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Statistical Analysis Plan

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Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Study to Evaluate the Safety and Efficacy of CT1812 in Participants with Mild to Moderate Alzheimer's Disease
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Document History

Final V1.0	18-Dec-2019 – Initial version
Final V2.0	Updated throughout to align with V6.0 of the protocol. "Subject" was replaced with "Participant" throughout. Removal of Per-Protocol Population, addition of Completers Population and PK Population throughout. Section 2.1.3 (Exploratory Objectives) was updated from "To identify and assess metabolites of CT1812 in plasma" to "To characterize the PK profile of CT1812 in plasma". Section 2.2.3 (Pharmacokinetic/Pharmacodynamic Endpoints) was updated to remove one of the PK endpoints "Plasma CT1812 metabolites". Section 3.1 (Overall Design) was updated to add the definition of Part A, Part B and Part C. Section 3.2 (Sample Size and Power) was updated to include 48 active-dosed participants in sample size. Section 3.7 (SOE) was updated to align with Protocol Amendment 6.0. Section 5 (Analysis Populations) was updated to include definition for All Subjects population, Completers Population and PK Population. Section 6 (General Issues for Statistical Analysis) was updated to include a section on the subgroups of interest. The previously defined subgroup based on CT1812 CSF concentration was removed. A statement was added to document that tables and figures will present data for each individual CT1812 dose group as well as a combined CT1812 dose group (100 mg + 300 mg together). Section 6.1.1 (Baseline) was updated to include the day of first dose in the definition of Baseline. Section 6.1.3 (Multiple Comparisons) was updated to include text that had previously been included in Section 8.3 (ADAS-Cog 14). Section 6.1.4 (Handling of Dropouts or Missing Data) was updated to clarify that only missing data for endpoints assessed at post baseline timepoints may be imputed using LOCF. Section 6.1.8 (Derived Variables) was updated to remove derivation of MMSE Total Score, added derivation of Modified Hachinski total score, ADCS-ADL total score, Number Cancellation total score and ADAS 13 total score. And updated definition of TEAE to include AEs with an onset date/time on the first dose of study drug. Section 6.1.9 (Data Adjustments/Handling/Conventions) was updated to include

	imputation for missing AE dates. Section 6.1.10 was added to define subgroups. Section 7.1 (Disposition of Participants and Withdrawals) was updated to remove summary of treatment discontinuation. Section 7.3 (Demographics and Other Baseline Characteristics) was updated to inlcude ApoE4 Status, ApoE Genotype, and Mini Mental State Exam (MMSE) Total Score in baseline characteristics summary. Also added clarification that demographic table for mITT population will be produced when mITT population is different from the Safety population. Section 8 (Efficacy Analysis) was updated to include details on which efficacy endpoints would be summarized using the Completers Population and the types of figures to be produced. Section 8.8 (Biomarker changes) was significantly updated to reflect the planned analyses for the final study analysis. Added rules for subgroup analyses. Added figures to be produced at final analysis. Section 9 (Safety and Tolerability Analysis) was updated throughout to include the visits at which by-visit summaries of safety data would be summarized (Section 9.3 Vital Signs, Section 9.4 ECGs and Section 9.5 PE). Section 9.2 (Clinical Laboratory Evaluations) was updated to include clarification to data sources from both local lab and central lab. Section 9.6 (C-SSRS) was updated to clarify the listing of suicidality data will only include data for participants with at least one occurrence of suicidal ideation or behavior during treatment. Section 9.7 (Prior and Concomitant Medications) was updated to include the definition of prior medications. Section 10 (Changes from Planned Analysis) was updated to include the All Subjects, mITT, Completers, and PK Populations and to document the removal of the Per-Protocol Population. Also added changes from protocol: composite z-score scales are added as one of the efficacy endpoints. Section 11.1 (PK and PD Analysis) was updated to remove the reference to exploratory biomarkers, as this information is already contained in Section 8.8 (Biomarker changes). Section 12 (References) was updated to remove references 4 and 5.

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Cognition Therapeutics, Inc. protocol number COG0201 (A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Study to Evaluate the Safety and Efficacy of CT1812 in Participants with Mild to Moderate Alzheimer's Disease), Version 6.0, dated 13-Jun-2023. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3] for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Cognition Therapeutics, Inc.'s study COG0201.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to:

- To assess the safety and tolerability of CT1812 in participants with mild to moderate Alzheimer's disease (AD).

2.1.2. Secondary Objective

The secondary objective of the study is to:

- To assess target engagement and identify pharmacodynamic effects of CT1812 on cerebrospinal fluid (CSF) biomarkers.

2.1.3. Exploratory Objectives

The exploratory objectives of the study are:

- To characterize the PK profile of CT1812 in plasma.

- To assess the efficacy of CT1812 as a treatment for mild to mode[redacted]

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- The incidence and severity of adverse events (AEs).
- The change in usage of concomitant medications.
- Changes in vital signs.
- Changes in physical exam findings.
- Changes in electrocardiogram findings.
- Changes in clinical laboratory testing (serum chemistry, hematology, urinalysis).
- Changes in the Columbia Suicide Severity Rating Scale (C-SSRS).

2.2.2. Efficacy Endpoints

The efficacy endpoints of this study include:

- Mini Mental State Exam (MMSE).
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) 11 and-ADAS-Cog 13 (delayed recall and Number Cancellation added to ADAS-11 in the ADAS-13).
- Neuropsychological Test Battery (NTB) including Trails A and B, Digit Span, and Letter and Category Fluency (COWAT and CFT).
- Alzheimer's Disease Cooperative Study (ADCS)-Clinical Global Impression of Change (CGIC).
- ADCS-Activities of Daily Living (ADCS-ADL).
- Composite z-score scales (Cognitive Composite score; Memory composite score; Attention composite score; Executive Function composite score).

2.2.3. Pharmacokinetic/Pharmacodynamic Endpoints

The pharmacokinetic (PK) endpoints of the study include the following:

- CT1812 CSF/plasma concentration ratio (end of study [EOS] only).
- Changes in pre-dose CT1812 plasma concentrations.

The pharmacodynamic (PD) endpoints of the study include:

- CSF- abeta, tau, phospho-tau, neurogranin, synaptotagmin, synaptosomal-associated protein 25 (SNAP25), Neurofilament Light Chain (NFL), and Aβ oligomers. Other exploratory target engagement biomarkers may also be evaluated.

3. Overall Study Design and Plan

3.1. Overall Design

This is a phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel group 26-week study of two doses of CT1812 in adults with mild to moderate AD.

Participants will be screened for eligibility by physical, laboratory, psychometric and neurologic examinations, and neuroimaging. Pre-drug CSF and blood samples will be obtained ≤42 days prior to randomization at Baseline/Day 1. After having met all inclusion criteria, and none of the exclusion criteria, participants will be randomized in a 1:1:1 ratio to one of three treatment arms (CT1812 at doses of 100 or 300 mg/day or placebo; up to n=48 per group). On clinic visit days, study drug will be taken in the clinic after all baseline procedures have been conducted. For days where there are no clinic visits, participants will ingest study drug each morning at home. Participants and their caregivers/study partner will return to the clinic for repeat psychometric/neurologic testing, safety procedures, and PK and PD sample collection at the intervals described below.

Participants will be enrolled in three parts of the study, referred to as Part A, Part B and Part C. Part A is defined as the first 24 participants enrolled in the trial, and an interim analysis will be conducted on these participants. Part B is defined as the 25th participant through the 62nd participant enrolled in the trial. Part C is defined as all participants enrolled after October 2021.

Participants in Part A and B will return to the clinic twice in the first week after baseline, weekly for 3 weeks, bimonthly until Day 70, then every 4 weeks until Day 182 (See Table 1). A follow-up visit will occur approximately 30 days after the end of treatment.

