Main Title

A Pilot Electroencephalography (EEG) Study to Evaluate the Effect of CT1812 Treatment on Synaptic Activity in Subjects With Mild to Moderate Alzheimer's Disease

Protocol Number: COG0202

Official Short Title:

Pilot Clinical Study of CT1812 in Mild to Moderate Alzheimer's Disease Using EEG

Clinical Study Protocol

FINAL Version 4.0

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Confidentiality Statement:

SIGNATURE PAGE FOR SPONSOR

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Approved by the following:

[redacted]

2/25/2022
Date

Chief Medical Officer and Study Director
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SIGNATURE PAGE FOR INVESTIGATOR

Study No. COG0202

Protocol Title: A Pilot Electroencephalography (EEG) Study to Evaluate the Effect of CT1812 Treatment on Synaptic Activity in Subjects With Mild to Moderate Alzheimer's Disease

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with all applicable regulations, including the International Conference on Harmonisation (ICH) Tripartite Guideline for Good Clinical Practice (GCP), and the Guidelines of the Declaration of Helsinki.

Investigator Name	**Signature**	**Date**

1 STUDY ORGANIZATIONAL STRUCTURE

Sponsor:	Cognition Therapeutics, Inc.
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2 PROTOCOL SYNOPSIS

TITLE:	A Pilot Electroencephalography (EEG) Study to Evaluate the Effect of CT1812 Treatment on Synaptic Activity in Subjects With Mild to Moderate Alzheimer's Disease
SPONSOR:	Cognition Therapeutics, Inc.
PROTOCOL NUMBER:	COG0202
CLINICAL STUDY PHASE:	2
STUDY DRUG PRODUCT:	CT1812

STUDY OBJECTIVES:

Primary:

- To evaluate the safety, tolerability, and pharmacokinetics (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 measurements, as reflected by relative theta power.

Exploratory: Cerebrospinal fluid

- Measure changes in exploratory cerebrospinal fluid (CSF) and plasma biomarkers, including synaptic damage biomarkers such as neurogranin, measured at baseline and through the end of each treatment period.
- To evaluate changes in cognitive and global functioning, as measured by the following:
    - Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog-14).
    - Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC).
    - Amsterdam Instrumental Activity of Daily Living Questionnaire (A-IADL-Q).
    - Neuropsychological test battery (NTB) that includes Category Fluency Test (CFT), Controlled Word Association Test (COWAT), Trail Making Test (TMT) Parts A & B, and Wechsler Memory Digit Span (VMDS).
    - 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 (AEC-c).

STUDY DESIGN:

This is a single-site, randomized, double-blind, placebo-controlled, 29-day, 2-period crossover Phase 2 study of 1 dose level of CT1812 (active) or placebo in adults with mild to moderate AD.

Screening procedures will occur on Days -42 to -1. Eligible participants will return to the study site at the Baseline/Day 1 visit and will be randomly assigned to either active study drug or placebo. Participants will return home and will take study treatment daily for 4 weeks (Day 1 through Day 29), followed by a 2-week washout period. Afterwards, participants will return to the study site to receive the crossover treatment (placebo or active) for the second treatment period of 29 days (Days 44 to 72). Participants will return to the study site 12 days after the final dose of study treatment for follow-up safety and laboratory assessments. The total duration of participant participation in the study, including the screening period, is up to 126 days. (For a detailed list of assessments, see **Table 1**: Schedule of Assessments.)

NUMBER OF PARTICIPANTS:

16 participants (8 randomized to 300 mg CT1812, 8 randomly assigned to placebo during each treatment period): the 8 participants randomly assigned to CT1812 in Treatment Period 1 will receive placebo in Treatment Period 2; the 8 participants randomly assigned to placebo in Treatment Period 1 will receive CT1812 in Treatment Period 2.

TARGET POPULATION:

INCLUSION CRITERIA:

Participants may be included in the study only if they meet all the following criteria:

1) Women of non-childbearing potential and men, aged 50 to 85 years, inclusive, with a diagnosis of mild to moderate Probable Alzheimer's Disease Dementia, according to the NIA-AA 2018 criteria and at least a 6-month history of decline in cognitive function documented in the medical record.
    i) Non-childbearing potential for women is defined as postmenopausal (last menses greater than 24 months) or undergone a documented bilateral tubal ligation or hysterectomy. If last menses less than 24 months, a serum follicle stimulating hormone (FSH) confirming post-menopausal status will be determined.
    ii) Male participants who are sexually active with a woman of child-bearing potential must agree to use condoms during the study and for 3 months after last dose. Female partners should also consider using an acceptable means of birth control, though it is not mandatory. Acceptable forms of birth control include abstinence, birth control pills, or any double combination of: intrauterine device (IUD), male or female condom, diaphragm, sponge, and cervical cap.
2) CSF meets CSF abeta 1-42 (abeta) and p-tau -181 criteria as defined below.

    CSF abeta 1-42 < 1000pg/ml (Elecsys assay) AND
    CSF p-tau 181 > 19 pg/ml (Elecsys Assay)

    OR:
    CSF abeta 1-42 < 1000pg/ml (Elecsys assay) AND
    p-tau -181 / abeta 1-42 ratio > 0.020

    OR:
    CSF p-tau 181 > 19 pg/ml (Elcsys Assay) AND
    p-tau -181 / abeta 1-42 ratio > 0.020

    Historical CSF results will be considered provided the results are consistent with the CSF thresholds required for inclusion and following discussion with the medical monitor; however, a lumbar puncture is still required as part of screening procedures.
3) Neuroimaging (MRI) consistent with the clinical diagnosis of Alzheimer's disease and without findings of significant exclusionary abnormalities (see exclusion criteria, number 4). A historical MRI, up to 1 year prior to screening, may be used as long as there have been no interval clinical neurologic events which may suggest a change in the MRI scan.
4) MMSE score of 18 to 26, inclusive.
5) No active depression and a GDS ≤ 6 (see exclusion criteria number 6).

6) Formal education of 8 or more years.
7) Participants must have a caregiver/ study partner who in the opinion of the site's Principal Investigator, has contact with the study participant for a sufficient number of hours per week to provide informative responses on the protocol assessments, oversee the administration of study drug, and is willing and able to participate in all study site visits and some study assessments. The caregiver/study partner must provide written informed consent to participate in the study.
8) Participants living at home or in the community (assisted living acceptable).
9) Participants must have no known history of difficulty swallowing capsules.
10) Stable pharmacological treatment of any other chronic conditions for at least 30 days prior to screening.
11) Must consent to apolipoprotein E (APOE) genotyping.
12) Participants shall be generally healthy with mobility (ambulatory or ambulatory-aided, i.e., walker or cane), vision and hearing (hearing aid permissible) sufficient for compliance with testing procedures.
13) Must be able to complete all screening evaluations.

EXCLUSION CRITERIA:

Participants will be excluded from the study if any of the following conditions apply:

1) Hospitalization (except for planned procedures) or change of chronic concomitant medication within 1 month prior to screening.
2) Participants living in a continuous care nursing facility.
3) Contraindications to the MRI examination for any reason.
4) MRI of the brain indicative of significant abnormality, including, but not limited to, prior hemorrhage or infarct > 1 cm^3, > 3 lacunar infarcts, cerebral contusion, encephalomalacia, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space-occupying lesion (e.g., abscess or brain tumor such as meningioma). Small incidental meningiomas may be allowed if discussed and approved by the Medical Monitor.
5) Clinical or laboratory findings consistent with:
    a) Other primary degenerative dementia, (dementia with Lewy bodies, fronto-temporal dementia, Huntington's disease, Creutzfeldt-Jakob Disease, Down syndrome, etc.).
    b) Other neurodegenerative condition (Parkinson's disease, amyotrophic lateral sclerosis, etc.).
    c) Seizure disorder.
    d) Other infectious, metabolic or systemic diseases affecting the central nervous system (syphilis, present hypothyroidism, present vitamin B12 or folate deficiency, other laboratory values etc.).

6) A current DSM-V diagnosis of active major depression, schizophrenia or bipolar disorder. Participants with depressive symptoms successfully managed by a stable dose of an antidepressant are permitted.
7) Clinically significant, advanced or unstable disease that may interfere with outcome evaluations, such as:
    a) Chronic liver disease, liver function test abnormalities or other signs of hepatic insufficiency (ALT, AST, alkaline phosphatase > 1.5 ULN, lactate dehydrogenase (LDH) > 1.5 x ULN).
    b) Respiratory insufficiency.
    c) Renal insufficiency eGFR < 50 mL/min based on the CKD-EPI Creatinine formula, https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr.
    d) Heart disease (myocardial infarction, unstable angina, heart failure, cardiomyopathy within 6 months before screening).
    e) Bradycardia (< 50/min.) or tachycardia (> 100/min.).
    f) Poorly managed hypertension (systolic > 160 mm Hg and/or diastolic > 95 mm Hg) or hypotension (systolic < 90 mm Hg and/or diastolic < 60 mm Hg).
    g) Uncontrolled diabetes in known diabetics, as defined by hemoglobin A1c (HbA1c) > 7.5.
8) History of cancer within 3 years of screening with the exception of fully excised non-melanoma skin cancers or non-metastatic prostate cancer that has been stable for at least 6 months.
9) Seropositive for human immunodeficiency virus (HIV).
10) History of acute/chronic hepatitis B or C and/or carriers of hepatitis B (seropositive for hepatitis B surface antigen [HbsAg] or anti-hepatitis C virus [HCV] antibody).
11) Clinically significant abnormalities in screening laboratory tests, including:
    a) Hematocrit less than 35% for males and less than 32% for females, absolute neutrophil cell count of <1500/uL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of < 120,000/uL; international normalized ratio (INR) > 1.4 or other coagulopathy, confirmed by repeat assessment of:
        i) Hematocrit.
        ii) Neutrophil count.
        iii) Platelet count.
12) Disability that may prevent the participant from completing all study requirements (e.g., blindness, deafness, severe language difficulty, etc.).
13) Within 4 weeks of screening visit or during the study, concurrent treatment with antipsychotic agents, antiepileptics, centrally active anti-hypertensive drugs (e.g., clonidine, l-methyl dopa, guanidine, guanfacine, etc.), sedatives, opioids, mood stabilizers (e.g., valproate, lithium); or benzodiazepines.

14) Any disorder that could interfere with the absorption, distribution, metabolism or excretion of drugs (e.g., small bowel disease, Crohn's disease, celiac disease, or liver disease).

15) Nootropic drugs, except AD medication (acetylcholinesterase inhibitors and memantine) that the participant should have been taking for no less than 3 months. New medications, including AD medication, should not be started during the study without consultation with the Medical Monitor.

16) Suspected or known drug or alcohol abuse, i.e., more than approximately 60 g alcohol (approximately 1 liter of beer or 0.5 liter of wine) per day.

17) Suspected or known allergy to any components of the study treatments.

18) Enrollment in another investigational study or intake of investigational drug within the previous 30 days or 5 half-lives of the investigational drug, whichever is longer.

19) Intake of drugs or substances potentially involved in clinically significant induction or inhibition of cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp) mediated drug interactions with CT1812, within 4 weeks or 5 half-lives of the interacting drug prior to administration of CT1812 and throughout the study. Grapefruit juice should be avoided in the 2 weeks prior to dosing and throughout the study. See Appendix A for a complete list of prohibited substances.

20) Exposure to immunomodulators, anti Aβ vaccines, passive immunotherapies for AD (e.g., monoclonal antibodies) within the past 180 days and/or exposure to beta secretase cleaving enzyme (BACE) inhibitors within the past 30 days.

21) Anticipated use of nonsteroidal anti-inflammatory drugs (NSAIDs) on more than 14 days during the study period.

22) Contraindication to undergoing lumbar puncture (LP) including, but not limited to: inability to tolerate an appropriately flexed position for the time necessary to perform an LP; INR > 1.4 or other coagulopathy; platelet count of < 120,000/μL; infection at the desired LP site; taking anti-coagulant medication within 90 days of screening (low-dose aspirin is permitted); degenerative arthritis of the lumbar spine; suspected non-communicating hydrocephalus or intracranial mass; and, prior history of spinal mass or trauma.

23) Any condition, which in the opinion of the Investigator or the Sponsor makes the participant unsuitable for inclusion.

LENGTH OF STUDY:

Participants will be screened up to 42 days prior to the Baseline/Day 1 visit. Each participant will receive active drug and placebo during this crossover 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. Total planned duration is up to 126 ± 2 days, including the up to 42-day screening period.

DOSAGE, DOSE FORM, AND ROUTE OF ADMINISTRATION:

CT1812 will be dosed at 300 mg/day for the active dose level.

CT1812 will be provided to participants as two hydroxypropyl methylcellulose (HPMC) capsules each containing 150 mg of CT1812. Matching placebo capsules will be provided. Study drug will be supplied in appropriately labeled bottles.

CT1812 will be administered orally.

EVALUATION CRITERIA:

Safety will be assessed via the monitoring of

- Adverse events.
- Physical examinations.
- Vital signs - BP, heart rate and body temperature.
- Electrocardiogram (ECG).
- Clinical laboratory tests:
  - Blood chemistry
  - Hematology
  - Urinalysis
  - Plasma.
- Affective and cognitive measures:
  - Columbia Suicide Severity Rating Scale (C-SSRS).
  - ADAS-Cog-14, ADCS-CGIC, A-IADL-Q, and an NTB that includes CFT, COWAT, TMT Parts A & B, and VMDS.

Pharmacokinetic assessments include:

- Serum CT1812 concentrations at specified timepoint. (See **Table 1 – Schedule of Assessments**).
- CSF: concentration of CT1812 at trough (24-hour postdose).

Pharmacodynamics assessments include:

- Analyses of plasma and CSF for biomarkers of target engagement or disease modification.

STATISTICAL CONSIDERATIONS:

Sample size justification:

For the endpoint of global relative theta power (the fraction of the total brain activity accounted for by theta wave frequency), the assumed within-subject standard deviation (SD) is equal to 3%. 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 between treatments of 2.5%.

