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# Protocol COG1201

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

ClinicalTrials.gov ID (NCT number): NCT05225415

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# A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2, 6-MONTH STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EXPLORATORY EFFICACY OF CT1812 IN SUBJECTS WITH MILD TO MODERATE DEMENTIA WITH LEWY BODIES

Protocol Number: COG1201

## Official Short Title:

Clinical Trial of CT1812 in Mild to Moderate Dementia with Lewy Bodies

## Clinical Study Protocol

**Version Number**: 3.0

**Issue Date:** 20 September 2022



## Confidentiality Statement:

## SIGNATURE PAGE FOR SPONSOR

Study No. COG1201

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Approved by the following:

[redacted] 9/22/2022

Anthony O. Caggiano, MD, PhD. Date
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## SIGNATURE PAGE FOR INVESTIGATOR

Study No. COG1201

Protocol Title: A randomized, double-blind, placebo-controlled, phase 2, 6-month study to evaluate the safety, tolerability and exploratory efficacy of CT1812 in subjects with mild to moderate Dementia with Lewy Bodies

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 PROTOCOL SYNOPSIS

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| **TITLE:** A randomized, double-blind, placebo-controlled, phase 2, 6-month study to evaluate the safety, tolerability, and exploratory efficacy of CT1812 in subjects with mild to moderate Dementia with Lewy Bodies |
| **SPONSOR:** Cognition Therapeutics Inc. |
| **PROTOCOL NUMBER:** COG1201 |
| **CLINICAL STUDY PHASE:** Phase 2 |
| **STUDY DRUG PRODUCT:** CT1812 |
| **STUDY OBJECTIVES:**<br><br>**Primary:**<br>• To assess the safety and tolerability of CT1812 as a treatment for mild to moderate Dementia with Lewy Bodies.<br><br>**Secondary:**<br>• To assess exploratory measures of efficacy at baseline, 3 months, and 6 months.<br>• To assess pharmacodynamic target engagement and potential biomarker evidence of disease modification.<br><br>**Exploratory:**<br>• To evaluate the efficacy of two doses of once-daily oral CT1812, administered for 6 - months in subjects with Dementia with Lewy Bodies.<br>• To evaluate the change in α-synuclein pathology in skin biopsies over the course of 6 months. |
| **STUDY DESIGN:**<br><br>This is a multi-center, randomized, double-blind, placebo-controlled, study in subjects with mild to moderate Dementia with Lewy Bodies. |

Subjects will be screened for eligibility by physical, laboratory, psychometric and neurologic examinations, and neuroimaging. Subjects may opt into collection of -pre-dose CSF. If a subject opts into CSF collection, this is to be completed along with screening procedures ≤ 42 days prior to randomization at Baseline/Day 1. After having met all inclusion criteria, and none of the exclusion criteria, subjects will be randomized equally to one of three treatment arms. On clinic visit days, study drug will be taken in the clinic after all baseline procedures have been conducted. For days where there are no clinic visits, subjects will ingest study drug each morning at home. Subjects and their caregivers/study partner will return to the clinic for repeat psychometric/neurologic testing, safety procedures and PK and PD sample collection at the intervals described below.

- Subjects will return to the clinic approximately every 2 weeks after their baseline visit until Day 70, then every four weeks until Day 182 (See Table 1). A safety follow-up visit will occur approximately 28 days after the end of treatment for all subjects that complete through Day 182.

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

**Safety Stopping Rules:**

Dosing may be terminated by the Sponsor at the recommendation of the DSMB (Data and Safety Monitoring Board) based on 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 subjects with the same or similar severe AE assessed as probably or possibly related to dosing with the investigational product.

Four or more subjects with the same or similar moderate AE which is possibly or probably related to dosing with investigational product.

The Sponsor and DSMB will review the available safety data and recommend whether dosing should continue, study drug administration should be terminated, or additional monitoring procedures or safety precautions need to be employed.

The study or a dose group may 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 subjects:

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 LFTs but has an elevation of ALT or AST >3 X ULN. These participants will have LFTs retested within 4 days after their last dose of study drug. If LFTs 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 SUBJECTS:**

Approximately 120 subjects randomized in a 1:1:1 ratio to 100 mg/day, 300 mg/day or placebo.

**TARGET POPULATION:**

**INCLUSION CRITERIA:**

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

1) Subjects or their Legally Authorized Representative (LAR) (or designee as applicable by local law) must provide written informed consent to the study procedures prior to any study procedures.
2) 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.
3) Men or women 50-85 years of age (inclusive), meeting criteria for probable DLB (as defined by the 4$^{th}$ report of the DLB Consortium- McKeith et al., 2017)
4) Men willing to comply with acceptable form of contraception or women of non-childbearing potential as defined below:
    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 childbearing 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 abstinence, birth control pills, or any double combination of: intrauterine device (IUD), male or female condom, diaphragm, sponge, and cervical cap.

5) MRI, or CT scan due to contraindication of MRI if approved by medical monitor) obtained during screening consistent with the clinical diagnosis of DLB and without findings of significant exclusionary abnormalities. 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.
6) MMSE 18-27 inclusive.
7) If receiving acetylcholinesterase inhibitors (AChEI), memantine or a combination of the two, must have been on a stable dose for at least 12 weeks before the screening visit, with no plans for dose adjustment during the study. Treatment-naive subjects can be entered into the study, but there should be no plans to initiate treatment with AChEIs or memantine from Screening to the end of the study.
8) Stable pharmacological treatment of any other chronic conditions for at least 30 days prior to screening.
9) Formal education of eight or more years.
10) Subjects living at home or in an assisted living facility.
11) Ability to swallow capsules.
12) Must consent to apolipoprotein E (ApoE) genotyping.
13) 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.
14) Must be able to complete all screening evaluations.

**EXCLUSION CRITERIA:**

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

1) Any neurological condition that may be contributing to cognitive impairment above and beyond those caused by the subject's DLB, including any co-morbidities detected by clinical assessment or MRI (or CT scan due to contraindication of MRI, if approved by medical monitor)
2) History of transient ischemic attacks or stroke within 12 months of screening.
3) Parkinsonian (extrapyramidal) features with Modified Hoehn and Yahr stage 4 or higher or any diagnosis of Parkinson's disease or parkinsonism that preceded cognitive decline by more than one year.
4) Hospitalization (except for planned procedures) or change of chronic concomitant medication within one month prior to screening.
5) Any major psychiatric diagnosis, including schizophrenia, bipolar disorder, and current major depressive disorder as per Diagnostic and Statistical Manual of Mental Disorders Fifth Edition.
6) Geriatric Depression Scale score >6. (Subjects with a GDS >6 may be allowable if the investigator does not believe the subject is clinically depressed. Investigators should contact the medical monitor to discuss eligibility.)
7) Subjects living in a continuous care nursing facility.
8) 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 the medical monitor on a case-by-case basis).
9) Screening MRI (or historical MRI or CT scan due to contraindication of MRI if approved by medical monitor) or historical MRI/CT scan, 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.

10) Clinical, laboratory findings or medical history consistent with:

a) Other primary degenerative dementia, (frontotemporal dementia, Huntington's disease, Creutzfeldt-Jakob Disease, Down syndrome, etc.).

b) Other neurodegenerative condition (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.).

11) 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 which requires the use of supplemental oxygen.

c) Renal insufficiency eGFR < 50 mL/min based on the CKD-EPI formula.

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 heart rate is below 50 beats/min or 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 $HbA_{1c}$ >7.5% in subjects with diabetes, only those subjects with known diabetes are required to get a $HbA_{1c}$ at screen.

12) 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.

13) Seropositive for human immunodeficiency virus (HIV).

14) 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).

15) 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

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

17) 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) 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) Stable use of clonazepam for at least 30 days as indicated for REM Sleep Behavioral Disorder (RBD)

c) Stable use of atypical antipsychotics (e.g., quetiapine, pimavanserin) for at least 30 days as indicated for delusions and hallucinations secondary to DLB.

18) 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).

19) Nootropic drugs except stable AD meds (acetylcholinesterase inhibitors or memantine).

20) 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.

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

22) 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.

23) 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.

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

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

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

**LENGTH OF STUDY:**

Each subject and caregiver will participate in a screening period of up to 42 days, followed by a double-blind treatment period of 182 (+/- 2) days and a follow up visit at day 210 (+/- 2) for a maximum 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 food.

**EVALUATION CRITERIA:**

A DSMB (Data and Safety and Monitoring Board) will oversee the safety of the trial. This committee will include independent experts, including an independent statistician. Safety data will be provided to the DSMB at quarterly intervals during the trial. The study clinician and study medical monitor will review trial safety data on a regular basis. 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 subjects 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, complete lipid panel.
- Columbia Suicide Severity Rating Scale (C-SSRS).

Efficacy Measures:

- Montreal Cognitive Assessment (MoCA).
- Cognitive Drug Research Battery (CDR).
- Clinician Assessment of Fluctuation (CAF).
- Epworth Sleepiness Scale (ESS).
- Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part III (MDS-UPDRS3).
- The Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC).
- ADCS-Activities of Daily Living (ADCS-ADL).
- Neuropsychiatric Inventory (NPI).

