REVISION HISTORY

Revisions to Version 5.0 (per Amendment 04)

Date: 01 Dec 2023

Change	Rationale	Affected Protocol Sections
CCI [redacted]	To expedite Cohort B recruitment; amyloid pathology will be confirmed retrospectively using CSF baseline samples	Synopsis • Inclusion Criteria • Statistical Methods ○ Study Endpoints ▪ Exploratory Endpoints Section 9.3.1 Section 9.7.1.1.3 Section 9.7.1.9
Changed collection of blood samples for PK assessments at Week 48 to Week 52 for Cohort B	Correction	Synopsis • Pharmacokinetic Assessments
Changed maximum infusion time for 3000 mg from 4 to 2 hours for Cohort B	Correction	Section 9.4.1
Removed CDR-SB and GDS assessments from Visits 2, 8, and 15 and EOS/ET Visits in Cohort B Schedule of Procedures/Assessments	Correction; CDR-SB and GDS already included in multiple cognitive and clinical assessments in the Schedule of Procedures/Assessments at Visits 2, 8, and 15 and EOS/ET Visits	Section 9.5.2.1
Added blood for E2814 PK and anti-E2814, clinical labs, and ECG as Unscheduled Visit(s) assessments for Cohort B	Assessments in Unscheduled Visits are up to the investigator's discretion if necessary.	Section 9.5.2.1
Added footnote n to blood for PGx in Cohort A Schedule of Procedures/Assessments; added footnote l to blood for PGx in Cohort B Schedule of Procedures/Assessments	Blood for confirmatory genetic testing will be taken during Screening if necessary.	Section 9.5.2.1
Added Outpatient Visits in the Cohort B Schedule of Procedures/Assessments at Visits 3, 4, 6, 7, 9, 10, 12, 13, and 15, and EOS/ET Visits and removed from Visit 2 (Day -1 to 1).	Correction; following the in-clinic visit on Day 1, all subsequent visits will be outpatient visits and will occur Q4W for the duration of the study for Cohort B	Section 9.5.2.1

Revisions to Version 5.0 (per Amendment 04)

Date: 01 Dec 2023

Change	Rationale	Affected Protocol Sections
Updated Cohort B Schedule of Procedures/Assessments footnote k	To clarify blood sampling time points for PK assessments	Section 9.5.2.1

Revisions to Version 4.0 (per Amendment 03)

Date: 28 Feb 2023

Change	Rationale	Affected Protocol Sections
Added new Cohort (B) and increased the number of subjects	To further evaluate safety and biomarker effects at the 3000 mg dose.	Synopsis • Study Design • Number of Subjects • Study Treatments • Duration of Treatment • Clinical Efficacy Assessments • Pharmacokinetic Assessments • Pharmacodynamic, Pharmacogenetic, and Other Biomarker Assessments • Safety Assessments • Immunogenicity Assessments • Sample Size Rationale Section 9.1 Section 9.1.1.1 Section 9.1.2.2 Section 9.2 Section 9.3 Section 9.4.1 Section 9.5.1.1 Section 9.5.1.1.4 Section 9.5.1.2 Section 9.5.1.3.1 Section 9.5.1.3.2 Section 9.5.1.4 Section 9.5.1.4.4 Section 9.5.1.4.5 Section 9.5.1.4.6 Section 9.5.1.4.7 Section 9.5.1.4.8

Revisions to Version 4.0 (per Amendment 03)

Date: 28 Feb 2023

Change	Rationale	Affected Protocol Sections
		Section 9.5.1.5 Section 9.5.2.1 Section 9.5.2.2
Clarified primary endpoint of change from baseline in CSF free and bound MTBR-tau and total MTBR-tau at 12 weeks is for Cohort A only	Clarification due to addition of Cohort	Synopsis • Statistical Methods Section 9.7.1.1.1
Added pharmacokinetic and anti-drug antibody blood sampling as required assessments at the Follow-up Visit	Correction	Synopsis • Pharmacokinetic Assessments • Immunogenicity Assessments Section 9.5.1.3.1 Section 9.5.1.3.2 Section 9.5.2.1

Revisions to Version 3.0 (per Amendment 02)

Date: 18 Oct 2022

Change	Rationale	Affected Protocol Sections
Added 4500 mg dose	Results to date from study E2814-A001-001 indicate that a dose of 4500 mg is acceptable for evaluation in subjects with Alzheimer's disease in order to inform clinical dose selection for Phase 3 studies	Synopsis • Study Design • Study Treatment Section 9.1 Section 9.1.2 Section 9.2 Section 9.4.1 Section 9.4.4 Section 9.4.5 Section 9.5.1.3.1 Section 9.5.1.3.2 Section 9.5.2.1
Added cerebrospinal fluid (CSF), biomarker, pharmacokinetic (PK), and immunogenicity sampling associated with the 1st 4500 mg dose	To collect data at the appropriate times related to the increased dose	Synopsis • Study Design • Pharmacokinetic Assessments • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Immunogenicity Assessments Section 9.5.1.3.1

Revisions to Version 3.0 (per Amendment 02)
Date: 18 Oct 2022

Change	Rationale	Affected Protocol Sections
		Section 9.5.1.3.2 Section 9.5.1.5 Section 9.5.2.1
Clarified that subjects must be on a stable dose of oral contraception for 100 days prior to dosing and continue on that dose throughout the study and for 16 weeks after study drug discontinuation	To correct error and ensure consistency in subject surveillance for 5 half-lives after study drug discontinuation	Synopsis • Exclusion Criteria Section 9.3.2
Allow the use of marijuana (including products containing tetrahydrocannabinol [THC]) as a concomitant medication if the investigator confirms that there is no suspected abuse or dependency related to marijuana and THC use will not prevent the subject from performing psychometric tests accurately	To allow for subject use during the study	Synopsis • Concomitant Drug Therapy Section 9.4.7
Allow Assessments for study visits that require positron emission tomography (PET), magnetic resonance imaging (MRI), and/or cognitive assessments to be completed over several days if needed provided all assessments are completed within the visit window	Clarification	Section 9.5.2.1
Updated sponsor address	Physical address change	Section 1
Updated signature page	Sponsor personnel changes	Protocol Signature Page

Revisions to Version 2.0 (per Amendment 01)
Date: 23 Nov 2021

Change	Rationale	Affected Protocol Sections
Edited the description of the timing of magnetic resonance imaging (MRI)	Revised for clarity	Synopsis • Safety Assessments Section 9.5.1.4

Revisions to Version 2.0 (per Amendment 01)

Date: 23 Nov 2021

Change	Rationale	Affected Protocol Sections
Added a row to the Schedule of Procedures/Assessments table to specify that Clinical Dementia Rating – Sum of Boxes (CDR-SB) is to be conducted at Screening	Added for clarity	Section 9.5.2.1

Revisions to Version 1.0 (per Amendment 01)

Date: 23 Nov 2021

The primary reason for the Amendment is to increase the dose of E2814 to be used in the Phase 2 part of this study.

Change	Rationale	Affected Protocol Sections
Introduction of a higher dose (3000 mg) in the Phase 2 Treatment Period	Following consultation with FDA and given the totality of the nonclinical data and clinical safety and target engagement (TE) data available to date, a higher dose does not pose an unacceptable risk and provides for the evaluation of a higher E2814 dose in subjects with Alzheimer's disease to inform clinical dose selection for Phase 3 studies.	Synopsis • Study Design • Study Treatments • Pharmacokinetic Assessments Section 9.1.2.1.2 Section 9.2 Section 9.4.1 Section 9.4.4 Section 9.4.5 Section 9.5.1.3.1 Section 9.5.2.1
Revised the schedule of lumbar puncture for cerebrospinal fluid (CSF) collection	Added a CSF collection to occur 12 weeks after initiation of the highest dose (3000 mg) to provide for the evaluation of target engagement and E2814 concentration at this dose.	Synopsis • Study Design • Pharmacokinetic Assessments • Pharmacodynamic Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2.1.2 Section 9.5.1.3.1 Section 9.5.1.3.2 Section 9.5.2.1
Revised the schedule of cognitive assessments	Shifted the schedule of cognitive tests to occur every 24 weeks throughout the study, as changes in cognition are not likely to be observable over shorter intervals and to reduce the burden for study subjects and partners.	Synopsis • Clinical Efficacy Assessments Section 9.5.1.2 Section 9.5.2.1
Deleted the requirement for a second informed consent	The study is a continuous study from the Phase 1b Treatment Period into the Phase 2 Treatment Period.	Section 9.5.2.1

Revisions to Version 1.0 (per Amendment 01)

Date: 23 Nov 2021

The primary reason for the Amendment is to increase the dose of E2814 to be used in the Phase 2 part of this study.

Change	Rationale	Affected Protocol Sections
scheduled for the start of the Phase 2 Treatment Period	Explanation of the dose increases in Phase 2 is provided in the initial consent, and a separate consent to increase dose is not required.	
Added time window allowances for scheduled assessments	To provide flexibility to subjects and study partners.	Section 9.5.2.1
Increased blood volume collected for PD analyses from 6 mL to 10 mL	To provide sufficient plasma volume for all proposed PD biomarker analyses	Synopsis • Pharmacodynamic Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.3.2
Corrected the PK sampling schedule to reflect that no PK sample is required on Day 84	Corrected for consistency throughout the protocol	Section 9.5.2.1 Section 9.5.1.3.1
Revised the time window allowance for vaccinations relative to dosing, and added instruction for the timing of COVID-19 vaccination relative to dosing	To allow flexibility for subjects to undergo vaccination during ongoing COVID-19 pandemic	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Increased the duration of contraception requirement post-dosing and required post-dose interval for reporting pregnancy or breast feeding	To maintain contraception and pregnancy reporting for 5 half-lives after the last dose	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.4.2
Increased the duration of the post-dose adverse event (AE) follow-up	To continue follow-up of AEs for 5 half-lives after the last dose	Section 9.5.1.4.1
Deleted collection of subjects' dates of birth	For consistency with Eisai Global Protocol template	Section 9.5.1.1.1
Revised the threshold of abnormal hepatic tests that may require reporting and additional evaluation for an underlying etiology	For consistency with Eisai Global Protocol template	Section 9.5.4.3.2
Revised the definition of the Safety Analysis Set for analysis	For consistency with Eisai Global Protocol template	Section 9.7.1.2
Editorial, internal consistency, and formatting revisions	Document quality	Throughout

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2814-G000-103
Study Protocol Title:	An Open-Label Phase 1b/2 Study to Assess Safety and Target Engagement of E2814 in Subjects with Mild to Moderate Cognitive Impairment due to Dominantly Inherited Alzheimer's Disease
Sponsor:	Eisai Inc. 200 Metro Boulevard Nutley, New Jersey 07110, US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire, AL10 9SN, UK
Sponsor's Investigational Product Name:	E2814
Indication:	Alzheimer's Disease
Phase:	1b/2
Approval Date:	V1.0 08 Dec 2020 (original protocol) V2.0 23 Nov 2021 (Amendment 01) V3.0 23 Nov 2021 (Amendment 01) V4.0 18 Oct 2022 (Amendment 02) V5.0 28 Feb 2023 (Amendment 03) V6.0 01 Dec 2023 (Amendment 04)
IND Number	139378
EudraCT Number	2020-005728-12
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2814