For the endpoint of CSF neurogranin assuming a true within-subject 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.

Safety analyses:

- AEs will be assessed by the Investigator for severity and will be coded for summarization using Medical Dictionary for Regulatory Activities (MedDRA® Version 22). Concomitant medications will be coded using WHO Drug Dictionary (enhanced) WHODrug Global (B3) 2019 Mar 1.

Adverse events (AEs) will be summarized by Medical Subject Headings (MeSH) Term and System, for each dose group (including placebo) and the incidence compared. Laboratory measures will be summarized by treatment group and timepoint, both as absolute values and as change from baseline, with descriptive statistics summarizing each group and timepoint. Similar presentations will be used for vital signs, ECG interval measurements, and changes from pre-treatment baseline.

Analyses of PK parameters and pharmacodynamics markers:

Standard non-parametric statistical analyses will be used to examine the relationships between dose and PK parameters.

Pharmacodynamics markers in CSF and CT1812 concentrations in serum and CSF will be summarized using appropriate descriptive statistics.

Additional statistical details will be provided in a prospective statistical plan.

Safety Stopping Rules

For all participants

The occurrence of any one of the following events will result in suspension of administration of study drug in all participants until safety information can be further reviewed by the Sponsor and Medical Monitor.

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

Under these circumstances, the Sponsor and Medical Monitor will review the available safety data and, in consultation with the site's Principal Investigator, recommend whether dosing should continue, or if study drug administration should be terminated, or if additional monitoring procedures or safety precautions need to be employed.

If a stopping rule is achieved, selective unblinding of the participants involved may be performed by the Sponsor to determine if the SAEs/AEs are isolated to a single dose group or if they occurred in placebo participants.

The study or a dose group may also be terminated if the Medical Monitor, Study Director and Sponsor, in consultation with the site's Principal Investigator, determine if any AEs have occurred that are intolerable or pose a medically unacceptable safety risk.

For individual participants

Participants who develop a severe AE or laboratory abnormality will not receive any additional doses and will be monitored until resolution of the AE or the return of laboratory abnormality to the acceptable screening value(s). Study drug may be re-initiated after consultation with Medical Monitor and Sponsor. Any participant with:

- Elevated ALT or AST greater than 5 X ULN should have dosing with study drug stopped and have laboratory tests repeated every 3-4 days until levels return to less than or equal to 1.5 X ULN. If the Medical Monitor and Investigator are in agreement, study drug may be continued while a confirmatory ALT/AST is obtained within 3 days. If the confirmatory ALT/AST tests are below 5 X ULN, study drug may be continued. The frequency of the laboratory tests may be modified after discussion with the Medical Monitor if the liver enzymes are in a decreasing trend.
- Elevated ALT or AST greater than 3 X ULN in combination with total bilirubin > 2 X ULN or INR > 1.5 X ULN OR an ALT or AST > 3 X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) should have dosing with study drug stopped and have laboratory testing repeated every 3 to 4 days. If the Medical Monitor and Investigator are in agreement, study drug may be continued while a confirmatory laboratory testing is obtained within 3 days. If these criteria are no longer met, study drug can be continued at the discretion of the Medical Monitor and Investigator. The frequency of the laboratory tests may be modified after discussion with the Medical Monitor if the laboratory tests are trending towards normal.
- An increase in serum creatinine by 0.3 mg/dL (24.4 micromol/L) or 150% of baseline, which is without clinical explanation of another etiology, will result in repeated serum chemistry testing within 3 to 7 days. If the serum creatinine elevation is confirmed on repeated testing the study drug will be discontinued. If the serum creatinine elevation resolves upon subsequent testing after study drug is discontinued the study drug may be restarted with serum creatinine monitoring at the discretion of the Medical Monitor and Investigator.
- An increase in serum calcium to ≥10.5 mg/dl (2.63 mmol/L), which is without clinical explanation of another etiology, will result in repeated serum chemistry testing within 3-7 days. If the serum calcium elevation is confirmed on repeated testing the study drug will be discontinued. If the serum calcium elevation resolves upon subsequent testing after study drug is discontinued the study drug may be restarted with serum calcium monitoring at the discretion of the Medical Monitor and Investigator.
- Note: Fractional excretion of calcium will be monitored in each participant and interpreted in conjunction with serum creatinine and serum calcium. Given

the ability of fractional excretion to fluctuate, no upper limit for discontinuing study drug based on fractional excretion of calcium has been set but it may be used as a stopping rule if persistent unexplained increases in fractional excretion of calcium are observed.

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3 GLOSSARY OF TERMS AND ABBREVIATIONS

Abbreviation	Description
Abeta, Aβ	amyloid beta
AD	Alzheimer's disease
ADAS-CGIC	Alzheimer's Disease Assessment Scale – Clinical Global Impression of Change
ADAS-Cog	Alzheimer's Disease Assessment Scale–cognitive subscale
ADAS-Cog-14	Alzheimer's Disease Assessment Scale–cognitive subscale
ADCS	Alzheimer's Disease Cooperative Study
AE	adverse event
A-IADL-Q	Amsterdam – Instrumental Activities of Daily Living questionnaire
AKI	acute kidney injury
ALT	alanine aminotransferase
AEC-c	Amplitude Envelope Correlation
APOE	gene that codes for apolipoprotein E
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-HCG	beta human chorionic gonadotropin
BACE	beta secretase cleaving enzyme
BP	systolic and diastolic blood pressure
BUN	blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
CFT	Category Fluency Test

CKD-EPI	Chronic Kidney Disease -Epidemiology Collaboration
C_{max}	maximum concentration
COWAT	Controlled Word Association Test
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
dL	deciliter
DSMB	data safety monitoring board
ECG	electrocardiogram
EEG	electroencephalography
EOS	end-of-study [visit]
F	Fahrenheit
FBR	future biomedical research
GCP	good clinical practice
GDS	Geriatric Depression Scale
GFR	glomerular filtration rate
h	hour(s)
Hba1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
hERG	human ether-à-go-go related gene
Hgb	hemoglobin
HIV	human immunodeficiency virus

HPMC	hydroxypropyl methylcellulose
Hz	Hertz
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
INR	international normalized ratio
IUD	intrauterine device
IRB	Institutional Review Board
KIM-1	kidney injury molecule -1
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LP	lumbar puncture
MeSH	Medical Subject Headings
MAD	multiple ascending dose
MCHC	mean corpuscular hemoglobin concentration
MCI	mild cognitive impairment
MCV	mean corpuscular volume
µg	microgram
mL	milliliter
mmol	millimolar
MMSE	Mini-Mental State Exam
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NIH	National Institutes of Health
NIA	National Institute on Aging

NSAIDs	nonsteroidal anti-inflammatory drugs
NTB	neuropsychological test battery
PD	pharmacodynamics
P-gp	P-glycoprotein
PGRMC1	Progesterone receptor membrane compound 1
PK	pharmacokinetic(s)
QD	once daily
SAE	serious adverse event
$t_{1/2}$	terminal half-life
TSH	thyroid stimulating hormone
TMT A & B	Trail Making Test A and B
ULN	upper limit of normal
VMDS	Wechsler Memory Digit Span

4 INTRODUCTION

4.1 Background

Synaptic dysfunction and loss caused by age-dependent accumulation of synaptotoxic beta-amyloid (Abeta) 1-42 oligomers is proposed to underlie cognitive decline in Alzheimer's disease (AD). Accumulation of Abeta protein leads to self-association, resulting in formation of oligomers. Cognition Therapeutics Inc. has demonstrated that Abeta oligomers bind saturably to a single high affinity site on the surface of neuronal synapses (Izzo et al 2014a, b). Once bound, these oligomers alter membrane trafficking rate and reduce surface expression of neuronal receptors critical for synaptic plasticity (Hsieh 2006, Lacor 2007). This leads to failure of long-term potentiation, reversible spine loss in neurons, and impaired cognitive performance that progresses throughout the course of AD (Shankar 2007, Zempel 2013). Cognition Therapeutics Inc. has identified a receptor not previously associated with AD that mediates the binding of Abeta oligomers to neurons, the sigma-2/PGRMC1 receptor (Izzo et al 2014a, b).

Cognition Therapeutics has discovered a series of highly brain penetrant, novel sigma-2/PGRMC1 antagonist molecules, including CT1812 that both prevent and competitively displace oligomer binding to neuronal synapses, prevent spine loss in neurons and prevent and treat oligomer-induced deficits in membrane trafficking in vitro. These antagonists displace endogenous human AD oligomers from brain tissue sections in a dose-dependent manner. Chronic administration of sigma-2/PGRMC1 antagonists at doses that reach brain concentrations corresponding to greater than 80% estimated receptor occupancy at the sigma-2/PGRMC1 receptor restore cognitive function in aged transgenic hAPP Swe/Ldn mice models of AD. These molecules work by allosteric antagonism of the sigma-2/PGRMC1 receptor protein or a protein closely associated with it to modulate oligomer binding site affinity, representing a novel previously unrecognized mechanism of action for disease-modifying Alzheimer's therapeutics.

CT1812 is a highly brain penetrant novel sigma-2/PGRMC1 antagonist molecule that prevents and displaces binding of Abeta42 oligomers to receptors on brain cells. In vitro, in-cultured rat neurons, CT1812 not only antagonizes binding of Abeta42 oligomers, but also prevents Abeta oligomer-induced membrane trafficking changes. Chronic treatment with this first-in-class, highly brain-penetrant, disease-modifying oligomer receptor antagonist restores aged AD model transgenic mouse performance to normal in multiple cognitive tests. Sponsor hypothesizes that chronic treatment with CT1812 could restore neuronal plasticity compromised by Abeta

oligomers, and thus improve cognitive function in patients throughout the course of AD. This approach is fundamentally different than that of other therapeutics in development (such as beta secretase cleaving enzyme [BACE] inhibitors) that focus on lowering the brain concentrations of beta amyloid protein. This product could provide the first clinical test of the hypothesis that cognitive decline in AD is related to toxic effects of Abeta oligomers on synaptic function.

There are no currently approved products for the treatment of prodromal mild cognitive impairment (MCI) or established AD that function by blocking the binding and pathological activity of soluble Abeta oligomers. While there are some approved drugs for other indications that demonstrate significant affinity at sigma-2/PGRMC1 receptors, unlike CT1812, these other drugs have significant activity at other pharmacological targets besides the sigma-2/PGRMC-1 receptor, which would make them undesirable therapeutic agents for this indication. None of these have been tested or approved for treating AD or cognitive impairment.

Cognition Therapeutics, Inc. is developing this oral formulation of CT1812 to treat AD and mild cognitive impairment.

Various techniques can be used to study brain activity and functional connectivity, but electroencephalography (EEG) is the only method that is available in almost every hospital. EEG is a non-invasive, cheap and reliable technique, making it a suitable tool for large interventional studies. Neuronal dysfunction caused by cerebral pathology, for example the deposition of toxic β-amyloid oligomers in AD, can be detected by EEG in various ways.

For this purpose, no specific task EEG data is required. Several minutes of routinely recorded artifact-free, resting-state, eyes-closed EEG data is sufficient for all analyses.

Measures expressing local brain activity are used often in the diagnostic evaluation of patients in clinical care. In patients with AD, the EEG shows distinct changes reflecting abnormalities of brain activity (Jeong 2004, Gouw et al 2017, de Waal et al 2012). In the earliest phase of AD, the EEG can be normal. With progression of the disease, there is a gradual, diffuse slowing of brain activity, reflected by changes of spectral power in conventional frequency bands. First, slow (theta; 4 - 8 Hz) activity increases and fast (beta, 13 - 30 Hz) activity decreases, followed by slowing and diminished reactivity of mid-range (alpha, 8 - 13 Hz) activity. In later stages, alpha activity decreases and finally very slow (delta, 0.5 - 4 Hz) power increases. In amyloid-positive patients who have no objective cognitive disturbances, global theta power has also been shown to be a predictive marker of future cognitive decline (Gouw et al 2017).

Since global theta activity (and in particular 'relative theta power') is the most powerful early-phase diagnostic EEG marker in AD patients, it will be included in this study as primary efficacy outcome measure. Because of their expected additional value in early AD, several measures reflecting changes in brain activity will be added for exploratory purposes: relative power in alpha and beta bands, global peak frequency, and theta/alpha ratio.

In addition to regional brain activity, communication between brain regions ("functional connectivity") can be derived from task-free EEG. For the investigation of synaptic function, functional connectivity markers are especially relevant. Recent clinical studies have shown promising results when using specific EEG connectivity measures for treatment monitoring.

A promising marker of functional connectivity is the so-called corrected Amplitude Envelope Correlation (AEC-c); it will be included as exploratory secondary endpoint (Hipp et al 2012, Colclough et al 2016). Built upon functional connectivity, more advanced graph theoretical network analysis can be performed to gain insight in changes in functional network integrity (i.e., topology, efficacy, robustness) during the AD disease process, but also during treatment periods. These can provide more insight into disease mechanisms. We will include a battery of state-of-the-art measures to characterize and compare overall functional brain network topology (minimum spanning tree analysis with measures diameter, tree hierarchy, leaf fraction, betweenness centrality and eccentricity), global efficiency (small world topology analysis with measures characteristic path length and clustering coefficient), sub-community detection (modularity analysis with measures Modularity index, number of modules, participation coefficient, within-module degree) (Rubinov & Sporns 2010, Stam et al 2014).

4.2 Nonclinical Experience

4.2.1 Nonclinical Pharmacology Studies

CT1812 is a lipophilic isoindoline formulated as a fumarate salt and is the result of a structure-based medicinal chemistry optimization program comprised of more than 300 analogs. CT1812's properties are fully described along with all preclinical studies in the Investigator Brochure. CT1812 has a high affinity at the target receptor sigma-2/PGRMC1 (S2), and is > 100-fold selective for this receptor over other receptors and ion channels. Dose-limiting toxicities at higher doses in both species appear to be hypercalcemia and renal tubular damage, both of which are non-invasively monitored via measurement of serum calcium and urinary markers of renal tubular injury such as kidney injury molecule 1 (KIM-1).

