Statistical Analysis Plan

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

SAP Version and date: Draft 3.0, 25-July-2023

STUDY DRUG:
CST-2032, CST-107

PREPARED FOR:

CuraSen Therapeutics, Inc.
930 Brittan Avenue, #306
San Carlos, CA 94070, USA

PREPARED BY:

[redacted]

Approval Signature Page

[redacted]

Document Author: [redacted] Date
Biostatistician II
Signature by Manager: [redacted]
Director, Biostatistics

Document Reviewer: [redacted] Date
Senior Biostatistician I

CuraSen Therapeutics, Inc.

Document Reviewer: [redacted] Date
Chief Medical Officer

Revision History

SAP Revision Chronology:

Version 1.0	16-February-2023	
Version 2.0	25-April-2023	Amend Section 4.5 Timing of Analysis for adjusted interim analysis timing.
Version 3.0	25-July-2023	Amend Section 2 Introduction for updated protocol and CRF versions. Amend Section 4.5 Timing of Analysis to include additional outputs. Amend Section 9.2 Secondary Endpoints and Analyses for planned analyses in case of model convergence issues, repeat analyses on the per protocol set, and addition of MoCA analyses.

Contents

1 ABBREVIATIONS

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
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
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
Cmax	Maximum concentration
CNR	Contrast-to-noise ratio
CNS	Central nervous system
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CST-107	Nadolol
DSMB	Data and Safety Monitoring Board
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5
DSST	Digital Symbol Substitution Test
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
EW	Early withdrawal
FAS	Full analysis set
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
MD	Mild Dementia
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
PKS	PK set
PO	By mouth/oral administration
PPS	Per protocol set
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
RBD1Q	REM Sleep Behavior Disorder 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

2 INTRODUCTION

The statistical analysis plan (SAP) details the planned statistical analysis methods required to address the study objectives as described in CuraSen's protocol CST2032/CST-107-CLIN-015: 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 SAP should be read in conjunction with the study protocol, case report form (CRF), and any other applicable study documents. This version of the SAP is based on the protocol CST2032-CST107-CLIN-015, Amendment 10 dated 11Jul2023 and CRF version 7.0 dated 31Mar2023. Changes to these documents may result in subsequent changes to the SAP. The final, sponsor-approved version of the SAP must occur prior to database lock.

2.1 Changes to the Planned Analysis

There is still no adjustment of Type I error but hypotheses are not designated in priority order for hierarchical testing.

3 STUDY OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
The primary objective of this study is to evaluate the safety and tolerability of CST-2032 when combined with CST-107.	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	
The secondary objectives of this study will evaluate the effects of CST-2032 when combined with CST-107 versus placebo on the following measures: 1. Cognition 2. Mood 3. Attention Deficit 4. Apathy 5. Overall clinical improvement 6. PK	The secondary endpoints will compare the effect of CST-2032 administered with CST-107 versus placebo on the following: • Cognitive tasks in the Cambridge Neuropsychological Test Automated Battery (CANTAB) and other cognitive measures: o Reaction Time (RTI) – attention o Verbal Recognition Memory (VRM) – episodic memory (verbal stimuli) o Adaptive Tracking Task (ATT) – visuospatial with strong attentional demand o 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 (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, $t_{1/2}$).
Exploratory	
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.	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, genetic variants involved in neurodegenerative disease including but not limited to apolipoprotein E4 (APOE4), leucine rich repeat linase2 (LRRK2), and glucocerebrosidase (GCase) protein

	(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 the Cognitive tasks in the Cambridge Neuropsychological Test Automated Battery (CANTAB) and other cognitive measures.

4 STUDY DESIGN

4.1 General Description

This is a Phase 2a, randomized, placebo-controlled, double-blind crossover study to evaluate the safety, tolerability and effects 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.

During each treatment period, subjects will receive 3 mg CST-107 or matching placebo on Day -1, followed by daily doses of 3 mg CST-2032 (co-administered with 3 mg CST-107) or matching placebo on Day 1 through Day 14. The study medications will be provided as oral tablets for CST-2032, CST-107, and corresponding matching placebos. Each treatment period will be separated by a washout period of at least 7 days and up to 21 days.

