full analysis set
FERT	Facial Expression Recognition Task
FOG	Freezing of Gait
FOG-Q	Freezing of Gait Questionnaire
FSH	Follicle-stimulating hormone
GDS	Geriatric Depression Scale
HADS	Hospital Anxiety and Depression Scale
HR	Heart rate
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen

HCV Ab	Hepatitis C antibody
HIV	Human immunodeficiency virus
HRV	Heart rate variability
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IRT	Interactive response technology
ITT	Intent to treat
IV	Intravenous
MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MHYS	Modified Hoehn & Yahr Scale
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NDD	Neurodegenerative disease
PAL	Paired Associates Learning
PD	Parkinson's Disease
PDD	Parkinson's Disease Dementia
PI	Principal Investigator
PK	Pharmacokinetic
PKS	PK set
PLR	Pupillary Light Reflex
PO	By mouth/oral administration
PPS	Per protocol set
QD	Once daily
RBD1Q	REM Sleep Behavior Disorder Single-Question Screen
RBD+PD	REM Sleep Behavior Disorder positive Parkinson's Disease
RTI	Reaction Time Index
RVP	Rapid Visual information Processing
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SART	Sustained attention response task
SOC	System organ class
SOP	Standard operating procedure
SRM	Safety review meeting
t1/2	Time to maximum observed drug concentration
TEAE	Treatment emergent adverse event
tmax	Time of maximum concentration
TP	Treatment Period
TSH	Thyroid-stimulating hormone
VRM	Verbal Recognition Memory
WAIS-IV	Wechsler Adult Intelligence Scale, Fourth Edition

2. INTRODUCTION

The statistical analysis plan (SAP) details the planned analysis required to satisfy the Clinical Study Report (CSR) of study number CST103/CST107-CLIN-011: A Phase II, Randomized, Placebo-Controlled, Double-Blind, Crossover Study of the Pharmacodynamic Effects of CST-103 co-administered with CST-107 on the Central Nervous System in Subjects with Neurodegenerative Disorders.

The content of this SAP is based on the protocol version 6.0 (Amendment 6 AUS-NZ) dated 18-Feb-2022 and protocol version 7.0 (Amendment 7 UK-EU) dated 18-Feb-2022 and CRF version 6.0 dated 27-Mar-2022.

2.1. Changes from the Protocol

While two separate protocols govern the trial in Australia/New Zealand and the United Kingdom/European Union, all analyses will be performed cumulatively among subjects across all regions, except for BioStamp and SART analyses which are only collected on subjects from Australia and New Zealand.

Additionally, the protocol states that approximately 20 subjects will be enrolled in Cohort A with RBD+PD or MCI and approximately 20 subjects will be enrolled in Cohort B with PDD or DLB. Due to the difficulty in recruiting patients with DLB and PDD the majority of the subjects recruited will be in Cohort A and the majority of these are RBD+PD subjects. Cohort B data will be captured in listings and summarized in the demographics, disposition, secondary endpoint analyses, and exploratory analyses tables.

3. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
The primary objective of this study is to identify a CNS signal in one of the planned pharmacodynamic measures after multiple oral doses of CST-103 in the presence of CST-107 in four populations of subjects with Neurodegenerative Disorders (NDD): Cohort A 1. Parkinson's Disease (PD) with REM Sleep Behavior Disorder (RBD) and Depressive Symptoms 2. Mild Cognitive Impairment (MCI) with Depressive Symptoms Cohort B 1. Dementia with Lewy Bodies (DLB) with Cognitive Fluctuations	The primary endpoints include: Cohort A: Change in Negative Emotional Bias in the Facial Expression Recognition Task Cohort B: Cognitive Fluctuations as measured by: 1. Spectral analysis of waking EEG 2. AUS/NZ Subjects Only: Activity Tracking 3. Pupillometry 4. Dementia Cognitive Fluctuation Scale (DCFS)

2. Parkinson's Disease Dementia (PDD) with Cognitive Fluctuations These pharmacodynamic assessments will compare the effect of CST-103 co-administered with CST-107 with that of placebo on the following: Cohort A: • Emotional Facial Processing Cohort B: • Cognitive fluctuations	
Secondary	
The secondary objectives for all subjects include the comparison of the effect of CST-103 co-administered with CST-107 with that of placebo on the following: 1. Cognition 2. AUS/NZ Subjects only: Movement and time spent sitting, standing and sleeping 3. Sleep 4. Pupillary reactivity 5. Mood Assessment 6. Safety and tolerability of CST-103 co-administered with CST-107 7. The pharmacokinetic (PK) profiles of CST-103 and CST-107	The secondary endpoints will compare the effect of CST-103 co-administered with CST-107 with that of placebo on the following: 1. Verbal fluency test (alphabet & category) 2. CANTAB cognitive assessments, with include the following: • Reaction Time (RTI) • Rapid Visual Information Processing (RVP) • Verbal Recognition Memory (VRM) Phase I • Adaptive Tracking Task (ATT) • Paired Associated Learning Task (PAL) • Stop Signal Task (SST) • Delayed Verbal Recall 3. AUS/NZ Subjects Only: Digital wearable device (BioStamp) data, which includes four key measures of interest: a) Activity and posture classifications, durations, and temporal patterns b) Sleep (duration, posture transitions, and activity counts) c) Autonomic function – heart rate variability (HRV) d) Temporal pedometry (daily step count, and gait cadence)

	4. Assessment of sleep using the digital device and Epworth Sleepiness Scale (ESS) 5. Change in pupillary diameter as measured using the pupillary light reflex test 6. Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS) 7. Adverse events (AE), electrocardiograms (ECGs), vital signs, laboratory safety tests (hematology, chemistry, and urinalysis) 8. Plasma PK parameters of CST-103 and CST-107 (including C_{max}, t_{max}, AUC_t. AUC_{inf}, $t_{1/2}$)
Exploratory	
The exploratory objectives are: 1. To characterize the effect of CST-103 co-administered with CST-107 on inflammatory biomarkers in blood, such as C-reactive protein and cytokine levels. 2. To characterize the effect of CST-103 co-administered with CST-107 on neurodegenerative biomarkers in the blood study as neurofilament light chain, total and phosphorylated tau protein, and amyloid-β (Aβ) peptides may also be measured 3. To characterize the effect of CST-103 co-administered with CST-107 on performance of a sustained attention task in subjects in Cohort B 4. To characterize the effect of CST-103 co-administered with CST-107 on Freezing of Gait (FOG) (for subjects with RBD+PD, PDD, and DLB). 5. To characterize the locus coeruleus volume and contract ratio (this is an optional objective based on imaging capabilities)	The exploratory endpoints are: 1. Changes in inflammatory biomarkers, such as C-reactive protein and cytokine levels, as measured prior to and after CST-103 co-administered with CST-107 may be determined. 2. Changes in neurodegenerative biomarkers, such as neurofilament light chain, total and phosphorylated tau protein, and amyloid-β (Aβ) peptides, as measured prior to and after CST-103 co-administered with CST-107 may be evaluated. 3. AUS/NZ Subjects Only: Performance on the Sustained Attention Response Task (SART) as measured prior to and after CST-103 co-administered with CST-107. 4. Assessment of FOG using the FOG-Q (for subjects with PBD+PD, PDD, and DLB). 5. The characterization of the brain imaging signal in the locus coeruleus complex using neuromelanin-sensitive MRI sequence. This is an optional

	endpoint based on imaging capabilities.