In vitro pharmacodynamics (PD) studies confirmed CT1812 target binding specificity, affinity and engagement, including the prevention and reversal of Aβ oligomer binding and the prevention of Aβ oligomer-induced synapse loss.

In vivo PD studies confirmed the desired consequences of target engagement, including cognitive improvements in an aged transgenic mouse model of AD following oral administration of an apparently tolerated dose of CT1812 daily for 9 weeks. Additional in vivo PD studies, using an Aβ oligomer detecting microelectrode in an aged transgenic mouse model of AD, demonstrated that administration of CT1812 caused an acute increase in soluble Aβ oligomers in the interstitial fluid of the hippocampus and a sustained increased in soluble Aβ oligomers in the CSF of the lateral ventricle of the brain. These increases in soluble Aβ oligomers occurred without a change in the amount of soluble Aβ 1-40, indicating that displacement of Aβ oligomers occurred following treatment with CT1812.

4.2.2 Nonclinical Pharmacokinetic Studies

Absorption of CT1812 following oral gavage administration to mice, rats and dogs appears to be very rapid, with brain concentrations exceeding those concurrently measured in plasma. The drug is highly protein-bound in plasma from rat, mouse, dog, and human, but only weakly bound to blood cells. Systemic exposures to CT1812 following oral administration to rats and dogs were greater than dose-proportional at high, toxicologically relevant dosages. Extensive first-pass metabolism appears to be via oxidation and/or direct glucuronidation.

Studies with human recombinant cytochrome P450 (CYP) isoforms show rapid metabolism ($t_{1/2}$ of 6.8 min) by CYP3A4, and slower metabolism ($t_{1/2}$ of 57 and 81 minutes) by CYP2D6 and CYP2C19. A direct glucuronide conjugate was also observed in vitro in human hepatocyte incubations, consistent with that observed in vivo in rats and dogs.

CT1812 was not an inhibitor of CYP1A2, CYP2B6, or CYP2C8, with less than 50% inhibition of activity observed at the highest concentration evaluated (10 μM). CT1812 was a weak inhibitor of CYP2C9, CYP2C19, CYP2D6, and CYP3A4, with IC_{50} values ranging from 4.4 to 38 μM. However, when evaluated in the context of systemic exposure data in humans, the drug-drug interaction liability from these effects was considered to be minimal. CT1812 was found to be an inducer of CYP3A4 (≥ 0.3 μM), suggesting a potentially clinically significant risk of drug-drug interactions with this isoform, but induction of CYP2B6 and CYP1A2 appear less likely. CT1812 does appear to be a substrate for p-glycoprotein (P-gp) and inhibits P-gp with an IC_{50} of 10 μM. This is considered to be potentially clinically significant, primarily due to the possibility of

interactions in the gastrointestinal (GI) tract. In vitro inhibition of the OATP1B1 transporter (IC_{50} of 11.5 μM) by CT1812 does not appear to be clinically relevant, when evaluated in the context of systemic exposure data in humans. As assessed per the FDA 2012 draft guidance for DDI evaluations, clinically relevant DDI are suggested via CT1812 effects on CYP3A4 and P-gp.

4.2.3 Nonclinical Safety Studies

Two hERG (human Ether-à-go-go Related Gene) assays were performed to assess effects of CT1812 on the rapidly activating delayed rectifier potassium channels (IKr) using channels stably transfected and over-expressed in Chinese Hamster Ovary cells. Using whole-cell patch clamp electrophysiology, CT1812 was tested in both studies in duplicate at concentrations of 1, 3, 10, and 30 μM. Mean IC_{50} values of 26 μM and 0.6 μM were determined in the first and second assay, respectively. Reasons for the differing results are unknown. However, no ECG effects were noted in the telemeterized dog cardiovascular safety study or in the multiple-dose dog pivotal toxicology study when tested up to high-dose mean C_{max} values of approximately 4 μM.

Safety pharmacology studies with rats revealed no apparent effects on central nervous system or pulmonary parameters, following single oral dosages that exceeded the maximum tolerated dose in this species.

General toxicology studies with rats and dogs following oral dosing of CT1812 revealed dose-limiting toxicity that manifested as degenerative changes in the proximal tubules of kidney, hypercalcemia, and vascular mineralization and/or degeneration involving multiple tissues and organs in each species. Tolerable and intolerable dosages and exposures, characterized with each species, informed the selection of dosages for this study.

Additionally, toxicology studies revealed several test article-related clinical laboratory changes, including elevated serum creatinine and/or BUN that correlated with mild weight loss, elevated serum calcium and reduced urinary specific gravity. The exact mechanism for these changes cannot be determined from those studies. Serum and urine tests will be performed in this study to evaluate the effect of study drug administration on renal function (including serum creatinine, serum calcium, and urine calcium).

Genetic toxicology studies revealed no positive responses in bacterial and mammalian in vitro assays, or in an in vivo mouse bone marrow micronucleus assay when tested up to maximally feasible dosages.

4.3 Clinical Experience

CT1812 has been administered safely with good tolerability in more than 60 healthy volunteers in a placebo-controlled Phase 1a study (COG0101). Six single (10-1120 mg) and 3 multiple dose cohorts (QD, 14 days, 280-840 mg) were observed under close in-patient stay (N = 6 to 8 treated, 2 placebo per cohort). Plasma concentrations of drug were shown to be approximately dose proportional across 2 orders of magnitude [0.13-14.93 mg (free base equivalent)/kg], and accumulation was minimal. Peak concentrations of CT1812 were reached within 1 to 2 hours and the plasma half-life was shown to be approximately 12 hours. Adverse events (AEs) were mostly mild to moderate in severity and principally included headache, nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, upper respiratory tract infection, lightheadedness, syncope, myalgia, dizziness, rash and pain at the lumbar puncture (LP) site in those participants who had LPs. There was only one AE of severe intensity (a serious adverse event [SAE] of upper respiratory tract infection) occurring in one participant in the 840 mg dose of the multiple ascending dose (MAD) study, believed to be unrelated to study drug based on a similar pattern of URTIs in participants receiving drugs other than CT1812 in the study unit during the same time period. One participant in the multiple dose cohort study developed a rash while on study drug. This participant showed improvement after discontinuing CT1812.

No evidence of renal toxicity has been observed to date based on routine measures of renal function (serum creatinine, BUN).

Four participants in the MAD study showed an increase in liver function tests below 3X the upper limit of normal (including one participant on placebo). Subsequent studies will closely monitor liver enzyme parameters to determine if these were sporadic findings or possibly drug-related.

A fed cohort (280 mg) single dose was compared to the fasting cohort of 280 mg and no significant food effect was observed. A multiple dose cohort of elderly (≥65 years old) healthy volunteers was dosed at 560 mg x 14 days, and their exposures were similar to the 840 mg younger healthy volunteer participants.

In COG0103, 15 healthy volunteers evaluated potential effects of CT1812 on the disposition of sensitive substrates of selected CYP isoenzymes CYP2C19 (omeprazole), CYP2C9 (tolbutamide), CYP2D6 (dextromethorphan), and CYP3A4/5 (midazolam). Participants were administered the probe drugs on Day -2; and followed by pharmacokinetic (PK) evaluations. On Days 1 through 6, each participant took CT1812 560 mg. The CT1812 dose on Day 6 was taken

concomitantly with the probe drug cocktail, and PK evaluation was conducted. No significant interaction was observed for isoenzymes 2C19 and 2C9. A weak drug interaction was observed between steady-state CT1812 and midazolam 4 mg (CYP3A4). Midazolam AUC_{last} and the AUC_{last} ratio (parent to metabolite) decreased by 24% and 28%, respectively, when midazolam 4 mg was taken with steady state CT1812 than when midazolam was taken alone. A weak drug interaction was observed between steady-state CT1812 and dextromethorphan 50 mg (CYP2D6), as indicated by a 1.75-fold and 2-fold increase in dextromethorphan AUC_{last} and C_{max}, respectively, following the combination treatment relative to dextromethorphan alone; however, the dextromethorphan/dextrorphan AUC_{last} ratio was similar between treatments. Based on the small magnitude of the interactions observed in this study for the isoenzymes CYP2D6 and CYP3A4, clinically meaningful implications are unlikely.

A Phase 1 study (COG0102) has completed enrollment in Australia, evaluating the safety and PK of 3 dose levels of CT1812 (90 mg, 280 mg, 560 mg) or matching placebo, administered once daily for 28 days in participants with mild to moderate Alzheimer's disease. This study enrolled 19 participants in a 1:1:1:1 ratio. In general, all doses were relatively well tolerated. There were no deaths or SAEs. All AEs were considered mild or moderate. While there was an increased frequency observed in total AEs with increasing dose, the small number of treated participants does not permit definitive conclusions regarding the incidence of AEs by dose in a larger study population. Specific AEs that were noted to occur with greater frequency at the 560 mg dose included transient lymphocytopenia, nausea, vomiting, headache, fatigue, and depression. These AEs resolved in most instances while treatment was ongoing; one participant at the 560 mg dose experienced an ALT increase of 4.7 X ULN that resolved to normal levels after discontinuation of study drug. Cognitive outcomes were similar across the treatment groups. Plasma CT1812 concentration increased approximately dose proportionally, with a dose dependent increase in CSF concentration. CSF concentrations at all tested doses were > 80% of estimated brain PGRMC-1 receptor occupancy, which was the threshold associated with efficacy in preclinical studies.

EEG measures the synchronous extracellular ion flow due to excitatory and inhibitory postsynaptic potentials in groups of synchronized cortical neurons. The effect of neuroactive agents that change synaptic function and/or these postsynaptic potentials can be measured by changes in EEG oscillatory activity. Local activity changes are commonly described using spectral power measures. In patients with AD, the EEG shows distinct changes in spectral power indicating diffuse slowing of brain activity with disease progression (Jeong 2004, Gouw et

al 2017). Treatment studies using task free EEG spectral measures show specific reversal of this oscillatory slowing to approved AD therapeutics (Gianotti et al 2008, Scheltens et al 2018). A short-term treatment study with rivastigmine resulted in decreased delta and theta absolute power (Adler and Brassen, 2001) whereas donepezil showed a decrease in global theta power (Brassen and Adler, 2003). A short-term decrease in theta power also predicted response to rivastigmine treatment after 6 months (Adler et al., 2004). Decreases in theta power were also observed with memantine (Baliboni 2013).

4.4 Rationale for Study

CT1812 was shown to be safe and well tolerated in a study of healthy volunteers and in Phase 1 studies of participants with mild to moderate Alzheimer's disease. This Phase 2 study is designed to identify measures of target engagement that reflect the rapid mechanism of action of CT1812 to restore synapse number to normal. We expect that the ability of CT1812 to rapidly restore synapse number to normal will result in a decrease in EEG theta power in AD patients in response to short-term treatment with CT1812.

4.4.1 Rationale for Selected Dose

Based on brain receptor occupancy studies in animals, the daily dose of 300 mg/day is projected to exceed 95% receptor occupancy. In a Phase 1 multiple dose, 2-week study, doses exceeding 300 mg/day were well-tolerated in both younger (aged ≤ 64 years) and older (aged ≥ 65 years) participants. In the phase 1 AD study, tolerability was also acceptable with no severe or serious AEs observed at doses exceeding 300 mg/day.

5 STUDY OBJECTIVES

5.1 Primary

- 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 through quantitative EEG, as reflected by relative theta power.

5.2 Exploratory

- Measure changes in exploratory 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 Alzheimer's Disease Assessment Scale–cognitive subscale-14 (ADAS-Cog-14); Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC); Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q); and, a neuropsychological test battery (NTB) that includes Category Fluency Test (CFT), Controlled Word Association Test (COWAT), Trail Making Test (TMT) Parts A & B, and Wechsler Memory Digit Span (VMDS).
- 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 (AEC-c).

6 STUDY TYPE AND DESIGN

6.1 Study Type

This is a single-site, randomized, double-blind, placebo-controlled, 29-day, 2-period, crossover Phase 2 study.

6.2 Endpoints

6.2.1 Exploratory Efficacy Endpoints

- EEG spectral measures, specifically relative theta (4-8 Hz) power.
- ADAS-Cog-14
- ADCS-CGIC
- A-IADL-Q
- NTB, which includes:
    - CFT
    - COWAT

- TMT A & B
- VMDS

- CSF protein concentration (AB42 and AB40 monomers, total tau, phospho-tau, neurogranin, and SNAP-25).

6.2.2 Safety Endpoints

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

6.2.3 Pharmacokinetic/Pharmacodynamic Endpoints

- **Pharmacokinetics**:
  - CT1812 CSF/plasma concentration ratio (end-of-study [EOS] only).
  - Changes in predose CT1812 plasma concentrations.

6.3 Study Design

This study is a single-site, randomized, double-blind, placebo-controlled, 2-period crossover study in 16 mild to moderate Alzheimer's patients (MMSE 18-26) who will receive 300 mg of CT1812 or placebo once daily. These patients will be organized in 2 groups of 8 patients each. The patients 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 patients 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 EEG, A-ADL-Q, and ADAS-Cog-14, supplemented with additional

cognitive tests including 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 PK and 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 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 study visit 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.

7 STUDY DRUG

7.1 Supply and Storage

CT1812 will be provided to the site pharmacy as a hydroxypropyl methylcellulose (HPMC) capsule containing 64 mg of CT1812 fumarate salt (equivalent to 150 mg of the CT1812 free base, respectively). Study drug will be provided in amber-colored, induction-sealed, screw-top bottles with desiccant packs.

All study drug (unopened and opened bottles) will be stored between 2 to 8 degrees Celsius.

Identical placebo capsules containing lactose monohydrate will also be supplied to match the CT1812 supplies in the same packaging and will require the same storage conditions (i.e., between 2 to 8 degrees Celsius).

