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Protocol COG0108

Official Title: A Phase 1, Open-Label Study to Assess the Absorption, Metabolism, Excretion, and Mass Balance of a Single Oral Dose of [14C]-CT1812 in Healthy Adult Male Subjects

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Clinical Protocol

A Phase 1, Open-Label Study to Assess the Absorption, Metabolism, Excretion, and Mass Balance of a Single Oral Dose of [^{14}C]-CT1812 in Healthy Adult Male Subjects

Celerion Project No.: CA35306

Sponsor Project No.: COG0108

Good Clinical Practices (GCP) Statement

This study is to be performed in full compliance with the protocol, GCP, and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Name	Description
15Dec2021 [redacted]	Final Protocol, Amendment 1 The amendment is being written to change the blood collection tube size from 5 mL for plasma CT-1812 and M6 pharmacokinetic assessment to 6 mL and from 1 mL for whole blood total radioactivity assessment to 2 mL due to commercial availability of the blood collection tubes. Therefore the total blood volume collected in the study will increase from 392 mL to 428 mL. Table 1 in Section 13.4 Blood Volume Drawn for Study Assessments was updated accordingly. In addition, Section 6 Study Events Flow Chart was revised to correct the following discrepancies: • Changed the footnotes of columns EOT/ET and FU to the correct footnotes; i.e., c and d, respectively. • Updated footnote "m" to be consistent with Section 13.3.6 Fecal Sampling and Processing.
02Dec2021 by [redacted]	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase 1, Open-Label Study to Assess the Absorption, Metabolism, Excretion, and Mass Balance of a Single Oral Dose of [^{14}C]-CT1812 in Healthy Adult Male Subjects

CELERION CLINICAL SITE AND PRINCIPAL INVESTIGATOR:

[redacted]

Signature: _____ Date: _____

PI's name:_____

Signature Page for VV-57813 v2.0

Reason for signing: Approve	[redacted]gator Date of signature: 17-Dec-2021 14:05:21 GMT+0000

Signature Page for VV-57813 v2.0

A Phase 1, Open-Label Study to Assess the Absorption, Metabolism, Excretion, and Mass Balance of a Single Oral Dose of [^{14}C]-CT1812 in Healthy Adult Male Subjects

SPONSOR AND SPONSOR'S REPRESENTATIVE:

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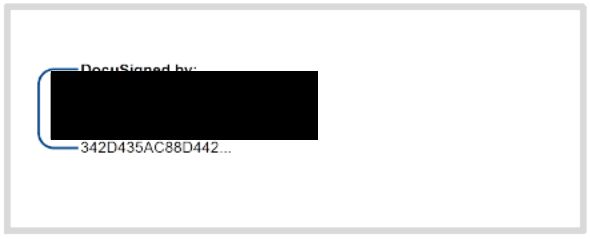
Signature: 

Date: 12/16/2021

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3 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact for Serious Adverse Event Reporting	[redacted]
Protocol Author	[redacted]
Certified Clinical Laboratory	[redacted]
Bioanalytical Laboratory for Pharmacokinetics, Total Radioactivity Analysis, and Metabolite Profiling	[redacted]
Bioanalytical Laboratory for Metabolite Identification	[redacted]

Pharmacokinetic and Statistical Analyses

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5 SYNOPSIS

Compound:	CT1812
Clinical Indication:	Alzheimer's Disease (AD) dementia or prodromal mild cognitive impairment (MCI) due to AD
Study Phase and Type:	Phase 1 – absorption, metabolism, excretion, and mass balance study
Study Objectives:	**Primary objectives:** • To determine the route(s) of elimination and the overall mass balance of CT1812 following a single oral dose of [^{14}C]-CT1812 administered in healthy adult male subjects. • To quantitate total radioactivity (TRA) concentration equivalents in whole blood, plasma, urine, and feces following a single oral dose of [^{14}C]-CT1812 administered in healthy adult male subjects. • To characterize the PK profile of CT1812 and its metabolite, M6, in plasma following a single oral dose of [^{14}C]-CT1812 administered in healthy adult male subjects. • To characterize the metabolite profile of CT1812 in plasma, urine, and feces following a single oral dose of [^{14}C]-CT1812 in healthy adult male subjects and identify the chemical identity of each metabolite accounting for more than 10% of circulating TRA. **Secondary objectives:** • [redacted]
Summary of Study Design:	This is an open-label, single-dose study to assess the absorption, metabolism, excretion, and mass balance for [^{14}C]-CT1812. Subjects will be admitted to the [redacted] on Day -1 and discharged from the [redacted] following completion of 168 hours postdose procedures (Day 8). On Day 1, subjects will receive a single oral dose of 300 mg CT1812 (2 capsules) with a microtracer dose of ~1 µCi [^{14}C]-CT1812 (1 capsule). Whole blood, plasma, urine, and fecal samples will be

	collected over 168 hours postdose (Day 8) to measure total radioactivity (all samples), CT1812 and M6 metabolite concentrations (plasma), and for metabolite profiling and identification (plasma, urine, and fecal samples). [redacted] will attempt to contact all subjects who received the study drug (including subjects who terminate early) using their standard procedures approximately 14 days after dosing to determine if any adverse event (AE) has occurred since the last visit.
Number of Subjects:	Eight (8), healthy, adult male subjects will be enrolled.
Dosage, Dosage Form, Route, and Dose Regimen:	Study drug will be supplied as capsules of nonradiolabeled CT1812 (powder) and capsules of radiolabeled [^{14}C]-CT1812 (powder/suspension). The study treatment will consist of 3 capsules: 2 capsules containing CT1812 [redacted] and 1 capsule containing ~1 µCi [^{14}C]-CT1812 ([redacted]®). Capsules will be administered orally under fasting conditions on Day 1 at Hour 0 with approximately 240 mL of water. Additional water, up to 50 mL, is permissible to facilitate swallowing multiple capsules.
Key Assessments:	**Mass Balance** TRA recovery and the percent of the radioactive dose excreted in the urine and feces will be assessed. Mass balance will be calculated as a sum of the percent of the TRA recovered in urine and feces relative to the administered radioactive dose minus any radioactive dose lost due to emesis (if any occurred). **Pharmacokinetics:** The following PK assessments will be evaluated, as appropriate: • TRA concentration equivalents ar[redacted] • TRA concentration equivalents [redacted]

