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Protocol COG1201

Official Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2, 6-Month Study to Evaluate the Safety, Tolerability and Exploratory Efficacy of CT1812 in Subjects with Mild to Moderate Dementia with Lewy Bodies

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Statistical Analysis Plan

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Approval

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

Signature	Date
[redacted] *Biostatistician II* Syneos Health	19 November 2024
[redacted] *Anthony Caggiano* *Chief Medical Officer, Head of R&D* Cognition Therapeutics, Inc.	20 November 2024

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
CAF	Clinician Assessment of Fluctuation
CDR	Cognitive Drug Research Battery
CI	Confidence Interval
CRF	Case report Form
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
Ct	Plasma Concentration at Date/Point in Time
DLB	Dementia with Lewy Bodies
ESS	Epworth Sleepiness Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	Intent-to-Treat
LS	Least Squares
LSM	Least Square Means
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MoCA	Montreal Cognitive Assessment Scale
NPI	Neuropsychiatric Inventory
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
PT	Preferred term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TLFs	Tables, Listings, and Figures
WHO	World Health Organization

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Study COG1201 (A Randomized, Double-Blind, Placebo-Controlled, Phase 2, 6-Month Study to Evaluate the Safety, Tolerability and Exploratory Efficacy of CT1812 in Subjects with Mild to Moderate Dementia with Lewy Bodies). The purpose of this statistical analysis plan (SAP) is to provide specific guidelines for the statistical analyses. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the SAP:

- Protocol, version 3.0, 20SEP2022
- Annotated electronic case report form (eCRF), version 7.0, 24MAR2024
- Data management plan, version 1, 02FEB2022

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to assess the safety and tolerability of CT1812 as a treatment for mild to moderate Dementia with Lewy Bodies (DLB).

3.2 Secondary Objectives

The secondary objectives of the study are:

- To assess exploratory measures of efficacy at Baseline, 3 months, and 6 months.
- To assess pharmacodynamic target engagement and potential biomarker evidence of disease modification.

3.3 Exploratory Objectives

- To evaluate the efficacy of 2 doses of once-daily oral CT1812, administered for 6 months in subjects with DLB.
- To evaluate the change in α-synuclein pathology in skin biopsies over the course of 6 months.

4. STUDY DESIGN AND PLAN

This is a multicenter, randomized, double-blind, placebo-controlled study in subjects with mild to moderate DLB.

Subjects will be screened for eligibility by physical, laboratory, psychometric and neurologic examinations, and neuroimaging. Subjects may opt into collection of pre-dose Cerebrospinal fluid (CSF). If a subject opts into CSF collection, this is to be completed along with screening procedures <= 42 days prior to randomization at Baseline/Day 1. After having met all inclusion criteria, and none of the exclusion criteria, subjects will be randomized equally to one of 3 treatment arms (CT1812 at doses of 100 mg/day, 300 mg/day or placebo, up to n=40 group). On clinic visit days, study drug will be taken in the clinic after all baseline procedures been conducted. On days where there are no clinic visits, subjects will take study drug each morning at home. Subjects and their caregivers/ study partner will return to the clinic for repeat psychometric/neurologic testing, safety procedures and pharmacokinetic (PK) and pharmacodynamic (PD) sample collection at the intervals described below.

Subjects will return to the clinic approximately every 2 weeks after their Baseline visit until Day 70, then every 4 weeks until Day 182. A safety follow-up visit will occur approximately 28 days after the end of treatment for all subjects that complete through Day 182.

Subjects who prematurely discontinue the study for any reason will be asked to attend an early termination visit within 2 weeks of the last dose of study drug.

Dosing may be terminated by the Investigator if in the best interest of the subject, by the Sponsor at the recommendation of the Drug Safety and Monitoring Board (DSMB) based on safety and tolerability data, or at the discretion of the Sponsor; as a result, there are no study-specific stopping rules defined in the protocol.

The occurrence of any one of the following events will result in a review of study safety information to date by the Sponsor and DSMB.

- Two occurrences of the same or similar serious adverse event (SAE) assessed as probably or possibly related to dosing with investigational product.
- Two or more different subjects with the same or similar severe adverse event (AE) assessed as probably or possibly related to dosing with the investigational product.
- Four or more subjects with the same or similar moderate AE which is possibly or probably related to dosing with investigational product.

The Sponsor and DSMB will review the available safety data and recommend whether dosing should continue, or if study drug administration should be terminated, or if additional monitoring procedures or safety precautions need to be employed. The study or a dose group may also be terminated if the Sponsor and DSMB determine that any AE(s) are occurring that are intolerable or pose a medically unacceptable safety risk.

5. DETERMINATION OF SAMPLE SIZE

The sample size is not based on statistical considerations but was chosen to provide preliminary information on the safety and efficacy of CT1812 when administered according to this protocol.

It should be noted that for the comparison of both active groups versus placebo a total sample size of 105 would have 80% power to detect a mean difference of 0.78 points in the change from baseline in Montreal cognitive assessment scale (MoCA) score assuming a standard deviation of 1.32 points (PASS 2020: Two Sample T-Test, alpha=0.05). To account for potential dropouts, a sample size of 120 subjects (40 subjects per arm) is planned.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables and listings. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) numbering convention will be used for all tables, listings, and figures (TLFs). Unless otherwise noted, all statistical testing will be 2-sided and performed at the 0.05 significance level. Tests for the key efficacy endpoint of change from baseline in MoCA score at Month 6 will be declared statistically significant if the calculated *P* values following the sequential testing hierarchy described in Section 10.7 are <0.05. No adjustments for multiple comparisons will be made for the statistical testing of any other endpoints.

Continuous variables will be summarized by presenting the number of observations, means, standard deviations (SDs), medians, minimums, and maximums. Other summaries (e.g., quartiles, 95% confidence intervals [CIs]) may be used as appropriate.

Categorical variables will be summarized by presenting counts and percentages of subjects in corresponding categories. All possible categories as defined in the eCRF should be populated, even if they have zero counts. Percentages for missing values are omitted and do not account for the percent calculation of other categories. Percentages are based on the total category count excluding the missing category if not otherwise mentioned. In certain tables (e.g., AEs), the total number of subjects is used as the denominator. Footnotes will specify the percent basis in those cases.

All summary tables will be presented by treatment group. Baseline summaries will also include a total summary column.

Individual subject data obtained from the eCRFs, external vendors, central and local clinical laboratory and any derived data will be presented by subject in data listings.

The analyses described in this plan are considered a priori, in that they have been defined before breaking the blind.

Any analyses performed after breaking the blind will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® statistical software, version 9.4 or higher (SAS Institute Inc). Tables, listings, and figures will be presented in RTF and PDF format.

The process for SAS program validation and quality control (QC) for programs and outputs is documented in the Synteract working instruction "SAS Programming Quality Control". Study-specific QC requirements can be found in APPENDIX B: SAS PROGRAMMING QUALITY CONTROL REQUIREMENTS.