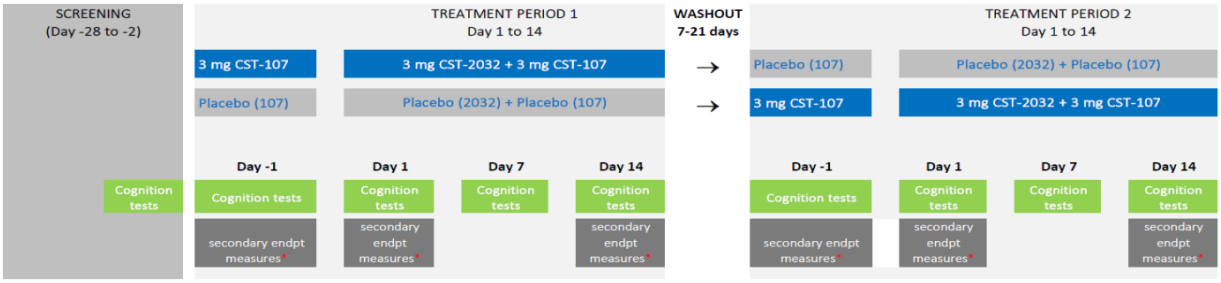
All subjects will complete clinical, cognitive and pharmacodynamic assessments during each treatment period as indicated in the Scheduled of Events in Appendix 2 of this SAP.

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

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.

Subjects will be enrolled at up to 20 clinical sites in the USA and New Zealand.

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.

4.2 Randomization and Blinding

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.

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.

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.

4.3 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.

4.4 Study Committees

4.4.1 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to assess participant safety at predetermined intervals (including an optional interim analysis) during the study as needed. Further details will be provided in the DSMB Charter.

4.5 Timing of Analyses

An unblinded interim analysis may be conducted after approximately 50% of subjects have completed Treatment Period 1. A subset of the analysis will be reviewed in closed DSMB sessions and all results will be reviewed by the unblinded CuraSen team. Results reviewed by the DSMB are marked in the table below with asterisks. All efforts will be made by data management to clean the data as much as possible for this analysis. It is expected that the following set of 24 outputs will be generated:

Number	Title	Population
14.1.1*	Subject Disposition	Intent to Treat Set
14.1.2*	Demographics and Baseline Characteristics	Intent to Treat Set
14.2.2.1.1*	Secondary Endpoint: CANTAB Observed and Change from Baseline Results by Timepoint	Full Analysis Set
14.2.2.1.2	Secondary Endpoint: CANTAB Observed and Change from Baseline Results by Timepoint – Subgroup Analysis	Full Analysis Set
14.2.2.1.3*	Secondary Endpoint: CANTAB Observed and Change from Baseline Results by Timepoint during Treatment Period 1	Full Analysis Set
14.2.2.1.4*	Secondary Endpoint: CANTAB Observed and Change from Baseline Results by Timepoint during Treatment Period 2	Full Analysis Set
14.2.2.1.5*	Secondary Endpoint: CANTAB Observed and Change from Baseline Results by Timepoint	Per Protocol Set
14.2.2.1.6	Secondary Endpoint: CANTAB Observed and Change from Baseline Results by Timepoint – Subgroup Analysis	Per Protocol Set
14.2.2.1.7*	Secondary Endpoint: CANTAB Observed and Change from Baseline Results by Timepoint during Treatment Period 1	Per Protocol Set
14.2.2.1.8*	Secondary Endpoint: CANTAB Observed and Change from Baseline Results by Timepoint during Treatment Period 2	Per Protocol Set

14.2.2.2.1*	Secondary Endpoint: Verbal Fluency Test Observed and Change from Baseline Results by Timepoint	Full Analysis Set
14.2.2.2.2	Secondary Endpoint: Verbal Fluency Test Observed and Change from Baseline Results by Timepoint – Subgroup Analysis	Full Analysis Set
14.2.2.3.1*	Secondary Endpoint: Digital Symbol Substitution Test Observed and Change from Baseline Results by Timepoint	Full Analysis Set
14.2.2.3.2	Secondary Endpoint: Digital Symbol Substitution Test Observed and Change from Baseline Results by Timepoint – Subgroup Analysis	Full Analysis Set
14.2.2.9.1*	Secondary Endpoint: Montreal Cognitive Assessment Observed and Change from Baseline Results by Timepoint	Full Analysis Set
14.2.2.9.2	Secondary Endpoint: Montreal Cognitive Assessment Observed and Change from Baseline Results by Timepoint – Subgroup Analysis	Full Analysis Set
14.3.1.1*	Overall Summary of Adverse Events	Safety Set
14.3.1.2*	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
14.3.1.3*	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Set
14.3.4.1.1*	Hematology – Observed Results and Change from Baseline by Timepoint	Safety Set
14.3.4.2.1*	Clinical Chemistry – Observed Results and Change from Baseline by Timepoint	Safety Set
14.3.4.2.2	Clinical Chemistry – Shifts from Baseline by Timepoint	Safety Set
14.3.5.1*	Vital Signs – Observed Results and Change from Baseline by Timepoint	Safety Set
14.3.6.1*	Electrocardiogram (ECG) – Observed Results and Change from Baseline by Timepoint	Safety Set

