Protocol: I5T-MC-AACP(a)

# A Phase 1, Open-Label Study to Characterize the Pharmacokinetics of Donanemab Following Intravenous Doses in Healthy Participants

NCT05567159

Approval Date: 12 Dec 2022

# Title Page



**Protocol Title:**

A Phase 1, Open-Label Study to Characterize the Pharmacokinetics of Donanemab Following Intravenous Doses in Healthy Participants

**Protocol Number:** I5T-MC-AACP

**Amendment Number:** a

**Compound:** LY3002813

**Brief Title:**

A Study to Characterize the Pharmacokinetics of Donanemab Following Intravenous Doses in Healthy Participants

**Study Phase:** Phase 1

**Acronym:** AACP

**Sponsor Name:** Eli Lilly and Company

**Legal Registered Address:** Eli Lilly and Company, Indianapolis, Indiana USA 46285

**Regulatory Agency Identifier Number:** IND: 109157

**Approval Date:** Protocol Electronically Signed and Approved by Lilly on date provided below.

**Document ID:** VV-CLIN-076261

**Medical Monitor Name and Contact Information will be provided separately.**



Approved on 12 Dec 2022 GMT

# Protocol Amendment Summary of Changes Table

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Original Protocol | 31-Aug-2022 |

## Amendment (a)

This amendment is considered to be nonsubstantial.

## Overall Rationale for the Amendment:

The protocol was amended to increase the number of participants who may enroll in the study to ensure the required number of subjects complete the study and to make minor procedural updates.

Minor changes were needed for consistency within the protocol and between the protocol and informed consent form (ICF).

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1 Synopsis | Updated number of participants who may be enrolled. | Approximately 40 participants may be enrolled to ensure the required number of subjects complete the study. |
| | Added "IV" when discussing study design and summary. | To be more specific regarding type of administration. |
| Section 1.3 Schedule of Activities | Added a note that height is measured at screening only. | There is no need for height to be measured at other timepoints. |
| Section 4.1 Overall Design | Updated number of participants who may be enrolled. | Approximately 40 participants may be enrolled. |
| | Added "IV" when discussing study design and summary. | To be more specific regarding type of administration. |
| Section 4.3 Justification for Dose | Added "IV" for the dose selected for this study. | To be more specific regarding type of administration. |
| Section 5.3 Lifestyle Considerations | Changed when participants should abstain from alcohol from "until after collection of the final PK sample" to "until leaving the CRU". | To align with alcohol restrictions set out in Exclusion Criteria 30 and in the ICF. |
| Section 8 Study Assessments and Procedures | Removed "in the CRF" from the line regarding recording of actual time. | Actual times need to be recorded, but not in the CRF. |
| Section 9.5 Sample Size Determination | Updated number of participants who may be enrolled. | Approximately 40 participants may be enrolled. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 10.7<br>Appendix 7 | Removed sentence stating that "This is documented as a screen failure in the CRF". | EMP does not capture screen failures in the CRF. |

Abbreviations: CRF = case report form; CRU = clinical research unit; EMP = Exploratory Medicine and Pharmacology; ICF = informed consent form; IV = intravenous; PK = pharmacokinetics.

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# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:**

A Phase 1, Open-Label Study to Characterize the Pharmacokinetics of Donanemab Following Intravenous Doses in Healthy Participants

**Brief Title:**

A Study to Characterize the Pharmacokinetics of Donanemab Following Intravenous Doses in Healthy Participants

**Regulatory Agency Identifier Number:**

IND: 109157

**Rationale:**

Study I5T-MC-AACP (AACP) will investigate the pharmacokinetics (PK) and safety of intravenous (IV) administration of donanemab in healthy participants every 2 weeks (Q2W) for 10 weeks at a 350 mg dose to support dosing regimens in future studies.

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To characterize the PK profile of donanemab following administration of 350 mg IV doses in healthy participants | • $AUC_{0\text{-}4Weeks}$<br>• $C_{max,ss}$, and<br>• $AUC_{t,ss}$ |
| Secondary | |
| • To investigate the safety and tolerability of donanemab following administration of 350 mg IV doses in healthy participants | • Incidence of treatment-emergent adverse events and serious adverse events |

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration versus time curve during a dosing interval at steady state; $AUC_{0\text{-}4Weeks}$ = area under the concentration versus time curve 0 to 4 weeks; $C_{max,ss}$ = maximum observed drug concentration during a dosing interval at steady state; IV = intravenous; PK = pharmacokinetic.

**Overall Design:**

This is a Phase 1, open-label study to evaluate the PK, safety, and tolerability of 350 mg donanemab administered as a single IV dose Q2W for 10 weeks in healthy participants. Approximately 40 participants may be enrolled so that approximately 25 participants complete the study. Participants will receive a single 350 mg dose of donanemab IV Q2W for 10 weeks.

After each dose administration, participants will remain in the clinical research unit (CRU) for up to 5 days. Participants will return to the CRU for regular outpatient visits until the next dose of donanemab. After the last dose of donanemab, participants will return for outpatient visits up to 12 weeks after the last dose.

**Brief Summary:**

The purpose of this study is to measure the PK of 350 mg donanemab IV administered Q2W for 10 weeks in healthy participants.

Study details include:

- The study duration will be up to 22 weeks.
- The treatment duration will be up to 10 weeks.
- The visit frequency will be Q2W.

**Study Population:**

Healthy participants will be enrolled in this study.

**Number of Participants:**

Approximately 40 participants will be enrolled to donanemab so that approximately 25 participants complete the study.

**Intervention Groups and Duration:**

Screening period: 28 days prior to enrollment into the study.

Treatment periods: On Day -1 prior to dosing of each of the 6 treatment periods, participants will be admitted to the CRU. On Day 1 of each treatment period, participants will be dosed with a single IV dose (350 mg) of donanemab Q2W for 10 weeks. After each dose administration, participants will remain in the CRU for up to 5 days.

Follow-up period: Up to 12 weeks after the last dose of donanemab.

**Ethical Considerations of Benefit/Risk:**

The following are the risks and discomforts associated with donanemab:

- amyloid-related imaging abnormalities (ARIA)
- treatment-emergent anti-drug antibodies (TE-ADAs), and
- infusion-related reactions (IRRs) and hypersensitivity.

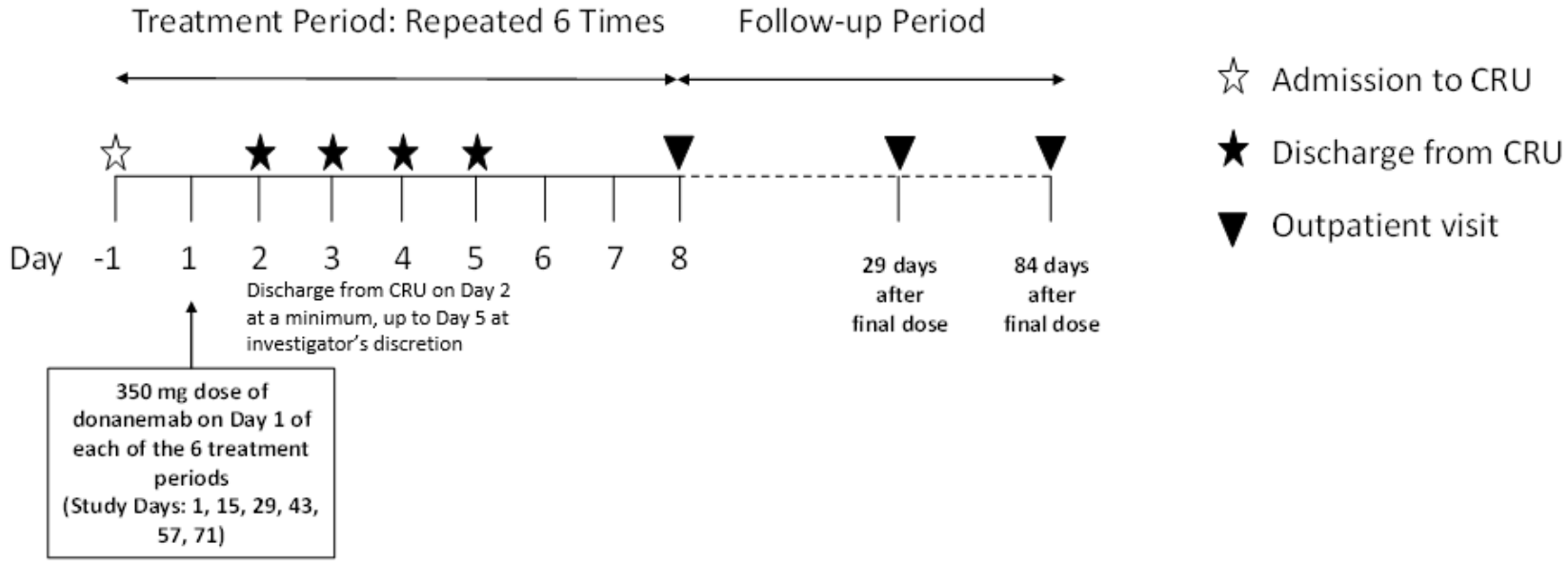
In this study (Study AACP), amyloid-related imaging abnormality–edema/effusions (ARIA-E) and amyloid-related imaging abnormality–hemorrhage/hemosiderin deposition (ARIA-H) events are not expected given the young healthy population being enrolled. These participants are expected to not have amyloid deposits in their brain and thus the risk of ARIA-E and ARIA-H is considered low.