Participants in Part C will return to the clinic on Day 7 and Day 14 after baseline, followed by twice-monthly visits until Day 70, then every four weeks until Day 182 (See Table 1). A follow up visit will occur approximately 30 days after the end of treatment.

Participants who prematurely discontinue the study for any reason will be asked to attend a final safety and efficacy visit.

Following an adequate clinical and non-clinical safety review of data from this initial cohort of participants, the protocol may be amended to expand enrollment and treatment duration to 12 months.

Participants who initially do not meet all enrollment criteria for this study may be permitted to re-screen. Re-screening may be permitted on a case-by-case basis following a discussion between the Principal Investigator (PI) and the Medical Monitor regarding whether a participant remains potentially eligible to participate in the study. A participant who is re-screened is not required to sign another ICF if the re-screening occurs within 30 days from the previous ICF signature date. There is no minimum period of time a participant must wait to re-screen for the study. The participant must meet all eligibility criteria at the time of re-screening in order to qualify for the study. Depending upon the time from the last screening visit, the Medical Monitor will determine what assessments need to be repeated.

The study start date is defined as the date on which the first Informed Consent is signed. A participant is considered to have completed the study if he/she has completed all study visits. The end of the study is defined as the date of the last visit or the date of the last procedure of the last participant in the study.

3.2. Sample Size and Power

The sample size justification in the protocol was as follows: for this trial, groups of 48 active-dosed participants per dose level are felt to give adequate sensitivity to detect AEs. A sample size of 48 active-dosed participants for each dose level (100 mg/day, 300 mg/day) has 91% power to detect at least one occurrence of any drug-related AE with a true prevalence in the treated population of 5%.

Additional participants may be added to replace participants with significant disruption to their visit schedule due to COVID or if there are unanticipated dropouts.

Additionally, for the primary exploratory efficacy analysis relating to the ADAS-COG 11 comparing the combined CT1812 treatment groups versus the placebo group, 48 participants per group provides 81% power to show a treatment difference of 3.0 points assuming a two-sided test at the alpha=0.05 level of significance, assuming a SD of 5.4 points, and a dropout rate of 15%.

3.3. Study Population

The study population will consist of male and female participants, 50 to 85 years of age (inclusive), with a diagnosis of mild to moderate AD according to the 2011 National Institute on Aging - Alzheimer's Association (NIA-AA) criteria and at least a 6-month decline in cognitive function documented in the medical record.

3.4. Treatments Administered

Participants who meet eligibility criteria will be randomized to one of three treatment arms (CT1812 at doses of 100 mg/day or 300 mg/day or placebo). Study drug will be administered orally once each morning (i.e., prior to 12 pm) for 6 months.

3.5. Method of Assigning Participants to Treatment Groups

Participants will be randomized in a 1:1:1 ratio to CT1812 100 mg/day, CT1812 300 mg/day or placebo. The placebo will be identical in appearance to the active CT1812. The unblinded statistician assigned to the trial will generate a randomization list with the appropriate number of 4--digit individual study identification numbers (IDs) for each arm, randomly assigned to one of the treatment arms.

3.6. Blinding and Unblinding

This is a double-blind study. All participants, investigators, and study personnel involved in the conduct of the study will be blinded to treatment assignment, with the exception of a specified unblinded statistician who will generate and have access to the randomization code. The unblinded study personnel will not otherwise participate in study procedures or data analysis prior to unblinding of the study data.

If a safety stopping rule (defined in Section 7.3.1 of the study protocol) is achieved, selective unblinding of the participants involved may be performed by the Sponsor to determine if the AEs (serious or otherwise) are isolated to a single dose group or if they occurred in placebo participants.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

[redacted]

Table 1: Schedule of Events

		Screen	Base-line													
	Study day(s)	**-60 to -1**	**1**	**3 (±1)**	**7 (±2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**42 (±2)**	**56 (±2)**	**70 (±2)**	**90 (±2)**	**98,126, 154 (±2)**	**172 (±2)**	**182 (±2)**	**210 (±2)**
	Visit(s)	**1**	**2**	**3***	**4**	**5**	**6***	**7**	**8**	**9**	**10**		**11,12 ,13**		**14**	**Safety Follow Up 15**
	Screening Tests															
1	Informed consent	X														
2	Inclusion/Exclusion Criteria	X	X													
3	Demography & Medical History	X														
4	Confirm AD diagnosis	X														
5	MMSE	X	X						X				X (Day 98)		X	
6	Modified Hachinski exam and GDS	X														
7	ApoE Status	X														
8	Optional whole blood sample for future biomedical research	X														
9	Screening Laboratories	X														
	Physical Exam, Vitals, ECG, Other															
10	Complete Physical Exam	X	X												X	
11	Brief Physical Exam			X	X	X	X	X	X	X	X		X			
12	Vital signs and weight	X	X	X	X	X	X	X	X	X	X		X		X	X
13	ECG (12-lead)	X	X					X		X			X (Day 98)		X	
14	MRI	X													X	
15	Amyloid PET Scan	X														

[redacted]

		Screen	Base-line													
	Study day(s)	**-60 to -1**	**1**	**3 (±1)**	**7 (±2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**42 (±2)**	**56 (±2)**	**70 (±2)**	**90 (±2)**	**98,126, 154 (±2)**	**172 (±2)**	**182 (±2)**	**210 (±2)**
	Visit(s)	**1**	**2**	**3***	**4**	**5**	**6***	**7**	**8**	**9**	**10**		**11,12 ,13**		**14**	**Safety Follow Up 15**
	Blood Draws, Urine Collection & Lumbar Puncture															
16	Chemistry & hematology	X	X	X	X	X	X	X	X	X	X		X		X	X
17	Serum cystatin C		X	X	X	X			X		X		X		X	X
18	PK and Exploratory Biomarkers Sampling	X EB only	X	X	X	X		X	X		X		X		X	
19	Serum biomarkers	X										X		X		
20	Coagulation testing (PT/INR)	X									X**		X (Day 154)			
21	Optional lumbar puncture (CSF Biomarker Sampling)	X											X (Day 98***)		X	
22	Urinalysis	X	X	X	X	X		X	X	X	X		X		X	
23	Pregnancy testing	X														
	Cognitive, Functional, and Safety Assessments															
24	C-SSRS	X	X	X	X	X	X	X	X	X	X		X		X	X
25	Cognitive Assessments and ADCS-ADL	X	X						X				X (Day 98)		X	
	ADCS-CGIC		X						X				X (Day 98)		X	
	Concomitant Medications, Adverse Events and Study Drug Administration															
26	Concomitant Medications	X	X	X	X	X	X	X	X	X	X		X		X	X
27	Adverse Events Assessment		X	X	X	X	X	X	X	X	X		X		X	X
28	Drug Accountability			X	X	X	X	X	X	X	X		X		X	

		Screen	Base-line													
	Study day(s)	**-60 to -1**	**1**	**3 (±1)**	**7 (±2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**42 (±2)**	**56 (±2)**	**70 (±2)**	**90 (±2)**	**98,126, 154 (±2)**	**172 (±2)**	**182 (±2)**	**210 (±2)**
	Visit(s)	**1**	**2**	**3***	**4**	**5**	**6***	**7**	**8**	**9**	**10**		**11,12 ,13**		**14**	**Safety Follow Up 15**
29	Drug Dispensation		X					X		X	X		X			
30	In office dose administration		X	X	X	X	X	X	X	X	X		X		X	

Abbreviations: AD = Alzheimer's disease; ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognition subscale; ADCS-ADL = ADCS-Activities of Daily Living Scale; ADCS-CGIC = ADCS-Clinical Global Impression of Change; ApoE = apolipoprotein E; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; GDS = Geriatric Depression Scale; LP = lumbar puncture; MMSE = Mini Mental State Exam; MRI = Magnetic Resonance Imaging scan; NTB = Neuropsychological Test Battery; PET = Positron Emission Tomography scan; PK = pharmacokinetic; PT/INR = prothrombin time and international normalized ratio

* Study Visit 3 (Day 3) and Visit 6 (Day 21) will not be performed for participants enrolled in Part C.