7.2 Packaging and Labeling

The label on the participant bottles will contain the following information in the English language:

- Protocol number: COG0202.
- Expiration date.

- Lot number.
- Contents.
- Weight.
- Storage conditions.
- The sentence, "For Clinical Trial Use Only."
- Name of the Investigator.
- Name, address and telephone number of the Sponsor.

7.3 Administration

CT1812 or matching placebo will be administered orally as a single daily dose for 29 days. Each dose CT1812 or matching placebo will consist of 2 capsules. All participants will ingest the first dose at the study site and be observed for 2 hours. Capsules will be swallowed with approximately 240 mL of water with or without food. Daily outpatient dosing should occur in the morning (i.e., prior to 12 pm/noon). To ensure appropriate specimen collection times relative to dosing on study site days, participants will be asked to bring their study drug to study site visits and to take their study drug at the study site upon the instruction of the site staff. On "Drug dispensing" study site visits drug accountability will be completed for the bottle returned by the participant and the "Dose administration at study site" will be taken for that visit from the newly assigned bottle.

7.3.1 Safety Stopping Rules

For all participants:
The occurrence of any one of the following events will result in suspension of administration of study drug in all participants until safety information can be further reviewed by the Sponsor and Medical Monitor.

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

Under these circumstances, the Sponsor and Medical Monitor will review the available safety data and, in consultation with the site's Principal Investigator, recommend whether dosing should continue, or if study drug administration should be terminated, or if additional monitoring procedures or safety precautions need to be employed.

If a stopping rule is achieved, selective unblinding of the participants involved may be performed by the Sponsor to determine if the SAEs/AEs are isolated to a single dose group or if they occurred in placebo participants.

The study or a dose group may also be terminated if the Medical Monitor, Study Director, and Sponsor, in consultation with the site's Principal Investigator, determine that any adverse event(s) are occurring that are intolerable or pose a medically unacceptable safety risk.

For individual participants:

Participants who develop a severe adverse event or laboratory abnormality will not receive any additional doses and will be monitored until resolution of the AE or the return of laboratory abnormality to the acceptable screening value(s). Study drug may be re-initiated after consultation with Medical Monitor and Sponsor. Any participant with:

- Elevated ALT or AST greater than 5 X ULN should have dosing with study drug stopped and have laboratory tests repeated every 3 to 4 days until levels return to less than or equal to 1.5 X ULN. If the Medical Monitor and Investigator are in agreement, study drug may be continued while a confirmatory ALT/AST is obtained within 3 days. If the confirmatory ALT/AST tests are below 5 X ULN, study drug may be continued. The frequency of the laboratory tests may be modified after discussion with the Medical Monitor if the liver enzymes are in a decreasing trend.
- Elevated ALT or AST greater than 3 X ULN in combination with total bilirubin > 2 X ULN or INR > 1.5 X ULN OR an ALT or AST > 3 X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) should have dosing with study drug stopped and have laboratory testing repeated every 3 to 4 days. If the Medical Monitor and Investigator are in agreement, study drug may be continued while a confirmatory laboratory testing is obtained within 3 days. If these criteria are no longer met, study drug can be continued at the discretion of the Medical Monitor and Investigator. The frequency of the laboratory tests may be modified after discussion with the Medical Monitor if the laboratory tests are trending towards normal.

- An increase in serum creatinine by 0.3 mg/dL (24.4 micromol/L) or 150% of baseline, which is without clinical explanation of another etiology, will result in repeated serum chemistry testing within 3 to 7 days. If the serum creatinine elevation is confirmed on repeated testing the study drug will be discontinued. If the serum creatinine elevation resolves upon subsequent testing after study drug is discontinued the study drug may be restarted with serum creatinine monitoring at the discretion of the Medical Monitor and Investigator.
- An increase in serum calcium to ≥10.5 mg/dl (2.63 mmol/L), which is without clinical explanation of another etiology, will result in repeated serum chemistry testing within 3 to 7 days. If the serum calcium elevation is confirmed on repeated testing the study drug will be discontinued. If the serum calcium elevation resolves upon subsequent testing after study drug is discontinued the study drug may be restarted with serum calcium monitoring at the discretion of the Medical Monitor and Investigator.
- Note: Fractional excretion of calcium will be monitored in each participant and interpreted in conjunction with serum creatinine and serum calcium. Given the ability of fractional excretion to fluctuate, no upper limit for discontinuing study drug based on fractional excretion of calcium has been set but it may be used as a stopping rule if persistent unexplained increases in fractional excretion of calcium are observed.

7.4 Drug Accountability

Participants will return all study bottles and unused study drug at each study site visit for drug accountability to be performed. The Investigator or their appointed designee is responsible for ensuring that deliveries of study drug are correctly dispensed and recorded, that the product is handled and stored safely and properly, and that it is only being given to participants in accordance with this protocol.

Sites will keep a current log of drug accountability recording:

- What drug supply was received from the Sponsor.
- What drug supply was dispensed to each participant.
- What drug supply is current in inventory.
- What drug supply was destroyed or returned to the Sponsor for destruction.

Note: Drug accountability is the responsibility of the Investigator; a written account will be required for all discrepancies.

The Sponsor's designated Monitor must verify all accountability records during periodic monitoring visits. Unused and used study drug must be stored on site until such accountability has taken place and authorization is received from the Sponsor or Sponsor's designee that the study drug may be returned or destroyed.

7.5 Overdose/Toxicity Management

No specific pharmacologic antagonist or antidote exists for CT1812. Therefore, overdose or clinical toxicity should be managed with supportive care and pharmacologic treatments directed at specific symptoms (i.e., benzodiazepines for agitation or antipyretics for fever).

7.6 Blinding, Randomization, and Matching Participants

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.

The non-blinded statistician assigned to the study will generate a list with the appropriate number of 4-digit individual study IDs randomly for each arm, randomly assigned to either active study drug or placebo.

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.

8 INVESTIGATORS, SITES AND DURATION

8.1 Investigator and Study Site

This single-center study will be conducted at the VU University Medical Center (VUmc) in Amsterdam, The Netherlands, under the Direction of Everard Vijverberg, MD, Ph.D.

8.2 Duration of Study

Screening procedures will occur on Days -42 to -1. Eligible participants will return to the study site at the Baseline/Day 1 visit to be randomly assigned to either active study drug or placebo. 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. The total duration of participant participation in the study, including the screening period, is up to 126 days.

8.3 Termination of Study

This study may be terminated at the discretion of the Sponsor.

9 STUDY POPULATION

9.1 Number of Participants

Up to 16 participants will be randomized.

9.2 Inclusion Criteria

Participants may be included in the study only if they meet all of the following criteria:

1) Women of non-childbearing potential and men, aged 50 to 85 years, inclusive, with a diagnosis of mild to moderate Alzheimer's disease according to the 2018 NIA-AA criteria and at least a 6-month history of decline in cognitive function documented in the medical record.

    i) Non-childbearing potential for women is defined as postmenopausal (last menses greater than 24 months) or undergone a documented bilateral tubal ligation or hysterectomy. If last menses less than 24 months, a serum follicle stimulating hormone (FSH) value confirming post-menopausal status may be used.

    ii) Male participants who are sexually active with a woman of child-bearing potential must agree to use condoms during the study and for 3 months after last dose. Female partners should also consider using an acceptable means of birth control, though it is not mandatory. Acceptable forms of birth control include abstinence, birth control pills, or any double combination of: intrauterine device (IUD), male or female condom, diaphragm, sponge, and cervical cap.

2) CSF meets CSF abeta 1-42 (abeta) and p-tau -181 criteria as defined below.

    CSF abeta 1-42 < 1000pg/ml (Elecsys assay) AND
    CSF p-tau 181 > 19 pg/ml (Elecsys Assay)

    OR:

CSF abeta 1-42 < 1000pg/ml (Elecsys assay) AND
p-tau -181 / abeta 1-42 ratio > 0.020

OR:
CSF p-tau 181 > 19 pg/ml (Elcsys Assay) AND
p-tau -181 / abeta 1-42 ratio > 0.020

Historical CSF results will be considered provided the results are consistent with the CSF thresholds required for inclusion and following discussion with the medical monitor; however, an LP is still required as part of screening procedures.

3) Neuroimaging (MRI) consistent with the clinical diagnosis of Alzheimer's disease and without findings of significant exclusionary abnormalities (see Section 9.3 exclusion criteria no. 4). An historical MRI, up to 1 year prior to screening, may be used as long as there have been no interval clinical neurologic events that may suggest a change in the MRI scan.
4) MMSE 18-26 inclusive.
5) Geriatric Depression Scale (GDS) ≤ 6 with no active depression (see Section 9.3 exclusion criteria no. 6).
6) Formal education of 8 or more years.
7) Participants must have a caregiver/study partner who in the opinion of the site's Principal Investigator, has contact with the study participant for a sufficient number of hours per week to provide informative responses on the protocol assessments, oversee the administration of study drug, and is willing and able to participate in all study site visits and some study assessments. The caregiver/ study partner must provide written informed consent to participate in the study.
8) Participants living at home or in the community (assisted living acceptable).
9) Participants must have no known history of difficulty swallowing capsules.
10) Stable pharmacological treatment of any other chronic conditions for at least 30 days prior to screening.
11) Must consent to apolipoprotein E (APOE) genotyping.
12) Participants shall be generally healthy with mobility (ambulatory or ambulatory-aided, i.e., walker or cane), vision and hearing (hearing aid permissible) sufficient for compliance with testing procedures.
13) Must be able to complete all screening evaluations.

9.3 Exclusion Criteria

Participants will be excluded from the study if any of the following conditions apply:

1) Hospitalization (except for planned procedures) or change of chronic concomitant medication within 1 month prior to screening.
2) Participants living in a continuous care nursing facility.
3) Contraindications to the MRI examination for any reason.
4) Screening MRI (or historical MRI, if applicable) of the brain indicative of significant abnormality, including, but not limited to, prior hemorrhage or infarct > 1 cm^3, > 3 lacunar infarcts, cerebral contusion, encephalomalacia, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space-occupying lesion (e.g., abscess or brain tumor such as meningioma).
5) Clinical or laboratory findings consistent with:
    a) Other primary degenerative dementia, (dementia with Lewy bodies, fronto-temporal dementia, Huntington's disease, Creutzfeldt-Jakob Disease, Down syndrome, etc.).
    b) Other neurodegenerative condition (Parkinson's disease, amyotrophic lateral sclerosis, etc.).
    c) Seizure disorder.
    d) Other infectious, metabolic or systemic diseases affecting the central nervous system (syphilis, present hypothyroidism, present vitamin B12 or folate deficiency, other laboratory values etc.).
6) A current DSM-V diagnosis of active major depression, schizophrenia or bipolar disorder. Participants with depressive symptoms successfully managed by a stable dose of an antidepressant are allowed entry.
7) Clinically significant, advanced or unstable disease that may interfere with outcome evaluations, such as:
    a) Chronic liver disease, liver function test abnormalities or other signs of hepatic insufficiency (ALT, AST, alkaline phosphatase > 1.5 ULN, lactate dehydrogenase (LDH) > 1.5 x ULN).
    b) Respiratory insufficiency.

c) Renal insufficiency eGFR < 50 mL/min based on the CKD−EPI formula, https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr

d) Heart disease (myocardial infarction, unstable angina, heart failure, cardiomyopathy within 6 months before screening).

e) Bradycardia (< 50/min.) or tachycardia (> 100/min.).

f) Poorly managed hypertension (systolic > 160 mm Hg and/or diastolic > 95 mm Hg) or hypotension (systolic < 90 mm Hg and/or diastolic < 60 mm Hg).

g) Uncontrolled diabetes in known diabetics, as defined by hemoglobin A1c (HbA1c) > 7.5.

8) History of cancer within 3 years of screening with the exception of fully excised non-melanoma skin cancers or non-metastatic prostate cancer that has been stable for at least 6 months.

9) Seropositive for human immunodeficiency virus (HIV).

10) History of acute/chronic hepatitis B or C and/or carriers of hepatitis B (seropositive for hepatitis B surface antigen [HbsAg] or anti-hepatitis C [HCV] antibody).

11) Clinically significant abnormalities in screening laboratory tests, including:

a) Hematocrit less than 35% for males and less than 32% for females, absolute neutrophil cell count of <1500/uL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of < 120,000/uL; **international normalized ratio** (INR) > 1.4 or other coagulopathy, confirmed by repeat assessment of:

i) Hematocrit.

ii) Neutrophil count.

iii) Platelet count.

12) Disability that may prevent the participant from completing all study requirements (e.g., blindness, deafness, severe language difficulty, etc.).

13) Within 4 weeks of screening visit or during the study, concurrent treatment with antipsychotic agents, antiepileptics, centrally active anti-hypertensive drugs (e.g., clonidine, l-methyl dopa, guanidine, guanfacine, etc.), sedatives, opioids, mood stabilizers (e.g., valproate, lithium); or benzodiazepines, with the following exception:

a) Low dose lorazepam may be used for sedation prior to MRI scan for those participants requiring sedation. At the discretion of the Investigator, 0.5 to 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. No more than a total of 2 mg lorazepam may be used for the MRI scan.

14) Any disorder that could interfere with the absorption, distribution, metabolism or excretion of drugs (e.g., small bowel disease, Crohn's disease, celiac disease, or liver disease).

15) Nootropic drugs except stable AD meds (acetylcholinesterase inhibitors and memantine).

16) Suspected or known drug or alcohol abuse, i.e., more than approximately 60 g alcohol (approximately 1 liter of beer or 0.5 liter of wine) per day.

17) Suspected or known allergy to any components of the study treatments.

18) Enrollment in another investigational study or intake of investigational drug within the previous 30 days or 5 half-lives of the investigational drug, whichever is longer.

19) Intake of drugs or substances potentially involved in clinically significant induction or inhibition of CYP3A4 or P-gp mediated drug interactions with CT1812, within 4 weeks or 5 half-lives of the interacting drug prior to administration of CT1812 and throughout the study. Grapefruit juice should be avoided in the 2 weeks prior to dosing and throughout the study. See Appendix A for a complete list of prohibited substances.

