Protocol Amendment I5T-MC-AACQ (a)

Investigating the Effect of Different Donanemab Dosing Regimens on ARIA-E and Amyloid Lowering in Adults with Early Symptomatic Alzheimer's Disease

NCT05738486

Approval Date: 26-May-2023

Title Page

Protocol Title:

Investigating the Effect of Different Donanemab Dosing Regimens on ARIA-E and Amyloid Lowering in Adults with Early Symptomatic Alzheimer's Disease

Protocol Number: I5T-MC-AACQ

Amendment Number: a

Compound: LY3002813

Brief Title:

Exploration of Different Donanemab Dosing Regimens

Study Phase: 3b

Acronym: TRAILBLAZER-ALZ 6

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s):

IND: 109157

EU trial number: 2022-502268-18-00

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

Document ID: VV-CLIN-114998

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*28-Oct-2022*

Amendment [a]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The main rationale for the amendment is to clarify the chosen dosing regimens for treatment arms 3 and 4 and other minor corrections/clarifications as stated below.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Updated visit frequency to every 2 weeks for the first 10 visits (V2-V10) and every 4 weeks thereafter	Correction per SoA
	Addition of "<5 half-lives prior to randomization" to an exclusion criterion about passive anti-amyloid immunotherapy	Clarification
1.2. Schema	Revised schema to align with every 2 weeks visit frequency for V2-V10, updated footnote [a] to align with visit frequency	Correction
1.3. Schedule of Activities	Period II – Q2W visit frequency	Alignment with Q2W visit frequency for V2-V10
	Period III - Clarify that V801 is not needed if more than 12 weeks have passed since last dose of IP at V25 or study discontinuation	Clarification
1.3.2. Period II – Treatment Visits 2-15	Orthostatic BP and pulse are measured at V2, V8, V12, V15, and unscheduled visits, sitting BP, pulse, and temperature will be measured at all visits	Clarification
	MRI notes edited to align with Q2W visit frequency	Alignment with Q2W visit frequency for V2-V10
	Removed footnote [a] to align with Q2W visit frequency	Alignment with Q2W visit frequency for V2-V10

Section # and Name	Description of Change	Brief Rationale
1.3.3. Period II – Treatment Visits 16-25	Amyloid PET scan note regarding ED visit revised to 3 months from last amyloid PET scan	Correction
4.1.1. Treatment Arms and Titration Regimen Outline	Treatment arms 3 and 4 established; removal of treatment arms 3 option 2 and 4 option 2 and the language around this	Clarification
	Removed "only if donanemab Q2W dosing regimen is chosen; otherwise these visits will be skipped"	Alignment with visit/dosing frequency
4.3. Justification for Dose	Built-in dosing pauses updated to align with current dosing regimens	Clarification
5.2. Exclusion Criteria	Addition of "<5 half-lives prior to randomization" to Exclusion Criterion 22	Clarification
6.3. Assignment to Study Intervention	Clarified stratification regarding PET scan results and *APOE* genotype	Clarification
8.2.1. Physical/Neurological Examinations	Addition of "neurological" to align with SoA	Correction to align with SoA
8.2.2. Vital Signs	Clarified vital signs, including temperature, will be measured at all visits	Clarification
	Clarified sitting BP is measured at all visits	Clarification
	Clarified orthostatic BP and pulse to be measured supine and standing	Clarification
8.2.5. Suicidal Ideation and Behavior Risk Monitoring	Corrected C-SSRS to be administered at V2 per the SoA	Correction to align with SoA
	Clarified study partner may be present in person or on phone for all days C-SSRS is administered	Clarification
8.4. Pharmacokinetics	Addition of PK sample collection regarding IP discontinuation	Clarification
9.3.1. General Considerations	Alignment with objective tables for 76 weeks (corresponding visit V25) assessment	Editorial

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Minor editorial changes	Clarification/editorial

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

Investigating the Effect of Different Donanemab Dosing Regimens on ARIA-E and Amyloid Lowering in Adults with Early Symptomatic Alzheimer's Disease

Brief Title:

Exploration of Different Donanemab Dosing Regimens

Regulatory Agency Identifier Numbers:

IND: 109157

EU trial number: 2022-502268-18-00

Rationale:

This study will investigate different donanemab dosing regimens and their effect on the frequency and severity of ARIA-E in adults with early symptomatic Alzheimer's disease (AD) and explore patient characteristics that might predict risk of ARIA.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To assess the effect of alternative donanemab dosing regimens versus the standard donanemab dosing regimen on ARIA-E frequency	Proportion of participants with any occurrence of ARIA-E by Week 24
Secondary	
To assess the effect of alternative donanemab dosing regimens versus standard donanemab dosing regimen on ARIA-E frequency	Proportion of participants with any occurrence of ARIA-E by Week 52
To assess the effect of alternative donanemab dosing regimens versus standard donanemab dosing regimen on brain amyloid deposition	Change from baseline in brain amyloid plaque deposition as measured by amyloid PET scan through • Week 24 • Week 52 • Week 76

To evaluate the effect of alternative donanemab dosing regimens on ARIA events	• Proportion of participants with any occurrence of ARIA-H by
	  ○ Week 24
	  ○ Week 52
	• ARIA-E and ARIA-H by severity

To assess peripheral PK and presence of anti-donanemab antibodies	• Serum PK of donanemab • ADAs against donanemab, including TE-ADAs and neutralizing antibodies

Abbreviations: Aß = amyloid-beta peptide; ADA = antidrug antibody; ARIA = amyloid-related imaging abnormalities; PK = pharmacokinetic.

Estimand

The primary clinical question of interest is:

> *What is the reduction in the frequency of ARIA-E events at Week 24 in participants with early symptomatic AD treated with an alternative donanemab dosing regimen compared to the standard donanemab dosing regimen, regardless of discontinuation or interruption of donanemab dosing for any reason and regardless of change in background AD medication?*

Overall Design

This is a multicenter, randomized, double-blind, Phase 3b study in adults with early symptomatic AD. Early symptomatic AD refers to the combination of 2 stages, mild cognitive impairment and mild AD dementia.

The study duration will be up to approximately 91 weeks and includes a

- screening period
- double-blind treatment period, and
- posttreatment follow-up.

The visit frequency is every 2 weeks for Visits 2-10 and every 4 weeks thereafter.

The treatment duration will be up to approximately 72 weeks.

If a participant meets amyloid plaque reduction criteria at Visit 12 (Week 24) or Visit 19 (Week 52), they will no longer receive treatment, and the study-site personnel may conduct Visits 13, 14, 16, 17, 18, 20, 21, 23, and 24 by telephone.

Brief Summary:

This study is intended to assess

- alternate donanemab dosing regimens that could potentially reduce the risk of ARIA-E frequency, severity, symptoms
- baseline and treatment response characteristics, including magnetic resonance imaging (MRI) and blood-based biomarkers, that might predict risk of ARIA-E, and

- amyloid lowering of alternate dosing regimens.

Magnetic resonance imaging of the brain will be used to check for evidence of ARIA-H or ARIA-E, and other clinically relevant safety findings.

Amyloid positron emission tomography (PET) scans provide a quantitative assessment of amyloid plaque deposition in the brain and can serve as a biomarker of clearance of amyloid deposits.

Part of the study eligibility criteria is determined by amyloid PET scans. Additional amyloid PET scans will be performed during the study.

Study partners

Each participant must have a study partner.

A second study partner may serve as backup. The study partners are required to accompany the participant for signing consent. Certain study visits require that a study partner is available by telephone if not accompanying the participant at the visit.

If a study partner must withdraw from study participation, a replacement may be allowed at the investigator's discretion.

Study Population:

In general, an individual may take part in this study if they

- Are 60 to 85 years of age, at the time of signing the informed consent.
- Have gradual and progressive change in memory function for ≥6 months from time of signing the informed consent.
- Have a Mini Mental State Examination (MMSE) score of 20 to 28 at Visit 1. The MMSE is a brief instrument used to assess cognitive function.
- Have an amyloid PET scan result that shows the presence of amyloid pathology.

In general, an individual may not take part in this study if they

- Have significant neurological disease affecting the central nervous system other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures, except febrile childhood seizures.
- Have a condition that in the investigator's opinion could interfere with the analyses of this study, or a current serious or unstable illness.
- Have a life expectancy of less than 24 months.
- Are not able to complete the MRI imaging procedures due to issues, such as claustrophobia, or have metal implants or a cardiac pacemaker.
- Are not able to complete the PET procedure or have sensitivity to the amyloid PET tracer used in the procedure.
- Have previously received donanemab or treatment before with passive anti-amyloid immunotherapy <5 half-lives prior to randomization.

Number of Participants:

Approximately 800 participants will be randomly assigned to 1 of 4 treatment arms in a 1:1:1:1 ratio.

Intervention Groups and Duration:

There will be 4 treatment arms in this study.

All participants will receive a dosing regimen that includes donanemab, but at different dose levels and frequency of dosing. Placebo is given at specific visits to preserve the blind for the different dosing regimens. All dosing is administered by intravenous infusion.

After Week 16, all participants are targeted to receive the maximum donanemab dose of 1400 mg monthly until they meet the dose stopping criteria or until the end of the study.