** Only required on Day 70 if the optional LP on Day 98 is planned.

***If a participant and investigator are agreeable, an additional LP may be performed at least 24 hours before the Day 98 visit.

If adequate volume is available, CSF will be stored for future evaluation of biomarkers of target engagement or disease modification. See Laboratory Procedures Manual for sample handling. See Section 11.5 for details. Obtained CSF should be sent for cell counts (white blood cells and red blood cells, with differential if either of the counts is abnormal), CSF protein, and CSF glucose at Screening, Day 98 (optional), and Day 182. If abnormalities are observed at Screening, they should be discussed with the Medical Monitor before randomizing the participant.

1. Informed consent must be obtained prior to the participant undergoing any study-specific procedures.
2. Review of all criteria detailed in Sections 9.2 and 9.3 of protocol.
3. Record demographic information, confirm ethnicity and obtain medical history.
4. Confirm AD diagnosis in accordance with McKhann 2011 criteria.
5. Mini Mental State Exam and Geriatric Depression Scale.
6. Perform Modified Hachinski Exam to screen for vascular dementia.
7. ApoE genetic testing is required for all participants.
8. Optional whole blood sample (~10 mL) for future biomedical research, including potential genetic analyses.
9. Screening labs include viral serology, Thyroid-stimulating hormone (TSH), Follicle-stimulating hormone (FSH) and Hemoglobin A1c (HbA1c).
10. Complete physical examination = thorough examination of all body systems, including height, weight, and neurological exam. Weight should be measured on the same scale each time. Height measured only at screening.

11. Brief physical examination = inquire about signs/symptoms, review of general appearance and brief review of body systems, including weight. Weight should be measured on the same scale each time.
12. Vital signs will include body temperature, systolic and diastolic BP, respiration rate and pulse rate. Weight should also be recorded. At Baseline and subsequent visits, vital signs are done at pre-dose.
13. ECG to be conducted during screening period, and approximately two hours post-dose (+/- 45 min) at specified visits.
14. MRI (or CT scan due to contraindication of MRI if approved by medical monitor) performed at screen (if an historical MRI is not used) and end of treatment.
15. Diagnostic confirmation by amyloid PET with florbetaben or another approved amyloid PET ligand. Diagnostic confirmation by cerebrospinal fluid (CSF) sample collected at Screen Lumbar Puncture, in place of the amyloid PET, will also be accepted.
16. Blood Chemistry and Hematology - Blood should be drawn within an hour of urine collection.
17. Serum cystatin C: Blood should be drawn within an hour of urine collection.
18. Plasma PK and Exploratory Biomarker Sampling: See Laboratory Procedures Manual for sample handling. PK will not be assessed at screen whereas the exploratory biomarker samples will be collected.
    Serum biomarker samples are collected at any point during screening at least 24 hours prior to the Baseline Visit. Serum biomarkers will also be collected at Day 90 (+/- 2 days) and Day 172 (+/- 2 days).
    This blood draw will be performed at a local lab. The local lab will include onsite laboratory facilities for collection and processing. Participants consented to Protocol version 2.0 on or after their Baseline visit are not required to have the Biomarker samples drawn on Day 90 or Day 172.
19. The serum samples should not be collected on the same day as the lumber puncture.
20. Coagulation testing includes prothrombin time and INR.
21. Optional lumbar puncture: Participants may opt to undergo lumbar puncture as part of screening, after all other eligibility criteria have been reviewed and approved by the medical monitor, at least 24 hours before the Baseline visit and again at Day 182 (the end of the dosing period). LP on the Day 182 visit should be performed minimally 24 hours prior to the other the Day 182 visit procedures (e.g., Day 181) and prior to dosing on that day. The optional screening visit lumbar puncture must not be performed without Medical Monitor approval.
22. Urine should not be first morning void. See Laboratory Procedures Manual for sample handling.
23. Pregnancy testing should include an assessment of FSH levels.
24. C-SSRS Screening/Baseline version used at screening visit, Since Last Visit version used at all other visits.
25. The ADAS-Cog 13, NTB, ADCS-ADL, and MMSE will be conducted during screening period, and prior to dosing at other visits. The ADCS-CGIC will be conducted beginning at Day 1, and all other visits with the cognitive assessments.
26. All concomitant medications will be recorded from screening through Day 210.
27. During Screening (post-consent), only SAEs related to a study-specific procedure will be collected. For all related AEs of moderate or severe intensity ongoing at the end of the study, follow-up will continue until the event has resolved to baseline severity, the event is assessed as stable by the Investigator, or the participant is lost to follow-up or the participants withdraws consent.
28. Study drug accountability will be performed via capsule count.
29. Dosing on non-study visit days will be self-administered at home. On “Drug Dispensation” clinic visits drug accountability will be completed for the bottle returned by the participants and the “in office dose administration” will be taken for that visit from the newly assigned bottle. Study drug can be administered with, or without food.
30. Participants will be administered the first dose in the clinic on Day 1. Doses on study visit days will also be administered in the clinic. Dose should be administered with or without food.

4. Statistical Analysis and Reporting

This SAP is based on the approved clinical study protocol, version 6.0, dated 12-Jun-2023.

This SAP addresses the safety and efficacy objectives of the study and describes the statistical methods that are to be used for the interim and final analysis of the completed study.

The reader of this SAP is encouraged to also read the clinical protocol, Drug Safety and Monitoring Board (DSMB) charter, and any other identified documents, for details on the planned conduct of the study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of participants (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Other statistics such as coefficient of variation (%CV), quartiles, confidence intervals (CIs), and number of missing values may be added as appropriate.

Categorical (qualitative) variable summaries will include the frequency and percentage of participants who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of participants in the study population within each treatment group, unless otherwise specified. The denominator for by-visit displays will be the number of participants in the relevant study population with non-missing data at each visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data. Measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and *P*-values will be reported. A *P*-value of ≤0.10 but >0.05 will be considered evidence of a trend. Corresponding 95% CIs will be presented for statistical tests.

4.2. Interim Analysis and Data Monitoring

After the first 24 participants have been randomized and completed their last study visits, the database for those participants will be frozen for purposes of an unblinded interim analysis of safety and efficacy data. All statistical outputs planned for the final analysis at the time of the interim analysis will be generated for the interim analysis. After the data for the first 24 participants is frozen, the unblinded statistician will provide randomization codes for these

participants only. These outputs will exclude any data from participants that are not part of the first 24 randomized participants. The data from the first 24 participants will also be included in the analysis of the final dataset.

A DSMB will oversee the safety of the trial. This committee will consist of 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. Additional details can be found in the DSMB charter.

5. Analysis Populations

The following analysis populations are planned for this study:

- **All Subjects:** The All Subjects population includes all participants who sign the ICF and get screened for the study.
- **Safety Population (SAF):** The Safety Population includes all participants who receive one or more doses of study medication.
- **Efficacy Modified Intent-To-Treat Population (mITT):** The Efficacy mITT Population includes all randomized participants who receive any amount of study drug and who have a baseline and at least one post-baseline assessment of the ADAS-Cog 11 total score.
- **Completers Population (CP):** The Completers Population includes all randomized participants who completed the study (i.e., who did not prematurely withdraw). There is no expectation that a participant included in the CP will have attended every single scheduled visit; as long as the participant completed the study, they will be included in the population.
- **Pharmacokinetic Population (PK):** The Pharmacokinetic Population includes all participants in the SAF who had at least one quantifiable concentration of CT1812.

