STATISTICAL ANALYSIS PLAN

Study Title:	A Pilot Electroencephalography (EEG) Study to Evaluate the Effect of CT1812 Treatment on Synaptic Activity with Mild to Moderate Alzheimer's Disease
Phase:	2
Protocol No.:	COG0202
Protocol Date(s):	Version 3.4: 19DEC2019 Version 4.0: 21FEB2022 *Protocol versions prior to V3.4 were not approved by the IRB and therefore are not applicable to list here.*
Analysis Plan Version and Date:	Final Version 1.0: 20January2023
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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

Prepared by:

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Review:

[redacted]

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the planned data summary and analysis of data from Protocol COG0202. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

1.1. STUDY OVERVIEW

This study is a single-site, randomized, double-blind, placebo-controlled, 2-period crossover study in 16 mild to moderate Alzheimer's participants (Mini-Mental State Exam [MMSE] 18-26) who will receive 300 mg of CT1812 or placebo once daily (QD). These participants will be organized in 2 groups of 8 participants each. The participants in one group will receive 29 days of treatment with CT1812 [Period 1] followed by a 14-day washout period, then 29 days treatment with placebo [Period 2]. The participants in the second group will receive placebo for 29 days during period 1, followed by a 14-day washout period, then CT1812 for 29 days during period 2. Change in synaptic function and cognition will be assessed by quantitative electroencephalography (EEG), Amsterdam Instrumental Activity of Daily Living Questionnaire (A-IADL-Q), and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog 14), supplemented with additional cognitive tests including Neuropsychological Test Battery (NTB) and a clinician's global impression at the end of Treatment Periods 1 and 2.

Participants will ingest study drug each morning at home with or without food, except on study site days when study drug will be administered at the study site. Participants and their study partners will return to the study site for repeat psychometric/neurologic testing, safety procedures and pharmacokinetic (PK) and pharmacodynamic (PD) sample collection at the intervals described below.

Up to 16 participants will be enrolled and will return to the study site on Days 1, 3, 8, 15, 22, and 29. A washout period will occur between days 30 to 43 followed by additional study site visits on Days 44, 46, 51, 58, 65, and 72. An end of study (EOS) follow-up visit will be completed on Day 84; approximately 12 days after the end of treatment.

Participants will be provided with 31 days of study drug to ensure treatment is continued up to the last Timepoint (Study days 29 ± 2 and 72 ±2).

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

1.2. SCHEDULE OF ASSESSMENTS

	Period	**Screen**	**Baseline**	**Treatment Period 1**					**Wash**	**Treatment Period 2**						**F/U**
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**	**10**	**11**	**12**	**13**	**14**
	Study day	**-42 to -1**	**1**	**3**	**8 (±2)**	**15 (±2)**	**22 (±2)**	**29 (±2)**	**30 to 43**	**44 (±2)**	**46 (±2)**	**51 (±2)**	**58 (±2)**	**65 (±2)**	**72 (±2)**	**84 (±2)**
1	Informed consent	X								X						
2	Inclusion/exclusion criteria	X	X													
3	Demography & medical history	X														
4	Confirm AD diagnosis	X														
5	MMSE, GDS	X														
6	MRI, Imaging	X														
7	Complete physical examination	X	X													X
8	Brief physical examination				X	X	X	X		X		X	X	X	X	
9	Vital signs	X	X		X	X	X	X		X		X	X	X	X	X
10	ECG (12-lead)	X	X			X				X		X				X
11	EEG		X					X		X					X	X
	Blood Draws & Lumbar Puncture															
12	APOE status	X														
13	Screening laboratories	X														
14	Chemistry, hematology, viral serology and lipid panel	X	X		X	X	X	X		X		X	X	X	X	X
15	Whole blood for FSH, if applicable	X														

	Period	Screen	Baseline	Treatment Period 1					Wash	Treatment Period 2						F/U
	Visit	1	2	3	4	5	6	7		8	9	10	11	12	13	14
	Study day	-42 to -1	1	3	8 (±2)	15 (±2)	22 (±2)	29 (±2)	30 to 43	44 (±2)	46 (±2)	51 (±2)	58 (±2)	65 (±2)	72 (±2)	84 (±2)
16	Whole blood for future biomedical research	X														
17	Blood and plasma for PK/PD sampling and exploratory biomarkers		a		b	b	b	a		a		b	b	b	a	c
18	Lumbar puncture	X						X							X	
	Urine collections															
19	Urinalysis	X	X			X		X		X			X		X	X
20	Pregnancy testing	X													X	
	Affective and cognitive assessments															
21	C-SSRS	X	X					X		X					X	
22	CGIC		X					X		X					X	
23	Neuropsychological test battery		X					X		X					X	
24	ADAS-Cog-14		X					X		X					X	
25	A-IADL-Q		X					X		X					X	
26	Drug dispensing		X							X						
27	Telephone check			X							X					
28	Concomitant medications	X	X	X	X	X	X	X		X	X	X	X	X	X	X
29	AE assessment		X	X	X	X	X	X		X	X	X	X	X	X	X
30	Medication compliance check			X	X	X	X	X			X	X	X	X	X	
31	Dose administration at study site		X		X	X	X	X		X		X	X	X	X	

	Period	Screen	Baseline	Treatment Period 1					Wash	Treatment Period 2						F/U
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**	**10**	**11**	**12**	**13**	**14**
	Study day	**-42 to -1**	**1**	**3**	**8 (±2)**	**15 (±2)**	**22 (±2)**	**29 (±2)**	**30 to 43**	**44 (±2)**	**46 (±2)**	**51 (±2)**	**58 (±2)**	**65 (±2)**	**72 (±2)**	**84 (±2)**
32	Dose administration at home			<----------X---------->						<----------X---------->						

ADAS-Cog-14 = Alzheimer's Disease Assessment Scale–cognitive subscale-14; AE = adverse event; A-IADL-Q = Amsterdam – Instrumental Activities of Daily Living questionnaire; APOE = apolipoprotein E; CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC); C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EEG = electroencephalography; EOS = end-of-study; FSH = follicle stimulating hormone; F/U = follow-up period; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Exam; PD = pharmacodynamics; PK = pharmacokinetics; TSH = thyroid stimulating hormone.