TE-ADAs have been observed after a single dose of donanemab across all dose levels assessed, including the single cohort of healthy participants in Study I5T-MC-AACC (AACC). Therefore, TE-ADAs will be carefully monitored in this study.

IRRs have been observed in Studies AACC, I5T-MC-AACD, and I5T-MC-AACG. All biological agents carry the risk of systemic allergic and hypersensitivity reactions and patients should be monitored for the occurrence of these reactions.

**Data Monitoring Committee: No**

## 1.2. Schema




Abbreviation: CRU = clinical research unit.

## 1.3. Schedule of Activities (SoA)

| Assessment Period | Screening | Treatment Periods 1-6 | | | | | | | Follow-up (Treatment Period 6) | | ED | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-28 to -2** | **-1** | **1** | **2** | **3** | **4** | **5** | **8** | **37** | **96** | | |
| Informed consent | X | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | | | | |
| Admission to CRU | | X | | | | | | | | | | |
| Discharge from CRU | | | | X | X | X | X | | | | | Discharge from CRU can be at a minimum of 2 days postdose and up to 5 days postdose at the discretion of the investigator. |
| Outpatient visit | | | | | | | | X | X | X | X | |
| Donanemab administration | | | X | | | | | | | | | |
| Medical history, demographics | X | | | | | | | | | | | |
| Weight, height, BMI | X | | | | | | | | | X | X | Height measured at screening only. |
| Physical examination, medical assessment | X | X | X | X | | | X[a] | | | X | X | [a] If discharge from CRU is on Days 2, 3, or 4, physical examination will be taken at the earlier CRU discharge visit.<br>Full physical exam at screening and Day -1 and symptom-directed medical assessment at other time points and as |

| Assessment Period | Screening | Treatment Periods 1-6 | | | | | | | Follow-up (Treatment Period 6) | | ED | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-28 to -2** | **-1** | **1** | **2** | **3** | **4** | **5** | **8** | **37** | **96** | | |
| | | | | | | | | | | | | deemed necessary by investigator. |
| Neurological examination | X | X | | 24 hr | | | X[b] | | X | X | X | [b] If discharge from CRU is on Days 2, 3, or 4, neurological examination will be taken at the earlier CRU discharge visit. |
| C-SSRS | X | X | | | | | | | | X | X | |
| Vital signs (supine): blood pressure, pulse rate, temperature | X | X | Predose, 6 hr | 24 hr | X | X | X | | X | X | X | Temperature should only be measured at screening and predose on Day 1. |
| 12-lead ECG | X | | Predose | | | | | | | X | X | Single 12-lead ECG. Time points may be added, if clinically indicated. |
| AE and concomitant medications | X | X | X | X | X | X | X | X | X | X | X | |
| Clinical laboratory tests | X | X | | 24 hr | | | | | | X | X | |
| Serology | X | | | | | | | | | | | HBV, HCV, and HIV |
| Ethanol and urine drug screen | X | X | | | | | | | | | | Ethanol test (urine or breath) may be repeated at other time points at the discretion of the investigator. |

| Assessment Period | Screening | Treatment Periods 1-6 | | | | | | | Follow-up (Treatment Period 6) | | ED | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-28 to -2** | **-1** | **1** | **2** | **3** | **4** | **5** | **8** | **37** | **96** | | |
| Pregnancy test | X | | | | | | | | | X | X | Females only. Serum pregnancy test at screening. Urine pregnancy test at all other time points. |
| Serum FSH | X | | | | | | | | | | | For postmenopausal females only. |
| PK sample | | X | Predose, End of infusion | 24 hr | 48 hr | 72 hr | 96 hr | X | X | X | X | PK sample and immunogenicity sample should be taken at the same time on Day -1. |
| Immunogenicity | | X[c] | | | | | | | X | X | X | [c] Immunogenicity sample taken on Day -1 of Treatment Periods 1, 2, 3 and 6. |
| Pharmacogenetics – apolipoprotein E genotype ε4 | | X | | | | | | | | | | Day -1 of Treatment Period 1 only. |

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BMI = body mass index; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hr = hour; PK = pharmacokinetics.

Note: Site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, follow this order of priority for procedures: ECG, vital signs, PK samples, ADA.

# 2. Introduction

LY3002813 (donanemab) is a humanized immunoglobulin (Ig) G1 antibody directed at the pyroglutamate formation of the third amino acid (N3pG) of amyloid beta (Aβ) epitope that is present only in brain amyloid plaques. It is being developed as a treatment to slow the progression of Alzheimer's disease (AD).

## 2.1. Study Rationale

Study I5T-MC-AACP (AACP) will investigate the pharmacokinetics (PK) and safety of intravenous (IV) administration of donanemab in healthy participants every 2 weeks (Q2W) for 10 weeks at a 350-mg dose to support dosing regimens in future studies.

## 2.2. Background

Alzheimer's disease is an age-related neurodegenerative disorder characterized by a progressive decline in cognitive function and a decline in ability to perform activities of daily living. It can ultimately lead to death due to complications of the disease. Strong genetic and biochemical evidence highlights a central role of the amyloid pathway in the pathogenesis of AD (Hardy and Selkoe, 2002).

Pathologic hallmarks of AD identified at autopsy include the presence of neuritic Aβ plaques, neurofibrillary tangles (Hyman et al. 2012), and neuronal loss in brain regions important for cognition, such as the hippocampus and temporal cortex (Selkoe 1991). Pathological data obtained from patients with AD demonstrate that extensive plaque deposition exists in the patient population well before the first memory complaint (Morris and Price 2001; Jack et al. 2010).

Immunotherapy is an increasingly promising therapeutic approach that is focused on using antibodies to facilitate clearance of pathogenetic peptides, such as the Aβ peptide (Avgerinos et al. 2021). The mechanism of action of donanemab is considered to be targeting and removal of existing amyloid plaques. The clinical strategy for donanemab is based on the amyloid hypothesis of AD, which states that the production and deposition of Aβ plaques is an early and necessary event in the pathogenesis of AD. Clinical support for this hypothesis comes from the demonstration that parenchymal Aβ levels are elevated before the diagnosis of AD. Furthermore, early in the disease, the presence of brain amyloid appears to increase the risk of conversion from mild cognitive impairment (MCI) to AD. It is implicit in this hypothesis that enhanced clearance of Aβ plaques will lead to amelioration of AD symptoms and slow progression of AD.

As of 05 January 2021, donanemab has been administered in 3 completed clinical studies (see below). A total of 243 participants have received at least 1 dose of donanemab. Of those 243 participants, donanemab has been administered to 6 healthy participants and in 237 study participants with MCI due to AD; mild to moderate AD or with early symptomatic AD and intermediate cerebral tau burden.

Two Phase 1 studies (Study I5T-MC-AACC [AACC] and Study I5T-MC-AACD [AACD]) have been conducted in participants with MCI due to AD and mild to moderate AD. In Study AACC, single IV dose of donanemab from 0.1 mg/kg to 10 mg/kg was administered in single-ascending

dose phase, and IV doses from 0.3 mg/kg to 10 mg/kg once per month for a total of 4 doses were administered in multiple-ascending dose phase. In addition, a single IV dose of 1 mg/kg donanemab was administered to a single cohort of healthy participants. In Study AACD, single and multiple doses from 10 mg/kg to 40 mg/kg were administered. In both studies, rapid and sustained reduction in cerebral amyloid plaques were observed with donanemab doses ≥10 mg/kg.

