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Document: Redacted Protocol COG0201

Official Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Study to Evaluate the Safety and Efficacy of CT1812 in Subjects With Mild to Moderate Alzheimer's Disease.

ClinicalTrials.gov ID (NCT number): NCT03507790

Protocol Date : Version 6.0_12 June 2023

CLINICAL STUDY PROTOCOL

Protocol Full Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Study to Evaluate the Safety and Efficacy of CT1812 In Subjects with Mild to Moderate Alzheimer's Disease
Protocol Number:	COG0201
Version:	6.0
Compound Number:	CT1812
Study Phase:	2
Sponsor Name and Address:	Cognition Therapeutics, Inc. 2500 Westchester Avenue Purchase, NY 10577 United States of America
Sponsor Approval Date:	12-June-2023

Confidentiality Statement

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GCP Statement

The study will be conducted according to the International Council on Harmonisation harmonized tripartite guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE FOR SPONSOR

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Approved by the following:

[redacted]

20-Jun-2023 | 10:21:22 EDT

Date

2500 Westchester Avenue
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SIGNATURE PAGE FOR INVESTIGATOR

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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, ICH and the Declaration of Helsinki.

Investigator Name	Signature	Date

1 STUDY ORGANIZATIONAL STRUCTURE

Sponsor:	Cognition Therapeutics, Inc.
Primary Sponsor Contact Head of Clinical Operations	[redacted] Executive Director - Clinical Operations Cognition Therapeutics, Inc. [redacted]
24-Hour Medical Monitor Coverage Medical Monitor	[redacted] Cognition Therapeutics, Inc. [redacted]

2 PROTOCOL SYNOPSIS

TITLE: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Study to Evaluate the Safety and Efficacy of CT1812 in Subjects with Mild to Moderate Alzheimer's Disease.

SPONSOR: Cognition Therapeutics Inc.

PROTOCOL NUMBER: COG0201

CLINICAL STUDY PHASE: Phase 2

STUDY DRUG PRODUCT: CT1812

STUDY OBJECTIVES:

Primary:

- To assess the safety and tolerability of CT1812 as a treatment for mild to moderate Alzheimer's disease.

Secondary:

- To assess target engagement and identify pharmacodynamic effects of CT1812 on CSF biomarkers.

Exploratory:

- To characterize the PK profile of CT1812 in plasma.
- To assess the efficacy of CT1812 as a treatment for mild to moderate Alzheimer's disease.

STUDY DESIGN:

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group 36 week multicenter Phase 2 study of two doses of CT1812 in adults with mild to moderate Alzheimer's Disease (AD).

Participants will be screened for eligibility by physical, laboratory, psychometric and neurologic examinations, and neuroimaging. Pre-drug CSF and blood samples will be obtained $\leq$ 42 days prior to randomization at Baseline/Day 1. After having met all inclusion

criteria, and none of the exclusion criteria, participants will be randomized to one of three treatment arms (CT1812 at doses of 100 or 300 mg/d or placebo, up to n=48 group). Participant

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

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

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

Participants who prematurely discontinue the study for any reason will be asked to attend a final safety and efficacy visit. Additional participants may be added to replace participants with significant disruption to their visit schedule due to COVID or if there are unanticipated dropouts.

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

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

Safety Stopping Rules:

Dosing may be terminated by the Sponsor at the recommendation of the DSMB (Data Safety and Monitoring Board) based upon safety and tolerability data, or at the discretion of the Sponsor; therefore, there are no study-specific stopping rules defined in this protocol.

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

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

The Sponsor and DSMB will review the available safety data and recommend whether dosing should continue, study drug administration should be terminated, or additional monitoring procedures or safety precautions need to be employed. Selective unblinding of participants in the study may be performed by the DSMB 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 DSMB determines that any adverse event(s) are occurring that are intolerable or pose a medically unacceptable safety risk.

In the case of an emergency, the Principal Investigator may unblind a participant without the Sponsor's approval, however, the Sponsor should be notified if a participant is unblinded as soon as possible.

For individual participants:

Any participant who develops the following liver function test (LFT) laboratory abnormalities will not receive any additional doses of study drug and will be monitored until the return of laboratory abnormality to the acceptable screening value(s).

- Elevated ALT or AST greater than 5 X Upper Limits of Normal (ULN)
- Elevated ALT or AST greater than 3 X ULN in combination with total bilirubin > 2 X ULN or INR > 1.5 X ULN
- Elevated 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%)

Serial monitoring of ALT/AST/bilirubin and INR will be performed, initially with repeat values within 4 days of discontinuation of study drug. If LFTs are still elevated 4 days post-study drug interruption, participants should have LFTs checked again 4 days later (+/- 1 day). The site investigator and Medical Monitor should agree to a plan for further LFT

monitoring depending on whether the LFTs are still increasing or trending towards normal. Repeat testing should be carried out until LFTs have normalized. The LFTs in this instance can also be run locally for more rapid turnaround.

In the event a reversible etiology is found to explain the elevated liver enzymes (such as a common bile duct stone), drug may be restarted following normalization of LFTs, and after discussion between the Medical Monitor and site PI. If an alternative etiology is not identified, dosing of the study drug will be permanently discontinued, and the participant will be withdrawn from the study.

Study drug will be temporarily discontinued if a participant does not achieve the aforementioned levels of elevated transaminases but has an elevation of ALT or AST >3 X ULN. These participants will have their liver function retested within 4 days after their last dose of study drug. If transaminases are still elevated 4 days post-study drug interruption, participants will have LFTs checked again 4 days later (+/- 1 day), and the site PI and Medical Monitor will agree to a plan for further monitoring of the findings. The LFTs in this instance can also be run locally for more rapid turnaround.

LFTs do not need to be intensively monitored when ALT and AST are ≤ 3 X ULN with no elevation of bilirubin, however the investigator and the Medical Monitor will formulate a plan for serial testing of LFTs. Cessation of dosing is not required in this circumstance but may be temporarily interrupted at the discretion of the investigator.

NUMBER OF PARTICIPANTS:

Up to approximately 144 participants randomized in a 1:1:1 ratio to 100 mg/day, 300 mg/day or placebo. Additional participants may be added to replace participants with significant disruption to their visit schedule due to COVID or if there are unanticipated dropouts.

TARGET POPULATION:

INCLUSION CRITERIA:

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

1) Men, and women of non-childbearing potential, 50-85 years of age inclusively, with a diagnosis of mild to moderate Alzheimer's disease according to the 2011 NIA-AA

criteria and at least a 6 month decline in cognitive function documented in the medical record.

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

ii) Male subjects who are sexually active with a woman of child-bearing potential must agree to use condoms during the trial and for 3 months after last dose unless the woman is using an acceptable means of birth control. Acceptable forms of birth control include birth control pills, or any double combination of: intrauterine device (IUD), diaphragm, sponge, and cervical cap. Periodic abstinence, coitus interruptus, exclusive use of spermicides and lactational amenorrhea method (LAM) are not acceptable contraceptive methods.

2) Diagnostic confirmation by amyloid PET with florbetaben or another approved amyloid PET ligand. Previous amyloid imaging study with a positive result will be accepted. If none is available, then amyloid PET will be conducted during screening. Diagnostic confirmation by a CSF sample collected at the optional screening visit lumbar puncture in place of amyloid PET will also be acceptable. Inclusion via CSF samples requires: low Aβ 42 OR low Aβ 42/40 ratio AND either increased total-tau OR increased phospho-tau based on the ranges established by the central lab.

3) Neuroimaging (MRI, or CT scan due to contraindication of MRI is approved by Medical Monitor) obtained during screening consistent with the clinical diagnosis of Alzheimer's disease and without findings of significant exclusionary abnormalities (see exclusion criteria, number 4). An historical MRI (or CT scan), up to 1 year prior to screening, may be used if there is no history of intervening neurologic disease or clinical events (such as a stroke, head trauma etc.) and the subject is without clinical symptoms or signs suggestive of such intervening events.

4) MMSE 18-26 inclusive.

5) No active depression and a GDS ≤6 (see exclusion criteria number 6). Subjects with a GDS >6 may be allowed to enroll if the investigator does not believe the subject is

clinically depressed. Investigators must contact the Medical Monitor to discuss eligibility.

6) Modified Hachinski ≤ 4.

7) Formal education of eight or more years.

8) Participants must have a caregiver/ study partner who in the opinion of the site principal investigator, has contact with the study subject 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 clinic visits and some study assessments. The caregiver/ study partner must provide written informed consent to participate in the study.

9) Participants living at home or in the community (assisted living acceptable).

10) Ability to swallow CT1812 capsules.

11) Stable pharmacological treatment of any other chronic conditions for at least 30 days prior to screening.

12) Participants must be capable of providing written informed consent to the study procedures and for use of protected health information [Health Insurance Portability and Accountability Act (HIPAA) and European General Data Protection Regulation (GDPR), if applicable]. Written informed consent also shall be obtained from the responsible caregiver. All consent processes must be undertaken in the presence of a witness and prior to any study procedures.

13) Must consent to apolipoprotein E (ApoE) genotyping for data analysis stratification.

14) 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.

15) 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 one month prior to screening.

2) Participants living in a continuous care nursing facility.