20) Exposure to immunomodulators, anti Aβ vaccines, passive immunotherapies for AD (e.g., monoclonal antibodies) within the past 180 days and/or exposure to BACE inhibitors within the past 30 days

21) Anticipated use of nonsteroidal anti-inflammatory drugs (NSAIDs) on more than 14 days from Baseline/Day 1 to Day 182. Contraindication to undergoing an LP including, but not limited to: inability to tolerate an appropriately flexed position for the time necessary to perform an LP; international normalized ratio (INR) > 1.4 or other coagulopathy; platelet count of < 120,000/μL; infection at the desired LP site; taking anti-coagulant medication within 90 days of screening (low-dose aspirin is permitted); degenerative arthritis of the lumbar spine; suspected non-communicating hydrocephalus or intracranial mass; prior history of spinal mass or trauma.

22) Any condition, which in the opinion of the Investigator or the Sponsor, makes the participant unsuitable for inclusion.

9.4 Withdrawal of Participants

A participant should be withdrawn from the study if any of the following occur:

1. Withdrawal of participant consent.
2. Investigator determines that withdrawal from the study is in the best interest of the participant.
3. Major protocol violation (i.e., circumstances where confounding conditions make it impossible to derive sound scientific or medical conclusions from the primary endpoint data generated on a participant).
4. Any condition, injury, or disease that becomes apparent during the study and necessitates the termination of the participant from the study; including events detailed in Section 7.3.1 - Safety Stopping Rules.
5. Administrative reason (e.g., termination of the clinical study by a regulatory agency or the Sponsor).

9.5 Participant Withdrawal Procedures

9.5.1 Follow-up Procedures for Participants Who Withdraw Prematurely

The date and the reason for study drug discontinuation or participant withdrawal from the study must be recorded on the Case Report Form. If the participant has received one or more doses of clinical study material, and has not withdrawn consent, the participant shall return for the EOS visit. The EOS visit for early terminations will occur within 2 weeks of the last dose.

9.6 Procedures for Replacing Participants Who Withdraw Prematurely

Participants who withdraw from the study prior to dosing may be replaced after consultation with the Sponsor. If a participant is replaced, instructions in Section 7.6 will be followed for randomization and assignment of a study number.

10 TREATMENT PLAN AND METHODS

10.1 Schedule of Assessments

Table 1 – 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														
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	

	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)**
	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	
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).
3. Record demographic information, confirm ethnicity, and obtain medical history.
4. Confirm AD diagnosis per the NIA-AA 2018 criteria for probable AD Dementia.
5. Mini-Mental State Exam and Geriatric Depression Scale.
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 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. 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, CSF will be

stored for future evaluation of biomarkers of target engagement or disease modification. See 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 ADCS-CGIC will be conducted on Days 1, 29, 44, and 72.
23. The NTB (CFT, COWAT, TMT Parts A & B, and 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 AEs.
28. All concomitant medications will be recorded from screening through the EOS visit.
29. During screening (after consent), only 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.

10.2 Visit Specific Procedures

10.2.1 Visit 1 / Screening

Screening must be performed within 42 days prior to Baseline (Day 1). The following procedures will be performed at the Screening visit:

- Obtain signed Informed Consent Form from both participant and caregiver/study partner.
- Evaluate participant eligibility against study inclusion/exclusion criteria (Section 9.3), including administration of the Mini-Mental State Exam (MMSE) and Geriatric Depression Scale (GDS).
- Record demographic information, confirm ethnicity, and obtain medical history.
- Confirm diagnosis per the NIA-AA 2018 criteria for probable AD Dementia.
- Perform MRI, unless an MRI taken within the past 12 months is available (see Section 13.1.9 for details).
- Perform complete physical examination (see Section 13.1.3 for details).
- Measure and record vital signs (see Section 13.1.4 for details).
- Perform 12-lead ECG (see Section 13.1.8 for details).
- Draw blood and prepare samples for APOE status. APOE genotype is associated with the risk and age of onset of AD. Blood samples (approximately 10 mL) to perform this testing will be collected and will be used to further understanding of response to CT1812. The genotyping is mandatory for participation in the study and the results will not be revealed to the Investigator, participant, and caregiver/study partner.
- Draw blood and prepare samples for the following: serum chemistry (including lipid panel), hematology; viral serology; HbA1c in known diabetics; and TSH. FSH in women who had their last menses less than 24 months prior to screening and who are not surgically sterile (see Section 13.1.5 for details). Abnormal results at

screening will exclude a participant unless the Investigator is aware of a specific reason that can explain the abnormality (e.g., elevated CPK 24 hours after strenuous exercise). If an abnormal lab remains abnormal on repeat, the participant will be excluded.

- Exploratory Biomarkers only, to be collected with other blood work.
- Optional whole blood sample collection for future biomedical research (FBR), including potential genetic analyses, if the participant gave specific consent (see Section 11.3.1).
- Collect urine sample for urinalysis (see Section 13.1.5 for details).

- Collect urine sample for β-HCG pregnancy test for post-menopausal women, aged < 60 years, with last menses less than 24 months. Pregnancy test must be negative prior to dosing.
  - Administer C-SSRS (see Section 13.1.7 for details).
  - Record concomitant medications.
  - Once screening results indicate participant is eligible for the study, the participant should undergo LP at least 24 hours before the Baseline/Day 1 visit (see Section 11.5 for details).
  - If eligible, schedule participant to return to the study site on Day 1 to initiate treatment.

10.2.2 Visit 2 / Study Day 1 – Baseline

The following baseline procedures will be conducted on Day 1:

<u>Predose assessments</u>

- Confirmation of eligibility from the Sponsor; confirm continued eligibility prior to dosing.
- Perform complete physical examination (see Section 13.1.3 for details).
- Measure and record vital signs at predose (see Section 13.1.4 for details).

- Administer NTB, affective and cognitive assessments, ADCS-CGIC, and the A-IADL-Q (see Section 12.1 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.5 for details).
- Collect blood samples for PK and exploratory biomarker analysis at 1 ± 0.25-hour predose and at 2 (± 0.25) hours postdose (PK only).
- Collect urine samples for urinalysis (see Section 13.1.5 for details).
- Record any new medical conditions, AEs, or changes in medications since screening.
- Perform EEG (see Section 12.2 for details).
- Observe the participant self-administer the study drug (or observe the study partner administer the study drug to the participant). The study drug may be administered with or without food. Confirm that the participant can swallow the study drug without difficulty.

Postdose assessments

- Administer C-SSRS "Since-Last-Visit" version (see Section 13.1.7).
- Administer ECG approximately 2 hours postdose. ECGs will be recorded using a digital ECG to provide machine-generated interval measurements.
- Dispense study drug supply and instructions for at home dosing.

10.2.3 Visit 3 / Study Day 3 – Telephone Wellness Check

The participant and/or study partner will be called via telephone for a wellness check.

- Ask participant and/or study partner if any new concomitant medications were taken since the previous visit and record them in the case report form (CRF).

- Ask participant and/or study partner if any AEs had occurred since the previous visit and record them in the CRF.
- Instruct participant to hold the Day 8 dose and return to the study site for Visit 4.

10.2.4 Visit 4 / Study Day 8

The participant will return to the study site.

Predose assessments

- Conduct drug accountability.
- Perform brief physical examination (see Section 13.1.3 for details).
- Measure and record vital signs at predose (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.5 for details).
- Collect blood samples for PK and exploratory biomarker analysis at 1 ± 0.25-hour predose.
- Administer Day 8 dose with or without food.

Postdose assessments

- Record any new medical conditions, AEs, or changes in medications since the previous visit.
- Instruct participant to hold the Day 15 dose and return to the study site for Visit 5.

10.2.5 Visit 5 / Study Day 15

The participant will return to the study site.

Predose assessments

- Conduct drug accountability.

- Perform brief physical examination (see Section 13.1.3 for details).
- Measure and record vital signs (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.5 for details).
- Collect blood samples for PK and exploratory biomarker analysis at 1 ± 0.25-hour predose.
- Collect urine samples for urinalysis (see Section 13.1.5 for details).
- Administer Day 15 dose with or without food.

Postdose assessments

- Record any new medical conditions, AEs, or changes in medications since the previous visit.
- Perform 12-lead ECG (see Section 13.1.8 for details).
- Instruct participant to hold the Day 22 dose and return to the study site for Visit 6.

10.2.6 Visit 6 / Study Day 22

Predose assessments

- Conduct drug accountability.
- Perform brief physical examination (see Section 13.1.3 for details).
- Measure and record vital signs at predose (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum chemistry and hematology, including coagulation (see Section 13.1.5 for details).
- Collect blood samples for PK and exploratory biomarker analysis at 1 ± 0.25-hour predose.

- Administer Day 22 dose with or without food.

Postdose assessments

- Record any AEs.
- Record any new medical conditions, AEs, or changes in medications since the previous visit.
- Instruct participant to hold the Day 29 dose and return to the study site for Visit 7.

10.2.7 Visit 7 / Study Day 29 (+/- 2 days)

The participant will return to the study site.

Predose assessments

- Drug accountability is completed.
- Administer C-SSRS "Since-Last-Visit" version postdose (see Section 13.1.7).
- Perform brief physical examination (see Section 13.1.3 for details).
- Measure and record vital signs at predose (see Section 13.1.4 for details).
- Administer CSSR, CGIC, NTB, ADAS-COG-14, and A-IADL-Q assessments (see Section 12.1 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.5 for details).
- Collect blood samples for PK and exploratory biomarker analysis at 1 (± 0.25) hour predose and 2, (± 0.25) hours postdose (PK only).
- Collect urine samples for urinalysis (see Section 13.1.5 for details).
- Record any new medical conditions, AEs, or changes in medications since the previous visit.

- Perform EEG (see Section 12.2 for details).
- Perform the LP procedure (see Section 11.5 for details).
- Administer last dose of study drug with or without food.

The assessments for day 29 may be split over two days (e.g., EEG and LP split from safety assessments, ECG, PK and cognitive assessments).

10.2.8 Days 30 to 43 – Washout Period

Participants will be instructed to return to study site for the Day 44 visit.

10.2.9 Visit 8 / Study Day 44

The participant will return to the study site and a new informed consent pertaining to the Treatment Period 2 will be obtained.

The assessments for Treatment Period 1 and Treatment Period 2 are identical, except a brief physical examination (not a complete physical examination) will be performed in the second treatment period.

Predose assessments

- Confirmation of eligibility from the Sponsor; confirm continued eligibility prior to dosing.
- Perform brief physical examination (see Section 13.1.3 for details).
- Measure and record vital signs at predose (see Section 13.1.4 for details).
- Administer CSSR, CGIC, NTB, ADAS-COG-14, and A-IADL-Q assessments (see Section 12.1 for details). Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.5 for details).
- Collect blood samples for PK and exploratory biomarker analysis at 1 ± 0.25-hour predose and at 2, (± 0.25) hours postdose (PK only).
- Collect urine samples for urinalysis (see Section 13.1.5 for details).

- Record any new medical conditions, AEs, or changes in medications since the Screening visit.
- Perform EEG (see Section 12.2 for details).
- Administer Day 44 dose with or without food.

Postdose assessments

- Administer C-SSRS "Since-Last-Visit" version (see Section 13.1.7).
- Administer ECG approximately 2 hours postdose. ECGs will be recorded using a digital ECG to provide machine-generated interval measurements.
- Dispense study drug supply and instructions for at home dosing.
- Instruct participant to NOT take the dose at home on the day of a study site visit. Explain that the study site staff will administer the study drug at the study site.

10.2.10 Visit 9 / Study Day 46 – Telephone Wellness Check

The participant and/or study partner will be called via telephone for a wellness check.

- Ask participant and/or study partner if any new concomitant medications were taken since the previous visit and record them in the case report form (CRF).
- Ask participant and/or study partner if any AEs had occurred since the previous visit and record them in the CRF.
- Instruct the participant to hold the dose for Study Day 51 and return to the study site for Visit 10.

10.2.11 Visit 10 / Study Day 51

The participant will return to the study site.

Predose assessments

- Conduct drug accountability.
- Perform brief physical examination (see Section 13.1.3 for details).
- Measure and record vital signs at predose (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.5 for details).
- Collect blood samples for PK and exploratory biomarker analysis at 1 ± 0.25-hour predose.
- Perform 12-lead ECG (see Section 13.1.8 for details). ECGs will be recorded using a digital ECG to provide machine-generated interval measurements.
- Administer Day 51 dose with or without food.

Postdose assessments

- Record any new medical conditions, AEs, or changes in medications since the previous visit.
- Instruct participant to hold the Day 58 dose and return to the study site for Visit 58.

10.2.12 Visit 11 / Study Day 58

The participant will return to the study site.

Predose assessments

- Conduct drug accountability.
- Perform brief physical examination (see Section 13.1.3 for details).
- Measure and record vital signs (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.5 for details).

- Collect blood samples for PK and exploratory biomarker analysis at 1 ± 0.25-hour predose.
- Collect urine samples for urinalysis (see Section 13.1.5 for details).
- Administer Day 58 dose with or without food.

Postdose assessments

- Record any new medical conditions, AEs, or changes in medications since the previous visit.
- Instruct participant to hold the Day 65 dose and return to the study site for Visit 12.

10.2.13 Visit 12 / Study Day 65

Predose assessments

- Conduct drug accountability.
- Perform brief physical examination (see Section 13.1.3 for details).
- Measure and record vital signs at predose (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum chemistry and hematology, including coagulation (see Section 13.1.5 for details).
- Collect blood samples for PK and exploratory biomarker analysis at 1 ± 0.25-hour predose.
- Administer Day 65 dose with or without food.

Postdose assessments

- Record any new medical conditions, AEs, or changes in medications since the previous visit.
- Instruct participant to hold the Day 72 dose and return to the study site for Visit 13.