One Phase 2 study (Study I5T-MC-AACG [AACG]) has been conducted in participants with early symptomatic AD and intermediate (low to medium) cerebral tau burden. In Study AACG, 700 mg of donanemab IV once every 4 weeks (Q4W) for first 3 doses followed by 1400 mg Q4W for up to 72 weeks was administered. Treatment with donanemab compared with placebo resulted in a significant slowing (32%; $p = 0.04$) of disease progression, as measured by the integrated Alzheimer's Disease Rating Scale (iADRS; Wessels et al. 2015), as well as deep and rapid reduction in amyloid plaque level.

Key safety findings from these completed studies included amyloid-related imaging abnormalities (ARIA), infusion-related reactions (IRR), and the presence of treatment-emergent anti-drug antibodies (TE-ADAs). The most common treatment-emergent adverse events (TEAEs) observed were:

- ARIA–edema/effusions (ARIA-E)
- ARIA–hemorrhage/hemosiderin deposition (ARIA-H)
- superficial siderosis of central nervous system
- IRRs
- fall
- headache
- dizziness
- upper respiratory tract infections, and
- urinary tract infection.

A high proportion of patients receiving donanemab have TE-ADA (92.2%; additional detail available in the IB). While patients experiencing hypersensitivity events were more likely to show high titer TE-ADA, a high titer was not predictive of adverse events (AEs).

Currently, Phase 3 Study I5T-MC-AACI in early symptomatic AD, Phase 2 Study I5T-MC-AACH in symptomatic AD, and Phase 3 Study I5T-MC-AACM in cognitively unimpaired participants with evidence of AD pathology are ongoing.

A detailed description of the chemistry, pharmacology, efficacy, and safety of donanemab is provided in the IB.

## 2.3. Benefit/Risk Assessment

The following are the risks and discomforts associated with donanemab:

- ARIA
- TE-ADAs
- IRR and,
- hypersensitivity.

Amyloid-related imaging abnormalities have been observed in patients with MCI or AD in completed Phase 1 studies, AACD and AACC, Phase 2 study AACG, and in the ongoing Phase 3 studies. Events of ARIA may be serious, or life threatening and could lead to permanent disability or death.

Incidences of ARIA-E occur spontaneously at rates of 0.1% to 1%. Incidences of ARIA-H occur spontaneously at rates of 10% to 20% (Ketter et al. 2017). Both spontaneously occur more frequently in apolipoprotein E genotype ε4 (ApoE4) carriers than noncarriers, and ARIA-E is a risk factor for the occurrence of ARIA-H. Both ARIA-E and ARIA-H occur more frequently with antibody therapies directed at amyloid and are considered a class effect. Other anti-amyloid antibodies in clinical development have demonstrated a dose-dependent risk for ARIA-E. Most of these cases are asymptomatic and have been detected by routine brain magnetic resonance imaging. When symptoms are present in association with these imaging abnormalities, they have been reported to include headache, vomiting, unsteadiness, dizziness, tremor, confusion, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures (Ostrowitzki et al. 2012; Sperling et al. 2012; VandeVrede et al. 2020; Mintun et al. 2021; Swanson et al. 2021). In most cases, these imaging abnormalities have not required treatment other than discontinuation of the investigational compound, typically resulting in resolution of imaging abnormalities. Infrequently, high-dose steroid therapy has been administered in the presence of prominent symptoms.

In this study (Study AACP), ARIA-E and ARIA-H events are not expected given the young healthy population being enrolled. These participants are expected to not have amyloid deposits in their brain and thus the risk of ARIA-E and ARIA-H is considered low.

Treatment emergent-ADAs and IRRs have been observed in studies, AACC, AACD, and AACG.

All biological agents carry the risk of systemic allergic/hypersensitivity reactions and patients should be monitored for the occurrence of these reactions. Clinical manifestations of these reactions may include but are not limited to the following:

- skin rash
- pruritus (itching)
- dyspnea
- urticaria (hives)
- angioedema (eg, swelling of the lips and/or tongue)
- hypotension, and
- anaphylactic reaction.

See IB Section 6.2.2.7 for more information regarding frequency of hypersensitivity reactions. There were no hypersensitivity reactions in healthy participants in Study AACC.

Treatment emergent-ADAs have been observed after a single dose of donanemab across all dose levels assessed and including the single cohort of healthy participants in the Study AACC. Therefore, TE-ADAs will be carefully monitored in this study.

There is no anticipated therapeutic benefit for the healthy participants in this study. However, participants may benefit from the screening procedures (through detection of unknown health issues) even if they receive no therapeutic benefit from the study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of donanemab may be found in the IB.

# 3. Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To characterize the PK profile of donanemab following administration of 350 mg IV doses in healthy participants | • $AUC_{0\text{-}4Weeks}$<br>• $C_{max,ss}$, and<br>• $AUC_{\tau,ss}$ |
| Secondary | |
| • To investigate the safety and tolerability of donanemab following administration of 350 mg IV doses in healthy participants | • Incidence of treatment-emergent adverse events and serious adverse events |
| Exploratory | |
| • To assess the effect of TE-ADAs on the PK of 350 mg IV donanemab | • Model parameters for the exposure-response relationship between donanemab serum concentrations and ADA titer |
| • To characterize immunogenicity of donanemab following administration of 350 mg IV doses in healthy participants | • Incidence of TE-ADA |

Abbreviations: ADA = anti-drug antibody; $AUC_{\tau,ss}$ = area under the concentration versus time curve during a dosing interval at steady state; $AUC_{0\text{-}4Weeks}$ = area under the concentration versus time curve 0 to 4 weeks; $C_{max,ss}$ = maximum observed drug concentration during a dosing interval at steady state; IV = intravenous; PK = pharmacokinetic; TE-ADA = treatment-emergent anti-drug antibodies.

# 4. Study Design

## 4.1. Overall Design

This is a Phase 1, open-label study to evaluate the PK, safety, and tolerability of 350 mg donanemab administered as a single IV dose Q2W for 10 weeks in healthy participants. Approximately 40 participants may be enrolled so that approximately 25 participants complete the study. Participants will receive a single 350 mg dose of IV donanemab Q2W for 10 weeks. After each dose administration, participants will remain in the clinical research unit (CRU) for up to 5 days. Participants will return to the CRU for regular outpatient visits until the next dose of donanemab. These visits will occur on Days 3, 4, 5, and 8 (unless the participant is still admitted to the CRU, in which activities for those days will be performed during the inpatient stay). After the last dose of donanemab, participants will return for outpatient visits up to 12 weeks after the last dose.

Screening may occur up to 28 days prior to enrollment into the study. Once the informed consent is signed by the participants, they will be assessed for eligibility and will undergo screening procedures outlined in the Schedule of Activities (SoA; Section 1.3).

Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. Eligible participants will be admitted to the CRU on Day -1 prior to dosing in each of the 6 treatment periods. On Day 1 of each treatment period, participants will be dosed with an IV dose of donanemab and remain in the CRU until discharge on Day 2, although participants may remain inpatient up to Day 5 of each treatment period at the discretion of the investigator. After dosing with 350 mg donanemab, participants will return to the CRU approximately 2 weeks later to be admitted at Day -1 of the subsequent period.

Safety and tolerability will be assessed through electrocardiograms (ECGs), clinical laboratory tests, vital sign measurements, recording of AEs, physical examination, and neurological examination. Additionally, immunogenicity will be assessed.

After discharge from the CRU after the final treatment period, participants will return for further outpatient assessments (safety, PK, and immunogenicity) until 12 weeks after the final dose.

## 4.2. Scientific Rationale for Study Design

**Blinding**

The study will be open label as the primary outcome is PK. Therefore, placebo treatment is not required. Although safety and tolerability is a secondary objective, the safety profile of donanemab is well understood and at higher doses than that administered in this study.

**Pharmacokinetic sampling**

Pharmacokinetic sampling time points have been selected to allow evaluation of PK sufficient to fulfill the study objectives.

**Study Population**

Healthy participants have been selected for this study as it has been demonstrated previously that the PK profile of donanemab is comparable between healthy participants and AD patients. In

addition, there are no patient-centric outcomes in this study so a healthy participant population is considered appropriate.

## 4.3. Justification for Dose

Donanemab 350 mg IV Q2W was selected for this study because this dose is within the dose range previously evaluated in Phase 1 and Phase 2 studies. A 350 mg dose of donanemab administered as a single IV dose is within the dose range previously evaluated in Phase 1 studies (Studies AACC and AACD). In Study AACC, doses of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg (equivalent to approximately 7 mg, 21 mg, 70 mg, 210 mg, and 700 mg, respectively) of donanemab were assessed. Doses at or below 3 mg/kg (210 mg) had lower than dose proportional exposure (with half-life ~ 4.7 days) whereas exposure following the single doses of donanemab between 10 mg/kg (700 mg) and 40 mg/kg (2800 mg) were shown to be dose proportional (with half-life of 11 days) in Study AACD.