Name of Active Ingredient: E2814

Study Protocol Title

An Open-Label Phase 1b/2 Study to Assess Safety and Target Engagement of E2814 in Subjects with Mild to Moderate Cognitive Impairment due to Dominantly Inherited Alzheimer's Disease

Site(s)

Four or more sites across the United States (US) and United Kingdom (UK)

Study Period and Phase of Development

First subject screened to last subject's last visit: Approximately 41 months (revised per Amendment 03)

Phase 1b/2

Objectives

Primary Objectives:

- To assess the safety and tolerability of intravenous (IV) infusions of E2814 in subjects with Dominantly Inherited Alzheimer's Disease (DIAD)
- To evaluate target engagement (TE) of E2814 on microtubule binding region (MTBR)-tau species in cerebrospinal fluid (CSF) in subjects with DIAD

Secondary Objectives:

- To assess the pharmacokinetics (PK) of E2814 in serum, plasma, and CSF
- To assess the immunogenicity (production of anti-E2814 antibody) of E2814
- To assess the effect of E2814 on CSF, blood, and imaging biomarkers

Exploratory Objectives:

cci [redacted]

Study Design

This is an open-label Phase 1b/2 study to evaluate the safety and TE of E2814 on MTBR-tau species in CSF following IV infusions of E2814 in DIAD subjects. Subjects in this study are confirmed mutation positive for genes known to be associated with DIAD. The mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid precursor protein (*APP*) that are associated with DIAD have very high penetrance (near 100%).

The study will consist of 2 Cohorts (A and B).

Cohort A

Cohort A consists of 2 phases: A Screening Phase and a Treatment Phase consisting of 3 periods: 1b, 2, and follow up.

- The Screening Phase will run from Day -60 to Day -2 during which the eligibility of the subject will be determined. Screening assessments will include tau Positron Emission Tomography (PET), amyloid PET, and safety magnetic resonance imaging (MRI) and genetic testing to confirm mutation status.
- The Phase 1b Treatment Period will initially allow 8 subjects to receive open-label treatment with 3 IV infusions of 750 mg E2814 every 4 weeks (Q4W) over 12 weeks. Subjects will check into the clinic on the day before dosing but will not be required to stay in the clinic overnight on Day -1 to Day 2, they may instead stay overnight at a nearby hotel and return to the clinic the next day. In addition, subjects will have outpatient visits on Days 15, 29, and 57. On conclusion of the Phase 1b Treatment Period, on Day 84, subjects will check into the clinic and will undergo safety assessments. Subjects will not be required to stay in the clinic overnight on Day 84 to Day 86, they may instead stay overnight at a nearby hotel and return to the clinic the next day. A CSF sample will be collected for assessment of TE and CSF concentrations of E2814 on Day 1 and Day 84. Subjects will then progress to the Phase 2 Treatment Period. Subjects who withdraw from the Phase 1b Treatment Period for reasons other than safety may be replaced.
- The Phase 2 Treatment Period will allow subjects who tolerated the 750 mg dose of E2814 and completed all assessments in the Phase 1b Treatment Period to receive a further 96 weeks of IV E2814 at an initial dose of 1500 mg Q4W for at least 3 doses (12 weeks) followed by a dose of 3000 mg Q4W for at least 3 doses (12 weeks), followed by a dose of 4500 mg Q4W for the remaining weeks. (revised per Amendments 01 and 02)
  - CCI [redacted]

  [redacted]

  [redacted]

  Following the in-clinic visit CCI [redacted], all subsequent visits will be outpatient visits and CCI [redacted] (revised per Amendments 01 and 02)

  CCI [redacted]

Cohort B (revised per Amendment 03)

Cohort B consists of 2 phases: A Screening Phase and a Treatment Phase consisting of 2 periods: 52-week Treatment Period and 12-week Follow Up Period.

CCI

During the Cohort A Phase 2 and Cohort B Treatment Periods, infusions will take place in the clinic. When the process for home infusion is established, and if allowed and conducted according to local guidelines, the investigator may assess for an individual subject if home infusions are suitable according to the following guidelines: If a subject has shown acceptable tolerability for the infusions, is considered by the investigator to be at low risk of developing adverse events (AEs) related to study drug infusion that may require acute medical treatment, and has shown no clinically significant findings on other safety measures related to study drug infusion during the Cohort A Phase 1b Treatment Period, or the first month or first dose of Cohort B treatment, he or she may be allowed to receive infusions at home keeping in accordance with the required infusion schedule, depending on the feasibility for blood sampling or cognitive assessments on the scheduled visits. (revised per Amendment 03)

The Follow-up Period for both Cohorts will follow subjects for a period of 12 weeks after the last dose for safety. (revised per Amendment 03)

Number of Subjects

Up to 8 subjects in Cohort A (revised per Amendment 03)

Up to 5 subjects in Cohort B (revised per Amendment 03)

Inclusion Criteria

1. Male or female, age 18 to 80 years at the time of informed consent
2. Individuals who are confirmed to be mutation positive for *PSEN1*, *APP*, or *PSEN2* gene that is associated with DIAD
3. CDR-SB score 5 to 12 at Screening
4. CCI
5. Able to undergo MRI, lumbar puncture (LP), PET, and complete all study-related testing and evaluations

6. Has a study partner who in the investigator's judgment is able to provide accurate information as to the subject's cognitive and functional abilities, who agrees to provide information at the study visits which require informant input for scale completion

Exclusion Criteria

1. Clinically significant illness that required medical treatment within 8 weeks before the 1st dose or a clinically significant infection that required medical treatment within 4 weeks before 1st dose
2. Females who are breastfeeding or pregnant at Screening or Baseline [redacted]
3. Females of child-bearing potential who:
   - Within 3 months before Screening, did not use a highly effective method of contraception, [redacted]
4. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's Alzheimer's disease (AD)
5. History of transient ischemic attacks, stroke, or seizures within 12 months of Screening
6. History of clinically important carotid or vertebrobasilar stenosis, plaque, or other prominent risk factor for stroke or cerebral haemorrhage (including atrial fibrillation and anticoagulation). Low dose aspirin (≤325 mg daily) is not exclusionary
7. Any current psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could interfere with study procedures in the subject
8. Geriatric Depression Scale (GDS) score greater than or equal to 8 at Screening

9. Contraindications to MRI scanning, including but not limited to pacemaker/cardiac defibrillator, neurostimulators, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners)
10. Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD
11. Other significant pathological findings on brain MRI at Screening, CCI [redacted]
12. Hypersensitivity to E2814 or any of the excipients, or to any monoclonal antibody treatment
13. Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study
14. With a bleeding disorder of current chronic use of anticoagulants (eg, warfarin, dabigatran, rivaroxaban, or apixaban) or of clopidogrel is exclusionary. Limited (occasional or isolated) use of anticoagulants/antiplatelet compounds in cases such as surgical procedures.
15. Have thyroid stimulating hormone outside of normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects whether or not they are taking thyroid supplements.
16. HgbA1c >8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes). Subjects may be rescreened after 3 months to allow optimization of diabetic control.
17. Abnormally low serum vitamin B12 levels for the testing laboratory CCI [redacted]
18. History of human immunodeficiency virus infection, history of hepatitis B infection within the past year, history of hepatitis C infection which has not been adequately treated, or history of spirochete infection of the central nervous system (eg, syphilis, Lyme, or borreliosis)
19. Any other clinically significant abnormalities in physical examination, vital signs, laboratory tests, or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety
20. Malignant neoplasms within 3 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects, or localized breast cancer in female subjects). Subjects who had malignant neoplasms but who have had at least 3 years of documented uninterrupted remission before Screening need not be excluded.
21. Answers "yes" to Columbia-Suicide Severity Rating Scale (C-SSRS) suicidal ideation Type 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit, or has been hospitalized or treated for any suicidal behavior in lifetime.

22. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening or a positive urine drug test at Screening. CCI [redacted]
23. Any other medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which in the opinion of the investigator could affect the subject's safety or interfere with the study assessments
24. Concurrent participation in a clinical study involving any anti-amyloid therapies (including any monoclonal antibody therapies) within 6 months before Screening
25. Concurrent participation in a clinical study involving any anti-tau therapies.
26. Participated in any other investigational medication or device study in the 3 months or 5 half-lives (whichever is longer) of the medication before Screening
27. Planned surgery which requires general anesthesia that would take place during the study. CCI [redacted]
28. Visual or hearing impairment that would prevent the subject from performing psychometric tests accurately.

Study Treatments

Cohort A

(revised per Amendment 03)

Phase 1b Treatment Dose: 750 mg E2814 Q4W for 3 doses (12 weeks)

Phase 2 Treatment Dose: 1500 mg E2814 Q4W for at least 3 doses (12 weeks) followed by 3000 mg E2814 Q4W for at least 3 doses (12 weeks), followed by 4500 mg Q4W for the remaining weeks for a total of 96 weeks (revised per Amendments 01 and 02)

Cohort B Treatment Dose: 3000 mg Q4W (revised per Amendment 03)

CCI [redacted]

Duration of Treatment

Cohort A (revised per Amendment 03)

Screening Period: approximately 8 weeks

Phase 1b Treatment Period: 12 weeks

Phase 2 Treatment Period: 96 weeks

Post-Treatment Follow-up Period: 12 weeks

Cohort B (revised per Amendment 03)

Screening Period: approximately 8 weeks

Treatment Period: 52 weeks

Post-treatment Follow-up Period: 12 weeks

Concomitant Drug/Therapy

Any medication (including over-the counter medications and vaccines) or therapy administered to the subject during the study will be recorded.

Stable doses of medication(s) for the treatment of non-excluded medical condition(s) will be permitted provided the dose has been stable for at least 30 days prior to Screening, if they are free of any clinically important side effects attributable to the drug.

CCI

[redacted]

Assessments

Clinical Efficacy Assessments

Cohort A

CCI

[redacted]

CCI [redacted]

Cohort B

CCI [redacted]

Pharmacokinetic Assessments

The date and time of each sample collected will be recorded. Serum and plasma concentrations of E2814 will be analyzed by population PK analysis to characterize the PK of E2814.

Cohort A

Blood samples (8 mL each, 4 mL for serum and 4 mL for plasma) for PK assessments will be collected according to the following schedule in the Phase 1b Treatment Phase (750 mg E2814 administration):

- Predose and immediately at the end of the 1st infusion on Day 1, and at 4, 8, and 24 hours after the end of the infusion
- Single samples will be collected during the outpatient visits on Day 15, Day 29 (predose), and Day 57 (predose).