* denotes outputs to be reviewed by the DSMB

The efficacy analyses may be performed on all subjects included in the interim analysis and/or, separately, for AD and/or PD subgroups in this set. Additionally, further analyses of PD-MCI, PD-MD, AD-MCI, and AD-MD subgroups may be undertaken in the efficacy analyses if sufficient subjects are enrolled. A final decision on the populations to be analyzed will be made prior to the

interim analysis based on the number of subjects enrolled with PD or AD, and within the further MCI or MD groups. For example, the Sponsor may elect to exclude a patient population from the interim analysis if the post-dose data are available for fewer than e.g., 25 subjects. The baseline and safety summaries will be performed on all subjects included in the interim analysis regardless of the patient population(s) selected for efficacy analysis.

To produce these outputs, a biostatistician and a statistical programmer from [redacted], separate from the primary study team, will be unblinded to treatment assignments and work within a restricted domain inaccessible to all other [redacted] members. No additional team members from [redacted] or CuraSen will become unblinded until after database lock and release of the live randomization list at the time of study completion. The unblinded statistician will be in attendance during the closed DSMB sessions for the purpose of presenting and interpreting the interim analysis results. Additional information regarding the roles, responsibilities, and objectives for the DSMB will be outlined within a DSMB charter, separate from this SAP.

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

5 ANALYSIS SETS/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 (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 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 (i.e., has no protocol deviations labeled as “major”). 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.

6 DATA ANALYSIS CONSIDERATIONS

6.1 General Data Handling

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

Study data will be recorded in eCRFs for all screened and randomized patients. The EDC vendor for this study is MedNet Solutions.

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

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

Unless stated otherwise, categorical data will be summarized by disease type, treatment sequence, and overall using frequency counts and percentages. Where applicable, 95% confidence intervals (CIs) will be provided. Unless otherwise stated, the denominator of percentages will be the number of participants in the population/treatment arm or the number with non-missing data.

- 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.

Relative to the number of digits after the decimal in the raw data, summary statistics will have the following number of digits after the decimal:

- Minimum and Maximum: same number of significant digits as the raw data
- Mean and Median: one additional decimal place to that reported for Minimum and Maximum
- SD or Standard Error (SE): 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 is 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.

6.2 Stratification and Covariates

There are no formal plans for analysis stratification.

6.3 Evaluation of Subgroups

All summaries and analyses will be performed by (PD) and (AD). Select secondary efficacy endpoints will be further analyzed by MCI and MD categories (PD-MCI, PD-MD, AD-MCI, and AD-MC).

6.4 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.

7 GENERAL CONSIDERATIONS

7.1 Reference Dates

- Screening date is defined as the eCRF provided date on which a subject was screened for trial entry and informed consent was obtained.
- Treatment start date is defined as the date of first dose of CST-2032 or matching placebo. Each treatment period will have a treatment start date (i.e., in order to determine AEs occurring during a treatment). Subjects commence dosing of CST-107 or matching placebo 1 day earlier and this will be considered Day -1.
- 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.

7.2 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.

7.3 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.

7.4 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.

7.5 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 in subject data listings.

8 STUDY SUBJECT DATA

8.1 Subject Enrollment and 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 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.

8.2 Protocol Deviations

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

Protocol waiver data will also be recorded and detailed in a data listing.

8.3 Demographic and Baseline Characteristics

Subject demographics using the ITT set will be summarized. 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, baseline height (cm), baseline weight (kg), and BMI (kg/m2). Data will be presented by disease criteria and sequence.