Ethical Considerations of Benefit/Risk:

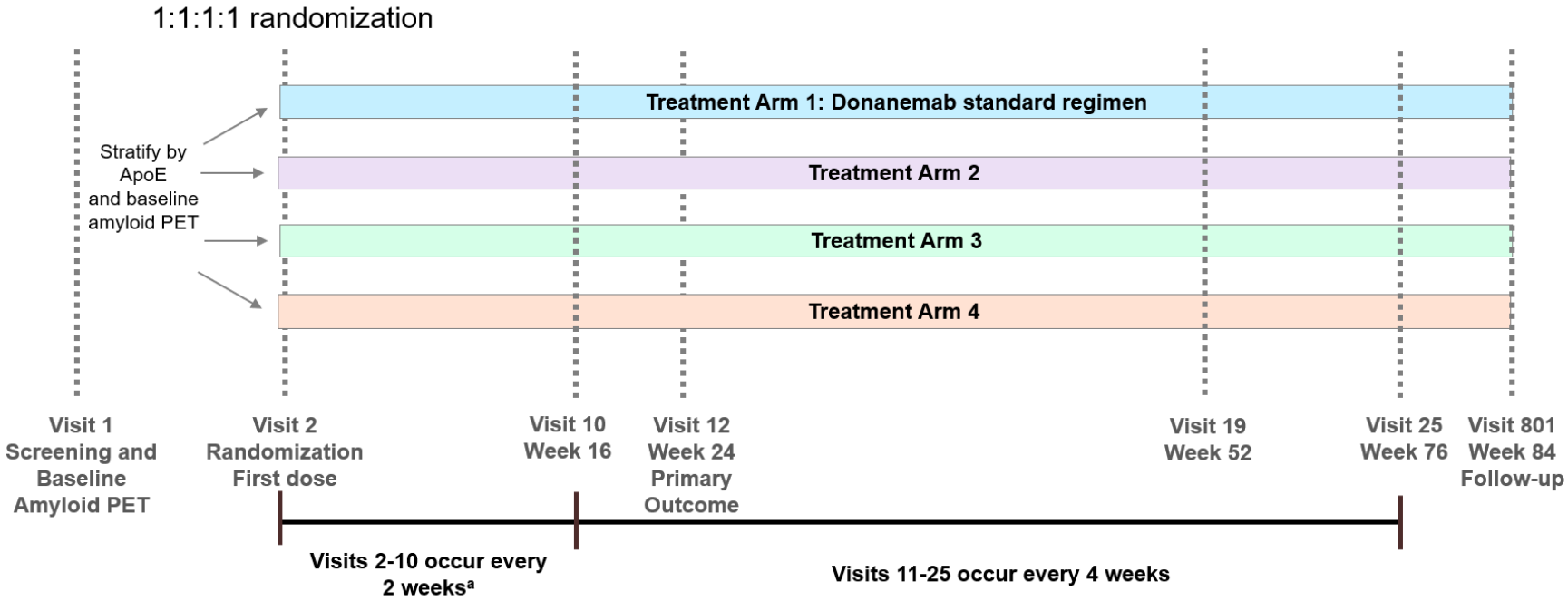
A potential key benefit for participation in this study is the delay in cognitive and functional decline associated with AD.

The potential risks associated with participation in this study are the occurrence of ARIA and infusion-related reactions. These risks are observed with beta amyloid plaque-targeted therapies, including donanemab.

Given the seriousness and limited treatments for AD, donanemab provides a clinically meaningful treatment alternative. Considering the measures taken to minimize risk to participants, the potential benefit-risk balance for this study is acceptable for testing different dosing regimens that may reduce the risk of ARIA.

Data Monitoring Committee: Yes

1.2. Schema



[a] The visit frequency is every 2 weeks for Visits 2-10, and every 4 weeks thereafter.

Note: If a participant meets amyloid plaque reduction criteria defined by the Sponsor, as measured by amyloid PET scan, at Visit 12 (Week 24) or Visit 19 (Week 52), the participant will discontinue study intervention and stay in the study for the remaining study visits.

1.3. Schedule of Activities (SoA)

Three tables describe the SoA.

Table 1 (Section 1.3.1) describes Period I Screening.

Table 2 (Section 1.3.2) describes Period II Treatment Visits 2-15.

Table 3 (Section 1.3.3) describes Period II Treatment Visits 16-25, the Early Discontinuation Visit, and Period III Posttreatment Follow-Up Visit 801.

Period I – Screening

Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.

Screening should not extend past 49 days. Sponsor may strictly control toward end of study enrollment. If the PET or MRI results are delayed due to technical or logistical circumstances, it is not considered a protocol deviation.

Period II – Treatment

The visit frequency is every 2 weeks for Visits 2-10, and every 4 weeks thereafter. See Section 4.1.1 for more treatment arm information.

Early discontinuation

If a participant discontinues the study before Visit 25, perform ED assessments. After the ED Visit, the participant proceeds to Period III to complete the follow-up visit, if possible.

Period III – Follow-up

Visit 801 occurs at least 12 weeks after the last dose of IP. V801 is not needed if more than 12 weeks have passed since last dose of IP at V25 or study discontinuation.

Telephone visits

If a participant meets amyloid plaque reduction criteria at Visit 12 or Visit 19 and discontinues study intervention, the study-site personnel may conduct Visits 13, 14, 16-18, 20, 21, 23, and 24 by telephone. See Sections 4.1.1 and 7.1 for details.

1.3.1. Period I - Screening

I5T-MC-AACQ	Period I Screening	Notes
Visit Number	**Visit 1**	
Day Relative to Randomization	-49 to -1	
Tolerance Interval for Visit (Days)	≤49 before Visit 2	
Entry and administrative procedures		
Informed Consent - Participant	X	The participant informed consent form must be signed before any protocol-specific tests or procedures are performed.
Informed Consent - Study Partner	X	The study partner informed consent form must be signed before any protocol-specific tests or procedures are performed.
Inclusion/exclusion review	X	Review inclusion and exclusion criteria as information becomes available.
Demographics	X	Includes year of birth, sex, ethnicity (where permissible), and race.
Preexisting conditions and medical history	X	Collect all ongoing conditions and medical history.
Substance use (alcohol, caffeine, tobacco use, and nicotine replacement)	X	
Concomitant medications	X	
Adverse events (AEs)	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3.
Safety assessments		
Height	X	
Weight	X	
Vital signs	X	Measure vital signs after the participant has been sitting at least 5 min, and before obtaining a local ECG tracing, or collection of blood samples for laboratory testing. Collect temperature with sitting vitals.
Physical/neurological examination	X	See the Manual of Operations for details.

I5T-MC-AACQ	Period I Screening	Notes
Visit Number	**Visit 1**	
Day Relative to Randomization	-49 to -1	
Tolerance Interval for Visit (Days)	≤49 before Visit 2	
ECG 12-lead (single, local)	X	Collect ECG before blood sample collection. Unscheduled ECGs may be performed at the discretion of investigator.
Patient-reported outcomes (paper)		
MMSE	X	Participants must meet MMSE criteria before any other screening procedures are performed. See Section 5.5 for rescreening criteria. Administer the MMSE prior to medical procedures that could be stressful to the participant, for example before a blood draw.
Laboratory tests and sample collections		Blood draws for screening should be collected at the same time.
Hematology	X	
Clinical Chemistry	X	
Urinalysis	X	
Apolipoprotein E (ApoE)	X	Results will not be provided to the investigators.
Plasma pTau	X	Results will not be provided to the investigators.
Stored samples		Collect only where available and allowed per local regulations.
Genetics Sample	X	
Exploratory Biomarker Samples	X	

I5T-MC-AACQ	Period I Screening	Notes
Visit Number	**Visit 1**	
Day Relative to Randomization	-49 to -1	
Tolerance Interval for Visit (Days)	≤49 before Visit 2	
Screening PET scans and MRI		
Amyloid PET	X	The participant should meet all other eligibility criteria before the amyloid PET scan and MRI. If imaging results are received after the screening window, the participant remains eligible contingent on meeting the other eligibility criteria. If the investigator feels it is necessary, they may repeat the screening labs. A historical amyloid PET scan may be submitted for eligibility if performed within 12 months of Visit 2, randomization. The acceptance of a historical scan is at the discretion of the Sponsor. See Section 8.2.7 for MRI details.
MRI of brain	X	
Randomization and dosing		
Register visit with IWRS	X	

1.3.2. Period II - Treatment Visits 2-15

I5T-MC-AACQ	Period II Treatment														Notes
Visit Number	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Week Relative to Randomization	0	2	4	6	8	10	12	14	16	20	24	28	32	36	
Tolerance Interval for Visit (Days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Administrative															
Inclusion/exclusion review	X														Confirm participant meets all Visit 1 eligibility criteria before proceeding to Visit 2 procedures.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Any event(s) that occur after signing the informed consent are considered AEs as defined in Section 10.3.
Safety Assessments															
Weight	X						X				X			X	
Vital signs and temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sitting BP, pulse, and temperature will be measured at all visits. In addition, orthostatic BP and pulse will be measured at V2, V8, V12, V15, and unscheduled visits. See Section 8.2.2. Note: Measure BP and pulse for suspected hypersensitivity events when able to do so. Do not collect if visit is conducted by telephone.