	• TRA concentration equivalents [redacted] • CT1218 and M6 concentrations in plasma [redacted] • Ratio of plasma CT1812 to TRA fo[redacted]. **Metabolite profiling:** CT1812 metabolite profiling will be performed on plasma, urine, and fecal samples. The percent of dose represented by each of the metabolites, if any, will be calculated using the radioactive concentration equivalent data combined with the metabolite profiling data. The percentage of each identified metabolite, if any, to TRA in the plasma will be estimated based on plasma metabolite profiling data. Metabolites accounting for more than 10% of circulating TRA will be identified. **Whole blood to plasma partitioning ratio:** The percentage of TRA in whole blood relative to plasma will be estimated at each time-matched determination of TRA in whole blood and plasma. **Safety:** Safety will be monitored through AEs, 12-lead electrocardiograms (ECGs), vital sign measurements, clinical laboratory tests, physical examinations, ophthalmic examinations, and Columbia-Suicide Severity Rating Scale (C-SSRS). AEs will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

6 STUDY EVENTS FLOW CHART

Study Procedures [a]	S [b]	Study Days																				EOT /ET [c]	FU [d]
Days →		-1	1											2		3	4	5	6	7	8		
Hours →		C-I [e]	P	0	0.5	1	2	3	4	6	8	12	16 [f]	24	36	48	72	96	120	144	168		
Administrative Procedures																							
Informed Consent	X																						
Inclusion/Exclusion Criteria	X	X																					
Medical History	X																						
Safety Evaluations																							
Full Physical Examination	X																						
Abbreviated Physical Examination		X																					
Symptom-driven Physical Examination [g]													X										
Height	X																						
Weight	X	X																					
C-SSRS Questionnaire	X																					X	
12-Lead ECG	X		X [h]											X								X	
Vital Signs (PR, BP, RR, and T)	X		X [h]											X		X						X	
Hem, Serum Chem [i], and UA	X	X												X								X	
Ophthalmic Examinations	X																					X	
Urine Drug and Alcohol Screen	X	X																					
Cotinine Screen	X																						
HIV/Hepatitis Screen	X																						
AE Monitoring	X	X																					X
ConMed Monitoring	X	X																					
Study Drug Administration/ PK																							
[^{14}C]-CT1812 Dosing				X																			
Blood for Plasma CT1812 and M6 PK			X [j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood for Whole Blood TRA			X [j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood for Plasma TRA			X [j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood for Plasma Metabolite Profiling and identification			X [j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine for Metabolite Profiling and TRA [k]			X [j]		X								X										
Feces for Metabolite Profiling and TRA [l]			X [m]		X								X										

Study Procedures [a]	**S** [b]	**Study Days**																				**EOT /ET** [c]	**FU** [d]
Days →		**-1**	1											2		3	4	5	6	7	8		
Hours →		**C-I** [e]	P	0	0.5	1	2	3	4	6	8	12	16 [f]	24	36	48	72	96	120	144	168		
Other Procedures																							
Confinement in the CRU		X																					
Visit	X																						

a For details on Procedures, refer to Section 13.

b Within 28 days prior to dosing.

c To be performed at discharge from CRU (EOT) or prior to ET from the study.

d The CRU will attempt to contact all subjects who received the study drug (including subjects who terminate the study early) using their standard procedures approximately 14 days after dosing to determine if any AE has occurred since the last study visit.

e Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU. Subjects may be admitted earlier than Day -1 for COVID-19 testing not related to study protocol as per CRU requirements.

f The 16-hour time point may be on Day 1 or Day 2 depending on the time of dosing on Day 1.

g Symptom-driven physical examinations may be performed at the PI's or designee's discretion.

h To be performed within 24 hours prior to dosing.

i Samples for serum chemistry will be obtained following a fast of at least 8 hours-at the time of screening, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to when the serum chemistry sample is taken.

j Predose samples should be stored separately, away from the postdose samples to avoid cross contamination.

k Urine collection for analysis of TRA and metabolite profiling will be conducted at the following intervals: predose, 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours postdose, and every 24 hours until Day 8 (168 hours postdose).

l Fecal collection for the analysis of TRA and metabolite profiling will be conducted predose and in 24-hours intervals for 168 hours postdose.

m The predose fecal sample is to be obtained within 48 hours prior to dosing. Predose samples should be stored separately, away from the postdose samples to avoid cross contamination.

Abbreviations: AE = Adverse event(s), BP = Blood pressure, C-I = Check-in, C-SSRS = Columbia-Suicide Severity Rating Scale, Chem = Chemistry, ConMeds = Concomitant medication, COVID-19 = Coronavirus Disease-2019, CRU = Clinical research unit, ECG = Electrocardiogram, EOT/ET = End-of-Treatment or early termination, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, P = Predose, PI = Principal Investigator, PK = Pharmacokinetics, PR = Pulse rate, RR = Respiratory rate, S = Screening, T = Temperature, TRA = Total radioactivity, UA = Urinalysis.

7 ABBREVIATIONS

Pharmacokinetic parameter abbreviations and definitions may be found in Sections 13.3.2, 13.3.5, and 13.3.7

µCi	Microcurie
Abeta	Beta amyloid
AD	Alzheimer's Disease
AE	Adverse event
AMS	Accelerator mass spectrometry
BMI	Body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central nervous system
COVID-19	Coronavirus Disease-2019
CRF	Case report form
[redacted]	[redacted]
CSF	Cerebrospinal fluid
%CV	Coefficient of variation
CYP	Cytochrome P450
ECG	Electrocardiogram
EDTRS	Early Treatment Diabetic Retinopathy Study
F	Absolute bioavailability
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPBCD	Hydroxypropyl-β-cyclodextrin
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
KRBC/PL	Ration of partitioning between red blood cells and plasma
LLOQ	Lower level of quantitation
MAD	Multiple ascending dose
MCI	Mild cognitive impairment
n	Sample size
No.	Number
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
PO	Per os; oral
QA	Quality Assurance
QD	Once daily
QTcF	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing, corrected QT interval by Fredericia.
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SEDDS	Self-emulsifying drug delivery system
TEAE	Treatment-emergent adverse events
TRA	Total radioactivity
US	United States
USA	United States of America

8 INTRODUCTION

8.1 Background

CT1812 is an oral formulation in current development for the treatment of Alzheimer's Disease (AD) dementia and Mild cognitive impairment (MCI) due to AD. Cognition Therapeutics, Inc., has discovered that oligomeric forms of the beta amyloid 1-42 (Abeta) protein binds specifically and reversibly to a single, saturable receptor site on neuronal synapses (Izzo 2014a; Cahill et al, 2016) and that brain penetrant small molecules that act as antagonists at the sigma-2 receptor can both prevent oligomer binding in vitro and displace bound oligomers from these receptor sites and stop synapse loss in vitro. Currently, there are no approved products for the treatment of MCI or established AD that function by blocking the binding and pathological activity of soluble Abeta oligomers. CT1812 is a brain penetrant drug designed to selectively target and displace the oligomeric form of Abeta (Abeta oligomers) bound to neuronal receptors at synapses by a new and differentiated mechanism of action. CT1812 not only prevents and displaces binding of amyloid-beta oligomers to neuronal synapses, but was shown to prevent and restore Abeta oligomer-induced synapse loss and reverses downstream alterations in neuronal trafficking in cultured rat neurons.