PK/PD Biomarkers:

- Pharmacokinetic: Plasma and CSF CT1812.
- Pharmacodynamic:
  - Plasma biomarkers such as Aβ, phospho-tau, α-synuclein, phospho-α-synuclein, α-synuclein oligomers will be examined. Other exploratory biomarkers may also be evaluated.
  - Optional CSF- CSF biomarkers such as Aβ, tau, phospho-tau, neurogranin, synaptotagmin, SNAP25 (synaptosomal-associated protein 25), Neuro Filament Light Chain (NFL), Aβ oligomers, α-synuclein, phospho-α-synuclein, α-synuclein oligomers will be examined. Other exploratory biomarkers may also be evaluated.

**STATISTICAL METHODS:**

**Analysis Populations**

The populations for analysis will include the enrolled population, safety population, intent-to-treat (ITT) population, pharmacokinetic (PK) population, and the pharmacodynamic (PD) population.

**Sample Size**

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

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

**Data Analysis**

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4 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 24 or higher). 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 WHO Drug Dictionary (enhanced) version March 2021 or higher. 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.

Exploratory analyses of potential change in α-synuclein pathology in skin biopsies over the course of 6 months will be conducted using appropriate statistical tests.

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

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# 2 GLOSSARY OF TERMS AND ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| (α-synO) | α-synuclein oligomers |
| Abeta/ Aβ | Amyloid beta |
| AChEI | acetylcholinesterase inhibitors |
| AD | Alzheimer's disease |
| ADCS-CGIC | Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change |
| ADCS-ADL | Alzheimer's Disease Cooperative Study – Activities of Daily Living |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AKI | acute kidney injury |
| 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 |
| CAF | Clinician Assessment of Fluctuation |
| CDR | Cognitive Drug Research Battery |
| $C_{max}$ | maximum concentration |
| CNS | central nervous system |

| Abbreviation | Description |
|---|---|
| CRF | Case report form |
| CSF | cerebrospinal fluid |
| $C_{ss}$ | steady state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CYP | cytochrome P450 |
| DDI | drug-drug interaction |
| dL | deciliter |
| DLB | Dementia with Lewy Bodies |
| DSMB | Data Safety Monitoring Board |
| ESS | Epworth Sleepiness Scale |
| ECG | electrocardiogram |
| EOS | end of study |
| F | Fahrenheit |
| FBR | Future Biomedical Research |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| GFR | glomerular filtration rate |
| 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 |

| Abbreviation | Description |
|---|---|
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IRB | Institutional Review Board |
| IKr | delayed rectifier potassium channels |
| kg | kilogram |
| KIM-1 | kidney injury molecule -1 |
| LAR | Legally Authorized Representative |
| LBD | Lewy body dementia |
| LP | lumbar puncture |
| LSM | Least square means |
| MAD | multiple ascending dose |
| MCHC | mean corpuscular hemoglobin concentration |
| MCI | mild cognitive impairment |
| MDS UPDRS Part III | Movement Disorder Society-United Parkinson's Disease Rating Scale Part III |
| MMRM | mixed model for repeated measures |
| MoCA | Montreal cognitive assessment scale |
| µg | microgram |
| mg | milligram |
| mL | milliliter |
| mM | milimole |
| mmol | millimolar |
| MMSE | Mini Mental State Exam |
| MRI | Magnetic Resonance Imaging |

| Abbreviation | Description |
|---|---|
| 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 |
| NPI | Neuropsychiatric Inventory |
| NSAIDs | nonsteroidal anti-inflammatory drugs |
| PD | pharmacodynamics |
| PDD | Parkinson's disease dementia |
| P-gp | p-glycoprotein |
| PK | pharmacokinetic |
| PRO | Patient reported outcome |
| QD | once daily |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| $t_{1/2}$ | terminal half life |
| TFF3 | trefoil factor 3 (an indicator of renal damage) |
| TK | toxicokinetic |
| $T_{max}$ | time to maximum concentration |
| ULN | upper limit of normal |
| WOCBP | Women of Childbearing Potential |
| Vd | volume of distribution |

# 3 INTRODUCTION

## *3.1 Background*

Dementia with Lewy bodies (DLB) is one of the most common causes of dementia. DLB, together with Parkinson's disease dementia (PDD), is a form of Lewy body dementia (LBD). Approximately 1.4 million Americans suffer from LBD, making it the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD). In addition to progressive dementia and motor deficits, patients with DLB endure a wide range of debilitating symptoms including cognitive fluctuations, recurrent visual hallucinations, and rapid-eye movement sleep behavior disorder. DLB patients have a short lifespan and rapid cognitive decline compared to AD and PDD patients. As a result, DLB is also associated with greater healthcare costs and caregiver burden than other forms of dementia. Unfortunately, no treatments are available to cure or slow the progression of DLB, making disease-modifying therapies for DLB a critical unmet medical need (Goldman 2020).

A hallmark of DLB is the accumulation of abnormal protein aggregates called Lewy bodies. Lewy bodies are primarily composed of α-synuclein fibrils and oligomers. Although the processes by which these aggregates form and spread through the brain are poorly understood, it is widely thought that the accumulation of α-synuclein is linked to synaptic dysfunction, neurodegeneration, and neuronal death.

Amyloid β (Aβ) is also linked to cognitive decline and markers of neurodegeneration in persons with DLB. While synucleinopathy is the defining feature of LBDs, amyloid plaques characteristic of AD are associated with the cognitive impairment in DLB. Approximately 80% of patients suffering from DLB have significant concentrations of Aβ-rich plaque deposits in their brains, in addition to α-synuclein pathology, at autopsy Aβ deposition correlates with cortical thinning, the severity of neurofibrillary tangles, and Lewy body inclusions. The combination of Aβ and α-synuclein deposition in PDD patients is associated with a shorter interval between development of dementia and onset of motor symptoms, as well as a shorter life span. Aβ deposition was linked to cognitive impairment in patients with DLB and PDD. Thus, Aβ-targeted therapies could limit cognitive decline in individuals with DLB.

The Sponsor (Cognition Therapeutics, Inc. [CogRx]) is developing CT1812, a first-in-class brain-penetrant small molecule that selectively clears toxic Aβ oligomers from the brain. CT1812 was identified through a phenotypic screening approach, in which it demonstrated an ability to prevent the binding and effects of Aβ oligomers (AβO) on mature neurons in culture (Izzo et al., 2014a; Izzo et al., 2014b). It displaces AβO bound to neuronal receptors at synapses and protects

synapses from toxic AβO effects. CT1812 accomplishes this by allosterically modulating a key protein regulator of oligomer receptors, the sigma-2 receptor complex, thus destabilizing the oligomer binding site and increasing the off-rate of AβO, which are then cleared into the cerebrospinal fluid (CSF). By inhibiting oligomer binding, CT1812 blocks downstream synaptotoxicity and restores memory to normal in aged transgenic mouse models of AD.

The sigma-2 receptor complex protein PGRMC1 also binds to α-synuclein monomer and oligomer in synaptosomes. Evidence suggests that α-synuclein oligomers (α-synO) are toxic to synaptic function and the process of autophagy, a vital cellular damage response mechanism. Importantly, CT1812 partially attenuates α-synO binding and internalization. By displacing both α-synO and AβO from neurons, CT1812 may relieve the synaptotoxic effects of these oligomers in DLB patients and is therefore a clinical candidate for this disease.

CT1812 is currently in clinical development for the treatment of AD. CT1812 has been demonstrated to be generally safe and well tolerated in Phase 1 trials in healthy volunteers (NCT02570997) and AD patients (NCT02907567). When administered once daily for 28 days to mild to moderate AD patients, CT1812 significantly reduces concentrations of synaptic degeneration markers in AD patient CSF (NCT02907567). The CT1812 mechanism of action has the potential to halt or slow cognitive decline, which will significantly alleviate the suffering of patients. This hypothesis is being tested in an ongoing six-month trial in mild to moderate AD patients (NCT03507790). The proposed clinical study in DLB patients will leverage these ongoing development efforts for AD and provide an opportunity to investigate a novel therapeutic candidate in an indication for which no disease-modifying treatments exist.



## *3.2 Nonclinical Experience*

### 3.2.1 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 Brochure. CT1812 has a high affinity at the target receptor sigma-2/PGRMC1 (S2) and is >100-fold selective for this receptor over other receptors and ion channels. Dose-limiting toxicities at higher doses in both species appear to be hypercalcemia and renal tubular damage, both of which are non-invasively monitored via measurement of serum calcium and urinary markers of renal tubular injury such as kidney injury molecule 1 (KIM-149,50).

*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.

### 3.2.2 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 drug-drug interaction (DDI) evaluations, clinically relevant DDI are suggested via CT1812 effects on CYP3A4 and P-gp.

### 3.2.3 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 mM. Mean $IC_{50}$ values of 26 mM and 0.6 mM 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.