Key for Table 1 Schedule of Assessments

1. Informed consent must be obtained prior to the participant undergoing any study-specific procedures.
2. Review all inclusion/exclusion criteria (see Section 9.3 of protocol).
3. Record demographic information, confirm ethnicity, and obtain medical history.
4. Confirm Alzheimer's Disease (AD) diagnosis per the National Institute on Aging- Alzheimer's Association (NIA-AA) 2018 criteria for probable AD Dementia.
5. Mini-Mental State Exam and Geriatric Depression Scale (GDS).
6. Magnetic resonance imaging (MRI) of the brain will be performed, unless an MRI taken within the past 12 months is available.
7. Complete physical examination: a thorough examination of all body systems, including height and weight. Weight should be measured on the same scale each time. Height may be measured only at screening.
8. 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.
9. Vital signs will include body temperature, systolic and diastolic blood pressure (BP), and heart rate. Vital signs will be collected prior to dose administration and 2 hours post dose on Days 1, 3, 8, 15, and 29 in Treatment Period 1 and on Days 44, 46, 51, 58, 65, and 72 in Treatment Period 2. Vital signs will be collected at all other visits when convenient during the visit.
10. Electrocardiogram (ECG) will be conducted during the screening period and on dosing days approximately 2 hours post dose.
11. Refer to the EEG manual for details.
12. Genetic testing for the apolipoprotein E (APOE) gene.
13. Screening labs, including TSH, hemoglobin A1c (HbA1c) and viral serology.
14. Blood chemistry (including lipid panel) and hematology: Blood should be drawn within an hour of urine collection. Collections on Days 22 and 65 include coagulation testing.
15. Whole blood for follicle stimulating hormone (FSH) in women who had their last menses less than 24 months prior to screening.
16. Whole blood for Future Biomedical Research (FBR) will be collected, provided the participant gives consent.
17. PK/PD Sampling:
    a. Collect 1 (± 0.25) hour predose (PK and Exploratory Biomarkers) and at 2 (± 0.25) hours post dose (PK only) on Days 1, 29, 44, and 72.
    b. Collect 1 (± 0.25) hour predose (PK and Exploratory Biomarkers) on Days 8, 15, 22, 51, 58 and 65.
    c. Collect once (PK and Exploratory Biomarkers) on Day 84 (follow-up visit).

Exploratory Biomarkers

Collect plasma for Exploratory Biomarkers predose at each visit where plasma for PK is collected.

18. Participants will undergo lumbar puncture (LP) as part of screening after all other eligibility criteria have been met and again at the end of each treatment period. During Treatment Period 1, final LP should be performed on Day 29 prior to dosing (or on Days 25 to 28 prior to dosing, if needed for scheduling purposes); during Treatment Period 2, the final LP should be performed on Day 72 prior to dosing (or on Days 68 to 71 prior to dosing, if needed for scheduling purposes). If adequate volume is available, cerebrospinal fluid (CSF) will be stored for future evaluation of biomarkers of target engagement or disease modification. See Protocol section 11.5 for details.
19. Urine should not be first morning void.
20. For post-menopausal women, aged < 60 years, with last menses within the preceding 24 months. The urine pregnancy test will be performed at the end of the screening period (within 24 hours of dosing on Day 1) and on Day 72. The pregnancy test must be negative prior to dosing.
21. C-SSRS ("Screening" version) will be administered during screening and "Since-Last-Visit" version on Days 1, 29, 44, and 72.
22. The Alzheimer's Disease Cooperative Study -Clinical Global Impression of Change (ADCS-CGIC) will be conducted on Days 1, 29, 44, and 72.
23. The NTB (Category Fluency Test [CFT], Controlled Word Association Test [COWAT], Trail Making Test [TMT] Parts A & B, and Wechsler Memory Digit Span [VMDS]) will be conducted during screening, and on Days 1, 29, 44, and 72.
24. The ADAS-Cog-14 version A will be conducted during screening, on Day 1, and Day 29; version B will be conducted on Day 44 and Day 72.
25. The A-IADL-Q will be conducted during screening, prior to the first dose on Day 1, and on Days 29, 44, and 72.
26. Study drug will be dispensed on the first day of Treatment Period 1 (Day 1) and on the first day of Treatment Period 2 (Day 44).
27. On Days 8 and 46, the participant and/or study partner will be called via telephone for a wellness check, including questions about concomitant medications and any Adverse Events (AEs).
28. All concomitant medications will be recorded from screening through the EOS visit.
29. During screening (after consent), only Serious Adverse Events (SAEs) related to a study-specific procedure will be collected. For all related AEs of moderate or severe intensity that are ongoing at the end of the study, follow-up will continue until one of the following has been met: the event has resolved to baseline severity; the event is assessed as stable by the Investigator; the patient is lost to follow-up; or the patient withdraws consent.
30. Participant must bring all remaining study drug to each study site visit to verify how many tablets of study drug have been taken.
31. Dosing on study site days will be administered by the study site staff. The dose may be administered with or without food.
32. Dosing on non-study site days will be administered at home. The dose may be administered with or without food.

1.3. GLOSSARY OF ABBREVIATIONS

AD	Alzheimer's Disease
ADAS-Cog-14	Alzheimer's Disease Assessment Scale-cognitive subscale
ADCS-CGIC	The Alzheimer's Disease Cooperative Study -Clinical Global Impression of Change
AE	adverse event
AEC-c	Amplitude Envelope Correlation-corrected
A-IADL-Q	Amsterdam Instrumental Activity of Daily Living Questionnaire
ALT	alanine transaminase
ALP	alkaline phosphatase
ANOVA	analysis of variance
APOE	apolipoprotein E
AST	aspartate aminotransferase
BLQ	Below limit of quantification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFT	Category Fluency Test
CGIC	Clinical Global Impression of Change
COWAT	Controlled Word Association Test
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
EEG	electroencephalography
EOS	end of study
FBR	future biomedical research
FSH	follicle stimulating hormone
GDS	Geriatric Depression Scale
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
JPE	Joint Permutation Entropy
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LP	lumbar puncture
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

MeSH	Medical Subject Headings
MMSE	Mini Mental State Exam
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging- Alzheimer's Association
NTB	Neuropsychological Test Battery
PD	pharmacodynamic
PK	pharmacokinetic
PLI	Phase Lag Index
PT/INR	prothrombin time
QD	once daily
QTcB	heart rate-corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SD	standard deviation
TEAE	treatment emergent adverse events
TMT	Trail Making Test
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VMDS	Wechsler Memory Digit Span
WHO	World Health Organization

2. OBJECTIVES

Primary Objectives:

- To evaluate the safety, tolerability, and PK of CT1812 following repeated dosing of CT1812 for 29 days.
- To evaluate the efficacy of CT1812 in restoring synaptic function in participants with mild to moderate Alzheimer's disease (AD) through quantitative EEG, as reflected by relative theta power.