7. NOTATION OF TREATMENT GROUPS AND VISITS

The following notation of treatment groups will be used throughout the report:

TABLE 1 NOTATION OF TREATMENT GROUPS

Full notation (as used in the study protocol)	Notation used throughout all tables, listings, and figures
100 mg/day of CT1812	CT1812 100 mg
300 mg/day of CT1812	CT1812 300 mg
100mg/day and 300mg/day of CT1812 combined	CT1812 Combined
Placebo	Placebo

TABLE 1 VISIT TERMINOLOGY

Visit	Notation used throughout all tables, listings, and figures
Screening, Days -42 through Day -1, Visit V1	Screening
Baseline, Day 1, Visit V2	Baseline
Day 14 (±2), Visit V3	Day 14
Day 28 (±2), Visit V4	Day 28
Day 42 (±2), Visit V5	Day 42
Day 56 (±2), Visit V6	Day 56
Day 70 (±2), Visit V7	Day 70
Day 98 (±2), Visit V8	Day 98
Day 126 (±2), Visit V9	Day 126
Day 154 (±2), Visit V10	Day 154
Early Termination, Day 182 (±2), Visit V11	Day 182
Safety Follow-up, Day 210 (+2), Visit V12	Follow-up

Analysis Days

Study days are measured from the date of first dose of randomized treatment.

Study days corresponding to measurements are calculated as:

- Assessment date – date of first exposure to treatment + 1 (if assessment date is on or after the date of first exposure to treatment)

- Assessment date – date of first exposure to treatment (if assessment date is before the date of first exposure to treatment)

8. ANALYSIS POPULATIONS

The populations for analysis will include the enrolled population, intent-to-treat (ITT) population, safety population, completers/compliers population, pharmacokinetic (PK) population, pharmacodynamics (PD) population, and the skin biopsy population.

- The enrolled population will include all subjects that signed the Informed Consent Form (ICF). Subject disposition summaries and data listings will be based on this population.

- The safety population will include all subjects in the ITT population who received at least one dose of study drug. Subjects in this population will be analyzed according to the treatment they received, regardless of which treatment they were randomly assigned. All safety and tolerability analyses will be based on this population and treatment assignment.

- The ITT population will include all subjects that were randomly assigned to study drug. Subjects in this population will be analyzed according to the treatment to which they were randomized, regardless of what treatment they received. All efficacy analyses will be based on this population and treatment assignment.

- The completers /compliers population will include all randomized subjects who completed the study (i.e., who did not prematurely withdraw) and had between 80%-120% compliance with study drug over the course of the study. There is no expectation that a subject included in the completers/compliers population will have attended every single scheduled visit; as long as the subject completed the study and met the study drug compliance criteria, they will be included in the population. Subjects in this population will be analyzed according to the treatment to which they were randomized, regardless of what treatment they received. This population will be used for sensitivity analyses of the efficacy endpoints.

The following subject populations will be used for PK/PD analyses:

- The PK population will include all subjects in the safety population who had at least 1 quantifiable concentration of CT1812.

- The PD population will include all subjects in the safety population who had an exploratory biomarker evaluation.

The following subject population will be used for the summarization of skin biopsy results:

- The skin biopsy population will include all subjects in the safety population with Syn-One Test skin biopsy results available.

9. STUDY DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND STUDY CONDUCT

9.1 Subject Disposition

Subject disposition information will be summarized by treatment group and overall. Summaries will include the number of subjects screened, enrolled, randomized, included in each analysis population, completing the study treatment, discontinuing study treatment and the reason for discontinuing study treatment, completing the study, discontinuing the study and the primary reason for study discontinuation.

9.2 Protocol Deviations

Major protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified before database lock and unblinding of individual subject treatment information. Major protocol deviations may include, but are not limited to:

- Randomized subjects who did not satisfy selected inclusion and exclusion criteria
- Randomized subjects who developed withdrawal criteria during the study but were not withdrawn
- Subjects who received the wrong treatment or an incorrect dose
- Subjects who missed visit or visit outside protocol window
- Subjects who missed assessment or assessment at incorrect time point
- Subjects who were administered prohibited medication

Major protocol deviations will be summarized by deviation category, deviation subcategory and treatment group for the ITT population.

9.3 Eligibility

A listing of subjects not fulfilling eligibility criteria will be presented.

9.4 Demographic and Baseline Characteristics

Demographic variables include age, sex, ethnicity, and race. Age will be calculated in years relative to the informed consent date.

Other baseline characteristics include height, weight, time since DLB diagnosis, BMI, Geriatric Depression Scale (GDS), MMSE scores, Modified Hoehn and Yahr Scale, Apolipoprotein Genotype, Amyloid Probability Score 2, and MDS-UPDRS3 Total Score.

Descriptive statistics will be presented for age, height, weight, and other continuous variables. Frequency counts and percentages will be presented for sex, ethnicity, and race. Demographic

and baseline characteristics will be listed for each subject and summarized descriptively by treatment group for the safety and ITT populations.

The time since DLB diagnosis is calculated by (date of first exposure to treatment - date of probable DLB Diagnosis + 1)/365.25.

An additional table will be produced to summarize baseline scores for efficacy assessments for the ITT population.

9.5 Medical History

The verbatim terms of the reported medical history conditions/events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1.

A summary table will be prepared by treatment group and overall for the ITT Population. The summary will show the system organ class (SOC) and preferred term (PT) ordered by descending frequency in the overall column by SOC and PT.

9.6 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms will be mapped to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification 3 and preferred names using the WHO Drug Global dictionary (enhanced) September 2021.

Partial dates will be imputed. For details on imputation rules, refer to Appendix A: Presentation of Data and Programming Specifications. Imputed dates are only used for classification of a medication as a prior or concomitant medication; no other calculation, such as durations, will be performed using imputed dates.

- Medications that started prior to the first dose of study drug will be considered prior medications, regardless of whether or not they were stopped prior to the first dose of study drug.
- Any medications continuing or starting after the first dose of study drug will be considered concomitant medications.
- If a medication starts prior to the first dose of study drug and continues after the first dose of study drug, it will be considered both prior and concomitant.

If the medication cannot be classified as a prior or concomitant medication, the medication will be considered as concomitant.

Prior and concomitant medications will be summarized for each treatment by ATC class 3 and preferred name for the ITT population. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than 1 medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if he/she reported 1 or more medications at that level. Each summary will be ordered by descending subject count in the total column by ATC level 3 and preferred name.

10. EFFICACY ANALYSES

All efficacy analyses will be based on the ITT population. As a sensitivity analysis, all efficacy endpoints will be summarized using the completers/compliers population.

10.1 Efficacy Endpoints

Efficacy endpoints are listed below:

- MoCA
- Epworth Sleepiness Scale (ESS)
- Clinician Assessment of Fluctuation (CAF)
- ADCS-Clinical Global Impression of Change (CGIC)
- ADCS-Activities of Daily Living (ADCS-ADL)
- Movement Disorder Society – United Parkinson's Disease Rating Scale Part III (MDS-UPDRS Part III)
- Cognitive Drug Research Battery (CDR)
- Neuropsychiatric Inventory (NPI)

10.1.1 Montreal Cognitive Assessment Scale (MoCA)

The MOCA is a brief dementia screening assessment that covers nine domains (Nasredinne et al., 2005). The MOCA has a 0-30 range with lower scores meaning more impairment. Total score is calculated by summing all sub-scores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal. Total score is obtained directly from CRF.