4. STUDY DESIGN

4.1. Study Design and Population

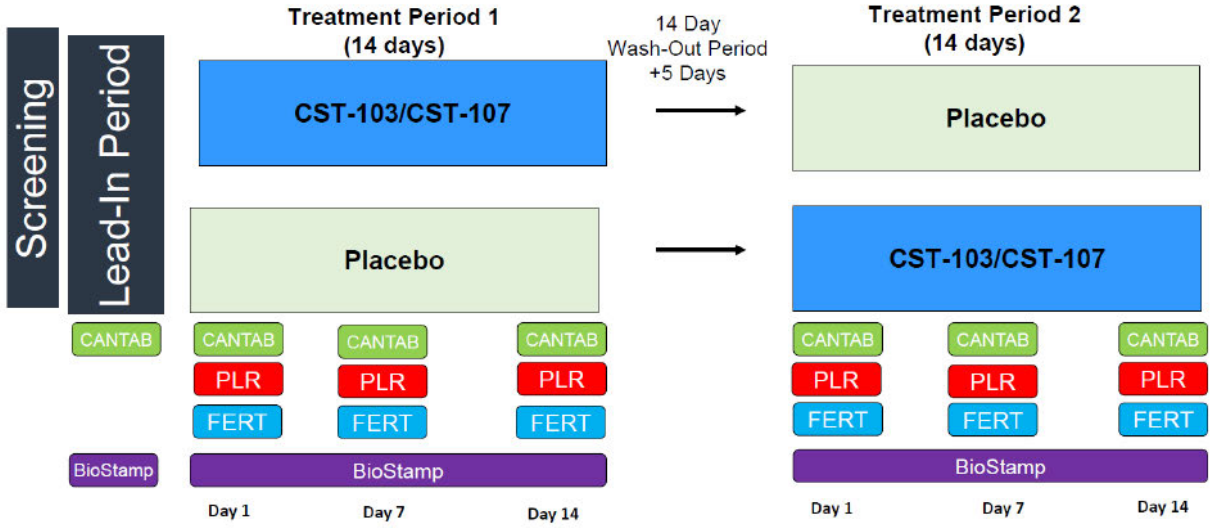
This is a Phase II, randomized, placebo-controlled, double-blind, crossover study on the CNS and pharmacodynamics effects of CST-103 co-administered with CST-107 in 4 subject populations with Neurodegenerative Disorders at up to ten clinical sites in Australia, New Zealand, and the United Kingdom.

Approximately 40 subjects will be enrolled in a 2 period, 2-way cross over design following study eligibility confirmation during the screening period. The number of subjects enrolled in each cohort may change as emerging data are reviewed from this and other studies. As noted in section 2.1, the majority of the subjects will be in RBD+PD group in Cohort A.

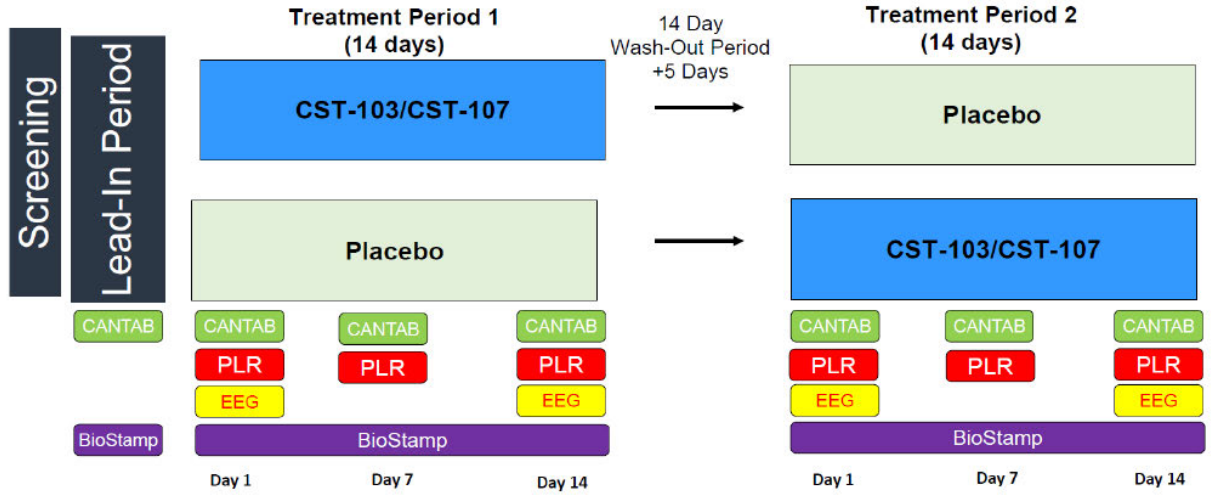
During each treatment period, subjects will receive daily doses of 80 µg CST-103 (administered as two 40 µg capsules) co-administered with 1 mg CST-107 (administered as one 1 mg capsule) or matching placebos for 14 days. Each treatment period will be separated by a washout period of 14 days (+5 day window)

The study duration will be approximately 12 weeks, which includes a Screening period of up to 21 days, a Lead-In Period of up to 14 days, the treatment/study period of 6 weeks (two 2-week treatment periods separated with a 2-week wash-out), and the Follow-Up Visit 2 weeks after the last study drug dose.

*Study Schema – Cohort A in RBD+PD or MCI Subjects**



*Study Schema – Cohort B in DLB or PDD Subjects**



**Biostamp devices will only be used for the Australia/New Zealand subjects but not for the UK or Belgian subjects.*

4.2. Randomization and Blinding

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

Randomization will be stratified by the following factors:

- Disease Criteria:

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

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

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

4.3. Sample Size Considerations

A total of approximately 40 subjects is planned in this crossover study. The sample size for the study parts are based on practical considerations. No formal hypothesis testing is planned.

The crossover design allows for an increased level of precision in estimates as compared to a parallel design with the same number of subjects. For primary and cognition related secondary endpoints, a sample size of 20 subjects in each cohort provides at least 80% power in this cross-over design to detect a treatment difference of 0.79*SD (active versus placebo) or larger for each endpoint of interest, where SD represents the standard deviation for the endpoint of interest.

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

4.4. Safety Review Meeting Committee

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

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

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

4.5. Interim Analysis

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

4.6. Timing of Analyses

The full set of analyses summarized in this SAP will be generated upon final study database lock.

5. DATA ANALYSIS CONSIDERATIONS

All analyses will be conducted based on SAS 9.4 or higher.

All data in the database will be presented in by-subject data listings.

Unless otherwise stated, all listings will be sorted by cohort, disease type, treatment sequence, subject number, and assessment date (and time, if available).

Unless stated otherwise, continuous data will be summarized by cohort, disease type, treatment sequence and overall based on n, mean, median, standard deviation (SD), minimum value, and maximum value.

Unless stated otherwise, categorical data will be summarized by cohort, disease type, treatment sequence and overall using n and percentage based on the number of nonmissing values.

- The number of missing values will be presented as a separate category with no percentage, but only if one or more subjects are missing data.
- Counts of zero will be presented without percentages.

Precision

- Mean and Median: one additional decimal place to that reported for Minimum and Maximum
- SD: two additional decimal places than the Minimum and Maximum
- Percentages: reported to one decimal place
- P-values will be reported to four decimal places. If the value is below 0.0001 it will be noted as < 0.0001; if the value above 0.9999 it will be noted as > 0.9999.