Observed exposure following a 350-mg dose of donanemab from this study will assess whether this exposure falls within linear or nonlinear exposure range compared with a 700- to 2800-mg dose range.

In participants with MCI due to AD or mild to moderate AD, including Japanese and non-Japanese, the following doses were generally well tolerated:

- up to 40 mg/kg, that is approximately 2800 mg as a single dose, and
- up to 20 mg/kg, that is approximately 1400 mg as multiple doses administered Q4W.

## 4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit.

# 5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only unless otherwise specified, and not continuously throughout the trial.

Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

**Age**

1. Participant must be 18 to 40 years of age inclusive, at the time of signing the informed consent.

**Type of Participant and Disease Characteristics**

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs, and cardiac monitoring

**Weight**

3. Body mass index (BMI) within the range of 19.0 to 32.0 kg/m$^2$ (inclusive).

**Sex and Contraceptive/Barrier Requirements**

4. Male or female

   Women of childbearing potential will be excluded from the study.

   Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Appendix 10.4.

**Informed Consent**

5. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

**Other Inclusions**

6. Clinical laboratory test results within normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
7. Venous access sufficient to allow IV drug delivery and blood sampling as per the protocol.
8. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures and research unit policies.

## 5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions**

9. Have a history of intracranial hemorrhage, cerebrovascular aneurysm or arteriovenous malformation, carotid, carotid artery occlusion, stroke or epilepsy or family history of dementia or Down's syndrome.
10. Have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, immunological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; or constituting a risk when taking the study medication; or of interfering with the interpretation of data.
11. Have allergies to either humanized monoclonal antibodies, diphenhydramine, epinephrine, or methylprednisolone.
12. Have had gamma globulin therapy within the last 6 months.
13. Have a history within the past 5 years of a primary or recurrent malignant disease.
14. Have a history of clinically significant multiple or severe drug allergies or severe posttreatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, exfoliative dermatitis).
15. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
16. Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS, and the ideation or behavior occurred within the past month.
17. Have a history or presence of psychiatric disorders considered to be clinically significant in the opinion of the investigator.
18. Have evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies.
19. Have spontaneously cleared hepatitis C virus (HCV) infection, defined as a positive HCV antibody test and a negative HCV RNA test. Participants with no history of HCV antibody (anti-HCV) treatment, may be eligible for inclusion in the study, provided they have no detectable HCV RNA at screening for this study.

20. Have a current infection with hepatitis B virus (HBV), that is, positive for hepatitis B surface antigen, polymerase chain reaction (PCR) positive for HBV DNA or both.
21. Are lactating.

**Prior/Concomitant Therapy**

22. Have used over-the-counter or prescription medications, including herbal medication, within 7 days prior to dosing.

**Prior/Concurrent Clinical Study Experience**

23. Are currently enrolled in, have completed or discontinued dosing within the last 30 days or 5 half-lives of investigational product from a clinical trial involving an investigational product; or are concurrently enrolled in any other type of medical research.
24. Have previously completed or withdrawn from this study or any other study investigating donanemab.

**Diagnostic Assessments**

25. Have screening clinical laboratory test results with unacceptable deviations that are judged to be clinically significant by the investigator.
26. Have an abnormality in the 12-lead ECG, abnormal blood pressure, and pulse rate considered clinically significant by the investigator.

**Other Exclusions**

27. Are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
28. Are Lilly employees or employees of third-party organizations involved with the study.
29. Known history of alcohol or drug abuse (as defined by the Diagnostic and Statistical Manual, fifth Edition, Text Revision) within 2 years prior to enrolling or a positive result regarding use of illicit drugs on the drug screening test.
30. Have an average weekly alcohol intake that exceeds 21 units for males and 14 units for females per week, or are unwilling to stop alcohol consumption [from 24 hours prior to dosing until leaving the CRU] (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).
31. Have donated blood of more than 400 mL within the last 3 months, or any blood donation (including apheresis) within the last 1 month, or total volume of blood donation within 12 months is 1200 mL at screening.
32. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.
33. Are pregnant or intend to become pregnant or to breastfeed during the study.
34. Smoke more than 10 cigarettes per day or are unable to abide by investigative site smoking restrictions.

## 5.3. Lifestyle Considerations

### 5.3.1. Meals and Dietary Restrictions

- Standard meals will be provided at all times while participants are resident at the CRU, as per the CRU's policy.

### 5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until leaving the CRU.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

### 5.3.3. Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

## 5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. If applicable, participants may be re-tested at the discretion of the investigator (eg, abnormal laboratory result) before being deemed a screen failure.

## 5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

Not applicable.

# 6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

## 6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

| | |
|---|---|
| **Intervention Name** | Donanemab |
| **Dosage Level(s)** | 350 mg Q2W |
| **Route of Administration** | IV infusion |

Abbreviations: IV = intravenous; Q2W = every 2 weeks.

**Packaging and labeling**

Study interventions will be supplied by the sponsor in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

### 6.1.1. Administration Details

Donanemab will be administered as slow IV infusion over at least 30 minutes. Resuscitation equipment, emergency drugs, and appropriately trained staff must be available during the infusion and for at least 4 hours after participants have completed their infusion.

#### 6.1.1.1. Management of Infusion Reactions

There is a risk of infusion reaction with any biological agent; therefore, all participants should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to:

- fever
- chills
- nausea
- headache
- bronchospasm
- hypotension
- angioedema
- throat irritation
- rash
- pruritus
- myalgia, and
- dizziness.

In the event that a significant infusion reaction occurs, the following guidance should be followed:

- The investigational product infusion should be slowed (eg, reduce infusion rate by 50% [eg, an infusion rate of 12 mL/h becomes 6 mL/h or slower]) or stopped, depending on the symptoms/signs present:
    - if slowed, the infusion should be completed at the slower rate, as tolerated
    - if determined by the investigator that the infusion should no longer continue, no further attempts to dose the participant should be made
- Supportive care should be employed in accordance with the symptoms/signs

If a participant's infusion reaction is sufficiently severe to discontinue the infusion, subsequent infusions may be administered with premedication at the discretion of the investigator following agreement with the Lilly clinical research physician (CRP) or clinical pharmacologist.

If a participant's infusion rate is reduced due to an infusion reaction, subsequent infusions may be administered at the discretion of the investigator following agreement with the Lilly CRP or clinical pharmacologist. If further infusions are administered, the infusion rate must not exceed the slowest rate used to complete the infusion on the occasion the infusion reaction occurred. Premedication may be administered at the discretion of the investigator.

If it is determined the participant should not receive further doses of investigational product, the participant should complete AE and other follow-up procedures per Section 1.3 of this protocol.

## 6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

## 6.3. Assignment to Study Intervention

This is an open-label study with only 1 treatment.

## 6.4. Blinding

Not applicable as this is an open-label study with only 1 treatment.

## 6.5. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The dose of donanemab and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and in the case report form (CRF).

## 6.6. Dose Modification

Dose adjustments are not permitted in this study.

## 6.7. Continued Access to Study Intervention after the End of the Study

Not applicable.

## 6.8. Treatment of Overdose

In the event of an overdose, the investigator or treating physician should:

- contact the medical monitor immediately
- closely monitor the participant for any AE/ serious adverse event (SAE) and laboratory abnormalities, and
- obtain a plasma sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis).

## 6.9. Prior and Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates, and
- dosage information including dose and frequency for concomitant therapy of special interest.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of ≤3 grams/day, is permitted for use in a 24-hour period at the discretion of the investigator. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required. Any additional medication used during the course of the study must be documented.

**COVID-19 Considerations**

Government guidance for Health Facilities should be followed when conducting visits.

The use of a severe acute respiratory syndrome coronavirus 2 of the genus Betacoronavirus (SARS-CoV-2) vaccine in participants treated with donanemab has not been studied by Lilly. However, given the risk posed by coronavirus disease 2019 (COVID-19) in the midst of this pandemic, decisions regarding the use of any vaccination, including approved/authorized for use vaccines, in participants treated with donanemab should be made at the discretion of the treating physician using their best clinical judgment and after careful consideration of risk benefit factors for the participant. If you have any questions regarding the type of vaccine that can be used for your clinical study participants, please contact your Centers for Disease Control and Prevention (CDC) or medical monitor for further instructions. Please have information on the vaccine(s) available in your country, prior to contacting your medical monitor.