8.1.1 Nonclinical

[redacted]

8.1.2 Clinical

Phase I clinical trial for single ascending dose (SAD) and multiple ascending dose (MAD) studies have been completed in healthy subjects (study number COG0101). This double-blind, placebo controlled, ascending dose, multi-cohort trial included a food effect arm at the 90 mg dose.

Pharmacokinetics

In the SAD part, each cohort consisted of 6 subjects who received a single dose of CT1812 and 2 subjects who received matching placebo. Following single-dose administration (10 mg, 30 mg, 90 mg [fed and fasted], 180 mg, 450 mg, and 1120 mg), Tmax was reached in 60 to 90 minutes. The median t½ ranged from 11.1 to 14.0 hours (coefficient of variance [%CV] from 14% to 39%) across the dose groups with no dose dependence. Individual t½ ranged from 7.1 to 19.3 hours. Plasma exposure (AUCinf) and Cmax were approximately dose proportional across 2 orders of magnitude. No appreciable differences in plasma AUC or Cmax were observed between fed and fasted cohorts given a 90 mg oral dose. No gender differences were detected.

In the MAD part, each cohort consisted of 8 subjects who received CT1812 and 2 subjects who received matching placebo once daily (QD) for up to 14 days. Following multiple-dose administration (280 mg and 560 mg [younger cohorts] and 560 mg [older cohort]), PK profiling was performed on samples drawn from participants on Day 3 and Day 14 of dosing. Tmax ranged from 0.5 to 4.0 hours with the median Tmax for each cohort ranging from 0.88 to 2.0 hours. The t½ ranged from 8.93 to 12.3 hours with no linear correlation with dose. Individual t½ ranged from 6.14 to 21.7 hours. Plasma exposure (AUC0-24,) and Cmax were approximately dose-proportional and showed modest accumulation compared to QD dosing in the SAD part. The healthy elderly subjects dosed with 560 mg of CT1812 for 14 days demonstrated mean plasma concentrations of CT1812 between that of the 560 mg and the 840 mg doses in healthy young subjects. Mean Cmax was 31% above, Tmax similar, and AUC0-24 was 58% above the 560 mg dose parameters in normal healthy young subjects. Cerebrospinal fluid (CSF) was drawn from participants in the 560 mg and 840 mg cohorts 23 hours after dosing on Days 7, 8, or 9 for determination of CT1812 concentrations. Subjects dosed with 560 mg had a mean (± standard deviation) CSF concentration of 8.01 (4.26) ng/mL. Subjects in the 840 mg cohort had a mean CSF concentration of 23.3 ng/mL. These results indicate CNS penetration of CT1812 following oral dosing. Multiple dose exposure of CT1812 corresponded to more than 20 times the expected minimum therapeutic dose (34 to 38 mg) while CSF analysis indicated that brain concentrations exceeded the minimum target expected to improve memory (>80% receptor occupancy).

Following CT1812 (90, 280, and 560 mg) administered QD to patients with mild to moderate AD for 28 days, preliminary PK analysis showed evidence of modest accumulation of CT1812 as indicated by plasma AUC values. Both AUC0-24 and Cmax estimates were higher on Day 28 than on Day 1, and pre-dose trough concentrations increased across the

dosing course, with steady-state levels generally attained by Day 7. Systemic exposure, as indicated by Cmax and AUC, increased approximately proportionally with dose; variability in PK parameters was high, with some individual values overlapping between dose groups. Lumbar punctures were performed on Day 28, 24 hours after the Day 27 dose. Mean steady-state predose CT1812 concentrations in the CSF increased with dose. Neurogranin levels, a synaptic damage marker that increases in the CSF of AD patients, significantly declined relative to screening levels in CT1812-treated patients by 17.6% compared to placebo-treated individuals, this finding is consistent with CT1812's mechanism of action and preclinical studies demonstrating the drug can prevent Abeta oligomer-induced synapse loss and return synapse number to normal. Synaptotagmin-1 levels, synaptic damage biomarker that is elevated in the CSF of AD patients, significantly declined by a mean of 63% in CT1812-treated patients on Day 28 compared to baseline values, whereas placebo treated values increased by a mean of 24%.

A fixed-sequence study to examine the effect of multiple-dose CT1812 administration on standard probes of CYP2C19 (Omeprazole), CYP2C9 (Tolbutamide), CYP2D6 (Dextromethorphan), and CYP3A4/5 (Midazolam) activity in healthy adult subjects was also conducted. Based on the small magnitude of change in PK parameters observed in this study for the isoenzymes CYP2D6 and CYP3A4, clinically meaningful interactions are unlikely except possibly for narrow therapeutic range CYP3A4 substrates. No significant interaction was observed for isoenzymes CYP2C19 and CYP2C9.

Safety

Single dose administration up to 1120 mg, and 14-day administration up to 840 mg/day were well tolerated. Adverse events reported to date have all been mild to moderate in severity, (with the exception of one serious adverse event [SAE] considered unrelated to study drug) and have mainly 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 one SAE following the 840 mg/day dose of the MAD investigation, an upper respiratory infection believed to be unrelated to study drug. There was one subject in the MAD investigation who developed a rash and showed improvement after discontinuing CT1812. Four (4) subjects in the MAD investigation showed an increase in liver function tests (LFTs) below 3 times the upper limit of normal (including one subject receiving placebo). These abnormalities resolved after the 14-day dosing period, with the exception of one subject who had an isolated rise of LFTs at Day 35. Lymphocytopenia was observed, at approximately Day 14 of dosing, in all cases it resolved with continuation of treatment except in one subject whose resolution was associated with drug cessation related to liver function test elevation. These cases were isolated to the 560 mg QD dose, and in 75% of cases were associated with non-specific malaise, which may suggest a stress-related response.