3) Contraindication to the MRI examination for any reason. CT scan may be substituted for an MRI if a subject is unable to tolerate an MRI or an MRI is contraindicated for medical reasons. The proposed CT scan will be approved by the Medical Monitor on a case-by-case basis.

4) Screening MRI (or historical MRI, or CT scan due to contraindication of MRI if approved by medical monitor) 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). If a small incidental meningioma is observed, the Medical Monitor may be contacted to discuss eligibility.

5) Clinical or laboratory findings consistent with:

   a. Other primary degenerative dementias such as dementia with Lewy bodies, frontotemporal 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. Subjects with depressive symptoms successfully managed by a stable dose of an antidepressant or antipsychotic would be allowed to enroll.

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, as calculated by the central laboratory.

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

e. Bradycardia (<50 beats/min.) or tachycardia (>100 beats/min.). If the heart rate is below 50 beats/min the subject may be eligible to enroll if the Investigator has determined that the heart rate < 50 beats/min is stable and not clinically significant. If the heart rate is above 100 beats/min, the heart rate assessment may be repeated to assess eligibility.

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 defined by HbA1c >7.5% in participants with diabetes. Only those subjects with known diabetes are required to get a HbA1c at screen.

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). Subjects who have evidence of resolved Hepatitis C infection (HCV RNA negative) may be considered following discussion with the Medical Monitor.

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 < 1500/uL (with the exception of a documented history of a chronic benign neutropenia), absolute lymphocyte count <900/ul or platelet cell count of < 120,000/uL; INR >1.4 or other coagulopathy, confirmed by repeat assessment of:

i. Hematocrit

ii. Neutrophil count

iii. Lymphocyte count

iv. Platelet count

v. PT/INR

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

13) Within 4 weeks of screening visit or during the course of 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 exceptions:

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 the 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.

b) Stable use of eszopiclone or zolpidem for sleep is allowed. Stable use of short-acting benzodiazepines and trazadone specifically as sleep aids are allowed.

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 or 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 indicated by elevated MCV significantly above normal value at screening.

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 five 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 five half-lives of the interacting drug prior to administration of CT1812 and throughout the course of the study. Grapefruit juice should be avoided in the two weeks prior to dosing and throughout the course of the study. See Appendix A for a complete list of prohibited substances. See Section 9.3.1 for handling of Paxlovid ™ administration for COVID infection during the study.

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

21) Any vaccination within one week of the baseline visit.

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

LENGTH OF STUDY:

Each participant and caregiver will participate in a screening period of up to 42 days, followed by a double-blind treatment period of 182 (+/- 7) days and a follow up visit at Day 210 for a total of 254 days of study participation.

DOSAGE, DOSE FORM, AND ROUTE OF ADMINISTRATION:

CT1812, 100 mg or 300 mg

Study Drug will be capsules of identical appearance containing either placebo or CT1812 fumarate.

Study drug will be taken by mouth once each morning with or without food.

EVALUATION CRITERIA:

A DSMB (Data and Safety and Monitoring Board) will oversee the safety of the trial. This committee will include three independent experts, including an independent statistician. Safety data will be provided to the DSMB at quarterly intervals during the trial. The study clinician and study Medical Monitor will review trial safety data biweekly and more frequently as the rate of enrollment and safety data warrant. Similarly, more frequent *ad*

hoc meetings of the DSMB will occur if ongoing safety data indicate interim meetings are indicated.

The DSMB will review the safety and tolerability of CT1812 of the participant enrolled in the study. They may also recommend additional safety and/or monitoring measures.

Safety and Tolerability Measures:

- Adverse events.
- Serious Adverse Events.
- Physical and neurological examinations.
- Vital signs - body temperature, systolic and diastolic blood pressure, pulse rate and respiration rate.
- Electrocardiogram (ECG).
- Clinical laboratory tests: hematology, biochemistry, coagulation, serology and urinalysis.
- Columbia Suicide Severity Rating Scale (C-SSRS).

Efficacy Measures:

- Mini Mental State Exam (MMSE).
- ADAS-cog 11 and ADAS-cog 13 (Delayed Recall and digit cancellation added to ADAS-11 in the ADAS-13).
- Neuropsychological Test Battery (NTB). NTB includes Trails A & B, Digit Span, Letter & Category Fluency (COWAT and CFT).
- ADCS-Clinical Global Impression of Change (CGIC).
- ADCS-Activities of Daily Living (ADCS-ADL).

Exploratory Measures:

- Pharmacokinetic: Plasma and CSF CT1812.
- Pharmacodynamic: CSF- Aβ, tau, phospho-tau, Neuro Filament Light Chain (NFL), neurogranin, synaptotagmin, SNAP25 (synaptosomal-associated protein 25) and

Aβ oligomers. Other exploratory target engagement biomarkers may also be evaluated.

STATISTICAL METHODS:

Analysis Populations

The safety population will include all participants receiving one or more doses of study treatment. Individual data for all enrolled participants will be presented in data listings, sorted by participant and dosing arm.

An interim analysis will be performed once the first 24 participants have completed six months of dosing. Details of the interim analysis can be found in the statistical analysis plan.

Study Sample Size

Groups of up to 48 participants per dose level are felt to give adequate sensitivity to detect adverse events. A sample size of 48 participants for each dose level (100 mg, 300 mg) has 91% power to detect at least 1 occurrence of any drug-related AE with a true prevalence in the treated population of 5%.

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

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

Data Analysis

All descriptive statistical analyses will be performed using the current version of SAS statistical software, unless otherwise noted.

Adverse Events will be assessed by the investigator for severity and will be coded for summarization using the current version of Medical Dictionary for Regulatory Activities (MedDRA®). Adverse Events will be summarized by Preferred Term and System Organ

Class, for each dose group (including placebo).

Laboratory measures will be summarized by treatment group and time-point both as absolute values and as change from baseline, with descriptive statistics summarizing each group and time point. Similar presentation will be used for vital signs and for ECG interval measurements, and changes from pre-treatment baseline.

Concomitant medications will be coded using the current version of WHO Drug Dictionary or Concomitant medications will be summarized and listed.

Efficacy endpoints will be summarized by treatment group and time-point using descriptive statistics as both absolute values and as change from baseline. Differences between treatment groups will be assessed using a mixed model for repeated measures (MMRM). The difference between each treatment group and the placebo at each time-point will be estimated based on the least square means (LSM) from the MMRM. Exploratory analyses of potential pharmacodynamics markers in CSF and plasma will be conducted using appropriate statistical tests.

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

Contents

List of Tables

3 GLOSSARY OF TERMS AND ABBREVIATIONS

Abbreviation	Description
Aβ	amyloid beta
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – cognition subscale
AE	adverse event
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
AKI	Acute kidney injury
ALT	alanine aminotransferase
APOE	gene which 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
CFT	Category Fluency Test
C_{max}	maximum concentration
CNS	central nervous system
COWAT	Controlled Word Association Test
CSF	cerebrospinal fluid

Abbreviation	Description
C_{ss}	steady state concentration
C-SSRS	Columbia Suicide Severity Rating Scale
dL	deciliter
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EOS	End of Study
F	Fahrenheit
FBR	Future Biomedical Research
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GFR	glomerular filtration rate
GMP	Good Manufacturing Practice
h	hour(s)
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
hERG	human Ether-à-go-go Related Gene
Hgb	hemoglobin
HIV	human immunodeficiency virus
IC50	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviation	Description
IVRS / IWRS	Interactive Voice Response Systems / Interactive Web Response Systems
kg	kilogram
KIM-1	kidney injury molecule -1
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
µg	microgram
mg	milligram
mL	milliliter
mmol	millimolar
MMSE	Mini Mental State Exam
MRI	Magnetic Resonance Imaging
MTD	maximum tolerated dose
NAG	N-acetyl-beta-D-glucosaminidase (an indicator of renal damage)
NIH	National Institutes of Health
NIA	National Institute on Aging
NTB	Neuropsychological Test Battery
PD	pharmacodynamics
PK	pharmacokinetic
QD	once daily
SAE	serious adverse event
$t_{1/2}$	terminal half life
TFF3	trefoil factor 3 (an indicator of renal damage)

Abbreviation	Description
TK	toxicokinetic
T_{max}	time to maximum concentration
ULN	upper limit of normal
Vd	volume of distribution

4 INTRODUCTION

4.1 Background

Synaptic dysfunction and loss caused by age-dependent accumulation of synaptotoxic beta-amyloid (Aβ) 1-42 oligomers is proposed to underlie cognitive decline in Alzheimer's Disease (AD). Accumulation of Aβ protein leads to self-association, resulting in formation of oligomers. Cognition Therapeutics Inc. has demonstrated that Aβ oligomers bind saturably to a single, high affinity site on the surface of neuronal synapses (Izzo et al 2014a; Izzo et al., 2014b). 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 Aβ 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 patient 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 Aβ42 oligomers to receptors on brain cells. In vitro, in cultured rat neurons, CT1812 not only antagonizes binding of Aβ42 oligomers, but also prevents Aβ 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 Aβ 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 Aβ 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 Aβ 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 mild to moderate AD and early AD / mild cognitive impairment.

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 over 300 analogs. CT1812's properties are fully described along with all preclinical studies in the Investigator's 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.

In vitro pharmacodynamic (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 CNS 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 trial.