### *3.3 Clinical Experience*

CT1812 has been administered safely with good tolerability in over 60 healthy volunteers in a placebo-controlled Phase 1a trial (COG0101). 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 subjects who had lumbar punctures. There was only one AE of severe intensity, being an SAE of upper respiratory tract infection, occurring in one subject 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 subject in the multiple dose cohort study developed a rash while on study drug. This subject showed improvement after discontinuing CT1812.

No evidence of renal toxicity was observed based on routine measures of renal function (serum creatinine, BUN) or cystatin C.

Four subjects in the MAD study showed an increase in liver function tests below 3X the upper limit of normal (including one subject 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 subjects.

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). Subjects were administered the probe drugs on Day -2 and PK evaluations performed. On Days 1 through 6, each subject 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 subjects with mild to moderate Alzheimer's disease. This study enrolled 19 subjects 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 subjects 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 subject 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.

A Phase 1 trial (COG0105) was a pilot study of Synaptic Vesicle Glycoprotein 2A (SV2A) PET ligand $^{11}$C-UCB-J to evaluate the effect of CT1812 treatment on synaptic density in subjects with Mild to Moderate Alzheimer's Disease. Eligible subjects were randomized in a 1:1:1 (300 mg CT1812: 100 mg CT1812: placebo) ratio. This was a 24-week treatment period, with an optional 24-week double blind extension period which was instituted after study startup; 23 subjects were dosed, 18 completed the original trial, and 13 rolled over to the double-blind extension.

Overall, CT1812 was generally well tolerated when delivered daily over a 24- or 48-week period in subjects with mild to moderate AD.

The most common TEAE in the CT1812 treatment arms was headache. Two subjects were withdrawn from the study due to TEAEs of liver function test increased (mild, probably related to

study treatment). In the CT1812 100 mg arm, two cases of post-dose neurological examination findings were assessed as clinically significant for coordination (bilateral ideomotor apraxia) and mental state (presence of delusions). There were 2 subjects (CT1812 100 mg and 300 mg treatment arms) with suicidal ideation as assessed by the C-SSRS.

A Phase 1 trial (COG0104) was a pilot study to evaluate the effect of CT1812 treatment on Aβ oligomer displacement into CSF in subjects with Mild to Moderate Alzheimer's Disease. Subjects were randomized to CT1812 560 mg/280 mg or placebo in a 1:1 ratio. A single dose was administered following insertion of an indwelling CSF lumbar catheter, and hourly CSF and plasma sampling was performed over a period of 24 hours to assess for oligomer displacement.

Overall, CT1812 was generally well tolerated in mild to moderate AD patients when delivered as a single dose of 560 mg.

There are several ongoing studies. COG0201 is a Phase 2 randomized, 6 month double-blind, placebo-controlled, parallel-group, study to evaluate the safety and efficacy of CT1812 in subjects with mild to moderate Alzheimer's disease with a target enrollment of 120 subjects. Subjects are randomized to one of three treatment arms (CT1812 at doses of 100 or 300 mg/d or placebo, n=40/group). To date 62 subjects have randomized. There have been several episodes of LFT elevation at various timepoints that have resolved following drug discontinuation or spontaneously. No SAEs have been considered drug-related.

COG0202 is a Phase 2 randomized, double-blind, placebo-controlled electroencephalography (EEG) study to evaluate the Effect of CT1812 Treatment on Synaptic Activity in Subjects with Mild to Moderate Alzheimer's Disease. This is a single-site, 16 subject, 29-day, 2-period crossover Phase 2 study of 1 dose level of CT1812 (300 mg) or placebo randomized in a 1:1 ratio. The purpose is to evaluate the efficacy of CT1812 in restoring synaptic function in subjects with mild to moderate Alzheimer's disease (AD) through quantitative EEG measurements, as reflected by relative theta power.

### *3.4 Rationale for Study*

CT1812 was shown to be safe and well tolerated in a study of healthy volunteers and in Phase 1 studies of subjects 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 DLB (the targeted clinical indication for CT1812). Randomized subjects 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

and potential change in α-synuclein pathology in skin biopsies over the course of 6-months are also included.

### *3.5 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) subjects. Transient increases in LFTS were noted in some subjects. Subjects were discontinued and LFTs returned to normal after discontinuation. In the phase 1 AD trial tolerability was also acceptable with no severe or serious adverse events observed at doses exceeding 300 mg/day.

## 4 STUDY OBJECTIVES

### *4.1 Primary Objectives*

- To assess the safety and tolerability of CT1812 as a treatment for mild to moderate Dementia with Lewy Bodies.

### *4.2 Secondary Objectives*

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

### *4.3 Exploratory Objectives*

- To evaluate the efficacy of two doses of once-daily oral CT1812, administered for 6 - months in subjects with Dementia with Lewy Bodies.

## 5 STUDY TYPE AND DESIGN

### *5.1 Study Type*

This is a multi-center, randomized, double-blind, placebo-controlled, study of 120 subjects with three dose arms: 100 mg/day and 300 mg/day of CT1812, vs placebo.

## *5.2 Endpoints*

### 5.2.1 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).

### 5.2.2 Efficacy Endpoints

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

### 5.2.3 Pharmacokinetic/Pharmacodynamic Endpoints

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

### *5.3 Study Design*

This is a multi-center, randomized, double-blind, placebo-controlled, study of 120 subjects has three dose arms: 100 mg/day and 300 mg/day of CT1812, vs placebo.

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

- Subjects will return to the clinic approximately every 2 weeks after their baseline visit until Day 70, then every four weeks until Day 182 (See Table 1). A safety follow-up visit will occur approximately 28 days after the end of treatment for all subjects that complete through Day 182.

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

#### 5.3.1 Re-screening Activities

Subjects who initially screen fail for this study may be permitted to re-screen. Re-screening may be permitted on a case-by-case basis following PI discussion with the Medical Monitor regarding whether a subject remains potentially eligible to participate in the study. A subject 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 subject must wait to re-screen for the study. The subject must meet all eligibility criteria at the time of re-screening in order to qualify for the study. Depending on the time from last screening, the medical monitor will determine what assessments need to be repeated.

# 6 STUDY DRUG

## *6.1 Supply and Storage*

Study drug formulated in hydroxypropyl methylcellulose (HPMC) capsules will be provided in bottles containing 65 capsules of 50 mg dose or 150 mg dose (based on freebase CT1812 fumarate salt) or its matching placebo. The bottles (original container) are induction sealed, child proof screw-top bottles with desiccant packs.

All study drug (unopened and opened bottles) will be stored refrigerated between 2°C to 8°C [35.6°F to 46.4°F] in their original bottles.

## *6.2 Packaging and Labeling*

The treatment label will include a study reference code, drug identifier, quantity of dosage units, and lot number at a minimum, as well as other pertinent information according to US FDA or 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.

## *6.3 Administration*

CT1812 or matching placebo will be administered orally as a single daily dose for 6 months. All subjects will take the first dose in the clinic with food and be observed for 2 hours. A single daily dose consists of 2 capsules of study drug. Two (2) capsules to be taken with 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, subjects 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 subject and the “in office dose administration” will be taken for that visit from the newly assigned bottle.

### 6.3.1 Safety Stopping Rules

Dosing may be terminated by the Sponsor at the recommendation of the DSMB (Drug 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 subjects with the same or similar severe AE assessed as probably or possibly related to dosing with the investigational product.
- Four or more subjects with the same or similar moderate AE which is possibly or probably related to dosing with investigational product.

The Sponsor and DSMB will review the available safety data and recommend whether dosing should continue, or if study drug administration should be terminated, or if additional monitoring procedures or safety precautions need to be employed.

The study or a dose group may also be terminated if the Sponsor and DSMB determine that any adverse event(s) are occurring that are intolerable or pose a medically unacceptable safety risk.

For individual subjects:

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 LFTs but has an elevation of ALT or AST >3 X ULN. These participants will have LFTs retested within 4 days after their last dose of study drug. If LFTs 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.



### *6.4 Accountability*

Subjects 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 subjects in accordance with this protocol.

Sites will keep a current log of drug accountability recording:

- Temperature logs for on-site storage refrigerator.
- What drug supply was received from the Sponsor.
- What drug supply was dispensed to each subject.
- 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.

### *6.5 Overdose/Toxicity Management*

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

### *6.6 Blinding, Randomization and Matching Subjects*

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 multiple digit individual study IDs for each arm, randomly assigned to either active or placebo treatment.

## 7 INVESTIGATORS, SITES AND DURATION

### *7.1 Investigator and Site*

This is a multi-center trial and will include up to approximately 30 qualified investigator sites.

### *7.2 Duration of Study*

Screening procedures will occur on Days -42 to -1. Eligible subjects will return to the clinic at Baseline/Day 1 visit for randomization into the trial. Daily dosing will continue through Day 182. The maximum total duration of subject participation in the study is up to 254 days including screening.