Exploratory Objectives:

- Measure changes in exploratory cerebrospinal fluid (CSF) and plasma biomarkers including synaptic damage biomarkers such as Neurogranin as well as disease progression biomarkers (such as Aβ40 and 42) measured at baseline and through the end of each treatment period.
- To evaluate changes in cognitive and global functioning, as measured by the following:
  - ADAS-Cog-14
  - ADCS-CGIC
  - A-IADL-Q
  - NTB that includes Category Fluency Test (CFT), Controlled Word Association Test (COWAT), Trail Making Test (TMT) Parts A & B, and Wechsler Memory Digit Span
- Evaluate additional quantitative EEG measures that have shown promise as diagnostic/treatment marker: relative alpha (8-13 Hz) and beta (13-30 Hz) power, theta/alpha power ratio, spectral peak frequency, and functional connectivity measures corrected Amplitude Envelope Correlation-corrected (AEC-c).

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

Based on the use of a two-sided one-sample (within-subject) comparison between CT1812 and placebo at the alpha=0.05 level of significance, a sample size of 16 participants provides 90% power to detect a mean difference in relative theta power between treatments of 2.5%.

For the endpoint of CSF Neurogranin, assuming a true within-subject standard deviation (SD) of 129.6 pg/mL and based on the use of a two-sided one-sample comparison at the alpha=0.05 level of significance, a sample size of 16 participants provides 90% power to detect a treatment difference of -105 pg/mL.

3.2. RANDOMIZATION AND MASKING

This is a double-blind, placebo-controlled study. Study treatment will consist of capsules of CT1812 and matching placebo. The placebo capsule will be identical in appearance to the active CT1812 capsule.

Treatment Sequence	Dosing Period 1 (Days 1-29)	Dosing Period 2 (Days 44-72)
CT1812/ Placebo	300 mg CT1812 (two 150mg capsules) QD	Placebo (two capsules) QD
Placebo/ CT1812	Placebo (two capsules) QD	300 mg CT1812 (two 150mg capsules) QD

The randomization schedule with the appropriate number of 4-digit individual study IDs randomly generated for each treatment sequence was prepared by a non-study statistician at Julius Clinical.

Should any participant withdraw from the study prior to study completion, the participant may be replaced, at the discretion of the Sponsor. The replacement participant will be given the same treatment assignment (by the unblinded statistician) as the withdrawn participant.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

No strata or covariates will be examined.

3.3.2. Examination of Subject Subsets

No subject subset analyses are planned for this study.

3.3.3. Multiple Testing and Comparisons

To control for multiplicity, a sequential testing procedure will be used on select exploratory EEG endpoints. If the primary efficacy endpoint is statistically significant, then the first exploratory EEG endpoint in the list below will be formally tested. If the first exploratory EEG endpoint is statistically significant, then the next exploratory EEG endpoint in the list will be formally tested. This will continue until all endpoints in the list below have been tested, or until non-significance is observed for an endpoint. Once a non-significant p-value result is reached, statistical testing will continue for the remaining endpoints, but the p-values that are generated will be considered nominal p-values.

The order of the testing will follow the order of the endpoints listed below:

1. Change from period baseline in global relative theta power (primary efficacy endpoint)
2. Change from period baseline in global alpha band AEC-c (exploratory endpoint)
3. Change from period baseline in global relative alpha power (exploratory endpoint)
4. Change from period baseline in global relative beta power (exploratory endpoint)

Following this procedure will not result in a need for alpha adjustments to conclude statistical significance. All tests will be performed at the 0.05 level.

3.3.4. Missing Data and Outliers

Laboratory and/or vital signs with missing units will be converted to standardized units by review of the original data value (e.g., a temperature with no unit, but a recorded value of 99.1 will be assumed to have a unit of Fahrenheit and standardized accordingly).

Should a treatment-emergent adverse event (TEAE) have missing severity or relationship, it will be classified as having a severity of 'SEVERE' and/or 'DRUG RELATED' in summary tables but the severity/relationship will appear as missing in listings.

3.3.5. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent or if a medication is concomitant). In such cases, incomplete dates will be imputed.

To minimize bias, the project statistician will impute dates in a systematic, but reasonable manner. All events associated with a given visit that have an incomplete date are assumed to have occurred on the date of the visit. For events not associated with a given visit (i.e., adverse events [AEs] and concomitant medications), the following rules for missing or partial event dates will be implemented:

- Missing start day, but month and year present:

  If the event occurs in the same month and year as the occurrence of study drug in Period 1, then the start day of the event will be assigned to the day of first dose of study drug in Period 1.

  If the event occurs in the same month and year as the occurrence of study drug in Period 2, then the start day of the event will be assigned to the day of first dose of study drug in Period 2.

  Otherwise, the start day will be set to the first day of the month.

- Missing start day and month, but year present:

  If the event occurs in the same year as study drug in Period 1, then the start date of the event will be assigned to Day 1 of Period 1.

  If the event occurs in the same year as study drug in Period 2, then the start date of the event will be assigned to Day 1 of Period 2.

  If the event occurs in the same year as study drug in both Period 1 and Period 2, then the start date of the event will be assigned to Day 1 of Period 1.

  Otherwise, the start day and month will be set to 01 January.

- Missing all components of a start date:

  Assign the date of Day 1 of Period 1.

However, if another date precludes the possibility (e.g., an end date for an AE cannot be prior to the start date of the AE, medication dates linked to an AE should be taken after the start of an AE), the closest date to Period Day 1 that is possible for the incomplete date will be used.

If a date has an unknown day, month, and year, the event will be assumed to have started/ended on the date of Period Day 1, unless another date precludes the possibility, in which case the closest date to Period Day 1 will be used.

3.3.6. Imputation of Alphanumeric Data

Should there be instances where a clinical laboratory parameter or PK concentration is reported with imbedded non-numeric characters, as for example, "<0.1" or ">10" the data will be imputed for the purpose of quantitative summaries. The actual values as reported in the database will be presented in data listings.

For incorporation in quantitative summaries, the following imputation rules will be employed:

For clinical laboratory values, the lower limit of quantification will be replaced with ½ the value of the lower limit. For example, < 0.1 will be replaced with 0.05. The upper limit of quantitation will be increased by one level of precision that precedes the value. For example, ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1".

PK concentration values that are below the level of quantification (BLQ) will be set to zero for summary tables. Individual values that are BLQ will be presented as "BLQ" in the concentration data listing.

3.3.7. Presentations by Timepoint

By-visit summaries will be presented according to the analysis period nominal visit (i.e., Day 1 of period through Day 29 and follow-up of period) based on the nominal visit from the CRF or laboratory data. If the visit is a discontinuation or unscheduled visit, the nominal visit will be assigned based on visit windows. Visit windows are based on the period day completed according to the table below.