10.1.2 Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a measure that assesses subjective sleepiness over the prior two weeks (Johns, 1991,1997). The ESS is a scale that queries the likelihood of dozing (i.e., 0= no chance of dozing, 1= slight chance of dozing, 2= moderate chance of dozing or sleeping, 3= high chance of dozing) in eight different circumstances. Total score sums up all sub-scores and can range from 0 to 24. A higher score is associated with increased sleepiness. An ESS score ≥10 is considered abnormal and consistent with excessive daytime sleepiness. Total score is obtained directly from CRF.

10.1.3 Clinician Assessment of Fluctuation (CAF)

Cognitive fluctuations are a core feature of DLB (McKeith et al., 2017) characterized by alterations in attention, alertness, and consciousness. The CAF is a screening questionnaire asked of an informant to capture frequency and duration of episodes to calculate a severity score (range 0-16 with higher scores representing more severe fluctuations (Walker et al., Sep 2000). If the fluctuating confusion is present, the frequency and duration of episodes of fluctuating confusion are both rated on a scale of 0-4, and these two scores are multiplied together to produce a severity score from 0-12 (0 representing no fluctuating confusion, 12 representing severe fluctuating confusion; a score of 16 would signify a continuous clouded state, which, by definition, would denote no fluctuation).

10.1.4 ADCS-Clinical Global Impression of Change (CGIC)

The Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC) was developed by the Alzheimer's Disease Cooperative study (ADCS) (Schneider et al., 1997). The ADCS-CGIC is a validated categorical measure of change in the patient's clinical condition between baseline and follow-up visits. It measures whether the effects of active treatment are substantial enough to be detected by a skilled and experienced clinician on the basis of a clinical interview and examination. The 7 responses and corresponding numeric scores for each response of the ADCS-CGIC are: Marked improvement (1), Moderate improvement (2), Minimal improvement (3), No change (4), Minimal worsening (5), Moderate worsening (6), Marked worsening (7). The observed scores at each visit will be summarized. A responder is defined as a subject who responded as "Marked improvement, Moderate improvement, Minimal improvement, No change" and non-responder is defined as a subject who responded as "Minimal worsening, Moderate worsening, Marked worsening".

10.1.5 ADCS-Activities of Daily Living (ADCS-ADL)

The ADCS-ADL (Galasko et al., 1997) is a 23-item informant-administered assessment of functional impairment in terms of activities of daily living. Informants respond to 23 questions about the patient's involvement and level of performance across items representing daily living. The questions range from basic to instrumental activities of daily living. Each item is rated from the highest level of independent performance to complete loss. Each response has a point value, and the total score is the summation of the numeric values. The total score range is from 0- 78 with lower scores indicating greater functional impairment. Total score is obtained directly from CRF.

10.1.6 Movement Disorder Society – United Parkinson's Disease Rating Scale Part III (MDS-UPDRS Part III)

The MDS-UPDRS3 is a gold standard assessment of the motor examination of parkinsonism (Goetz et al., 2008), a core feature of DLB (McKeith et al., 2017). The motor exam covers 18 motor signs associated with parkinsonism covering bradykinesia, rigidity, tremor, and gait with a range of scores from 0-136, with higher scores supporting more severe symptoms. A score of 6

or greater suggest the presence of parkinsonism (Goetz et al., 2008). Total score is obtained directly from CRF.

10.1.7 Cognitive Drug Research Battery (CDR)

The CDR System is an automated test system designed to precisely measure and profile such patterns of changes to cognition. The CDR System has been specifically developed to assess both enhancement and impairment of human cognitive function. The assessment procedures developed for the CDR System definitively measure changes in the following major areas of cognitive function: Attention, vigilance and information processing; Working memory; Verbal and non-verbal episodic secondary memory; and Executive function. The composite scores for each cognitive function will be calculated and provided from the data vendor (Signant Health) following the derivations provided in Appendix D.

10.1.8 Neuropsychiatric Inventory (NPI)

The NPI assesses common behaviors associated with dementia. A structured interview of the caregiver is used to assess 12 behavior domains. For each item within a domain, the symptom frequency is rated as: 1, occasionally; 2, often; 3, frequently; 4, very frequently and the symptom severity is rated as: 1, mild; 2, moderate; 3, marked. The total domain score is calculated as the sum of the frequency scores multiplied by the severity scores for each item assessed within a domain and is obtained directly from CRF. The total NPI score is obtained by adding the domain scores for each of the 12 domains, and ranges from 0 to 144 (144 is the worst possible score). The higher the total score, the more severe the symptoms. Additionally, a caregiver distress score is recorded for each behavior domain ("How emotionally distressing do you find this behavior?") and is rated on a 0- to 5-point scale where 0 is 'Not at all' and 5 is 'Very severely or extremely'. The total caregiver distress score is calculated as the sum of the individual caregiver distress scores recorded for the 12 behavior domains and ranges from 0 to 60. The total score and total distress score are both collected from two separate fields in CRF: Total Score A-J, Total Score A-L, Total Distress Score A-J, Total Distress Score A-L.

10.2 Baseline Values

Unless otherwise noted, baseline is defined as the last non missing value recorded before or on the date of first dose of study drug. Unscheduled visits will be used in the determination of baseline values, when applicable.

For all efficacy assessments, baseline will be considered as the latest assessment conducted within 6 hours after the first dose of study drug.

10.3 Adjustments for Covariates

Baseline value of the efficacy endpoints that will be analyzed will be included as covariate in the models.

10.4 Handling of Dropouts or Missing Data

Data in summary tables will be summarized by the nominal visit collected in the electronic data capture (EDC) system. The Day 182 (End of Study or early termination) label in the EDC system is used for both Day 182 End of Study and early termination visits. A participant will only have their Day 182 data included in the summary tables if it occurs on or after study Day 170. Participants who early terminate before study day 170 will have their early termination visit data listed only. No imputations will be made for missing values. Summaries will be based on observed data only.

10.5 Interim Analysis and Data Monitoring

No interim analysis is planned for this study.

A DSMB will oversee the safety of the trial. This committee will include independent experts, including an independent statistician. Safety data will be provided to the DSMB at quarterly intervals during the trial. The study clinician and study medical monitor will review trial safety data biweekly and more frequently as the safety data warrant. Similarly, more frequent ad hoc meetings of the DSMB will occur if ongoing safety data indicate interim meetings are indicated.