8.4 Clinical and Cognitive Scales

The Montreal Cognitive Assessment (MoCA) 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) 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 PD 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 5.3.6.8 of the study protocol.

The REM Sleep Behavior Disorder Single-Question Screen (RBD1Q) 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.)?” RBD1Q will be evaluated for all subjects but used to assess eligibility for only PD subjects.

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

8.5 Medical History

Medical history among the ITT set will be summarized and listed by Medical Dictionary for Regulatory Activities (MedDRA 24.1) system organ class (SOC) and preferred term (PT), and verbatim term as collected in the study database.

8.6 Prior, Concomitant, and Rescue Medication

The incidence of medication use will be summarized by WHO Drug Dictionary (B3 2021-09-01) anatomic therapeutic chemical (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 and prior to the start of CST-2032 or matching placebo on Day 1). Concomitant medications are those which have been identified to have been taken at any point after first dose. Subjects who are administered rescue medications are those which have been administered rescue nadolol when there is an intolerable HR/BP increase. Prior, concomitant, and rescue medication use will be summarized separately and presented by disease and treatment group.

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

8.7 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 follow:

Duration of Exposure (days) = Date of Last Dose – Date of First Dose + 1

In addition, subjects will be assessed for compliance to drug dosing for CST-2032 and CST-107 based on number of tablets 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-2032 or placebo tablets are expected to be taken during each treatment period, per protocol (i.e., two tablets once daily beginning on Day 1). Summaries will be presented by treatment (i.e., Placebo and CST-2032/CST-107) based on each subject's exposure to each treatment.

- 15 CST-107 or placebo tablets are expected to be taken during each treatment period, per protocol (i.e., one tablet once daily beginning on Day -1). Summarized will be presented by treatment (i.e., Placebo and CST-2032/CST-107) based on each subject's exposure to each treatment.

Drug exposure will be summarized by 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 dispensed and returned, and compliance will be listed.

9 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.

9.1 Primary Endpoint and Analyses

The SAF will be used for all primary endpoint analyses unless otherwise stated otherwise. The primary objective of this study is to evaluate the safety and tolerability of CST-2032 when combined with CST-107. Further details regarding safety analyses can be found in Section 11.

9.2 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.

CANTAB

Cognition function is assessed using the following CANTAB tests:

- Reaction Time (RTI)
- Verbal Recall Memory (VRM)
- 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 on Day -1 (Baseline), and 3 hours after dosing on Days 1, 7, and 14 of each treatment period. Summaries will be presented by disease type and treatment sequence.

There are eighteen 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.
- VRM Free Recall Distinct Stimuli Mean – P1.1-1.3: The mean of times a subject repeats a word that was shown during the presentation phase in the P1.3 immediate free recall stage. The measurement name for this parameter in the files downloaded from the CANTAB portal is VRMFRDM.
- VRM Free Recall Distinct Stimuli Median – P1.1-1.3: The median number of distinct words that are correctly recalled from the presentation phase by the subject during the P1.1-1.3 immediate free recall stages. The measurement name for this parameter in the files downloaded from the CANTAB portal is VRMFRDMD.
- 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 SSTSSRT.
- 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.

Additionally, 3 more verbal recall parameters will be derived for analysis:

- VRM Free Recall Distinct Stimuli Mean Errors – P1.1-1.3: For each recording of VRMFRDM, a new record will be derived as the value of VRMFRDM subtracted from 18. The parameter decode will be VRMFRDME.
- VRM Delayed Free Recall Distinct Stimuli Errors – P2.1: For each recording of VRMFR21D, a new record will be derived as the value of VRMFR21D subtracted from 18. The parameter decode will be VRMFR21E.
- VRM Delayed Recognition Total Correct Errors – P2.2: For each recording of VRMD22TC, a new record will be derived as the value of VRMD22TC subtracted from 36. The parameter decode will be VRMD22TE.

For all 21 parameters, observed values at each assessment and changes from baseline will be summarized using descriptive statistics on the FAS and PPS. In addition to the descriptive statistic summaries, 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: 3 hrs post-dose, Day 7: 3 hrs post-dose, Day 14: 3 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. If there are convergence issues, alternative covariance structures may be used including autoregressive of order 1 (AR1) and compound symmetry (CS). The effect size will be estimated using Cohen's D: difference in means / pooled SD. This analysis will be performed using AD and PD as subgroups, and again using AD-MCI, AD-MD, PD-MCI, and PD-MD as subgroups.