Table 1: Visit Windows for Discontinuation and Unscheduled Visits

CRF Visit	Analysis Period	Analysis Visit	Period Target Day	Period Window Days
Baseline	1	Day 1 (Baseline Period 1)	1	≤ 1
Day 3	1	Day 3	3	2-5
Day 8	1	Day 8	8	6-11
Day 15	1	Day 15	15	12-18
Day 22	1	Day 22	22	19-25
Day 29	1	Day 29	29	26-41
Day 44	2 (1)	Day 1 (Baseline Period 2)/ Follow-up (Period 1)	1 (44)	≤ 1 (42-46)
Day 46	2	Day 3	3	2-5
Day 51	2	Day 8	8	6-11
Day 58	2	Day 15	15	12-18
Day 65	2	Day 22	22	19-25
Day 72	2	Day 29	29	26-38
Day 84 Follow-up	2	Post-Treatment Follow-up (Period 2)	41	39-43

If assessments are collected multiple times within a given visit window, the scheduled visit, if available, will be used for summary presentations. If no scheduled visit is available, then the result closest to the scheduled visit date will be used for summary presentations. If two unscheduled measurements (discontinuation or unscheduled visit) have the same distance to the expected date, the earlier value will be used. If a subject has multiple non-missing unscheduled values on the same date, then the last one is used, as determined by the time collected, if available.

3.3.8. Definitions and Terminology

Age
The age of a subject in years will be reported as collected on the CRF.

Analysis Period
Analysis Period is the stage of the study during which treatment is administered and assessments are being conducted. Given the crossover design in which each unique participant receives two treatments in a randomly ordered sequence, Analysis Period 1 is the subset of study days between the start of dosing for the initial treatment in the sequence until the dosing for Period 2, the second treatment in the sequence. Analysis Period 2 is the subset of study days between the start of dosing for the second treatment up to the final follow-up visit. For nominal visits, Day 1 of Analysis Period 2 will also be the follow-up visit for Analysis Period 1, to allow for symmetry of the visits for each period (see Table 1). For events without nominal visits, such as AEs, the event will be assigned to an analysis period based on the date the event occurred.

Treatment Period
The treatment period is the period during which a participant receives the first dose through the last dose of study drug (CT1812 or placebo). There are two treatment periods in this study. The first treatment period (29 days) will be followed by a 14-day washout. Immediately after the washout, there will be a second treatment period for 29 days, followed by a 12-day safety follow-up period.

Study Day 1 (Baseline)
Study Day 1 is the day study drug (either CT1812 or placebo) is first initiated during the study.

Period Day 1
Period Day 1 in each analysis period is the earliest day that study drug is administered within that period.

Study Day
Study Day is defined relative to Study Day 1 (Baseline). Thus, the study day of an event is calculated as:

Study Day =Event Date – Date of Study Day 1 (+1 if event date is after Date of Day 1)

This calculation will result in negative study days being assigned to visit occurring prior to the start of study drug (CT1812 or placebo) and positive study days being assigned on or after the start of study drug (CT1812 or placebo). There will be no Day 0 value to match the schedule of events.

Period Day
Within each analysis period, Period Day is defined relative to Period Day 1. Thus, the period day of an event is calculated as:

Period Day = Event Date – Date of Period Day 1 (+1 if event date is after Period Day 1)

This calculation will result in negative period days being assigned to visit occurring prior to treatment with study drug within each period, and positive study days being assigned on or after the start of study drug.

Period Last Dose of Study Drug
Last Dose of Study Drug is defined as the last date that the subject received study drug for a given treatment period as recorded on the Dosing CRF.

Days on Study
Days on Study is the number of days from Study Day 1 to the date of study completion or early termination as recorded on the CRF and calculated as:

Days on Study = Final Day on Study – Study Day 1 + 1.

Duration of Exposure (days)
Duration of Exposure (days) is the number of days from Period Day 1 to the Period Last Dose of Study Drug. This does not include the washout period.

Duration of Exposure = Period Last Dose of Study Drug – Period Day 1 + 1.

Cumulative Dose of Study Drug
The cumulative dose of study drug is calculated in milligrams and is calculated as the sum of each daily dose of study drug within a given treatment period as recorded in the CRF.

Study Drug Compliance
Compliance (%) will be calculated for each treatment period as the Total Number of Capsules Taken divided by the Expected Number of Capsules Taken*100, defined as follows:

- Total Number of Capsules Taken
  Per participant, per study drug, calculated as the number of tablets dispensed minus (the number of tablets returned + the number of tablets lost).
  - The number of tablets dispensed for a treatment period is equal to the number of tablets dispensed at the first visit in the treatment period (for Period 1, this is Visit 2 [Baseline]; for Period 2, this is Visit 8).
  - The number of tablets returned for a treatment period is equal to the number of tablets returned at the last visit in the treatment period (for Period 1, this is Visit 6; for Period 2, this is Visit 12).
  - The number of tablets lost for a treatment period is equal to the cumulative number of reported lost tablets during the treatment period.

- Expected Number of Capsules Taken
  For participants that begin Period 2 dosing, the expected number of capsules in Period 1 is 29 days * 2 capsules/day = 58 capsules. Otherwise, if the participant does not enter Period 2, or discontinues during Period 2, the expected number of capsules taken during the period will be equal to the number of days from date of Period Day 1 to the date of Period Last Dose of Study Drug multiplied by 2.

Study Timepoint
Study Timepoint is the nominal visit as recorded on the CRF.

Study Baseline Value

For purposes of analysis, the study baseline value is defined as the last value obtained prior to initiation of Period 1 study drug (CT1812 or placebo). Should the baseline visit value be obtained after the first dose of study drug (CT1812 or placebo) or if this value is not available at Study Day 1, then the most recent value obtained prior to earliest initiation of study drug (CT1812 or placebo) will be used for the study baseline value.

Period Baseline Value

For purposes of analysis of data within each treatment/analysis period, the baseline value will be defined as the last valid evaluation completed before the study drug administration within each analysis period. For all CSF and plasma biomarker endpoints, the baseline value for both Period 1 and Period 2 will be the study baseline value.

Change from Study Baseline

Change from Study baseline for a given endpoint is defined as the Study Time Point X value minus the Study Baseline Value.

Change from Period Baseline

Change from Period Baseline for a given endpoint is defined as the Study Time Point X value minus the Period Baseline Value. For all CSF and plasma biomarker endpoints, the change from Period Baseline value will be equal to the change from study baseline value.