10.6 Examination of Subgroups

The following subgroups are defined for this study:

Subgroup	**Definition/Levels**
Sex	Male, Female
MMSE at Baseline	18-24, 25-27
Age	<Median age, >=Median age
Amyloid positivity at Screening	The C2N Amyloid Probability Score 2 (APS2) in plasma will be used. The APS2 score will be calculated (by C2N) at screening/baseline in plasma. If the APS2 is >47.5, the participant will be included in the amyloid-biomarker positive subgroup. Otherwise, the participant will be included in the amyloid-biomarker negative subgroup. If a participant does not have the APS2 score available, then classification will be based on the plasma pTau217/Tau217 ratio only. If the pTau217/Tau217 ratio is >4.2, the participant will be included in the amyloid-biomarker positive subgroup. Otherwise, the participant will be included in the amyloid-biomarker negative subgroup.

	Note: The APS2 score is an output that takes into account plasma pTau217/Tau217 and the plasma Aβ42/40 ratio to predict the presence of brain amyloid >25 centiloids via PET.
Parkinsonian features at Baseline based on MDS-UPDRS	<Median baseline MDS-UPDRS3 total score, >=Median baseline MDS-UPDRS3 total score
Parkinsonian features at Baseline based on Modified Hoehn and Yahr Scale	Baseline Modified Hoehn and Yahr stage <=2 Baseline Modified Hoehn and Yahr stage >2
Acetylcholinesterase (AChE) inhibitors and/or memantine use during the study	Yes: Participant took these medications during the treatment period No: Participant did not take these medications during the treatment period The following medications will be considered for this subgroup: Any medication containing donepezil (Aricept, Namzaric), rivastigmine (Exalon), galantamine (Razadyne, Reminyl), or tacrine (Cognex) is considered an AChE inhibitor. Any medication containing memantine (Namenda, Namzaric) is considered memantine.
ApoE status at Baseline	Positive, Negative. If genotype ApoE or phenotype ApoE contains E4, then ApoE status is considered Positive. Otherwise Negative.
Skin biopsy sum total composite score at Baseline	Positive: Baseline skin biopsy sum total composite score >0 Negative: Baseline skin biopsy sum total composite score =0
Plasma pTau217/Tau217 ratio at Baseline	This subgroup will consist of three levels: • Amyloid-biomarker positive, Baseline pTau217/Tau217 ratio < median • Amyloid-biomarker positive, Baseline pTau217/Tau217 ratio >= median

	• Amyloid-biomarker negative In the subset of subjects included in the amyloid-biomarker positive subgroup, the median Baseline pTau217/Tau217 ratio value will be determined using the data received from C2N. The subjects in the amyloid-biomarker positive subgroup will then be split into two groups based on their Baseline pTau217/Tau217 ratio value (< median, >= median). All subjects in the amyloid-biomarker negative subgroup will be included in the "Amyloid-biomarker negative" group, regardless of their Baseline pTau217/Tau217 ratio value.

10.7 Multiple Comparison/Multiplicity

Although the assessment of efficacy is considered a secondary objective of this study, the key efficacy endpoint is defined as the change from baseline in MoCA score at 6 months. The primary analysis of this key efficacy endpoint will be based on the comparison of both CT1812 treatment groups combined vs. placebo. If the result of this analysis is statistically significant ($p<0.05$), then formal statistical testing will proceed as follows in a sequential manner:

1. CT1812 300mg/day vs. placebo
2. CT1812 100mg/day vs. placebo

If the comparison of CT1812 300mg/day vs. placebo is statistically significant ($p<0.05$) then the comparison of CT1812 100mg/day vs. placebo will be formally tested. If the comparison of CT1812 300mg/day vs. placebo is not statistically significant ($p\geq0.05$) then the result of the analysis of CT1812 100mg/day vs. placebo will be interpreted descriptively.

No adjustments for multiplicity will be made for the testing of the other endpoints evaluated in this study.

10.8 Multicenter Studies

This is multicenter study, with approximately 30 qualified investigator sites participating. Approximately 120 subjects will be randomly assigned, leading to approximately 4 subjects per site.

The expected low number of subjects at some sites does not allow for the site to be included as a covariate in the statistical model.

11. METHODS OF EFFICACY ANALYSIS

11.1 Montreal Cognitive Assessment Scale (MoCA)

The primary efficacy comparison will test the following hypotheses:

H_0: The change from baseline in MoCA score at Month 6 is equal when comparing both active treatment groups (combined) versus Placebo.
H_1: The change from baseline in MoCA score at Month 6 is different when comparing both active treatment groups (combined) versus Placebo.

Baseline and both observed values and change from baseline values for Day 28, Month 3, and Month 6 will be summarized by treatment group using descriptive statistics.

The difference between treatment groups (combined CT1812 vs. placebo) will be assessed using a mixed model for repeated measures (MMRM) with change from baseline values at Day 28, Month 3, and Month 6 as the response values, treatment group (CT1812 100 mg, CT1812 300 mg, placebo), time point, and a treatment group by time point interaction as fixed effects, subject as a random effect, and baseline value as a covariate. An unstructured covariance structure will be applied, and the denominator degrees of freedom will be computed using the Kenward-Roger method. If the model does not converge using the unstructured covariance structure, the autoregressive (order 1) AR(1) structure will be used. If the AR(1) structure also does not converge, other covariance structures deemed appropriate to fit the data will be used. The least square means (LSM), standard errors, LSM differences between combined CT1812 and placebo, 95% CIs for the LSM differences, and p-values at each post-Baseline time point will be presented.

The pairwise comparisons of each CT1812 group and placebo will be performed from the same model in a similar manner to what is described above.

Plots of mean MoCA score change from baseline with standard deviation over time, plots of LS mean MoCA score (from MMRM model) change from baseline with 95% CI over time, and spaghetti plots of individual subject MoCA score change from baseline over time will be provided. These three plots will be repeated using the completers/compliers population.

Subgroup analysis will be done for MoCA scores using subgroups defined in Section 10.6.

A listing for individual MoCA scores will be presented.

11.2 Epworth Sleepiness Scale (ESS)

The ESS total score will be analyzed as described in Section 11.1. Plots of mean ESS total score change from baseline with standard deviation over time, plots of LS mean ESS total score (from MMRM model) change from baseline with 95% CI over time, and spaghetti plots of individual

subject ESS total score change from baseline over time will be provided for the ITT population only. A listing for individual ESS scores will be presented.

11.3 Clinician Assessment of Fluctuation (CAF)

The CAF severity score will be analyzed as described in Section 11.1. Plots of mean CAF severity score change from baseline with standard deviation over time, plots of LS mean CAF severity score (from MMRM model) change from baseline with 95% CI over time, and spaghetti plots of individual subject CAF severity score change from baseline over time will be provided for the ITT population only. A listing for individual CAF scores will be presented.

11.4 ADCS-Clinical Global Impression of Change (CGIC)

The CGIC outcome will be summarized for each treatment by time point (Day 28, Month 3 and Month 6). The summary will present the number and percentage of subjects in each outcome. Additionally, the continuous score, derived using the numeric score of each outcome response, will be summarized at each visit using descriptive statistics. Statistical modeling will be performed using an MMRM model similar to what is described in Section 11.1 but with the observed ADCS-CGIC values at Day 28, Month 3, and Month 6 as the response values.