Refer to the Investigator's Brochure (IB) for detailed background information on CT1812 (IB, Version 5.0).

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

The disposition of any drug in the body is controlled by physiological processes affecting absorption, metabolism, and excretion. The most efficient and well-established approach to elucidate these processes is a mass balance study in which the drug dose is administered in radiolabeled form, followed by collection and analysis of different biological matrices for radioactivity using liquid scintillation count and determination of drug concentration using conventional liquid chromatography-tandem mass spectrometry and metabolite profile using liquid chromatography with radiometric detection. The PK, metabolic pathways, and routes of elimination of CT1812 have been evaluated in vitro and in vivo in preclinical species (IB, Version 5.0). In this study the TRA of [^{14}C]-CT1812 will be measured using accelerator mass spectrometry (AMS).

Additionally, the PK profile of CT1812 in humans has been evaluated in healthy subjects (in a SAD and MAD investigation [Study COG0101]). Currently, the biotransformation/metabolism and excretory pathways of CT1812 in humans are not known.

The aim of this study is to characterize the plasma exposure, clearance pathways, and excretion routes for CT1812 and its metabolites in healthy male subjects following oral administration. Based on data in healthy subjects, the average t½ of CT1812 following single oral administration in the fasted state for doses from 10 mg to 1120 mg (Study COG0101) ranged from 11.1 to 14 hours, thus, it is expected that more than 90% of the radioactivity should be eliminated within 168 hours postdose, the sampling duration in this study.

8.2.2 Rationale for the Dose Selection

The single dose consisting of 300 mg (~1 µCi) [^{14}C]-CT1812 oral capsules chosen for this study is expected to provide sufficient mass of drug, and sufficient specific radioactivity (using AMS analysis), for detection and analysis of parent drug and/or metabolites in whole blood, plasma, urine, and fecal samples, as applicable, with CT1812 exposures that are in a safe and pharmacologically active range. Single doses of CT1812 (10 mg – 1120 mg), administered previously to healthy subjects appeared to be safe and well tolerated with the majority of events reported being mild in severity.

The effective dose of radiation for a human male following a single oral administration of 1 µCi of [^{14}C]-CT1812, was calculated to be 0.036 mrem. The effective dose is <20 x than what the average American receives in one day from natural background radiation (NCRP, 2009). Estimated radiation doses from a 1 µCi oral administration of [^{14}C]-CT1812 are below the radiation dose limits set forth in 21 Code of Federal Regulations (CFR) 361 for the whole body, active blood-forming organs, lens of the eye, gonads, and any other organ. The extrapolated 0.036 mrem effective dose represents 0.0012% of the FDA limit (3000 mrem to the whole body, active blood-forming organs, lens of the eye, or gonads). Based on these results, a dose of 1 µCi of [^{14}C]-CT1812 can be administered to a human and be recognized as safe under FDA guidelines (CFR Title 21, 2019).

8.3 Risks and/or Benefits to Subjects

Based on the clinical safety data available from healthy subject studies, the oral dose of CT1812 administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study, as it is a single dose administered according to the dosing recommendations in the IB and was found to be safe and well tolerated (IB, Version 5.0).

The estimated total radiation dose and the tissue specific exposure from a single oral administration of ~1 µCi [^{14}C]-CT1812 are below the radiation dose limits set forth by the Food and Drug Administration (FDA) (see Section 8.2.2). Thus, the health risk resulting from exposure to radiation in the study drug is very low.

The safety monitoring practices employed by this protocol (i.e., AE questioning, 12-lead ECG, vital signs, clinical laboratory tests, ophthalmic examinations, and C-SSRS) are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs (TEAEs).

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

9 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To determine the route(s) of elimination and the overall mass balance of CT1812 following a single oral dose of [^{14}C]-CT1812 administered in healthy adult male subjects.	TRA recovery and the percent of the radioactive dose excreted in the urine and feces.
To quantitate TRA concentration equivalents in whole blood, plasma, urine, and feces following a single oral dose of [^{14}C]-CT1812 administered in healthy adult male subjects.	TRA concentration equivalents in whole blood and plasma a[redacted]
To characterize the PK profile of CT1812 and its metabolite, M6, in plasma following a single oral dose of [^{14}C]-CT1812 administered in healthy adult male subjects.	CT1812 and M6 metabolite concentrations in plasma a[redacted]:
To characterize the metabolite profile of CT1812 in plasma, urine, and feces following a single oral dose of [^{14}C]-CT1812 in healthy adult male subjects and identify the chemical identity of each metabolite accounting for more than 10% of circulating TRA.	CT1812 metabolite profiling and chemical identification in plasma, urine, and fecal samples containing sufficient amounts of radioactivity.

[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is an open-label, single-dose study to assess the absorption, metabolism, excretion, and mass balance for [^{14}C]-CT1812.

Eight (8) healthy male subjects will be enrolled.

Screening of subjects will occur within 28 days prior to dosing.

Subjects will be admitted to the [redacted] on Day -1 and discharged from the [redacted] following completion of 168 hours postdose procedures (Day 8).

On Day 1, subjects will receive a single oral dose of 300 mg CT1812 (2 capsules) with a microtracer dose of ~1 µCi [^{14}C]-CT1812 (1 capsule). Whole blood, plasma, urine, and fecal samples will be collected over 168 hours postdose (Day 8) to measure TRA (all samples), CT1812 and M6 metabolite concentrations (plasma), and for metabolite profiling and identification (plasma, urine, and fecal samples).

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Discontinued subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement and Follow-Up

Subjects will be housed on Day -1, at the time indicated by the [redacted], until completion of 168 hour procedures. Subjects may be admitted earlier than Day -1 for Coronavirus Disease-2019 (COVID-19) testing not related to study protocol as per [redacted] requirements. A subject may be required to remain at the [redacted] for longer at the discretion of the Principal Investigator (PI) or designee.

The [redacted] will attempt to contact all subjects who received the study drug (including subjects who terminate early) using their standard procedures approximately 14 days after dosing to determine if any AE has occurred since the last visit.

10.1.2 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure, i.e., the follow-up contact, outlined in the Study Events Flow Chart (Section 6).

A subject is considered to have completed the study if he has completed the last scheduled procedure, i.e., the follow-up contact, shown in the Study Events Flow Chart (Section 6).

11 STUDY POPULATION

11.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male, 19-55 years of age, inclusive, at the Screening visit.