Time Since Diagnosis (years)

(Date of informed consent – date of diagnosis + 1)/365.25

Adverse Event (AE)

An AE is any untoward medical occurrence in a participant or clinical investigation participant undergoing a study procedure or administration of a study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding per the Investigator), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. A related AE is an AE with a causality rating of “possible” or “probable” and a not related AE is an AE with a causality rating of “unlikely” or “unrelated”. A pretreatment AE is any AE occurring during the pretreatment period (between informed consent and initiation of a study drug). A post-study AE is an AE occurring more than 30 days after the date of last dose.

Treatment-emergent Adverse Event

TEAEs are all AEs occurring during the treatment periods or a pretreatment AE that worsens in intensity during either treatment period. TEAEs will be categorized into which study period they occurred. An AE with onset date on or after the initiation of study drug in Period 1 and before dosing with study drug for Period 2, or before follow-up contact if Period 2 dosing is not initiated, is considered a Period 1 TEAE. An AE with onset date on or after the initiation of study drug in Period 2 through the follow-up visit is considered a Period 2 TEAE.

Treatment Related AE

A TEAE with relationship recorded as “possible” or “probable” on the CRF.

Concomitant Medications

Concomitant medications are those medications taken on or after the date the study drug was initiated. This definition includes medications started prior to the initiation of study drug but continuing concomitantly with study drug. Medications taken during a washout period will be applied to the treatment immediately prior. Medications taken across multiple treatment periods will be assigned to both treatment periods.

Prior Medications

Prior medications are those medications taken and discontinued prior to the initiation of study drug.

Columbia-Suicide Severity Rating Scale (C-SSRS) Score

The C-SSRS is comprised of 10 categories with binary responses to indicate a presence or absence of the behavior. The 10 categories 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

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

Categories 1-5 represent suicide ideation and categories 6-10 represent suicidal behavior. Each category is scored as 1 (present) if there is a positive response in the category and a 0 (absent) if there are no positive responses in the category.

Self-Injurious Behavior Without Suicidal Intent During Treatment

A participant will be categorized as having self-injurious behavior without suicidal intent if there is an occurrence of non-suicidal self-injurious behavior on the C-SSRS – SINCE LAST VISIT CRF at any post-baseline visit within a given treatment period.

Baseline C-SSRS Score

Baseline represents the pre-treatment assessment of recent history (i.e., study baseline), with elements of suicidal ideation assessed over the prior 6 months and elements of suicidal behavior assessed over the prior two years. It is scaled from 0 (no suicidal ideation or behavior) to 10 (completed suicide).

3.4. TIMING OF ANALYSES

The final analysis will be completed after the last participant completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

4. ANALYSIS POPULATIONS

The populations for analysis will include the Enrolled Population, Safety Population, the Pharmacokinetic (PK) Population and the Pharmacodynamic (PD) Population.

- Enrolled Population: The Enrolled Population includes all participants who signed the informed consent form and obtained a participant number.
- Safety Population: The Safety Population includes all randomized participants who receive one or more doses of study drug. The Safety Population will be used for all efficacy and safety data summaries.
- PK Population: The PK population is comprised of all randomized participants who receive at least one dose of study drug and have at least one PK concentration of CT1812. The PK population will be used for all PK data summaries.
- PD Population: The PD population is comprised of all randomized participants who receive at least one dose of study drug and have at least one pharmacodynamic assessment. The PD population will be used for all PD data summaries.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data. Unless stated otherwise, the term "descriptive statistics" refers to number of participants (n), mean, median, SD, Q1, Q3, minimum and maximum for continuous data and frequencies and percentages for categorical data.

Unless otherwise specified, participant accountability and baseline characteristics (e.g., participant disposition, demographics, baseline characteristics, and protocol deviations) will be summarized by randomized treatment sequence *(*CT1812/Placebo or Placebo/CT1812). Safety and efficacy data will be summarized by actual treatment received (CT1812 or placebo).

All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted by randomized treatment sequence, participant, and treatment received/date of occurrence.

The statistical analyses will be conducted with the SAS® System version 9.4 or higher. All analyses will be subject to formal verification procedures. Specifically, results from summary tables and listings will be verified utilizing independent programming prior to issuance of the draft statistical report. Figures will be independently verified via programming or hand checked in accordance with PharPoint SOP PRG 008. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

5.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject disposition will be presented. The number of participants enrolled, randomized, treated (Safety Population), included in PK and PD populations, completed the study, and discontinued

from the study will be provided. The primary reasons for study discontinuation at any point will be presented by randomized treatment sequence and overall for the Enrolled population. The number of days on study will be summarized using descriptive statistics.

The following demographics and disease characteristics will be summarized by randomized treatment sequence and overall for the Safety Population:

- Age
- Sex
    - Females of child-bearing potential
- Race
- Ethnicity
- Height
- Weight
- Body mass index (BMI)
- Years of education
- National Institute on Aging - Alzheimer's Association (NIA-AA) Diagnosis
- Time since diagnosis (years)
- Screening MMSE total score
- Baseline ADAS-Cog-14 total score
- Baseline A-IADL-Q total score
- Screening apolipoprotein E (ApoE) status

Medical history will be mapped to a system organ classification (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0, or more recent version available at the time of database lock and listed by randomized treatment sequence and subject.

A listing of ApoE status at Screening will be produced for the Enrolled population.

5.2. EXTENT OF EXPOSURE

Duration of exposure, cumulative dose of study drug received, and treatment compliance will be summarized by treatment received for all participants.

5.3. EFFICACY ANALYSIS

5.3.1. Primary Efficacy Endpoint

The primary endpoint is global relative theta (4-8 Hz) power obtained through EEG assessment at Day 1, Day 29 of Treatment Period 1, and at Days 44 and 72 (Day 1 and Day 29 of Treatment Period 2) of the study. EEGs are also assessed at Day 84 (Follow-up Visit) however the Day 84 results will be excluded from the statistical models described in the following sections as the Day 84 measurements are only applicable to the last treatment each subject received.

5.3.2. Primary Efficacy Analysis

Brain activity using EEG will be gathered with eyes closed during 15-minute task free sessions. Spectral analyses will be conducted by Fast Fourier Transformation using BrainWave performed to

obtain the relative and absolute power in the delta (0.5-4 Hz), theta (4-8 Hz), alpha 1 (8-10 Hz), alpha 2 (10-13 Hz), and beta (13-30 Hz) frequency bands, as well as peak frequency. Global power per frequency band will be obtained by averaging spectral measures of all electrodes and regional power will be calculated in frontal, central, temporal and parieto-occipital regions. Before statistical analysis, the log transformation (log base 10) will be applied to normalize the distribution of the absolute power values.