The following PK samples will be taken during the Phase 2 Treatment Period (1500 mg, 3000 mg, and 4500 mg E2814 administration) (revised per Amendments 01 and 02):

- Predose and immediately at the end of the infusion on Day 85 and at 4, 8, and 24 hours after the end of the infusion
- Predose and immediately at the end of the infusion on Day 169 and predose every 12 weeks thereafter (revised per Amendment 03)
- Predose and immediately after the end of infusion on the day of 1st dose of 4500 mg and predose 12 weeks after the 1st dose of 4500 mg (revised per Amendment 03)
- At the End of Study Visit/Early Termination and Follow-up Visits (revised per Amendment 03)

CSF samples will be collected via LP predose on Day 1 and Day 84 (Week 12 [this collection can occur on Day 85 as long as it occurs predose]). Thereafter, LP sampling will occur 12 weeks after each dose titration on Day 169 (CCI [redacted]), Day 253 (CCI [redacted]; and at the End of Study/Early Termination Visit for PK assessments. (revised per Amendments 01, 02, and 03)

Cohort B

Blood samples (8 mL each, 4 mL for serum and 4 mL for plasma) for PK assessments will be collected according to the following schedule: (revised per Amendment 03)

- Predose and immediately at the end of the infusion on Day 1 and predose at Weeks 12, 24, 36, and 52 (revised per Amendment 04)
- At the End of Study/Early Termination and Follow-up Visits

CSF samples will be collected via LP predose on Day 1, and predose at Week 24 and Week 52. (revised per Amendment 03)

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

A pharmacogenomic (PGx) blood sample (6 mL) for confirmatory *PSEN1*, *APP*, or *PSEN2* gene mutation testing will be taken during Screening.

In addition, in all consented subjects except where prohibited by regional or local laws, the PGx samples may be used to identify genetic factors that may influence a subject's exposure to treatment, as well as genetic factors that may have an effect on clinical response or potential AEs related to treatment, and to explore the role of genetic variability in response. These findings may be used for identification and validation of new drug targets and for potential diagnostic development.

Cohort A

Blood samples (10 mL each) for plasma PD biomarkers will be collected (revised per Amendment 02):

- Predose and immediately at the end of the infusion on Days 1, 29, 57, and 85
- On Day 15
- Predose on Day 169 and every 12 weeks thereafter
- Predose on the day of 1st dose of 4500 mg and 12 weeks after the 1st dose of 4500 mg
- At the End of Study/Early Termination Visit

Cohort B

Blood samples (20 mL each) for plasma PD biomarkers will be collected (revised per Amendment 03):

- Predose on Day 1 and at Weeks 12, 24, 36
- At the End of Study/Early Termination Visits

CSF samples will be collected via LP at Predose on Day 1, and predose at Week 24 and End of Study/Early Termination Visit.

<u>CSF and Blood Plasma Biomarkers:</u>

CSF and blood plasma concentrations of AD-related biomarkers CCI [redacted] will be measured.

<u>Imaging Biomarkers</u>

Cohort A

CCI [redacted]

Cohort B

CCI [redacted]

[redacted]

Safety Assessments

For the Phase 1b and Phase 2 Treatment Periods and the Cohort B Treatment Period, safety will be assessed by monitoring and recording all AEs; regular monitoring of hematology, clinical

chemistry, and urine values; periodic measurement of vital signs and ECGs; periodic evaluation of suicidality using the C-SSRS, and performance of physical examinations. (revised per Amendment 03)

Cohort A

Safety MRIs will be conducted at Screening (Visit 1), at Visit 6, Visit 18 (Week 60) and at the End of Study/Early Termination Visit. (revised per Amendment 02)

Cohort B

Safety MRIs will be conducted at Screening, Week 24, and Week 52. (revised per Amendment 03)

Immunogenicity Assessments

CCI [redacted]

Bioanalytical Methods

CCI [redacted]

Statistical Methods

Study Endpoints

Primary Endpoints

- Incidence of treatment-emergent adverse events and serious adverse events, laboratory parameters, vital signs, and ECGs
- Change from baseline in CSF free and bound MTBR-tau and total MTBR-tau at 12 weeks in Cohort A (revised per Amendment 03)

Secondary Endpoints

- Serum and plasma PK parameters following dosing on Days 1 and 85
- CSF E2814 concentrations

- Serum (or plasma) anti-E2814 antibody concentration
- Change from baseline in CSF and/or plasma biomarkers including t-tau and phosphorylated tau biomarkers
- Change from baseline in tau PET signal

Exploratory Endpoints

CCI [redacted]

Analysis Sets

The Safety Analysis Set is the group of all allocated subjects who received at least 1 dose of study drug . At least 1 laboratory, vital sign, or ECG measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required. This is the analysis population used for all safety analyses which will be based on as-treated principle. (revised per Amendment 01)

The PK Analysis Set is the group of subjects who received at least 1 dose of study drug and had sufficient PK data to derive at least 1 PK parameter.

The PD Analysis Set is the group of subjects who received at least 1 dose of study drug and had sufficient PD data to derive at least 1 PD parameter.

The definition of these analysis sets is the same for both the Phase 1b and Phase 2 Treatment Periods; actual determination of these analysis sets will be made separately for each study period.

Efficacy Analyses

Change from baseline in cognitive assessments will be summarized by visit.

Pharmacokinetic Analyses

The PK analysis will be performed on the PK Analysis Set. Serum and plasma concentrations of E2814 will be tabulated by nominal sampling time and summarized by dose using summary statistics in Cohort A and Cohort B. Serum and plasma concentration-time profiles will be plotted. (revised per Amendment 03)

Serum and plasma E2814 PK parameters will include (but not be limited to) C_{max}, time to reach maximum drug concentration (t_{max}) and area under the concentration-time curve from zero time to the end of the dosing interval ($AUC_{(0\text{-}672h)}$) on Days 1 and 85 in Cohort A. (revised per Amendment 03)

CCI [redacted]

Pharmacodynamic Analyses

CCI [redacted]

CCI [redacted]

Pharmacokinetic-Pharmacodynamic Analyses

CCI [redacted]

Safety Analyses

Evaluation of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, ECGs, C-SSRS and physical examinations (including a psychiatric evaluation). Safety data from the Phase 1b Period of Cohort A will be summarized separately from the Phase 2 Treatment Period of Cohort A and Cohort B. TEAEs will be summarized by dose. (revised per Amendment 03)

Descriptive statistics (eg, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent for categorical variables) of the laboratory, vital signs, and ECGs, and changes from baseline will be evaluated by dose.

Interim Analyses

Not applicable.

Sample Size Rationale

No formal sample size calculations have been performed. For this Phase 1b/Phase 2 study, up to 13 subjects (up to 8 subjects in Cohort A and up to 5 subjects in Cohort B) are considered adequate to evaluate the initial safety and PK in symptomatic DIAD subjects and to establish evidence of TE. (revised per Amendment 03)

3 TABLE OF CONTENTS

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LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AD	Alzheimer's disease
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
APP	amyloid precursor protein
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
COVID-19	coronavirus 2019
CRA	clinical research associate
CRF	Case Report Form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse event
DIAD	Dominantly Inherited Alzheimer's Disease
DIAN-TU	Dominantly Inherited Alzheimer Network-Trial Unit
FAS	Functional Assessment Scale
FCSRT	Free and Cued Selective Reminding Test
GDS	Geriatric Depression Scale
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
ICF	informed consent form

Abbreviation	Term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
mAb	monoclonal antibody
MAC-Q	Memory Assessment Questionnaire
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
MTBR	microtubule binding region
NFT	neurofibrillary tangles
NOAEL	no observed adverse effect level
NPI-Q	Neuropsychiatric Inventory–Questionnaire
PD	Pharmacodynamic
PET	Positron Emission Tomography
PGx	pharmacogenomic
PI	principal investigator
PK	pharmacokinetic
PSEN1	presenilin 1
PSEN2	presenilin 2
PT	Preferred term
Q4W	every 4 weeks
sAD	sporadic AD
SAD	single ascending dose
SAE	serious adverse event

Abbreviation	Term
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
TE	target engagement
TEAE	treatment-emergent adverse events
TEMAV	treatment-emergent markedly abnormal laboratory value
THC	tetrahydrocannabinol
t_{max}	time to reach maximum drug concentration
t-tau	total tau
ULN	upper limit of normal
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WMS-R	Wechsler Memory Scale-Revised

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (GCP), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in Clinical research associates [CRAs], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

Where appropriate, at the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013

- ICH E6 Guideline for GCP (Committee for Proprietary Medicinal Products/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH

- Title 21 of the United States Code of Federal Regulations regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 Code of Federal Regulations Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject or guardian, in accordance with applicable professional standards and local laws/regulations or legally acceptable representative, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 4 or more investigational sites in the United States (US) and United Kingdom (UK).

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Pathology of Alzheimer's Disease

Tau proteins, which belong to the family of microtubule-associated proteins, are mainly expressed in neurons and found in the axons and dendrites. Tau proteins play an important role in the assembly of tubulin monomers into microtubules to constitute the cytoskeleton and serve as tracks for axonal transport. Tau proteins are translated from a single gene located on chromosome 17, with alternative mRNA splicing leading to the formation of 6 different tau isoforms, of which 5 are found in the human adult brain. The isoforms differ, with having either 3 (R1, R3, and R4) or 4 (R1–R4) repeat-regions in the carboxy(C)-terminal part and variable occurrence of microtubule binding region (MTBR). The amino(N)-terminal domain, which establishes links between microtubules and other parts of the cytoskeleton, or the plasma membrane, has a variable occurrence of 0, 1, or 2 inserts of 29 amino acids (Falcon, et al., 2015).

Tau proteins are the key constituent of intracellular fibrillar lesions described in Alzheimer's disease (AD) and other neurodegenerative disorders, referred to as tauopathies. Aggregation of hyperphosphorylated tau into insoluble paired helical filaments that accumulate in nerve cells is a critical process in the formation of neurofibrillary tangles (NFTs), which is a hallmark pathological finding in AD, a secondary tauopathy (Fitzpatrick, et al., 2017). NFTs are also a pathological finding in primary tauopathies, such as Frontotemporal Lobar Degeneration linked to chromosome 17, Corticobasal Degeneration, Pick's disease, Progressive Supranuclear Palsy, and Argyrophilic grain disease, among others. Recent in vitro and in vivo research on the development of paired helical filaments and NFTs has shown that the pathophysiological tau process appears to be initiated by the occurrence of extracellular tau seeds. These small soluble tau seeds trigger the spread of tau pathology across the brain, possibly in a transynaptic manner, inducing the formation of intracellular insoluble tau aggregates, thereby driving the development of NFT pathology (Goedert and Spillantini, 2017, Noble, et al., 2013, and von Bergen, et al., 2000). In AD, NFTs occur in a neuroanatomically characteristic pattern of increasing severity, generally defined according to the Braak stages I to VI, which correlate well with progressive neuronal loss and clinical decline. Consequently, selective targeting and removal of tau seeds is expected to stop or slow down disease progression in tauopathy.