Unless otherwise noted, statistical inference will be based on a 5% significance level (i.e. 95% confidence intervals will be produced).

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of duration of treatment.

Numbering for data displays will be based on ICH E3.

5.1. Stratification and Covariates

There are no formal plans for analysis stratification.

5.2. Evaluation of Subgroups

There are no formal plans for examining subgroups.

5.3. Multiple Comparisons and 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.

6. GENERAL DATA HANDLING CONVENTIONS

6.1. Reference Dates

- Screening date is defined as the eCRF provided date on which a subject was screened for trial entry.
- Treatment start date is defined as the date of first dose of study drug. Each treatment period will have a treatment start date (i.e., in order to determine AEs occurring during a treatment).
- Treatment end date is defined as the date of last dose of study drug.
- Safety data, such as AEs and laboratory assessments will use the treatment start date as a reference date.
- Study day will be based on treatment start date as a reference date.

6.2. Study Day and Duration Variables

Study day or duration calculations will generally be defined as the following, assuming non-missing dates:

- date of interest – reference date + 1, when the date of interest >= reference date;
- otherwise, date of interest – reference date.

If either date is missing, reference day or duration calculations will not be performed. Date imputation will be performed as identified in Section 6.4.

In general, study day will be based on the treatment start date as the reference. As such, study day would either have a negative value if collected before dosing or a positive value if collected on or after the day of drug dosing; there will be no study day zero.

Duration of time is dependent on reference dates and will be calculated in a manner similar to that of the reference date calculation, assuming that dates of interest will strictly follow reference dates (e.g., no negative values). For example, duration of time in study is defined as the end of study date – informed consent date + 1. Duration of treatment is defined as treatment end date – treatment start date + 1, where treatment end date is the date of last dose of study drug.

6.3. Baseline and Post-Baseline Changes

Unless stated otherwise, baseline and post-baseline change values will be based on the following:

- Baseline will be based on the last non-missing value collected prior to or on the treatment start date and time. Post-baseline values will be those collected after the treatment start date and time.
- Change from baseline is defined as: value – baseline value.

6.4. Missing Data and Data Imputation Rules

All attempts will be made by the Data Management team to ensure completeness of data. Generally, missing data will not be imputed, and will be presented as collected in the study database.

In cases where adverse event (AE) or medication dates are missing, the imputation methods described in Appendix 1 will be used to determine flags for treatment-emergent events, and concomitant medications.

Other missing data methods will be proposed within the respective analysis section, as needed.

6.5. Multiple Assessments and Visit Windows

Nominal visits (e.g. those identified by the study CRF) will be the basis of summarization and statistical analysis; no visit date windowing will be conducted. Unscheduled data may be included in summaries of specific abnormalities any time post-baseline and subject data listings.

7. STUDY SUBJECT DATA

7.1. Analysis Populations

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 (SAF): All subjects who received at least 1 dose of study drug (CST-103/CST-107 or placebo). Subjects will be reported based on the treatment and dose received. The Safety Set will be used for the reporting of safety analyses.

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

Per-Protocol Set (PPS): A subset of the Full Analysis Set who sufficiently complied with the protocol. The analysis set will only include subjects without protocol deviations classified as "major". The Per Protocol Set may be used for selected safety analyses.

BioStamp Set (BSS): A subset of the Full Analysis Set who have at least one BioStamp measurement during the baseline period each of the post-baseline periods. The BioStamp Set will be used for demographics and the BioStamp related endpoints.

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

7.2. Subject Disposition

Subject disposition will be summarized using the ITT set. Summaries will include the number and percent of subjects: screened, enrolled, in each analysis population, completing the study, and discontinuing study prematurely, including a description of the reason for early withdrawal. Reasons for withdrawal will include the following:

- Adverse Event
- Lost to follow-up
- Subject withdrew consent
- Protocol violation/non-compliance
- Investigator decision
- Study terminated by sponsor
- Pregnancy
- Study burden
- Tested positive for COVID-19
- Fear of contracting COVID-19
- Other

Data will be presented by study cohort, disease criteria, and sequence.

Screen failures, analysis populations, and final subject disposition status will be listed. Visit dates and reasons for visits not done will also be listed.

7.3. Protocol Deviations

Protocol deviations will be recorded and detailed in a data listing. Deviations will be identified as major or minor, as evaluated by the monitoring team.

7.4. Demographic and Baseline Characteristics

Subject demographics using the ITT set will be summarized, and repeated on the BSS. These will include age, sex (Male / Female), child-bearing potential (Yes / No), ethnicity (Hispanic or Latino / Not Hispanic or Latino), race (American Indian or Alaska Native / Asian / Black or African American / Native Hawaiian or Pacific Islander / White / Other), years of education, country (United Kingdom/Belgium / Australia/New Zealand), baseline height (cm), baseline weight (kg), and BMI (kg/m^2). Data will be presented by study cohort, disease criteria, and sequence.

Clinical and Cognitive Scales
The Montreal Cognitive Assessment (MoCA, for all subjects) is a brief cognitive screening tool and includes measures of expressive and receptive language, memory, and praxis. There are items that screen executive functions and working memory. The scores range from 0 to 30 with scores lower than 26 suggesting cognitive disorder.

The Digital Symbol Substitution Test (DSST, for MCI subjects only) integrates complex neuropsychological processes and measures aspects of cognitive function, including cognitive and psychomotor speed, attention, visual scanning, and executive function. The maximum attainable score is 135, with higher scores indicating better performance. Further details of the test can be found in Section 5.3.6.1 of the study protocol.

The Modified Hoehn and Yahr Scale (MHYS, for RBD+PD, DLB, and PDD subjects only) is a clinician-completed rating scale that is used to describe the symptom progression of PD. It parses PD into 5 stages, with the additional of stages 1.5 and 2.5 to account for the intermediate course of PD. Details on staging can be found in Section 5.3.6.3 of the study protocol.

The REM Sleep Behavior Disorder Single-Question Screen (RBD1Q, for RBD+PD subjects only) is a single "yes-no" question 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.)?"

MoCA and DSST, MHYS, and RBD1Q data will be summarized in the demographics and baseline characteristics tables and listed by subject.

Descriptions of the Hospital Anxiety and Depression Scale (HADS) can be found in section 8.2 below, and descriptions of Neuromelanin-MRIs can be found in section 8.3 below. Baseline HADS depression and anxiety subscores and neuromelanin MRI contrast-to-noise (by scanner type) will be summarized in the demographics and baseline characteristics table.

These demographic and baseline data will be listed. Additionally, drugs of abuse and alcohol findings and serology data will be listed.

7.5. Medical History

Medical history among the ITT set will be summarized and listed by Medical Dictionary for Regulatory Activities (MedDRA 23.1) system organ class (SOC) and preferred term (PT), and verbatim term as collected in the study database.

7.6. Prior and Concomitant Medication

The incidence of medication use will be summarized by WHO Drug Dictionary (B3, 2020-09-01) anatomic therapeutic chemical classification (ATC) Level 2 classification (i.e., therapeutic main group) and preferred name. A subject will be counted only once at each level of reporting. Prior medications are those which have been identified to have been discontinued prior to the treatment start date (e.g. taken exclusively during the pre-therapy period). Concomitant medications are those which have been identified to have been taken at any point after first dose. Concomitant medication use will be summarized on the ITT set and presented by study cohort, disease type, and sequence, as applicable.