2. Male subjects must follow protocol specified contraception guidance as described in Section 11.4.5.

3. Continuous non-smoker who has not used tobacco/nicotine-containing products for at least 3 months prior to dosing.

4. Body mass index (BMI) ≥18.0 and ≤30.0 kg/m^2 at the Screening visit (subjects must not have experienced a weight loss or gain of >10% within 4 weeks of dosing).

5. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the PI/designee at the Screening visit.

6. History of a minimum of 1 bowel movement per day.

7. Able to swallow multiple capsules.

8. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol.

11.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Evidence of disease that, in the opinion of the PI/designee, may influence the outcome of the study within 4 weeks before dosing; e.g., psychiatric disorders, cancer, seizures, or disorders of the GI tract, liver, kidney, respiratory system, endocrine system, hematological system, neurological system, or cardiovascular system, or subjects who have a congenital abnormality in metabolism.

2. Clinically significant illness, in the opinion of the PI/designee, that requires medical treatment within 8 weeks prior to dosing, or a clinically significant infection that requires medical treatment within 4 weeks prior to dosing.

3. Any history of GI surgery that may affect PK profiles of CT1812, e.g., hepatectomy, nephrectomy, gastric bypass, digestive organ resection. Subjects with a history of appendectomy may be included at the discretion of the PI/designee and Sponsor.

4. Has evidence of a clinically significant abnormality in physical examination findings, vital signs, or clinical laboratory determinations (congenital nonhemolytic

hyperbilirubinemia [e.g., suspicion of Gilbert's syndrome is not acceptable]) at the Screening visit or Check-in.

5. Has a clinically significant ECG abnormality, including a marked prolonged QT interval corrected by Fridericia's method (QTcF; e.g., a repeated demonstration of a QTcF interval >450 msec) at the Screening visit or Check-in, or a family history of prolonged QTc syndrome or sudden death or angina, or has history of congestive heart failure, poorly controlled hypertension, clinically significant arrhythmia, hypotension, any form of heart block (history of or on ECG at the Screening visit or Check-in), bundle branch block, symptomatic ectopy, unstable arrhythmias including atrial fibrillation, frequent supraventricular or ventricular ectopy, or a PR >210 msec or QRS duration >120 msec on ECG at the Screening visit or Check-in.

6. Estimated creatinine clearance <80 ml/min/1.73 m^2 at the Screening visit by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

7. Known history of clinically significant allergy to CT1812 or excipients at the Screening visit.

8. Has been diagnosed with acquired immune deficiency syndrome, or tests positive for human immunodeficiency virus (HIV), Hepatitis B virus surface antigen (HBsAg), or Hepatitis C virus (HCV) at the Screening visit.

~~9.~~ Has a history of alcohol use disorder within the 2 years before the Screening visit.

10. Positive urine drug or alcohol results at the Screening visit or Check-in.

11. Positive cotinine result at the Screening visit.

12. Unable to refrain from or anticipates the use of:

    - Any drugs, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to dosing except for those allowed in Section 11.4.1.

    - Any drugs known to be significant inducers of CYP2D6 and CYP3A4 and/or P-gp, including St. John's Wort, for 28 days prior to dosing. Appropriate sources (e.g., Flockhart Table™) will be consulted to confirm lack of PK/pharmacodynamic interaction with study drug.

13. Donation of blood or significant blood loss within 56 days prior to dosing.

14. Plasma donation within 7 days prior to dosing.

15. Poor peripheral venous access.

16. Recent history (within 2 weeks of Day -1) of abnormal bowel movements, such as diarrhea, loose stools, or constipation.

17. Has exposure to significant diagnostic or therapeutic radiation (e.g., serial X-ray, computed tomography scan, barium meal) or current employment in a job requiring radiation exposure monitoring within 12 months prior to Check-in.

18. Has participated in a radiolabeled drug study where exposures are known to the PI within the previous 3 months prior to admission to the clinic for this study or participated in a radiolabeled drug study where exposures are not known to the PI within the previous 6 months prior to admission to the clinic for this study. The total 12-month exposure from this study and a maximum of 3 other previous radiolabeled studies within 3 to 12 months prior to this study will be within the CFR recommended levels considered safe, per United States (US) Title 21 CFR 361.1 i.e., less than 5000 mrem whole-body annual exposure with consideration given to the half-lives of the previous radiolabeled study drugs received.

19. Has previously participated in a CT1812 investigational study.

20. Evidence or history of active suicidal thoughts (Type 4 or 5 on the C-SSRS) in the 6 months preceding the screening visit; or have a history of a suicide attempt in the previous 2 years, or more than 1 lifetime suicide attempt; or are at serious suicide risk per the PIs clinical judgment.

21. Has any condition that would, in the opinion of the PI/designee or Sponsor, make the subject unsuitable for the study or is, in the opinion of the PI/designee, not likely to complete the study for any reason.

22. Participation in another clinical study within 30 days prior to dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.

11.3 Early Termination of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the PI or designee for the following reasons:

- AEs.
- Difficulties in blood collection.

A subject may be withdrawn by the PI (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

Subjects who withdraw from the study early following dosing will be requested to remain confined to the [redacted] at least until Day 8.

11.4 Lifestyle Considerations

11.4.1 Medications and Supplements Restrictions

Prior concomitant medications (including prescription and non-prescription medications, herbal remedies, or vitamin supplements) will be prohibited as listed in the exclusion criteria in Section 11.2 and throughout the study.

After dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

A mild laxative (i.e., Milk of Magnesia®, Colace®) or prune juice may be used to help with bowel movements if necessary, at the discretion of the PI/designee, except for the first 4 hours postdose.

Eye drops for retinal examination will be permitted to facilitate the ophthalmic assessments.

If deviations occur, the PI or designee in consultation with the Sponsor if needed will decide on a case by case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

11.4.2 Meals and Dietary Restrictions

11.4.2.1 Meals

Water (except water provided with dosing) will be restricted 1 hour prior to and 1 hour after dosing, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Subjects will fast overnight for at least 10 hours prior to dosing. Subjects will continue the fast for at least 4 hours postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the [redacted], subjects will be required to fast from all food and drink except water between meals and snacks (with exception for mild laxative [i.e., Milk of Magnesia®, Colace®] or prune juice which may be given at the discretion of the PI/designee at any time excluding the first 4 hours following dosing).

Each meal and/or snack served at the [redacted] will be standardized and will be similar in caloric content and composition and will be taken at approximately the same time.

11.4.2.2 Dietary Restrictions

The consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Grapefruit/Seville orange (or products containing these): 14 days prior to dosing and throughout the period of sample collection.