7.2 Compound Overview

The Therapeutic Innovation Group compound "C"-E2814 is a novel immunoglobulin G subclass 1a monoclonal antibody (mAb) that binds with high affinity to 2 epitopes in the 4R region and one epitope in the 3R region of tau. Critically, E2814 has been shown to bind to the MTBR, a region on tau that is found in the vast majority of tau species and considered to be required for tau seeding to occur. E2814 has been shown to inhibit tau aggregation in vitro, while the murine form of E2814 (7G6) has shown the ability to reduce the transmission of tau species in vivo, even in a model containing just 1 of the 2 binding sites normally found in the 4R isoform of the tau protein (Roberts, et al., 2020). The proposed mechanism for drug effect in humans is that E2814 will bind to the assumed low amounts of extracellular MTBR-containing tau and thereby inhibit further tau aggregation and accelerate its clearance, such as mAb mediated uptake and phagocytosis in microglia.

The target clinical indication for E2814 is AD, which represents the most common tauopathy with a significant global disease burden, exerting a devastating effect on patients and their families and having a considerable impact on healthcare systems. However, development of highly effective AD treatments has been hampered by the lack of surrogate biomarkers, slow course of cognitive and clinical decline, variability in clinical phenotype, and variability when measuring cognition and functional impairments in AD. These challenges are especially difficult since validated diagnosis of AD in the absence of symptoms has not yet been achieved. Prevention trials thus must be long and large due to inability to predict if and when cognitive symptoms will start, lack of functional impairment, and difficulties identifying an at-risk study population prior to symptomatic cognitive decline.

In order to address key AD prevention trial design challenges through utilizing a population almost certain to develop AD – the Dominantly Inherited AD (DIAD) population, the Dominantly Inherited Alzheimer Network-Trial Unit (DIAN-TU) designed and executed a pioneering prevention trial for the DIAD population (Bateman, et al., 2017). The DIAD population represents a unique group for study since the genetic mutations in these individuals are thought to underlie the pathophysiologic changes inherent in AD. In addition, the impact of age-related changes on cognitive function and brain pathology are minimized since cognitive impairment occurs at a younger and predictable age based on family history. Changes in cognitive, clinical, biochemical, and structural measures in DIAD are similar to sporadic AD (sAD), suggesting that a common pathophysiology exists between DIAD and sAD. Therefore, treatment trials in DIAD are likely to provide further insights into underlying mechanisms of the common pathophysiology.

Regarding tau pathology for the comparison between DIAD and sAD, the distribution of NFT pathology appears similar between DIAD and sAD and the molecular and 3-dimensional structure of the tauopathies are identical (Fitzpatrick, 2017). Further, recent studies in the DIAN consortium have demonstrated similar distributions of tau Positron Emission Tomography (PET) signals in DIAD and sAD. Thus, the distribution and type of tau pathology among DIAD and sAD are analogous. This evidence strongly suggests that the temporal order and progression of pathophysiological, cognitive, and clinical changes are

shared in DIAD and sAD. Therefore, DIAD presents a unique opportunity to examine experimental disease modifying therapies for AD. Patients can be identified for whom the likelihood of future dementia is essentially certain and therapy can be initiated at predictable times in relation to measurable disease biomarkers. Moreover, in light of the diagnostic reliability and consequent population homogeneity, such studies require fewer patient participants and shorter total study lengths relative to trials in sAD.

The findings from the previous randomized clinical trials for anti-amyloid antibodies in the DIAN-TU platform are viewed as the supportive reason to explain testing tau-based agents in DIAD subjects and may represent the best possibility for measurable benefit in either biomarker outcomes or cognitive decline. Given this situation, Eisai's anti-tau antibody (E2814) has been selected as one candidate for the next step of the DIAN-TU Trials.

7.3 Study Rationale

The proposed study is an open-label Phase 1b/2 study to evaluate the safety and target engagement (TE) of 2 different doses of E2814 on MTBR-tau species in cerebrospinal fluid (CSF) in subjects with DIAD and exhibiting mild to moderate cognitive impairment. This study will target individuals who are known to have a disease-causing mutation confirmed by the genetic testing. The study will also assess the pharmacokinetic (PK), immunogenicity, and other pharmacodynamic (PD) effects of E2814. No formal sample size calculations have been performed. For this Phase 1b/Phase 2 study, up to 8 subjects in Cohort A and up to 5 subjects in Cohort B are considered adequate to evaluate the initial safety and PK in symptomatic DIAD subjects and to establish evidence of TE. (revised per Amendment 03)

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objectives of the study are:

- To assess the safety and tolerability of intravenous (IV) infusions of E2814 in subjects with DIAD
- To evaluate TE of E2814 on MTBR-tau species in CSF in subjects with DIAD

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the PK of E2814 in serum, plasma, and CSF
- To assess the immunogenicity (production of anti-E2814 antibody) of E2814
- To assess the effect of E2814 on CSF, blood, and imaging biomarkers

8.3 Exploratory Objectives

The exploratory objectives of the study are:

CCI [redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E2814-G000-103 is an open-label Phase 1b/2 study to evaluate the safety and TE of E2814 on MTBR-tau species in CSF following IV infusions of E2814 in DIAD subjects. CCI [redacted]

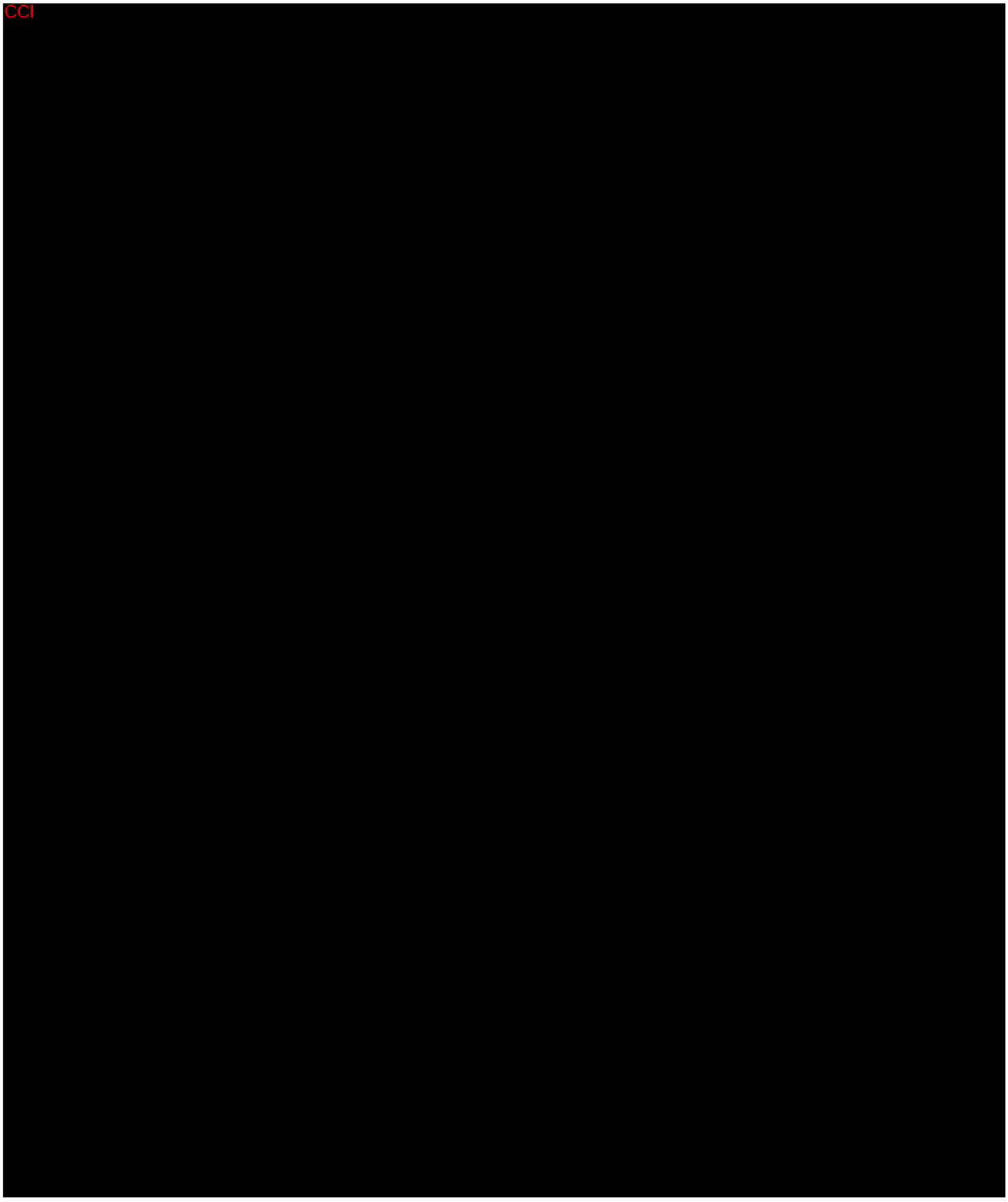
The study will consist of 2 Cohorts (A and B). (revised per Amendment 03)

Cohort A consists of 2 phases: A Pretreatment Phase consisting of a Screening Period and a Treatment Phase consisting of 3 periods: 1b, 2, and follow up. (revised per Amendment 03)

Cohort B will consist of a Pretreatment Phase and a Treatment Phase consisting of 2 periods (52-week Treatment Period and 12-week Follow Up Period). (revised per Amendment 03)

The end of the study will be the date of the last study visit for the last subject in the study.

An overview of the study design is presented in Figure 1 (Cohort A) and Figure 2 (Cohort B). (revised per Amendment 03)



9.1.1 Pretreatment Phase

9.1.1.1 Screening Period

Cohort A Screening Period (revised for Amendment 03)

Screening will occur between Day –60 and Day –2. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any Screening procedures or assessments. Screening assessments will include tau PET, amyloid PET, and safety magnetic resonance imaging (MRI) and genetic testing to confirm mutation status. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Cohort B Screening Period (revised for Amendment 03)

Screening will occur between Day -60 and Day -2. The purpose and assessments are the same as for the remainder of the subjects except that amyloid PET will not be done in Cohort B subjects.