All prior and concomitant medication data will be listed including the verbatim and preferred drug name and ATC Level 2. Procedures and non-med therapies will also be listed.

7.7. Study Drug Exposure and Compliance

Drug exposure will be summarized as a continuous variable in the Safety Set. The duration of drug exposure will be calculated as follows:

$$\text{Duration of Exposure (days)} = \text{Date of Last Dose} - \text{Date of First Dose} + 1$$

In addition, subjects will be assessed for compliance to drug dosing for CST-103 and CST-107 based on number of tablets/capsules dispensed and returned will be provided. The total number of tablets taken will be calculated as the sum of tablets dispensed minus the sum of tablets returned.

- 28 CST-103 or placebo capsules are expected to be taken during each treatment period, per protocol (i.e., two capsules once daily). Summaries will be presented by treatment (i.e., Placebo and CST-103/CST-107) based on each subjects' exposure to each treatment.
- 14 CST-107 or placebo capsules are expected to be taken during each treatment period, per protocol (i.e., one capsule once daily). Summarized will be presented by treatment (i.e., Placebo and CST-103/CST-107) based on each subjects' exposure to each treatment.

Drug exposure will be summarized by cohort, disease type, and treatment taken at time of data collection.

Study drug administration data, including date and time of doses, location of dosing, total number of tablets/capsules dispensed and returned, and compliance will be listed.

8. ENDPOINT ANALYSES

All inferential analyses are exploratory in nature given that this study was not powered based on any statistical assumptions. All efficacy data will be presented by cohort, disease type, and treatment assigned at the time of data collection.

8.1. Primary Endpoint and Analyses

Cohort A

Analyses of FERT data will be summarized in a separate analysis plan.

Cohort B

Due to the small sample size, all primary endpoint data for Cohort B subjects will be listed only using the FAS.

Waking EEG

Analyses of waking EEG data will be summarized in a separate analysis plan.

Activity Tracking (AUS/NZ Subjects Only)

The BioStamp nPoint device will be worn continuously for the 7 days prior to the Treatment Period 1 through the Day 1 visit (Baseline period), and re-dispensed at each of the Day 1 Visits in both periods, worn for 14 days, and removed on Day 14. During each of the three periods in which the subject wears the device, the device calculates 49 cumulative metrics for each day worn within the period. The metrics are then aggregated by study period (Baseline period, Treatment Period 1, Treatment Period 2). The 7 metrics related to activity tracking/classification are:

- Percent Wake Time defined as the percentage of sensor wear time spent awake. All time not spent awake is time spent asleep (identified in the raw data as wake_percent).
- Percent Moving Time defined as the percentage of waking time spent moving (sum of walking and other) (identified in the raw data as moving_percent).
- Percent Moving Other Time defined as the percentage of time spent moving but not walking (identified in the raw data as moving_other_percent).
- Percent Walking Time defined as the percentage of time spent walking

- Moving Activity Count defined as the activity counts per hour during moving periods (identified in the raw data as activity_moving).
- Resting Activity Count defined as the activity counts per hour during resting periods
- Wake Activity Count defined as the activity counts per hour during moving and resting periods (identified in the raw data as activity_resting).

All BioStamp aggregated data will be listed.

Pupillometry

The PLR test will be conducted for each eye in duplicate prior to first dose on Day 1 (Baseline), and 4 hours post dose on Day 1, Day 7, and Day 14 of each treatment period. Results from the duplicate measurements and across eyes will be averaged (i.e., the four pre-dose measurements on Day 1 [left eye occasions 1 and 2; right eye occasions 1 and 2] will be averaged). Parameters collected include initial pupil diameter (INIT), diameter at end of constriction (END), average constriction velocity (ACV), maximum constriction velocity (MCV), averaged dilated velocity (ADV) and time to reach 75% of initial resting diameter during pupillary dilation (T75).

All pupillometry data will be listed.

Dementia Cognitive Fluctuation Scale (DCFS)

The DCFS is a questionnaire consisting of 17 items that queries confusion, differences in functioning through the day, sleep patterns and problems, varying levels of alertness, and clarity of thought/communication. The DCFS will be administered during screening, on Day 1 (Baseline), and on Day 14 of each treatment period.

Responses for all 17 items and domain scores will be reported in by-subject listings.

8.2. Secondary Endpoints and Analyses

The FAS will be used for all secondary endpoint analyses unless stated otherwise. All inferential analyses are exploratory in nature given that this study was not powered based on any statistical assumptions.

<u>Cohort A and Cohort B</u>

CANTAB

Cognition function is assessed using the following CANTAB tests:

- Reaction Time (RTI)
- Verbal Recall Memory (VRM) Phase 1
- Adaptive Tracking Task (ATT)
- Paired Associates Learning Task (PAL)
- Stop Signal Task (SST)

- Delayed Verbal Recall

The cognitive assessments measured as part of the CANTAB tests will be administered prior to dosing on Day 1 (Baseline), and 4 hours after dosing on Days 1, 7, and 14 of each treatment period. Summaries will be presented by cohort, disease type, and treatment sequence.

Absolute values of each key measure at each assessment and changes from baseline will be summarized using descriptive statistics on the FAS. There are sixteen key measures based on the Measures Description downloaded from the CANTAB portal and as described by Cambridge Cognition, which are:

- RTI Median Five-Choice Movement Time: The median time taken for a subject to release the response button and select the target stimulus after it flashed yellow on screen, measured in milliseconds. The measurement name for this parameter in the files downloaded from the CANTAB portal is RTIFMDMT.
- RTI Median Five-Choice Reaction Time: The median duration it took for a subject to release the response button after the presentation of a target stimulus, measured in milliseconds. The measurement name for this parameter in the files downloaded from the CANTAB portal is RTIFMDRT.
- PAL First Attempt Memory Score: The number of times a subject chose the correct box on their first attempt when recalling the pattern locations. The measurement name for this parameter in the files downloaded from the CANTAB portal is PALFAMS.
- PAL Number of Patterns Reached: The number of patterns presented to the subject on the last problem they reached. The measurement name for this parameter in the files downloaded from the CANTAB portal is PALNPR.
- PAL Total Errors (Adjusted): The number of times the subject chose the incorrect box for a stimulus on assessment problems (PALTE), plus an adjustment for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach. The measurement name for this parameter in the files downloaded from the CANTAB portal is PALTEA.
- VRM Free Recall Distinct Stimuli – P1.1: The total number of distinct words that are correctly recalled from the presentation phase by the subject during the P1.1 immediate free recall stage. The measurement name for this parameter in the files downloaded from the CANTAB portal is VRMFR11D.
- VRM Free Recall Distinct Stimuli – P1.2: The total number of distinct words that are correctly recalled from the presentation phase by the subject during the P1.2 immediate free recall stage. The measurement name for this parameter in the files downloaded from the CANTAB portal is VRMFR12D.
- VRM Free Recall Distinct Stimuli – P1.3: The total number of distinct words that are correctly recalled from the presentation phase by the subject during the P1.3 immediate free recall stage. The measurement name for this parameter in the files downloaded from the CANTAB portal is VRMFR13D.
- VRM Delayed Free Recall Distinct Stimuli – P2.1: The total number of distinct words that are correctly recalled from the presentation phase by the subject during the P2.1

delayed free recall stage. The measurement name for this parameter in the files downloaded from the CANTAB portal is VRMFR21D.