I5T-MC-AACQ	Period II Treatment														Notes
Visit Number	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Week Relative to Randomization	0	2	4	6	8	10	12	14	16	20	24	28	32	36	
Tolerance Interval for Visit (Days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Administrative															
Physical/neurological examination	X						X				X			X	See the Manual of Operations for details. Note any clinically significant changes from baseline on the AE CRF.
Clinician-administered Assessments (Paper)															
C-SSRS screening/baseline	X														AE collection should occur prior to the collection of the C-SSRS.
C-SSRS since last assessed			X		X		X		X	X	X	X	X	X	
Laboratory tests and sample collections															Collect samples before dosing, unless indicated below. See Section 10.2 for details of testing included in panels.
Hematology	X						X				X			X	
Clinical Chemistry	X						X				X			X	
High-sensitivity C-Reactive Protein	X		X		X		X				X			X	
Neurofilament Light chain	X		X		X		X				X			X	Collect only where available and allowed per local regulations.
Glial fibrillary acidic protein	X		X		X		X				X			X	
sTREM2	X		X		X		X				X			X	
Amyloid-Beta 40 and 42	X		X		X		X				X			X	
Plasma pTau	X		X		X		X				X			X	
Pharmacokinetic Samples (Predose)			X		X		X				X				Sample may be collected from the IV site prior to the infusion.

I5T-MC-AACQ	Period II Treatment														Notes
Visit Number	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Week Relative to Randomization	0	2	4	6	8	10	12	14	16	20	24	28	32	36	
Tolerance Interval for Visit (Days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Administrative															
Pharmacokinetic Samples (Postdose)	X		X				X				X				Collect within 30 min after the end of infusion. Collect from different arm than one used for the infusion.
Immunogenicity Samples	X		X		X		X				X				Collect before the infusion when applicable and possible.
Stored Samples															
Exploratory Biomarker Samples	X		X		X		X				X			X	Collect before the infusion where allowed per local regulations.
Other Safety Measures															
MRI of brain			X				X				X				**Visit 4:** Perform and review MRI before the Visit 4 dose and at least 21 days after the first infusion. **Visit 8:** Perform and review MRI before the Visit 8 dose. **If dosing was missed in visits before Visit 8**: perform and review an additional MRI before seventh dose . See Section 8.2.7.1 for MRI sequence details for each visit. Unscheduled MRIs may be performed at the discretion of investigator.
Additional Efficacy Measures															
Amyloid PET scan											X				

I5T-MC-AACQ	Period II Treatment														Notes
Visit Number	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Week Relative to Randomization	0	2	4	6	8	10	12	14	16	20	24	28	32	36	
Tolerance Interval for Visit (Days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Administrative															
Randomization and Dosing															
Randomization using IWRS	X														
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study intervention using IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Administer study intervention	X	X	X	X	X	X	X	X	X	X	X	X	X	X	The participant must be observed for a minimum of 30 min following the end of each infusion. Visits 2 to 10: Dosing intervals must be more than 7 days apart. Visits 10 to 15: Dosing intervals must be greater than or equal to 21 days apart.

1.3.3. Period II - Treatment Visits 16-25, the Early Discontinuation Visit, and Period III Posttreatment Follow-Up Visit 801

I5T-MC-AACQ	Period II Treatment											Period III	Notes
Visit Number	16	17	18	19	20	21	22	23	24	25	ED	801	
Week Relative to Randomization	40	44	48	52	56	60	64	68	72	76		84	
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±14	
Administrative													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3.
Safety Assessments													
Weight				X			X			X	X		
Vital signs and temperature	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.2.2. For unscheduled visits, measure orthostatic BP and pulse. Do not collect if visit is conducted by telephone.
Physical/neurological examination				X			X			X	X		See the Manual of Operations for details. Note any clinically significant changes from baseline on the AE CRF.
Clinician-Administered Assessments (Paper)													
C-SSRS since last assessed	X	X	X	X	X	X	X	X	X	X	X	X	AE collection should occur prior to the collection of the C-SSRS.
Laboratory Tests and Sample Collections													Collect samples before dosing, unless indicated below. See Section 10.2 for details of testing included in panels.
Hematology				X			X			X	X		

I5T-MC-AACQ	Period II Treatment											Period III	Notes
Visit Number	16	17	18	19	20	21	22	23	24	25	ED	801	
Week Relative to Randomization	40	44	48	52	56	60	64	68	72	76		84	
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±14	
Clinical Chemistry				X			X			X	X		
High-sensitivity C-Reactive Protein				X			X			X	X		
Neurofilament light chain				X			X			X	X		Collect only where available and allowed per local regulations.
Glial fibrillary acidic protein				X			X			X	X		
sTREM2				X			X			X	X		
Amyloid-Beta 40 and 42				X			X			X	X		
Plasma pTau				X			X			X	X		
Pharmacokinetic Samples (Predose)				X									May be collected from the IV site before the infusion.
Pharmacokinetic Samples (Postdose)				X									Collect within 30 min of infusion completion. Collect from different arm than one used for the infusion.
Pharmacokinetic Samples (Random)										X	X	X	Do not collect if the last infusion was >6 months prior to the scheduled visit.
Immunogenicity Samples				X						X	X	X	Collect before infusion when applicable and possible.
Stored Samples													
Exploratory Biomarker Samples				X			X			X	X		Collect before infusion unless not allowed or possible due to local regulation.

I5T-MC-AACQ	Period II Treatment											Period III	Notes
Visit Number	16	17	18	19	20	21	22	23	24	25	ED	801	
Week Relative to Randomization	40	44	48	52	56	60	64	68	72	76		84	
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±14	
Other Safety Measures													
MRI of the brain				X							X		See Section 8.2.7.1 for MRI sequence details for each visit. Unscheduled MRIs may be performed at the discretion of investigator. ED Visit: Conduct only if ED occurs more than 6 wk from the previous MRI.
Additional Efficacy Measures													
Amyloid PET scan				X						X	X		ED Visit: Conduct only if ED occurs after 3 or more months from the last amyloid PET scan.
Randomization and Dosing													
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study intervention using IWRS	X	X	X	X	X	X	X	X	X				
Administer study intervention	X	X	X	X	X	X	X	X	X				The participant must be observed for a minimum of 30 min following the end of each infusion. Dosing intervals must be more than 21 days apart.

Abbreviations: AE CRF = AE case report form; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; ED = early discontinuation; IWRS = interactive web-response system; IV = intravenous; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; Q2W = every 2 weeks; sTREM2 = soluble triggering receptor expressed on myeloid cells 2.

2. Introduction

LY3002813 (donanemab) is a humanized immunoglobulin 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 AD.

The donanemab clinical development program for the proposed indication currently comprises

- almost 400 participants in 3 completed studies - Studies AACC, AACD, and AACG, and
- approximately 3000 participants in ongoing studies.

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

2.1. Study Rationale

This study will investigate different donanemab dosing regimens and their effect on the frequency and severity of ARIA-E in adults with early symptomatic AD and explore patient characteristics that might predict risk of ARIA.

2.2. Background

ARIA

ARIA-E and ARIA-H are considered a class effect with antibody therapies directed at amyloid, and APOE ε4 carriers (heterozygotes or homozygotes) have a greater risk for ARIA-E and ARIA-H than noncarriers.

Patients with ARIA are usually asymptomatic. However, ARIA may be serious or life-threatening and could lead to permanent disability or death. When asymptomatic, ARIA may be detected by routine brain MRI. When symptoms are present in association with imaging abnormalities, symptoms include, but are not limited to

- headache
- vomiting
- dizziness
- tremor
- confusion
- visual or speech disturbances, or
- alteration of consciousness.

See the IB, Section 6.1 for more details.

ARIA events in clinical studies with donanemab

Amyloid-related imaging abnormalities were observed in completed Phase 1 studies, AACD and AACC, Phase 2 Study AACG, and in the ongoing Phase 3 study, AACI.

The ARIA events from the Phase 2 completed study are summarized below. Further details can be found in Sections 5.2.1.1.4.2, 5.2.1.2.4.2, and 5.2.1.3 of the IB.

Phase 2 Study AACG ARIA events

Study AACG was a Phase 2, double-blind, placebo-controlled study in participants with early symptomatic AD with intermediate brain tau burden. In Study AACG, ARIA (-E, -H, or both) was observed in a higher percentage of participants treated with donanemab, compared to participants treated with placebo. A majority of ARIA-E and ARIA-H events were first observed within 12 weeks of treatment initiation, with most events observed by 24 weeks.

ARIA-E occurred in 26.7% of participants treated with donanemab, with 6.1% of cases being symptomatic. Symptoms associated with ARIA-E included, but were not limited to, worsening of headache, altered mental status, confusion, and difficulty expressing themselves. Serious symptomatic ARIA-E requiring hospitalization occurred in 1.5% of participants treated with donanemab.

Donanemab dosing regimen

The standard donanemab dosing regimen used in the clinical studies to date is described in Section 4.1.1. This study will evaluate different dosing regimens compared to the standard donanemab dosing regimen for the potential to reduce ARIA. In addition, it will measure amyloid removal and explore novel imaging and blood biomarkers that may be related to or predict ARIA (See Section 4.1.1).

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential risks for this study

ARIA

Amyloid-related imaging abnormalities have been observed with beta amyloid plaque-targeted therapies, including donanemab. ARIA can be detected by brain MRI. ARIA is usually asymptomatic with these therapies, though serious events can occur.