Additionally, using treatment period 1 and treatment period 2 data separately, all 21 parameters will have observed value and change from baseline summarized, and a mixed effects model with change from baseline as the dependent variable, baseline as a covariate, timepoint (i.e., Day 1:3 hrs post-dose, Day 7: 3 hrs post-dose, Day 14: 3 hrs post-dose), disease type, and treatment as fixed effects, and subject as a random effect will be evaluated. The least square means, least

square mean differences, and associated p-values will be presented. AR1 and CS covariance structures may be explored if there are convergence issues. The effect size will be estimated using Cohen's D: difference in means / pooled SD. These analyses will be presented by AD and PD subgroups and no further subgroup categorization. The analyses will be presented on the FAS and repeated on the PPS.

Bar plots of the arithmetic mean of observed values with error bars of the standard error of the mean, arithmetic mean of change from baseline with error bars of the standard error bars of the mean change, and least square mean change with error bars of the standard error will be produced for the following CANTAB parameters:

- VRM Free Recall Distinct Stimuli Mean – P1.1-1.3 (VRMFRDM)
- VRM Free Recall Distinct Stimuli – P1.1 (VRMFR11D)
- VRM Free Recall Distinct Stimuli – P1.2 (VRMFR12D)
- VRM Free Recall Distinct Stimuli – P1.3 (VRMFR13D)
- VRM Delayed Free Recall Distinct Stimuli – P2.1 (VRMFR21D)
- VRM Delayed Recognition Total Correct – P2.2 (VRMD22TC)

Bar plots of the least square mean change with error bars of the standard error only will be produced for the following CANTAB parameters:

- PAL Total Errors (Adjusted) (PALTEA)
- RTI Median Five-Choice Reaction Time (RTIFMDRT)
- RTI Median Five-Choice Movement Time (RTIFMDMT)
- ATT Difficulty Multiplier Mean (ATT2BDM)
- SST Stop Signal Reaction Time (SSTSSRT)

All plots will be presented separately for AD and PD subjects.

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

Phonological verbal fluency (pVFT)

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

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.

The pVFTs will be administered on Day -1 (Baseline), Day 1, Day 7, and Day 14 of each treatment period. Summary statistics of observed values 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 1, 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. AR1 and CS covariance structures may be explored if there are convergence issues. The effect size will be estimated using Cohen's D: difference in means / pooled SD. This analysis will be performed using AD and PD as subgroups, and again using AD-MCI, AD-MD, PD-MCI, and PD-MD as subgroups. The analysis will be presented on the FAS and repeated on the PPS.

Bar plots of the least square mean change of Alphabet and Category scores with error bars of the standard error will be produced, separated by AD and PD.

All pVFT data will be listed.

Facial Expression Recognition Task (FERT)

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

Digital Symbol Substitution Test (DSST)

The DSST will be administered on Day -1 (Baseline), Day 1, Day 7, and Day 14 of each treatment period. Summary statistics of the total score observed values 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. AR1 and CS covariance structures may be explored if there are convergence issues. The effect size will be estimated using Cohen's D: difference in means / pooled SD. This analysis will be performed using AD and PD as subgroups, and again using AD-MCI, AD-MD, PD-MCI, and PD-MD as subgroups. The analysis will be presented on the FAS and repeated on the PPS.

A bar plot of the least square mean change of DSST total score with error bars of the standard error will be produced, separated by AD and PD.

All DSST data will be listed.

Geriatric Depression Scale – 30 questions (GDS-30)

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 1, 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 1, 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. AR1 and CS covariance structures may be explored if there are convergence issues. The effect size will be estimated using Cohen's D: difference in means / pooled SD.