- VRM Delayed Recognition Total Correct – P2.2: The total number of target words that the subject correctly recognizes, plus the total number of distractor words that the subject correctly rejects in the P2.2 delayed recognition phase. The measurement name for this parameter in the files downloaded from the CANTAB portal is VRMD22TC.
- ATT Euclidean Distance Mean (Phase 2B): The mean Euclidean distance between Target x/y and Finger Touch x/y coordinates, calculated in pixel over the entire 2B assessed phase of the task. This measure is only calculated during the times that either 'Finger Lift' and/or Multi-touch' are not occurring. The measurement name for this parameter in the files downloaded from the CANTAB portal is ATT2BEM.
- ATT Euclidian Distance Standard Deviation (Phase 2B): The standard deviation of the Euclidean distance between Target x/y and Finger Touch x/y coordinates, calculated in pixels over the entire 2B assessed phase of the task. This measure is only calculated during the times that either 'Finger Lift' or 'Multi-touch' are not occurring. The measurement name for this parameter in the files downloaded from the CANTAB portal is ATT2BESD.
- ATT Difficulty Multiplier Mean (Phase 2B): The mean of the difficulty multiplier calculated over the entire 2B assessed phase of the task. This measure is only calculated during the times that either 'Finger/Lift' and/or 'Multi-touch' are not occurring. The measurement name for this parameter in the files downloaded from the CANTAB portal is ATT2BDM.
- ATT Difficulty Multiplier Standard Deviation (Phase 2B): The standard deviation of the difficulty multiplier calculated over the entire 2B assessed phase of the task. This measure is only calculated during the times that either 'Finger Lift' and/or 'Multi-touch' are not occurring. The measurement name for this parameter in the files downloaded from the CANTAB portal is ATT2BDSD.
- SST Stop Signal Reaction Time: The estimate of time where an individual can successfully inhibit their responses 50% of the time. This covert measurement is sampled from the length of time between the go stimulus and the stop stimulus at which the subject is able to successfully inhibit their response on 50% of the trials. We can infer that this is the time before which all actions become ballistic and the subject is no longer able to cancel their action selection. The measurement name for this parameter in the files downloaded from the CANTAB portal is SSTSRT.
- SST Median RT: All Go Trials: The median reaction time taken across all the valid Go trials in the task. The measurement name for this parameter in the files downloaded from the CANTAB Portal is SSTMRTG.

In addition to the descriptive statistic summaries for the above, for each parameter, a mixed effects model approach will be used to evaluate treatment effect. The model will include change from baseline as the dependent variable, baseline as a covariate, treatment sequence, period, timepoint (i.e, Day 1: 4 hrs post-dose, Day 7: 4 hrs post-dose, Day 14: 4 hrs post-dose), disease type, and treatment as fixed effects, and subject as a random effect. The least square means will be summarized, as well as the least square mean difference between treatments, where the

corresponding p-value for this LS mean difference will be provided. All inferential analyses are exploratory in nature given that this study was not powered based on any statistical assumptions.

Line plots detailing individual subject results of the ATT parameters will be produced.

All CANTAB data, which includes 80 total measurements, will be listed on the FAS.

Verbal Fluency Test

The 'ALPHABET' and 'CATEGORY' tests from the Brief and Simple Index of Cognition (BASIC) tests are used in this study. For the ALPHABET task, subjects are given one 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.

Similar to the CANTAB data, descriptive summaries for the ALPHABET and CATEGORY total scores (identified in the raw data as AAACCPT and CAACCPT, respectively) and change from baseline will be provided at each collection timepoint (i.e, Day 1: 4 hrs post-dose, Day 7: 4 hrs post-dose, Day 14: 4 hrs post-dose), and a mixed effects model with change from baseline as the dependent variable, baseline as a covariate, treatment sequence, period, timepoint, disease type, and treatment as fixed effects, and subject as a random effect. The LS mean, LS mean difference, and p-value for the difference will be reported.

Verbal fluency data will be listed on the FAS.

BioStamp (AUS/NZ Subjects Only)

In addition to activity tracking/classification, the BioStamp nPoint device will continuously track posture (classifications, durations, and temporal patterns), sleeping patterns (duration, posture, transitions, and activity counts), autonomic function (heart rate variability (HRV)), and temporal pedometry via daily step count and gait cadence. There are 29 daily metrics calculated by the BioStamp device related to posture, sleeping patterns, autonomic function, and temporal pedometry. These metrics are then aggregated by study period (Baseline period, Treatment Period 1, Treatment Period 2).

- Posture:
    - Percent Resting Time defined as the percentage of waking time spent resting (sum of lying, sitting, and standing) (identified in the raw data as resting_percent).
    - Percent Lying Time defined as the percentage of waking time spent lying (identified in the raw data as resting_lying_percent).
    - Percent Sitting Time defined as the percentage of waking time spent sitting (identified in the raw data as resting_sitting_percent).
    - Percent Standing Time defined as the percentage of waking time spent standing (identified in the raw data as resting_standing_percent).

    - Percent Upright Posture defined as the percentage of resting time when the patient's posture was classified as upright. All time not classified as upright is classified as leaning (identified in the raw data as upright_posture_percent).
- Sleeping patterns:
    - Average Sleep Duration as defined by average hours of sleep for days that include sleep periods (identified in the raw data as avg_sleep_duration).
    - Average Sleep Posture Transitions as defined by the average number of sleeping posture transitions that occur per hour during sleep (identified in the raw data as sleeping_posture_transitions_rate).
    - Sleeping Activity Counts as defined by activity counts per hour during sleeping periods (identified in the raw data as activity_sleeping).
- Autonomic function:
  Heart Rate Variability (HRV) is computed for each activity period using two methods, LF/HF which is a ratio of low frequency to high frequency and RMSSD which is the root mean square of the successive differences. For each of the 8 metrics below, a set of descriptive statistics is computed (coefficient of variation, minimum, maximum, mean, 5^{th} , 25^{th}, 75^{th}, 95^{th} percentiles, standard deviation), and the mean of each parameter will be assessed using the mixed modeling described later on:
    - Sleeping HRV LF_HF (identified in the raw data as hrv_lfhf_sleeping).
    - Sleeping HRV RMSSD (identified in the raw data as hrv_rmssd_sleeping).
    - Resting HRV LF_HF (identified in the raw data as hrv_lfhf_resting).
    - Resting HRV RMSSD (identified in the raw data as hrv_rmssd_resting).
    - Moving HRV LF_HF (identified in the raw data as hrv_lfhf_moving).
    - Moving HRV RMSSD (identified in the raw data as hrv_rmssd_moving).
    - Waking HRV LF_HF (identified in the raw data as hrv_lfhf_wake).
    - Walking HRV RMSSD (identified in the raw data as hrv_rmssd_wake).

- Temporal pedometry:
    - Average Gait Cadence as defined as steps per minute during walking (identified in the raw data as avg_gate_cadence).
    - Step Count Rate as defined as step counts per hour during periods classified as walking (identified in the raw data as step_count_rate).