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 trial to evaluate the effect of study drug administration on renal function (including serum creatinine, serum calcium, 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 over 60 healthy volunteers in a placebo-controlled Phase 1a trial (COG 0101). Six single (10-1120 mg) and three multiple dose cohorts (QD, 14 days, 280-840 mg) were observed under close inpatient stay (N=6-8 treated, 2 placebo per cohort). Plasma concentrations of drug were shown to be approximately dose proportional across two 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 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 site in those participants who

had lumbar punctures. There was only one AE of severe intensity, being an SAE of upper respiratory tract infection, occurring in one participant in the 840 mg dose of the MAD study, believed to be unrelated to study drug based on a similar pattern of URTIs in subjects 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 or hypercalcemia has been observed based on routine measures of renal function (serum creatinine, BUN) or cystatin C.

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 PK evaluations performed. 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 1a/2 trial (COG0102) evaluated the safety and pharmacokinetics of three doses of once-a-day CT1812 (90 mg, 280 mg, 560 mg) dosed for 28 days in participants with mild to moderate Alzheimer's disease. This study enrolled 19 participants in a 1:1:1:1 ratio of these doses vs. placebo. In general, all doses were relatively well tolerated, with no 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 which 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 which 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.

For additional information about the clinical study program, please refer to the current Investigator Brochure.

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 evaluate the safety of two doses of CT1812 administered once daily for 6 months in adults aged 50 to 85 who have been diagnosed with mild to moderate Alzheimer's disease (the targeted clinical indication for CT1812). Randomized participants will receive 100 mg of CT1812, 300 mg of CT1812, or placebo once daily for 182 days. Exploratory endpoints that evaluate the effect of CT1812 on biomarkers are also included.

4.5 Rationale for Selected Doses

Based on brain receptor occupancy studies in animals, the daily dose of 300 mg/day is projected to exceed 95% occupancy while the 100 mg/day dose is projected to exceed 80% receptor occupancy. In the Phase 1 multiple dose 2-week trial, doses exceeding 300 mg/day were well-tolerated in both younger (≤ 64 years of age) and older (≥ 65 years of age) s. In the phase 1 AD

trial, tolerability was also acceptable with no serious adverse events observed at doses exceeding 300 mg/day.

5 STUDY OBJECTIVES

5.1 Primary Objectives

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

5.2 Secondary Objectives

- To assess target engagement and identify pharmacodynamic effects of CT1812 on CSF biomarkers.

5.3 Exploratory Objectives

- To assess the efficacy of CT1812 as a treatment for mild to moderate Alzheimer's disease.
- To characterize the PK profile of CT1812 in plasma.

6 STUDY TYPE AND DESIGN

6.1 Study Type

This is a multi-center Phase 2, randomized, double-blind, placebo-controlled, parallel-group study.

6.2 Endpoints

6.2.1 Safety Endpoints

- The incidence and severity of adverse events.
- The change in usage of concomitant medications.
- Changes in vital signs.
- Changes in physical exam findings.
- Changes in electrocardiogram findings.
- Changes in clinical laboratory testing (serum chemistry, hematology, urinalysis).

- Changes in the Columbia Suicide Severity Rating Scale (C-SSRS).

6.2.2 Efficacy Endpoints

- Mini Mental State Exam (MMSE).
- ADAS-cog 11 and ADAS-cog 13 (Delayed Recall and digit cancellation added to ADAS-11 in the ADAS-13).
- Neuropsychological Test Battery (NTB). NTB includes Trails A & B, Digit Span, Letter & Category Fluency (COWAT and CFT).
- ADCS-Clinical Global Impression of Change (CGIC).
- ADCS-Activities of Daily Living (ADCS-ADL).

6.2.3 Pharmacokinetic/Pharmacodynamic Endpoints

- **Pharmacokinetics**:
  - CT1812 CSF/plasma concentration ratio (end of study only).
  - Changes in pre-dose/trough level CT1812 plasma concentrations.
- **Pharmacodynamics**:
  - CSF- Aβ, tau, phospho-tau, neurogranin, synaptotagmin, SNAP25 (synaptosomal-associated protein 25), Neuro Filament Light Chain (NFL), Aβ oligomers. Other exploratory target engagement biomarkers may also be evaluated.

6.3 Study Design

This is a double-blind, placebo-controlled parallel-group trial in adults with mild to moderate AD. Participants will be screened for eligibility by physical, laboratory and psychometric and neurologic examinations, neuroimaging, and pre-drug CSF and blood samples obtained ≤42 days prior to randomization at Baseline/Day 1. After having met all inclusion criteria, and none of the exclusion criteria, participants will be randomized to one of three treatment arms (CT1812 at doses of 100 or 300 mg/d or placebo, n=48/group). The first dose of study drug will be administered in the clinic after all baseline procedures have been conducted. With the exception of clinic visits days, for the remainder of study days, participants will ingest study drug each morning at home with or without food. Participants and their caregivers/study partner will

return to the clinic for repeat psychometric/neurologic testing, safety procedures and PK and PD sample collection at the intervals described below.

Up to 144 participants will be enrolled.

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

Participants in Part C will return to the clinic for Visit 3 on Day 7 and Day 14 after baseline, followed by twice-monthly visits until Day 70, then every four weeks until Day 182 (See Table 1). A follow up visit will occur approximately 30 days after the end of treatment.

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

6.3.1 Re-Screening Activities

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

7 STUDY DRUG

7.1 Supply and Storage

Study drug will be provided in bottles containing capsules of CT1812 active equivalent to 50 mg or 150 mg of the CT1812 free base and its matching placebo. Study drug will be provided in bottles with desiccant packs. The treatment label on the bottle will include a study reference code (protocol number), drug identifier, quantity of capsules, and lot number at minimum, as well as pertinent information according to local regulations. The expiry or use-by date will be stored in the IRT (IVRS/IWRS) or according to local regulations. Study drug should not be used after the

expiry or use-by date. All packaged and labelled supplies will be formally released in accordance with both Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

The study drug should be stored in its original packaging at refrigerated temperatures (2 °C- 8 °C [32 °F -40 °F]), with daily minimum and maximum temperature logs maintained at the site. The investigator, or an approved representative (e.g., pharmacist), will ensure that all study drugs are stored and dispensed in accordance with local regulations concerning the storage and administration of investigational drugs. All drug supplies must be kept in a secure locked area under recommended storage conditions with access limited to those authorized by the investigator.

7.2 Administration

CT1812 or matching placebo will be administered orally as a single daily dose for 6 months. All participants will ingest the first dose in the clinic and be observed for 2 hours. A single daily dose consists of 2 capsules of study drug. Two (2) capsules will be swallowed with ~240 mL of water with or without food. Daily outpatient dosing should occur in the morning (i.e., prior to 12 pm). To ensure appropriate specimen collection times relative to dosing on clinic days, participants will be asked to bring their study medication to clinic visits and to take their medication at the clinic upon the instruction of the site staff. On "Drug Dispensation" clinic visits drug accountability will be completed for the bottle returned by the participant and the "in office dose administration" will be taken for that visit from the newly assigned bottle.

7.2.1 Safety Stopping Rules

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

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

- Two occurrences of the same or similar serious adverse event (SAE) assessed as probably or possibly related to dosing with investigational product.
- Two or more different 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 DSMB will review the available safety data and recommend whether dosing should continue, or if study drug administration should be terminated, or if additional monitoring procedures or safety precautions need to be employed. Selective unblinding of the participants in the study may be performed by the Sponsor and DSMB 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 Sponsor and DSMB determine that any adverse event(s) are occurring that are intolerable or pose a medically unacceptable safety risk.

For individual participants:

Any participant who develops the following liver function test (LFT) laboratory abnormalities 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).

- Elevated ALT or AST greater than 5 X Upper Limits of Normal (ULN)
- elevated ALT or AST greater than 3 X ULN in combination with total bilirubin > 2 X ULN or INR > 1.5 X ULN
- 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%)

Serial monitoring of ALT/AST/bilirubin and INR will be performed, initially with repeat values within 4 days of discontinuation of study drug. If LFTs are still elevated 4 days post-study drug interruption, participants should have LFTs checked again 4 days later (+/- 1 day). The site investigator and Medical Monitor should agree to a plan for further LFT monitoring depending on whether the LFTs are still increasing or trending towards normal. Repeat testing should be carried out until LFTs have normalized. The LFTs in this instance can also be run locally for more rapid turnaround.

In the event a reversible etiology is found to explain the elevated liver enzymes (such as a common bile duct stone), drug may be restarted following normalization of LFTs, and after discussion between the Medical Monitor and site PI.

Study drug will be temporarily discontinued if a participant does not achieve the aforementioned levels of elevated transaminases but has an elevation of ALT or AST >3 X

ULN. These participants will have their liver function retested within 4 days after their last dose of study drug. If transaminases are still elevated 4 days post-study drug interruption, participants will have LFTs checked again 4 days later (+/- 1 day), and the site PI and Medical Monitor will agree to a plan for further monitoring of the findings. The LFTs in this instance can also be run locally for more rapid turnaround.

LFTs do not need to be intensively monitored when ALT and AST are ≤ 3 X ULN with no elevation of bilirubin, however the investigator and the Medical Monitor will formulate a plan for serial testing of LFTs. Cessation of dosing is not required in this circumstance but may be temporarily interrupted at the discretion of the investigator.