Infusion-related reactions and hypersensitivity

Infusion-related reactions, including anaphylaxis and other immediate hypersensitivity reactions, were associated with donanemab infusion. These reactions may occur with the first or subsequent infusions of donanemab and typically occur during infusion or within 30 minutes postinfusion.

Procedural risks

MRI

MRI scans will be performed as routine safety monitoring during the study. AEs with MRI procedures are rare. However, the procedure involves a strong, magnetic pulsed gradient field which presents risks for participants with metal implants or other accessory medical devices, such as pacemakers, stents, cochlear implants. Participants with such devices should not have an MRI procedure performed unless it has been confirmed that conditions are appropriate for safe use.

The confined space of the MRI testing environment may cause some participants to experience claustrophobia, and some participants may find remaining still to be difficult for the duration of the imaging process.

PET scans

PET scans will be performed during the study. A PET scan uses a radioactive tracer. Multiple PET scans increase exposure to radiation, and at high levels, radiation has been shown to increase the risk of malignancy. As with MRI, the confined space of the PET testing environment may cause some participants to experience anxiety or claustrophobia.

See Section 8.1.1 for additional details, including expected radiation exposure.

More detailed information about the known and expected benefits and risks of the ß-amyloid tracers can be found in the

- United States Package Insert for florbetapir F18 Injection (Amyvid™ package insert, 2012)
- Summary of Product Characteristics for florbetapir F18 (Amyvid SmPC, 2021)
- United States Package Insert for florbetaben (Neuraceq™ package insert, 2014), and
- Summary of Product Characteristics for florbetaben (Neuraceq SmPC, 2021).

Management of risks for this study

ARIA

To reduce the risk of serious ARIA, participants with evidence of ARIA-E, >4 cerebral microhemorrhages, >1 area of cortical superficial siderosis, any macrohemorrhage, or severe white matter disease in screening MRI are excluded. Management of ARIA risk is covered in Section 8.3.3.1, which describes temporary or permanent study intervention discontinuation and MRI scanning guidance.

Infusion-related reactions and hypersensitivity

Most IRRs occur during the infusion or within 30 minutes. Participants will be monitored for at least 30 minutes after each infusion. Additional management of hypersensitivity is covered in Sections 7.1 and 8.3.3.2.

2.3.2. Benefit Assessment

Delay in cognitive and functional decline is a key potential benefit for donanemab, demonstrated by rapid and deep clearance of amyloid (Shcherbinin, et al. 2022), a surrogate endpoint likely to predict clinical benefit.

In Study AACG, donanemab was statistically significantly better than placebo in slowing disease progression as measured by the iADRS. The effect size at endpoint was 0.29, resulting in a 32% slowing of decline (Mintun, et al. 2021).

2.3.3. Overall Benefit-Risk Conclusion

Overall, given the seriousness and limited disease-modifying treatments for AD, donanemab provides a clinically meaningful treatment alternative. The risks of donanemab, appropriately managed with the proposed approaches, are outweighed by the demonstrated effect on a surrogate biomarker likely predictive of a clinical benefit in those with AD.

Considering the measures taken to minimize risk to participants, the potential benefit-risk balance for this study is acceptable for testing different dosing regimens that may reduce the risk of ARIA.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To assess the effect of alternative donanemab dosing regimens versus the standard donanemab dosing regimen on ARIA-E frequency	Proportion of participants with any occurrence of ARIA-E by Week 24
Secondary	
To assess the effect of alternative donanemab dosing regimens versus standard donanemab dosing regimen on ARIA-E frequency	Proportion of participants with any occurrence of ARIA-E by Week 52
To assess the effect of alternative donanemab dosing regimens versus standard donanemab dosing regimen on brain amyloid deposition	Change from baseline in brain amyloid plaque deposition as measured by amyloid PET scan through • Week 24 • Week 52 • Week 76
To evaluate the effect of alternative donanemab dosing regimens on ARIA events	• Proportion of participants with any occurrence of ARIA-H by o Week 24 o Week 52 • ARIA-E and ARIA-H by severity
To assess peripheral PK and presence of anti-donanemab antibodies	• Serum PK of donanemab • ADAs against donanemab, including TE-ADAs and neutralizing antibodies
Tertiary/Exploratory	
To explore characteristics that predict risk of ARIA-E and ARIA-H	• Association between exploratory MRI imaging sequences and the occurrence and severity of ARIA events • Association between blood-based biomarkers and the frequency and severity of ARIA events o NfL o pTau o Aß levels (40 and 42)

Objectives	Endpoints
	○ GFAP ○ sTREM2, and ○ hsCRP.
To evaluate the effect of alternative donanemab dosing regimens on IRR	• IRR events frequency and severity

Abbreviations: Aß = amyloid-beta peptide; ADA = antidrug antibody; ARIA = amyloid-related imaging abnormalities; hsCRP = high-sensitivity C-reactive protein; GFAP = glial fibrillary acidic protein; IRR = infusion-related reactions; NfL = neurofilament light chain; PK = pharmacokinetic; pTau = phosphorylated tau; sTREM2 = soluble triggering receptor expressed on myeloid cells 2.

Primary estimand/coprimary estimand

The primary clinical question of interest is:

> *What is the reduction in the frequency of ARIA-E events at Week 24 in participants with early symptomatic AD treated with an alternative donanemab dosing regimen compared to the standard donanemab dosing regimen, regardless of discontinuation or interruption of donanemab dosing for any reason and regardless of change in background AD medication?*

The estimand is described by the following attributes:

- **Population** - Participants with early symptomatic AD
- **Endpoint** - Occurrence of ARIA-E by Week 24
- **Treatment condition** - 4 randomized treatment arms of donanemab with varying dosing schemes
- **Population-level summary** - The relative reduction in proportion of participants with ARIA-E events in the alternative donanemab regimen compared to the standard donanemab regimen
- **Intercurrent events** - "Discontinuation or interruption of donanemab dosing for any reason" and "change in background AD medication." No other intercurrent events are considered
- **Estimand strategy** - Treatment policy. Data will be collected and analyzed regardless of postrandomization events in the first 24 weeks of the trial. This strategy will be implemented by a Bayesian logistic regression model
- **Rationale for estimand** - The study primary objective is to evaluate the effect of alternative donanemab dosing regimens versus the standard donanemab dosing regimen on ARIA-E rate

4. Study Design

4.1. Overall Design

This is a multicenter, randomized, double-blind, Phase 3b study in adults with early symptomatic AD.

This study includes a

- screening period
- double-blind treatment period, and
- posttreatment follow-up.

See the SoA for visit schedule, procedural and assessment details (Section 1.3).

4.1.1. Treatment Arms and Titration Regimen Outline

All participants will receive a dosing regimen that includes donanemab, but at different dose levels and frequency of dosing. Placebo is given at specific visits to preserve the blind for the different dosing regimens.

This table describes the planned dosing regimens for the first 16 weeks. After Week 16, all participants are targeted to receive 1400 mg monthly of donanemab until they meet the dose stopping criteria or until the end of the study.

Visit Number	2	3	4	5	6	7	8	9	10
Study Week	0	2	4	6	8	10	12	14	16
Treatment Arm	**Dose (mg)**								
1 standard regimen	700	PBO	700	PBO	700	PBO	1400	PBO	1400
2	700	PBO	PBO	PBO	1400	PBO	1400	PBO	1400
3	350	PBO	700	PBO	1050	PBO	1400	PBO	1400
4	350	350	350	350	350	350	700	700	1400

Abbreviations: PBO = placebo.

Telephone visits

If a participant meets amyloid plaque reduction criteria at Visit 12 (Week 24) or Visit 19 (Week 52), and discontinues study intervention (Section 7.1), the study-site personnel may conduct Visits 13, 14, 16, 17, 18, 20, 21, 23, and 24 by telephone.

4.1.2. Study Partners

Each participant must have a study partner as described in Section 5.1.

A second study partner may serve as backup. The study partners are required to accompany the participant for signing consent. Visits requiring the collection of AEs and concomitant medications must have a study partner available by telephone if not accompanying the participant at a visit.

If a study partner must withdraw from study participation, a replacement may be allowed at the investigator's discretion. The replacement will need to sign a separate informed consent on the first visit that they accompany the participant.

4.2. Scientific Rationale for Study Design

Study AACQ is a multicenter, randomized, double-blind study of donanemab in participants with early symptomatic AD, where early symptomatic AD refers to the combination of 2 stages, mild cognitive impairment and mild AD dementia. This study is intended to assess

- alternate donanemab dosing regimens that could potentially reduce the risk of ARIA-E frequency, severity, symptoms
- baseline and treatment response characteristics, including MRI and blood-based biomarkers, that might predict risk of ARIA-E, and
- amyloid lowering of alternate dosing regimens.

Characterizing the frequency, severity, onset, and resolution of ARIA events, in relation to dosing, is an important overall goal in understanding the benefit/risk of using amyloid lowering treatments for patients with early symptomatic AD.

In Study AACQ, all participants will receive donanemab, but at different dose levels and frequency of dosing (See Section 4.1.1.). Placebo is given at specific visits to preserve the blind for the different dosing regimens.

Study AACQ allows all participants to continue or change their symptomatic AD standard of care concomitant medications during the study.

Physical and neurological examinations, MRI assessments, and assessments of SIB are included to facilitate a comprehensive safety evaluation, in addition to AE reporting, safety measures such as laboratory assessments, immunogenicity testing, vital signs, and weight monitoring.