9.1.2 Treatment Phase

During the Cohort A Phase 2 and Cohort B Treatment Periods, infusions will take place in the clinic. When the process for home infusion is established, and if allowed and conducted according to local guidelines, the investigator may assess for an individual subject if home infusions are suitable according to the following guidelines: If a subject has shown acceptable tolerability for the infusions, is considered by the investigator to be at low risk of developing AEs related to study drug infusion that may require acute medical treatment, and has shown no clinically significant findings on other safety measures related to study drug infusion during the Cohort A Phase 1b Treatment Period or the first month or first dose of Cohort B treatment, he or she may be allowed to receive infusions at home keeping in accordance with the required infusion schedule, depending on the feasibility for blood sampling or cognitive assessments on the scheduled visits. (revised per Amendment 03)

9.1.2.1 Cohort A

9.1.2.1.1 PHASE 1B TREATMENT PERIOD

The Phase 1b Treatment Period will initially allow 8 subjects to receive open-label treatment with 3 IV infusions of 750 mg E2814 every 4 weeks (Q4W) over 12 weeks. Subjects will check into the clinic on the day before dosing but will not be required to stay in the clinic overnight on Day -1 to Day 2, they may instead stay overnight at a nearby hotel and return to the clinic the next day. In addition, subjects will have outpatient visits on Days 15, 29, and 57. On conclusion of the Phase 1b Treatment Period, on Day 84, subjects will check into the clinic and will undergo safety assessments. Subjects will not be required to stay in the clinic overnight on Day 84 to Day 86, they may instead stay overnight at a nearby hotel and return to the clinic the next day. A CSF sample will be collected for assessment of TE and CSF concentrations of E2814 on Day 1 and Day 84. Subjects will then progress to the Phase 2 Treatment Period. Subjects who withdraw from the Phase 1b Treatment Period for reasons other than safety may be replaced.

9.1.2.1.2 PHASE 2 TREATMENT PERIOD

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[redacted]

9.1.2.2 Cohort B (revised per Amendment 03)

All subjects in Cohort B will be administered 3000 mg of E2814 Q4W for up to 52 weeks. All visits will be outpatient or home infusion visits and will occur Q4W for the duration of the study. A CSF sample will be collected at baseline, Week 24, and Week 52. Samples will be used to analyze PD effects of E2814 on biomarkers associated with AD. The

concentrations of E2814 in postdose samples will also be assessed. Subjects will also undergo safety MRI, tau PET scans, and cognitive assessment at Visit 2, Week 24, and the End of Study/Early Termination Visit. For subjects who discontinue early, early termination CSF collection and tau PET scan will be performed, unless these assessments were performed within the previous 3 months.

9.1.2.3 Follow-Up Period

The Follow-up Period will follow all subjects for a period of 12 weeks after the last dose for safety.

9.2 Discussion of Study Design, Including Choice of Control Groups

The study will consist of 2 cohorts (A and B) (revised per Amendment 03):

Cohort A will consist of 2 phases:

1. The Phase 1b component of Cohort A will evaluate IV infusions of 750 mg E2814 (an intermediate dose of E2814) Q4W for 3 doses (12 weeks) to assess safety, tolerability, TE, PK, and immunogenicity of E2814.
2. The Phase 2 component of Cohort A will be initiated to receive a further 96 weeks of IV E2814 at an initial dose of 1500 mg Q4W for at least 3 doses (12 weeks), followed by 3000 mg Q4W for at least 3 doses (12 weeks), followed by 4500 mg Q4W for the remaining weeks. (revised per Amendments 01 and 02) Subjects must complete the Phase 1b component before they enter the Phase 2.

Cohort B will receive IV E2814 at a dose of 3000 mg Q4W for up to 52 weeks. (revised per Amendment 03)

In both Cohorts, pharmacogenomic (PGx) samples will be collected and may be used to explore heterogeneity in clinical features of disease including differences in baseline characteristics as well as PK, PD, and/or safety-related outcomes. For this compound, there is no expectation that any of these endpoints will be impacted by PGx variability on the absorption, distribution, metabolism, and elimination of E2814. PGx samples from this study may be used for future exploratory analyses which are not limited to this protocol or project. Findings may also be used, after pooling with samples across studies or projects as appropriate, for identification and validation of new drug targets and for potential diagnostic development. (revised per Amendment 03)

9.3 Selection of Study Population

Up to 13 subjects (up to 8 subjects in Cohort A and up to 5 subjects in Cohort B) will be enrolled at approximately 4 or more sites in the US and UK. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug. (revised per Amendment 03)

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Male or female, age 18 to 80 years at the time of informed consent
2. Individuals who are confirmed to be mutation positive for *PSEN1*, *APP*, or *PSEN2* gene that is associated with DIAD
3. CDR-SB score 5 to 12 at Screening
4. CCI [redacted]
5. Able to undergo MRI, LP, PET, and complete all study-related testing and evaluations
6. Has a study partner who in the investigator's judgment is able to provide accurate information as to the subject's cognitive and functional abilities, who agrees to provide information at the study visits which require informant input for scale completion

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Clinically significant illness that required medical treatment within 8 weeks before the 1st dose or a clinically significant infection that required medical treatment within 4 weeks before 1st dose
2. Females who are breastfeeding or pregnant at Screening or Baseline CCI [redacted]
3. Females of childbearing potential who:
   - Within 3 months before Screening, did not use a highly effective method of contraception, CCI [redacted]

NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

4. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
5. History of transient ischemic attacks, stroke, or seizures within 12 months of Screening
6. History of clinically important carotid or vertebrobasilar stenosis, plaque, or other prominent risk factor for stroke or cerebral haemorrhage (including atrial fibrillation and anticoagulation). Low dose aspirin (≤325 mg daily) is not exclusionary
7. Any current psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could interfere with study procedures in the subject
8. Geriatric Depression Scale (GDS) score greater than or equal to 8 at Screening
9. Contraindications to MRI scanning, including but not limited to pacemaker/cardiac defibrillator, neurostimulators, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners)
10. Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD
11. Other significant pathological findings on brain MRI at Screening, [redacted]
12. Hypersensitivity to E2814 or any of the excipients, or to any mAb treatment
13. Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study
14. With a bleeding disorder of current chronic use of anticoagulants (eg, warfarin, dabigatran, rivaroxaban or apixaban) or of clopidogrel is exclusionary. Limited (occasional or isolated) use of anticoagulants/antiplatelet compounds in cases such as surgical procedures.
15. Have thyroid stimulating hormone outside of normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects whether or not they are taking thyroid supplements.

16. HgbA1c >8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes). Subjects may be rescreened after 3 months to allow optimization of diabetic control.
17. Abnormally low serum vitamin B12 levels for the testing laboratory [redacted]
18. History of human immunodeficiency virus (HIV) infection, history of hepatitis B infection within the past year, history of hepatitis C infection which has not been adequately treated, or history of spirochete infection of the central nervous system (eg, syphilis, Lyme, or borreliosis)
19. Any other clinically significant abnormalities in physical examination, vital signs, laboratory tests, or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety
20. Malignant neoplasms within 3 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects, or localized breast cancer in female subjects). Subjects who had malignant neoplasms but who have had at least 3 years of documented uninterrupted remission before Screening need not be excluded.
21. Answers "yes" to Columbia-Suicide Severity Rating Scale (C-SSRS) suicidal ideation Type 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit, or has been hospitalized or treated for any suicidal behavior in lifetime.
22. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening or a positive urine drug test at Screening. [redacted]
23. Any other medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which in the opinion of the investigator could affect the subject's safety or interfere with the study assessments
24. Concurrent participation in a clinical study involving any anti-amyloid therapies (including any mAb therapies) within 6 months before Screening
25. Concurrent participation in a clinical study involving any anti-tau therapies.
26. Participated in any other investigational medication or device study in the 3 months or 5 half-lives (whichever is longer) of the medication before Screening
27. Planned surgery which requires general anesthesia that would take place during the study. [redacted]

28. Visual or hearing impairment that would prevent the subject from performing psychometric tests accurately.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

9.4 Treatments

9.4.1 Treatments Administered

Cohort A:

- Phase 1b: 750 mg E2814 administered as a 1-hour intravenous infusion (maximum infusion time 2 hours, if needed) Q4W. Duration of treatment will be 12 weeks.
- Phase 2: 1500 mg or 3000 mg E2814 administered as a 1-hour intravenous infusion (maximum infusion time 2 hours, if needed) Q4W for at least 3 doses (12 weeks) followed by 3000 mg Q4W for at least 3 doses (12 weeks), then 4500 mg Q4W for the remaining weeks. The 4500 mg doses will be administered as a 2-hour intravenous infusion (maximum infusion time 4 hours, if needed) Q4W. Total duration of treatment will be 96 weeks. (revised per Amendments 01, 02, and 03)

Cohort B: 3000 mg administered as a 1-hour IV infusion (maximum infusion time 2 hours, if needed) Q4W. (revised per Amendment 04) Duration of treatment will be 52 weeks. (revised per Amendment 03)

The duration of the Post-Treatment Follow-up Period in both cohorts will be 12 weeks. (revised per Amendment 03)

9.4.2 Identity of Investigational Product

Investigational products, ie, test drug will be supplied by the sponsor in labeled containers.

9.4.2.1 Chemical Name of E2814

- Test drug code: E2814
- Generic name: Not available.
- Chemical name: Not applicable
- CCI
- [redacted]

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

E2814 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive E2814. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

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One of the primary objectives of this study is to confirm TE in subjects with DIAD. Furthermore, this study is designed to investigate whether the safety profile of E2814 in subjects with DIAD is similar to the safety profile in healthy subjects in Study 001.

CCI

9.4.5 Selection and Timing of Dose for Each Subject

The 750, 1500, and 3000 mg doses will be administered as a 1-hour IV infusion (maximum infusion time 2 hours, if needed) Q4W. The 4500 mg doses will be administered as a 2-hour IV infusion (maximum infusion time 4 hours, if needed) Q4W. (revised per Amendments 01, 02, and 03)

9.4.6 Blinding

This study will not be blinded.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the counter medications and vaccines) or therapy administered to the subject during the study will be recorded.

Stable doses of medication(s) for the treatment of non-excluded medical condition(s) will be permitted provided the dose has been stable for at least 30 days prior to Screening, if they are free of any clinically important side effects attributable to the drug.

Stable doses of cholinesterase inhibitors and/or memantine will be permitted if they have been taking these medications for at least 90 days prior to Screening and has been on a stable dose for at least 60 days prior to Screening.

Flu, shingles, pneumococcal and hepatitis B, and other vaccines can be administered at least 2 weeks before the 1st administration of the study drug in Phase 1b Treatment Period. Once study drug dosing initiates, no vaccines should be administered before the 3rd infusion. Thereafter, the vaccines can be administered during Phase 2 Treatment Period and Follow-up Period. Vaccination should be timed such that it will be administered at least 7 days after the previous infusion and at least 7 days before the next infusion of the study drug. (revised per Amendment 01)

COVID-19 vaccination will not be allowed from 7 days before dosing and until 7 days after each dose. Where possible, subjects should be encouraged to receive their full course of COVID-19 vaccination prior to 7 days before initiation of dosing in this study. (revised per Amendment 01)

The use of marijuana (including products containing tetrahydrocannabinol [THC]) is allowed during the study if the investigator confirms that there is no suspected abuse or dependency related to marijuana and THC use will not prevent the subject from performing psychometric tests accurately. (revised per Amendment 02)

The following concomitant drugs and therapies are not permitted before Screening and until the last visit during the Treatment Period:

a. Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the Treatment Period
b. Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before Screening and until the last visit during the Treatment Period

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number

- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, or a completed Investigator and Site Information Form
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572 or Investigator and Site Information Form
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement.
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority. As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and, together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and

documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Screening Assessments

Screening assessments will be conducted as specified in the Schedule of Procedures/Assessments (Table 4 or Table 5). Assessments scheduled to be conducted at the Screening Visit (Visit 1) only, are described below (Sections 9.5.1.1.1 through 9.5.1.1.4). (revised per Amendment 03)

9.5.1.1.1 DEMOGRAPHY

Subject demography information will be collected at the Screening Visit. Demography information includes age, sex, race/ethnicity. (revised per Amendment 01)

9.5.1.1.2 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions Case Report Form (CRF).