### *7.3 Use of Remote Measures in Extenuating Circumstances*

Study visits should be performed in the clinic as specified in Section 9 and Table 1 if possible. However, under extenuating circumstances, after consultation with and approval by the medical monitor, specific alternative measures may be implemented (e.g., if a subject is unable to travel to the study site due to safety concerns and/or local restrictions related to COVID-19 or other emerging events) in order to ensure the safety of subjects, site investigators, and site personnel while maintaining compliance with GCP and minimizing impact to the integrity of the study. The Screening Visit, Day 1 (Baseline), Days 28, 56, 70, 154 and 182 must be performed in the clinic.

The following remote measures may be implemented. Additional details can be found in the Study Reference Manual.

- Consent or reconsent may be obtained remotely in writing (or verbally, with follow-up written confirmation), as allowed by local regulations.
- Study drug may be shipped directly from the site to the subject, as applicable and as allowed by local regulations.
- Study visits (except for those noted above) may be conducted as in-home visits by qualified personnel.
- Study assessments to evaluate safety may be performed or overseen by qualified personnel conducting the in-home visits.

### *7.4 Termination of Study*

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

## 8 STUDY POPULATION

### *8.1 Number of Subjects*

Approximately 120 subjects will be randomized.

### *8.2 Inclusion Criteria*

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

1) Subjects or their Legally Authorized Representative (LAR) (or designee as applicable by local law) must provide written informed consent to the study procedures prior to any study procedures.

2) 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.

3) Men or women 50-85 years of age (inclusive), meeting criteria for probable DLB (as defined by the 4$^{th}$ report of the DLB Consortium, McKeith et al., 2017).

4) Men willing to comply with acceptable form of contraception or women of non-childbearing potential as defined below:

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 childbearing 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 abstinence, birth control pills, or any double combination of: intrauterine device (IUD), male or female condom, diaphragm, sponge, and cervical cap.

5) MRI (or CT scan due to contraindication of MRI, if approved by medical monitor) obtained during screening consistent with the clinical diagnosis of DLB and without findings of significant exclusionary abnormalities. An historical MRI (or CT scan), up to 1 year prior to screening, may be used as long as 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.

6) MMSE 18-27 inclusive.

7) If receiving acetylcholinesterase inhibitors (AChEI), memantine or a combination of the two, must have been on a stable dose for at least 12 weeks before the screening visit, with no plans for dose adjustment during the study. Treatment-naive subjects can be entered into the study, but there should be no plans to initiate treatment with AChEIs or memantine from Screening to the end of the study.

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

9) Formal education of eight or more years.

10) Subjects living at home or in an assisted living facility.

11) Ability to swallow capsules.

12) Must consent to apolipoprotein E (ApoE) genotyping.

13) 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.

14) Must be able to complete all screening evaluations.

### *8.3 Exclusion Criteria*

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

1) Any neurological condition that may be contributing to cognitive impairment above and beyond those caused by the subject's DLB, including any co-morbidities detected by clinical assessment or MRI (or CT scan due to contraindication of MRI, if approved by medical monitor).
2) History of transient ischemic attacks or stroke within 12 months of screening.
3) Parkinsonian (extrapyramidal) features with Modified Hoehn and Yahr stage 4 or higher or any diagnosis of Parkinson's disease or parkinsonism that preceded cognitive decline by more than one year.
4) Hospitalization (except for planned procedures) or change of chronic concomitant medication within one month prior to screening.
5) Any major psychiatric diagnosis, including schizophrenia, bipolar disorder, and current major depressive disorder as per Diagnostic and Statistical Manual of Mental Disorders Fifth Edition.
6) Geriatric Depression Scale score $\geq 6$. (Subjects with a GDS >6 may be allowable if the investigator does not believe the subject is clinically depressed. Investigators should contact the medical monitor to discuss eligibility.)
7) Subjects living in a continuous care nursing facility.
8) Contraindication to the MRI examination for any reason or, in lieu of an MRI, if the subject is unwilling or unable to undergo a CT scan, or if the CT scan is not approved by the medical monitor. (Note: 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 the medical monitor on a case-by-case basis).
9) Screening MRI (or CT scan due to contraindication of MRI if approved by medical monitor) or historical MRI/CT scan, 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.
10) Clinical, laboratory findings or medical history consistent with:

a) Other primary degenerative dementia, (frontotemporal dementia, Huntington's disease, Creutzfeldt-Jakob Disease, Down syndrome, etc.).

b) Other neurodegenerative condition (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.).

11) 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 which requires the use of supplemental oxygen.

c) Renal insufficiency eGFR < 50 mL/min based on the CKD-EPI formula.

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

e) Bradycardia (<50 beats/min.) or tachycardia (>100beats/min.). If heart rate is below 50 beats/min or 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 $HbA_{1c}$ >7.5% in subjects with diabetes, Only those subjects with known diabetes are required to get a $HbA_{1c}$ at screen.

12) 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.

13) Seropositive for human immunodeficiency virus (HIV).

14) 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).

15) 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

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

17) 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) 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) Stable use of clonazepam for at least 30 days as indicated for REM Sleep Behavioral Disorder (RBD)

c) Stable use of atypical antipsychotics (e.g., quetiapine, pimavanserin) for at least 30 days as indicated for delusions and hallucinations secondary to DLB.

18) 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).

19) Nootropic drugs except stable doses of acetylcholinesterase inhibitors or memantine.

20) 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.

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

22) 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.

23) 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 course of study.

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

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

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



## *8.4 Withdrawal of Subjects*

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

1) Withdrawal of subject consent.

2) Investigator determines that withdrawal from the study is in the best interest of the subject.

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 subject).

4) Any condition, injury, or disease that becomes apparent during the study and necessitates the termination of the subject from the study; including events detailed in Section 6.3.1-Safety Stopping Rules.

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

## *8.5 Subject Withdrawal Procedures*

### 8.5.1 Follow-up Procedures for Subjects Who Withdraw Prematurely

The date and the reason for study drug discontinuation or subject withdrawal from the study must be recorded on the Case Report Form. If the subject has received one or more doses of study

drug, and has not withdrawn consent, the subject shall return for the Early Termination Visit. The Early Termination Visit will occur within 2 weeks of the last dose.

### *8.6 Procedures for Replacing Subjects Who Withdraw Prematurely*

Subjects who withdraw from the study will not be replaced.

## 9 TREATMENT PLAN AND METHODS

### *9.1 Table 1, Schedule of Assessments*

| | | Visit 1 Screen Day -42 to -1 | Visit 2 Baseline Day1 | Visit 3 Day 14 (±2) | Visit 4 Day 28 (±2) | Visit 5 Day 42(±2) | Visit 6 Day 56 (±2) | Visit 7 Day 70 (±2) | Visit 8 Day 98 (±2) | Visit 9 Day 126 (±2) | Visit 10 Day 154 (±2) | Visit 11 Early Term Day 182 (±2) | Visit 12 Safety Follow Up Day (210 +2) 30 days post treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Informed consent | X | | | | | | | | | | | |
| 2 | Inclusion/Exclusion Criteria | X | X | | | | | | | | | | |
| 3 | Demography, Education History, Alcohol and Drug History & Medical History | X | | | | | | | | | | | |
| 4 | Confirm DLB diagnosis | X | | | | | | | | | | | |
| 5 | MMSE, GDS | X | | | | | | | | | | | |
| 6 | ApoE Status | X | | | | | | | | | | | |
| 7 | Screening laboratories | X | | | | | | | | | | | |
| 8 | Complete Physical Exam | X | X | | | | | | | | | X | |
| 9 | Brief Physical Exam | | | | X | | X | | X | | X | | |
| 10 | ECG (12-lead) | X | X | | X | | | | X | | | X | |
| 11 | MRI | X | | | | | | | | | | | |
| 12 | Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X |
| 13 | Safety labs (chem, hem, U/A) | X | X | X | X | X | X | X | X | X | X | X | X |
| 14 | PK blood sampling | | X | | X | | X | | X | | X | X | |
| 15 | PD plasma biomarkers | X | X | | X | | | | X | | | X | |
| 16 | Whole blood sample for future biological research | | X | | | | | | | | | | |
| 17 | Coagulation testing (PT/INR) | X | | | | | | | | | X | | |
| 18 | Optional Lumbar puncture | X | | | | | | | | | | X | |
| 19 | Optional CSF biomarkers | X | | | | | | | | | | X | |
| 20 | Syn-One Skin Biopsy | X | | | | | | | | | | X | |
| 21 | Pregnancy testing and FSH for women that are not surgically sterile | X | | | | | | | | | | | |
| 22 | C-SSRS | X | X | | X | | X | | X | | X | X | X |
| 23 | Training on the CDR System (x2) | X | | | | | | | | | | | |
| 24 | MOCA, CDR** ADCS-ADL, NPI, ADCS-CGIC, MDS-UPDRS Part III | | X | | X | | | | X | | | X | |
| 25 | CAF, ESS | X | X | | X | | | | X | | | X | |
| 26 | Modified Hoehn and Yahr | X | | | | | | | | | | | |
| 27 | Concomitant Meds | X | X | X | X | X | X | X | X | X | X | X | X |
| 28 | Adverse Events assessment | | X | X | X | X | X | X | X | X | X | X | X |
| 29 | Drug Accountability | | | X | X | X | X | X | X | X | X | X | |
| 30 | Dispense study drug | | X | | X | | X | | X | | X | | |
| 31 | Study drug given in clinic with food | | X | | X | | X | | X | | X | X | |