11.4.3 Caffeine, Alcohol, and Tobacco Restrictions

Subjects will refrain to use the following:

- Xanthines/Caffeine-containing foods or beverages: 24 hours prior to dosing and throughout the period of sample collection (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction).
- Alcohol-containing foods or beverages: 48 hours prior to dosing and throughout the period of sample collection.
- Tobacco/nicotine containing products: at least 3 months prior to dosing and throughout the period of sample collection.

11.4.4 Activity Restrictions

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures. Should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Specific measures will be taken to prevent the subject from missing a urine collection by strictly controlling and providing access to designated restrooms only. Subjects will be asked to void prior to entering the shower.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from the Screening visit until completion of the study.

Should any subject withdraw or be withdrawn from the study, he will be cautioned against activities requiring mental alertness, judgment and physical coordination such as driving, operating machinery, or power equipment for a period of 24 hours postdose.

11.4.5 Contraception Requirements

11.4.5.1 Guidance for Subjects

Subjects must agree to the following method of contraception:

A non-vasectomized subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study from dosing until 90 days after dosing. No restrictions are required for a vasectomized subject provided his vasectomy has been performed 4 months or more prior to dosing.

A subject who has been vasectomized less than 4 months prior to dosing must follow the same restrictions as a non-vasectomized subject.

The subject must agree not to donate sperm from dosing until 90 days after dosing.

12 TREATMENTS

12.1 Treatments Administered

Study drug will be supplied as capsules of nonradiolabeled CT1812 (powder) and capsules of radiolabeled [^{14}C]-CT1812 (powder/suspension).

The study treatment will consist of 3 capsules: 2 capsules containing CT1812 ([redacted] and 1 capsule containing ~1 µCi [^{14}C]-CT1812 ([redacted]).

Capsules will be administered orally under fasting conditions on Day 1 at Hour 0 with approximately 240 mL of water. Additional water, up to 50 mL, is permissible to facilitate swallowing multiple capsules.

The pharmacy at the [redacted] will provide the [^{14}C]-CT1812 dose in individual unit dose containers for each subject.

Subjects will be instructed not to crush, split, or chew the capsules.

The exact clock time of dosing will be recorded.

12.2 Dose Modification

The dose and administration of the study drug to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 11.3.

12.3 Method of Treatment Assignment

Each subject will be assigned a unique identification number upon the Screening visit. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of dosing, different from the screening number.

If replacement subjects are used, the replacement subject number will be 100 more than the original (e.g., Subject No. 101 will replace Subject No. 1). Subjects will be replaced at the discretion of the Sponsor if less than 6 subjects are available for evaluation.

12.4 Blinding

This is an open-label study.

12.5 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

13 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the blood (for whole blood and/or plasma), urine, and feces collections for TRA, the blood (for plasma) CT1812 and M6 concentrations, and the blood (for plasma), urine, and feces collections for metabolite profiling, as applicable, are the critical parameters and need to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

13.1 Screening

Within 28 days prior to dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and history of tobacco use will be recorded. Each subject will have a 12-lead ECG, vital sign measurements (pulse rate, blood pressure, temperature, and respiratory rate), clinical laboratory tests, ophthalmic, C-SSRS, and physical examination.

13.2 Safety Assessments

13.2.1 Physical Examination

Full and abbreviated physical examinations and symptom driven physical examination(s) will be performed as outlined in the Study Events Flow Chart (Section 6). Additional symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

An abbreviated physical examination will include at the minimum, examination of respiratory, cardiovascular, and GI systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs.

13.2.2 Standard Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and pulse rate will be measured as outlined in the Study Events Flow Chart (Section 6). Additional vital signs may be taken at any other times, if deemed necessary by the PI or designee.

Blood pressure and heart rate measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g. nausea, dizziness) or if deemed necessary by the PI or designee.

Vital signs will be measured within 24 hours prior to Day 1 dosing for the predose time point. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

13.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

13.2.4 Ophthalmic Examinations

Ophthalmic examinations will be performed as outlined in the Study Events Flow Chart (Section 6). Additional ophthalmic examinations may be taken at any other times, if deemed necessary by the PI or designee. Ophthalmic examinations will include the following tests:

- Best-corrected visual acuity using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (refraction only required if subjects does not have his corrective lenses or contact lenses)
- Slit lamp exam
- Intraocular pressure measurement with applanation tonometry
- Dilated fundus retinal exam

13.2.5 Body Weight

Body weight (kg) will be reported as outlined in the Study Events Flow Chart (Section 6).

13.2.6 Columbia Suicide Severity Rating Scale

The C-SSRS is a questionnaire scale to detect emergent suicide symptoms (suicidal ideation or actual suicidal behavior) during the course of this study. Assessments will be performed according to the Study Events Flow Chart (Section 6). At Screening, the C-SSRS Baseline/Screening version will be administered; at all other time points, as applicable, the Since Last Visit version will be administered. Additional C-SSRS assessments may be performed at other times if deemed necessary. The C-SSRS is to be administered at the site by an appropriately qualified/trained individual and a copy of the questionnaire to be used will be kept in the study binder. In addition, subjects who at any time during this study spontaneously report AEs of suicidal ideation or suicidal behavior, either as an outpatient or during visit interviews, must be assessed by the PI or designee and referred for further mental health evaluation as clinically indicated.

13.2.7 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology

- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

Serum Chemistry *

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Chloride
- Calcium
- Glucose (fasting)
- Creatinine **
- Lactic dehydrogenase
- Creatine phosphokinase

Urinalysis

- pH
- Specific gravity
- Protein ***
- Glucose
- Ketones
- Bilirubin
- Blood ***
- Nitrite***
- Urobilinogen
- Leukocyte esterase ***

Additional Tests

- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiates
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Urine cotinine

* Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample is taken.

** At the Screening visit, creatinine clearance will be calculated using the CKD-EPI formula.

*** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

13.2.8 Adverse Events

13.2.8.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

13.2.8.2 Monitoring

Subjects will be monitored for adverse reactions to the study formulations and/or procedures throughout the study, from the time of signing the ICF until the follow-up contact. Prior to release, subjects will be asked how they are feeling. At the follow-up contact, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee.

Treatment of serious adverse events (SAEs) will be performed by a licensed health care professional, either at Celerion or at a nearby hospital emergency room where appropriate medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as fatal, not recovered/not resolved recovered/resolved, recovered/resolved with sequelae, recovering/resolving.