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

Conners Adult Attention Deficit Hyperactivity Disorder Scale (ADHD) Rating Scale, short form, self-report (CAARS)

The CAARS is a 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. Individuals are asked to rate themselves on a range of symptoms and behaviors associated with ADHD as adults using a 4-point scale: 0=Not at all/never; 1=Just a little/once in a while; 2=Pretty much/often; 3=Very much/very frequently. The CAARS will be administered on Day -1 (Baseline), Day 1, and Day 14 of each treatment period. Total score will be derived as the sum of results from the 26 questions at each visit and can range from 0 to 78. Subscales will be derived as follows:

- Inattention/Memory Problems: sum of scores from questions 3, 5, 17, 18, and 21
- Hyperactivity/Restlessness: sum of scores from questions 4, 6, 10, 11, and 23
- Impulsivity/Emotional Lability: sum of scores from questions 1, 7, 8, 13, and 20
- Problems with Self-Concept: sum of scores from questions 9, 15, 16, 25, and 26
- ADHD Index: sum of scores from questions 2, 7, 8, 9, 11, 12, 14, 17, 19, 22, 24, and 26

Summary statistics of the 5 subscales and 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 1, 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. AR1 and CS covariance structures may be explored if there are convergence issues. The effect size will be estimated using Cohen's D: difference in means / pooled SD.

All CAARS data, including responses to individual questions, will be listed.

Starkstein Apathy scale short form (SAS-6)

The SAS-6 is a 6-item questionnaire read by an examiner to measure the severity of apathetic symptoms. Each question has four possible answers: "not at all," "slightly," "some," or "a lot" which are scored on a 4-point Likert scale (range: 0–3). Total scores will be derived the summation of scored responses (higher scores indicate more severe apathy) from each question and can range from 0 to 18. The SAS-6 will be administered on Day -1 (Baseline), Day 1, 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 1, 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. AR1 and CS covariance structures may be explored if there are convergence issues. The effect size will be estimated using Cohen's D: difference in means / pooled SD.

All SAS-6 data, included responses to individual questions, will be listed.

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

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. Further details of the test can be found in Section 5.3.7.4 of the study protocol. The ADCS-CGIC will be administered on Screening (Baseline) and Day 14 of each treatment period. Scores range from 1 (marked improvement) to 7 (marked worsening), where 4 indicates no change. Summary statistics of scores at Day 14 will be presented. A mixed model with the score as the outcome, fixed effects for treatment sequence, period, timepoint (i.e., 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. AR1 and CS covariance structures may be explored if there are convergence issues. The effect size will be estimated using Cohen's D: difference in means / pooled SD.

All ADCS-CGIC data will be listed.

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. The Color Trails Test will be administered on Day -1 (Baseline), Day 7, and Day 14 of each treatment period at selected sites. Summary statistics of completion times for Part 1, Part 2, and their time difference 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 and 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. AR1 and CS covariance structures may be explored if there are convergence issues. The effect size will be estimated using Cohen's D: difference in means / pooled SD.

A bar plot of the least square mean change of the Part 2 completion time with error bars of the standard error will be produced, separated by AD and PD.

All Color Trails Test data will be listed.

Montreal Cognitive Assessment (MoCA)

Details of MoCA are outlined in section 8.4 of this SAP. The MoCA will be collected at Screening (Baseline) and Day 14 of each treatment period. Summary statistics of the MoCA-MIS Score and MoCA Total Score 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 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. AR1 and CS covariance structures may be explored if there are convergence issues. The effect size will be estimated using Cohen's D: difference in means / pooled SD. This analysis will be performed using AD and PD as subgroups, and again using AD-MCI, AD-MD, PD-MCI, and PD-MD as subgroups.

All MoCA data will be listed.

9.3 Exploratory Endpoints and Analyses

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

Neurodegenerative Biomarkers

Neurodegenerative biomarkers including neurofilament light chain, total and phosphorylated tau protein, and amyloid-β (Aβ) peptides will also be collected at Screening and Day 14 of each treatment period. If data is available descriptive statistics of the neurodegenerative biomarkers and change from baseline to Day 14 will be summarized. Additionally, genetic biomarkers including APOE4, LRRK2, and GBA may be collected at Screening and descriptive statistics may be tabulated if numeric. All biomarker data will be listed.