If a subject has at least 5 days of sensor wear within each period, the metrics will be aggregated for each period to obtain a single value. Descriptive statistics of the 17 metrics noted above, as well as the 7 activity metrics noted in Section 8.1 above, and change from baseline will be reported for both Cohort A and Cohort B subjects. A mixed model with change from baseline period as the dependent variable, baseline period value as a covariate, treatment sequence, post-baseline period (i.e., 1, 2), disease type, and treatment as fixed effects, and subject as a random effect will be analyzed for these posture, sleep, autonomic function, activity tracking, and temporal pedometry parameters for all subjects and LS means, LS mean differences, and p-values will be presented.

Epworth Sleepiness Scale (ESS)

The ESS is an 8-item, self-administered questionnaire in which subjects are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in 8 different activities. The total score is the sum of the 8 item scores, with scores ranging from 0 (no daytime sleepiness) to 24 (high sleep propensity in daily life). The ESS will be administered on Day 1 (Baseline), Day 7, and Day 14 of each treatment period. Descriptive statistics of total scores and change from baseline will be reported. Additionally, a mixed model will be used to evaluate the treatment effect. The model will include change from baseline as the dependent variable, fixed effects for baseline, treatment sequence, period, timepoint (i.e., Day 7, Day 14), disease type, and treatment, and a random subject effect. LS mean, LS mean difference, and LS mean difference p-value will be reported.

ESS data, including responses to individual questions, will be provided in a listing.

Pupillary Diameter

Summary statistics of the observed values (averages by occasion) and change from baseline for the parameters listed in Section 8.1 (INIT, END, ACV, MCV, ADV, T75) will be reported. In addition, to assess the treatment difference between CST-103/CST-107 and placebo, a mixed model with baseline, treatment sequence, period, timepoint (i.e., Day 1: 4 hrs post-dose, Day 7: 4 hrs post-dose, Day 14: 4 hrs post-dose), disease type, and treatment as fixed effects, and a random subject effect, will be analyzed, with the LS mean, LS mean difference, and p-value for the LS mean difference will be reported for each pupillometry parameter noted above.

Geriatric Depression Scale (GDS)

The GDS is a 30-item self-administered yes/no question test constructed for brief screening of depression in elderly persons. Total scores are the summation of scored responses (responses indicating worsening depression equate to 1, and responses indicating lessening depression equate to 0) from each question. Scores greater than 9 are considered suspect for depression. The GDS will be administered on Day 1 (Baseline), Day 7, and Day 14 of each treatment period. Summary statistics of total scores and change from baseline will be presented. A mixed model with change from baseline as the outcome, baseline as a covariate, fixed effects for treatment sequence, period, timepoint (i.e., Day 7, Day 14), disease type, and treatment, and subject as a random effect will be analyzed. LS mean, LS mean difference and its associated p-value will be reported.

All GDS data, included responses to individual questions, will be listed.

Hospital Anxiety and Depression Scale (HADS)

HADS is a 14-item questionnaire with subscales for anxiety and depression. Subjects are given 14 questions in multiple-choice format, seven about depressive symptoms and seven about anxiety symptoms and are asked to give a score from 0 to 3 where 0 is the least depressed/anxiety option and 3 the most. Depression and Anxiety sub-scores are recorded in the electronic database and are calculated as the sum of responses to the 7 questions within the

category. HADS will be administered on Day 1 (Baseline) and Day 14 of each treatment period. Summary statistics of sub-scores and changes from baseline will be reported. A mixed model to assess the treatment effect, including fixed effects baseline, treatment sequence, period, timepoint (i.e., Day 14), disease type, and treatment, and random subject effect will be analyzed, and LS means, LS mean differences, and associated p-value will be presented.

HADS data will be listed.

8.3. Exploratory Endpoints and Analyses

The FAS will be used for all exploratory endpoint analyses unless stated otherwise.

Cohort A and Cohort B

Inflammatory Biomarkers

Inflammatory biomarkers include C-reactive protein and cytokine levels and will be collected at Day 1 (Baseline) and Day 14 of each treatment period. Descriptive statistics of observed values and change from baseline will be presented for both biomarkers. Inflammatory biomarker data will also be listed.

Neurodegenerative Biomarkers

Neurodegenerative biomarkers including neurofilament light chain, total and phosphorylated tau protein, and amyloid-β (Aβ) peptides will also be collected at Day 1 (Baseline) and Day 14 of each treatment period. Similar to inflammatory biomarker data, descriptive statistics of the neurodegenerative biomarkers and change from baseline to Day 14 will be summarized. All neurodegenerative biomarker data will be listed.

Sustained Attention to Response Task (SART, Cohort B AUS Subjects from Site 502 only)

SART is a computer-based go/no-go task that requires participants to withhold behavioral response to a single, infrequent target presented among a background of frequent non-targets. The subject is asked to respond to the non-target and inhibit their response to the target. Parameters collected include error rate and reaction time. The SART will be administered prior to dosing on Day 1 (Baseline) and 3 hours post-dose on Days 1 and 14 of each treatment period. SART data will be reported in by-subject listings.

Freezing of Gait Questionnaire (FOG-Q, RBD+PD, DLB, and PDD Subjects Only)

The FOG-Q assesses Freezing of Gait (FOG) and consists of six items borrowed from the Gait and Falls Questionnaire. Each question ranges from 0 to 4, with higher scores indicating worsening gait. FOG-Q will be administered on Day 1 (Baseline) and Day 14 of each treatment

period. Summary statistics of responses to each of the six question and change from baseline will be reported. FOG-Q data will additionally be listed.

Neuromelanin MRI Scan

The neuromelanin-sensitive MRI sequence is optional depending on the imaging facility's capabilities, and can be performed at Screening. If not performed at Screening, it may be performed at the Follow-up visit or at any other convenient time during the study. Neuromelanin will be measured to evaluate its suitability as a biomarker of locus coeruleus integrity.

MRI data will be listed.

9. PHARMACOKINETICS

Details regarding PK sampling, including scheduled timepoint and actual date and time of blood draws will be listed. Additional analyses of PK data will be summarized in a separate analysis plan.

10. SAFETY

All safety analysis reporting will be based on the Safety Set. All safety summaries except for laboratory summaries will be presented by cohort, disease type, and treatment taken at time of data collection. Lab summaries will be presented by cohort, disease type, and treatment sequence.

10.1. Adverse Events

Adverse events (AEs) will be recorded from the signing informed consent through end of study. AEs will also be assessed for severity, relationship to study drug, and seriousness. AEs will be considered treatment-emergent if their onset occurs following the date of first dose up to the study completion date. Each TEAE will also be categorized according to the treatment period in which it occurs, in order to attribute and summarize an AE based on treatment received at time of event (i.e., during placebo or active treatment). Events that occur during the washout period between Treatment Period 1 and 2 will be attributed to the treatment received in Period 1, and events occurring after Treatment Period 2 up to the End of Study visit will be attributed to the treatment received in Period 2.

Any missing severity assessments will be assumed to be severe, missing relationship assessments will be assumed to be related, and missing seriousness assessments will be assumed as serious.

An overview of AEs will be produced, including counts and percentages of subjects with any incidences of: treatment-emergent AEs (TEAEs), serious AEs (SAEs), related AEs, unrelated AEs, AEs by maximum severity, AEs leading to treatment withdrawal and AEs leading to death.

Adverse events will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA 23.1) for reporting by system organ class (SOC) and preferred term (PT) in descending order of overall incidence.