Collection of race and ethnicity data

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

The standard donanemab dosing regimen has a titration schedule of 700 mg IV Q4W for the first 3 doses and then 1400 mg IV Q4W. This study will investigate alternative dosing regimens that may potentially reduce the frequency and/or severity of ARIA-E.

The doses and frequency were selected based on human safety, efficacy, PK, and PD data from Phase 1-3 studies.

The goal is to investigate at least 3 additional dose regimens in addition to the standard donanemab regimen. The dosing regimen options are detailed in Section 4.1.1. These dosing regimens include either built-in dosing pause of 8 weeks between infusions, or administering a lower dose more frequently (Q2W), resulting in a lower maximum concentration but with the same monthly exposure compared to the standard donanemab regimen. All of the dosing regimens are anticipated to result in robust plaque clearance.

It is hypothesized that 8-week dosing interval will allow time for potential asymptomatic ARIA to resolve and may decrease the risk of ARIA exacerbation (Salloway et al. 2022).

Administering a lower dose, compared with the standard donanemab regimen, will result in a lower maximum concentration (C_{max}). It is hypothesized that a lower C_{max} and a slower increase in serum concentration may reduce ARIA risk (Hayato et al. 2020; Salloway et al. 2022).

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 or last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if the participant has completed all periods of the study, including the last scheduled procedure shown in the SoA.

5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

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. Are 60 to 85 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Have gradual and progressive change in memory function reported by the participant or informant for ≥6 months from time of signing the informed consent.
3. Have an MMSE score of 20 to 28 (inclusive) at Visit 1.
4. Have an amyloid PET scan result from central read, consistent with the presence of amyloid pathology. A historical amyloid PET scan may be submitted for consideration for eligibility if performed ≤12 months of Visit 2, randomization. The acceptance of a historical scan is at the discretion of the Sponsor.

Sex and contraceptive/barrier requirements

5. Women not of childbearing potential and males may participate in this 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

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusion criteria

7. Have a study partner who will provide written informed consent to participate, is in frequent contact with the participant, and will accompany the participant to study visits or be available by telephone at designated times. See Section 4.1.2 for details on study partners.
8. Are reliable and willing to make themselves available for the duration of the study and are able and willing to follow study procedures.

5.2. Exclusion Criteria

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

Medical conditions

9. Have significant neurological disease affecting the central nervous system other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures, except febrile childhood seizures.
10. Have a condition that in the investigator's opinion could interfere with the analyses of this study, or a current serious or unstable illness, including
    - cardiovascular
    - hepatic
    - renal
    - gastroenterologic
    - respiratory
    - endocrinologic
    - neurologic other than AD
    - psychiatric
    - immunologic, or
    - hematologic.
11. Have a life expectancy of less than 24 months.
12. Have a presence or history of malignant neoplasms within the past 5 years prior to Visit 1.
    Exceptions:
    - non-metastatic basal- or squamous-cell skin cancer
    - Stage 0 non-invasive carcinoma of the cervix
    - Stage 0 non-invasive prostate cancer, or
    - other cancers with low risk of recurrence or spread.
13. Are in the investigator's opinion, actively suicidal and deemed a significant risk for suicide.
14. Have a diagnosis of alcohol or drug use disorder, except tobacco use disorder, within 2 years of Visit 1.
15. Have a history of clinically significant multiple or severe drug allergies, significant atopy, or severe posttreatment hypersensitivity.

Imaging, vital signs, electrocardiograms, laboratory tests, and physical examination

16. Have a screening MRI that shows evidence of significant abnormality suggesting another potential etiology for progressive dementia or a clinically significant finding that may impact the participant's ability to safely participate in the study.
17. Have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants or a cardiac pacemaker.

18. At Visit 1, have a centrally read MRI demonstrating the presence of
    - ARIA-E
    - >4 cerebral microhemorrhages
    - >1 area of cortical superficial siderosis
    - any macrohemorrhage, or
    - severe white matter disease.
19. Have a contraindication to the PET procedure or sensitivity to the amyloid PET tracer.
20. Have present or planned exposure to ionizing radiation that, in combination with the planned administration of study PET ligands, would result in a cumulative exposure that exceeds local recommended exposure limits.
21. Have laboratory values, in relation to the reference range, of
    ALT ≥2.5X ULN
    AST ≥2.5X ULN
    ALP ≥2.0X ULN, or
    TBL >1.5X ULN, except for participants diagnosed with Gilbert's syndrome.

Prior/concomitant therapy

22. Have had prior treatment with a passive anti-amyloid immunotherapy <5 half-lives prior to randomization.
23. Have received active immunization against Aβ in any other study.
24. Have previously received donanemab.

Prior/concurrent clinical study experience

25. Are currently enrolled in any other interventional clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
26. Have participated in a clinical study involving an investigational study intervention and have received an intervention within the last 30 days of Visit 1.
27. Have previously completed or withdrawn from this study. This does not apply to participants who are allowed to rescreen before randomization in this study.

Other exclusion criteria

28. Are investigator site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
29. Are Lilly employees or are employees of third-party organizations involved in the study that require exclusion of their employees, or have study partners who are Lilly employees or are employees of third-party organizations that require exclusion of their employees.

5.3. Lifestyle Considerations

Blood donation

Participants should refrain from donating blood or blood products from the time of their screening visit until 6 months following the last dose of study intervention.

Alcohol consumption

Participants should avoid excessive use of alcohol from the screening visit until the study ends. Excessive alcohol consumption is defined for men as consuming an average of more than 3 drinks per day or more than 21 drinks per week. For women, excessive use of alcohol is defined as consuming an average of more than 2 drinks per day or more than 14 drinks per week.

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. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who screen fail for an MMSE >28 may be rescreened once after 24 weeks if the investigator feels there has been further cognitive decline. If an individual is rescreened, a new participant number is assigned, and the individual must sign a new ICF.

Individuals who screen fail due to non-eligible imaging results, may not be rescreened.

Other reasons for screen failure will require Sponsor approval for rescreen.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable for this study. All entry criteria must be met within the specified visit intervals in the SoA.

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 or 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	Placebo	Florbetapir	Florbetaben
Dosage Level(s)	350 mg 700 mg 1050 mg 1400 mg	Not applicable	See Section 8.1.1	See Section 8.1.1
Route of Administration	IV infusion	IV infusion	IV infusion	IV infusion
Authorized as defined by EU Clinical Trial Regulation	Not authorized in the EU	Authorized and not used according to EU authorization	Authorized as Amyvid® and not used according to EU authorization Not authorized in EU[a]	Authorized and not used according to EU authorization

[a] Florbetapir solution for injection is manufactured in the EU per an MA as well as per an IMPD. There are different drug product-manufacturing sites in the EU MA compared to the IMPD. The manufacture of florbetapir solution for injection according to both an MA and an IMPD enables a more robust and larger area of supply for clinical trial sites throughout Europe.

Florbetapir and florbetaben are amyloid PET tracers being used as AxMPs to aid in the assessment of study eligibility, endpoints, and dose stopping criteria.

Donanemab administration

Intervention is administered by IV infusion over a minimum of 30 minutes. Other detailed preparation and administration instructions for infusion information may be found in the Pharmacy Preparation Instructions.

Safety supplies when dosing

Resuscitation equipment and rescue medications must be available wherever intervention is administered.

Packaging and labeling

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

6.2. Preparation, Handling, Storage, and Accountability

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.

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.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

Randomization

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, the login information and directions for the IWRS will be provided to each site.

Participants will be randomly assigned to 1 of 4 treatment groups in a 1:1:1:1 ratio.

Participants will be stratified at baseline by amyloid PET scan results (≥24.1 and <54 centiloids; ≥54 and <79 centiloids; ≥79 and <107 centiloids; ≥107 centiloids) and *APOE* genotype (heterozygous carrier, homozygous carrier, and noncarrier).

6.4. Blinding

This is a double-blind study. Blinding will be maintained throughout the conduct of the study, as described in the separate Blinding and Unblinding Plan.

To maintain this blind, an otherwise uninvolved party, such as an unblinded pharmacist or other unblinded qualified individual, will be responsible for the preparation and dispensation of all study intervention according to the Pharmacy Preparation Instructions.

The Sponsor may be unblinded to treatment assignments prior to the completion of the study if interim analyses that include safety analyses, futility, early efficacy, and sample size re-estimation are conducted. If performed, operational details and a quantitative framework to provide information for these decisions will be prespecified and documented in a separate analysis plan.

Sites, participants, and study partners will remain blinded to treatment assignment throughout the duration of the study.

Emergency unblinding

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.

If a participant's intervention assignment is unblinded, the Sponsor must be notified immediately within 24 hours of this occurrence. The date and reason that the blind was broken must be recorded.

Discontinuation from the study in case of unblinding

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from the Sponsor for the participant to continue in the study.

6.5. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention 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 CRF.

Any infusion at which 75% or more of the infusion solution is given will be considered a complete infusion. If a participant attends a visit but does not receive a complete infusion, for example, due to technical complications, every effort should be made to complete the infusion within 24 hours of preparation, except if an infusion reaction occurs that prevents rechallenge. If less than 75% of the infusion solution is given, this must be recorded as an incomplete infusion on the CRF.