Z-scores

Z-scores will be calculated for the observed values of select CANTAB, pVFT, and DSST endpoints using the formula: z = (observed value - normative mean) / normative SD. Normative means and standard deviations can be found in Appendix 3, and specifics on which parameters will be used in z-score derivations (ATT2BDM, PALTEA, RTIFMDRT, SSTSSRT, and VRMFR11D) are in section 9.2 in the CANTAB section. Z-scores will also be derived for the Alphabet and Category total scores of pVFT and the DSST total score. For the endpoints of PALTEA, RTIFMDRT and SSTSSRT, in which higher scores reflect poor performance, the sign of z-scores will be reversed by multiplying the calculated z-score by -1. Hence a positive z-score will reflect an outcome better than the norm and a negative z-score will reflect an outcome worse than the norm. In the case of the adaptive tracking test in the CANTAB, normative data are from prior studies conducted by CuraSen. For endpoints for which multiple norms are shown in Appendix 3, pooled estimates of the normal mean and SD, weighted by the sample size, will be used to calculate the z-scores. Z-scores for DSST will use norms based on the age of the subject. Normative data for the CANTAB, VFT, and DSST endpoints are summarized in Appendix 3. Normative data for the verbal fluency tests, DSST and most of the tests within the CANTAB are defined from published studies in which the tests were administered in an approximately similar manner as the CLIN-011 study. Normative data are based on untreated, approximately age matched cognitively normal populations, except for the Stop Signal Test where data are only available for a young adult population are available.

Summary statistics of z-scores and change from baseline for subjects with a baseline deficit will be presented for each of the 5 CANTAB parameters marked. Baseline deficit is defined as having a baseline z-score less than -0.5. Subjects with baseline values greater than or equal to -0.5 will not be summarized. Additionally, a mixed model approach will be used to evaluate treatment effect. The model will include change from baseline in z-score as the dependent variable, baseline as a covariate, treatment sequence, period, timepoint (i.e., Day 1: 3 hrs post-

hose, Day 7: 3 hrs post-dose, Day 14: 3 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.

Summary statistics of z-scores and change from baseline for subjects with a baseline deficit for the two pVFT parameters will also be presented. Baseline deficit is defined as having a baseline z-score less than -0.5, and subjects with baseline values greater than or equal to -0.5 will not be summarized. Additionally, a mixed model with z-score change from baseline as the dependent variable, baseline as a covariate, treatment sequence, period, timepoint (i.e., Day 1, Day 7, Day 14), disease type, and treatment as fixed effects, and subject as a random effect will be analyzed, with the least square means, least square mean difference, and corresponding p-value will be provided.

Summary statistics of z-scores and change from baseline for subjects with a baseline deficit for DSST total score will be presented. Baseline deficit is defined as having a baseline z-score less than -0.5, and subjects with baseline values greater than or equal to -0.5 will not be summarized. Additionally, a mixed model with z-score change from baseline as the dependent variable, baseline as a covariate, treatment sequence, period, timepoint (i.e., Day 1, Day 7, Day 14), disease type, and treatment as fixed effects, and subject as a random effect will be analyzed, with the least square means, least square mean difference, and corresponding p-value will be provided.

10 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.

11 SAFETY

11.1 Adverse Events

Adverse events (AEs) will be recorded from the time of randomization 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 and time of first dose of CST-2032 or matching placebo 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 24.1) 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

11.2 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, and white blood cell (WBC) count with differential, reticulocyte count.
- Clinical chemistry: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, calcium, bicarbonate, serum creatinine, creatinine phosphokinase (CPK), glucose, lipase, amylase, 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: calculated creatinine clearance according to the Cockcroft-Gault equation.
- 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.

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:

- 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.
- COVID-19: SARS-CoV-2 (Screening only)

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

11.3 Vital Signs

Vital signs will include the following: systolic and diastolic blood pressure (mmHg); heart rate (beats/min), temperature (ºC), and respiratory rate (breaths/min).

Observed values and changes from screening/baseline for vital signs will be summarized at each visit and time point. Summaries will be presented by treatment at the time of data collected (i.e., Placebo and CST-2032/CST-107). If multiple collections occur for the same visit and timepoint in two positions, the values will be averaged.

All vital sign data will be listed.

Box plots of observed results or change from baseline at each visit for heart rate, systolic blood pressure, and diastolic blood pressure results for each treatment group may be generated.

11.4 Electrocardiogram (ECG)

ECG parameters include: Heart rate, PR interval, RR interval, QRS interval, QT interval, QTcB interval, and QTcF interval. Observed values and changes from baseline for ECG parameters will be summarized at each visit and time point. The baseline measurement may include up to 9 repeat observations, and all repeats will be averaged to obtain a single baseline value. Any ECG parameters taken in triplicate post-baseline will be averaged within timepoint.

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 $\leq$ 500 msec
- QTcF > 500 msec
- QTcF change from baseline of $\leq$ 30 msec

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

For parameters collected as triplicate measurements, the average of the non-missing measurements will be summarized.