Summaries of adverse events by SOC and PT will include the following types:

- TEAEs;
- SAEs; and
- Related AEs.

A summary of TEAEs by SOC, PT, and maximum severity will also be prepared.

A comprehensive listing of all AEs will be provided in a by-subject data listing. In addition, the following listings will be provided:

- SAEs;
- Related AEs; and
- AEs leading to study drug termination

10.2. Clinical Laboratory Evaluations

Hematology and clinical chemistry will be reported based on the International System of Units (SI). The following laboratory evaluations will be summarized using descriptive statistics:

- **Hematology**: hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential, and reticulocyte count.
- **Clinical chemistry**: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, calcium, bicarbonate, serum creatinine, creatinine phosphokinase (CPK), glucose, lipase, phosphate, potassium, sodium, total bilirubin, total cholesterol, total protein, triglycerides, and uric acid. Additionally, the following chemistry parameters collected at Screening only will be included in these outputs: thyroid-stimulating hormone (TSH) and calculated creatinine clearance according to the Cockcroft-Gault equation.

Observed values and changes from screening/baseline, when applicable, for the above laboratory evaluations will be summarized at each visit.

This data will also be summarized in shift tables of baseline to each visit based on range categories of low (below lower limit of normal [LLN], normal, and high [above upper limit of normal [ULN]).

All laboratory results will be provided in subject data listings. The following additional results will be included in these listings:

- **Urinalysis and microscopy**: 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.
- **Serology**: HIV Ab, HbsAg, HbsAb, and HCV Ab (Screening only).
- **Immunology**: SARS-CoV-2 (Screening only).
- **Pregnancy and FSH Tests**: Both urine and serum pregnancy tests will be presented.
- **Urine Drug and Alcohol tests**: Drug tests will include amphetamine, barbiturates, cocaine, opiates.

Box plots of observed results or change from baseline at each visit for potassium and glucose results for each treatment group may be generated.

10.3. Vital Signs

Vital signs will include the following: systolic and diastolic blood pressure (mmHg); heart rate (beats/min), temperature (^{o}C), and respiratory rate (breaths/min). Any vital signs taken in triplicate will be averaged within timepoint.

Observed values and changes from screening/baseline for vital signs will be summarized at each visit and time point. For parameters collected as triplicate measurements, the average of the non-missing measurements will be summarized.

Summaries will be presented by treatment at the time of data collected (i.e., Placebo and CST-103/CST-107).

All vital sign data will be listed.

Box plots of observed results or change from baseline at each visit for heart rate results for each treatment group may be generated.

10.4. Electrocardiogram (ECG)

ECG parameters include: Heart rate, PR interval, RR interval, QRS interval, QT interval and QTcF. Observed values and changes from baseline for ECG parameters will be summarized at each visit and time point.

Electrocardiograms (ECGs) will be interpreted using the following categories: Normal; Abnormal Not Clinically Significant; and Abnormal, Clinically Significant.

Clinical interpretation will also be summarized at each visit and time point.

Additionally, the number and percentage of subjects in each of the following QTcF categories will be tabulated by visit and timepoint:

- QTcF $\leq$ 450 msec
- 450 msec < QTcF $\leq$ 480 msec

- 480 msec < QTcF ≤ 500 msec
- QTcF > 500 msec
- QTcF change from baseline of ≤ 30 msec
- QTcF change from baseline of > 30 msec and ≤ 60 msec
- QTcF change from baseline of > 60 msec

Box plots of observed results or change from baseline at each visit and timepoint for QTcF results for each treatment group may be generated.

10.5. Physical Examinations

Physical examinations will be presented in subject data listings. The following body systems will be assessed:

- General appearance
- Head, Neck, Thyroid
- Ears, Eyes, Nose, Throat, Mouth
- Chest (excluding breasts)
- Respiratory
- Cardiovascular
- Lymph nodes
- Abdomen
- Skin, Hair, Nails
- Musculoskeletal
- Neurological
- Other

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

The Columbia-Suicide Severity Rating Scale measures four elements: the severity of ideation, the intensity of ideation, behavior and lethality. The C-SSRS consists of 10 categories, with a binary response option (yes/no). Categories include:

1. Wish to be Dead
2. Non-specific Active Suicidal Thoughts
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5. Active Suicidal Ideation with Specific Plan and Intent
6. Preparatory Acts or Behavior
7. Aborted Attempt
8. Interrupted Attempt
9. Actual Attempt (nonfatal)
10. Completed Suicide.

The C-SSRS will be completed at Day 1 (Baseline), Day 7, Day 14, and Follow-Up. The outcome of the C-SSRS is a numerical score obtained from the 10 categories stated above.

In addition, three C-SSRS composite indicator variables will be calculated as follows:

(1) C-SSRS suicidal ideation indicator

A composite indicator of C-SSRS suicidal ideation (Items 1-5 above) will be calculated as:

- IF the response to any one of the five suicidal ideation questions is "Yes", THEN set the suicidal ideation indicator equal to 1.
- OTHERWISE, set the suicidal ideation indicator equal to 0.

(2) C-SSRS suicidal behavior indicator

A composite indicator of C-SSRS behavior ideation (Items 6-10 above) will be calculated as:

- IF the response to any one of the five suicidal behavior questions is "Yes", THEN set the suicidal behavior indicator equal to 1.
- OTHERWISE, set the suicidal behavior indicator equal to 0.

(3) C-SSRS suicidal ideation or behavior indicator

A composite indicator of C-SSRS suicidal ideation or behavior will be calculated as:

- IF the response to any one of the 5 suicidal ideation questions or any of the 5 suicidal behavior questions is "Yes", THEN set the suicidal ideation or behavior indicator equal to 1.
- OTHERWISE, set the suicidal ideation or behavior indicator equal to 0.

The C-SSRS will be evaluated in the Safety Set based on methods described by Nilsson. The number and percentage of subjects with any suicidal ideation and/or suicidal behavior following the first dose of study drug will be tabulated.

For the composite endpoint of suicidal ideation, the number and percent of subjects who experience any one of the five suicidal ideation events at least once during treatment through follow-up will be tabulated.

For the composite endpoint of suicidal behavior, the number and percent of subjects who experience any one of the five suicidal behavior events at least once during treatment through follow-up will be tabulated.

For the composite endpoint of suicidal ideation or behavior, the number and percent of subjects who experience any one of the ten suicidal ideation or behavior events at least once during treatment through follow-up will be tabulated.

Results from the C-SSRS will be presented in a listing.