Missed infusions should be recorded on the CRF. If at any time it is discovered that the participant has not completed proper dosing during the titration phase, the Sponsor should be contacted prior to the subsequent infusions to discuss the possibility of completing a proper titration phase, if needed.

6.6. Dose Modification

Dose reductions are not allowed in this study.

If a participant develops ARIA during the titration period, the investigator may decide not to increase the dose as described in the Manual of Operations.

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

This section is not applicable for this study.

6.8. Treatment of Overdose

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted
- closely monitor the participant for any AE or SAE and laboratory abnormalities, and
- obtain a plasma sample for analysis of study intervention if requested by the medical monitor.

6.9. Prior and Concomitant Therapy

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, or herbal supplements, 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.

Contact the medical monitor if there are any questions regarding concomitant or prior therapy.

Medications for Alzheimer's disease

Permitted treatments

Permitted treatments during the study include

- use of approved or standard-of-care symptomatic treatments for AD
- initiation, change, or discontinuation of symptomatic treatments, when medically indicated, and
- nonmedication treatments for AD, such as behavioral management.

Prohibited treatments

These therapies are not allowed during the study:

- Passive anti-amyloid immunotherapies, such as
  - gantenerumab
  - lecanemab, or
  - aducanumab.
- Immunoglobulin G therapy, also known as gamma globulin or intravenous immunoglobulin.

Medications for infusion reactions

If an infusion reaction occurs, medications managing the reaction may be administered at the discretion of the investigator or designee, according to local practice guidelines.

If the need for concomitant medication arises, inclusion or continuation of the participant may be at the discretion of the investigator or designee.

Concomitant therapy administered to treat an infusion reaction or as premedication for infusions should be documented in addition to completion of the Hypersensitivity, Anaphylactic, and Infusion-Related Reactions CRF.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If study intervention is permanently discontinued, the participant should remain in the study for safety evaluations and biomarker collection, as shown in the SoA.

A participant may be permanently discontinued from study intervention if

- the participant or participant's designee requests to discontinue the study intervention
- the participant requires an excluded treatment
- the participant answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS
- the participant 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
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons or for severe noncompliance to the study protocol, and
- ARIA (See Sections 7.1.2 and 8.3.3.1 for details).

Additional guidance

Systemic hypersensitivity reactions

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from study intervention. See Section 7.1.3 for information on rechallenge in the case of systemic hypersensitivity reactions.

Amyloid plaque reduction

If a participant meets amyloid plaque reduction criteria defined by the Sponsor, measured by amyloid PET scan, at Visit 12 (Week 24) or Visit 19 (Week 52), the participant will discontinue study intervention and stay in the study for the remaining study visits.

7.1.1. Liver Chemistry Stopping Criteria

Interrupting study intervention based on elevated liver tests

The study intervention should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.6), if 1 or more of the conditions in this table occur.

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 wk	
ALT or AST >3x ULN and either TBL >2x 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 >2x ULN
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL >2x 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 >2x ULN
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA 2009 and other consensus guidelines, with minor modifications.	

Abbreviations: INR = international normalized ratio; ULN = upper limit of normal.

Resuming study intervention after elevated liver tests

Resumption of the study intervention 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, non-drug etiology is identified. Otherwise, the study intervention should be permanently discontinued.

7.1.2. Temporary Discontinuation

Temporary discontinuation from study intervention is allowed due to

- hospitalization
- personal or exceptional circumstances (See Section 10.7)
- certain incidences of ARIA, or
- evaluation of an AE.

If temporary discontinuation is due to an AE, the investigator should report the event to the medical monitor.

If temporary discontinuation of study intervention occurs, the investigator or designee determines if and when the study intervention may be restarted. See the Manual of Operations for temporary discontinuation guidance.

Temporary discontinuation of intervention due to ARIA

The investigator may temporarily discontinue intervention if the participant develops treatment-emergent ARIA-H or ARIA-E to an extent deemed clinically significant by the investigator.

Reinitiating intervention can be considered after resolution of ARIA-E and stabilization of ARIA-H-imaging findings and the resolution of any associated symptoms. Both the decision to stop and restart intervention may be discussed with the Sponsor-designated medical monitor.

See the Manual of Operations for temporary discontinuation guidance.

See Section 6.6 for dose modification considerations.

See Section 8.3.3.1 for details on adverse event reporting for ARIA-E and ARIA-H.

7.1.3. Rechallenge in Cases of Systemic Hypersensitivity or Infusion-related Reactions

Dosing rechallenge is contraindicated in participants that have experienced a suspected or possible anaphylactic reaction, a reaction involving 2 or more organ systems, for example, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems, that occurs very close to a prior dose (Sampson et al. 2006).

For systemic hypersensitivity reactions or IRRs, 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. Any premedication given will be documented as a concomitant therapy.

Prior to initiating premedication or rechallenging, the investigator may consult with the Sponsor.

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 for any reason or without providing any reason
- at the request of the participant's designee, for example, 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

- if the participant requires a ferromagnetic implant or insertion of a cardiac pacemaker that is not MRI compatible.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and follow-up, 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 they repeatedly fail 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 randomly assigned, 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 (Section 1.3).

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.

8.1. Efficacy Assessments

8.1.1. Amyloid PET Scan

Amyloid PET scans provide a quantitative assessment of amyloid plaque deposition in the brain and can serve as a biomarker of clearance of amyloid deposits.

Part of the study eligibility criteria is determined by amyloid PET scans. Additional amyloid PET scans will be performed as indicated in the SoA (Section 1.3).

Personnel blinded to treatment allocation will assess the change in amyloid burden using the PET scan.

Site investigators, participants, and study partners will not be informed of the results of PET scans obtained following randomization as they relate to the study. Any findings that may be of potential medical concern will be provided for appropriate follow-up.

PET scan procedures

Specific imaging acquisition protocols designed to ensure consistency across sites will be provided in a PET Imaging Manual.

Participants must minimize movement during each PET procedure, which can last 10 to 30 minutes for each scan. Most state-of-the-art imaging systems are designed to reduce head motion and participant discomfort.

PET scan safety

The primary risk related to PET scans is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion will be provided in the ICF.

Only 1 of the ß-amyloid tracers, either florbetapir F18 or florbetaben F18, will be used at a given amyloid PET scan visit.

The table below shows the effective radiation dose from the PET scans.

	Effective Dose (mSv) per Scan[a]	Number of Scans in First Year	Effective Dose (mSv) for Scans in First Year	Number of Scans in Second Year	Effective Dose (mSv) for Scans in Second Year	Sum of Effective Dose (mSv) for Years 1 and 2
Florbetapir F18 Scan (10 mCi IV)	7.43	2	14.86	2	14.86	29.72
Florbetaben F18 Scan (8.1 mCi IV)	6.2	2	12.4	2	12.4	24.8

Abbreviations: CT = computerized tomography; ED = early discontinuation; IV = intravenous infusion; PET = positron emission tomography.

[a] Dose shown includes radiation exposure from the radiotracer and assumes a nonclinical CT scan is obtained (estimated at 0.4 mSv) as part of the PET scan attenuation correction process when the scan is done on a PET/CT scanner. A clinical CT scan is not needed during the PET scan session and, because it will add additional radiation exposure, it is not recommended.

Number of scans allowed

In the event a repeat scan is required, for example, the scan is not analyzable, 1 additional scan may be received in 1 year.

In the event of an ED scan, up to 1 additional scan may be received in 1 year.

The maximum number of scans per year is 3.

8.1.2. Screening Mini Mental State Examination

The MMSE is a brief instrument used to assess cognitive function in participants (Folstein et al. 1975). The MMSE will be used for screening in this study. See Section 5.1.

The instrument measures orientation, memory, and attention and the ability of the participant to name objects, follow verbal and written commands, write a sentence, and copy figures. The range for the total MMSE score is 0 to 30, with lower scores indicating greater level of impairment.

8.2. Safety Assessments

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

8.2.1. Physical/Neurological Examinations

A complete physical examination will include, at a minimum, assessments of these systems:

- cardiovascular
- respiratory
- gastrointestinal, and
- neurological.

Height and weight will also be measured and recorded at screening and then just weight thereafter.

The investigator may conduct a complete physical/neurological examination at any time a participant presents with physical complaints and is considered necessary. See details in the Manual of Operations.

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

8.2.2. Vital Signs

Vital signs, including temperature, will be measured at all visits. Vital sign measurements include blood pressure, pulse, and temperature.

For each participant, conduct vital signs measurements according to the SoA (Section 1.3).

Measure vital signs before

- obtaining an ECG tracing
- collection of blood samples for laboratory testing, or
- the start of infusion.
- if possible, during an IRR or suspected hypersensitivity once participant is stabilized.

Sitting blood pressure and pulse will be measured after 5 minutes in the sitting position at all visits. In addition, orthostatic blood pressure and pulse will be measured supine and standing at designated visits, as detailed in the SoA (Section 1.3).

For orthostatic blood pressure monitoring, participants should be supine for at least 5 minutes and then stand for at least 3 minutes prior to taking the respective measurements. If the participant feels unable to stand, only supine vital signs will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms.

8.2.3. Electrocardiograms

For each participant, collect a single 12-lead digital ECG according to the SoA. Record the ECG before collecting any blood. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

If deemed clinical necessary, ECGs may be obtained at additional times.

ECGs will be interpreted by the investigator or qualified designee at the study site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets the study entry criteria and for immediate participant management, if any clinically relevant findings are identified.