Please consult the vaccine product label for further information regarding associated risks and precautions, and guidance from your local regulatory agency. Hypersensitivity events have been reported in association with certain vaccines, in close temporal relation to the application. Taking this into consideration, it is recommended that study drug not be administered sooner than 5 days before or after a vaccination.

As with all other concomitant medications, please ensure you record applicable information regarding an individual's receipt of vaccination(s) in the participant's source documents, and then follow the CRF instructions for concomitant medications for appropriate capture of vaccine administration in the CRFs. Please record each administration date of the vaccine (each time) as a concomitant medication in the CRF. If the participant is vaccinated outside of your facility, please request and record information such as manufacturer and dose date, when available. Any possible related AEs from the vaccination should be reported according to the Lilly Adverse Event/Serious Adverse Event reporting guidance and to the appropriate manufacture, according to local practice.

# 7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Participants discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per Section 1.3 of this protocol.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

## 7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the SoA. A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study,
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons
- if the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

In addition, study drug may be discontinued if participants

- answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or
- answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

### 7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of the study intervention for abnormal liver tests **should be considered** by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT (alanine aminotransferase ) or AST (aspartate aminotransferase) >5× for healthy participants upper limit of normal (ULN)
- ALT or AST >3× ULN for healthy participants sustained for more than 2 weeks or
- ALT or AST >3× ULN and total bilirubin level (TBL) >2× ULN or international normalized ratio (INR) >1.5 or
- ALT or AST >3× ULN the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3× ULN

- ALP >2.5× ULN and TBL >2× ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Participants who discontinue from study intervention due to the abnormal liver tests will undergo monitoring as described in Appendix 10.6.

**Interrupting study drug based on liver test elevations in participants with normal or near-normal baseline liver tests**

In study participants with normal or near normal baseline liver tests (ALT, AST, ALP <1.5× ULN), the study drug should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.8.1) if one or more of these conditions occur:

| Elevation | Exception |
|---|---|
| ALT or AST >5× ULN | |
| ALT or AST >3× ULN and either TBL >2× ULN or INR >1.5 | For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2× ULN. |
| ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) | |
| ALP >3×ULN, when the source of increased ALP is the liver | |
| ALP >2.5× ULN and TBL >2× ULN | For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2× ULN. |
| ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) | |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Source: [FDA] United States Food and Drug Administration. Drug-induced liver injury: premarketing clinical evaluation: guidance for industry. July 2009. Accessed August 26, 2022. https://www.fda.gov/media/116737/download

**Interrupting study drug based on elevated liver tests in participants with abnormal baseline liver tests**

In study participants with abnormal baseline liver tests (ALT, AST, ALP ≥1.5× ULN), the study drug should be **interrupted** if one or more of these conditions occur:

| Elevation | Exception |
|---|---|
| ALT or AST >3× baseline | |
| ALT or AST >2× baseline and either TBL >2× ULN or INR >1.5 | For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2× ULN. |
| ALT or AST >2× baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) | |
| ALP >2.5× baseline, when the source of increased ALP is the liver | |
| ALP >2× baseline and TBL >2× ULN | For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2× ULN. |
| ALP >2× baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) | |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Source: [FDA] United States Food and Drug Administration. Drug-induced liver injury: premarketing clinical evaluation: guidance for industry. July 2009. Accessed August 26, 2022. https://www.fda.gov/media/116737/download

**Resuming study drug after elevated liver tests**

Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited nondrug etiology is identified. Otherwise, the study drug should be discontinued.

## 7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request
- at the request of the participant's designee (eg, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons

- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

## 7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

# 8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Section 1.3 lists the SoA, detailing the study procedures and their timing (including tolerance limits for timing). The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded.
- Appendix 10.2 lists the laboratory tests that will be performed for this study.
- Appendix 10.2.1 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.
- Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

## 8.1. Efficacy Assessments

Not applicable.

## 8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

### 8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- Symptom-directed physical assessment may be conducted at other visits as mentioned in SoA and as clinically indicated. Symptom-directed physical examinations may also be conducted at other visits, as determined by the investigator, if a participant presents with complaints.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3).
- Additional vital signs may be measured during the study if warranted.
- Blood pressure and pulse rate should be measured after at least 5 minutes supine.
- Unscheduled orthostatic vital signs should be assessed if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes. If the participant feels unable to stand, only the supine vital signs will be recorded.
- Body temperature should be measured as indicated in the SoA, or any time that it is clinically indicated.

### 8.2.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT interval (QTc).
- For each participant, ECGs should be collected according to the SoA (Section 1.3).
- Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of the investigational product, should be reported to Lilly, or its designee, as an AE via the eCRF.
- Electrocardiograms must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.
- Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

### 8.2.4. Clinical Safety Laboratory Tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within the follow-up period after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then report the information as an AE.

### 8.2.5. Pregnancy Testing

Pregnancy testing will be performed as specified in the SoA.

### 8.2.6. Neurological Examination

A neurological examination will be performed by the investigator (or designee) at the time points specified in the SoA. If clinically significant abnormalities are noted at these time points, additional examinations should be performed as clinically necessary. The examiner should be familiar with the participant’s baseline examination. Elements of the examination may include inspection for tremors, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign.

The table below presents the scoring of the neurological examination findings.

| Score | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Tremor | Absent | Visible with limb extension and/or careful inspection | Visible without limb extension | Interferes with motor function | |
| Nystagmus | Absent | 1 to 3 beats on lateral gaze | >3 beats on lateral gaze | Present on forward gaze | |
| Reflexes (brachial or patellar) | Normal | Trace | Absent | Increased | Clonic |
| Finger-nose | Normal | Abnormal | | | |
| Romberg sign | Absent | Present | | | |

### 8.2.7. Suicidal Ideation and Behavior Risk Monitoring

**C-SSRS**

Columbia-Suicide Severity Rating Scale is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. The C-SSRS will be performed by the investigator (or designee) at the time points specified in the SoA.

Donanemab is considered to be a central nervous system-active drug. Participants being treated with donanemab should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

In the clinical trials with donanemab to date, there has been no association between donanemab treatment and suicidal ideation.

When informed consent or assent has been given, families and caregivers of participants being treated with donanemab should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and intervention emergent suicidal ideation and behavior will be monitored during Study AACP using the C-SSRS.

### 8.2.8. Safety Monitoring

The Lilly clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or CRP will periodically review

- trends in safety data
- laboratory analytes
- AEs, including monitoring of incidence of any nature of any neurological symptoms, infusion related reaction, and allergic or hypersensitivity reactions,
- ECGs,
- neurological examinations, and
- physical examinations.

When appropriate, the Lilly clinical pharmacologist or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

#### 8.2.8.1. Hepatic Safety

**Close hepatic monitoring**

Laboratory tests (Appendix 6 [Section 10.6]), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

| If a participant with baseline results of... | develops the following elevations: |
|---|---|
| ALT or AST <1.5× ULN | ALT or AST ≥3× ULN |
| ALP <1.5× ULN | ALP ≥2× ULN |
| TBL <1.5× ULN | TBL ≥2× ULN (except for patients with Gilbert's syndrome) |
| ALT or AST ≥1.5× ULN | ALT or AST ≥2× baseline |
| ALP ≥1.5× ULN | ALP ≥2× baseline |
| TBL ≥1.5× ULN | TBL ≥1.5× baseline (except for patients with Gilbert's syndrome) |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (eg, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the

participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

**Comprehensive hepatic evaluation**

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

| If a participant with baseline results of... | develops the following elevations: |
|---|---|
| ALT or AST <1.5× ULN | ALT or AST ≥3× ULN with hepatic signs/symptoms[a], or<br>ALT or AST ≥5× ULN |
| ALP <1.5× ULN | ALP ≥3× ULN |
| TBL <1.5× ULN | TBL ≥2× ULN (except for patients with Gilbert's syndrome) |
| ALT or AST ≥1.5× ULN | ALT or AST ≥2× baseline with hepatic signs/symptoms[a], or<br>ALT or AST ≥3× baseline |
| ALP ≥1.5× ULN | ALP ≥2× baseline |
| TBL ≥1.5× ULN | TBL ≥2× baseline (except for patients with Gilbert's syndrome) |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio (PT-INR); tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (eg, ultrasound or computed tomography scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

**Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study**

Additional hepatic safety data collection in hepatic safety CRF should be performed in study participants who meet 1 or more of the following 5 conditions:

- Elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests (if baseline ALT <1.5× ULN)
    - In participants with baseline ALT ≥1.5× ULN, the threshold is ALT ≥3× baseline on 2 or more consecutive tests
- Elevated TBL to ≥ 2x ULN (if baseline TBL <1.5× ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5× ULN, the threshold should be TBL ≥2× baseline
- Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5× ULN)
    - In participants with baseline ALP ≥1.5× ULN, the threshold is ALP ≥2× baseline on 2 or more consecutive blood tests
- Hepatic event considered to be an SAE
- Discontinuation of study drug due to a hepatic event

Note: the interval between the two consecutive blood tests should be at least 2 days.