6. General Issues for Statistical Analysis

Table and figure outputs based on the Safety Population and all listings will be presented by actual treatment received. Table and figure outputs based on the PK Population will be presented by actual treatment received. Table and figure outputs based on the mITT Population and Completer Population will be presented by randomized treatment.

Generally, all table and figure outputs will present individual CT1812 dose groups (100 mg, 300 mg) and the pooled CT1812 dose group (100 mg and 300 mg together) in addition to placebo.

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last non-missing observation recorded on or before the first dose of study drug will be used

as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

The efficacy models will include APOE ε4 (+ or −) status at baseline as covariates. Participants with ambiguous APOE results will be classified as positive for the efficacy analyses.

6.1.3. Multiple Comparisons

Although all of the clinical efficacy analyses for this study are exploratory in nature, the ADAS-Cog 11 least square mean change from baseline analysis is considered the primary exploratory analysis of interest compared to the other clinical efficacy analyses. The primary exploratory analysis of the ADAS-Cog 11 will compare the least square mean change from baseline value for the two active arms combined to the least square mean change from baseline value for the placebo arm at day 182, using a two-sided test at the alpha=0.05 level of significance. If the primary exploratory analysis of the ADAS-Cog 11 is statistically significant, then the following comparisons will be made using the least square mean change from baseline values and the same model as for the primary analysis:

1) 300 mg CT1812 versus placebo;

2) 100 mg CT1812 versus placebo.

Each comparison will be conducted using a two-sided test at the alpha=0.05 level of significance. This fixed sequence testing procedure will control the overall level of significance for this outcome.

All other clinical efficacy analyses will be conducted using two-sided tests at the alpha=0.05 level of significance. No adjustments will be made for multiple comparisons and all other p-values will be considered nominal.

6.1.4. Handling of Dropouts or Missing Data

If a participant is missing one, two, or three individual components of the Cognitive Composite score at a time point, the Cognitive Composite score will be computed using the average of the participant's non-missing components at the time point. If a participant is missing four or more individual components at a time point, the Cognitive Composite score will not be derived at that time point.

For the interim analysis, missing data for endpoints assessed at multiple time points will be imputed using the last observation carried forward (LOCF) approach.

For the final analysis, missing data for endpoints assessed at multiple time points and analyzed using repeated measures models will not be imputed. Missing data for endpoints assessed at post baseline timepoints may be imputed using LOCF for the purpose of analyzing data using an Analysis of Covariance (ANCOVA) model when the MMRM model fails to converge.

For the interim and final analyses, missing data for endpoints assessed at only one post-baseline time point will not be imputed.

6.1.5. Outlier Values and Values below the Limit of Quantitation

Some biomarker analyses may require removal of participants whose values are outliers or who have values at certain time points that are below the limit of quantitation. Decisions regarding inclusion or exclusion of participant values at particular timepoints will be made prior to database lock (DBL) and unblinding of data.

6.1.6. Analysis Visit Windows

Data in summary tables will be summarized by the nominal visit collected in the electronic data capture (EDC) system. The Day 182 (EOS or early termination [ET]) label in the EDC system is used for both Day 182 EOS visits and ET visits. A participant will only have their Day 182 data included in the summary tables if it occurs after study Day 170. Participants that early terminate before study Day 170 will have their ET visit listed only.

6.1.7. Pooling of Sites

Not applicable.

6.1.8. Derived Variables

- Change from baseline = value at current time point – value at baseline.
- Treatment-emergent AE (TEAE) = any AE with an onset date/time on or after the first dose of study drug.
- Modified Hachinski total score = the sum of the individual 8 item scores. Items 1, 6, 7 & 8 attract a score of 2-points if present (range of 0-8). Items 2, 3, 4 & 5 attract a score of 1-point if present (range of 0-4). The total score ranges from 0 – 12.
    - The sites were originally responsible for manually calculating the total score and entering it into the clinical study database. To ensure accuracy, it was decided to re-derive this total score in the ADaM dataset.
- ADCS-ADL total score = the sum of the individual 23 item scores. The score ranges from 0-78.
    - The sites were originally responsible for manually calculating the total score and entering it into the clinical study database. To ensure accuracy, it was decided to re-derive this total score in the ADaM dataset
- The ADAS-13 total score = the sum of all 13 individual items (word recall; commands; constructional praxis; delayed word recall; naming objects and fingers; ideational praxis; orientation; word recognition; remembering test instructions; spoken language; word finding; comprehension of spoken language; and number cancellation).
    - The score for the number cancellation item was originally set up to be derived within the clinical study database, however prior to database lock, an error was discovered in the derivation of this item score. This error subsequently impacts

the derivation of the ADAS-13 total score, which was also originally set up to be derived within the clinical study database.

- As a result, both the number cancellation item score and the ADAS-13 total score will be re-derived in the ADaM dataset for analysis purposes as follows:
- The number cancellation score will be derived in two steps:
  - Step 1: Calculate the preliminary number cancellation item score as (number of targets hit) – [(number of errors) + (number of times to remind to task)]
  - Step 2: Take the preliminary number cancellation item score calculated in Step 1 and re-scale as follows:
    - If number cancellation item score is ≥ 30 then re-scale as 0
    - If 24 ≤ number cancellation item score ≤ 29 then re-scale as 1
    - If 18 ≤ number cancellation item score ≤ 23 then re-scale as 2
    - If 12 ≤ number cancellation item score ≤ 17 then re-scale as 3
    - If 6 ≤ number cancellation item score ≤ 11 then re-scale as 4
    - If 0 ≤ number cancellation item score ≤ 5 then re-scale as 5
      - Number cancellation item scores < 0 will be re-scaled as 5
  - The resulting final number cancellation item score will range from 0 to 5.
- The ADAS-13 total score will be derived as the sum of the 13 individual items, but using the score for the number cancellation item which has been re-derived as described above.

- The ADAS-11 total score is the sum of 11 individual items excluding delayed recall and number cancellation.
- The Cognitive Composite score will be calculated using z-scores of the below items. The z-scores will be derived by calculating the baseline mean and standard deviation of each individual component for all participants. A z-score within each component will be derived for each participant at each timepoint by subtracting the corresponding baseline mean and then dividing by the corresponding baseline SD. The Cognitive Composite score will be set as the mean of the 10 individual z-scores (5 ADAS-COG scores and 5 NTB scores) within each participant and timepoint. If a participant is missing one, two, or three scores at a particular timepoint, the missing scores will be set as the average non-missing z-score of all participants at that timepoint within each component when deriving the Cognitive Composite score. If a participant is missing four or more individual components at each timepoint, the Cognitive Composite score will not be derived.
  - ADAS-COG
    - Word recall (scored on a 0 to 10 range), average of trials I, II, and III. If at least one of the trials is missing, this component will be considered missing. The sign of the z-score for this component will be reversed when deriving the Cognitive Composite score as it is the total words not recalled that is being recorded. This test is a key measure of episodic memory.

- Orientation (0 to 8). The sign of the z-score for this component will be reversed when deriving the Cognitive Composite score as the recorded score for this test is the number of items answered incorrectly. This measure is an index of the study participant's episodic memory and a single item of semantic memory (their name).

- Delayed Word Recall (0 to 10). The sign of the z-score for this component will be reversed when deriving the Cognitive Composite score as it is the total words not recalled that is being recorded.

- Word Recognition (0 to 24). The sign of the z-score for this component will be reversed when deriving the Cognitive Composite score. This is a further test of episodic memory using a word recognition paradigm of 12 true positive targets and 12 foil items. While the possible score for this measure is 0 to 24, the standard ADAS-Cog score is capped at a maximum worst score of 12.