Key for Table 1, Schedule of Assessments

Abbreviations: DLB = Dementia with Lewy Bodies, PROs= Patient Reported Outcomes, MoCA = Montreal Cognitive Assessment Scale, CAF= Clinician Assessment of Fluctuation, ESS = Epworth Sleepiness Scale, MDS-UPDRS part III = Movement Disorder Society – United Parkinson's Disease Rating Scale Part III, ADCS-CGIC = The Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change, ADCS-ADL= The Alzheimer's Disease Cooperative Study - Activities of Daily Living, MMSE = Mini Mental State Exam, CDR= Cognitive Drug Research Battery, ApoE = apolipoprotein E, C-SSRS = Columbia Suicide Severity Rating Scale, ECG=electrocardiogram, GDS = Geriatric Depression Scale, PK=pharmacokinetic, NPI = Neuropsychiatric Inventory

1. Informed consent for subject and caregiver must be obtained prior to the subject undergoing any study-specific procedures.
2. Review of all criteria detailed in Sections 8.2 and 8.3
3. Record demographic information, confirm ethnicity and obtain medical history, drug and alcohol history, and education history.
4. Confirm DLB diagnosis in accordance with criteria based on the 4th report of the DLB Consortium (McKeith et al., 2017). See Appendix B.
5. Perform MMSE and GDS (see sections 11.1.8 and 11.1.7).
6. APOE genetic testing is required for all subjects (see section 9.2.1).
7. Screening labs include viral serology, TSH, FSH (for female subjects that are not surgically sterile) and HbA1c (for diabetic subjects only).
8. Complete physical examination = thorough examination of all body systems (including neurological exam), including height and weight. Weight should be measured on the same scale each time. Height measured only at screening (see section 12.1.2).
9. 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 12.1.2).
10. ECG to be conducted during screening period, and approximately one to two hours post-dose at specified visits (see section 12.1.7).
11. MRI (or CT scan due to contraindication of MRI if approved by medical monitor) performed at screen (if an historical MRI/CT scan is not used) (see section 12.1.8).
12. Vital Signs: body temperature, systolic and diastolic blood pressure, pulse rate and respiration rate
13. Safety labs – Blood Chemistry, Hematology and Urinalysis – Blood should be drawn within an hour of urine collection (see section 12.1.4).
14. Collect PK samples. See Section (see section 10.2) for timing of sample collection. See Laboratory Procedures Manual for sample handling.
15. Collect PD plasma biomarker samples. See Section (see section 10.2) for timing of sample collection. See Laboratory Procedures Manual for sample handling. If the PD sample cannot be collected prior to dosing on Day 1 baseline, the subject may not receive the first dose of study drug. Dosing will be delayed until this successful collection of this pre-dose baseline sample.
16. Whole blood sample collected for future biologic research (see section 10) See Laboratory Procedures Manual for sample handling
17. Coagulation testing includes prothrombin time (PT) and INR (see section 12.1.4).
18. Optional lumbar puncture: For subjects opting to undergo lumbar puncture, the procedure should be performed 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 within t–e – 2-day visit window minimally 24 hours prior to the Day 182 visit procedures (e.g., Day 181) and prior to dosing on that day (see section 10.3).

19. 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 10.3)
    CSF should be sent for cell counts, if such testing is available (white blood cells and red blood cells, with differential if either of the counts is abnormal), CSF protein, and CSF glucose at Screening and Day 182. If abnormalities are observed at Screening, they should be discussed with the medical monitor before randomizing the subject.
20. Subjects will undergo Syn-One Test™ punch biopsy during the screening period once all other screening procedures are complete with this procedure to occur at least 24 hours before the Baseline visit.
21. Pregnancy testing for female subjects that are not surgically sterile (see section 12.1.6)
22. C-SSRS Screening/Baseline version used at screening visit, Since Last Visit version used at all other visits and will be administered prior to dosing (see section 11.1.12).
23. The CDR system requires two training sessions to be conducted at least 30 minutes apart during the screening period. These trainings can be done at the screening visit or scheduled on separate days during the screening period.
24. The PROs/assessments will all be completed prior to dosing and procedures during the study visit (see section 11.1).
25. The CAF and ESS will be administered prior to dosing and procedures during the study visit (see section 11.1.2 and 11.1.3).
26. The Modified Hoehn and Yahr will be administered at screening prior to other procedures (see section 11.1.1).
27. All concomitant medications will be recorded from screening through Day 210 (see section 9.3).
28. 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 patient is lost to follow-up or the patient withdraws consent (see section 12).
29. Drug accountability must be performed at each visit with the exception of screening, baseline and day 210 (safety follow up) (see section 6.4).
30. Where drug is dispensed, the remainder of the previous bottle should be collected and retained by the site.
31. Study drug should be administered in clinic with food.

## *9.2 Visit Specific Procedures*

### 9.2.1 Visit 1 / Screening

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

- Subjects or their Legally Authorized Representative (LAR) (or designee as applicable by local law) must provide written informed consent to the study procedures prior to any study procedures. The caregiver must also provide written informed consent at this time.
- Evaluate subject eligibility against study inclusion/exclusion criteria.
- Confirm DLB diagnosis (see section Appendix B).
- Record demographic information, confirm ethnicity, alcohol and drug history, educational history and obtain medical history.
- Administer the Mini-Mental State Exam (MMSE) and Geriatric Depression Scale (GDS)
- Administer Modified Hoehn and Yahr
- Administer CAF and ESS
- Administer C-SSRS Screening/Baseline version
- Perform complete physical examination with neurological examination
- Measure and record vital signs
- Perform 12-lead ECG
- MRI (or CT scan due to contraindication of MRI, if approved by medical monitor), unless an historical MRI/CT scan is used.
- Draw blood and prepare samples for APOE status. Apolipoprotein E (ApoE) genotype is associated with the risk and age of onset of DLB. 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 subject and caregiver.
- Draw blood and prepare samples for coagulation testing (PT/INR), 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), Blood should be drawn within an hour of urine collection. Abnormal results at screening will exclude a subject 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 subject will be excluded. Collect blood sample for exploratory biomarker samples

- Collect blood samples for exploratory plasma biomarker analysis
- 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
- Record concomitant medications
- Once all above screening assessments are completed, complete the subject eligibility form located in the study manual and submit to the medical monitor.
- If a subject opts in to the lumbar puncture, the subject should undergo the lumbar puncture (CSF biomarkers to be collected during this procedure) at least 24 hours before the Baseline visit.
- Once all other screening activities are complete, the subject should undergo the Syn-One Test™ skin biopsy at least 24 hours prior to the baseline visit.
- During the screening period, subjects will need to be trained on how to use the CDR system. This is an automated battery amenable to measurement of cognitive deficits in patients with DLB (McKeith et al. 2000; Wesnes et al. 2014). It consists of 10 performance tasks measuring attention, working memory, episodic memory, and executive function, performed by the patient on a laptop. Two training sessions need to be conducted at least 30 minutes apart during the screening period to allow patients to become familiar with the procedure, reduce test anxiety, reduce learning effects, and produce a stable baseline. These trainings can be done at the screening visit or scheduled on separate days during the screening period.
- If eligible, schedule subject to return to the clinic on Day 1 to initiate CT1812 dosing.

### 9.2.2 Visit 2 / Study Day 1 – Baseline

The following procedures will be conducted on Day 1:

Pre-dose Assessments:

- Confirm continued eligibility prior to dosing.
- Administer MOCA, CDR, ADCS-ADL, NPI, ADCS-CGIC, MDS-UPDRS Part III, CAF and ESS
- Administer C-SSRS Since Last Visit version
- Perform complete physical examination with neurological examination
- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and hematology Blood should be drawn within an hour of urine collection.
- Collect whole blood sample for future biomedical research including potential genetic analyses
- Collect blood samples for PK and exploratory plasma biomarker analysis
- Collect urine samples for urinalysis
- Record any new medical conditions, AEs, or changes in medications since the Screening visit.
- Administer study drug with food.

Post-dose Assessments

- Record ECG ~1- 2 hours post-dose
- Dispense study drug supply and instructions for at home dosing.
- Instruct subject to return for Day 14 visit including instructions to bring study drug to the Day 14 visit

### 9.2.3 Visit 3 Study Day 14

The subject will return to the clinic for the following assessments:

- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and hematology. Blood should be drawn within an hour of urine collection.
- Collect urine samples for urinalysis,
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability, return study drug to the subject for continued dosing
- Instruct subject to return for Day 28 visit including instructions to hold dose on morning of Day 28 visit and to bring study drug with them

### 9.2.4 Visit 4 Study Day 28

The subject will return to the clinic for the following assessments:

Pre-dose Assessments:

- Administer MOCA, CDR, ADCS-ADL, NPI, ADCS-CGIC, MDS-UPDRS Part III, CAF and ESS
- Administer C-SSRS Since Last Visit version
- Perform brief physical examination
- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and hematology.) Blood should be drawn within an hour of urine collection
- Collect blood samples for PK and exploratory plasma biomarker analysis

- Collect urine samples for urinalysis
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability
- Collect remaining drug in old bottle.
- Administer Day 28 dose with food.