7.3 Drug Accountability

Participants will return all study bottles and unused study drug at each clinic 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.

7.4 Overdose/Toxicity Management

No specific pharmacologic antagonist or antidote exists for CT1812 or sigma-2 modulators in general. 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).

7.5 Blinding, Randomization and Matching Participants

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

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

Should any participant withdraw from the study prior to study completion, the participant may be replaced, at the sponsor's discretion. 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 Site

This is a multi-center trial and will include up to approximately 25 qualified investigator sites in Australia, Czech Republic, Netherlands, Spain, and the United States.

8.2 Duration of Study

Screening procedures will occur on Days -42 to -1. Eligible participants will return to the clinic at Baseline/Day 1 visit for randomization into the trial. Daily dosing will continue through week 26. The total duration of participant participation in the study is up to 254 days including screening.

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

9.2 Inclusion Criteria

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

1) Men, and women of non-childbearing potential, 50-85 years of age inclusively, with a diagnosis of mild to moderate Alzheimer's disease according to the 2011 NIA-AA criteria and at least a 6 month decline in cognitive function documented in the medical record.

   i) Non-childbearing potential for women is defined as postmenopausal (last natural menses greater than 24 months) or undergone a documented bilateral tubal ligation or hysterectomy. If last natural menses occurred less than 24 months ago, a serum FSH value confirming post-menopausal status can be employed.

   ii) Male subjects who are sexually active with a woman of child-bearing potential must agree to use condoms during the trial and for 3 months after last dose unless the woman is using an acceptable means of birth control. Acceptable forms of birth control include birth control pills, or any double combination of: intrauterine device (IUD), diaphragm, sponge, and cervical cap. Periodic abstinence, coitus interruptus, exclusive use of spermicides and lactational amenorrhea method (LAM) are not acceptable contraceptive methods.

2) Diagnostic confirmation by amyloid PET with florbetaben or another approved amyloid PET ligand. Previous amyloid imaging study with a positive result will be accepted. If none is available, then amyloid PET will be conducted during screening. Diagnostic confirmation by a CSF sample collected at the optional screening visit lumbar puncture in place of amyloid PET will also be acceptable. Inclusion via CSF samples requires the following: low Aβ 42 OR low Aβ 42/40 ratio AND either increased total-tau OR increased phospho-tau.

3) Neuroimaging (MRI, or CT scan due to contraindication of MRI if approved by Medical Monitor) obtained during screening consistent with the clinical diagnosis of Alzheimer's disease and without findings of significant exclusionary abnormalities (see exclusion criteria, number 4). An historical MRI (or CT scan), up to 1 year prior to screening, may be used if there is no history of intervening neurologic disease or clinical events (such as a stroke, head trauma etc.) and the subject is without clinical symptoms or signs suggestive of such intervening events.

4) MMSE 18-26 inclusive.

5) No active depression and a GDS ≤6 (see exclusion criteria number 6). Subjects with a GDS >6 may be allowed to enroll if the investigator does not believe the subject is clinically depressed. Investigators must contact the Medical Monitor to discuss eligibility.

6) Modified Hachinski ≤4.

7) Formal education of eight or more years.

8) Subjects must have a caregiver/ study partner who in the opinion of the site principal investigator, has contact with the study subject 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 clinic visits and some study assessments. The caregiver/ study partner must provide written informed consent to participate in the study.

9) Subjects living at home or in the community (assisted living acceptable).

10) Ability to swallow CT1812 capsules.

11) Stable pharmacological treatment of any other chronic conditions for at least 30 days prior to screening.

12) Subjects must be capable of providing written informed consent to the study procedures and for use of protected health information [Health Insurance Portability and Accountability Act (HIPAA) and European General Data Protection Regulation (GDPR), if applicable]. Written informed consent also shall be obtained from the responsible caregiver. All consent processes must be undertaken in the presence of a witness and prior to any study procedures.

13) Must consent to apolipoprotein E (ApoE) genotyping for data analysis stratification.

14) Subjects 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.

15) Must be able to complete all screening evaluations.

9.3 Exclusion Criteria

Subjects 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 one month prior to screening.

2) Subjects living in a continuous care nursing facility.

3) Contraindication to the MRI examination for any reason. CT scan may be substituted for an MRI if subjects are unable to tolerate an MRI or an MRI is contraindicated for medical reasons, if the proposed CT scan is discussed and approved by Medical Monitor on a case-by-case basis.

4) Screening MRI , or CT scan due to contraindication of MRI, if approved by Medical Monitor (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). If a small incidental meningioma is observed, the Medical Monitor may be contacted to discuss eligibility.

5) Clinical or laboratory findings consistent with:

   a) Other primary degenerative dementia, (dementias such as dementia with Lewy bodies, frontotemporal 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. Subjects with depressive symptoms successfully managed by a stable dose of an antidepressant would be allowed to enroll.

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, as calculated by the central laboratory.

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

e) Bradycardia (<50 beats/min.) or tachycardia (>100 beats/min.). If the heart rate is below 50 beats/min the subject may be eligible to enroll if the Investigator has determined that the heart rate < 50 beats/min is stable and not clinically significant. If the heart rate is above 100 beats/min, the heart rate assessment may be repeated to assess eligibility.

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 defined by HbA1c >7.5 in subjects with diabetes. Only those subjects with known diabetes are required to get a HbA1c at screen.

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). Subjects who have evidence of resolved Hepatitis C infection (HCV RNA negative) may be considered following discussion with the Medical Monitor.

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, absolute lymphocyte count <900/ uL), or platelet cell count of <120,000/uL; INR >1.4 or other coagulopathy, confirmed by repeat assessment of:

i) Hematocrit

ii) Neutrophil count

iii) Lymphocyte count

iv) Platelet count

v) PT/INR

12) Any disability that may prevent the subject 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 exceptions:

a) 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 to 1 mg may be given orally prior to an MRI 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.

At the discretion of the investigator, lorazepam or another anxiolytic may be administered as per local standard of care prior to MRI scan or optional lumbar puncture. Note neurocognitive testing should not be done within 24 hours of administration of conscious sedation.

b. The stable use of zolpidem or eszopiclone for sleep is allowed.

c. Stable use of short-acting benzodiazepines and trazadone, specifically as sleep aids are allowed.

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 or 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 indicated by elevated MCV significantly above normal value at screening.

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 five 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 five half-lives of the interacting drug prior to administration of CT1812 and throughout the course of the study. See Appendix A for a complete list of prohibited substances. See Section 9.3.1 for handling of Paxlovid™ administration for COVID infection during the study.

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

21) Any vaccination within one week of the baseline visit.

22) Any condition, which in the opinion of the investigator or the sponsor makes the subject 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 7.2.1 - Safety Stopping Rules.

5) Administrative reason (e.g., termination of the clinical study by a Regulatory Agency or the Sponsor).

Every effort should be made to retain participants in the study. Study staff should try to address participant concerns prior to early termination.

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 trial material, and has not withdrawn consent, the participant shall return for the End of Study (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 7.5 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

		Screen	Base-line													
	Study day **Visit**	-60 to -1 1	1 2	3 (±1) 3*	7 (±2) 4	14 (±2) 5	21 (±2) 6*	28 (±2) 7	42(±2) 8	56 (±2) 9	70 (±2) 10	90 (±2)	98, 126, 154 (±2) 11,12, 13	172 (±2)	182 (±2)/ 14	210 (±2) Safety Follow Up 15
	Screening Tests															
1	Informed consent	X														
2	Inclusion/Exclusion Criteria	X	X													
3	Demography & Medical History	X														
4	Confirm AD diagnosis	X														
5	MMSE	X	X						X				X (D98)		X	
6	Modified Hachinski exam and GDS	X														
7	ApoE Status	X														
8	Optional whole blood sample for future biomedical research	X														
9	Screening Laboratories	X														
	Physical Exam, Vitals, ECG, Other															
10	Complete Physical Exam	X	X												X	
11	Brief Physical Exam			X	X	X	X	X	X	X	X		X			
12	Vital signs and weight	X	X	X	X	X	X	X	X	X	X		X		X	X
13	ECG (12-lead)	X	X					X		X			X (D98)		X	
14	MRI	X													X	
15	Amyloid PET Scan	X														

		Screen	Base-line													
	Study day **Visit**	-60 to -1 1	1 2	3 (±1) 3*	7 (±2) 4	14 (±2) 5	21 (±2) 6*	28 (±2) 7	42(±2) 8	56 (±2) 9	70 (±2) 10	90 (±2)	98, 126, 154 (±2) 11,12, 13	172 (±2)	182 (±2)/ 14	210 (±2) Safety Follow Up 15
	Blood Draws, Urine Collection & Lumbar Puncture															
16	Chemistry & hematology	X	X	X	X	X	X	X	X	X	X		X		X	X
17	Serum cystatin C		X	X	X	X			X		X		X		X	X
18	PK and Exploratory Biomarkers Sampling	X EB only	X	X	X	X		X	X		X		X		X	
19	Serum biomarkers	X										X		X		
20	Coagulation testing (PT/INR)	X									X**		X (D 154)			
21	Optional lumbar puncture	X											X (D98) ***		X	
22	Urinalysis	X	X	X	X	X		X	X	X	X		X		X	
23	Pregnancy testing	X														
	Cognitive, Functional, and Safety Assessments															
24	C-SSRS	X	X	X	X	X	X	X	X	X	X		X		X	X
25	Cognitive Assessments and ADCS-ADL	X	X						X				X (D98)		X	
	ADCS-CGIC		X						X				X (D98)		X	
	Concomitant Medications, Adverse Events and Study Drug Administration															
26	Concomitant Meds	X	X	X	X	X	X	X	X	X	X		X		X	X
27	Adverse Events Assessment		X	X	X	X	X	X	X	X	X		X		X	X
28	Drug Accountability			X	X	X	X	X	X	X	X		X		X	
29	Drug Dispensation		X					X		X	X		X			
30	In office dose administration		X	X	X	X	X	X	X	X	X		X		X	