- Number Cancellation (raw score 0 to 40, subsequently re-scaled to a 5-point scale [0-5]). In this task, the participant is asked to cross off as many target digits as possible in 45 seconds. The score is derived as the number of incorrectly crossed-off items and the number of reminders given subtracted from the number of items correctly crossed off. The resulting score (0-40) is then re-scaled to a 5-point scale (0-5) as described earlier in this section. NTB

  - COWAT – This test of working memory and executive function yields a key metric referred to as 'Total number of acceptable words'. This is obtained by calculating how many of the study participant's responses are deemed acceptable according to the scoring rules. The total score for COWAT is the sum of the number of accepted words for each of the 3 tests (three letters). The score range for this test is typically between 0 and 80, though floor performance (a score of 0) is vanishingly rare in mild-to-moderate stage AD participants.

  - CFT – This is a further test of working memory and executive function that yields a key metric referred to as 'Total number of acceptable words'. This is obtained by calculating how many of the study participant's responses are deemed acceptable according to the scoring rules. The usual performance range for this test is between 0 and 40.

  - Digit Span – This is a brief measure of working memory, especially in the Digits Backwards section. The key metric is 'Total number of trials correct', which is the number of sequences correctly recalled. The range of the test is 0 to 24 and both floor and ceiling effects are rare.

  - Trail Making Test (TMT) A – This is essentially a measure of attention, as successful completion relies on quickly and accurately connecting numbered circles in an ascending sequence. The key metric for analysis

purposes is 'Time taken for completion'. Errors and time taken once again both contribute to performance. However, because errors incur a time penalty, it is not necessary to analyze both metrics. The sign of the z-score for this component will be reversed when deriving the Cognitive Composite score.

- Trail Making Test (TMT) B – This is the more complex component of the TMT in which successful completion relies on the study participant accurately connecting the numbered and lettered circles. Study participants are required to alternate between numbers and letters in an ascending sequence. The key metric for analysis purposes is again 'Time taken for completion'. As with TMT A, because errors incur a time penalty, it is not necessary to factor in errors for analysis purposes. The sign of the z-score for this component will be reversed when deriving the Cognitive Composite score.

- The Memory composite score will be a composite z-score average similar to the Cognitive Composite score but will only be derived using the average of the ADAS-Cog Word Recall, Orientation, Delayed Word Recall, and Word Recognition items. If a participant is missing any of the four items at a timepoint, this composite score will not be derived.
- The Attention composite score will be a composite z-score average derived using the average of the Number Cancellation and TMT A items. If a participant is missing either of the two items at a timepoint, this composite score will not be derived.
- The Executive function composite score will be a composite z-score average derived using the average of the COWAT, CFT, Digit Span, and TMT B items. If a participant is missing any of the four items at a timepoint, this composite score will not be derived.

6.1.9. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P*-values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P*-value less than 0.0001 occurs, it will be shown in tables as < 0.0001. If a *P*-value greater than 0.9999 occurs, it will be shown in tables as > 0.9999.

Adverse events and medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus available at the time of database lock.

Prior and concomitant medications will be coded using the latest version of World Health Organization - Drug Dictionary Enhanced (WHO-DDE) available at the time of database lock.

A treatment-related AE is any AE with a relationship to the study drug of probable or possible.

If it is necessary to calculate a participant's age from the (partial or complete) date of birth

(DOB) and the date of the Baseline Visit, the floor function will be used to ensure the participant has an integer age.

If partial AE dates or partial medication dates occur, the convention for replacing missing dates for the purposes of calculating derived variables is as follows:

For partial AE and medication start dates:

- If the year is unknown, then do not impute the date but instead assign a missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of first application date and the end date (if present) is after first dose date, or AE/medication is ongoing, then impute as the month and day of the first application date. If this produces a date after the AE/medication end date, assign 01 January.
    - Otherwise, assign 01 January.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the first dose date, then impute as the day of the first dose date. If this produces a date after the AE/medication end date, assign 01.
    - Otherwise, assign 01.

For partial AE and medication end dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the year is known but the month or month and day is unknown, then:
    - If the year matches the year of the last date of the study (date of last contact if participant is lost to follow-up; date of completion or early termination otherwise), then impute as the month and day of the last date of the study.
    - Otherwise, assign 31 December.
- If the year and month are known, but day is unknown, then:
    - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.
    - Otherwise, assign the last day of the month.

In general, for quantitative laboratory values reported as '<X' or '≤X', the lower limit of quantitation (LLOQ) will be used for analysis (i.e., the value of X will be used in the analysis for lab values reported as '<X' or '≤X'). Similarly, for quantitative laboratory values reported as '>X' or '≥X', the upper limit of quantitation (ULOQ) will be used for analysis (i.e., the value of X will be used in the analysis for lab values reported as '>X' or '≥X').

For analysis purposes, repeat laboratory test results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeated laboratory value will be used for data analysis.

Data missing in the exploratory analysis of phospho-tau proteins will be handled according to the SAP provided by Proteome Sciences.

6.1.10. Subgroups

The following subgroups are defined for this study:

Subgroup	**Definition/Levels**
Measurable PK at Multiple Timepoints	If a participant randomized to CT1812 has measurable (>BLOQ) CT1812 concentrations at 7 or more post-baseline timepoints at which PK was assessed, then they are included in the subgroup. All participants randomized to placebo with CT1812 concentrations BLOQ at all post-baseline timepoints at which PK was assessed are included in the subgroup. Analyses will summarize all participants who meet the criteria to be included in the subgroup. It is not of interest to compare participants who meet the criteria for inclusion in this subgroup vs. those who don't.
Sex	Male, Female
MMSE at Baseline	18-21, 22-26
Age	<65, >=65
ApoE Status at Baseline	Positive, Negative. If genotype ApoE or phenotype ApoE contains E4, then ApoE status is considered Positive. Otherwise Negative.
pTau217 at Baseline	<Median, >=Median Median value is determined based on all participants combined (regardless of treatment group). This subgroup is based on plasma biomarker samples (not CSF).
Pre/Post COVID	Pre-COVID: Includes participants who completed or prematurely withdrew from the study prior to March 10, 2020. Post-COVID: All remaining participants
Region	US, ex-US (EU + AUS)
Acetylcholinesterase (AChE) inhibitors and/or memantine	Yes: Participant took these medications during the treatment period No: Participant did not take these medications during the treatment period

Subgroup	Definition/Levels
use during the study	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.

7. Study Participants and Demographics

7.1. Disposition of Participants and Withdrawals

The number of participants randomized and treated will be summarized by treatment group. The number and percentage of participants in the Safety, mITT, Completers, and PK Populations will be summarized by treatment group. The number and percentage of participants who completed the study and who prematurely discontinued the study will be summarized by treatment group. The reasons for study discontinuation will also be summarized.

All disposition information will be listed.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Demographic variables such as age, sex (including child-bearing potential for female), ethnicity, and race, and baseline characteristics such as height, weight, and body mass index (BMI), highest Level of Education, ApoE4 Status, ApoE Genotype, and Mini Mental State Exam (MMSE) Total Score will be summarized by treatment group for the Safety and mITT (if different from Safety) Populations.

Categorical variables, such as sex, ethnicity, race, and level of education will be summarized using frequencies and percentages. Continuous variables such as age, height, weight, and BMI will be summarized using mean, SD, median, minimum, and maximum.

Medical history will be coded using the latest version of MedDRA at the time of database lock. Medical history information will be listed only.

Demographic information will also be listed.

7.4. Exposure and Compliance

For all of the below formulas, *i* = individual participant for the entire treatment period.

- Total days of exposure will be calculated as:

$$\sum_i Days\ on\ Study\ Drug$$

- Study drug compliance will be calculated as:

$$\frac{\sum_i Actual\ Capsules\ Taken}{\sum_i Planned\ Capsules} \times 100$$

Compliance will be calculated using drug accountability data over the entire treatment period for each participant, up to treatment completion or discontinuation. Planned capsules will be calculated as 2 × the number of days between the first and last dose of study drug (inclusive).