The primary efficacy variable, global relative theta power, is defined as the percentage of total brain activity accounted for by theta wave frequency.

Global relative theta power will be quantified and summarized descriptively (observed values, change from the pre-treatment values) by treatment and time point using the Safety Population.

The change from period baseline in global relative theta power within each period will be analyzed using a linear mixed model with fixed effects for treatment group (CT1812 or placebo), sequence, and period, and a random effect for subject within sequence. The sample model code is as follows:

```
PROC MIXED;
CLASS TREATMENT PERIOD SEQUENCE SUBJECT;
MODEL CHANGE = TREATMENT PERIOD SEQUENCE;
REPEATED/ TYPE=UN SUB = SUBJECT(SEQUENCE);
LSMEANS TREATMENT / DIFF CL E ALPHA = 0.05;
RUN;
```

The comparison between CT1812 and placebo will be made using a two-sided test at the alpha=0.05 level of significance.

5.3.3. Exploratory Efficacy Endpoints and Analysis

All exploratory endpoints will be provided in data listings.

5.3.3.1. Cerebrospinal fluid and plasma biomarkers

CSF and plasma biomarkers will be measured at study baseline and at the end of each treatment period. The complete list of biomarkers to be assessed is as follows:

CSF: Ab42, pTau181, tTau, Ab40, Ab42/40 ratio, pTau217, NFL, Neurogranin, SNAP-25, GFAP, YKL-40, sTREM2, NXTP2, VAMP2

Plasma: pTau181, pTau217, Ab40, Ab42, Ab42/40 ratio, NFL, GFAP

Observed values and changes from study baseline for each biomarker will be summarized by treatment using the PD Population. The change from study baseline for each biomarker will be analyzed in a manner similar to what is described for the analysis of the primary endpoint, i.e., using a linear mixed model for repeated measurements with fixed effects for treatment group (CT1812 or placebo), sequence, and period, and a random effect for subject within sequence. Comparisons between CT1812 and placebo for each parameter will be made using two-sided tests at the alpha=0.05 level of significance.

For each of the CSF and plasma biomarkers, line plots will be created to summarize the mean (SD) values over time for each treatment sequence. Additionally, spaghetti plots will be created to

summarize the CSF and plasma biomarker data for each subject, using symbols and/or different line types to distinguish between the treatment sequences.

An additional analysis will be conducted for each biomarker for the subset of subjects in the PD population who were randomized into the Placebo/CT1812 treatment sequence. Observed and change from baseline to the end of Treatment Period 1 values will be summarized using descriptive statistics.

5.3.3.2. ADAS-Cog-14 Score

The ADAS Cog-14 includes the 11 tasks of the ADAS cog subscale (ADAS-Cog), plus 3 tasks for delayed word recall, maze, and digit cancellation tasks (Kueper 2018). The ADAS Cog-14 scores are based on the number of errors made on each item and compiled into a sum score. Higher scores represent more severe impairment.

Scores for each task and total score are as recorded in the CRF. The total score is derived as the sum of the scores from the 11 tasks of the ADAS-Cog plus the scores for the 3 additional tasks. The ADAS-Cog-14 total score and changes from period baseline will be summarized by treatment. The change from period baseline in the total score will be analyzed in a manner similar to what is described for the analysis of the primary endpoint.

5.3.3.3. ADCS-CGIC Score

The ADCS-CGIC assessment 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 clinician uses a worksheet to interview the participant and determine the rating. The ADCS-CGIC rating is made on a 7-point scale where the lowest score (1) indicates marked worsening, and the highest score (7) indicates marked improvement. The ADCS-CGIC assessment scores at the end of each Treatment Period will be summarized by treatment. Since the ADCS-CGIC value is a measure of the change from baseline, the algebraic change from baseline will not be calculated for the ADCS-CGIC summary table.

The number and percentage of participants recording each of the ADCS-CGIC responses will be presented for each treatment group. Additionally, the mean (SD) value for each treatment group will be presented. The distribution of responses will be analyzed using a generalized linear model based on the multinomial distribution. The sample model code is as follows:

```
PROC GENMOD;
CLASS TREATMENT PERIOD SEQUENCE SUBJECT;
MODEL RESPONSE = TREATMENT PERIOD SEQUENCE / DIST=MULTINOMIAL;
REPEATED SUBJECT=SUBJID(SEQUENCE) / TYPE=UN;
CONTRAST ‘CT1812 vs PLACEBO’ TREATMENT 1 -1;
RUN;
```

5.3.3.4. A-IADL-Q

The A-IADL-Q is an adaptive and computerized questionnaire designed to assess impairments in instrumental activities of daily living (IADL) in (early) dementia. The scoring of this questionnaire is performed by an external vendor (Brain Research Center). The A-IADL-Q Total score and

changes from period baseline will be summarized by treatment. The change from period baseline in total score will be analyzed in a manner similar to what is described for the analysis of the primary endpoint.

5.3.3.5. Neuropsychological Test Battery (NTB)

The NTB will consist of the following assessments: CFT, COWAT, TMT Parts A & B, and Wechsler Memory Digit Span.

- For CFT, the total generated words and number of accepted words will be summarized.
- For COWAT, the number of correct words in each of the 3 timed tests will be summarized.
- For TMT, the time to complete test (seconds) and number of errors for each part (A, B) will be summarized.
- For Wechsler Memory Digit Span, the total items correct and length for both forward and backwards tests will be summarized.

The assessments as described in the bulleted list above and changes from period baseline will be summarized by treatment. The change from period baseline for each assessment will be analyzed in a manner similar to what is described for the analysis of the primary endpoint.

5.3.3.6. Other EEG Outcome Variables

The following EEG parameters will be summarized and analyzed in a manner similar to how the primary efficacy analysis will be conducted:

- Alpha AEC-c (global)
- Alpha relative power (global)
- Beta relative power (global)
- Mean peak frequency parieto-occipital
- Global theta/alpha ratio
- Alpha MST betweenness centrality maximum BC
- Alpha MST (diameter global, eccentricity global, leaf fraction global, tree hierarchy global)
- Alpha AEC-c (central, frontal, parieto-occipital, temporal)
- Alpha Joint Permutation Entropy (JPE) (global, central, frontal, parieto-occipital, temporal)
- Alpha relative power (central, frontal, parieto-occipital, temporal)
- Alpha Phase Lag Index (PLI) (global, central, frontal, parieto-occipital, temporal)
- Alpha absolute power (global, central, frontal, parieto-occipital, temporal)
- Beta MST betweenness centrality maximum BC
- Beta MST (diameter global, eccentricity global, leaf fraction global, tree hierarchy global)
- Beta AEC-c (global, central, frontal, parieto-occipital, temporal)
- Beta JPE (global, central, frontal, parieto-occipital, temporal)
- Beta PLI (global, central, frontal, parieto-occipital, temporal)
- Beta relative power (central, frontal, parieto-occipital, temporal)
- Beta absolute power (global, central, frontal, parieto-occipital, temporal)
- Delta MST betweenness centrality maximum BC
- Delta MST (diameter global, eccentricity global, leaf fraction global, tree hierarchy global)