The proportion of subjects classified as CGIC responders and non-responders will be summarized at each visit by treatment group.

Plots of mean ADCS-CGIC score change from baseline with standard deviation over time, plots of LS mean ADCS-CGIC score (from MMRM model) change from baseline with 95% CI over time, and spaghetti plots of individual subject ADCS-CGIC score change from baseline over time will be provided for the ITT population only.

Subgroup analysis will be done for the continuous ADCS-CGIC score using subgroups defined in Section 10.6.

A listing for individual ADCS-CGIC outcomes will be presented.

11.5 ADCS-Activities of Daily Living (ADCS-ADL)

The ADCS-ADL total score will be analyzed as described in Section 11.1. Plots of mean ADCS-ADL total score change from baseline with standard deviation over time, plots of LS mean ADCS-ADL total score (from MMRM model) change from baseline with 95% CI over time, and spaghetti plots of individual subject ADCS-ADL total score change from baseline over time will be provided for the ITT population only.

Subgroup analysis will be done for ADCS-ADL total score using subgroups defined in Section 10.6. A listing for individual ADCS-ADL scores will be presented.

11.6 Movement Disorder Society – United Parkinson's Disease Rating Scale Part III (MDS-UPDRS Part III)

The MDS-UPDRS Part III total score will be analyzed as described in Section 11.1. Plots of mean MDS-UPDRS Part III total score change from baseline with standard deviation over time, plots of LS mean MDS-UPDRS Part III total score (from MMRM model) change from baseline with 95% CI over time, and spaghetti plots of individual subject MDS-UPDRS Part III total score change from baseline over time will be provided for the ITT population only. A listing for individual MDS-UPDRS Part III scores will be presented.

11.7 Cognitive Drug Research Battery (CDR)

The CDR composite scores will be analyzed as described in Section 11.1. The descriptive summary will be performed for each of the individual task measures. The descriptive summary and analysis will be performed for each of the composite scores (Power of Attention, Continuity of Attention, Cognitive Reaction Time, Response Variability, Quality of Working Memory, Quality of Episodic Secondary Memory, Speed of Memory, Quality of Memory). The calculation of composite scores is described in Appendix D.

Plots of mean CDR composite scores change from baseline with standard deviation over time, plots of LS mean CDR composite scores (from MMRM model) change from baseline with 95% CI over time, and spaghetti plots of individual subject CDR composite scores change from baseline over time will be provided for the ITT population only.

A listing for each individual task measures and composite score in CDR will be presented.

11.8 Neuropsychiatric Inventory (NPI)

The total NPI score for all domains (Total Score A-L), the total NPI score excluding Sleep and Appetite and eating disorders (Total Score A-J), the total distress score (Total Distress Score A-L), and the total distress score excluding Sleep and Appetite and eating disorders (Total Distress Score A-J) will be analyzed similarly as described in Section 11.1. The descriptive summary and statistical testing will also be performed for each of the 12 domain scores (Delusions, Hallucinations, Agitation/Aggression, Depression/Dysphoria, Anxiety, Elation/Euphoria, Apathy/Indifference, Disinhibition, Irritability/Lability, Aberrant Motor Behavior, Sleep, and Appetite and eating disorders), and for the caregiver distress scores for each of the 12 domains.

The total NPI score for all domains (Total Score A-L), the total NPI score excluding Sleep and Appetite and eating disorders (Total Score A-J), the total distress score (Total Distress Score A-L), and the total distress score excluding Sleep and Appetite and eating disorders (Total Distress Score A-J) will be summarized graphically. Plots of mean change from baseline with standard deviation over time, plots of LS mean (from MMRM model) change from baseline with 95% CI over time, and spaghetti plots of individual subject change from baseline over time will be provided for the ITT population only.

A listing for each individual subscale score in NPI will be presented.

12. PHARMACOKINETIC ANALYSES

Plasma CT1812 concentrations collected prior to dosing will be summarized for each sampling day with descriptive statistics.

All PK listings, individual and mean pre-dose concentrations, PK tables and figures, and all statistical analyses will be presented using the PK population.

Pharmacokinetic Endpoints:

- CT1812 CSF/plasma concentration ratio (EOS only).
- Predose CT1812 plasma concentrations.

12.1 Data Handling

Blood samples will be collected on Days 1, 28, 56, 98, 154, and 182 at the protocol-specified times (within 1.25 hours prior to dosing, i.e., pre-dose samples) for the determination of CT1812 concentrations in plasma.
The raw plasma concentration data will be handled as follows:

For summary tables and figures for plasma concentrations:

- For all pre-dose samples, the sampling time will be set to zero.
- Any CT1812 concentration that is reported as below the lower limit of assay quantitation (BLQ) will be set to zero.

12.2 Presentation of Plasma Concentrations

Individual plasma concentration results:

A raw data listing will be provided displaying the concentration as reported and nominal and actual sampling times relative to the start dose of study drug. Results will be displayed using 3 significant digits.

Summary statistics of plasma concentrations:

The plasma concentrations for CT1812 will be summarized by dose group and the nominal time point of the pre-dose samples collected on Days 1, 28, 56, 98, 154, and 182 using descriptive statistics (n, arithmetic mean, SD, coefficient of variation (CV) % of arithmetic mean, median, minimum, maximum, geometric mean, and CV % for the geometric mean).

Results will be displayed using 3 significant digits.

The CV % for the geometric mean will be calculated using the following formula:

$$CV\ (\%) = 100 * \sqrt{e^{SD^2} - 1}$$

where SD is of the natural-log transformed data.

Figures:

An overlay of individual and mean profiles of pre-dose concentrations on Days 1, 28, 56, 98, 154, and 182 will be provided for each dose group on linear scales.

Mean profiles of pre-dose concentrations on Days 1, 28, 56, 98, 154, and 182 will be provided for each dose group on a linear scale and may be presented with or without error bars.

Scatter plots of individual pre-dose concentrations on Days 1, 28, 56, 98, 154, and Day 182 versus BMI, weight, age and gender will be provided for each dose group for both plasma and CSF. Pearson correlation coefficients and p-values will be provided.

Individual PK Endpoints:

A raw data listing will be provided displaying the individual CT1812 CSF/plasma concentration ratio results will be displayed using 3 significant digits.

Summary statistics of PK Endpoints:

CT1812 CSF/plasma concentration ratio will be summarized by dosing group using descriptive statistics (n, arithmetic mean, SD, CV% for the arithmetic mean, median, minimum, maximum, geometric mean, and CV% for the geometric mean). Results will be displayed using 3 significant digits.

13. PHARMACODYNAMICS ANALYSES

13.1 Data Handling and Biomarker Measurements

CSF biomarkers: Samples will be collected at screening and Day 182/End of Study.

CSF biomarker being assessed in this study are a-synuclein using **Amprion's** αSyn seed amplification assay (**αS-SAA**)

Plasma biomarkers: Samples will be collected at screening, baseline, Day 28, Day 98, Day 182.