10.2.14 Visit 13 / Study Day 72 (+/- 2 days)

The participant will return to the study site.

The assessments for day 72 may be split over two days (e.g., EEG and LP split from safety assessments, ECG, PK and cognitive assessments).

Predose assessments

- Drug accountability is completed.
- Administer C-SSRS "Since-Last-Visit" version postdose (see Section 13.1.7).
- Perform brief physical examination (see Section 13.1.3 for details).
- Measure and record vital signs at predose (see Section 13.1.4 for details).
- Administer CSSR, CGIC, NTB, ADAS-COG-14, and A-IADL-Q assessments (see Section 12.1 for details). Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.5 for details).
- Collect blood samples for PK and exploratory biomarker analysis at 1 (± 0.25) hour predose and 2, (± 0.25) hours postdose (PK only).
- Collect urine samples for urinalysis (see Section 13.1.5 for details).
- Collect urine sample for β-HCG pregnancy test for post-menopausal women, aged < 60 years, with last menses less than 24 months.
- Record any new medical conditions, AEs, or changes in medications since the previous visit.
- Perform EEG (see Section 12.2 for details).
- Perform the LP procedure (see Section 11.5 for details).
- Administer last dose of study drug with or without food.

Postdose Assessments

- Participant is reminded to return for Visit 14 / Study Day 84 / EOS visit.

10.2.15 Visit 14 / Study Day 84 / End-of-Study Visit

The following procedures will be conducted on Day 84 / EOS Visit:

- Perform complete physical examination (see Section 13.1.3 for details).
- Measure and record vital signs (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.5 for details).
- Collect a blood sample for PK and exploratory biomarker analysis (only 1 collection).
- Collect urine samples for urinalysis (see section 13.1.5)
- Record any new medical conditions and AEs.
- Perform EEG (see Section 12.2 for details).
- Record ECG (see Section 13.1.8 for details).
- Record any AEs.
- Record changes in medications.

10.3 Concomitant Medications and Other Restrictions

All medications mentioned in the exclusion criteria (Section 9.3) are expressly prohibited at any time during the study. Exceptions to the list of excluded medications may be made on a case-by-case basis if discussed and approved by the Medical Monitor in advance. Intake of drugs or substances potentially involved in clinically significant CYP3A4 or P-gp mediated drug interactions with CT1812, within 4 weeks or 5 half-lives of the interacting drug prior to administration of CT1812 and throughout the study are prohibited. Grapefruit juice should be avoided in the 2 weeks prior to dosing and throughout the study. See Appendix A for a list of these prohibited substances.

Participants may be on stable doses (at least 30 days prior to screening) of an acetylcholinesterase inhibitor and/or memantine and continue these medications during the study. Participants may be on a stable dose (at least 60 days prior to screening) of an SSRI antidepressant and may continue this medication during the study.

11 SAMPLE COLLECTION

11.1 Volume of Blood Collected

The total volume of blood collected from each participant during this study will be up to 360 mL.

11.2 Blood Sampling for PK and Exploratory Biomarkers

Blood samples for the measurement of plasma CT1812 levels and exploratory biomarkers will be drawn at the following times during the study:

- Day -42 to-1 Exploratory Biomarkers only, to be collected with other blood work.
- Days 8, 15, 22, 51, 58, and 65 collect 1 (± 0.25) hour predose only.
- Days 1, 29, 44, and 72 collect 1 (± 0.25) hour predose (PK and Exploratory Biomarkers) and 2 (± 0.25) hours postdose (PK only).
- Day 84 (follow-up visit): PK and Exploratory Biomarkers.

Refer to Laboratory Manual for collection procedures and sampling handling.

11.3 Handling, Shipping, Storage, and Analysis of Blood Samples

Please refer to the Laboratory Procedures Manual for the processing of blood samples for PK and biomarker analyses.

11.3.1 Samples for Future Biomedical Research (FBR)

Specimens obtained for Future Biomedical Research (FBR) will be collected, tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form.

Participant blood specimens collected during this study may be stored for up to 15 years and used to further the knowledge of CT1812. A whole blood sample (approximately 10 mL) for future biomedical research will be collected during screening from participants who consent to have this specimen drawn. Research performed on this sample may include genetic analyses (e.g., DNA, gene expression profiling [ribonucleic acid], proteomics, metabolomics, or other analytes). Banked blood specimens may be used in the future to determine whether certain genotypes are correlated with the safety or efficacy of CT1812 or to answer emerging research questions not described elsewhere in the protocol.

Participants in this study will not be identified by name in CRFs, study-related forms, study reports, or any related publications and this de-identification applies to all FBR specimens. Consistent with all patient information, information related to FBR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form signed by the patient, unless permitted or required by law.

Data derived from FBR specimen analysis on individual participants will generally not be provided to study Investigators unless a request for research use is granted.

After collection at the site, de-identified specimens obtained for FBR will be transferred to Cognition Therapeutics and stored in a secure, long-term storage facility at -80° C for up to 15 years. After 15 years, the samples will be destroyed, and archived information will be discarded per local/country regulation. Sampling procedures, storage conditions, and shipment instructions are provided to the sites in the separate laboratory procedures manual.

Data generated from de-identified FBR specimens will be available for inspection upon request by representatives of national and local health authorities, and monitors, representatives, and collaborators, as appropriate.

Samples of de-identified FBR specimens, genetic research data and associated clinical data derived from the de-identified FBR samples may be shared with researchers who are not participating in the study or submitted to government or other health research databases for sharing with other researchers for the purpose of better understanding Alzheimer's disease and/or the study drug and/or other treatments.

The Investigator should document whether or not the participant has given consent to participate by completing the FBR Sample Informed Consent.

In the event of death or loss of competence of a participant who is participating in the Research, the participant's specimen and data will continue to be used unless permission to use the de-identified FBR specimens is withdrawn.

11.4 Pharmacokinetic Endpoints

The following CT1812 pharmacokinetic assessments will be made based on serial predose concentrations in plasma and CSF:

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

11.5 Cerebrospinal Fluid

11.5.1 Collection

Cerebrospinal fluid (CSF) is being collected at screening, Day 29, and Day 72 in this study to evaluate CSF concentrations of CT1812 following repeated dosing of CT1812 and potential effects on CSF biomarkers (abeta, tau, phospho-tau, NFL, neurogranin, synaptotagmin, SNAP25, or other exploratory biomarkers).

A qualified physician will perform the LPs to collect CSF. Before commencing the LP, the clinician will ensure that there are no contraindications to the procedure. Diagnostic confirmation by additional 2 mL CSF sample will be collected at the screening LP.

Samples of CSF collected at each timepoint should be sent to a local lab for cell counts (white blood cells and red blood cells, with differential if either of the counts is abnormal), CSF protein, and CSF glucose. If abnormalities at screening are observed, they should be discussed with the Medical Monitor before randomizing the participant.

The Investigator may in the event of a failed LP elect attempt a repeat LP under fluoroscopy or CT scan or to obtain the assistance of an anesthesiologist, if these options are available at their IRB approved facility. Should the screening LP be unsuccessful, this would not preclude participation in the study, sub sequentially scheduled LPs unless there are contraindications based on the screening attempt.

11.5.2 Timing of CSF Collection

Samples of CSF will be collected via LP during screening with a minimum of 24 hours before the Baseline visit and predose on Days 29 and 72. Regardless of which day the LP is performed, cognitive testing for that day should be completed prior to the LP, which should be followed by study drug dosing for that day.

11.5.3 Volume of CSF Collected

The volume of CSF collected from each participant during this study will be approximately 45 mL, (15 mL at each of the specified timepoints).

11.5.4 Handling, Shipping, Storage and Analysis of CSF

Please refer to the Laboratory Procedures Manual for the handling of CSF samples. Participant CSF specimens collected during this study may be stored for up to 15 years and used to further the knowledge of CT1812.

12 EFFICACY ASSESSMENTS

12.1 Affective and Cognitive Measures

12.1.1 Alzheimer's Disease Assessment Scale-cognitive subscale

The Alzheimer's Disease Assessment Scale (ADAS), a rating instrument, was developed in the early 1980s; it was designed specifically to evaluate the severity of cognitive and noncognitive behavioral dysfunctions characteristic of persons with Alzheimer's disease (Rosen 1984). The ADAS-cog subscale (ADAS-cog) consists of 11 tasks, which assess multiple cognitive domains, including memory, language, praxis, and orientation; its primary purpose is to be an index of global cognition in response to antidementia therapies. The ADAS Cog-14 includes the 11 tasks of the ADAS-Cog, plus delayed word recall, maze, and digit cancellation tasks (Kueper 2018).

12.1.2 Geriatric Depression Scale

The GDS is a depression screening assessment designed to identify depression in the elderly (Sheikh and Yesavage 1986). The short-form 15-item questionnaire with Yes and No answers queries participant's energy, attitude toward life, mood, etc. Participant eligible for this study must not have a score about 6 out of 15. Often symptoms of depression can mask or mimic some symptoms of Alzheimer's disease, therefore it is important to rule out participation of those who may be suffering from acute depression.

12.1.3 Mini-Mental State Exam

The Mini-Mental State Exam (MMSE) (Folstein et al. 1975) is a brief, screening instrument often used in clinical studies to assess dementia severity. The MMSE assess 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.

12.1.4 Neuropsychological Test Battery (NTB)

NTB will consist of the CFT, COWAT, TMT Parts A & B, and VMDS.

12.1.5 Alzheimer's Disease Cooperative Study -Clinical Global Impression of Change

The Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC) was developed by the Alzheimer's Disease Cooperative study (ADCS) (Schneider et al 1997). The 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 subject and study partner, 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 judgments with face validity. At follow-up visits, the clinician uses a similar set of forms to re-interview the patient and caregiver/study partner. The ADCS-CGIC rating is made on a 7-point scale similar to other global change scales, where a higher 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. The ADCS-CGIC will be completed by an independent rater (not the rater completing the cognitive or other assessments) where available at the site.

12.1.6 Amsterdam Instrumental Activity of Daily Living Questionnaire

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 questionnaire is completed by a caregiver, such as a relative or friend.

12.2. *Other: Pharmacodynamic Assessments*

Plasma, and CSF will be stored for future evaluation of biomarkers of target engagement or disease modification. Specimens collected during this study may be stored for up to 15 years and used to further the knowledge of CT1812.

12.2 EEG Recordings

EEGs will be recorded on OSG digital equipment (BrainRT™; OSG BV, Rumst, Belgium); A-D precision (Analog to digital conversion) 20-bit, sample frequency 500 Hz, AgCl-electrodes, recording montage- Fz, hardware filters (0.27 – 100 Hz). EEG data in patients will be obtained during a 15-minute task free session with closed eyes. An EEG assessment will be conducted at Day 1 and at Day 29 of Treatment Period 1, and at Day 44 and 72 (Day 1 and Day 29 of Treatment Period 2) of the study (Table 1). Twenty-one (21) channels of the standard 10-20 system will be recorded: Fp2 / Fp1, F8 / F7, F4/ F3, A2 / A1, T4 / T3, C4 / C3, T6 / T5, P4 / P3, O2 / O1, Fz, Cz, Pz, an ECG- and a respiration channel. Raw data are recorded using a montage with Fz as the common reference electrode. Electrode impedance will be checked before and after the recording and is kept below 5 KOhm. The following online filter settings are used: high pass 0.16 Hz, low pass 70 Hz, no notch filter. A sample frequency of 500 Hz and analog to digital conversion precision of 12 bit will be used. The recording is carefully monitored by an experienced EEG technician to minimize artefacts and to prevent drowsiness.

13 Safety Assessments

13.1.1 Safety Oversight

A study safety monitoring committee will oversee the safety of the study. This committee will include the study director, the Sponsor's Medical Monitor, and the site's Principal Investigator. Safety data (lab reports, AEs) will be provided to the safety committee to review at monthyl intervals during the study. The committee will meet, at minimum, once quarterly to discuss study safety data.

13.1.2 Adverse Events

AEs will be captured from the start of study-related procedures at Visit 1 (including diagnostic assessments or signing of ICF) onward during the course of this study. Important medical events and conditions occurring prior to this period are not AEs; they will be captured within the medical chart and in the Medical History section of the Case Report Form.

13.1.3 Physical Examination

At study visits in which a complete physical examination is required, the Investigator should perform a thorough examination of all body systems (exception: genitourinary and reproductive should be symptom-directed). At study visits in which a brief physical examination is required, the Investigator should inquire about signs/symptoms, general appearance, eyes (pupillary reaction, ophthalmoscopy, eye movements), oral mucosa, heart and pulses, lungs, abdomen (liver/spleen), kidneys, and neurological (symptom-directed and may include mental state, speech, gait/posture, arm swinging, facial movements, tongue, muscle wasting (power and tone), coordination, reflexes, and sensation).

Height should be measured at screening. Weight should be measured on the same scale at each visit. The Investigator must ensure that the scale is properly calibrated prior to study initiation.

13.1.4 Vital Signs

Vital signs will include body temperature, systolic and diastolic 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..Blood pressure and pulse rate recordings will be made after the study patient has been at rest for ≥5 minutes in either a sitting or a semi-supine position. As part of vital signs, the participant's weight should be measured.

13.1.5 Clinical Laboratory Tests

Hematology testing will include 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]) will be performed at screening and Days 22 and 65, prior to visits where LPs will be performed.

Serum chemistry analyses will include 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 will include osmolality, creatinine, calcium, sodium, turbidity, color, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocytes, and microscopic particles. Urine should not be first morning void. Microscopic examination will be performed if urinalysis results are abnormal for bacteria, casts, epithelial cells, erythrocytes, or leukocytes. Urine should be collected within 1 hour of blood draws for hematology and chemistry panels. Trace protein will be considered positive.

13.1.5.1 Screening Laboratory Tests

The following will be performed to confirm participant eligibility at screening:

- Viral serology: hepatitis B antigen, anti-hepatitis C antibody and anti-HIV antibodies.
- FSH testing will be conducted in women who had their last menses less than 24 months prior to screening and who are not surgically sterile.
- Thyroid stimulating hormone (TSH)
- HbA_{1c} will be conducted in known diabetics.
- Folate and B12 are optional at discretion of the Investigator if there is suspicion of deficiency.