#### 8.2.8.2. Hypersensitivity Reactions Including Infusion Related Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the Hypersensitivity, Anaphylactic, and Infusion Related Reactions CRFs.

Locations where study participants are receiving investigational product should have appropriately trained medical staff and appropriate medical equipment and rescue medications available. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

If a participant experiences a systemic hypersensitivity reaction or infusion related reaction either involving two or more organ systems (eg, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems), or that is severe, additional blood and urine samples should be collected as close to the event as possible, as described in Appendix 2 (Section 10.2.2). Tryptase and when applicable urine N-methylhistamine should be repeated in approximately 4 weeks to obtain postevent baseline. Laboratory results are provided to the sponsor via the central laboratory.

#### 8.2.8.3. Dosing Rechallenge and Premedication for Infusions

Premedication for dosing is not planned. Dosing rechallenge is contraindicated in participants that have experienced a suspected or possible anaphylactic reaction (eg, reaction involving 2 or more organ systems [eg, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems] occurring in close proximity to dosing), in a prior dose (Sampson et al. 2006). For infusion related reactions which are not suspicious for anaphylaxis, after review of the data, and at the investigator's discretion, the participant may be rechallenged. If rechallenge is planned, the

participant may be premedicated for subsequent doses at the investigator discretion and according to local practice guidelines. Prior to initiating premedication, the investigator may consult with the sponsor. Any premedication given will be documented as a concomitant therapy.

## 8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3 (Section 10.3):

- AEs
- SAEs, and
- Product complaints (PCs)

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

### 8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

| Event | Collection Start | Collection Stop | Timing for Reporting to Sponsor or Designee | Mechanism for Reporting | Back-up Method of Reporting |
|---|---|---|---|---|---|
| **Adverse Event** | | | | | |
| AE | signing of the informed consent form (ICF) | participation in study has ended | As soon as possible upon site awareness | AE CRF | N/A |
| **Serious Adverse Event** | | | | | |
| SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures | signing of the ICF | start of intervention | Within 24 hours of awareness | SAE paper form | SAE paper form |
| SAE and SAE updates – after start of study intervention | start of intervention | participation in study has ended | Within 24 hours of awareness | SAE paper form | SAE paper form |
| SAE[a] – after participant's study participation has ended **and** the investigator becomes aware | After participant's study participation has ended | N/A | Promptly | SAE paper form | N/A |
| **Pregnancy** | | | | | |
| Pregnancy in female participants and female partners of male participants | After the start of study intervention | 60 days following the after final dose | Within 24 hours (see Section 8.3.2) | Pregnancy paper form | Pregnancy paper form |

| Event | Collection Start | Collection Stop | Timing for Reporting to Sponsor or Designee | Mechanism for Reporting | Back-up Method of Reporting |
|---|---|---|---|---|---|
| **Product Complaints** | | | | | |
| PC associated with an SAE or might have led to an SAE | Start of study intervention | End of study intervention | Within 24 hours of awareness | Product Complaint form | N/A |
| PC not associated with an SAE | Start of study intervention | End of study intervention | Within 1 business day of awareness | Product Complaint form | N/A |
| Updated PC information | — | — | As soon as possible upon site awareness | Originally completed Product Complaint form with all changes signed and dated by the investigator | N/A |
| PC (if investigator becomes aware) | Participation in study has ended | N/A | Promptly | Product Complaint form | |

Abbreviations: AE = adverse event; ICF = informed consent form; N/A = not applicable; PC = product complaints; SAE = serious adverse event.

[a] Serious adverse events should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

#### 8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading AE collection should occur prior to the collection of the C-SSRS.

If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

### 8.3.2. Pregnancy

**Collection of pregnancy information**

*Male participants with partners who become pregnant*

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive donanemab.
- After learning of a pregnancy in the female partner of a study participant, the investigator will
  - obtain a consent to release information from the pregnant female partner directly, and
  - within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

  The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

*Female participants who become pregnant*

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

Prior to continuation of study intervention following pregnancy, the following must occur:

- The sponsor and the relevant Institutional Review Board (IRB)/Independent Ethics Committee (IEC) give written approval.
- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and the participant's offspring.

## 8.4. Pharmacokinetics

- Venous blood samples of approximately 4 mL will be collected for measurement of serum concentrations of donanemab as specified in the SoA (Section 1.3).
- A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

## 8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

## 8.6. Genetics

A blood sample for DNA isolation will be collected from participants.

See Appendix 5 (Section 10.5) for Information regarding genetic research and Appendix 1 (Section 10.1.11) for details about sample retention and custody.

## 8.7. Biomarkers

Biomarkers are not evaluated in this study.

## 8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against donanemab. Antibodies may be further characterized for their ability to neutralize the activity of donanemab. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of donanemab. All samples for immunogenicity should be taken predose when applicable and possible.

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies (ADAs) in the presence of donanemab at a laboratory approved by the sponsor.

Treatment-emergent ADAs are defined in Section 9.3.6.

Samples will be retained for a maximum of 15 years after the last participant visit, if local regulations allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to donanemab. Any samples remaining after 15 years will be destroyed.

## 8.9. Health Economics

Health economics and health economics parameters are not evaluated in this study.

# 9. Statistical Considerations

The statistical analysis plan will be finalized prior to first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

## 9.1. Statistical Hypotheses

Not applicable.

### 9.1.1. Multiplicity Adjustment

Not applicable.

## 9.2. Analyses Sets

The following populations are defined:

| Population | Description |
|---|---|
| Entered | All participants who sign the informed consent form |
| Pharmacokinetic | All enrolled participants who received at least 1 full dose of donanemab and have baseline and at least one postbaseline evaluable pharmacokinetic sample. Participants will be analyzed according to the intervention they actually received. |
| Safety | All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received |

### 9.2.1. Study Participant Disposition

A detailed description of participant disposition will be provided at the end of the study.

### 9.2.2. Study Participant Characteristics

Demographic and baseline characteristics will be summarized.

## 9.3. Statistical Analyses

### 9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of the Sponsor or its designee.

Pharmacokinetic analyses will be conducted on data from all participants who receive at least 1 dose of the investigational product and have evaluable PK data.

Safety analyses will be conducted for all enrolled participants who received study intervention, whether or not they completed all protocol requirements.

Summary statistics, data tabulations, and data graphs will be provided as deemed appropriate.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety, immunogenicity, and population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the statistical analysis plan, where appropriate. Adjustments to the planned analyses are described in the final clinical study report.

### 9.3.2. Primary Endpoint Analyses: Pharmacokinetic Analyses

#### 9.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for donanemab will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum drug concentration ($C_{max,ss}$) and area under the concentration versus time curve 0 to 4 weeks ($AUC_{0\text{-}4Weeks}$) and during a dosing interval at steady state ($AUC_{\tau,ss}$) following multiple dosing of donanemab. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

Noncompartmental analysis will be conducted, and PK parameter estimates of maximum observed drug concentration ($C_{max}$), area under the concentration versus time curve from time 0 to infinite time ($AUC_{0\text{-}\infty}$), area under the concentration versus time curve from time 0 to last measured concentration ($AUC_{0\text{-}tlast}$), clearance and half-life will be reported for donanemab. Exposure ($AUC_{0\text{-}4Weeks}$) will be calculated. Other noncompartmental parameters may be reported, as appropriate.

Exploratory graphical analyses relating donanemab serum exposure and immunogenicity may be conducted.

### 9.3.3. Secondary Endpoint(s) Analyses

The incidence of TEAEs and SAEs to investigate the safety and tolerability of donanemab following IV administration of donanemab in healthy participants Q2W for 10 weeks at a 350 mg dose will be listed and/or summarized.

### 9.3.4. Exploratory Analyses

The number of TEAEs will be reported. The frequency and percentage of participants with preexisting ADAs and with TE-ADAs to donanemab will be tabulated. The relationship between the presence of TE-ADAs and serum donanemab concentration may be assessed.