Plasma biomarkers being assessed during this study are as follows: at baseline, Day 98 and Day 182, whereas some biomarkers are being assessed only at screening (V1) (C2N; Precivity AD2)

Biology	Biomarker	Biofluid	Timepoint to be analyzed	Assay Method
Core Biomarker	**PrecivityAD2**	Plasma	Screening	LC-MS
	pTau181	Plasma	Baseline Day 98 End of the study*	Simoa
	pTau217	Plasma		Simoa
	Aβ42, Aβ40, Aβ42/40 ratio	Plasma		Simoa
Neuroinflammation	**GFAP**	Plasma		Simoa
Neurodegeneration	**NFL**	Plasma		Simoa
DLB progression	**Total α-Syn**	Plasma		IMR
	Phospho-α-Syn	Plasma		IMR
	DDC	Plasma		Simoa

13.2 Presentation of Plasma and CSF Biomarkers

Tables

The biomarkers for CT1812 will be summarized using descriptive statistics (n, mean, SD, median, min, max) for observed (at each time point including baseline) and change from baseline values for each plasma biomarker. For CSF biomarker, we will present the n (%) of subjects with each result (Detected, Not Detected, Indeterminate) at Baseline. The percentages should be based on the number of subjects with a CSF biomarker result available. This will be summarized by treatment group (placebo, CT1812 100mg, CT1812 300mg, pooled CT1812 100mg+300mg). The change from baseline values for each plasma biomarker will be analyzed as follows:

- Assuming data for more than 1 post-baseline sample is available, then the MMRM will be used with change from baseline at each post-baseline visit values as the response values, treatment group (CT1812 100mg, CT1812 300mg, placebo), time point, and treatment group by time point interaction as fixed effects, subject as a random effect, and baseline value as a covariate. The least square means (LSM), standard errors, LSM differences vs. placebo, 95% CIs for the LSM differences, and p-values at each post-baseline time point will be presented. If only 1 post-baseline sample is available, then the ANCOVA model detailed below will be used.

- If only 1 post-baseline sample is available, then the ANCOVA will be used with change from baseline value at Day 182/End of Study as the response value, treatment group (pooled CT1812 100mg vs. placebo; separately for each individual CT1812 300mg, dose group vs. placebo) as fixed effect, and baseline value as a covariate. The LSM, standard errors, LSM differences vs. placebo, 95% CIs for the LSM differences, and p-values at Day 182 will be presented.

Correlation analyses: Pearson correlation analyses will be performed for:

1. The Sum Total Composite Score from the skin biopsy and plasma biomarkers, using observed values at each time point as well as change from baseline values
2. Plasma PK parameters and plasma biomarkers, using observed values at each time point as well as change from baseline in plasma biomarker values
3. Plasma biomarkers, observed and change from baseline, correlated with observed values at each time point and change from baseline cognitive and functional clinical outcome measures (i.e., MOCA, ESS, CAF, CGIC (observed values only), ADCS-ADL, MDS-UPDRS Part III, CDR, NPI).

Subgroup analyses:

The tabular summaries described above for plasma biomarkers only will be repeated by subgroup. However, the subgroup analyses will only be conducted if there are a minimum number of subjects in each treatment group/subgroup level:

- If less than 10 subjects fall into any one treatment group/level of a subgroup, then the corresponding summary/analysis for that subgroup will not be conducted.
- If at least 10 subjects fall into all treatment groups/levels of the subgroup, then the corresponding summary/analysis for that subgroup will be conducted.
- These rules will be applied separately for the subgroup analyses which compare individual CT1812 dose groups vs. placebo and for those which compare the pooled CT1812 dose group vs. placebo. It is possible that these criteria will not be met for the analysis based on individual CT1812 dose groups, but once the CT1812 dose groups are pooled, the criteria are met.

The subgroups of interest for plasma biomarkers are:

Subgroup	**Definition/Levels**
MMSE at Baseline	18-24, 25-27
Amyloid positivity at Baseline	The C2N Amyloid Probability Score 2 (APS2) in plasma will be used. The APS2 score will be calculated (by C2N) at screening/baseline in plasma. If the APS2 is >47.5, the participant will be included in the amyloid-biomarker positive subgroup. Otherwise, the participant will be included in the amyloid-biomarker negative subgroup. If a participant does not have the APS2 score available, then classification will be based on the plasma pTau217/Tau217 ratio only. If the pTau217/Tau217 ratio is >4.2, the participant will be included in the amyloid-biomarker positive subgroup. Otherwise, the participant will be included in the amyloid-biomarker negative subgroup. Note: The APS2 score is an output that takes into account plasma pTau217/Tau217 and the Aβ42/40 ratio to predict the presence of brain amyloid >25 centiloids via PET.
Skin biopsy sum total composite score at Baseline	Positive: Baseline skin biopsy sum total composite score >0 Negative: Baseline skin biopsy sum total composite score =0

Figures:

Spaghetti plots displaying individual subject-level data of observed values over time for each plasma biomarker by treatment group (placebo, CT1812 100mg, CT1812 300mg) will be provided.

Line plots displaying the mean (± SD) observed values over time (all time points, including baseline) for each plasma biomarker by treatment group (placebo, CT1812 100mg, CT1812 300mg, Pooled CT1812 100mg+300mg) will be provided.

Line plots displaying the mean (± SD) change from baseline values over time for each plasma biomarker by treatment group (placebo, CT1812 100mg, CT1812 300mg, Pooled CT1812 100mg+300mg) will be provided.

Line plots displaying the LSM (±95% CI) change from baseline values for each plasma biomarker by treatment group (placebo, CT1812 100mg, CT1812 300mg, Pooled CT1812 100mg+300mg) will be provided.

Vertical scatter plots displaying the individual subject-level data of change from baseline values at Day 98 and Day 182/End of Study for each plasma biomarker by treatment group (placebo, CT1812 100mg, CT1812 300mg) will be provided.

Listings:

All individual subject-level plasma and CSF biomarker data will be presented in data listings.

14. SKIN BIOPSY DATA ANALYSES

14.1 Observed Change from Baseline of the Sum Total Composite Score

Sum Total Composite Score is derived at each visit across the 3 biopsy sites for each subject. It is calculated as the sum of the posterior cervical P-SYN composite score, the distal thigh P-SYN composite score, and the distal leg P-SYN composite score. Assuming the subject had all 3 sites biopsied, the sum total composite score has a range of 0 to 36. If a subject is missing one or two of the biopsy site composite scores, then the sum total composite score is calculated as the sum of the available scores which are then stretched/scaled to fit the 0-36 range. If a subject is missing all three biopsy site composite scores, then the sum total composite score is left as missing. The summary table will present descriptive statistics for the observed value at each visit (baseline and end of study), the change from baseline to end of study, and then an ANCOVA analysis comparing the change values for each dose group vs. placebo. The ANCOVA model as described in Section 13.2 should include the baseline sum total composite score as a covariate.

15. SAFETY ANALYSES

All safety analyses will be based on the safety population.