13.1.5.2 Confirmation of Postmenopausal Status

A serum test for FSH will be done in women, aged < 60 years, who are post-menopausal with last menses occurring in the preceding 24 months. A urine pregnancy test will also be completed, and participants may not enter or continue in the study if pregnant. Additionally, women with an FSH test that is inconsistent with a postmenopausal state may not participate in the study.

13.1.6 Acute Kidney Injury Biomarker Testing

Acute kidney injury (AKI) is an abrupt loss of kidney function in the absence of volume depletion that develops within 7 days. In rat and dog toxicology studies of CT1812, dose-limiting toxicity consistently included hypercalcemia and microscopic findings of kidney proximal tubule degeneration. In dogs (the more sensitive species on the basis of exposures at the maximum tolerated dose [MTD] for changes in kidney function), increases in serum BUN and creatinine and lower urinary specific gravity were noted; each functional assessment fully recovered at all dose levels. Given these findings, kidney function will be monitored closely and at each point of

routine chemistry and hematology testing to observe physiologic changes as well as early indicators of AKI.

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13.1.7 Columbia Suicide Severity Rating Scale

Consistent with FDA regulatory guidance (FDA 2012), any occurrence of suicide-related thoughts and behaviors will be assessed. The Columbia Suicide Severity Rating Scale (C-SSRS) (Posner 2011) includes suggested questions to elicit the type of information needed to determine if a suicide-related thought or behavior occurred. It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent." The scale identifies behaviors that may be indicative of an individual's intent to commit suicide. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician and appropriate action undertaken. The "Screening" version will be used during screening, and the "Since-Last-Visit" version will be used at Visits 2, 7, 8, and 13.

13.1.8 12-lead Electrocardiogram

ECGs will be recorded using a digital ECG to provide machine-generated interval measurements.

13.1.9 MRI

The imaging specialist at the study site's MRI facility is responsible for determining if a patient is contraindicated from having this procedure. Listed below are some common conditions that may preclude the participant from having MRI scans. However, this list should not be used as a substitute for local clinical standards of care. The ultimate decision to perform the MRI rests with the site radiologist, the Investigator, and the standards set by the local IRB/IEC:

- Participants who have a history of claustrophobia.
- Participants with a pacemaker, epicardial pacemaker wires, MRI-incompatible cardiac valve prostheses, and MRI-incompatible vascular clips less than 2 months old or MRI-incompatible aneurysm clips of any age.
- Participants with MRI-incompatible cochlear implants.
- Participants with spinal nerve stimulators.
- Participants with an infusion pump.

- Participants with metallic fragments in the eyes/orbits or in the vicinity of the brain or major neurovascular structures of the body.
- Participants with an employment history that involves exposure to welding, unless absence of metallic fragments is documented by X-ray examination as per institutional practice.
- Participants who have shrapnel at any place in their body.

13.2 Adverse Events

13.2.1 Definitions

Adverse event

An adverse event (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), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug.

Related adverse event

A related AE is an AE with a causality rating of "possible" or "probable."

Not related Adverse Event

A not related AE is an AE with a causality rating of "unlikely" or "unrelated."

Laboratory abnormality

A laboratory abnormality is any clinically significant laboratory abnormality suggesting a disease or organ toxicity and which is of a severity requiring active management (i.e., changes of dose, discontinuation of drug, more frequent follow-up, medical treatment or a diagnostic investigation). Laboratory abnormalities are also considered AEs, if clinically significant.

Pretreatment adverse events

A pretreatment AE is any AE occurring during the pretreatment period (between informed consent and initiation of a study drug).

Post-study Adverse Event

A post-study AE is an AE occurring up to 30 days after Treatment Period 2.

Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are all AEs occurring during the treatment periods or a pretreatment AE that worsens in intensity during either treatment period.

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).

Serious Adverse Event

An SAE is any untoward medical occurrence that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect observed in any offspring of the participant conceived during treatment with the study drug or is an important medical event. See Section 14 for more details on SAEs.

13.2.2 Collection and Rating of Adverse Events

During the study (i.e., from the signing of the ICF through the Follow-up Visit plus 30 days for any SAE) all AEs, irrespective of the relatedness to the study drug, will be collected and reported on the Adverse Event Report Form. The seriousness criteria should not be confused with the intensity of the event. In case of an SAE, a Serious Adverse Event Report Form must be completed in the eCRF within 24 hours of identifying an SAE.

Overdoses and medication errors in the presence of clinical consequences should be recorded as AEs. The clinical consequence should be reported as "[enter AE]" due to overdose."

13.2.2.1 Onset Date

The onset date is the date when the first sign(s) or symptom(s) were first noted. For example, if the AE is an abnormal laboratory test (such as "platelets low"), the onset date is the date when the sample was taken. If the participant was hospitalized for meningitis, and symptoms such as fever, headache and nausea started the day before the hospitalization, the onset date is the day symptoms presented versus day of hospitalization.

13.2.2.2 Assessment of Intensity

The intensity of each AE will be rated according to the following 3-point scale:

- **Mild:** Awareness of signs or symptoms, but no disruption of usual activity.
- **Moderate**: Event sufficient to affect usual activity (disturbing).
- **Severe**: Inability to work or perform usual activities (unacceptable).

13.2.2.3 Relationship to Study Drug

The causal relationship of the study drug to an AE will be rated according to the following 4-point scale:

- **Unrelated:** Clearly and incontrovertibly due only to extraneous causes and does not meet criteria listed under possible or probable.
- **Unlikely:** Does not follow a reasonable temporal sequence from administration; may have been produced by the participant's clinical state or by environmental factors or other therapies administered.
- **Possible:** Follows a reasonable temporal sequence from administration; may have been produced by the participant's clinical state or by environmental factors or other therapies administered.
- **Probable:** Clear temporal association with improvement on cessation of study drug or reduction in dose. Reappears upon re-challenge or follows a known pattern of response to the study drug.

13.2.2.4 Action Taken

The action taken toward the study drug in response to an AE will be listed as one of the following:

- **None:** No change in study drug dosage was made.
- **Reduced:** Dose of study drug was reduced.
- **Discontinued** The study drug was permanently stopped.

13.2.2.5 Outcome of Adverse Event

The outcome of an AE will be recorded as one of the following:

- **Recovered:** Fully recovered or the condition has returned to the level observed at baseline.
- **Recovered with sequelae:** Resulted in persistent or significant disability or incapacity; the nature of the sequelae should be specified.
- **Not recovered.**
- **Death.**

13.2.3 Adverse Event Follow-up

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the participant.

Any participant who has any AE (whether serious or non-serious) or, in the Investigator's opinion, clinically significant abnormal laboratory test values will be evaluated by the Investigator or a monitoring physician and will be treated and followed until the symptoms or values return to normal or acceptable levels, as judged by the Investigator and the Sponsor.

AEs that are unresolved at the EOS visit or upon early withdrawal will be tracked at least weekly by site staff until resolution, for 30 days, or until the participant is lost to follow-up (defined as failure to respond to 3 phone messages left on separate days and 1 certified letter requesting follow-up).

Participants will be instructed to inform site staff of any AEs occurring during the 30-day period after discharge or early withdrawal.

Any follow-up information available at the time of the participant's end--of-study visit will be included in the clinical study report.

Any SAE that is considered to be unexpected and related to the study drug occurring after the EOS visit should be forwarded to the Sponsor. These cases will be handled and submitted as expedited reports but will not be included in the clinical study report.

Note:

Any unanticipated serious adverse events (SAEs) that are 'related' should be reported to the National Institute on Aging within 48 hours of knowledge of the event.

14 Serious and Other Significant Adverse Events

14.1.1 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that:

- **Results in death.** Death is not an event per se but rather an outcome. Note that any event resulting in a fatal outcome must be fully documented and reported, including deaths that occur within 30 days after treatment ends and irrespective of the causal relationship to the study drug.

- **Is life-threatening.** Life-threatening refers to an AE in which the participant was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death, if it was more severe.

- **Requires in-patient hospitalization or prolongation of existing hospitalization.** Hospitalization means that the participant was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Overnight stays for observation; stays at the emergency room, or treatment on an outpatient basis do not constitute a hospitalization. However, medical judgment must always be exercised and, when in doubt, the case should be considered serious (i.e., if the case fulfills the criterion for a medically important event). Hospitalization for administrative or social purposes does not constitute an SAE. Hospital admissions and/or surgical operations planned before study inclusion are not considered AEs if the illness or disease existed before the participant were enrolled in the study, provided that the condition did not deteriorate during the study.

- **Results in persistent or significant disability/incapacity.** Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. If in doubt, the decision should be left to medical judgment by the Investigator.

- **Is a congenital anomaly/birth defect.** Any congenital anomaly or birth defect observed in any offspring of the participant conceived during treatment with the study drug.

- **Is an important medical event.** Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important.

An AE caused by an overdose or medical error is considered serious if a criterion listed in the definitions above is fulfilled.

The following are not considered SAEs:

- A pre-existing condition that is present prior to or at the start of the study that did not worsen.

- Hospitalizations for treatment which were elective or preplanned, for a pre-existing condition unrelated to the indication under study that did not worsen.

- Admission to a hospital or other institution for general care, not associated with any deterioration in condition.

14.1.2 Serious Adverse Event Reporting by the Investigator to the Sponsor

During screening (after consent), only SAEs related to a study-specific procedure will be collected.
Any SAE that occurs after a participant has been enrolled in the study, whether or not related to study drug, must be reported to the Sponsor or its designee immediately (within 24 hours).

The procedure for reporting SAEs, regardless of causal relationship is as follows:

- Within 24 hours if the investigator's knowledge of an SAE, the site must notify the Sponsor or its designee by completing the AE form in the eCRF and selecting "Serious". The Sponsor or its designee will be notified automatically by EDC that an SAE has been entered.
- The initial SAE report should provide as much of the required information as is available at the time. The following minimum information is required for reporting an SAE: event verbatim term, seriousness criterion, investigator causality and an event outcome.

Submission of the SAE via the eCRF should not be delayed in order to collect additional information to complete the form.

The investigator should notify the local IRB/IEC of SAEs occurring at the site and other adverse events reports received from Sponsor or its designee in accordance with local procedures, if required. **CRO Medical Monitor Contact Information:**

The Medical Monitor is available 24/7 for site contact. Medical Monitor contact details will be provided directly to the clinical site.

14.1.3 Handling of Follow-up Information

Follow-up information may be required, or additional information may be received by the Sponsor (e.g., evolution of the SAE, other signs or symptoms, final diagnosis, final outcome, hospital discharge summary, or autopsy report). The same procedures and timelines as for initial reporting, listed above, should be followed for any follow-up information. If necessary, the study site will be visited to collect additional information.

Follow-up information is required on all SAEs until one of the following criteria is satisfied:

- The final outcome of the case is known.
- The event is resolved, or the medical condition of the participant is stabilized.
- No further information is available.
- Sponsor assessment has been finalized.

14.1.4 Reporting and Follow-up of Pregnancy

When an Investigator becomes aware of the pregnancy of a female participant, the Investigator must withdraw the participant from the study and follow the pregnancy until termination or until the child is 1 month old. The pregnancy will be reported immediately by telephone and by faxing a completed Pregnancy Report to the Sponsor within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator should notify the Sponsor or the Sponsor's agent of the outcome of the pregnancy by submitting a follow-up Pregnancy Report. Additionally, if the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE Report Form to the Sponsor within 24 hours of knowledge of the event.

14.1.5 Expedited Reporting of Serious Adverse Events

14.1.5.1 Responsibilities

The Sponsor is responsible for ensuring the timely reporting of SAEs to Regulatory Authorities and all Investigators who participate in the clinical development program of the study drug. It is the responsibility of the Investigator to provide the Sponsor with the case information such that reporting timeline demands of applicable Regulatory Authorities can be met.

14.1.5.2 Expedited Reporting

All AEs that are serious, unexpected, and considered related to the study drug judged by either Sponsor or the Investigator require expedited reporting. All available information relevant to the evaluation of the SAE will be reported. Serious adverse events will be considered reportable regardless of whether or not the study drug was used in accordance with the provisions in the protocol.

Adverse events which are serious, but expected, or those which are not associated with the study drug will only be subject to expedited reporting if they are required to be reported to an authority according to national requirements.

In addition, any unanticipated serious adverse events (SAEs) that are 'related' will be reported by the Sponsor to the United States National Institutes of Health within 48 hours of knowledge of the same.

14.1.5.3 Timelines

Fatal or life-threatening serious unexpected related cases require rapid reporting. Regulatory Authorities shall be notified as soon as possible but no later than 7 calendar days after first knowledge by the Sponsor representative, followed by as complete a report as possible within 8 additional calendar days.

Serious unexpected related cases that are not fatal or life-threatening must be submitted as soon as possible, but no later than 15 calendar days after first knowledge by the Sponsor representative that the case meets the minimum criteria for expedited reporting.

It is the responsibility of the Investigator to support Sponsor activities needed to meet the aforementioned timelines for Regulatory Authority reporting in the event of an SAE.

15 Statistical Methods

15.1 General Overview of the Statistical Analysis Plan

Individual data for all enrolled participants will be presented in data listings, sorted by participant and dosing arm.

15.2 Sample Size Justification

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 between treatments of 2.5%.

For the endpoint of CSF neurogranin, assuming a true within-subject 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.

15.3 Analysis Populations

The safety population will include all participants receiving one or more doses of study treatment.

15.4 Data Analysis

EEG Data Analysis: Five artefact-free epochs recorded in an awake state with eyes closed will be selected for each recording. Before analyses, the EEG recording will be referenced to a montage with an average reference. Spectral analyses will be conducted by Fast Fourier Transformation using BrainWave, a program by Professor Dr. C.J. Stam: http://home.kpn.nl/stam7883/brainwave.html. The following spectral measures will be calculated for each electrode: relative and absolute power in the delta (0.5 – 4Hz), theta (4 – 8 Hz), alpha 1 (8 – 10 Hz), alpha 2 (10 – 13 Hz), and beta frequency band (13 – 30 Hz) and 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 may be applied to normalize the distribution of absolute power values.