Study drug exposure and compliance information will also be listed.

8. Efficacy Analysis

All efficacy analyses are exploratory in nature. The intent of this plan is to run the analysis of covariance (ANCOVA) model described in section 8.1 at the time of the interim analysis and the mixed-model repeated measures (MMRM) model described in section 8.1 at the time of the final analysis. However, if the MMRM model fails to converge, the ANCOVA analysis (with both observed and observed + LOCF values) will be run in place of the MMRM model for the final analysis. A Day 182 visit will be considered out-of-window if it does not occur between study day 171 and study day 193 (inclusive).

For the final analysis, all efficacy analyses will be run using the mITT population and a subset of the efficacy parameters (ADAS-Cog 11, ADCS-ADL, MMSE, ADCS-CGIC) will be summarized using the Completers Population as a sensitivity analysis.

All figures will be based on the mITT population only. The following figures will be produced for each efficacy parameter (ADAS-Cog 11, ADCS-ADL, MMSE, ADCS-CGIC and the composite z-scores: Cognitive Composite score; Memory Composite score; Attention Composite score; and Executive Function Composite score):

- Line plot of change from baseline values.
- Line plot of least square mean change from baseline values.
- By-participant spaghetti plots of the change from baseline values.

8.1. Composite z-scores

The composite z-scores (Cognitive Composite score; Memory Composite score; Attention Composite score; and Executive Function Composite score) defined in Section 6.1.8 will have their observed values and change from baseline summarized by visit.

Mean change from baseline within each of the four composite z-scores will be analyzed using a MMRM analysis with treatment as the main effect, visit, baseline z-score of the corresponding composite score, APOE ε4 (+ or -) status at baseline, and treatment by visit as an interaction term. All post-baseline analysis visits will be included in the model (Day 42, Day 98, and Day

182). An unstructured covariance matrix will be used to model the within-participant errors. The Kenward-Roger approximation will be used to estimate degrees of freedom.

The least squares (LS) mean change from baseline will be presented along with the associated 95% Confidence Interval (CI) within each treatment group. In comparing treatments (CT1812 100 mg/day minus placebo, CT1812 300 mg/day minus placebo, and the CT1812 groups combined versus placebo), LS mean differences in change from baseline will be presented along with associated 95% CIs and pairwise treatment *P*-values.

In the case of convergence issues, other covariance structures will be considered including (but not limited to) Toeplitz, compound symmetry (CS) and autoregressive (AR[1]) with each model fit to find the covariance structure with the best fit. The fit statistics will be compared for all covariance structures and the structure with the smallest Akaike information criterion will be retained as the preferred model.

For the interim analysis, ANCOVA model at each visit will be run in place of the MMRM. This model will include treatment as the main effect, baseline z-score of the corresponding composite scores, and APOE ε4 (+ or −-) status at baseline. For endpoints where LOCF is used, the analyses will be repeated using only observed data.

The composite z-scores will also be listed.

8.2. Mini Mental State Exam (MMSE)

The MMSE is a brief, screening instrument often used in clinical trials to assess dementia severity. The MMSE assesses several aspects of memory and cognitive functioning including orientation, attention, concentration, comprehension, recall, and praxis. The total possible score is 30, with high scores indicating less impairment.

Descriptive summaries of observed values and changes from baseline in the MMSE total score will be calculated by visit.

Change from baseline for MMSE will be analyzed using the same MMRM model described in Section 8.1, with the MMSE score in place of the composite score.

For the interim analysis, an ANCOVA model at each visit will be run using the same effects described in Section 8.1, with baseline MMSE score in place of the composite baseline score. For endpoints where LOCF is used, the analyses will be repeated using only observed data.

For the final analysis, MMSE will be summarized and analyzed for both the mITT Population and the Completers Population. Additionally, the change from baseline in MMSE will be summarized and analyzed for each subgroup defined in Section 6.1.10 using the mITT Population. For the subgroup analysis by ApoE status at Baseline, the APOE covariate will be excluded from the statistical model.

Results for MMSE will be listed.

8.3. Alzheimer's Disease Assessment Scale-Cognition Subscale (ADAS-Cog 14)

The ADAS-Cog 14 is a widely used general cognitive measure in clinical trials of AD. The ADAS-Cog was developed as an outcome measure for dementia interventions; its primary

purpose was to be an index of global cognition in response to antidementia therapies. The ADAS-Cog assesses multiple cognitive domains including memory, language, praxis, and orientation. For this study, 13 items of the ADAS-Cog 14 will be assessed.

Descriptive summaries of observed values and changes from baseline in the ADAS-Cog 13 (ADAS-13) total score and ADAS-Cog 11 (ADAS-11) total score will be calculated by visit.

ADAS-13 and ADAS-11 change from baseline will be analyzed using the same MMRM model described in Section 8.1, with baseline ADAS-13 or ADAS-11 score in place of the composite baseline score.

For the interim analysis, an ANCOVA model at each visit will be run using the same effects described in Section 8.1, with baseline ADAS-13 or ADAS-11 score in place of the composite baseline score. For endpoints where LOCF is used, the analyses will be repeated using only observed data.

For the final analysis, ADAS-13 and ADAS-11 will be summarized and analyzed for both the mITT Population and the Completers Population. Additionally, the change from baseline in ADAS-13 and ADAS-11 will be summarized and analyzed for each subgroup defined in Section 6.1.10 using the mITT Population. For the subgroup analysis by ApoE status at Baseline, the APOE covariate will be excluded from the statistical model.

ADAS-Cog results will also be listed.

8.4. Neuropsychological Test Battery (NTB)

The NTB consists of TMT A and TMT B, Digit Span, COWAT, and CFT. The TMT A and TMT B marking duration in seconds, Digit Span, CFT, and COWAT, tests will be summarized by visit and treatment. The composite scores for each item defined in Section 6.1.8 will be summarized by visit and treatment.

The change from baseline for each NTB component score will be analyzed using the same MMRM model described in Section 8.1.

For the interim analysis, an ANCOVA model at each visit will be run using the same effects described in Section 8.1. For endpoints where LOCF is used, the analyses will be repeated using only observed data.

Results for NTB will also be listed.

8.5. ADCS-Clinical Global Impression of Change (ADCS-CGIC)

The ADCS-CGIC was developed by the Alzheimer's Disease Cooperative Study (ADCS). The scale consists of a format with which a clinician may address clinically relevant overall change, including 15 areas under the domains of cognition, behavior, and social and daily functioning. The rater, at baseline, interviews the participant and caregiver/informant, using a form that comprehensively lists relevant symptoms potentially useful in judging change, and makes notes for future reference. There are few requirements to fulfill during the interview, but clinical assessment of mental status is to be made. By allowing raters to use the forms in an unstructured manner, this scale may facilitate clinical judgements with face validity. At follow-up visits, the

clinician uses a similar set of forms to re-interview the participant and caregiver/informant. The ADCS-CGIC rating is made on a 7-point scale similar to other global change scales, where a lower score indicates marked improvement. The ADCS-CGIC value is a measure of the change from baseline and therefore the algebraic change from baseline is not calculated for the ADCS-CGIC. As available at the site, the ADCS-CGIC will be completed by an independent rater (not the rater completing the cognitive or other assessments).

Descriptive numeric summaries of observed values in the ADCS-CGIC will be calculated by visit.

Observed values for ADCS-CGIC will be analyzed using the same MMRM model described in Section 8.1. Since an ADCS-CGIC result is not collected at baseline, no baseline covariate will be included in the model.

For the interim analysis, an ANCOVA model at each visit will be run using the same effects described in Section 8.1, with no baseline covariate in the model. For endpoints where LOCF is used, the analyses will be repeated using only observed data.