15.1 Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), which are defined as those AEs that occurred on or after the date of first dose and those existing AEs that worsened during the study. If it cannot be determined whether the AE is treatment emergent due to a partial

onset date, then it will be counted as such. Verbatim terms in the eCRFs will be mapped to SOCs and PTs using MedDRA.

Summary tables that are presented by relationship to investigational product will consider any TEAE that is assessed by the principal investigator as probably or possibly related to investigational product to be related to investigational product. TEAEs considered unlikely or not related to investigational product will be considered unrelated to investigational product in summary tables. TEAEs with a missing relationship will be considered related to investigational product in all summary tables.

Summary tables that are presented by severity will consider TEAEs with missing severity as having a severity of severe.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PTs will be ordered by descending subject count in the total column by SOC and PT. Summaries of the following types will be presented:

- Overall summary of TEAEs that contains an overview of each of the following:
    - Subjects experiencing any TEAE and the total number of TEAEs
    - Subjects experiencing any TEAE considered related to investigational product and the total number of TEAEs considered related to investigational product
    - Subjects experiencing a treatment-emergent SAE and the total number of treatment-emergent SAEs
    - Subjects experiencing a treatment-emergent SAE related to investigational product and the total number of treatment-emergent SAEs related to investigational product
    - Subjects experiencing any TEAE with an outcome of death and the total number of TEAEs with an outcome of death
    - Subjects experiencing a TEAE with a severity of severe and the total number of TEAEs with a severity of severe
    - Subjects experiencing a TEAE with a severity of severe that is related to investigational product and the total number of TEAEs with a severity of severe that is related to investigational product
    - Subjects experiencing a TEAE leading to discontinuation of investigational product and the total number of TEAEs leading to discontinuation of investigational product
    - Subjects experiencing a TEAE related to investigational product leading to discontinuation of investigational product and the total number of TEAEs related to investigational product leading to discontinuation of investigational product

- Subjects experiencing a TEAE leading to discontinuation of study and the total number of TEAEs leading to discontinuation of study
- Subjects experiencing a TEAE related to investigational product leading to discontinuation of study and the total number of TEAEs related to investigational product leading to discontinuation of study

In addition to the overall TEAE summary the following summaries will be presented.

- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA SOC and PT
- Subject incidence of TEAEs by MedDRA SOC, PT, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity will be considered severe for this summary.
- Subject incidence of TEAEs by MedDRA SOC, PT, and maximum relationship to study drug (related/not related). Related AEs are those reported as "Probable" or "Possible," and unrelated AEs are those reported as "Unlikely" or "Not Related." At each level of subject summarization, a subject is classified according to the maximum relationship if the subject reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA SOC and PT
- Subject incidence of TEAEs leading to death by MedDRA SOC and PT
- Subject incidence of TEAEs leading to discontinuation of investigational product by MedDRA SOC and PT
- Subject incidence of TEAEs leading to discontinuation of study by MedDRA SOC and PT
- Subject incidence of non-serious TEAEs and total number of unique non-serious TEAEs by MedDRA SOC and PT

Separate listings of treatment-emergent AEs, treatment-emergent SAEs, AEs leading to death, and AEs leading to investigational product discontinuation will be presented.

15.2 Extent of Exposure

Investigational product exposure will be summarized for each treatment using the total number of doses taken, total dose received, the duration of treatment, and the number and percentage of subjects who had a dose interruption. Duration of treatment is defined as the last dose date minus the first dose date plus 1.

The total dose received formulated in hydroxypropyl methylcellulose (HPMC) capsules will be provided in bottles containing 65 capsules of 50 mg dose or 150 mg dose (based on freebase

CT1812 fumarate salt) or its matching placebo. Subjects are expected to take 2 capsules per day. Total dose received will be calculated by (50 mg or 150 mg) × actual number of used capsules in total.

Investigational product compliance will be calculated as follows:

- Compliance (%): (actual number of capsules taken in total) / (number of prescribed capsules to be taken) × 100
- Actual number of capsules taken in total: Sum of Number of Capsules Taken
- Number of prescribed capsules to be taken: duration of study drug administration (days) × 2 capsules per day
- Duration of study drug administration (days) = date of last administration – date of first administration + 1

Investigational product compliance will be presented as descriptive statistics, also will be summarized by treatment group using counts and percentages as categorized below:

- >100%
- >90% to 100%
- >80% to 90%
- ≤80%

15.3 Clinical Laboratory Evaluation

Laboratory parameters (serum chemistry, hematology, coagulation, and continuous urinalysis parameters) will be summarized using descriptive statistics at baseline and at each post baseline time point. Changes from baseline will also be summarized.

In addition, shift tables relative to the laboratory normal range (i.e., low-normal-high at baseline versus low-normal-high at post baseline) will be provided to assess changes in serum chemistry and hematology laboratory values from baseline to each post baseline time point.

Subjects with elevated ALT, AST, ALT or AST ≥ 3 × ULN, ALT, AST, ALT or AST ≥ 5 × ULN, ALT, AST, ALT or AST ≥ 10 × ULN, and ALT, AST, ALT or AST ≥ 20 × ULN will be summarized. Categories will be cumulative, i.e. a subject with an elevation of AST ≥ 5 × ULN will also appear in the categories ≥ 3 × ULN.

Separate listings for chemistry, hematology, coagulation, liver function, and urinalysis results will be presented.

15.4 Vital Signs

Vital signs and other measures (systolic and diastolic blood pressure, temperature, respiration rate, pulse rate, weight) will be summarized using descriptive statistics at baseline and at each postbaseline time point. Changes from baseline will also be summarized.

Separate listings for vital signs results will be presented.

15.5 Physical Examination

Physical examination results will be summarized as normal, abnormal – not clinically significant, or abnormal – clinically significant using descriptive statistics at baseline and at each postbaseline time point.

Physical examination results will be presented in a listing.

15.6 Electrocardiogram

ECG parameters (ventricular rate, RR, PR, QRS, QT, QTcF and QTcB) will be summarized using descriptive statistics at baseline and at each post baseline time point. Changes from baseline will also be summarized. Interpretation results will present the number and percentage of normal, abnormal not clinically significant, and abnormal clinically significant results at each visit.

In addition, a categorical summary of abnormal corrected QT interval values will be presented. At each time point, the number of subjects with QTcF values of >450 ms, >480 ms, and >500 ms will be presented. At each postbaseline time point, the number of subjects with change from baseline values in QTcF of >30 ms and >60 ms will be presented.

Electrocardiogram results will be presented in a listing.

15.7 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire used to measure the presence and intensity of suicidal ideation and behavior. C-SSRS Screening/Baseline version used at Screening Visit and the since Last Visit version used at all other visits and will be administered prior to dosing. The C-SSRS includes “yes” or “no” responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

Suicidal Ideation items include:

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior items include:

Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Endpoints:

Composite endpoints based on the above categories are defined as follows:

- Suicidal **ideation**: A "yes" answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal **behavior**: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.
- Suicidal **ideation or behavior**: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

Tables will include results from the Suicidal Ideation and Suicidal Behavior sections of the C-SSRS. Frequencies and percentages of participants with a response of "Yes" at any post-Baseline point as well as by study visit on the Suicidal Ideation and Suicidal Behavior items will be summarized by treatment received. A listing will be produced to present all C-SSRS data for subjects with any post-baseline suicidal ideation or behavior.