### 9.3.5. Safety Analyses

#### 9.3.5.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs will be presented by severity and by association with investigational product as perceived by the investigator. Adverse events reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

#### 9.3.5.2. Statistical Evaluation of Safety

All study intervention and protocol procedure AEs and SAEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. The incidence of symptoms will be presented by severity and by association with the study intervention as perceived by the investigator. Symptoms reported to have occurred prior to randomization will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities. The number of AEs and SAEs will be reported.

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. The safety parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

### 9.3.6. Immunogenicity Assessments

Treatment-emergent ADAs are defined as those with either

- a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA), or
- those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency of neutralizing antibodies may also be tabulated in TE ADA+ participants, when available.

The relationship between the presence of antibodies and the PK parameters and pharmacodynamic response including safety and efficacy to donanemab may be assessed.

### 9.3.7. Other Analyses

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide.

## 9.4. Interim Analysis

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

Access to safety, PK, and immunogenicity data may occur on an ongoing basis throughout the study. The purpose of these reviews is to inform the design of subsequent studies.

## 9.5. Sample Size Determination

Approximately 40 participants may be enrolled so that approximately 25 participants complete the study. The sample sizes described are customary for Phase 1 studies evaluating safety, PK, and immunogenicity and is not powered on the basis of statistical hypothesis testing.

# 10. Supporting Documentation and Operational Considerations

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
  - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

### 10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or the participant's legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

### 10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

### 10.1.5. Committees Structure

Not applicable.

### 10.1.6. Dissemination of Clinical Study Data

**Communication of Suspended or Terminated Dosing**

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

**Reports**

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

**Data**

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

### 10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Source data may include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

**Data Capture System**

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture systems will be stored at third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

Data from complaint forms submitted to the Sponsor will be encoded and stored in the global product complaint management system.

### 10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.7.

### 10.1.9. Study and Site Start and Closure

**First Act of Recruitment**

The study start date is the date on which the clinical study will be open for recruitment of participants.

**Study or Site Termination**

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

### 10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

### 10.1.11. Investigator Information

Not applicable.

### 10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of donanemab or after donanemab become(s) commercially available.

| **Sample Type** | **Custodian** | **Retention Period After Last Patient Visit*** |
|---|---|---|
| Long-term storage samples | Sponsor or Designee | 15 years |
| Pharmacokinetic | Sponsor or Designee | 2 years |
| Genetics | Sponsor or Designee | 15 years |
| Immunogenicity | Sponsor or Designee | 15 years |

## 10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the local laboratory.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

## Safety Laboratory Tests

| **Hematology** | **Clinical Chemistry** |
|---|---|
| Hematocrit | Sodium |
| Hemoglobin | Potassium |
| Erythrocyte count (RBC) | Bicarbonate |
| Mean cell volume | Chloride |
| Mean cell hemoglobin | Glucose (random) |
| Mean cell hemoglobin concentration | Blood urea nitrogen (BUN) or urea[c] |
| Leukocytes (WBC) | Creatinine |
| Platelets | Uric acid |
| | Total cholesterol |
| Differential WBC [Absolute counts] of: | Total protein |
| Neutrophils | Albumin |
| Lymphocytes | Total bilirubin |
| Monocytes | Alkaline phosphatase (ALP) |
| Eosinophils | Aspartate aminotransferase (AST) |
| Basophils | Alanine aminotransferase (ALT) |
| | Creatine kinase (CK) |
| **Urinalysis**[a] | Gamma-glutamyl transferase (GGT) |
| Specific gravity | |
| pH | |
| Protein | |
| Glucose | |
| Ketones | Ethanol testing[d] |
| Bilirubin | Urine drug screen[d] |
| Urobilinogen | Hepatitis B surface antigen[b] |
| Blood | Hepatitis C antibody[b,e] |
| Nitrite | HIV[e] |
| Microscopic examination of sediment[b] | Pregnancy test[f] |
| | FSH (postmenopausal females only)[b] |

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

Note: Results of these assays will be validated by the local laboratory at the time of testing.

[a] Performed by dipstick. Microscopic examination to be performed if dipstick is abnormal for blood, protein, or nitrates.

[b] Performed at screening only.

[c] Either BUN or urea will be tested, whichever is feasible.

[d] Urine drug screen and ethanol (urine or breath) level performed at screening and at admission to the clinical research unit.

[e] Participants with a positive hepatitis C antibody test result can have a confirmatory hepatitis C RNA test.

[f] In females only. Serum pregnancy test at screening and urine pregnancy test will be performed at other timepoints as indicated in SoA or at investigator's discretion.

### 10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

**Protocol I5T-MC-AACP Sampling Summary**

| Purpose | Blood Volume per Sample (mL) | Number of Blood Samples | Total Volume (mL) |
|---|---|---|---|
| Screening tests[a] | 45 | 1 | 45 |
| Clinical laboratory tests[a] | 12.5 | 13 | 162.5 |
| Pharmacokinetics | 4 | 50 | 200 |
| Immunogenicity | 10 | 6 | 60 |
| Pharmacogenetics | 10 | 1 | 10 |
| Total | | | 477.5 |
| Total for clinical purposes [rounded up to nearest 10 mL] | | | 480 |

[a] Additional samples may be drawn if needed for safety purposes.

### 10.2.2. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

**Purpose of collecting samples after a systemic hypersensitivity event**

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

**When to collect samples after a systemic hypersensitivity event occurs**

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return-to-baseline values.

| Timing | Laboratory Test [a] |
|---|---|
| Collect from 30 minutes to 4 hours after the start of the event.<br>● Note: The optimal collection time is from 1 to 2 hours after the start of event. | Total tryptase<br>complements (C3, C3a, and C5a)<br>cytokine panel (IL-6, IL-1β, IL-10 or any cytokine panel that includes these 3 cytokines) |
| Collect only if not already collected on the same day as the event.<br>● Note: If collecting, collect up to 12 hours after the start of the event. | donanemab (LY3002813) ADA<br>donanemab (LY3002813) concentration |

Abbreviations: ADA = anti-drug antibodies; IL = interleukin.

[a] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

### What information to record

Record the date and time when the samples are collected.

### Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

# 10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## 10.3.1. Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. |

| **Events Meeting the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. |

| **Events <u>NOT</u> Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.<br>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.<br>• Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). |

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.3.2. Definition of SAE

**An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:**

**a. Results in death**

**b. Is life-threatening**

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

**f. Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to

prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 10.3.3. Definition of Product Complaints

**Product Complaint**

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

### 10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

**AE, SAE, and Product Complaint Recording**

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

  Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship/
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB, in their assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

### 10.3.5. Reporting of SAEs

**SAE Reporting via an Electronic Data Collection Tool**

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section) or to the medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SAE Report.

**SAE Reporting via Paper Form**

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the medical monitor or the SAE coordinator.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE Report.

### 10.3.6. Regulatory Reporting Requirements

**SAE Regulatory Reporting**

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

# 10.4. Appendix 4: Contraceptive and Barrier Guidance

## 10.4.1. Definitions

| | Definition |
|---|---|
| Women of childbearing potential (WOCBP) | Adult females are considered WOCBP unless they are WNOCBP.<br>Any amount of spotting should be considered menarche. |
| Women not of childbearing potential (WNOCBP) | Females are considered WNOCBP if they<br>• have a congenital anomaly such as Müllerian agenesis<br>• are infertile due to surgical sterilization, or<br>• are postmenopausal.<br>Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy. |
| Postmenopausal state | The postmenopausal state is defined as a woman:<br>• at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or<br>• aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or<br>• 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or<br>• aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. |

[a] Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

### Females

| Topic | Condition |
|---|---|
| Pregnancy testing | Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure. See the protocol Schedule of Activities for subsequent pregnancy testing requirements. |
| Contraception | Abstinence or 2 effective forms of contraception where at least 1 form is highly effective, maintained for at least 5 half-lives plus 30 days |

## 10.4.2. Contraception Guidance

**For male participants:**

- Males may participate in this study.
- No male contraception is required except in compliance with specific local government study requirements.

**For female participants:**

- Women of childbearing potential are excluded from the study.
- Women not of childbearing potential may participate in this study.

See Appendix 4, Section 10.4.1 for definitions.