- Delta AEC-c (global, central, frontal, parieto-occipital, temporal)
- Delta JPE (global, central, frontal, parieto-occipital, temporal)
- Delta PLI (global, central, frontal, parieto-occipital, temporal)
- Delta relative power (global, central, frontal, parieto-occipital, temporal)
- Delta absolute power (global, central, frontal, parieto-occipital, temporal)
- Theta MST betweenness centrality maximum BC
- Theta MST (diameter global, eccentricity global, leaf fraction global, tree hierarchy global)
- Theta AEC-c (global, central, frontal, parieto-occipital, temporal)
- Theta JPE (global, central, frontal, parieto-occipital, temporal)
- Theta PLI (global, central, frontal, parieto-occipital, temporal)
- Theta relative power (global, central, frontal, parieto-occipital, temporal)
- Theta absolute power (global, central, frontal, parieto-occipital, temporal)
- Total power (global, central, frontal, parieto-occipital, temporal)

The following parameters will be log-transformed (log base 10) for the purposes of summarization and analysis:

- Alpha absolute power (global, central, frontal, parieto-occipital, temporal)
- Beta absolute power (global, central, frontal, parieto-occipital, temporal)
- Delta absolute power (global, central, frontal, parieto-occipital, temporal)
- Theta absolute power (global, central, frontal, parieto-occipital, temporal)

5.4. PHARMACOKINETIC ANALYSES

5.4.1. PK Endpoints

The following CT1812 PK assessments will be made based on concentrations in plasma:

- CT1812 CSF/plasma concentration ratio (end of study only)
- Changes in CT1812 plasma concentrations versus time
- Plasma CT1812 metabolite MP (CP199) versus time

5.4.2. PK Analysis

Plasma concentrations of CT1812 and its primary metabolite M6 (CP199) as reported by the analytical laboratory will be summarized by timepoint using descriptive statistics. Plasma concentrations are collected 1 hour pre-dose and 2 hours post dose on Study Days 1, 29, 44 and 72. On Study Days 8, 15, 22, 51, 58, and 65, concentrations are collected 1 hour pre-dose only and again on Day 84 for a follow-up visit. Summaries will include mean, standard deviation, geometric mean, coefficient of variation (CV), median, minimum, and maximum. The PK parameters to be evaluated are T_{max}, $T_{1/2}$, C_{max}, C_{min}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$. Figures depicting the mean plasma concentrations by time (linear and semi-log) will be generated. PK parameters will be derived in a validated Phoenix WinNonlin version 6.3 by noncompartmental analysis of plasma concentration data using sampling times.

CT1812 CSF/plasma concentration ratio at end-of-study will be summarized by treatment and included in a data listing.

Plasma CT1812 and CP199 concentrations will be listed.

5.5. SAFETY

Values for all safety variables will be listed by treatment sequence, participant, actual treatment received, and timepoint (as applicable).

5.5.1. Adverse Events

Adverse events will be mapped to a SOC and PT using MedDRA Version 22.0, or more recent version at the time of database lock.

The occurrence of TEAEs will be summarized by SOC and PT for each treatment.

Separate summaries will be provided for:

- Overall summary of TEAEs
- TEAEs
- Serious adverse events (SAEs)
- TEAEs related to study drug
- TEAEs by greatest severity
- TEAEs leading to the discontinuation of study drug
- TEAEs leading to death

If a participant experiences multiple events that map to a single term, the greatest severity grade according to the Investigator and strongest investigator assessment of relation to study medication will be assigned to the term for the appropriate summaries. Missing onset dates, severity and relationship will be imputed as previously outlined in Sections 3.3.4 and 3.3.5.

All AEs reported will be listed for individual participants showing both verbatim and MedDRA coded terms. All AEs that occurred prior to the initiation of study treatment will be excluded from the tables but will be included in the listings.

5.5.2. Clinical Laboratory Assessments

Clinical laboratory values and change from period baseline will be summarized by treatment and timepoint. Laboratory results will be categorized as Low/Normal/High based on reference ranges. Shifts in laboratory result category from baseline will be summarized by treatment. Summaries will include:

- Hematology and coagulation
    - Red blood cell count, erythrocyte mean corpuscular hemoglobin concentration (MCHC), erythrocyte MCV, hematocrit, hemoglobin, leukocyte count, and absolute counts of monocytes, neutrophils, basophils, eosinophils, and platelets. Coagulation testing (prothrombin time [PT/INR])
- Serum Chemistry and lipids
    - Glucose, calcium, albumin, total protein, sodium, potassium, bicarbonate, chloride, magnesium, blood urea nitrogen (BUN), creatinine, creatine kinase, alkaline

phosphatase, ALT, AST, bilirubin, lipase, lactate dehydrogenase (LDH), and phosphorus as well as a complete lipid panel consisting of (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL] and triglycerides

- Urinalysis
    - Osmolality, creatinine, calcium, sodium, turbidity, color, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocytes, and microscopic particles.

The number of participants with the following post-baseline liver, kidney, and calcium laboratory abnormalities will be summarized by treatment and timepoint:

- ALT/AST >1.5x upper limit of normal (ULN), >3x ULN, >5x ULN, >10x ULN, >20x ULN
- Total Bilirubin >1x ULN, >1.5x ULN, >2x ULN
- ALT >3x ULN and (Bilirubin >2x ULN or INR >1.5x ULN) *
- AST >3x ULN and (Bilirubin >2x ULN or INR >1.5x ULN) *
- ALT or AST >3x ULN and (Bilirubin >2x ULN or INR >1.5x ULN) *
- ALT and AST >3x ULN and (Bilirubin >2x ULN or INR >1.5x ULN) *
- Serum Calcium ≥ 2.62 mmol/L (10.5 mg/dL)
- Serum Creatinine increase from period baseline of > 26.5 umol/L (>0.3 mg/dL)

* For these conditions, the elevated values must have all occurred at the same visit in order to meet the criteria for the abnormality.

All laboratory values (including screening viral serology (hepatitis B antigen, anti-hepatitis C antibody and anti-HIV antibodies), FSH testing, THS, HbA1c, Folate and B12) will be listed and values outside the normal range will be indicated in the listing.