15.8 Impact of COVID-19

Cases where SARS-CoV-2 coronavirus disease 2019 (COVID-19) had an impact on the study conduct of this trial will be presented in a listing.

16. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The following analyses in this SAP are different from Protocol version 3.0.

- The following analysis populations are included in this SAP but are not defined in the protocol: enrolled population, completers/compliers population, skin biopsy population. These populations have been added in order to facilitate summaries of data using applicable subject subsets of data.

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18. APPENDICES

APPENDIX A: PRESENTATION OF DATA AND PROGRAMMING SPECIFICATIONS

General

- Specialized text styles, such as bold, italics, borders, shading, and superscripted and subscripted text will not be used in tables, figures, and data listings (TFLs) unless they add significant value to the TLF.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as nonprintable control characters and printer- or font-specific characters, will not be used in a TLF.
- Hexadecimal character representations are allowed (e.g., μ, α, and ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes must be used sparingly and add value to the TLF.

Tables

- With the exception of PK data, means and medians will be presented to 1 decimal place more than the raw data. Standard deviations will be presented to 2 decimal places more than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper CI values must be presented to 1 decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25% and 75%) must be presented to 1 decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to 4 decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be:
  - "Source: xxx", where xxx indicates the source table number(s), if applicable (in case aggregated results, such as the mean or median, are plotted), source listing(s) (in case individual responses are plotted), and/or source dataset(s) (e.g., ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".

Figures

- Legends will be used for all figures with more than 1 variable or item displayed.
- Figures will be in black and white but can be in color to add value to the clarity and readability of a figure. Lines must be wide enough to see the line after being copied.
- The last footnotes will be:
  - "Source: xxx", where xxx indicates the source listing number(s) and/or source dataset(s) (e.g., ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".

Listings

- If not otherwise specified, all data listings will be sorted by treatment, center, subject number, visit, and date/time, as appropriate.
- All date values will be presented in a SAS® statistical software, version 9.4 or higher (SAS Institute Inc) date format (eg, 29AUG2001).
- All observed time values will be presented using a 24-hour clock format (HH:MM:SS) (eg, 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be "PROGRAM SOURCE: ...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".

Missing or Incomplete Dates (i.e., Adverse Events and Concomitant Medications)

The most conservative approach will be systematically considered. If the adverse event (AE) onset date is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e., considered a treatment-emergent AE) except if the partial onset date or other data, such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant medication.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of the first dose of study drug, provided the start month and year are the same as the date of the first dose of study drug and stop date is either after the date of the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of the first dose of study drug, provided the start year is

the same as the date of the first dose of study drug and stop date is either after the date of the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013).

- If the start date is completely missing and stop date is either after the date of the first dose of study drug or completely missing, then the start date will be estimated to be equal to the date of the first dose of study drug. Otherwise, the start date will be estimated to be the first day of the same year as the stop date. All other non-AE and nonconcomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing, and January 1 will be used if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day of resolution of the event will be assumed to be the last day of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the day of resolution of the event will be assumed to be the last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date of the event is completely missing or event is continuing, the event resolution will be assumed to be after the first dose of study drug, and the stop date will be imputed using the last known date on the study.

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Days: A duration expressed in days between 1 date (date1) and another later date (date2) is calculated using the following formula: duration in days = date2 – date1 + 1
- Months: A duration expressed in months is calculated using the INTCK function of SAS using the following formula: months = intck('month', 'date1'd, date2'd, 'continuous')
- Years: A duration expressed in years between 1 date (date1) and another later date (date2) is calculated using the following formula: duration in years = intck('year', 'date1'd, 'date2'd, 'continuous')
- Height: Height entries made in inches are converted to centimeters using the following formula: height (cm) = height (in) × 2.54
- Weight: Weight entries made in pounds are converted to kilograms using the following formula: weight (kg) = weight (lb.)/2.2046
- Temperature: Temperature entries in degrees Fahrenheit are converted to degrees centigrade using the following formula: temperature (° C) = 5/9 × [temperature (° F) – 32]

- Body Mass Index (BMI): BMI is calculated using height and weight using and is calculated using the following formula: BMI (kg/m^2) = weight (kg) / [[height (cm) / 100]^2]
- Change from baseline: Change from baseline will be calculated using the following formula: change = postbaseline value – baseline value
- Percent change from baseline: Percent change from baseline will be calculated using the following formula: percent change from baseline = (postbaseline value – baseline value)/baseline value × 100.

APPENDIX B: SAS PROGRAMMING QUALITY CONTROL REQUIREMENTS

Derived datasets are independently programmed by 2 programmers. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study analysis dataset specifications provided to the client at study conclusion.

Tables and listings are independently reprogrammed by a second programmer.

Listings are checked for consistency against corresponding tables, figures, and derived datasets.

The entire set of TLFs is checked for completeness and consistency prior to its delivery to the client by the lead biostatistician and a senior level, or above, reviewer.

APPENDIX C: LIST OF TABLES, LISTINGS, AND FIGURES

The following proposal for Sections 14 and 16.2 is completed according to ICH E3 guidelines. The heading numbers and description are in **bold**. Minor changes from this planned index do not need to be amended in the statistical analysis plan.

APPENDIX D: CDR COMPOSITE SCORES

Variable Name	Signant Health Item Name	Format	Unit	Description
Power of Attention	POW_ATT	Num(7.0)	msec	SRT+VIGRT+CRT
Continuity of Attention	CONT_ATT	Num(5.1)		(VIGACC*0.45)+(CRTACC*0.5)-VIGFA
Cognitive Reaction Time	COGRT	Num(5.0)	msec	CRT-SRT
Response Variability	POWATTCV	Num(7.0)	%	(SRTSD/SRT*100)+(CRTSD/CRT*100)+(VIGSD/VIGRT*100)
Quality of Working Memory	QL_WORK	Num(6.3)		SPMSI+NWMSI

Variable Name	Signant Health Item Name	Format	Unit	Description
Quality of Episodic Secondary Memory	QL_EPIS	Num(7.1)		(DRECOACC+DRECNACC–100) +(DPICOACC+DPICNACC–100) +((IRCL– IRCLERR)*100/15) +((DRCL–DRCLERR)*100/15)
Speed of Memory	SPEEDMEM	Num(7.0)	msec	SPMRT+NWMRT+DRECRT+DPICRT
Quality of Memory	QL_MEM	Num(5.1)		(SPMOACC + SPMNACC-100) + (NWMOACC + NWMNACC-100) + (DRECOACC+DRECNACC–100) +(DPICOACC+DPICNACC–100) +((IRCL– IRCLERR)*100/15) +((DRCL–DRCLERR)*100/15)