Statistical analysis: As noted in section 4.1, global theta activity (and in particular global relative theta power, i.e., the fraction of the total brain activity accounted for by theta wave frequency) is the most powerful early-phase diagnostic EEG marker in AD patients. As noted in section 5.1, a primary study objective of this study is to evaluate the efficacy of CT1812 in restoring synaptic function in participants with mild to moderate Alzheimer's disease through the use of quantitative EEG, as reflected by relative theta power. Relative theta power is included in this study as a primary efficacy outcome measure. As noted in the synopsis and in section 15.2, for the endpoint of global relative theta power, the assumed within-subject standard deviation (SD) is equal to 3%. 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 between treatments of 2.5%. Because of their expected additional value in early AD, several additional EEG measures reflecting changes in brain activity will be added for exploratory purposes: relative power in alpha and beta bands, global peak frequency, and theta/alpha ratio. All the quantitative EEG outcome variables, including the primary efficacy outcome measure of global relative theta power, will be analysed using the analysis of variance (ANOVA) model for a 2-period, 2-treatment crossover study described by Senn (1993, pages 63-64).[30] Comparisons between CT1812 and placebo will be made using two-sided tests at the alpha=0.05 level of significance. This study and the quantitative EEG measures that are included in it are exploratory in nature and any positive EEG efficacy findings may be expected to be confirmed in larger subsequent trials. For this reason, no correction for multiple comparisons are planned.

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.3 or higher), unless otherwise noted. AEs will be assessed by the Investigator for severity and will be coded for summarization using Medical Dictionary for Regulatory Activities (MedDRA® Version 10.1 or higher). Concomitant medications will be coded using WHO Drug Dictionary (enhanced) Format C, 15 Aug 2005 or more recent updated version.

Adverse events will be summarized by Medical Subject Headings (MeSH) Term for each dose group (including placebo), and the incidence compared. Laboratory measures will be summarized by treatment group and timepoint, both as absolute values and as change from baseline, with descriptive statistics summarizing each group and timepoint. Similar presentations will be used for vital signs, ECG interval measurements, and changes from pre-treatment baseline.

Analyses of PK parameters and pharmacodynamics markers:

Standard non-parametric statistical analyses will be used to examine the relationships between dose and PK parameters.

Pharmacodynamics markers in CSF and CT1812 concentrations in serum and CSF will be summarized using appropriate descriptive statistics.

Additional statistical details will be provided in a prospective statistical plan.

15.5 Missing, Unused and Spurious Data

No imputation will be applied for missing data. Only non-missing values will be used for analyses.

16 Study Management

16.1 Protocol Amendment and Protocol Deviation

16.1.1 Protocol Amendment

Administrative amendments to the protocol will be classed as amendment of typographical errors, clarifications of confusing wording, and other minor modifications including but not limited to name, address, and contact information changes that have no impact on the safety of the participant or the science of the study. Administrative amendments will be submitted to the Institutional Review Board (IRB) for information only. The Sponsor will ensure that acknowledgement is received and filed. Otherwise, an amendment will be classed as a substantial amendment and will be submitted to the appropriate Regulatory Authorities and the IRB for approval.

16.1.2 Protocol Deviations

No deviations from the protocol are anticipated. Should a non-anticipated protocol deviation occur, the Sponsor must be informed as soon as possible. All deviations and the reasons for the deviation will be documented by the Investigator or designated staff. Reporting of protocol deviations to the IRB and in accordance with applicable Regulatory Authority mandates is the responsibility of the Investigator.

16.1.3 Protocol Waivers

The Sponsor will not grant protocol waivers for this study.

16.2 Ethics and Regulatory Aspects

16.2.1 Ethical Conduct of the Study and Regulatory Guidelines

To ensure the ethical conduct of this clinical study, each Investigator is expected to conduct the study in accordance with the protocol; the United States IND regulations specified under 21 CFR 11, 50, 54, 56, and 312; the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP); and the Guidelines of the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with all national, state and local laws of applicable Regulatory Authorities.

The responsibilities of the Sponsor, the Medical Monitor, and the Investigator will be as defined in the ICH GCP consolidated guideline, and applicable regulatory requirements in the country where the study takes place. The Investigator is responsible for adhering to the GCP responsibilities of investigators, for dispensing the study drug in accordance with the approved protocol or a signed amendment, and for the secure storage and safe handling of study drug and other study materials throughout the study.

16.2.2 Institutional Review Board and Regulatory Approval

An Institutional Review Board (IRB) will review this study protocol and any amendments The IRB will also review the written participant information sheet and the Informed Consent Form (ICF), their updates (if any), and any written materials given to the participants. A listing of the membership of the IRB and the name of the committee chair(s) or IRB registry (accreditation) number will be documented within the Investigator File and Trial Master File of the Sponsor.

Regulatory permission to perform the study must be obtained in accordance with applicable regulatory requirements. All ethics approvals must be obtained, and regulatory obligations met before a participant commencing any study-related procedures, including screening tests for eligibility.

16.2.3 Participant and Study Partner Informed Consent

Potential participants and his/her caregiver/study partner will be informed about the study both verbally and in writing. Each participant and his/her study partner will be provided with a written participant information sheet that has been approved by the IRB and will be given a reasonable

time to consider the study and ask any questions they have regarding the study. The study partner will consent to providing information about the participant, managing drug administration, and attending all study site visits. The written participant information sheet and ICF must be in a language that the participant can understand.

Only the Investigator, a medically qualified sub-investigator or a suitably qualified and trained authorized person may be involved in the informed consent process.

The Investigator or suitable designee will obtain a freely given, written consent from each participant and his/her study partner after an appropriate explanation of the aims, methods, potential hazards, and any other aspects of the study that are relevant to the decision of the participant to participate. The Investigator will explain that the participant is completely free to refuse to enter the study or withdraw from it at any time, without any consequences for their further care and without the need to justify.

The ICF and study partner consents must be signed and dated by the participant and study partner before commencing any study-related procedures, including screening tests for eligibility. The participant and study partner will receive copies of the written participant information sheet, the ICF, and study partner consent form.

Each participant will be informed that the Sponsor's study monitor, a Quality Assurance Auditor mandated by the Sponsor, or a Health Authority Inspector, in accordance with applicable regulatory requirements, may review his or her source records and health data. Data protection will be handled in compliance with national and local regulations.

If new safety information becomes available and results in significant changes in the risk to benefit assessment, the written participant information sheet will be revised or updated where necessary. Under these circumstances, all participants (including those already being treated) should be informed of the new information, given a copy of the revised form, and allowed to reevaluate their consent to continue in the study.

16.3 End of Study and Regulatory Notification

The study can be terminated in part or in whole at the discretion of the FDA, an applicable Regulatory Authority or the Sponsor.

At the end of the study, the IRBs and Regulatory Authorities will be notified by the Sponsor according to applicable regulatory requirements.

16.4 Data Protection and Confidentiality

The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirement(s).

16.5 Monitoring

The study will be monitored to ensure that the study is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site visits will be made at appropriate times during the study. The Sponsor's monitors must have direct access to source documentation in order to check the consistency of the data recorded in the CRFs.

The Investigator will make available to the Monitor all source documents, medical records, and source data necessary to complete CRFs. Also, the Investigator will work closely with the Sponsor's monitors and as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

16.6 Quality Assurance and Quality Control

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, the site's Principal Investigator is responsible for the accuracy, completeness, and reliability of the study data presented to the Sponsor.

Prior to the study initiation, the Sponsor will explain the protocol, Investigator's Brochure, and CRFs to Investigators. Also, the Monitor will be available to explain applicable regulations and answer any questions regarding the conduct of the study.

At its discretion, the Sponsor may conduct audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions.

The study site may also be compelled to an inspection by a Regulatory Authority.

16.7 Source Data

Source data are defined as information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Source documents are the original data, documents, and records. Examples include hospital records, laboratory reports, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, other radiographic depictions or displays, and participant files, as well as records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical study. The Primary Investigator and Sponsor (or designee) must review all source documents for compliance with GCP.

Study-specific data sheets may be used to document source information that would normally not be collected and documented in the routine management of the participant. The Investigator or designee must verify and sign all data sheets used for source documentation. The signed study-specific data sheets must be stored and archived in the participant's study records (preferably) or in the Investigator File.

The Investigator will permit study-related monitoring, audit(s), IRB review(s), and regulatory inspection(s), with a direct access to all the required source documents and associated records.

17 Data and Record Keeping

17.1 Case Report Forms

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on participant profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data. The Investigator's clinical staff will review all data listings for outliers, data inconsistencies, and spelling errors.

During the study, the Sponsor's study monitor will make site visits to review protocol compliance, compare CRFs against individual participant's medical records, assess drug

accountability, and ensure that the study is being conducted according to pertinent regulatory requirements.

Electronic data capture (EDC) entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained. Checking the EDC for completeness and clarity and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out giving due consideration to data protection and medical confidentiality.

17.2 Record Keeping

Study records and source documents need to be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application of CT1812 in an ICH region, whichever is the longest time period. The Sponsor will be notified prior to the planned destruction of any study related source documents.

18 Financing and Insurance

Financial aspects of the study are addressed in a separate clinical study agreement.

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

19 Use of Data and Publication Policy

Both the use of data and the publication policy are detailed within the clinical study agreement.

The Investigator should be aware that intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be pursuant to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or designee. With respect to such rights, the Sponsor or designee will solely own all right and interest in any materials, data and intellectual property rights developed by the Investigator and others performing the clinical study described in this protocol, participant to the terms of any such agreement. In order to facilitate such ownership, the Investigator will be required to assign all such inventions either to the Institution where the study is conducted or directly to the Sponsor or their designee, as will be set forth in the clinical study agreement. This agreement will not preclude the reporting of any required data to Regulatory Authorities.

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21 APPENDICES

Appendix A – Prohibited Medications - Cytochrome P450 Drug Interaction Table

In addition to the medications detailed in various exclusion criteria (Section 9.3), the following medications are restricted within 4 weeks of screening visit and during the study. Exceptions to the list of excluded medications may be made on a case-by-case basis, if discussed and approved by the Sponsor's Medical Monitor in advance.

- Antipsychotic agents.
- Antiepileptics.
- Centrally active anti-hypertensive drugs (e.g., clonidine, l-methyl dopa, guanidine, guanfacine, etc.).
- Sedatives.
- Opioids.
- Mood stabilizers (e.g., valproate, lithium); or benzodiazepines, with the following exception: Low-dose lorazepam may be used for sedation prior to MRI scan for those subjects requiring sedation. At the discretion of the Investigator, 0.5 mg to 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. No more than a total of 2 mg lorazepam may be used for the MRI scan.
- Nootropic drugs (except stable AD medications: acetylcholinesterase inhibitors and memantine), e.g., Gingko biloba extract.
- Moderate to strong inhibitors or inducers of CYP3A4. See Appendix A for a complete list of restricted medications.
- All hormonal contraceptives and hormone replacement therapies (oral, injectable, transdermal, or implanted).
- Calcium channel blockers (only diltiazem and verapamil are excluded).
- Coumadin® or other anticoagulant medications.
- Digoxin.
- Inability to separate dosing of CT1812 by at least 6 hours (before or after) from the participant's concomitant medications that are sensitive or are narrow therapeutic index: substrates of CYP3A4; P-glycoprotein (P-gp); loperamide; vinblastine; or talinolol.
- Exposure to immunomodulators, anti Aβ vaccines, passive immunotherapies for AD (e.g., monoclonal antibodies) within the past 180 days and/or exposure to BACE inhibitors within the past 30 days.

Below are partial listings of specific medications excluded in COG0202. Most of these categories are represented in exclusion criteria (see Section 9.3). This list might not be all-inclusive for specific categories of medications. Check with the Sponsor's Medical Monitor if there are questions.

Barbiturates	**Nonbenzodiazepine hypnotics**	**Antipsychotics**
benzylbutylbarbiturate butalbital amobarbital pentobarbital secobarbital sodium thiopental phenobarbital **Benzodiazepines** clonazepam diazepam estazolam flunitrazepam lorazepam midazolam nitrazepam oxazepam triazolam temazepam chlordiazepoxide alprazolam clobazam clorazepate etizolam.	eszopiclone zaleplon zolpidem zopiclone **Opioids** tramadol tapentadol morphine hydromorphone oxymorphone oxycodone hydrocodone methadone propoxyphene meperidine fentanyl codeine carfentanil.	olanzapine clozapine thiothixene haloperidol fluphenazine prochlorperazine trifluoperazine loxapine quetiapine asenapine **Other** glutethimide sodium oxybate (Xyrem®) **First-generation antihistamines** *The following should not be used within 24 hours of cognitive testing:* diphenhydramine dimenhydrinate doxylamine promethazine hydroxyzine brompheniramine chlorpheniramine.

3A4,5,7 INHIBITORS	3A4,5,7 INDUCERS	CYP3A Substrates with narrow therapeutic range
HIV Antivirals:	carbamazepine	alfentanil
indinavir	efavirenz	astemizole
nelfinavir	nevaripine	cisapride
ritonavir.	phenobarbital	cyclosporine
	phenytoin	dihydroergotamine
clarithromycin	pioglitazone	ergotamine
itraconazole	rifabutin	fentanyl
ketoconazole	rifampin	pimozide
nefazodone	St. John's wort	quinidine
erythromycin	troglitazone.	sirolimus
grapefruit juice		tacrolimus
verapamil		terfenadine.
suboxone		
diltiazem.		

Sensitive P-gp Substrate:
digoxin.

Source:

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "http://medicine.iupui.edu/clinpharm/ddis/clinical-table" Accessed: 17 Apr 2016.