For the final analysis, ADCS-CGIC will be summarized and analyzed for both the mITT Population and the Completers Population. Additionally, the observed values for ADCS-CGIC will be summarized and analyzed for each subgroup defined in Section 6.1.10 using the mITT Population. For the subgroup analysis by ApoE status at Baseline, the APOE covariate will be excluded from the statistical model.

Results of ADCS-CGIC will also be listed.

Additionally, frequencies and percentages in the ADCS-CGIC will be summarized by visit. Cochran-Mantel-Haenszel mean score statistics, using rank scores, and stratified by ApoE status, will be used to assess the difference in ADCS-CGIC responses at each visit between the CT1812 dose levels and placebo.

8.6. ADCS-Activities of Daily Living (ADCS-ADL)

The ADCS-ADL is a 23-item informant-administered assessment of functional impairment in terms of activities of daily living. Informants respond to 23 questions about the participant'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. The total score range is from 0 to 78 with lower scores indicating greater functional impairment.

Descriptive summaries of observed values and changes from baseline in the ADCS-ADL total score will be calculated by visit.

Change from baseline for ADCS-ADL will be analyzed using the same MMRM model described in Section 8.1, with the ADCS-ADL score in place of the composite score.

For the interim analysis, an ANCOVA model at each visit will be run using the same effects described in Section 8.1, with baseline ADCS-ADL score in place of the composite baseline score. For endpoints where LOCF is used, the analyses will be repeated using only observed data.

For the final analysis, ADCS-ADL will be summarized and analyzed for both the mITT Population and the Completers Population. Additionally, the change from baseline in ADCS-ADL will be summarized and analyzed for each subgroup defined in Section 6.1.10 using the mITT Population. For the subgroup analysis by ApoE status at Baseline, the APOE covariate will be excluded from the statistical model.

Results of ADCS-ADL will also be listed.

8.7. Cognitive Composite Score and its Components

Descriptive summaries of observed values and changes from baseline will be calculated by visit. The results will also be listed.

8.8. Biomarker Changes

Targeted measurements of several protein biomarkers in CSF and plasma will be made, including the following:

Biology	**Biomarker**	**Biofluid**
AD progression disease	Aβ42, Aβ40, Aβ42/40 ratio	CSF, plasma
	Total Tau	CSF
	pTau181	CSF, plasma
	pTau217	plasma
	Brain derived Tau (BD-Tau)	plasma
Synaptic function	Neurogranin	CSF
	Synaptotagmin 1, SNAP25	CSF
Neuroinflammation	GFAP	CSF, plasma
Neurodegeneration	NFL	CSF, plasma
Other	Alpha-Syn	CSF

For Aβ40 and Aβ42, it is expected to see decreases in the change from baseline values with CT1812 treatment at 6 months. For all remaining biomarkers, it is hypothesized that changes will be observed over the 6-month treatment period.

Descriptive summaries of observed values and changes from baseline for each plasma and CSF

biomarker will be calculated by visit.

Plasma samples will be analyzed at baseline (V2), V11 (Day 98), and Day 182. Assuming data for more than one post-baseline sample is available, the change from baseline for each plasma biomarker will be analyzed using the same MMRM model described in Section 8.1. If only one post-baseline sample is available, then the ANCOVA model detailed below will be used.

For the interim analysis, for analysis of the CSF biomarkers at the final analysis, and in the scenario where only one post-baseline plasma biomarker sample is available at the final analysis, an ANCOVA model of change from baseline values will be run using the same effects described in Section 8.1. For CSF, only screening (V1) and V14 (Day 182) biomarker samples were collected and biomarkers will be measured in CSF from V1 and V14 and will be analyzed in the final analysis.

For the analysis of phospho-tau proteins performed for the interim analysis only, ANOVA analysis of the log2 (fold change from baseline) will be used to assess significance of drug effects.

For the final analysis, the change from baseline in each biomarker will be summarized and analyzed for the "Measurable PK at Multiple Timepoints" subgroup. Additionally, for just the Aβ40 and Aβ42 biomarkers, the change from baseline will be summarized and analyzed by the "MMSE at Baseline" subgroup. The following rules will apply to the subgroup analyses:

- If less than 10 participants 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 participants 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.

For the final analysis, the following figures will be produced:

- Spaghetti plots displaying individual participant-level data of observed values over time for each plasma and CSF biomarker by treatment group (placebo, CT1812 100 mg, CT1812 300 mg). The mean value for each treatment group will be overlayed and presented as a bold line in the body of the figure. These will be formatted as 3-panel, side-by-side plots, where each treatment group is presented in their own panel and all on the same Y-axis.
- Line plots displaying the mean (±SD) observed values over time for each plasma and CSF biomarker by treatment group (placebo, CT1812 100 mg, CT1812 300 mg, pooled CT1812 100 mg+300 mg).
- Line plots displaying the mean (±SD) change from baseline values over time for each plasma biomarker by treatment group (placebo, CT1812 100 mg, CT1812 300 mg, pooled CT1812 100 mg+300 mg).
- Line plots displaying the mean (±SD) change from baseline values at Day 182 for each CSF biomarker by treatment group (placebo, CT1812 100 mg, CT1812 300 mg, pooled

CT1812 100 mg+300 mg) and plotted in this order from left to right in the figure.

- Line plots displaying the LS mean (±95% CI) change form baseline values for each plasma and CSF biomarker by treatment group (placebo, CT1812 100 mg, CT1812 300 mg, pooled CT1812 100 mg+300 mg) and plotted in this order from left to right in the figure.
- Vertical scatter plots displaying the individual participant-level data of change from baseline values at Day 182 for each CSF biomarker by treatment group (placebo, CT1812 100 mg, CT1812 300 mg, pooled CT1812 100 mg+300mg) and plotted in this order from left to right in the figure.

All biomarker data will also be listed.

8.9. Other Exploratory Efficacy Analyses

Pearson correlation coefficients will be used to assess associations between biomarkers and cognitive and behavioral changes (ADAS-13, ADAS-11, Memory Composite, Attention Composite, NTB individual items, Executive Function Composite, Cognitive Composite, MMSE, ADCS-ADL, and ADCS-CGIC). Correlations will be calculated for baseline biomarker values and baseline efficacy measures. Additionally, correlations between change from baseline in by-visit biomarker values and change from baseline in efficacy scales will be calculated, and correlations between observed values in by-visit biomarker values and observed values in efficacy scales will be calculated.

CT1812 concentrations in CSF and plasma will also be correlated with changes from baseline in biomarkers and cognitive measures.

Additional analyses and correlations may be explored as well (e.g., possibly including age, gender, education and ApoE) and will be discussed in the clinical study report (CSR).

9. Safety and Tolerability Analysis

Safety assessments will be performed at scheduled timepoints throughout the study and include physical examination, vital signs, ECGs, standard clinical laboratory testing (serum chemistry, hematology, urinalysis), C-SSRS, prior and concomitant medications (CMs), and AEs.

All safety analyses will be performed on the Safety Population by actual treatment received.

9.1. Adverse Events

Treatment-emergent AEs will be summarized in all AE tables. A TEAE is defined as any AE with an onset date/time on or after the first dose of study drug. All AE summary tables will include the number and percentage of participants with an AE within a category, system organ class (SOC), or preferred term (PT).

An overall summary of the number and percentage of participants with TEAEs will be provided by treatment group. Frequencies and percentages of the following will be included: with any TEAE, participants with any TEAE related to treatment, participants with any TEAE leading to

treatment discontinuation, participants with any serious treatment emergent AE (SAE), participants with any SAE related to treatment, and participants with any TEAE leading to death.