Key for Table 1

Abbreviations: AD = Alzheimer's disease; ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognition subscale; AKI = acute kidney injury; ApoE = apolipoprotein E; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End of Study; GDS = Geriatric Depression Scale; MMSE = Mini Mental State Exam; NTB = Neuropsychological Test Battery PK = pharmacokinetic

1. Informed consent must be obtained prior to the subject undergoing any study-specific procedures.
2. Review of all criteria detailed in Sections 9.2 and 9.3.
3. Record demographic information, confirm ethnicity and obtain medical history.
4. Confirm AD diagnosis in accordance with McKhann 2011 criteria.
5. Mini Mental State Exam and Geriatric Depression Scale.
6. Perform Modified Hachinski Exam to screen for vascular dementia.
7. APOE genetic testing is required for all participants.
8. Optional whole blood sample (~10 mL) for future biomedical research including potential genetic analyses (see section 11.3).
9. Screening labs include viral serology, TSH, FSH and HbA1c. See Section 13.1.4 for details.
10. Complete physical examination = thorough examination of all body systems, including height, weight and neurological exam. Weight should be measured on the same scale each time. Height measured only at screening. See Section 13.1.2 for details.
11. Brief physical examination = inquire about signs/symptoms, review of general appearance and brief review of body systems, including weight. Weight should be measured on the same scale each time. See Section 13.1.2 for details.
12. Vital signs will include body temperature, systolic and diastolic BP, respiration rate and pulse rate. Weight should also be recorded. At Baseline and subsequent visits, vital signs are done at pre-dose. See Section 13.1.3 for details.
13. ECG to be conducted during screening period, and approximately one to two hours post-dose (+/- 45 min) at specified visits. See Section 13.1.7 for details.
14. MRI (or CT scan due to contraindication of MRI if approved by medical monitor) performed at screen (if an historical MRI is not used) and end of treatment. See Section 13.1.8 for details.
15. Diagnostic confirmation by amyloid PET with florbetaben or another approved amyloid PET ligand. Diagnostic confirmation by CSF sample collected at Screen Lumbar Puncture, in place of the amyloid PET, will also be accepted.
16. Blood Chemistry and Hematology - Blood should be drawn within an hour of urine collection. See Section 13.1.4 for details.
17. Serum cystatin C: Blood should be drawn within an hour of urine collection.
18. Plasma PK and Exploratory Biomarker Sampling: See Section 11 for timing of sample collection. See Laboratory Procedures Manual for sample handling. PK will not be assessed at screen whereas the exploratory biomarker samples will be collected.

Serum biomarker samples are collected at any point during screening at least 24 hours prior to the Baseline Visit. Serum biomarkers will also be collected at Day 90 (+/- 2 days) and Day 172 (+/- 2 days).

This blood draw will be performed at a local lab. The local lab will include onsite laboratory facilities for collection and processing. Participants consented to Protocol version 2.0 on or after their Baseline visit are not required to have the Biomarker samples drawn on Day 90 or Day 172.

19. The serum samples should not be collected on the same day as the lumbar puncture.
20. Coagulation testing includes prothrombin time and INR.

    **Only required on Day 70 if the optional LP on Day 98 is planned.
21. Optional lumbar puncture: Participants may opt to undergo lumbar puncture as part of screening, after all other eligibility criteria have been reviewed and approved by the medical monitor, at least 24 hours before the Baseline visit and again at Day 182 (the end of the dosing period). LP on the Day 182 visit should be performed minimally 24 hours prior to the other the Day 182 visit procedures (e.g. Day 181) and prior to dosing on that day. (See section 11.5.2 Timing of CSF collection). The optional screening visit lumbar puncture must not be performed without Medical Monitor approval.

    ***If a participant and investigator are agreeable, an additional LP may be performed at least 24 hours before the Day 98 visit. (See section 11.5.2 Timing of CSF collection)

    If adequate volume is available, CSF will be stored for future evaluation of biomarkers of target engagement or disease modification. See Laboratory Procedures Manual for sample handling. See Section 11.5 for details. Obtained CSF should be sent for cell counts (white blood cells and red blood cells, with differential if either of the counts is abnormal), CSF protein, and CSF glucose at Screening, Day 98 (optional), and Day 182. If abnormalities are observed at Screening, they should be discussed with the Medical Monitor before randomizing the participant.
22. Urine should not be first morning void. See Laboratory Procedures Manual for sample handling. See Section 13.1.4 for details.
23. Pregnancy testing should include an assessment of FSH levels. See Section 13.1.4.1 and 13.1.4.2
24. C-SSRS Screening/Baseline version used at screening visit, Since Last Visit version used at all other visits. See Section 13.1.6.
25. The ADAS-Cog 13, NTB, ADCS-ADL, and MMSE will be conducted during screening period, and prior to dosing at other visits. The ADCS-CGIC will be conducted beginning at Day 1, and all other visits with the cognitive assessments.
26. All concomitant medications will be recorded from screening through Day 210.
27. During Screening (post-consent), only SAEs related to a study-specific procedure will be collected. For all related AEs of moderate or severe intensity ongoing at the end of the study, follow-up will continue until the event has resolved to baseline severity, the event is assessed as stable by the Investigator, or the participant is lost to follow-up or the participant withdraws consent.
28. Study drug accountability will be performed via capsule count.
29. Dosing on non-study visit days will be self-administered at home. On "Drug Dispensation" clinic visits drug accountability will be completed for the bottle returned by the participant and the "in office dose administration" will be taken for that visit from the newly assigned bottle. Study drug can be administered with, or without food.
30. Participants will be administered the first dose in the clinic on Day 1. Doses on study visit days will also be administered in the clinic. Study drug can be administered with, or without food.

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

10.2 Visit Specific Procedures

10.2.1 Visit 1 / Screening

The Screening visit must be performed within 60 days prior to Day 1 – Baseline. The following procedures will be performed at the Screening visit:

- Obtain signed Informed Consent Form from both participant and caregiver or study partner and Responsible Person if applicable.
- Evaluate participant eligibility against study inclusion/exclusion criteria including administration of the Mini-Mental State Exam (MMSE) and Geriatric Depression Scale (GDS).
- Diagnostic confirmation by amyloid PET with florbetaben or another approved amyloid PET ligand. Diagnostic confirmation by a CSF sample collected at the screening visit lumbar puncture in place of amyloid PET will also be acceptable.
- Record demographic information, confirm ethnicity and obtain medical history.
- Perform Modified Hachinski exam.
- Perform complete physical examination (see Section 13.1.2 for details).
- Measure and record vital signs (see Section 13.1.3 for details).
- Perform 12-lead ECG (see Section 13.1.7 for details).
- Draw blood and prepare samples for APOE status. Apolipoprotein E (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 utilized to further understanding of response to CT1812. The genotyping is mandatory for participation in the study and the results will not be revealed to either the investigator or participant and caregiver.
- Optional whole blood sample collection for future biomedical research including potential genetic analyses (see Section 11.3).
- Draw blood and prepare samples for serum chemistry, hematology, viral serology, TSH, FSH (in women who had their last natural menses less than 24 months prior to screening

and who are not surgically sterile) and HbA1c (in known diabetics) (see Section 13.1.4 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). Should an abnormal lab remain abnormal on repeat the participant will be excluded.

- Collect blood sample for exploratory biomarker samples (see Section 11.2 for details).
- Collect serum sample on Days – 60 to -2 (see Section 11.2 for details and the laboratory manual). This sample should not be collected on the same day as the optional lumbar puncture and must be at least 24 hours prior to baseline.
- Collect urine sample for β-HCG pregnancy test for women who are not postmenopausal (last natural menses was less than 24 months ago) that are not surgically sterile).
- Collect urine sample for urinalysis (see Section 13.1.4 for details).
- MRI (unless an historical MRI is used Or CT scan due to contraindication of MRI, if approved by Medical Monitor).
- Record concomitant medications.
- Administer cognitive assessments and ADCS-ADL (see Section 12.1 for details).
- Administer C-SSRS (see section 13.1.6 for details).
- Once all above screening assessments are completed, complete and submit to the study Medical Monitor the participant eligibility form.
- Once the participant is approved by the Medical Monitor to proceed, if the participant elects to undergo the lumbar puncture, it must be performed at least 24 hours before the Baseline visit (see Section 11.5 for details). If the site is using analysis of LP results as a condition of eligibility, the results must be returned to the site and approval given by the Medical Monitor to proceed to the Baseline visit. The optional lumbar puncture must not be performed without Medical Monitor approval.
- If eligible, schedule participant to return to the clinic on Day 1 to initiate CT1812 dosing.