Post-dose Assessments:

- Record ECG ~1- 2 hours post -dose).
- Dispense study drug supply and instructions for at home dosing
- Instruct subject to return for Day 42 visit including instructions to bring study drug with them to the Day 42 visit

### 9.2.5 Visit 5 Subject Day 42

The subject will return to the clinic for the following assessments:

- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and Blood should be drawn within an hour of urine collection.
- Collect urine samples for urinalysis
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability, return study drug to the subject for continued dosing
- Instruct subject to return for Day 56 visit including instructions to hold dose on morning of Day 56 visit and to bring study drug with them

### 9.2.6 Visit 6 Study Day 56

The subject will return to the clinic.

Pre-dose Assessments:

- Administer C-SSRS Since Last Visit version
- Perform brief physical examination
- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and hematology Blood should be drawn within an hour of urine collection.
- Collect blood samples for PK
- Collect urine samples for urinalysis
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability
- Administer Day 56 dose with food.

Post-dose Assessments:

- Dispense study drug supply and instructions for at home dosing
- Instruct subject to return for Day 70 visit including instructions to bring study drug with them to the Day 70 visit

### 9.2.7 Visit 7 Study Day 70

The subject will return to the clinic for the following assessments:

- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and hematology Blood should be drawn within an hour of urine collection.

- Collect urine samples for urinalysis
- Record any AEs.
- Record changes in medications.
- Conduct drug accountability, return study drug to the subject for continued dosing
- Instruct subject to return for Day 98 visit including instructions to hold dose on morning of Day 98 visit and to bring study drug with them

### 9.2.8 Visit 8 Study Day 98

The subject will return to the clinic.

Pre-dose Assessments:

- Administer MOCA, CDR, ADCS-ADL, NPI, ADCS-CGIC, MDS-UPDRS Part III, CAF and ESS
- Administer C-SSRS Since Last Visit version
- Perform brief physical examination
- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and hematology. Blood should be drawn within an hour of urine collection.
- Collect blood samples for PK and exploratory plasma biomarker analysis
- Collect urine samples for urinalysis
- Record any AEs
- Record changes in medications
- Conduct drug accountability
- Collect any remaining drug in old bottle

- Administer Day 98 dose with food

Post-dose Assessments:

- Record ECG ~1- 2 hours post-dose
- Dispense study drug supply and instructions for at home dosing
- Instruct subject to return for the Day 126 Study Visit

### 9.2.9 Visit 9 Study Day 126

The subject will return to the clinic for the following assessments:

- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and hematology Blood should be drawn within an hour of urine collection.
- Collect urine samples for urinalysis
- Record any AEs
- Record changes in medications
- Conduct drug accountability, return study drug to the subject for continued dosing
- Instruct subject to return for Day 154 visit including instructions to hold dose on morning of Day 154 visit and to bring study drug with them

### 9.2.10 Visit 10 Study Day 154

The subject will return to the clinic.

Pre-dose Assessments:

- Administer C-SSRS Since Last Visit version
- Perform brief physical examination
- Measure and record vital signs

- Draw blood and prepare sample for serum chemistry and hematology. Blood should be drawn within an hour of urine collection
- Draw blood for coagulation testing
- Collect blood samples for PK
- Collect urine samples for urinalysis
- Record any AEs
- Record changes in medications
- Conduct drug accountability
- Administer Day 154 dose with food

Post-dose Assessments:

- Dispense study drug supply and instructions for at home dosing
- Instruct subject to return for the relevant Day 182 Study Visit Including instructions to hold dose on morning of next visit and to bring remaining study drug with them

### 9.2.11 Visit 11 Study Day 182 / Early Termination

The subject will return to the clinic.

- Within the -2-day window for scheduling assessments:
- If the subject opted into the lumbar puncture, perform lumbar puncture, and collect CSF a minimum of 24 hours before the Day 182 / Early Termination Visit
- The subject should undergo the Syn-One Test™ skin biopsy at least 24 hours prior to the Day 182 / Early Termination Visit

Pre-dose Assessments:

- Administer MOCA, CDR, ADCS-ADL, NPI, ADCS-CGIC, MDS-UPDRS Part III, CAF and ESS
- Administer C-SSRS Since Last Visit version

- Perform complete physical examination with neurological examination
- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and hematology. Blood should be drawn within an hour of urine collection.
- Collect blood samples for PK and exploratory biomarker analysis
- Collect urine samples for urinalysis
- Record any AEs
- Record changes in medications
- Conduct drug accountability) and collect all remaining drug from subject
- Administer last dose of study drug with food

Post-dose Assessments

- Record ECG ~1-2 hours post-dose
- Instruct subject to return for Day 210, safety follow up visit

Any subject that discontinues prematurely should complete Visit 11/Day 182 as an Early Termination visit. For subjects prematurely discontinuing, an early termination visit should be scheduled within 2 weeks of the last dose of study medication. If early termination visit is 3 or more days from the last dose, PK sampling should not be done. The remainder of the assessments below should be performed.

### 9.2.12 Study Day 210 / Safety Follow-up Visit

The subject will return to the clinic.

- Administer C-SSRS Since Last Visit version
- Measure and record vital signs
- Draw blood and prepare sample for serum chemistry and hematology

- Collect urine samples for urinalysis
- Record any AEs
- Record changes in medications

### *9.3 Concomitant Medications and Other Restrictions*

All medications mentioned in the exclusion criteria (Section 8.3) 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 are prohibited. 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. As noted in Appendix A, The P-glycoprotein (P-gp) substrate drugs loperamide and talinolol must be separated from dosing of CT1812 (before or after) by 6 hours. If this is not feasible, the subject cannot participate in the study.

Subjects 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. Subjects may be enrolled on stable doses (at least 30 days prior to screening) of atypical antipsychotics (e.g., quietapine, pimavanserin) and clonazepam; however, such subjects should be monitored for potential changes in symptoms related to the use of these medications as a result of possible drug-drug interactions. Dose adjustments to these medications may be considered if indicated.

#### 9.3.1 Concomitant COVID-19 Treatment Restrictions

- If a subject is treated for COVID-19 infection, the following recommendations would allow the subject to remain in the trial.
    - If the subject is prescribed Paxlovid ™, CT1812 dosing should be held coinciding with the day Paxlovid ™ is first administered. CT1812 should not be administered for the 5-day course of Paxlovid ™, in addition to 7 additional days (12 days total holding of CT1812) to allow for regeneration of the 3A4 isoenzyme. Normal dosing of CT1812 can then resume.

- If a subject 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.

# 10 SAMPLE COLLECTION

## *10.1 Blood Sampling for PK and Exploratory Plasma Biomarkers*

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

- Day 1 (baseline) whole blood sample collection for Future Biomedical Research (FBR) (pharmacogenomics) including potential genetic analyses (see section 10.2). Within 1.25 hours prior to dosing
- PK: Days: 1, 28, 56, 98, 154, and 182: within 1.25 hours prior to dosing.
- PD plasma biomarkers: Screening and Days: 1, 28, 98, and 182: within 1.25 hours prior to dosing
    - Note: If the PD sample cannot be collected prior to dosing on Day 1 baseline, the subject may not receive the first dose of study drug. Dosing will be delayed until this successful collection of this pre-dose baseline sample.



## *10.2 Handling, Shipping, Storage and Analysis of Blood Samples*

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

Subject blood specimens collected during this study may be stored for up to 15 years and used to further the knowledge of CT1812. The whole blood sample (~10 mL) for Future Biomedical Research (FBR) will be collected at Day 1 from subjects. 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 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.

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

Data derived from FBR specimen analysis on individual subjects 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.

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

## *10.3 Optional Cerebrospinal Fluid*

### 10.3.1 Collection

Cerebrospinal fluid (CSF) is being collected from subjects that consent to this optional procedure at screen and Day 182. This is being collected to evaluate CSF concentrations of CT1812 following repeated dosing of CT1812 and potential effects on CSF biomarkers [Aβ, tau, phospho-tau, neurogranin, synaptotagmin, SNAP25 (synaptosomal-associated protein 25), Neuro Filament Light Chain (NFL), Aβ oligomers, α-syn, phospho-α-syn, α-syn oligomers]. Other exploratory biomarkers may also be evaluated.

As an optional procedure, CSF will be collected via lumbar puncture (LP). A qualified clinician will perform the LPs.

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

Obtained CSF collected at Screen and 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 such testing is available. If abnormalities at screen are observed, they should be discussed with the medical monitor before randomizing the subject.

The investigator may in the event of a failed LP elect to attempt a repeat LP under fluoroscopy or CT scan or to obtain the assistance of an anesthesiologist, if these options are available at their IRB approved facility. Fluoroscopy or CT can be used during the first attempt if that is the standard of care at the institution, or the subject's anatomy suggests use of these measures would be prudent..