8.2.4. Clinical Safety Laboratory Tests

See 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 or 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 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, for example, SAE or AE or dose modification, then report the information as an AE.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Participants should be monitored appropriately and observed closely for 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.

Families and caregivers of participants should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of SIB and to report such symptoms immediately to the study investigator.

Baseline assessment of SIB and intervention emergent SIB will be monitored during the study using the C-SSRS.

C-SSRS

The C-SSRS is a scale that captures the occurrence, severity, and frequency of SIB 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 "Baseline" version will be used at Visit 2. C-SSRS "Since Last Assessed" (Full version) scale will be administered at the subsequent visits as indicated in the SoA. C-SSRS must be administered by the clinician or appropriately trained study-site staff.

One study partner is requested to be present (in person or on the phone) on all days the C-SSRS is administered.

Timing of collection and AE monitoring

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.

8.2.6. Hepatic Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests, 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 1 or more of the conditions in this table occur.

If a participant with baseline results of...	Develops the following elevations…
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert's syndrome)

What to do if the abnormal condition persists or worsens

If the abnormality persists or worsens, the investigator, in consultation with the Lilly-designated medical monitor, should initiate clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests. At a minimum, this evaluation should include physical examination and a thorough medical history, including

- symptoms
- recent illnesses, for example, 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.

Frequency of monitoring

Initially, monitoring of symptoms and hepatic biochemical tests should be done 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 laboratory results stabilize.

Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of the conditions in this table occur.

If a participant with baseline results of...	**Develops the following elevations…**
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs or symptoms[a], or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs or symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

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

What a comprehensive evaluation should include

At a minimum, this evaluation should include

- physical examination and a thorough medical history, as outlined above
- tests for
    - prothrombin time, INR
    - viral hepatitis A, B, C, or E, and
    - autoimmune hepatitis, and
- an abdominal imaging study, for example, ultrasound or CT scan.

Based on the participant'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

Collect additional hepatic safety data in hepatic safety CRFs if a study participant develops a hepatic event considered to be an SAE or discontinues study intervention due to a hepatic event or meets 1 of the conditions described in this table.

If a participant with baseline results of...	**Develops the following elevations…**
ALT <1.5x ULN	ALT to ≥5x ULN on 2 or more consecutive blood tests
ALT ≥1.5x ULN	ALT ≥3x baseline on 2 or more consecutive blood tests
TBL <1.5x ULN	TBL ≥2x ULN, except for participants with Gilbert's syndrome
TBL ≥1.5x ULN	TBL ≥2x baseline
ALP <1.5x ULN	ALP ≥2x ULN on 2 or more consecutive blood tests
ALP ≥1.5x ULN	ALP to ≥2x baseline on 2 or more consecutive blood tests

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

8.2.7. Magnetic Resonance Imaging

Magnetic resonance imaging of the brain will be performed according to the SoA and as clinically indicated. The investigator may perform unscheduled MRIs if necessary.

This technology will be used to check for evidence of ARIA-H or ARIA-E, and other clinically relevant safety findings.

MRI sequence details for the study are in Section 8.2.7.1.

MRI scan reviews

The local review

The standard MRI sequences will be reviewed by the investigator or qualified designee for immediate participant management.

The exploratory MRI sequences should not be reviewed locally and will not impact participant management.

The central review

All MRI standard and exploratory sequences should be sent to centralized MRI vendor.

The safety central review will only be based on the standard MRI sequences.

Specific analyses of the scans, including assessments of ARIA-H and ARIA-E, will be interpreted by the centralized MRI vendor for data analysis and report-writing purposes.

Results of centrally read MRIs regarding participant care or safety will be reported back to the investigator.

Determination of MRI eligibility criteria

Any clinically significant findings noted by the initial review by the investigator at screening that result in a diagnosis should be recorded as a preexisting condition or AE.

The centralized MRI vendor will determine final MRI eligibility at screening and will report the MRI results to the investigator as “does” or “does not” meet MRI eligibility criteria.

8.2.7.1. MRI Sequence Details for the Study

The standard sequences will be used to determine participant eligibility, care and safety.

The exploratory sequences will be used for exploratory analyses only and will not be used for participant management.

This table provides MRI sequences and their timing throughout the study.

Sequences	**Study Visits**						
	Screening/Before first infusion[a]	**Visit 4 Week 4**	**Visit 8 Week 12**	**Visit 12 Week 24**	**Visit 19 Week 52**	**ED**	**UV**
Standard							
2D FLAIR	**X**	**X**	**X**	**X**	**X**	**X**	**X**
2D T2	**X**	**X**	**X**	**X**	**X**	**X**	**X**
GRE	**X**	**X**	**X**	**X**	**X**	**X**	**X**
DWI	**X**	**X**	**X**	**X**	**X**	**X**	**X**
3D T1	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Exploratory							
3D FLAIR	X	X	X	X	X	X	X
3D T2	X	X	X	X	X	X	X
DTI[b]	X	X	X	X	X	X	X
SWI[b]	X	X	X	X	X	X	X
Task-Fmri[b]	X						

Abbreviations: DTI = diffusion tensor imaging; DWI = diffusion-weighted imaging; ED = early discontinuation visit; FLAIR = fluid-attenuated inversion recovery; Fmri = functional magnetic resonance imaging; GRE = gradient echo; SWI = susceptibility weighted imaging; UV = unscheduled visit.

[a] Performed either with screening MRI or another time prior to first infusion at Visit 2.

[b] Perform when or where available.

Note: standard sequences denoted by bold text and shaded cells.

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

The definitions of the following events can be found in Section 10.3:

- AEs
- SAEs, and
- 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 intervention.

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 or contacts. All SAEs and AEs of special interest as defined in Section 8.3.3 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 PCs, 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 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	Backup Method of Reporting
Adverse Event					
AE	Signing of the 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 or after receiving PET tracer	Signing of the ICF	Start of intervention	Within 24 hr of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hr of awareness	SAE CRF	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 partners of male participants	After the start of study intervention	90 days after the last dose	Within 24 hr (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	Backup 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 hr 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	

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

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 study intervention.

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.

8.3.3. Adverse Events of Special Interest

Specific safety topics of interest for this study include, but are not limited to

- ARIA, and
- hypersensitivity, immediate and non-immediate, including IRRs and anaphylaxis.

The topics listed above, as well as other topics that may be subsequently determined by the Sponsor, will be subject to enhanced surveillance activities.

8.3.3.1. Amyloid-Related Imaging Abnormalities (ARIA)

While most cases of ARIA are asymptomatic, serious and life-threatening cases have been reported. Available data suggest serious cases are most likely to occur early in dosing, after the first, second, or third infusion of standard donanemab dosing.

Symptoms possibly associated with ARIA

Symptoms present in association with these imaging abnormalities may include, but are not limited to, 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).

Guidance for when a participant develops symptoms suggestive of ARIA

If a participant simultaneously develops more than 1 of the symptoms suggestive of ARIA-E, then perform an unscheduled MRI. A single symptom suggestive of ARIA-E of sufficient severity may also warrant an unscheduled MRI.

See Section 8.2.7 for additional instructions when conducting MRIs.

MRI sequences for detecting ARIA

If symptoms are reported, and ARIA-E is suspected, then the abnormality is best detected by FLAIR sequences on MRI.

If symptoms are reported, and ARIA-H is suspected, then the abnormality is best detected with the T2 gradient-recalled echo on MRI.

Guidance if ARIA is present

If ARIA is present, repeat MRIs are recommended every 4 to 6 weeks until resolution of ARIA-E or stabilization of ARIA-H.

For asymptomatic or mild symptoms, the participant can be observed; for moderate symptoms associated with ARIA-E, the use of oral or IV steroids can be considered. In the case of severe symptoms associated with ARIA-E, it is recommended to hospitalize the participant for close observation and consider the use of IV steroids such as high-dose dexamethasone or a similar agent. See Manual of Operations and Section 7.1.2 for more guidance.

ARIA-E reporting

If ARIA-E is present on MRI, the investigator will complete the CRF regarding the presence or absence of symptoms related to the ARIA-E and report the ARIA-E as an adverse event in the Adverse Events CRF.

Temporary and permanent discontinuation of intervention guidance

See Section 7.1.2 and the Manual of Operations for temporary and permanent discontinuation of intervention guidance.

8.3.3.2. Hypersensitivity Reactions

Hypersensitivity

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 designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, sites should measure blood pressure, temperature and pulse, when able to do so, and collect additional blood samples as described in Section 10.2.1. Laboratory results are provided to the Sponsor via the central laboratory.

8.4. Pharmacokinetics

Serum samples will be collected for measurement of serum concentrations of study intervention as specified in the SoA. If IP infusion is permanently discontinued but the participant remains in the study, 1 PK sample should be collected at the soonest scheduled visit regardless if PK sample collection is on the SoA at that visit. Dosing dates and times should be collected. Subsequent PK sample collection should follow the protocol SoA unless the scheduled visit exceeds 6 months since discontinuation of infusions. No additional PK sample collection is required once the participant exceeds 6 months since discontinuation of infusions.

The timing of sampling may be altered during the course of the study based on newly available data, for example, 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.

Bioanalytical samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism, protein binding, or bioanalytical method development or validation work.

See Section 10.1.12 for details about sample retention and custody.