13.2.8.3 Reporting

All AEs that occurred during this clinical study will be recorded. All clinically significant abnormal laboratory results should be reported as AEs.

The PI or designee will review each event and assess its relationship to drug treatment (likely, probably, possibly, unlikely or unrelated).

Each sign or symptom reported will be graded on a 3-point severity scale (mild, moderate, or severe), and the date of onset, time of onset, and outcome of each event will be noted.

The following definitions will be used for rating the severity of AEs:

Mild	The AE is easily tolerated and does not interfere with daily activity.
Moderate	The AE interferes with daily activity, but the subject is still able to function. Medical intervention may be considered.
Severe	The AE is incapacitating and requires medical intervention.

13.2.8.4 Serious Adverse Event

If any AEs are serious, as defined by the Food and Drug Administration (FDA) CFR, Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

If a SAE occurs to a subject on this study, contact the Sponsor personnel listed in Section 3.

13.3 Pharmacokinetic Assessments

13.3.1 Blood Sampling and Processing

Blood samples for the determination of TRA in whole blood and plasma, CT1812 and M6 concentrations in plasma, and metabolite profiling in plasma will be collected at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

Predose samples should be handled, processed, analyzed, and stored separately away from the postdose samples to avoid cross contamination.

Instruction for blood sampling, collection, processing, and sample shipment will be provided separately.

13.3.2 Pharmacokinetic Parameters

PK parameters for whole blood and plasma TRA concentration equivalents and for plasma CT1812 and metabolite M6, will be calculated, as appropriate:

AUC0-t:	The area under the concentration versus time curve, from time 0 to the time of the last common time point "t", where t is the last common time point at which plasma TRA and plasma CT1812 are quantifiable in all subjects.
AUC0-24:	The area under the concentration versus time curve, from time 0 to the 24-hour time point.
AUC0-last:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-last plus the ratio of the last measurable concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 - AUC0-last/AUC0-inf)*100.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero concentrations).

t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.
CL/F:	Apparent total clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf (parent only).
Vz/F:	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as Dose/(AUC0-inf x Kel) (parent only).

No value for Kel, AUC0-inf, AUC%extrap, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations, or who have an AE of vomiting that occurs at or before 2 times the median Tmax.

13.3.3 Whole Blood to Plasma Partitioning Ratio

The percentage of TRA in whole blood relative to plasma (i.e., whole blood:plasma partitioning ratio) will be estimated at each time-matched determination of TRA in whole blood and plasma collected at the scheduled time points as delineated in the Study Events Flow Chart (Section 6).

13.3.4 Urine Sampling and Processing

Urine for determination of TRA and metabolite profiling will be collected at the specified intervals delineated in the Study Events Flow Chart (Section 6).

Prior to the predose sample collection, each subject will be instructed as to urine collection methods. All urine during an interval is to be collected.

On Day 1, a spot collection will be obtained prior to dosing for the predose sample. Subjects will be asked again to empty their bladder within approximately 15 minutes prior to dosing, and no urine will be collected at this time unless it is needed for the predose sample. Only one predose urine sample will be collected on Day 1.

Subjects will be encouraged to void at the end of each collection interval. If they do void at any time during the collection interval, the time should be documented. Should this be the case, subjects need to void again at the end of the collection period, as scheduled. However, should subjects be unable to void, this will be documented as well.

Urine will be refrigerated during the collection intervals. At the end of each interval, urine will be pooled and thoroughly mixed. Total urine volume will be weighed and recorded.

Predose samples should be handled, processed, analyzed, and stored separately away from the postdose samples to avoid cross contamination.

Instructions for urine sampling, collection, processing, and sample shipment will be provided separately.

13.3.5 Urine Pharmacokinetic Parameters

PK parameters for urine TRA will be calculated as follows:

Ae(u):	Amount of TRA excreted in urine within a given collection interval.
CumAe(u):	Cumulative amount of TRA excreted in urine.
%Dose(u):	Percent of administered radioactive dose excreted in urine within a given collection interval.
Cum%Dose(u):	Cumulative percent of administered radioactive dose recovered in urine.
CLr:	Renal clearance. CLr = CumAe(u)/AUC0-inf, where both CumAe and AUC are determined over matched time interval.

13.3.6 Fecal Sampling and Processing

Fecal samples for the determination of TRA and metabolite profiling will be collected at the specified intervals delineated in the Study Events Flow Chart (Section 6).

The predose fecal sample is to be obtained within 48 hours prior to dosing. Subjects will be asked to bring a fecal sample at Check-in (if produced within 48 hours prior to dosing). Feces produced between Check-in and dosing will also be collected as a predose sample with the sample produced nearest to dosing to be retained as the only predose sample.

All fecal samples will be collected and stored individually for analysis of TRA and for metabolite profiling. The samples will be weighed at the time of collection. Multiple fecal samples from a given subject in a given interval will be pooled into a single sample at the time of homogenization.

Predose samples should be handled, processed, analyzed, and stored separately away from the postdose samples to avoid cross contamination.

Instructions for fecal sampling, collection, processing, and sample shipment will be provided separately.

13.3.7 Fecal Pharmacokinetic Parameters

PK parameters for feces TRA will be calculated as follows:

Ae(f):	Amount of TRA excreted in feces within a given collection interval.
CumAe(f):	Cumulative amount of TRA excreted in feces.

%Dose(f):	Percent of administered radioactive dose excreted in feces within a given collection interval.
Cum%Dose(f):	Cumulative percent of administered radioactive dose recovered in feces.

13.3.8 Emesis

Collection containers (pre-weighed) for emesis will be available for subjects participating in the study at all times following dosing until discharge from the clinic. Subjects will be instructed at the beginning of the study that they should use one of the designated containers if emesis occurs following [^{14}C]-CT1812 dosing. If emesis occurs following [^{14}C]-CT1812 dosing and the subject has been able to collect the emesis in the designated container, it will be weighed and recorded, labeled with subject identification, time, and date, and analyzed for TRA. The subject may continue the study with permission from the Sponsor; however, subject data will be excluded from the PK or mass balance calculations if the AE of vomiting occurs at or before 2 times the median Tmax.

13.3.9 Future Research

No additional analysis is planned to be performed on the PK blood/urine samples for possible future research. Any additional research on these samples unspecified by this protocol will require approval from the subjects.

13.3.10 Analytical Method

Samples from all subjects will be assayed even if the subjects do not complete the study.