### 10.3.2 Timing of Optional CSF Collection

After a subject has consented to participate in the optional lumbar puncture, samples for the measurement of CT1812 levels in CSF will be collected via lumbar puncture at least 24 hours before the Baseline visit, pre-dose, at least 24 hours prior to the Day 182 visit (within the visit window) in order to not impact the cognitive assessments performed on those visit days. **Regardless of which day the LP is performed, study drug dosing for that day should be completed in the clinic, following the LP.**

### 10.3.3 Volume of Optional CSF Collected

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

### 10.3.4 Handling, Shipping, Storage and Analysis of Optional CSF

Please refer to the Laboratory Procedures Manual for the handling of CSF samples. Subject 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.

## *10.4 Syn-One Test™ Skin Biopsy*

Using biopsy kits provided by CND Life Sciences, Inc. (CND), punch biopsies will be taken to assess presence of phosphorylated alpha-synuclein. The biopsy will be performed during the screening period once all other screening procedures are complete with this procedure to occur at least 24 hours before the Baseline visit. Three-millimeter punch biopsies will be taken from the distal leg, the distal thigh, and the posterior cervical region after local anesthesia with 1% lidocaine. Given the national lidocaine shortage, suitable substitutes are lidocaine with epinephrine (1.0% or 2.0% lidocaine with 1:100,000 epinephrine), lidocaine without epinephrine, or bupivacaine.

Any subject with a history of reaction to local anesthetic will be exempt from the procedure.

Any subject that as previously had a Syn-One Test™ does not need to have this procedure repeated. Results from this biopsy will be entered into the eCRF by the site staff.

Any subject that was randomized into the study prior to the implementation of the Syn-One Test™ is exempt from this procedure.

### 10.4.1 Results from the Syn-One Test™

Subjects and study site staff will be blinded to the results of the Syn-One Test™ until after the subject has completed their participation in the study.

### 10.4.2 Handling, Shipping and Analysis of Syn-One Skin Test™

Please refer to the standard practice guidelines provided by CND Life Sciences, Inc. (CND), for detailed instructions for processing and shipping biopsy samples.

Samples will be placed in labeled tubes of Zamboni fixative and shipped overnight to CND. The skin biopsies will be dual immunostained for protein gene product 9.5 and phosphorylated alpha-synuclein.

# 11 SCREENING, EFFICACY AND SAFETY ASSESSMENTS

## *11.1 Affective and Cognitive Measures*

### 11.1.1 Modified Hoehn and Yahr

The Modified Hoehn and Yahr Scale (Yahr and Hoehn 1967) is used to measure how Parkinson's symptoms progress and to stage the level of disability. The scale includes stages 0 to 5 with 0 being no signs of disease and 5 indicating the person is wheelchair or bedbound and in need of assistance.

### 11.1.2 Clinician Assessment of Fluctuation (CAF)

Cognitive fluctuations are a core feature of DLB (McKeith et al., 2017) characterized by alterations in attention, alertness, and consciousness. The CAF is a screening questionnaire asked of an informant to capture frequency and duration of episodes to calculate a severity score (range 0-16 with higher scores representing more severe fluctuations (Walker et al., Sep 2000). The CAF is highly correlated with electrophysiologic measures and with computerized tests of cognitive performance (the CDR) (Walker et al., Apr 2000).

### 11.1.3 Epworth Sleepiness Scale (ESS)

Excessive daytime sleepiness is a common feature in DLB and is a major component of the symptoms of cognitive fluctuations (Ferman et al., 2004, 2014). The Epworth Sleepiness Scale (ESS) is a measure that assesses subjective sleepiness over the prior two weeks (Johns, 1991, 1997). The ESS is a scale that queries the likelihood of dozing (i.e., 0= no chance of dozing, 1= slight chance of dozing, 2= moderate chance of dozing or sleeping, 3= high chance of dozing) in eight different circumstances. An ESS score ≥10 is considered abnormal and consistent with excessive daytime sleepiness. DLB patients have higher mean ESS scores compared to dementia etiologies (DLB 13.9 ± 5, bvFTD 9.6 ± 8, AD 8.8 ± 5, $p<0.05$). An ESS score ≥10 was significantly more likely to occur in DLB compared to bvFTD or AD (DLB 81% vs. bvFTD 47% vs. AD 45%, $p<0.01$) (Boeve et al., 2019).

### 11.1.4 Cognitive Drug Research Battery (CDR)

Marked impairments in and fluctuation of attention are characteristic of dementia with Lewy bodies (DLB) (Ballard et al., 2001). Cognitive correlates of fluctuations may be best captured with computerized assessments of attention, reaction time, and vigilance. The CDR is a computerized battery that captures simple and choice reaction time, cognitive reaction time, vigilance, and power of attention (Ballard et al., 2002). The CDR has been used in dementia clinical trials for DLB (Wesnes et al., 2002) and AD (Simpson, Surmon, Wesnes, & Wilcock, 1991).. The CDR should be administered at the time points listed in the Schedule of Activities. Baseline visit should be schedule at a time of the day that is repeatable for the following visits. Additionally, two training sessions will be conducted at least 30 minutes apart during the screening period to allow patients to become familiar with the procedure, reduce test anxiety, reduce learning effects, and produce a stable baseline. These trainings can be done at the screening visit or scheduled on separate days during the screening period.

### 11.1.5 Movement Disorder Society – Unified Parkinson's Disease Rating Scale -Part III (MDS-UPDRS3)

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

### 11.1.6 Montreal Cognitive Assessment (MOCA)

The MOCA is a brief dementia screening assessment that covers nine domains (Nasredinne et al., 2005). It has been validated for use in detecting cognitive impairment in Parkinson's disease (Gill, Freshman, Blender & Ravina, 2008), Parkinson's disease dementia (Biundo et al., 2016 & Wang et al., 2013) and DLB (Biundo et al., 2016). The MOCA has a 0-30 range with lower scores meaning more impairment. During 1-year of follow-up, the percentage of relative standard deviation was 21% and the MOCA may be better suited to study cognitive change in DLB than tests such as the Mini Mental State Exam (Folstein, Folstein & McHugh, 1975) due to the lack of ceiling and floor effects (Biundo et al., 2016).

### 11.1.7 Geriatric Depression Scale

The Geriatric Depression Scale (GDS) (Sheikh & 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 subject's energy, attitude toward life, mood, etc. Subjects 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 Dementia, therefore it is important to rule out participation of those who may be suffering from acute depression. Subjects with a GDS >6 may be allowable if the investigator does not believe the subject is clinically depressed. Investigators should contact the medical monitor to discuss eligibility.

### 11.1.8 Mini Mental State Exam

The Mini Mental State Exam (MMSE) (Folstein et al., 1975, 2010) is a brief, screening instrument often used in clinical trials to assess dementia severity. The MMSE assess several aspects of memory and cognitive functioning including orientation, attention, concentration, comprehension, recall, and praxis. The total possible score is 30, with high scores indicating less impairment.

### 11.1.9 Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) (Cummings et al., 1994, 1997) was developed to assess for common behaviors associated with dementia. A structured interview of the caregiver is used to assess 12 behavior domains including delusions, hallucinations, dysphoria, euphoria, anxiety, agitation/aggression, apathy, irritability/lability, disinhibition, and aberrant motor behavior as well as sleep and appetite/eating disorders. Screening questions are asked regarding behaviors which have occurred over the past month. If an affirmative response is given, more detailed information is acquired pertaining to the frequency on a 4-point scale and severity on a 3-point scale of the behavior. There is also a 6-point caregiver distress scale.

### 11.1.10 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 subject 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 patient 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.

### 11.1.11 ADCS-Activities of Daily Living (ADL)

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

### 11.1.12 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 et al., 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.

# 12 SAFETY ASSESSMENTS

## *12.1 Assessment of Safety*

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



**EVALUATION CRITERIA:**

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

- 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).

### 12.1.1 Adverse Events

Adverse events will be captured from the start of study-related procedures at Visit 1 (including diagnostic assessments or signing of ICF) and during the 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.

### 12.1.2 Physical and Neurological Examinations

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.

### 12.1.3 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 patient has been at rest for ≥5 minutes in either a sitting or a semi-supine position. As part of vital signs, the subject's weight should be measured.

### 12.1.4 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.

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.

In instances where either the AST or ALT are 2x the ULN these tests will be repeated and documented as an unscheduled visit.

Blood draws should occur within 1 hour of urine collection.

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. It should not be first morning void. Trace protein will be considered positive.

### 12.1.5 Screening Laboratory Tests

The following will be performed to confirm subject 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

### 12.1.6 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. Subjects 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.

### 12.1.7 12-lead Electrocardiogram

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

### 12.1.8 MRI

The imaging specialist at the study site's MRI facility is responsible for determining if a patient is contraindicated from having this procedure. The following is a list of some common conditions that may preclude the patient 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 for an MRI 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).