9.5.1.1.3 VIRAL TESTS

A (6 mL) sample of blood will be taken for hepatitis B core antibody (HBcAb), hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb) and HIV tests at the Screening Visit. Test dates and results will be recorded in the medical records at the study site.

9.5.1.1.4 DRUG, COTININE, AND ALCOHOL TESTS

Urine Drug and Cotinine Test

A sufficient urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 4 or Table 5). This sample will be tested for common drugs of use/abuse: eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids (as a group), benzodiazepines, barbiturates, and amphetamines. (revised per Amendment 03)

Breath Alcohol Test

The breath alcohol test will be performed according to the investigational site's SOP at Screening.

9.5.1.2 Clinical Efficacy Assessments

Cohort A

CCI [redacted]

Cohort B

CCI [redacted]

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

The date and time of each sample collection will be recorded. Serum and plasma concentrations of E2814 will be analyzed by population PK analysis to characterize the PK of E2814. (revised per Amendment 03)

Serum, plasma, and CSF concentrations of E2814 will be measured by validated electrochemiluminescence assays and/or by a validated immunoprecipitation/purification followed by liquid chromatography with tandem mass spectrometry, if available. Anti-E2814 antibodies will be measured by a validated electrochemiluminescence assay.

See Laboratory Manual for a description of collection, handling, and shipping procedures for PK samples.

Cohort A

Blood samples (8 mL each, 4 mL for serum and 4 mL for plasma) for PK assessments will be collected according to the following schedule in the Phase 1b Treatment Period (750 mg E2814 administration):

- Predose and immediately at the end of the 1st infusion on Day 1, and at 4, 8, and 24 hours after the end of the infusion
- Single samples will be collected during the outpatient visits on Day 15, Day 29 (predose), and Day 57 (predose).

The following PK samples will be taken during the Phase 2 Treatment Period (1500 mg, 3000 mg, and 4500 mg E2814 administration) (revised per Amendments 01 and 02):

- Predose and immediately at the end of the infusion on Day 85 and at 4, 8, and 24 hours after the end of the infusion
- Predose and immediately at the end of the infusion on Day 169 and predose every 12 weeks thereafter
- Predose and immediately after the end of the of the infusion on the day of the 1st dose of 4500 mg and predose 12 weeks after the 1st dose of 4500 mg
- At the End of Study/Early Termination and Follow-up Visits (revised per Amendment 03)

CSF samples will be collected via LP predose on Day 1 and Day 84 (Week 12 [this collection can occur on Day 85 as long as it occurs predose]). Thereafter, LP sampling will occur 12 weeks after each dose titration on Day 169 CCI Day 253 CCI and the End of Study/Early Termination Visit for PK assessments. (revised per Amendments 01, 02, and 03)

Cohort B

Blood samples (8 mL each, 4 mL for serum and 4 mL for plasma) for PK assessments will be collected at the following timepoints (revised per Amendment 03):

- Predose and immediately at the end of the infusion on Day 1 and predose at Weeks 12, 24, 36, and 52
- At the End of Study/Early Termination and Follow-up Visits

CSF samples will be collected via LP predose on Day 1, Week 24, and Week 52. (revised per Amendment 03)

9.5.1.3.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker, Assessments

Pharmacodynamic Assessments

CSF samples collected as outlined in Section 9.5.1.3.1 will be used to evaluate MTBR-tau TE (free/bound MTBR-tau species) and CSF concentration of E2814 as well as for assessment of biomarker endpoints. (revised per Amendments 01 and 02)

Cohort A

Blood samples (10 mL each) for plasma PD biomarkers will be collected (revised per Amendments 01 and 02):

- Predose and immediately at the end of the infusion on Days 1, 29, 57, and 85
- On Day 15
- Predose on Day 169 and every 12 weeks thereafter
- Predose on the day of the1st dose of 4500 mg and predose 12 weeks after the 1st dose of 4500 mg
- At the End of Study/Early Termination Visit

Cohort B

Blood samples (20 mL each) for plasma PD biomarkers will be collected (revised per Amendment 03):

- Predose and on Day 1 and at Weeks 12, 24, and 36
- At the End of Study/Early Termination Visit

CSF samples will be collected via LP at Predose on Day 1, and predose at Week 24, and End of Study/Early Termination Visit. (revised per Amendment 03)

Pharmacogenomic Assessments

A PGx blood sample (6 mL) for confirmatory *PSEN1*, *APP*, or *PSEN2* gene mutation testing will be taken during Screening.

In addition, in all consented subjects except where prohibited by regional or local laws, the PGx samples may be used to identify genetic factors that may influence a subject's exposure to treatment, as well as genetic factors that may have an effect on clinical response or potential AEs related to treatment, and to explore the role of genetic variability in response. These findings may be used for identification and validation of new drug targets and for potential diagnostic development.

CSF and Blood Plasma Biomarkers:

CSF and blood plasma concentrations of AD-related biomarkers [redacted] will be measured.

Imaging Biomarkers

[redacted]

9.5.1.4 Safety Assessments

For the Cohort A Phase 1b and Phase 2 Treatment Periods and the Cohort B Treatment Period, safety assessments will consist of monitoring and recording all AEs; regular monitoring of hematology, clinical chemistry, and urine values; periodic measurement of vital signs and ECGs; periodic evaluation of suicidality using the C-SSRS, and performance of physical examinations as detailed in Table 4 or Table 5. In Cohort A, Safety MRIs will be conducted at Screening (Visit 1), Visit 6, Visit 18 (Week 60, Day 421), and at the End of Study/Early Termination Visit. (revised per Amendment 02) In Cohort B, safety MRIs will be conducted at Screening, Week 24, and Week 52. (revised per Amendment 03)

9.5.1.4.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2814.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit. Refer to Section 9.5.4.1 for the time period after the end of treatment for serious adverse event (SAE) collection.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the AE CRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the clinical assessment of suicidality, C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE.

All AEs must be followed for 16 weeks after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. (revised per Amendment 01)

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.4.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment

- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.4.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be

captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the 1st report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.4.3 STUDY-SPECIFIC ADVERSE EVENTS

The study-specific events, infusion reaction, should always be considered AEs and reported on the AE CRF and on the event-specific CRFs designed to collect additional information on specific events.

Infusion Reactions

Any infusion-related reaction should be graded and managed according to the recent Common Terminology Criteria for Adverse event (CTCAE), Version 5.0, grading of allergic/hypersensitivity reactions/cytokine release, as follows:

- Grade 1: mild reaction, infusion interruption not indicated, systemic intervention not indicated
- Grade 2: oral intervention indicated (eg, antihistamines, nonsteroidal anti-inflammatory drugs, corticosteroids)
- Grade 3: prolonged reaction or recurrence of symptoms, bronchospasm, hospitalization indicated for clinical sequelae, IV intervention indicated
- Grade 4: life-threatening consequences; urgent treatment needed
- Grade 5: death

Infusion reactions of any grade outlined above (Grade 1 to 5) should be reported as AEs of special interest.

If a Grade 2 infusion reaction occurs, the infusion may be stopped (as deemed appropriate by the investigator) and the subject treated with antihistamines, corticosteroids, anti-inflammatory drugs, or other medications as medically indicated.

If a Grade 3 or higher infusion reaction occurs, the infusion should be immediately stopped and the subject should be treated with antihistamines, corticosteroids, anti-inflammatory drugs, IV fluids, or other medications and treatment as medically indicated.

9.5.1.4.4 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, clinical chemistry, and urinalysis, are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 4 or Table 5) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. (revised per Amendment 03)

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), fibrinogen, prothrombin time, aPTT, INR
Clinical chemistry	
Electrolytes	Calcium, chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Blood chemistry	Free T3, free T4, TSH, Vitamin B12, methylmalonic acid, C-reactive protein
Other	Albumin, total cholesterol, globulin, glucose, lactate dehydrogenase, inorganic phosphorus, total protein, protein fraction, triglycerides, uric acid, HbA_{1c}, hepatitis viral screen (HBcAb, HBsAg, HCVAb), HIV
Urinalysis	Glucose, ketones, occult blood, pH, protein, sediment (RBCs, WBCs, bacteria, casts, crystals, epithelial cells), specific gravity

HbA_{1c} levels and viral screen will be done at Screening only.
Total fibrinogen levels (measured in plasma using immunological methods) and functional fibrinogen (measured in plasma using the Clauss method) will be determined.
aPTT = activated partial thromboplastin time, HbA1c = glycosylated hemoglobin, HBcAb = hepatitis B core antibody, HBcAg = hepatitis B core antigen, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HIV = human immunodeficiency virus, INR = international normalized ratio, RBC = red blood cell, WBC = white blood cell.

Clinical laboratory tests will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless

otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Local laboratories will perform tests to qualify subjects for entry into the study. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the AE CRF [see Section 9.5.4.3.2]).

9.5.1.4.5 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), height (cm) and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 4 or Table 5) by a validated method. BP and pulse will be measured after the subject has been supine or semi-supine for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. (revised per Amendment 03)

9.5.1.4.6 PHYSICAL EXAMINATIONS

Comprehensive and abbreviated physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 4 or Table 5). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from Screening physical examination findings that meet the definition of an AE will be recorded on the AEs CRF (see Section 9.5.1.4.1). (revised per Amendment 03)

Comprehensive Physical Examination

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. The subject will be queried regarding physical status and subjective symptoms as well. A urogenital examination will only be required in the presence of clinical symptoms related to this region.

Abbreviated Physical Examination

Health status will be assessed by brief evaluation of the head, eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination.

9.5.1.4.7 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 4 or Table 5). (revised per Amendment 03)

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs CRF.

9.5.1.4.8 OTHER SAFETY ASSESSMENTS

Suicidality

An assessment of suicidality using the C-SSRS will be performed as designated in the Schedule of Procedures/Assessments (Table 4 or Table 5). (revised per Amendment 03)

Pregnancy Test

A serum β-hCG test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A 6-mL sample of blood will be taken at designated time points as specified in the Schedule of Procedures/Assessments (Table 4 or Table 5).