Plasma concentrations of CT1812 and metabolite M6 will be determined using validated analytical methods. Whole blood, plasma, urine, and feces TRA will be determined with liquid scintillation counting or AMS detection. Profiling and identification of metabolites in plasma, urine, and where possible, feces will be conducted using standard laboratory procedures. Specifics of the analytical methods will be provided in separate documents.

13.4 Blood Volume Drawn for Study Assessments

Table 1: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Volume per Aliquot (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, and serology)	1	12.5	-	12.5
On-study hematology and serum chemistry	3	12.5	-	37.5
Blood for plasma CT-1812 and M6 PK	18	6	2 mL (1 mL primary +1 mL backup)	108
Blood for plasma TRA	18	3	1 mL (0.5 mL primary and 0.5 mL backup)	54
Blood for plasma metabolite profiling and identification	18	10	4 mL (2 mL primary +2 mL backup)	180
Blood for whole blood TRA	18	2	2 mL (1 mL primary 1 mL backup)	36
Total Blood Volume (mL)→				428**

* Represents the largest collection tube that is expected to be used (a smaller tube may be used).

** If additional PK and safety analysis is required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

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14 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

14.1 Sample Size Determination

The sample size of 8 healthy male subjects was selected without statistical considerations and in order to have complete data from 6 subjects available for evaluation. It has been determined adequate to meet the study objectives. This sample size is limited based on clinical considerations for this type of study and in order to limit exposure to radioactivity.

14.2 Population for Analyses

PK Population: All subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations or an AE of vomiting as described) will be included in the statistical analysis.

Safety Population: All subjects who received the dose of the study drug will be included in the safety analysis.

14.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

14.3.1 Pharmacokinetic Analyses

14.3.1.1 Descriptive Statistics

The TRA (whole blood, plasma, urine, feces, and if applicable emesis), CT1812 and M6 metabolite concentrations (plasma), and PK parameters listed in Sections 13.3.2, 13.3.5 and 13.3.7 will be summarized using appropriate descriptive statistics which will be fully outlined in the SAP.

14.3.1.2 Mass Balance

Total radioactivity recovery and the percent of the radioactive dose excreted in the urine and feces will be assessed. Mass balance will be calculated as a sum of the percent of the TRA recovered in urine and feces relative to the administered radioactive dose minus any radioactive dose lost due to emesis (if any occurred).

14.3.1.3 Metabolite Profiling

CT1812 metabolite profiling will be performed on plasma, urine, and fecal samples containing sufficient amounts of radioactivity. The percent of dose represented by each of the metabolites, if any, will be calculated using the radioactive concentration equivalent data combined with the metabolite profiling data. The percentage of each identified metabolite, if any, to TRA in the plasma will be estimated based on plasma metabolite profiling data. Metabolites accounting for more than 10% of circulating TRA will be identified.

14.3.1.4 Whole Blood and Plasma Partitioning Ratio

The percentage of TRA in whole blood relative to plasma will be estimated at each time-matched determination of TRA in whole blood and plasma.

14.3.2 Safety Analyses

All safety data will be populated in the individual case report forms (CRFs), and will be listed by subject in the final report.

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities® available at Celerion and summarized by treatment for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, severity, and relationship to treatment will be provided.

Safety data including ECGs, vital signs assessments, ophthalmic examinations, and clinical laboratory results will be summarized by time point of collection.

C-SSRS data will be listed by subject.

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

Prior and concomitant medications will be listed by subject and coded using the most current version of the World Health Organization drug dictionary available at Celerion.

Medical history will be listed by subject.

15 STUDY ADMINISTRATION

15.1 Ethics

Institutional Review Board

This protocol will be reviewed by Advarra IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant to International Council for Harmonisation (ICH) guidelines, and may be reached at:

Advarra IRB
6100 Merriweather Drive, Suite 600
Columbia, Maryland 21044, USA
Tel.: +1 410 884-2900

15.1.1 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], November 2016).

15.1.2 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

15.1.3 Confidentiality

All members of the PI's staff have signed confidentiality agreements with Celerion. By signing this protocol, the PI and Celerion staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential.

The PI must guarantee the privacy of the subjects taking part in the study. Subjects will be identified throughout documentation and evaluation by a unique subject study number. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. If subject name appears on any study document, it must be redacted before the copy of the documents is supplied to the Sponsor. Any information concerning the subjects (clinical notes, identification numbers, etc.) must be kept on file by the PI who will ensure that it is revealed only to the Sponsor, IRB, or regulatory authorities for the purposes of trial monitoring, auditing or official inspections. As required, in the case of an event where medical expenses are the

responsibility of the Sponsor, personal information i.e., full name, social security details etc. may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data protection laws.

15.2 Termination of the Study

Celerion reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

15.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, and GCP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the study report.

Clinical data will undergo quality control prior to clinical database lock. Edit checks are performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

15.4 Direct Access to Source Data/Documents

Celerion will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6][R2] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

15.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of CT1812 and [^{14}C]-CT1812 to allow completion of this study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused CT1812 and [^{14}C]-CT1812 will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

15.6 Data Handling and Record Keeping

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the PI. The final signed CRFs are provided to the Sponsor in the format as decided between Celerion and the Sponsor (e.g., electronically, compact disc, flashdrive, secure file transfer protocol). This will be documented in the data management plan (if applicable).

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Celerion until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

15.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.8 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor’s written consent to publish the article.

16 REFERENCES

Cahill MA, Jazayeri JA, Catalano SM, et al. 2016. The emerging role of progesterone receptor membrane component 1 (PGRMC1) in cancer biology. Biochim Biophys Acta. pii: S0304-419X(16)30049-X. doi: 10.1016/j.bbcan.2016.07.004. [Epub ahead of print] Review. PMID: 27452206).

Food and Drug Administration: Code of Federal Regulation (CFR) Title 21. Part 361 Prescription Drugs for Human Use Generally Recognized as Safe and Effective and not Misbranded: Drugs Used in Research (April 2019). Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=361.1. Accessed on 17Dec2020.

Investigator's Brochure (Version 5). Cognition Therapeutics, Inc., CT1812, September 2021.

Izzo NJ, Staniszewski A, To L et al. 2014(a). Alzheimer's therapeutics targeting Amyloid beta 1-42 oligomers I: Abeta 42 oligomer binding to specific neuronal receptors is displaced by drug candidates that improve cognitive deficits. PLoS ONE 9(11): e0111898.

National Council on Radiation Protection and Measurements (NCRP) Report No. 160, Ionizing Radiation Exposure of the Population of the United State, National Council on Radiation Protection and Measurements, March 2009.