10.2.2 Visit 2 / Study Day 1 – Baseline

The following procedures will be conducted on Day 1:

Pre-dose Assessments:

- Confirm continued eligibility prior to dosing.
- Perform cognitive testing (see Section 12.1 for details).
- Perform MMSE.
- Perform complete physical examination (see Section 13.1.2 for details).
- Measure and record vital signs (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum cystatin C (see Section 13.1.5.1 for details).
- Collect blood samples for PK and exploratory biomarker analysis (see Section 11.2 for timing of sample collection).
- Collect urine samples for urinalysis (see Section 13.1.4 for details).
- Record any new medical conditions, AEs, or changes in medications since the Screening visit.
- Administer C-SSRS Since Last Visit version (see Section 13.1.6).
- Administer study drug with or without food.

Post-dose Assessments

- Record ECG ~ 1 - 2 hours post -dose (see Section 13.1.7 for details).
- Dispense study drug supply and instructions for at home dosing.

- For participants in Part A and B: Instruct participant to return for Day 3 visit including instructions to hold dose on morning of Day 3 visit.
- For participants in Part C: Instruct participant to return for Day 7 visit including instructions to hold dose on morning of Day 7 visit.

10.2.3 Visit 3 / Study Day 3 (Performed ONLY for participants enrolled in Part A and B)

The participant will return to the clinic.

Pre-dose Assessments:

- Perform brief physical examination (see Section 13.1.2 for details).
- Measure and record vital signs at pre-dose (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum cystatin C (see Section 13.1.5.1 for details).
- Collect blood samples for PK and exploratory biomarker analysis (see Section 11.2 for timing of sample collection).
- Collect urine samples for urinalysis (see Section 13.1.4 for details).
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability.
- Administer C-SSRS Since Last Visit version pre-dose (see Section 13.1.6).
- Administer Day 3 dose with or without food and return study drug bottles to participant, along with at-home instructions.

Post-dose Assessments:

- Instruct participant to return for the Day 7 study visit with instructions to hold dose on morning of Day 7 visit.

10.2.4 Visit 4 / Study Day 7

The participant will return to the clinic.

Pre-dose Assessments:

- Perform brief physical examination (see Section 13.1.2 for details).
- Measure and record vital signs (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum cystatin C (see Section 13.1.5.1 for details).
- Collect blood samples for PK and exploratory biomarker analysis (see Section 11.2 for timing of sample collection).
- Collect urine samples for urinalysis (see Section 13.1.4 for details).
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability.
- Administer C-SSRS Since Last Visit version (see Section 13.1.6).
- Administer Day 7 dose with or without food.

Post-dose Assessments:

- Instruct participant to return for the Day 14 study visit, including instructions to hold dose on morning of Day 14 visit.

10.2.5 Participant Visit 5 / Study Day 14

The participant will return to the clinic.

Pre-dose Assessments:

- Perform brief physical examination (see Section 13.1.2 for details).
- Measure and record vital signs (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum cystatin C (see Section 13.1.5.1 for details).
- Collect blood samples for PK and exploratory biomarker analysis (see Section 11.2 for timing of sample collection).
- Collect urine samples for urinalysis (see Section 13.1.4 for details).
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability.
- Administer C-SSRS Since Last Visit version (see Section 13.1.6).
- Administer Day 14 dose with or without food.

Post-dose Assessments:

- For participants in Part A and B: Instruct participant to return for the Day 21 visit with instructions to hold dose on morning of Day 21 visit.
- For participants in Part C, instruct participant to return for the Day 28 visit with instructions to hold dose on morning of Day 28 visit.

10.2.6 Participant Visit 6 / Study Day 21 (Performed ONLY for participants enrolled in Part A and B)

Pre-dose Assessments:

- Perform brief physical examination (see Section 13.1.2 for details).
- Measure and record vital signs at pre-dose (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability.
- Administer C-SSRS Since Last Visit version pre-dose (see Section 13.1.6).
- Administer Day 21 dose with or without food.

Post-dose Assessments:

- Instruct participant to return for the Day 28 visit with instructions to hold dose on morning of Day 28 visit.

10.2.7 Visit 7 / Study Day 28

The participant will return to the clinic.

Pre-dose Assessments:

- Perform brief physical examination (see Section 13.1.2 for details).
- Measure and record vital signs (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Collect urine samples for urinalysis (see Section 13.1.4 for details).

- Collect blood samples for PK and exploratory biomarker analysis (see Section 11.2 for timing of sample collection).
- Drug dispensation.
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability.
- Administer C-SSRS Since Last Visit version (see Section 13.1.6).
- Administer Day 28 dose with or without food.

Post-dose Assessments:

- Perform a 12 lead ECG – approximately 2 hours post-dose (see Section 13.1.7).
- Instruct participant to return for the Day 42 visit with instructions to hold dose on morning of Day 42 visit and to bring study drug with them.

10.2.8 Participant Visit 8 / Study Day 42

The participant will return to the clinic.

Pre-dose Assessments:

- Perform cognitive testing (see Section 12.1 for details).
- Perform MMSE.
- Perform brief physical examination (see Section 13.1.2 for details).
- Measure and record vital signs (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum cystatin C (see Section 13.1.5.1 for details).

- Collect urine samples for urinalysis (see Section 13.1.4 for details).
- Collect blood samples for PK and exploratory biomarker analysis (see Section 11.2 for timing of sample collection).
- Administer C-SSRS Since Last Visit version (see Section 13.1.6).
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability.
- Administer Day 42 dose with or without food.

Post-dose Assessments:

- Instruct participant to return for the Day 56 visit with instructions to hold dose on morning of Day 56 visit and to bring study drug bottle with them.

10.2.9 Participant Visit 9 / Study Day 56

The participant will return to the clinic.

Pre-dose Assessments:

- Perform brief physical examination (see Section 13.1.2 for details).
- Measure and record vital signs (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Collect urine samples for urinalysis (see Section 13.1.4 for details).
- Drug dispensation.
- Record any AEs.
- Record changes in medications.

- Conduct drug accountability on returned bottle.
- Administer C-SSRS Since Last Visit version pre-dose (see Section 13.1.6).
- Administer Day 56 dose.

Post-dose Assessments:

- Perform a 12 lead ECG – approximately 2 hours post-dose (see Section 13.1.7).
- Instruct participant to return for the Day 70 visit with instructions to hold dose on morning of Day 70 visit and to bring study drug with them.

10.2.10 Participant Visit 10 / Study Day 70

The participant will return to the clinic.

Pre-dose Assessments:

- Perform brief physical examination (see Section 13.1.2 for details).
- Measure and record vital signs at pre-dose (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Draw blood for coagulation testing (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum cystatin C (see Section 13.1.5.1 for details).
- Collect blood samples for PK and exploratory biomarker analysis. (see Section 11.2 for timing of sample collection).
- Collect urine samples for urinalysis (see Section 13.1.4 for details).
- Drug dispensation.
- Administer C-SSRS Since Last Visit version pre-dose (see Section 13.1.6).
- Record any AEs.

- Record changes in medications.
- Conduct drug accountability on returned bottle.
- Administer Day 70 dose with or without food.

Post-dose Assessments:

- Instruct participant to go to a local lab at Day 90 for serum collection.

10.2.11 Participant Study Day 90, Serum Collection

- Collect serum sample on Day 90 (+/- 2 days) (see Section 11.2 for details and the laboratory manual).

participant

10.2.12 Visits 11, 12 and 13 / Study Days 98, 126 and 154

Pre-dose Assessments:

- Perform cognitive testing – Day 98 only (see Section 12.1 for details).
- Perform MMSE – Day 98 only.
- If a participant and investigator are agreeable, an additional LP may be performed at least 24 hours before the Day 98 visit (see Section 11.5 for details).
- Perform brief physical examination (see Section 13.1.2 for details).
- Measure and record vital signs (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Draw blood for coagulation testing – Day 154 only (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum cystatin C (see Section 13.1.5.1 for details).

- Collect blood samples for PK and exploratory biomarker analysis (see Section 11.2 for timing of sample collection).
- Collect urine samples for urinalysis (see Section 13.1.4 for details).
- Administer C-SSRS Since Last Visit version (see Section 13.1.6).
- Drug dispensation.
- Administer dose with or without food.
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability on returned bottle.

Post-dose Assessments:

- Record 12-lead ECG – Day 98 only, approximately 2 hours post-dose (see Section 13.1.7 for details).
- On Day 154, Visit 13 instruct participant to go to a local lab at Day 172 for serum collection.

10.2.13 Participant Study Day 172, Serum Collection

Collect serum sample on Day 172 (+/- 2 days) (see Section 11.2 for details and the laboratory manual).

10.2.14 Participant Visit 14 / Study Day 182, End of Study Treatment Early Termination

This visit should be used as the Early Termination visit should the participant discontinue the study earlier than the Study Day 210 visit.

The participant will return to the clinic.

Pre-dose Assessments:

- Perform cognitive testing (see Section 12.1 for details).
- Perform MMSE.