11. REFERENCES

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12. APPENDICES

12.1. APPENDIX 1: Partial Date Conventions

Algorithm for Treatment Emergence of Adverse Events

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= follow-up / end of study, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= follow-up / end of study, assign as concomitant
	Missing	If stop date is missing, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= follow-up / end of study, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= follow-up / end of study, assign as concomitant
	Missing	If stop date is missing, assign as concomitant
Missing	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	If stop date is missing, assign as concomitant

12.2. APPENDIX 2: Protocol Schedule of Events

AUS and NZ Subjects: Schedule of Events for Each Treatment Period

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

	Screening	Lead-In	Treatment Periods 1 & 2[1]			Follow-Up
	Day -28 to Day -8	**Day -14 to Day -1**	**Day 1**	**Day 7[2] (±1)**	**Day 14/EW[3, 4] (±1)**	**~2 Weeks after Last Dose of Study Drug or EW**
Serum or urine pregnancy test[9]			X		X	X
SARS-CoV-2 status assessment[10]	X	X				
PK sample[11]			X		X	
Pharmacodynamic sample collection			X		X	
C-SSRS	X		X[24]	X	X	X
DSST[12, 13]	X					
Dementia Cognitive Fluctuation Scale	X		X		X	
Modified Hoehn & Yahr Scale (MHYS)[12, 15]	X					
HADS[18]	X		X		X	
Freezing of Gait Questionnaire (FOG-Q)[12, 15]			X		X	
RBD1Q[17, 18]	X					
MoCA[12]	X					
Epworth Sleepiness Scale (ESS)[18]		X	X	X	X	
Geriatric Depression Scale (GDS)[18]			X	X	X	

	Screening	Lead-In	Treatment Periods 1 & 2[1]			Follow-Up
	Day -28 to Day -8	**Day -14 to Day -1**	**Day 1**	**Day 7[2] (±1)**	**Day 14/EW[3, 4] (±1)**	**~2 Weeks after Last Dose of Study Drug or EW Visit[3]**
CANTAB[19]		X	X	X	X	
Pupillary Light Reflex (PLR) Test[20]			X	X	X	
EEG[21]			X		X	
Sustained Attention to Response Task (SART)[21]			X		X	
Facial Recognition Task (FERT) [16, 22]			X	X	X	
BioStamp digital device [23]		X	→	→	→	
CST-103+CST-107 or matching placebo administration			→	→	→	
Neuromelanin MRI scan	X[25]					X[25]
Assessment of AEs		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X

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

[1] Wash-out period between Treatment Periods 1 & 2 is 14 (+ 5) days.
[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.
[3] Should there be factors and/or conditions which would make a site visit unnecessarily difficult and/or potentially unsafe for a subject, some visits and/or procedures may be performed by alternate arrangement, e.g., visits in the subject's home, virtual visits.
[4] Subjects who withdraw from the study prior to completion of dosing should complete Day 14 safety assessments at the time of withdrawal.
[5] Vital signs to include BP, HR, respiration rate, and oral/tympanic temperature; triplicate BP and HR measurements (separated by approximately 1 minute) after subject is supine for 5 minutes; vital signs will be obtained at every study visit as follows:

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

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

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

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

[8] Safety labs to include hematology, chemistries, and urinalysis. Subjects should be fasting for 8 hours for the safety labs.

[9] At Screening, serum β-hCG pregnancy test for females of childbearing potential; an FSH test will be performed for postmenopausal women. Females of childbearing potential will have serum or urine pregnancy tests (per standard site practice) on Day 1, Day 14 and at the Follow-Up visit.

[10] Subjects to be assessed for current infection per local site standard procedure.

[11] PK sample timepoints (CST-103/CST-107) in each treatment period:

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

[12] The DSST, DCFS, MHYS, FOG-Q, and MoCA to be done by a qualified clinical rater.

[13] MCI subjects only

[14] Cohort B only; DLB and PDD subjects

[15] RBD+PD, DLB and PDD subjects only

[16] Cohort A only; MCI and RBD+PD subjects

[17] RBD+PD subjects only

[18] The RBD1Q, ESS, HADS, and GDS are per subject self-report.

[19] First administration of CANTAB is to familiarize the subject with the tests and equipment. The CANTAB should be administered after completion of FERT for Cohort A, and after completion of EEG for Cohort B at the following timepoints in each treatment period:

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

[20] The PLR test will be conducted after the CANTAB. The PLR test will be performed at the following timepoints in each treatment period:

4. Day 1:
   1. Prior to first dose
   2. After post dose CANTAB
5. Day 7: After post dose CANTAB
6. Day 14: After post dose CANTAB

[21] Cohort B only: First assessment with EEG on Day 1 pre-dose is to obtain a baseline for each period. The EEG will be conducted on Day 14 in clinic (~1 hour). EEG will be conducted at the following timepoints in each treatment period:

- Day 1:
  - Prior to dosing
  - 3 hours (±15 mins) after dosing
- Day 14: After dosing (up to 3 hours)

Cohort B (select sites only): First administration of Sustained Attention to Response Task (SART) is to obtain baseline for each period (it will be conducted only at a subset of sites). SART will be conducted at the following timepoints in each treatment period:

- Day 1:
  1. Prior to dosing
  2. 3 hours (±15 mins) after dosing such as to occur during the EEG collection period
- Day 14: After dosing (up to 3 hours) such as to occur during the EEG collection period

[22] Cohort A only: FERT will be conducted at the following timepoints in each treatment period:

- Day 1: Prior to dosing
- Day 7: After dosing

- Day 14: After dosing

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

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

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

UK/Belgium Subjects: Schedule of Events for Each Treatment Period

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

	Screening	**Lead-In**	**Treatment Periods 1 & 2[1]**			**Follow-Up**
	Day -28 to Day -8	**Day -14 to Day -1**	**Day 1**	**Day 7[2] (±1)**	**Day 14/EW[3, 4] (±1)**	**~2 Weeks after Last Dose of Study Drug or EW Visit[3]**
Serum or urine pregnancy test[9]			X		X	X
SARS-CoV-2 status assessment[10]	X	X				
PK sample[11]			X		X	
Pharmacodynamic sample collection			X		X	
C-SSRS	X		X[23]	X	X	X
DSST[12, 13]	X					
Dementia Cognitive Fluctuation Scale (DCFS)[12,14]	X		X		X	
Modified Hoehn & Yahr Scale (MHYS)[12, 15]	X					
HADS[18]	X		X		X	
Freezing of Gait Questionnaire (FOG-Q)[12, 15]			X		X	
RBD1Q[17, 18]	X					
MoCA[12]	X					
Epworth Sleepiness Scale (ESS)[18]		X	X	X	X	
Geriatric Depression Scale (GDS)[18]			X	X	X	

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

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

[1] Wash-out period between Treatment Periods 1 & 2 is 14 (+ 5) days.
[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.
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- Screening
- Lead-In
- Day 1 of each treatment period:
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  - 1 hour (±30 mins) after dosing
  - 4 hours (±30 mins) after dosing
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  - Day 7: After dosing (up to 4 hours)
  - Day 14: After dosing (up to 4 hours)
- Cohort B:
  - Day 1:
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    2. 4 hours (±30 mins) after dosing
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- Day 14: After post dose CANTAB

[21] Cohort B only: First assessment with EEG on Day 1 pre-dose is to obtain a baseline for each period. The EEG will be conducted on Day 14 in clinic (~1 hour). EEG will be conducted at the following timepoints in each treatment period:

- Day 1:
  1. Prior to dosing
  2. 3 hours (±15 mins) after dosing
- Day 14: After dosing (up to 3 hours)

Cohort B (select sites only): First administration of Sustained Attention to Response Task (SART) is to obtain baseline for each period (it will be conducted only at a subset of sites). SART will be conducted at the following timepoints in each treatment period:

- Day 1:
  1. Prior to dosing
  2. 3 hours (±15 mins) after dosing such as to occur during the EEG collection period
- Day 14: After dosing (up to 3 hours) such as to occur during the EEG collection period

[22] Cohort A only: FERT will be conducted at the following timepoints in each treatment period:

- Day 1: Prior to dosing
- Day 7: After dosing
- Day 14: After dosing

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

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