Examples of highly effective, effective, and unacceptable methods of contraception can be found below.

| Methods | Examples |
|---|---|
| Highly effective contraception (less than 1% failure rate) | • female sterilization<br>• combination oral contraceptive pill<br>• progestin-only contraceptive pill (mini-pill)<br>• implanted contraceptives<br>• injectable contraceptives<br>• contraceptive patch (only women <198 pounds or 90 kg)<br>• total abstinence<br>• vasectomy (if only sexual partner)<br>• fallopian tube implants (if confirmed by hysterosalpingogram)<br>• combined contraceptive vaginal ring, or<br>• intrauterine devices |
| Effective contraception | • male or female condoms with spermicide<br>• diaphragms with spermicide or cervical sponges<br>• barrier method with use of a spermicide<br>  ○ condom with spermicide<br>  ○ diaphragm with spermicide, or<br>  ○ female condom with spermicide |
| Ineffective forms of contraception whether used alone or in any combination | • spermicide alone<br>• periodic abstinence<br>• fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal)<br>• withdrawal<br>• postcoital douche, or<br>• lactational amenorrhea |

## 10.5. Appendix 5: Genetics

**Use/Analysis of DNA**

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to donanemab and related diseases. They may also be used to develop tests/assays including diagnostic tests related to donanemab and/or interventions of this drug class. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for apolipoprotein E genotype ε4. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to donanemab or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on donanemab or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

## 10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

### Hepatic Evaluation Testing

See Section 8.2.8.1 for guidance on appropriate test selection.

Testing by an investigator-designated local laboratory should be performed for all testing defined by this guidance.

The local laboratory must be qualified in accordance with applicable local regulations.

| **Hepatic Hematology Panel** | **Hepatic Clinical Chemistry Panel** |
|---|---|
| Hemoglobin | Total bilirubin |
| Hematocrit | Direct bilirubin |
| Erythrocytes (RBCs - red blood cells) | Alkaline phosphatase (ALP) |
| Leukocytes (WBCs - white blood cells) | Alanine aminotransferase (ALT) |
| Differential: | Aspartate aminotransferase (AST) |
| Neutrophils, segmented | Gamma-glutamyl transferase (GGT) |
| Lymphocytes | Creatine kinase (CK) |
| Monocytes | **Other Chemistry** |
| Basophils | Acetaminophen |
| Eosinophils | Acetaminophen protein adducts |
| Platelets | Alkaline phosphatase isoenzymes |
| Cell morphology (RBC and WBC) | Ceruloplasmin |
| **Hepatic Coagulation Panel** | Copper |
| Prothrombin time, INR (PT-INR) | Ethyl alcohol (EtOH) |
| **Hepatitis A virus (HAV) testing:** | Haptoglobin |
| HAV total antibody | Immunoglobulin IgA (quantitative) |
| HAV IgM antibody | Immunoglobulin IgG (quantitative) |
| **Hepatitis B virus (HBV) testing:** | Immunoglobulin IgM (quantitative) |
| Hepatitis B surface antigen (HbsAg) | Phosphatidylethanol (Peth) |
| Hepatitis B surface antibody (anti-HBs) | **Urine Chemistry** |
| Hepatitis B core total antibody (anti-HBc) | Drug screen |
| Hepatitis B core IgM antibody | Ethyl glucuronide (EtG) |
| HBV DNA [b] | **Other Serology** |
| **Hepatitis C virus (HCV) testing:** | Anti-nuclear antibody (ANA) |
| HCV antibody | Anti-smooth muscle antibody (ASMA) [a] |
| HCV RNA [b] | Anti-actin antibody [c] |
| **Hepatitis D virus (HDV) testing:** | Epstein-Barr virus (EBV) testing: |
| HDV antibody | EBV antibody |
| **Hepatitis E virus (HEV) testing:** | EBV DNA [b] |
| HEV IgG antibody | Cytomegalovirus (CMV) testing: |
| HEV IgM antibody | CMV antibody |
| HEV RNA [b] | CMV DNA [b] |
| **Microbiology** | Herpes simplex virus (HSV) testing: |
| Culture: | HSV (Type 1 and 2) antibody |
| Blood | HSV (Type 1 and 2) DNA [b] |
| Urine | Liver kidney microsomal type 1 (LKM-1) antibody |

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio; PT-INR = prothrombin time-international normalized ratio.

[a] Not required if anti-actin antibody is tested.

[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

## 10.7. Appendix 7: Provisions for Changes in Study Conduct During Exceptional Circumstances

**Implementation of this appendix**

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

**Exceptional circumstances**

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

**Implementing changes under exceptional circumstances**

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

**Considerations for making a change**

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

**Informed consent**

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits," and
- provision of their personal or medical information required prior to implementation of these activities.

**Changes in study conduct during exceptional circumstances**

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

***Remote visits***

*Types of remote visits*

**Telemedicine:** Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, AEs and concomitant medications.

**Other alternative locations:** Participants may visit local hospital other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include but are not limited to safety monitoring (physical examination, vital signs, ECG, body temperature, neurological examinations), sample collections for clinical laboratory tests.

*Data capture*

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

*Safety reporting*

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints remain unchanged.

*Return to on-site visits*

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

***Screening period guidance***

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 28 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 28 days from screening visit to randomization visit: the participant will proceed to the next study visit per the usual Schedule of Activities, provided that randomization visit must be conducted within 28 days from first screening visit.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 28 days from screening visit to randomization visit: The participant must be discontinued because of screening interruption due to an exceptional circumstance. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual Schedule of Activities should

be followed, starting at screening visit to ensure participant eligibility by randomization visit.

***Adjustments to visit windows***

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

**Documentation**

*Changes to study conduct will be documented*

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

*Source documents at alternate locations*

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

## 10.8. Appendix 8: Abbreviations and Definitions

| Term | Definition |
|---|---|
| **Aβ** | amyloid beta |
| **abuse** | Use of a study intervention for recreational purposes or to maintain an addiction or dependence |
| **AD** | Alzheimer's disease |
| **ADA** | anti-drug antibody |
| **AE** | adverse event |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **ApoE4** | apolipoprotein E genotype ε4 |
| **ARIA** | amyloid-related imaging abnormalities |
| **ARIA-E** | ARIA–edema/effusions |
| **ARIA-H** | ARIA–hemorrhage/hemosiderin deposition |
| **AST** | aspartate aminotransferase |
| **$AUC_{0\text{-}4Weeks}$** | area under the concentration versus time curve 0 to 4 weeks |
| **$AUC_{0\text{-}\infty}$** | area under the concentration versus time curve from time 0 to infinity |
| **$AUC_{0\text{-}tlast}$** | area under the concentration versus time curve from time 0 to last measured concentration |
| **$AUC_{\tau,ss}$** | area under the concentration versus time curve during a dosing interval at steady state |
| **BMI** | body mass index |
| **CDC** | Centers for Disease Control and Prevention |
| **$C_{max}$** | maximum observed drug concentration |
| **$C_{max,ss}$** | maximum observed drug concentration during a dosing interval at steady state |
| **complaint** | A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system. |
| **Compliance** | Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements. |
| **COVID-19** | coronavirus disease 2019 |

| | |
|---|---|
| **CRF** | case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant. |
| **CRP** | clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer. |
| **CRU** | clinical research unit |
| **C-SSRS** | Columbia-Suicide Severity Rating Scale |
| **ECG** | electrocardiogram |
| **enroll** | The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment. |
| **Enter** | Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives. |
| **HBV** | hepatitis B virus |
| **HCV** | hepatitis C virus |
| **HIV** | human immunodeficiency virus |
| **iADRS** | integrated Alzheimer's Disease Rating Scale |
| **IB** | Investigator's Brochure |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **IEC** | Independent Ethics Committee |
| **Ig** | immunoglobulin |
| **IMP** | Investigational Medicinal Product (see also "investigational product")<br>A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial. |
| **informed consent** | A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. |
| **INR** | international normalized ratio |
| **investigational product** | A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP." |

| | |
|---|---|
| **IRB** | Institutional Review Board |
| **IRR** | infusion-related reactions |
| **IV** | intravenous |
| **MCI** | mild cognitive impairment |
| **N3pG** | pyroglutamate formation of the third amino acid |
| **participant** | Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control |
| **PC** | product complaint |
| **PCR** | polymerase chain reaction |
| **PK** | pharmacokinetics |
| **PT-INR** | prothrombin time-international normalized ratio |
| **Q2W** | every 2 weeks |
| **Q4W** | every 4 weeks |
| **QTc** | corrected QT interval |
| **SAE** | serious adverse event |
| **SARS-CoV-2** | severe acute respiratory syndrome coronavirus 2 of the genus Betacoronavirus |
| **screen** | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. |
| **SIB** | suicidal ideation and behavior |
| **SoA** | Schedule of Activities |
| **TBL** | total bilirubin level |
| **TE-ADA** | treatment-emergent anti-drug antibodies |
| **TEAE** | Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment. |
| **ULN** | upper limit of normal |

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| Approval | PPD<br>Medical Director<br>12-Dec-2022 17:51:43 GMT+0000 |

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