9.5.1.5 Immunogenicity Assessments

Cohort A

Immunogenicity will be assessed by measuring the presence of anti-E2814 antibodies predose on Days 1, 15, 29, 57, 85, 169 and every 12 weeks thereafter; predose on the day of the 1st dose of 4500 mg and 12 weeks after the 1st dose of 4500 mg; and at the End of Study/Early Termination and Follow-up Visits. (revised per Amendments 02 and 03)

Cohort B

Immunogenicity will be assessed by measuring the presence of anti-E2814 antibodies predose, on Day 1, and at Weeks 12, 24, 36, and at the EOT/ET and Follow-up Visits. (revised per Amendment 03)

CCI [redacted]

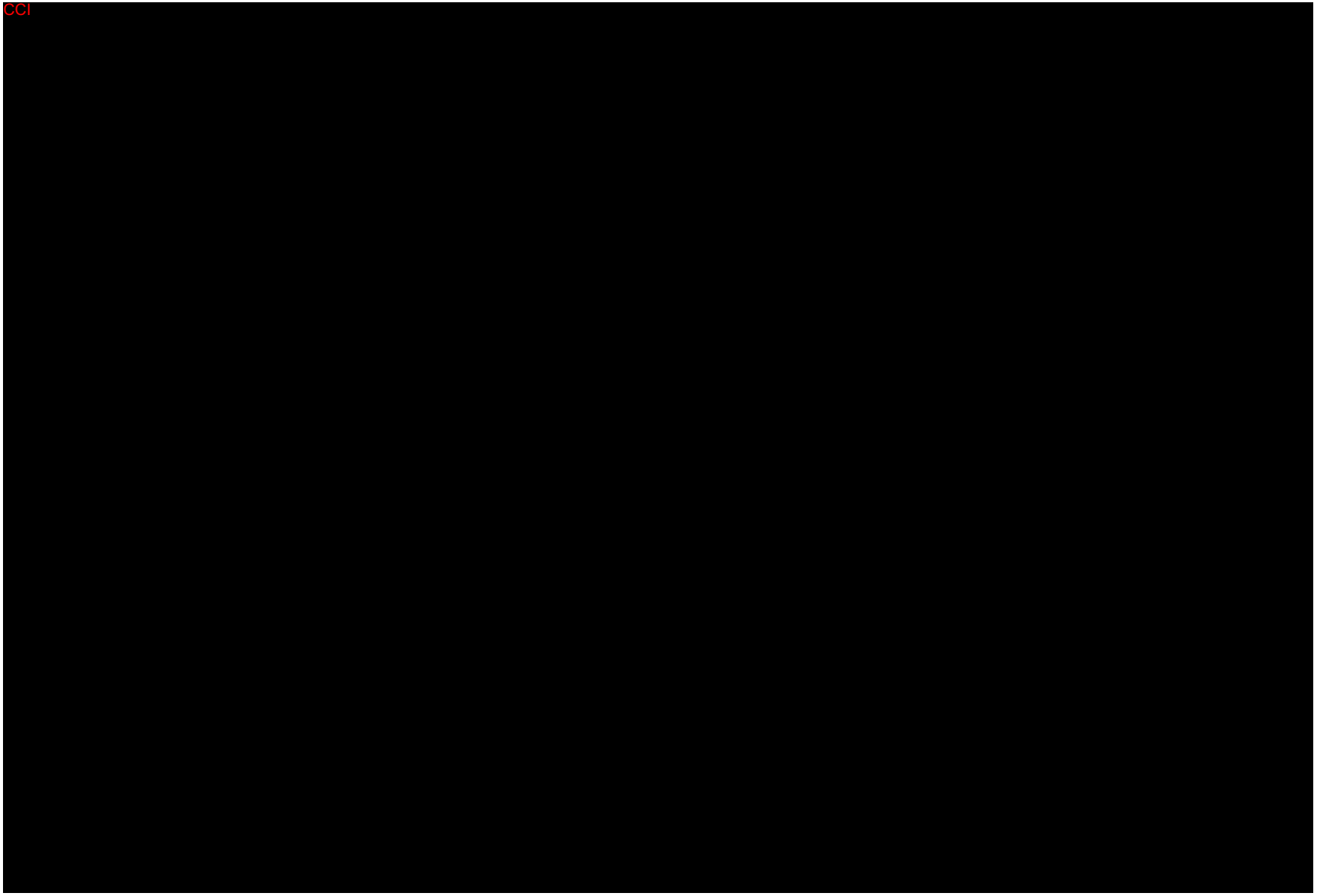
9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 and Table 5 present the schedule of procedures/assessments for the study. (revised per Amendment 03)

CCI

[redacted]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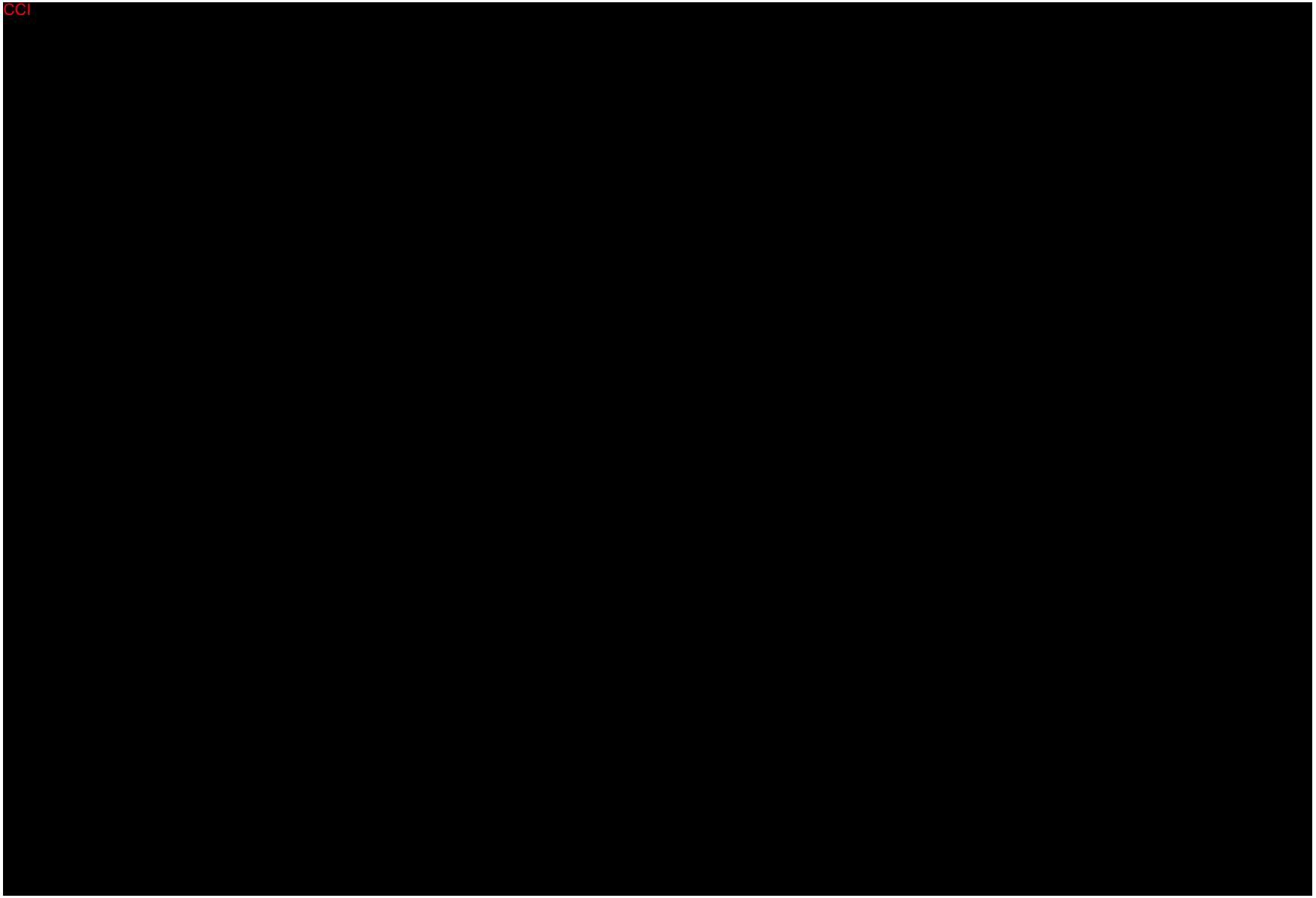
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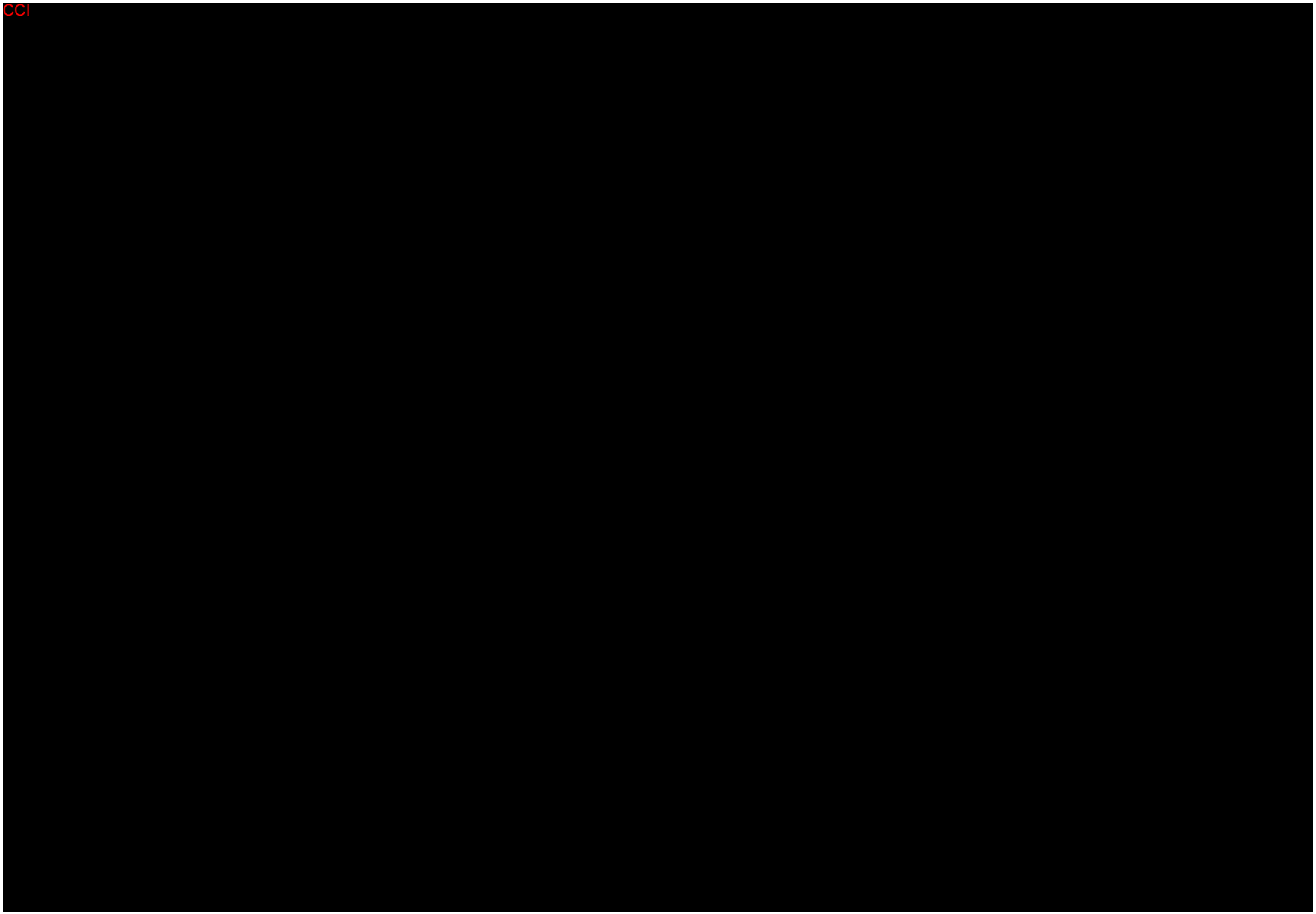
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9.5.2.2 Description of Procedures/Assessments Schedule