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

11.5 Physical Examinations

Physical examination abnormalities 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

11.6 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 Screening(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.

12 REFERENCES

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH E3 Guideline: Structure and content of clinical study reports questions & answers (R1). 2012.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf. Accessed 13 Jan 2016.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports E3. Step 4. 1995. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf. Accessed 13 Jan 2016.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH E9: Statistical principles for clinical trials. 1998. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf . Accessed 15 June 2016.

PhUSE CSS Development of Standard Scripts for Analysis and Programming Working Group. Analyses and Displays Associated with Demographics, Disposition, and Medications in Phase 2-4 Clinical Trials and Integrated Summary Documents. 2014. http://www.phusewiki.org/wiki/images/c/c9/CSS_WhitePaper_DemoDispMed_v1.0.pdf . Accessed 03 Jan 2017.

PhUSE CSS Development of Standard Scripts for Analysis and Programming Working Group. Analyses and Displays Associated to NonCompartmental Pharmacokinetics – With a Focus on Clinical Trials. 2014. http://www.phusewiki.org/wiki/images/e/ed/PhUSE_CSS_WhitePaper_PK_final_25March2014.pdf . Accessed 31 Dec 2016.

Nilsson ME, Suryawanshi S, Gassmann-Mayer C, Dubrava S, McSorley P, and Jiang K. (2013). Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide. Retrieved from http://www.cssrs.columbia.edu/documents/ScoringandDataAnalysisGuide_Feb2013.pdf.

13 APPENDICES

13.1 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 if day unknown or 31st December if day and month 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

13.2 APPENDIX 2: Protocol Schedule of Events

	Screening	**Treatment Periods 1 & 2[1]**				**End of Study**
	Day -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 genetic variant, LRRK2, GBA (optional and where applicable)	X					
Neurodegeneration biomarkers	X				X	
PK sample[11]				X		
RBD1Q, MHYS[12]	X					

	Screening	Treatment Periods 1 & 2[1]				End of Study
	Day -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]
MoCA[12]	X				X	
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	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 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 apartduring 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.

13.3 APPENDIX 3: Normative Data for Cognition Tests Used in this SAP

Test	Test Code	Mean Result	Standard Deviation	N	Population	Reference
DSST (2 min)	N/A	70.0	16.3	Subset of N=2200, from Wechsler 2008	35-44y	Wisdom et al 2012
		65.0	16.0		45-54y	
		59.5	15.5		55-64y	
		54.4	15.5		65-69y	
		49.5	15.5		70-74y	
		44.5	16.0		75-79y	
Verbal Fluency – Alphabet (items per minute)	AAACCPT	15.3	4.6	365	Healthy adults, mean age 41y, average 14.2 years of edu, 55% female	Harrison et al 2000
Verbal Fluency – Category (items per minute)	CAACCPT	17.9	6.8	46	Healthy adults >=65y	
Adaptive Tracking Test	ATT2BDM	4.8	0.45	8	Healthy 55-75y	CST2032-CLIN-001 (Cohort D2)
		5.2	0.29	16	Healthy 55-75y	CST103-CST139-CLIN-010 (Part D)
Paired associates learning test (PAL)	PALTEA	34.3	16.7	1349	Healthy adults 57-84y	Abbott et al 2018
		25.8	18.9	1204	Atherosclerosis and LDL >70mg/dL, 40-85y (mean=62.7y), 72% male, 92% white, 12.7y education, 74% on beta blockers. Excl: dementia and MCI	Guigliano et al 2017
5-choise Reaction time interval (TRI)	RTIFMDRT	327.7	43.6	1502	Healthy adults 57-84y	Abbott et al 2018
		355.9	71.7	1204	Atherosclerosis and LDL >70mg/dL, 40-85y (mean=62.7y), 72% male, 92% white, 12.7y education, 74% on beta blockers. Excl: dementia and MCI	Guigliano et al 2017
		370	54.5	488	Female twins, 42-72y at BL, mean age 55.5y	
Stop signal test – reaction time	SSTSSRT	180.09	32.08	36	Control group: 72% men, mean age=31.6y	Martoni et al 2018
Immediate Verbal Recall	VRMFR11D	8.15	2.32	91	Healthy, 29% male, mean age=65y	Bensalem et al 2019
		8.43	2.18	98		