5.5.3. 12-Lead Electrocardiogram

ECGs will be conducted on the screening day and dosing days approximately 2 hours post dose. Pulse rate, respiratory rate, QT, QTcB, and QTcF and corresponding changes from study baseline will be summarized by treatment and timepoint using descriptive statistics. All ECG values will be listed, and abnormal or clinically significant results will be indicated in the listing.

5.5.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary Enhanced Global (B3) Mar 2021, or more recent version at the time of database lock. Prior and concomitant medications will be presented in a data listing. Concomitant medications will be attributed to a treatment period (as described in Section 3.3.7) and summarized by treatment.

5.5.5. Physical Examination

Abnormal physical examination results will be listed.

5.5.6. Vital Signs

Body temperature, systolic and diastolic blood pressure, heart rate, weight, and BMI values and changes from period baseline will be summarized by treatment and timepoint. Vital signs will be listed.

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

The maximum post-baseline results from the C-SSRS will be summarized by treatment. The maximum of each subscale (suicidal ideation [Categories 1-5], suicidal behavior [Categories 6-10], suicidal ideation or behavior [Categories 1-10], and self-injurious behavior without suicidal intent) will be presented. All results from the C-SSRS will be reported in a listing. The "Screening" version will be used during screening, and the "Since-Last-Visit" version will be used at all subsequent visits.

5.5.8. Other Safety Analyses

MRI, MMSE, GDS and pregnancy results will be listed.

6. PROTOCOL DEVIATIONS

Deviations considered important per Investigator will be presented by category and subcategory of deviation and by treatment using the Safety Population. Any deviation from the protocol will be listed. The type of deviation along with a description and any additional comments about the deviation will be listed.

7. CHANGES IN THE PLANNED ANALYSES

This analysis plan defines three additional populations not pre-specified in the protocol: Enrolled Population, PK Population and PD Population. These populations were needed for summarizing participant disposition and for analyses of PK and PD data, respectively.

The protocol states that AEs will be summarized by Medical Subject Headings (MeSH) Term, however MedDRA alone will be used for the coding of AEs.

The protocol states that all the quantitative EEG outcome variables, including the primary efficacy outcome measure of global relative theta power, will be analyzed using the analysis of variance (ANOVA) model for a 2-period, 2-treatment crossover study described by Senn (1993, pages 63-64). Because the methods are identical in the case of a balanced design and because using a mixed model repeated measures approach with SAS PROC MIXED is less sensitive to imbalance between treatment arms and allows exploration of the UN (unstructured) structure, the analysis was conducted using PROC MIXED.

Acute kidney biomarker testing is mentioned in Section 13.1.6 of the study protocol, however these assessments were not conducted during the study. As such, there are no data to report.

Section 3.3.3 of this SAP prespecifies 3 exploratory EEG endpoints which are considered to be of relative importance for this study. This section also details a sequential testing procedure which will be followed in order to address multiplicity in the analysis of the primary and these select exploratory EEG endpoints.

Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

8. REVISION HISTORY

Date	Revision	Rationale

9. REFERENCES

Kueper JK, Speechley M, Montero-Odasso M. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review. J Alzheimers Dis. 2018;63(2):423-444. doi: 10.3233/JAD-170991. PMID: 29660938; PMCID: PMC5929311.

10. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8.
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population due to missing data.
    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, will be noted.
    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted by treatment group, subject number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- Numerical Values: The presentation of numerical values will adhere to the following guidelines:
    - Raw measurements will be reported to the number of decimal places as captured electronically or on the CRFs.
    - Standard deviations will be reported to two decimal places beyond the number of decimal places the original parameter is presented.
    - Means will be reported to the one decimal place places beyond the number of decimal places the original parameter is presented.

- Calculated percentages will be reported with no decimals.

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HH:MM).

11. PROPOSED TABLES, LISTINGS, AND FIGURES

Summary Tables

Accountability and Baseline Characteristics

14.1.1.1 Subject Disposition – Enrolled Population
14.1.2.1 Demographics and Baseline Characteristics – Safety Population
14.1.2.2 Baseline Disease Characteristics – Safety Population
14.1.3 Important Protocol Deviations/Violations – Safety Population
14.1.4 Drug Exposure and Compliance – Safety Population

Efficacy

14.2.1.1 Hierarchical Testing for Primary and Selected Exploratory Efficacy Endpoints – Safety Population
14.2.1.2 Change in EEG Measurement of Global Relative Theta Power by Timepoint – Safety Population
14.2.1.3 Change in EEG Measurements of Alpha Band AEC-c, Global Relative Alpha Power, and Global Relative Beta Power by Timepoint – Safety Population
14.2.1.4 Change in Other EEG Measurements by Timepoint – Safety Population
14.2.2.1 Change in ADAS-Cog-14 Total Score by Timepoint – Safety Population
14.2.2.2 Summary of ADCS – Clinical Global Impression of Change (CGIC) Assessment Scores by Timepoint – Safety Population
14.2.2.3 Change in Amsterdam IADL Questionnaire Assessment (A-IADL-Q) Total Score by Timepoint – Safety Population
14.2.2.4 Change in Neuropsychological Test Battery Results by Timepoint – Safety Population

Safety

14.3.1.1 Summary of Treatment-Emergent Adverse Events – Safety Population
14.3.1.2 Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term – Safety Population
14.3.1.3 Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Greatest Severity – Safety Population
14.3.1.4 Treatment-Emergent Adverse Events Related to Study Drug by MedDRA System Organ Class and Preferred Term – Safety Population
14.3.1.5 Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term – Safety Population
14.3.1.6 Treatment-Emergent Adverse Events Leading to the Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term – Safety Population
14.3.1.7 Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class and Preferred Term – Safety Population
14.3.2.1 Change in Clinical Chemistry and Lipid Laboratory Values by Timepoint – Safety Population
14.3.2.2 Change in Hematology and Coagulation Laboratory Values by Timepoint – Safety Population
14.3.2.3 Change in Serology Laboratory Values by Timepoint – Safety Population

14.3.2.4 Change in Urinalysis Laboratory Values by Timepoint – Safety Population
14.3.2.5 Summary of Abnormal Post-Baseline Hepatic and Other Select Laboratory Values – Safety Population
14.3.2.6 Shift in Clinical Chemistry and Lipid Laboratory Values by Timepoint – Safety Population
14.3.2.7 Shift in Hematology and Coagulation Laboratory Values by Timepoint – Safety Population
14.3.2.8 Shift in Urinalysis Laboratory Values by Timepoint – Safety Population
14.3.3 Change in Vital Signs by Timepoint – Safety Population
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