The incidence of TEAEs will be summarized with frequencies and percentages by the following:

- PT in descending order of frequency
- SOC and PT
- SOC, PT, and maximum severity (Mild; Moderate; Severe)
- SOC, PT, and maximum relationship to study drug (Not Related; Related)

Incidences other than the PT summary will be presented alphabetically by SOC and PT. Participants with multiple events within the same SOC and PT will be counted once per SOC and PT. TEAEs with a missing severity will be considered severe and TEAEs with a missing relationship to study drug will be considered related. AEs with a relationship of study drug of possibly or probably related will be considered related.

All AEs will be presented in a listing. AEs that are treatment emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to treatment discontinuation, by treatment group, SOC, and PT will be provided for the Safety Population.

A data listing of AEs leading to study drug discontinuation will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by SOC and PT and presented by treatment.

9.2. Clinical Laboratory Evaluations

9.2.1. Protocol-Required Safety Laboratory Tests

Hematology testing will include erythrocyte (red blood cell count), erythrocyte mean corpuscular hemoglobin concentration (MCHC), erythrocyte mean corpuscular volume (MCV), hematocrit, hemoglobin, and absolute counts of leukocytes, lymphocytes, monocytes, neutrophils, basophils, eosinophils, and platelets. Coagulation testing (prothrombin time [PT/INR]) will be performed at screening and Day 154 only.

Serum chemistry analyses will include glucose, calcium, albumin, protein, sodium, potassium, bicarbonate, chloride, magnesium, fractional calcium excretion, blood urea nitrogen (BUN), creatinine, creatine kinase, alkaline phosphatase, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), bilirubin, lipase, lactate dehydrogenase (LDH), and phosphate.

Urinalysis will include osmolality, creatinine, calcium, erythrocytes, leukocytes, sodium, specific

gravity, pH, specimen appearance (turbidity), color, protein, glucose, ketones, bilirubin, hemoglobin, urobilinogen, nitrite, and microscopic particles. Trace protein will be considered positive. Urine samples that did not have preservative added prior to lab analysis will be listed only.

All summaries of laboratory values from local and central lab will be presented using SI units. Observed hematology, chemistry, and urinalysis values and changes from baseline at each visit will be summarized by treatment received. Shifts from baseline regarding low/normal/high values will also be summarized by treatment received.

Shift tables summarizing the most extreme post-baseline shift for each participant within each lab parameter will be presented, with low and high results considered more extreme than normal. If a participant has both a low and high post-baseline result within a parameter, they will be counted within both the low and high rows.

The incidence of post-baseline ALT values >=3xULN, AST values >=3xULN, and AST or ALT values >=3xULN will be summarized.

All chemistry, hematology, and urinalysis data will be listed.

Screening laboratory tests such as viral serology, thyroid stimulating hormone, follicle-stimulating hormone, HbA1c, Folate, B12, and urine pregnancy test results will be listed only.

9.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for systolic blood pressure (SBP [mmHg]), diastolic blood pressure (DBP [mmHg]), heart rate (beats/min), respiration rate (breaths/min), body temperature (C), weight (kg), and body mass index (kg/m2) by visit and treatment group.

All vital sign results will be listed.

9.4. Electrocardiograms

Descriptive summaries will be presented for ECG measures of PR interval (msec), RR interval (msec), QRS interval (msec), QT interval (msec), QTc interval (both Fredericia's and Bazett's correction methods), and HR. These summaries will be presented by visit and treatment group.

The frequency and percentage of participants with normal, clinically significant abnormal, and not clinically significant abnormal ECG results will be summarized for the Safety Population by treatment group and visit.

All ECG results will be listed.

9.5. Physical Examination

Frequencies and percentages of participants with normal, clinically significant abnormal, and not clinically significant abnormal physical exam findings will be summarized within the following body systems: general appearance, eyes, oral mucosa, heart, lungs, abdomen (liver/spleen), kidneys, neurological, and other. The following visits will be included:

Baseline, Day 3 (Visit 3), Day 7 (Visit 4), Day 14 (Visit 5), Day 21 (Visit 6), Day 28 (Visit 7), Day 42 (Visit 8), Day 56 (Visit 9), Day 70 (Visit 10), Day 98 (Visit 11), Day 126 (Visit 12), Day 154 (Visit 13).

All physical exam results will be listed.

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

The C-SSRS is routinely used to quantify the severity of suicidal ideation and behavior. Both the ideation and behavior subscales are sensitive to change over time.

Two versions of the C-SSRS will be used in this study: the Screening version and the Since Last Visit version. The Screening version of the C-SSRS assesses lifetime suicidal ideation and behavior. The Since Last Visit version of the C-SSRS assesses suicidal thoughts or behaviors the participant may have had since the last time the C-SSRS was administered.

At the screening visit, the C-SSRS Screening version will be administered. At all subsequent visits, the C-SSRS Since Last Visit version will be administered.

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). Assign a score of 0 if no ideation is present.

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 below:

- 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.

Baseline is defined as the most severe ideation and behavior reported in the past 6 months prior to the first dose of study drug. Suicidality data collected on the C-SSRS will be listed for all participants with at least one occurrence of suicidal ideation or behavior during treatment. 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 point as well as by study visit on the Suicidal Ideation and Suicidal Behavior items will be summarized by treatment received.

Additionally, shifts of whether participants experienced suicidal ideation, behavior, or both from pre-treatment to post-treatment will be summarized in a shift table. An additional shift table of maximum ideation from pre-treatment to post-treatment will also be provided.

All C-SSRS data will be listed.

9.7. Prior and Concomitant Medications

Medications used in the study will be summarized as follows:

- Medications that started prior to the first dose of study drug will be considered prior medications whether they were stopped prior to the first dose of study drug.
- Any medications continuing or starting post the first dose of study drug will be concomitant.
- If a medication starts prior to the first dose and continues after the first dose of study drug, it will be considered both prior and concomitant.

Summaries of medications and therapies will be presented in tabular form using the Therapeutic Indication (ATC level 3) as an upper classification and the preferred drug name as a lower classification level. All medications will be summarized by the number and percentage of participants taking each medication and sorted by descending counts (overall) in the upper classification term and the lower classification term within the upper. For each participant, the medication will be counted only once within the upper classification level and only once within the lower classification level.

Prior and concomitant medication listings will include start and stop dates, medication name, route, dose, dose frequency, and reason for use.

10. Changes from Planned Analysis

Four additional analysis populations are defined in this SAP but are not defined in the study protocol: All Subjects Population, mITT Population, Completers Population, and PK Population. These analysis populations have been added to enable the summary of disposition, the primary analysis of efficacy data (mITT), a sensitivity analysis of efficacy data (Completers), and analysis of PK data (PK). The Per-Protocol Population, also not defined in the study protocol but included in V1.0 of the SAP, was removed.

The score for the number cancellation item was originally set up to be derived within the clinical

study database, however prior to database lock, an error was discovered in the derivation of this item score. This error subsequently impacts the derivation of the ADAS-13 total score, which was also originally set up to be derived within the clinical study database. As a result, both the number cancellation item score and the ADAS-13 total score will be re-derived in the ADaM datasets for analysis purposes.

The Modified Hachinski total score and ADCS-ADL total score were originally calculated and entered into the study database by the sites. To ensure accuracy, it was decided to re-derive these total scores in the ADaM dataset.

Composite z-score scales (Cognitive Composite score; Memory composite score; Attention composite score; Executive Function composite score) are added to efficacy endpoints and their derivation are included in Section 6.1.8.

11. Other Planned Analysis

11.1. Pharmacokinetic and Pharmacodynamic Analysis

Pharmacokinetic parameters such as CT1812 cerebrospinal fluid (CSF)/plasma concentration ratio, and CT1812 plasma concentrations will be summarized by treatment or treatment and visit where applicable using the PK Population. Analysis of pharmacodynamic parameters are detailed in Section 8.8 (Biomarker Changes).

12. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
3. The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.