- Perform complete physical examination (see Section 13.1.2 for details).
- Measure and record vital signs (see Section 13.1.3 for details).
- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum cystatin C (see Section 13.1.5.1 for details).
- Collect blood samples for PK and exploratory biomarker analysis (see Section 11.2 for timing of sample collection).
- Collect urine samples for urinalysis (see Section 13.1.4 for details).
- Optional: Perform lumbar puncture pre-dose (note: lumbar puncture may be performed pre-dose on Day 178, 179, 180 or 181 for ease of scheduling) (see Section 11.5 for details).
- Administer C-SSRS Since Last Visit version (see Section 13.1.6).
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability on returned bottle.
- Administer Day 182 dose with or without food.

Post-dose Assessments:

- Perform 12-lead ECG ~ 2 hours post-dose (see Section 13.1.7 for details).
- Perform MRI.

10.2.15 Study Day 210 – Safety Follow-up Visit

- Measure and record vital signs (see Section 13.1.3 for details).

- Draw blood and prepare sample for serum chemistry and hematology (see Section 13.1.4 for details).
- Draw blood and prepare sample for serum cystatin C (see Section 13.1.5.1 for details).
- Administer C-SSRS Since Last Visit version (see Section 13.1.7).
- 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 five half-lives of the interacting drug prior to administration of CT1812 and throughout the course of the study. Grapefruit juice should be avoided in the two weeks prior to dosing and throughout the course of 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.

10.3.1 Concomitant COVID-19 Treatment Restrictions

If a participant is treated for COVID-19 infection, the following recommendations would allow the participant to remain in the trial:

- Administration of the COVID-19 antiviral treatment Paxlovid™ (nirmatrelvir tablets, ritonavir tablets) will restrict concomitant administration of CT1812 because the ritonavir component is a potent CYP450 3A4 inhibitor. If a participant starts Paxlovid™ treatment, CT1812 dosing will be held for a total of twelve days starting with Paxlovid™ treatment initiation (Day 1). This time covers the five-day course of Paxlovid™ administration and

seven days to allow for regeneration of CYP450 3A4. CT1812 dosing as per protocol requirements will resume after the 12-day hold (Day 13). If a participant is prescribed Lagevrio™ (molnupiravir), the preclinical data indicates it is neither metabolized by CYP isoenzymes, nor does it interact with them. Therefore, no cessation of CT1812 is required if Lagevrio™ is employed.

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 420 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 -60 to-1 Exploratory Biomarkers only, to be collected with other blood work.
- Days 1, 7, 14, 28, 42, 70, 98, 126, 154, and 182: within 1.25 hours prior to dosing.
- Three serum samples at Screening (Days -60 to -2 days), Day 90 (± 2 days), and at Day 172 (± 2 days) (see Laboratory Manual for collection and handling details.) These samples will be collected at a local lab. The local lab will include onsite laboratory facilities for collection and processing.
- Optional lumbar punctures are not to be performed on the same day as the serum samples.

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.

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 (~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.

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.

Participants in Study COG0201 will not be identified by name in CRFs, study-related forms, study reports, or any related publications and this deidentification applies to all FBR specimens. Consistent with all participant 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 participant, 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, deidentified 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 deidentified 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 deidentified FBR specimens, genetic research data and associated clinical data derived from the deidentified 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 deidentified FBR specimens is withdrawn.

11.4 Pharmacokinetic Endpoints

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

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

11.5 Cerebrospinal Fluid

11.5.1 Collection

Lumbar punctures are optional in this study, however, a lumbar puncture at screening may be required for eligibility if a historical PET scan is not available. Cerebrospinal fluid (CSF) is being collected at screen and Day 182 in this study to evaluate CSF concentrations of CT1812 following repeated dosing of CT1812 and potential effects on CSF biomarkers (Aβ, tau, phospho-tau, NFL, neurogranin, synaptotagmin, SNAP25 or other exploratory biomarkers). If a participant and investigator are agreeable, an additional LP may be performed at least 24 hours before the Day 98 visit and prior to dosing on that day to evaluate CSF concentrations of CT1812 following repeated dosing of CT1812 and potential effects on CSF biomarkers (Aβ, tau66phospho-tau, NFL, neurogranin, synaptotagmin, SNAP25 or other exploratory biomarkers).

Diagnostic confirmation by additional 2 ml CSF sample collected at Screen Lumbar Puncture, in place of the amyloid PET, will be accepted.

CSF will be collected via lumbar puncture (LP). A qualified physician will perform the LPs.

Before commencing the LP, the clinician will ensure that there are no contraindications to the procedure.

Obtained CSF collected at optional Screen, optional Day 98 and optional Day 182 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 Screen are observed, they should be discussed with the Medical Monitor before randomizing the participant.

In the event of a failed lumbar puncture, the investigator may elect to attempt a repeat LP under fluoroscopy or to obtain the assistance of an anesthesiologist, if these options are available at their IRB approved facility.

If the LP at screening is unable to be performed, this will not preclude participation in the study, provided the participant otherwise qualifies based on amyloid PET criteria and meets all other eligibility criteria. If a screening LP is not performed, no other protocol-required LPs should be performed.

11.5.2 Timing of CSF Collection

Samples for the measurement of CT1812 levels in CSF will be collected via optional lumbar puncture during screening at least 24 hours before the Baseline visit, pre-dose, at least 24 hours prior to the Day 98 visit, and pre-dose, at least 24 hours prior to the Day 182 visit in order to not impact the cognitive assessments performed on those visit days. **Regardless of which day the optional LP is performed, study drug dosing for that day should be completed in the clinic, following the LP.**

Optional lumbar punctures are not to be performed on the same day as the serum samples.

11.5.3 Volume of CSF Collected

The volume of CSF collected from each participant during this study will be approximately 10-12 mL at each of the specified time points.

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-Cognition Subscale

The Alzheimer's Disease Assessment Scale-Cognition Subscale (Rosen 1984) is a widely used general cognitive measure in clinical trials of Alzheimer's disease. The ADAS-Cog was developed as an outcome measure for dementia interventions; its primary purpose was to be an index of

global cognition in response to antidementia therapies. The ADAS-Cog assesses multiple cognitive domains including memory, language, praxis, and orientation. For this study, an ADAS-Cog version that includes 13 items will be included however the original ADAS-Cog 11 version will be used as the principal exploratory clinical efficacy measure.

12.1.2 Geriatric Depression Scale

The Geriatric Depression Scale (GDS) (Sheikh and Yesavage 1986) is a depression screening assessment designed to identify depression in the elderly. The short-form 15-item questionnaire with Yes and No answers queries participant's energy, attitude toward life, mood, etc. Participants eligible for this study must not have a score above 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. Participants with a GDS >6 may be allowed to enroll if the investigator does not believe the participant is clinically depressed. Investigators must contact the Medical Monitor to discuss eligibility.

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

12.1.4 Neuropsychological Test Battery (NTB)

The Neuropsychological Test Battery will consist of the Trails A & B, Digit Span, Letter & Category Fluency tests (COWAT and CFT).

12.1.5 ADCS-Clinical Global Impression of Change (CGIC)

The Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC) was developed by the Alzheimer's Disease Cooperative study (ADCS) (Schneider et al 1997). The scale consists of a format with which a clinician may address clinically relevant overall change, including 15 areas under the domains of cognition, behavior, and social and daily functioning. The rater, at baseline, interviews the participant and caregiver/informant, using a form that comprehensively lists relevant symptoms potentially useful in judging change, and makes notes for future reference. There are few requirements to fulfill during the interview, but clinical assessment of mental status is to be made. By allowing raters to use the forms in an

unstructured manner, this scale may facilitate clinical judgments with face validity. At follow-up visits, the clinician uses a similar set of forms to re-interview the participant and caregiver/informant. The ADCS-CGIC rating is made on a 7-point scale similar to other global change scales, where a 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 ADCS-Activities of Daily Living (ADL)

The ADCS-ADL (Galasko, 1997) is a 23-item informant-administered assessment of functional impairment in terms of activities of daily living. Informants respond to 23 questions about the participant's involvement and level of performance across items representing daily living. The questions range from basic to instrumental activities of daily living. Each item is rated from the highest level of independent performance to complete loss. The total score range is from 0-78 with lower scores indicating greater functional impairment.

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.

13 Safety Assessments

13.1 Assessment of Safety

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

EVALUATION CRITERIA:

The DSMB will review the safety and tolerability of CT1812 of the participant enrolled in the study. They may also recommend additional safety and/or monitoring measures. Safety and tolerability measures:

- Adverse events.
- Serious Adverse Events.
- Physical and neurological examinations.
- Vital signs - body temperature, systolic and diastolic blood pressure, pulse rate and respiration rate.
- Electrocardiogram (ECG).
- Clinical laboratory tests: hematology, biochemistry, coagulation, serology and urinalysis.
- Columbia Suicide Severity Rating Scale (C-SSRS).

13.1.1 Adverse Events

Adverse events 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.

13.1.2 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.

13.1.3 Vital Signs

Vital signs include body temperature, systolic and diastolic blood pressure, pulse rate and respiration rate. Body temperature will only be recorded once daily. Blood pressure and pulse rate recordings will be made after the study participant 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.