## *12.2 Adverse Events*

### 12.2.1 Definitions

**Adverse Event**

An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigation subject 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 subject 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-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the study drug or is an important medical event. See Section 14 for more details on SAEs.

#### 12.2.2 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) 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".

*12.2.2.1 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 subject 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.

*12.2.2.2 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).

*12.2.2.3 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 subject'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 subject'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.

*12.2.2.4 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.

*12.2.2.5 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**

### 12.2.3 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 subject.

Any subject 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 subject 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).

Subjects 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 subject'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.

# 13 Serious And Other Significant Adverse Events

## *13.1 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 subject 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 subject 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 subject 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 subject 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 subject 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.

### 13.1.1 Serious Adverse Event Reporting by the Investigator to the Sponsor

Any SAE that occurs after a subject 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 subject signs the ICF until 30 days after last treatment with the study drug.

**Sponsor Representative and Contact Information for SAE Reporting:**

safety.fax@synteract.com

### 13.1.2 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 subject is stabilized.
- No further information is available.
- Sponsor assessment has been finalized.

## *13.2 Reporting and Follow-up of Pregnancy*

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

## *13.3 Expedited Reporting of Serious Adverse Events*

### 13.3.1 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.

### 13.3.2 Expedited Reporting

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

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

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

*13.3.2.1 Timelines*

Fatal or life-threatening serious unexpected and 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 and 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.

# 14 Statistical Methods

## *14.1 General Overview of the Statistical Analysis Plan*

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term “descriptive statistics” refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. Individual data for all enrolled subjects will be presented in data listings, sorted by dosing arm and subject.

The statistical analyses will be conducted with the SAS® software package version 9.4 or higher.
The remainder of this section is a summary of the planned statistical analyses for the efficacy and safety data collected in this protocol. Full details of these analyses will be included in the statistical analysis plan (SAP). The SAP will be developed and finalized before database lock and will include the subject populations for analyses, and procedures for accounting for missing data.



## *14.2 Sample Size*

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

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

## *14.3 Analysis Populations*

The populations for analysis will include the enrolled population, intent-to-treat (ITT) population, safety population, pharmacokinetic (PK) population, and the pharmacodynamic (PD) population.

The enrolled population represents all subjects that signed the informed consent form. This

population is being used for presentation of subject disposition, as well as for all listings.

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

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

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

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

### *14.4 Data Analysis*

#### 14.4.1 Initial Subject Characteristics

Demographic data and baseline characteristics will be listed for each subject and summarized descriptively by treatment group.

#### 14.4.2 Safety Analyses

Adverse events (AEs) will be assessed by the investigator for severity and will be coded for summarization using Medical Dictionary for Regulatory Activities (MedDRA® Version 24 or higher). The occurrence of AEs will be summarized by treatment using MedDRA system organ classification, preferred terms, and severity. Separate summaries of AEs, serious AEs, AEs related to study drug, and AEs leading to study discontinuation will be summarized by Preferred Term and System Organ Class.

Concomitant medications will be coded using WHO Drug Dictionary (enhanced) March 2021 or higher and summarized.

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.

Results from Columbia Suicide Severity Rating Scale (C-SSRS) will be listed.

Results from physical exam findings will be listed.

### 14.4.3 Efficacy Analyses

Continuous efficacy endpoints will be summarized by treatment group and time-point using descriptive statistics as both absolute values and change from baseline. Differences between treatment groups will be assessed using a mixed model for repeated measures (MMRM) with treatment group, time-point, and a treatment group by time-point interaction as fixed effects, subject as a random effect, and baseline value as a covariate. The difference between the combined CT1812 group versus placebo at each time-point will be estimated based on the least square means (LSM) from the MMRM. The pairwise comparisons of each CT1812 group and placebo will be created in a similar manner.

Each efficacy endpoint will be listed.

### 14.4.4 Other Analyses

Pharmacokinetic and exploratory biomarker analyses will be described in the SAP.



## 15 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 subject or the science of the study. Administrative amendments will be submitted to the Institutional Review Board (IRB) for information only. The Sponsor will ensure that acknowledgement is

received and filed. Otherwise, an amendment will be classed as a substantial amendment and will be submitted to the appropriate Regulatory Authorities and the IRB for approval.

#### 16.1.2 Protocol Deviations

No deviations from the protocol are anticipated. Should a non-anticipated protocol deviation occur, the Sponsor must be informed as soon as possible. All deviations and the reasons for the deviation will be documented by the Investigator or designated staff. Reporting of protocol deviations to the IRB and in accordance with applicable Regulatory Authority mandates is 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; 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 Study 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 subject information sheet and the Informed Consent Form (ICF), their updates (if any), and any written materials given to the subjects. 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 subject is exposed to any study-related procedure, including screening tests for eligibility.

### 16.2.3 Subject and Caregiver Informed Consent

Potential subjects and his/her caregiver will be informed about the study both verbally and in writing. Each subject and his/her caregiver will be provided with a written subject 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 subject, managing drug administration, and attending all clinic visits. The written subject information sheet and ICF must be in a language that the subject 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 subject 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 subject to participate. The Investigator will explain that the subject 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 subject and caregiver before exposure to any study-related procedure, including screening tests for eligibility. The subject and caregiver will receive copies of the written subject information sheet and the ICF and caregiver consent form.

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

If new safety information becomes available and results in significant changes in the risk to benefit assessment, the written subject information sheet will be revised or updated where necessary. Under these circumstances, all subjects (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 subjects 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. 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 Study Monitor source documents, medical records, and source data necessary to complete CRFs. In addition, the Investigator will work closely with the Study 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 Study 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, subject 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 subject. 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 subject'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 subject profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data.

During the study, a study monitor (CRA) will make site visits to review protocol compliance, compare eCRFs against individual subject'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 subject 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 subject 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, subject 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

Appendix B - Key Criteria from Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium.

# Appendix A – Prohibited Medications

The following medications are restricted within 4 weeks of screening visit and during the course of 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 with the exception of atypical antipsychotic agents e.g., quetiapine and pimavanserin (see exclusion criteria and concomitant medications sections)
- 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:
  At the discretion of the investigator, low dose lorazepam or another anxiolytic may be administered as per local standard of care prior to MRI scan or optional lumbar puncture. At the discretion of the investigator. Note neurocognitive testing should not be done within 24 hours of administration of conscious sedation.
- Nootropic drugs (except stable doses of acetylcholinesterase inhibitors or memantine), e.g., Gingko biloba extract.
- Moderate to strong inhibitors or inducers of CYP3A4. See the table below 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 (Prohibited only for subjects participating in optional lumbar puncture)
- Digoxin
- Inability to separate dosing by at least 6 hours (before or after) of CT1812 from subject medications which are sensitive or narrow therapeutic index substrates of CYP3A4, or substrates of P-glycoprotein (P-gp); Loperamide, Vinblastine or Talinolol. See Section 9.3.1 for handling of Paxlovid ™ administration for COVID infection during the course of study.
- Any prior exposure to immunomodulators, anti Aβ vaccines, anti Aβ passive immunotherapies for (e.g monoclonal antibodies) and/or exposure to BACE inhibitors within the past 30 days.

Below is a **partial** list of specific medications excluded unless otherwise noted. **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 | | Olanzapine |
| Butalbital | Eszopiclone | Clozapine |
| Amobarbital | Zaleplon | Thiothixene |
| Pentobarbital | Zolpidem | Haloperidol |
| Secobarbital | Zopiclone | Fluphenazine |
| Sodium thiopental | | Prochlorperazine |
| Phenobarbital | **Opioids** | Trifluoperazine |
| | | Loxapine |
| **Benzodiazepines** | Tramadol | Asenapine |
| | Tapentadol | |
| Diazepam | Morphine | **Other** |
| Estazolam | Hydromorphone | |
| Flunitrazepam | Oxymorphone | Glutethimide |
| Lorazepam | Oxycodone | sodium oxybate (Xyrem®) |
| Midazolam | Hydrocodone | |
| Nitrazepam | Methadone | **First Generation Antihistamines** |
| Oxazepam | Propoxyphene | |
| Triazolam | Meperidine | |
| Temazepam | Fentanyl | *Should not be used within 24 hours of cognitive testing* |
| Chlordiazepoxide | Codeine | Diphenhydramine |
| Alprazolam | Carfentanil | Dimenhydrinate |
| Clobazam | | Doxylamine |
| Clorazepate | | Promethazine |
| Etizolam | | 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 – Key Criteria from Diagnosis and Management of Dementia with Lewy Bodies: Fourth consensus report of the DLB Consortium.

Probable DLB can be diagnosed if:
a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or
b. Only one core clinical feature is present, but with one or more indicative biomarkers.

Core clinical features (The first 3 typically occur early and may persist throughout the course.)

- Fluctuating cognition with pronounced variations in attention and alertness.
- Recurrent visual hallucinations that are typically well formed and detailed.
- REM sleep behavior disorder, which may precede cognitive decline.
- One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Indicative biomarkers

- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
- Abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy.
- Polysomnographic confirmation of REM sleep without atonia.



McKeith IG et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017 Jul 4;89(1):88-100