See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

See Table 4 and Table 5 for the timing of the procedures and assessments to be performed during the study. A window of ±7 days will be permitted for all visits after Visit 2. The visit windows should be calculated from the day of 1st dose (Day 1). If a permitted visit window is used, every effort should be made to bring the subject back in line with the prespecified visit schedule at subsequent visits. Assessments for study visits that require PET, MRI, and/or cognitive assessments may be completed over several days if needed provided all assessments are completed within the visit window. (revised per Amendments 01, 02, and 03)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in Phase 1b/Phase 2 studies.

The safety assessments to be performed in this study, including hematology analyses, clinical chemistry tests, urinalysis, radiologic studies, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected for 100 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 16 weeks of last study treatment, (or any partner's pregnancy of a male subject in which the estimated date of conception is either before the last visit or within 16 weeks of last study treatment), or any exposure to study drug through breastfeeding during study treatment or within 16 weeks of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study. A subject who becomes pregnant may remain in the study if the investigator judges that the potential benefit to the subject outweighs any potential risk to the subject or the fetus and the subject gives informed consent for the further participation.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the AE CRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse and Intentional Overdose, even if asymptomatic, are always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the AE CRF.

9.5.4.3.2 Reporting of Abnormal Hepatic Tests of Clinical Interest

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the AE CRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."

- Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value that is greater than or equal to 3× the upper limit of normal (ULN) or if elevated greater than the ULN at baseline, then 3× the baseline for the subject

  AND

- Elevated total bilirubin lab value that is greater than or equal to 2× the ULN or if elevated greater than the ULN at baseline, then 1.5× the baseline for the subject

  AND AT THE SAME TIME

- Alkaline phosphatase lab value that is less than 2× the ULN

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve. (revised per Amendment 01)

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

AEs will be reported by the sponsor or a 3rd party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 4).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

Subjects who withdraw from the Phase 1b Treatment Period for reasons other than safety may be replaced. A subject removed from the study for any reason during the Phase 2 Treatment Period may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 or Investigator and Site Information Form must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to 3rd parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

- Incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECGs
- Change from baseline in CSF free and bound MTBR-tau and total MTBR-tau at 12 weeks in Cohort A (revised per Amendment 03)

9.7.1.1.2 SECONDARY ENDPOINTS

- Serum and plasma PK parameters following dosing on Days 1 and 85
- CSF E2814 concentrations
- Serum (or plasma) anti-E2814 antibody concentration
- Change from baseline in CSF and/or plasma biomarkers including total tau (t-tau) and phosphorylated tau biomarkers
- Change from baseline in tau PET signal

9.7.1.1.3 EXPLORATORY ENDPOINTS

CCI

[redacted]

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set is the group of all allocated subjects who received at least 1 dose of study drug. At least 1 laboratory, vital sign, or ECG measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required. This is the analysis population used for all safety analyses which will be based on as-treated principle. (revised per Amendment 01)

The PK Analysis Set is the group of subjects who received at least 1 dose of study drug and had sufficient PK data to derive at least 1 PK parameter.

The PD Analysis Set is the group of subjects who received at least 1 dose of study drug and had sufficient PD data to derive at least 1 PD parameter.

The definition of these analysis sets is the same for both the Phase 1b and Phase 2 Treatment Periods; actual determination of these analysis sets will be made separately for each study period.

9.7.1.3 Subject Disposition

The number of subjects administered each dose of E2814 along with the number in each of the analysis sets will be presented overall and by cohort. (revised per Amendment 03)

The number of subjects completing the study will be presented overall and by cohort. (revised per Amendment 03)

Subjects who prematurely terminate their participation in the study will be summarized by their primary reason for study termination.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized by dose using descriptive statistics overall and by cohort. Continuous demographic and baseline variables include age, height and weight; categorical variables include sex, age group, and race. (revised per Amendment 03)

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded using the World Health Organization Drug Dictionary (Sep 2020). Prior medications will be defined as medications that stopped before the 1st dose of study drug. Concomitant medications will be defined as medications that (1) started before the 1st dose of study drug and were continuing at the time of the 1st dose of study drug, or (2) started on or after the date of the 1st dose of study drug up to 100 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

Change from baseline in cognitive assessments will be summarized by visit.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK analysis will be performed on the PK Analysis Set. Serum and plasma concentrations of E2814 will be tabulated by nominal sampling time and summarized by dose using summary statistics in Cohort A and Cohort B. Serum and plasma concentration-time profiles will be plotted. (revised per Amendment 03)

Serum and plasma E2814 PK parameters will include (but not be limited to) C_{max}, time to reach maximum drug concentration (t_{max}) and area under the concentration-time curve from zero time to the end of the dosing interval ($AUC_{(0-672h)}$) on Days 1 and 85 in Cohort A. (revised per Amendment 03)

An integrated population analysis of E2814 PK will be performed by pooling data from Cohort A and Cohort B, and from all available studies. For population PK, the details will be described in a separately prepared analysis plan and its report, and the results will be provided in a separate report. (revised per Amendment 03)

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The PD Analysis Set will be used for both the listings and summaries of all biomarker CSF and plasma measurements (ie, free and bound MTBR-tau, total-MTBR-tau, and other biomarker assessments as data permit). Biomarker measurements (fluid and imaging) and change from baseline will be summarized by time point and dose and presented graphically.

These analyses will be done for CSF, plasma and serum. Dose-response relationships will be evaluated.

9.7.1.7.3 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

The relationship between PK and PD will be evaluated by visual inspection using plots. This may include but is not limited to the graphical exploration of the PK/TE relationship between E2814 concentrations and MTBR-tau binding in CSF.

PGx analyses may be performed and reported separately. Details of these analyses will be described in a separate analysis plan, and the results will not be included in the clinical study report.

9.7.1.8 Safety Analyses

Evaluation of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, ECGs, C-SSRS, and physical examinations. Safety data from the Phase 1b period of Cohort A will be summarized separately from the Phase 2 Treatment Period of Cohort A and Cohort B. TEAEs will be summarized by dose. (revised per Amendment 03)

Descriptive statistics (eg, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent for categorical variables) of the laboratory, vital signs, and ECGs, and changes from baseline will be evaluated by dose.

9.7.1.8.1 EXTENT OF EXPOSURE

Extent of exposure to study drug will be presented in subject data listings.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 21.0 or higher).

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by dose. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by system organ class (SOC) and preferred term (PT). A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each dose. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each dose. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each dose. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.4, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and dose using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the Treatment Period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. A listing of subjects with markedly abnormal laboratory values will be generated, which will be ordered by dose and subject.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, body temperature, weight) and changes from baseline will be presented by dose and visit.

9.7.1.8.5 ELECTROCARDIOGRAMS

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by dose and visit to end of treatment.

9.7.1.8.6 OTHER SAFETY ANALYSES

Subject data listings of viral tests, pregnancy tests, urine drug, breath alcohol and cotinine tests will be provided.

9.7.1.9 Other Analyses

The number (percentage) of subjects with positive and negative ADA and ADA titer categories (eg, >0, 5, 25, 125) by visit and dose will be summarized. In addition, the correlation between ADA titer and PK profile will be evaluated using descriptive statistics and summary plots at a minimum.

Change from baseline in tau PET and amyloid PET (Cohort A only; revised per Amendment 04) will be summarized by visit.

9.7.2 Determination of Sample Size

No formal sample size calculations have been performed. For this Phase 1b/Phase 2 study, up to 8 subjects in Cohort A and up to 5 subjects in Cohort B are considered adequate to evaluate the initial safety and PK in symptomatic DIAD subjects and to establish evidence of TE. (revised per Amendment 03)

9.7.3 Interim Analysis

Not applicable.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as interactive voice and web response system, x-rays, and other imaging reports (eg, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source
- Electronic Patient-Reported Outcome by self-reported measures

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following item(s), the data recorded directly on the CRF are to be considered source data:

- Reasons for discontinuation of study treatment
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)
- Reasons for dose modification
- Indication for prior/concomitant medication

- Sampling times for drug concentrations
- Sampling times for clinical laboratory tests

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 for US sites), Investigator and Site Information Form (for non-US sites), ICFs, and IRB/IEC correspondence. In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 15 years following the completion of the study.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
ALT	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
AST	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN if baseline was normal; 1.0 – 1.5×baseline if baseline was abnormal	>1.5 – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 10.0×ULN if baseline was normal; 3.0 – 10.0×baseline if baseline was abnormal	>10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium <LLN - 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	<6.0 mg/dL <1.5 mmol/L Ionized calcium <0.8 mmol/L; life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium >ULN - 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	>13.5 mg/dL >3.4 mmol/L Ionized calcium >1.8 mmol/L; life-threatening consequences
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 - 3.0×baseline; >1.5 – 3.0×ULN	>3.0×baseline; >3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 2.5×ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Glucose, serum-high (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	life-threatening consequences; urgent intervention indicated
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L; intervention initiated	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	125-129 mmol/L and asymptomatic	<125 – 129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN without physiologic consequences	N/A	>ULN with physiologic consequences	life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 5.0. Published: 27 Nov 2017.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2814-G000-103
Study Protocol Title:	An Open-Label Phase 1b/2 Study to Assess Safety and Target Engagement of E2814 in Subjects with Mild to Moderate Cognitive Impairment due to Dominantly Inherited Alzheimer's Disease
Investigational Product Name:	E2814
IND Number	139378
EudraCT Number	2020-005728-12

SIGNATURES

Authors:

PPD Study Director and Medical Monitor PPD Eisai Inc	Date
PPD Clinical Pharmacologist PPD Eisai Ltd.	Date
PPD Primary Statistician PPD Eisai Ltd	Date

INVESTIGATOR SIGNATURE PAGE

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I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local GCP guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

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