13.1.4 Clinical Laboratory Tests

Hematology testing will include red blood cell count, erythrocyte mean corpuscular hemoglobin concentration (MCHC), erythrocyte mean corpuscular volume (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 Day 154 only, unless an optional LP is planned for Day 98, in which case coagulation testing should also be performed on Day 70 in preparation for the LP.

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.

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 one hour of blood draws for hematology and chemistry panels. Should not be first morning urine. Trace protein will be considered positive.

13.1.4.1 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.
- Thyroid stimulating hormone (TSH).
- Follicle-stimulating hormone (FSH) testing will be conducted in women who had their last natural menses less than 24 months prior to screening) and who are not surgically sterile.

- HbA_{1c} will be conducted in known diabetics.
- Folate and B12 are optional at discretion of the investigator if there is suspicion of deficiency.

13.1.4.2 Pregnancy Tests

A urine pregnancy test and FSH will be performed at screening to rule out existing pregnancy in women who had their last natural menses less than 24 months prior to screening and who are not surgically sterile. to document a postmenopausal state. 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.

13.1.5 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.

To date, hypercalcemia has not been identified in any CT1812 clinical studies. Serum creatinine and calcium levels will continue to be monitored during routine laboratory testing, but hypercalcemia is not considered to be a potential risk with CT1812 treatment.

13.1.5.1 Serum Cystatin C

Cystatin C is a low molecular weight (approximately 13.3 KD) protein, encoded by the CST3 gene, which is used as a biomarker of kidney disease. It is removed from the bloodstream by glomerular filtration in the kidneys. Cystatin C is suggested to be a better marker for GFR than the serum creatinine marker as its serum concentration is not affected by other factors such as age, gender and body mass. If kidney function and glomerular filtration rate (GFR) decline, the blood levels of cystatin C rise. Serum levels of cystatin C are a more precise test of kidney function (GFR) than serum creatinine levels (Dharnidharka 2002). Serial determinations of Cystatin C will be monitored during the trial to assess for integrity of kidney function and assist in determination whether any additional steps/studies are required.

13.1.6 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 qualified study clinician and appropriate action undertaken. The Screening/Baseline version will be used during the screening visit, and the Since Last Visit version will be used at all subsequent visits.

13.1.7 12-lead Electrocardiogram

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

13.1.8 MRI

The imaging specialist at the study site's MRI facility is responsible for determining if a subject is contraindicated from having this procedure. The following is a list of some common conditions that may preclude the subject from having MRI scans. However, this 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 standard set by the local IRB/IEC:

- Subjects who have a history of claustrophobia.
- Subjects 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.
- Subjects with MRI-incompatible cochlear implants.
- Subjects with spinal nerve stimulators.
- Subjects with an infusion pump.
- Subjects with metallic fragments in the eyes/orbits or in the vicinity of the brain or major neurovascular structures of the body.
- Subjects with an employment history that involves exposure to welding, unless absence of metallic fragments is documented by X-ray examination as per institutional practice. Subjects who have shrapnel at any place in their body.

In lieu of an MRI, a CT scan may be substituted if subjects are unable to tolerate an MRI or an MRI is contraindicated for medical reasons. Any proposed CT scan must be discussed with and approved by the Medical Monitor on a case-by-case basis.

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 considered related to the study drug or not.

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 the treatment period.

Treatment-emergent Adverse Events

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

Treatment Period

The treatment period is the period during which a participant receives study drug (i.e., first dose through last dose).

Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that results in death, is life-threatening, requires in-participant 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 course of 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 and transmitted to the Sponsor or designee.

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

Adverse events 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 clinically significant (in the Investigator's opinion) abnormal laboratory test values will be evaluated by the Investigator or a monitoring physician and will be treated and followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator and the Sponsor.

Adverse events that are unresolved at end of study 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 three phone messages left on separate days and one 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 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 end of study 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 SAE will be reported to NIH by the sponsor within 48 hours of the time when the Sponsor becomes aware of the event

14 Serious And Other Significant Adverse Events

14.1.1 Definition of a Serious Adverse Event

A serious adverse event 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. Over-night 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

Any SAE that occurs after a participant has entered the study, whether related to study drug or not, must be reported to the CRO immediately (within 24 hours) via e-mail at the address noted below. A completed Serious Adverse Event Report Form with as much detail as possible must be included with the email. The Investigator must report all SAEs occurring from the time the participant signs the ICF until 30 days after last treatment with the study drug.

Sponsor Representative and Contact Information for SAE Reporting:

[redacted]

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. Pregnancy in a study participant or in a partner of a study participant, occurring after randomization, although not an AE, is considered an immediately reportable event. It must be reported immediately by telephone and by emailing 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 emailing a completed SAE Report Form to the Sponsor within 24 hours of knowledge of the event.

The sponsor will monitor pregnancies of female participants and female partners of male participants.

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 participant 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.

An interim analysis will be performed once the first 24 participants have completed six months of dosing. Details of the interim analysis can be found in the statistical analysis plan.

15.2 Number of Participants Chosen for This Study

For this trial groups of 48 active-dosed participants per dose level are felt to give adequate sensitivity to detect adverse events. A sample size of 48 active-dosed participants for each dose level (100 mg, 300 mg) has 91% power to detect at least 1 occurrence of any drug-related AE with a true prevalence in the treated population of 5%. Additional participants may be added to replace participants with significant disruption to their visit schedule due to COVID or if there are unanticipated dropouts.

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

15.3 Analysis Populations

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

15.4 Data Analysis

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 Preferred Term and System, for each dose group (including placebo) and the incidence compared. Laboratory measures will be summarized by treatment group and time-point both as absolute values and as change from baseline, with

descriptive statistics summarizing each group and time point. Similar presentation will be used for vital signs and for ECG interval measurements, and changes from pre-treatment baseline.

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) or Independent Ethics Committee (IEC) 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. Requests for deviations must be made in advance with the Sponsor. 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 an Investigator responsibility.

16.1.3 Protocol Waivers

Protocol waivers will not be granted by the Sponsor in 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; local regulations or 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 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 its secure storage and safe handling throughout the study.

16.2.2 Institutional Review Board and Regulatory Approval

The study protocol and any amendments will be reviewed by an Independent Review Board. The IRB will 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 consulted 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.

The 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 is exposed to any study-related procedure, including screening tests for eligibility.

16.2.3 Participant and Caregiver Informed Consent

Potential participants and his/her caregiver will be informed about the study both verbally and in writing. Each participant and his/her caregiver 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 to ask any questions they have regarding the study. The caregiver will consent to providing information about the participant, managing drug administration, and

attending all clinic 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 their suitable designee will obtain a freely given, written consent from each participant and his/her caregiver after an appropriate explanation of the aims, methods, potential hazards, and any other aspects of the study which 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 to withdraw from it at any time, without any consequences for their further care and without the need to justify.

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

Each participant will be informed that a 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. Monitors must have direct access to source documentation in order to check the consistency of the data recorded in the Case Report Forms (CRF).

The Investigator will make available to the Monitor source documents, medical records, and source data necessary to complete CRFs. In addition, the Investigator will work closely with the Monitor as needed and 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, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Principal or Qualified Investigator generating the data.

Prior to the study initiation, the Sponsor will explain the protocol, Investigator's Brochure, and CRFs to Investigators. In addition, the Monitor will be available to explain applicable regulations and to 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 center 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, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study. All source documents must be reviewed by the PI and the sponsor (or designee) for compliance with GCP.

Study-specific data sheets may be used to document source information that would not normally be collected and documented in the routine management of the participant. Data sheets used for source documentation must be verified and signed by the Investigator or a delegated study site team member and must be stored and archived in the participant's clinic 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. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

During the study, a study monitor (CRA) will make site visits to review protocol compliance, compare eCRFs against individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements.

Electronic CRF 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 eCRFs for completeness, 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 participant to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or their 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. 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

Appendix B - Time-Restricted Medications

Appendix A – Prohibited Medications - Cytochrome P450 Drug Interaction Table

In addition to the medications detailed in Section 9.3 (Exclusion Criteria) 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 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 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.
- Nootropic drugs (except stable AD medications: acetylcholinesterase inhibitors and memantine)
- 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 by at least 6 hours (before or after) of CT1812 from participant medications which are sensitive or narrow therapeutic index substrates of CYP3A4, or substrates of P-glycoprotein (P-gp); Loperamide, Vinblastine or Talinolol.
- Any prior exposure to immunomodulators, anti Aβ vaccines, passive immunotherapies for AD (e.g. monoclonal antibodies) and/or exposure to BACE inhibitors within the past 30 days.

Below is a **partial** list of specific medications excluded in COG0201 unless otherwise noted. Most of these categories are represented in Exclusion 14. **This list may not be all-inclusive for specific categories of medications. Check with the Medical Monitor if there are questions.**

Barbiturates	**Nonbenzodiazepine Hypnotics**	**Antipsychotics**
Benzylbutylbarbiturate Butalbital Amobarbital Pentobarbital Secobarbital Sodium thiopental Phenobarbital **Benzodiazepines (use is acceptable if on a stable dose during the trial specifically used as a sleep aid)** 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** *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

From: 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 April, 2016].

Appendix B – Time-Restricted Medications

The following drugs must be separated from dosing of CT1812 (before or after) by 6 hours. If this is not feasible, the participant cannot participate in the study:

P-glycoprotein (P-gp) substrates
Loperamide
Talinolol