8.5. Pharmacodynamics

The amyloid PET scan pharmacodynamic evaluations are described in Section 8.1.1.

8.6. Genetics

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

See Section 10.5 for information regarding genetic research and Section 10.1.12 for details about sample retention and custody.

Apolipoprotein E genotyping

An additional mandatory blood sample for *APOE* genotyping will be collected as shown in the SoA. Neither participants nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results.

8.7. Biomarkers

Samples for biomarker research will be collected at the times specified in the SoA (Section 1.3), where local regulations allow. Sample test type is specified in Section 10.2.

Samples will be used for research on the drug target, disease process, variable response to study intervention, pathways associated with AD, mechanism of action of donanemab or research methods, or in validating diagnostic tools or assay(s) related to AD or other neurological conditions.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Samples will be retained per Section 10.1.12.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA, venous blood samples will be collected to determine antibody production against donanemab. Antibodies may be further characterized or evaluated 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 ADAs in the presence of donanemab at a laboratory approved by the Sponsor.

Treatment-emergent ADAs are defined in Section 9.3.7. If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE ADA positive, additional samples may be taken for up to approximately 1 year after last dose.

Samples will be retained per Section 10.1.12.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

The SAP will be finalized prior to the first unblinding, and it will include a 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

The primary objective of Study AACQ is to assess the effect of alternative donanemab dosing regimens compared to the standard donanemab dosing regimen on reducing the proportion of participants with occurrence of any ARIA-E event by 24 weeks.

The primary analysis will be performed when all participants in the Safety Analysis Set (See Section 9.2) have had an opportunity to complete the Week 24 visit.

The primary analysis will be a Bayesian logistic regression model for the primary endpoint of ARIA-E rate by Week 24. Note that throughout the document the term "ARIA-E rate" refers to the proportion of participants with any ARIA-E occurrence by a specific time point, and the same applies for the definition of ARIA-H rate.

A mixture prior specification will be used to enable a formal dynamic use of historical data from other donanemab clinical studies for the ARIA-E rate by Week 24 in the standard dosing regimen. The Bayesian approach will compare the primary outcome, ARIA-E rate by Week 24, across the alternative donanemab dosing regimens. A Bayesian CSF will be established of the following form:

> *Probability of at least X% relative reduction in ARIA-E rate by Week 24 with at least one of the alternative donanemab regimens compared to standard donanemab regimen > probability threshold.*

The Bayesian approach will be used to calculate the posterior probability of at least X% reduction in ARIA-E rates by Week 24 in each alternative donanemab regimen with respect to the standard regimen. If the posterior probability for at least 1 alternative regimen exceeds the prespecified probability threshold, the study will have met its primary endpoint.

The exact CSF will be prespecified in the study SAP prior to the first unblinding of the primary endpoint. The margin of X% relative reduction in ARIA-E rate for the alternative regimens will be determined based on the clinical judgment. The probability threshold will be set to have a desired confidence level for the relative benefit of the alternative regimens, or to achieve the desired operating characteristics under a range of plausible scenarios of truth for the treatment effect. These scenarios include the null scenario where the alternative regimens would have similar ARIA-E frequency as the standard regimen.

9.1.1. Multiplicity Adjustment

Unless otherwise specified in the study SAP, no adjustments for multiplicity will be performed.

9.2. Analyses Sets

Participant Analysis Set / Population	Description
Entered	All participants who sign the ICF.
Enrolled/intent-to-treat	All participants randomly assigned to study treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.
Safety analysis set	All participants randomly assigned to study treatment and who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment group to which they were assigned.

9.3. Statistical Analyses

9.3.1. General Considerations

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

All analyses related to safety, including analyses for the primary endpoint, will be based on the Safety Analysis Set.

The analysis for the secondary objective related to amyloid plaque deposition will be based on the Safety Analysis Set unless otherwise specified in the SAP.

To allow for evaluation of the primary and secondary hypotheses at 24, 52, and 76 weeks, the assessments of corresponding primary and secondary objectives are expected to occur after all participants in the Safety Analysis Set have had the opportunity to complete visits 12, 19, and 25, respectively, including PET and MRI assessments. Data collected during the immunogenicity and safety follow-up period will be summarized and analyzed separately.

For analyses using historical data, the sources of historical data and analysis considerations will be described in the SAP.

When change from baseline is assessed, participants will be included in the analysis only if both a baseline and a postbaseline measure are available. Unless otherwise defined, a baseline measure is the last non-missing observation collected prior to the first administration of study medications.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Any adjustments to the planned analyses will be described in the final CSR.

9.3.2. Primary Endpoint Analysis

Unless otherwise specified in the SAP, the primary endpoint will be based on the ARIA-E events as diagnosed by the scheduled or unscheduled MRIs up to and including Visit 12.

The primary analysis will use a Bayesian logistic regression model to estimate and compare the relative reduction in ARIA-E rates by Week 24 for the alternative donanemab regimens versus the standard donanemab regimen. The logistic regression model will include the fixed effects for treatment, ApoE e4 status, and baseline amyloid level. The treatment effects will be presented in terms of the estimated odds ratios and relative reduction in ARIA-E rates by Week 24 for the alternative regimens relative to the standard regimen. The Bayesian CSF for the primary analysis will be defined in the SAP, and the 95% credible intervals will be provided for the key parameters of interest.

The primary analysis model will have the ability to leverage information on the ARIA-E rate of the standard donanemab regimen by Week 24 through the construction of an informative prior using historical data. A mixture prior specification will be used to dynamically incorporate information based on the similarity in the ARIA-E rates of the standard regimen by Week 24 compared to the historical data. The details of the analysis model along with the prior information and the details about the sources of historical data will be outlined in the SAP.

A secondary analysis using the Bayesian logistic regression model for the primary endpoint will be fit using data from Study AACQ only, that is, in the absence of using historical data on the ARIA-E rate by Week 24.

9.3.3. Secondary Endpoints Analysis

Descriptive statistics will be presented for all primary and secondary ARIA-related endpoints. Bayesian modeling as described above for the primary endpoint will be performed for the secondary endpoint of ARIA-E frequency at 52 weeks. Further modeling may be performed on the other ARIA-related endpoints, such as ARIA-H, and will be described in the SAP.

The frequency and severity of ARIA-E and of ARIA-H events will be summarized by symptomatic and asymptomatic events.

Time to first occurrence of ARIA-E or other ARIA-related events, such as symptomatic ARIA-E, may be analyzed and compared across the donanemab dosing regimens using a log-rank test for survival data. Participants who do not experience the event by the end of the study or drop out prior to the end of the study will be censored at their latest available time point. A Cox proportional-hazards model may also be used to analyze the data on time to event of first ARIA-related incidence. Details of these analyses along with the endpoints will be provided in the SAP.

To assess the effect of each alternative donanemab dosing regimen versus standard donanemab dosing regimen on brain amyloid deposition, a test of non-inferiority will be performed on the mean absolute change from baseline in brain amyloid plaque, from the amyloid PET scan, at Weeks 24, 52, and 76. Further details on defining margins for non-inferiority analyses will be described in the SAP.

9.3.4. Tertiary/Exploratory Endpoints Analysis

The analyses of tertiary endpoints will be specified in the SAP.

9.3.5. Safety Analyses

An overview of AEs, including the number and percentage of participants who died, experienced SAEs, and discontinuations from study treatment due to an AE and TEAE, will be provided for all 4 dosing regimens. TEAE in the Safety Analysis Set will be defined as events that first occurred or worsened on or after the day of first infusion.

Laboratory measurements will be analyzed using continuous data (change from baseline) and categorical or ordinal data (proportion of treatment-emergent abnormalities). If there are multiple records of laboratory measurements at baseline or postbaseline visit, the last record will be used.

Vital sign measurements and weight will be analyzed using continuous data (change from baseline) and categorical data (proportion of potentially clinically significant changes). Vital sign measurements include systolic and diastolic blood pressure and pulse, orthostatic diastolic and orthostatic systolic blood pressures and orthostatic pulse, and temperature.

Hypersensitivity and IRR will be analyzed by:

- **Potential immediate** – defined as TEAEs occurring on the date of infusions, or for which a hypersensitivity follow-up form indicates the event occurred within 24 hours of study intervention administration, and
- **Potential non-immediate** – defined as TEAEs that are not immediate but occur prior to the administration of a subsequent infusion.

The number and percentage of participants who experienced a TEAE of hypersensitivity or IRR will be reported across the 4 treatment groups.

Analysis of C-SSRS data

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 (CUIMC 2016).

9.3.6. Pharmacokinetic Analyses

Compartmental modeling of donanemab PK data using nonlinear, mixed-effects modeling or other appropriate software may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported.

Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. If appropriate, data from other studies of donanemab may be used in this analysis.

The PK/PD relationships between serum donanemab concentration, ARIA incidence rate, or PD markers activity may be explored graphically. The relationship between the presence of antibodies to donanemab and PK, PD, safety, and/or efficacy may be assessed graphically. Additional modeling may be performed based on the results of the graphical analyses.

Analyses will be detailed in a separate population PK/PD Analysis Plan.

9.3.7. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with treatment-emergent ADA to donanemab may be tabulated.

Treatment-emergent ADAs are defined as participants

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

For the treatment-emergent ADA-positive participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies to donanemab may be tabulated in treatment-emergent ADA-positive participants.

The relationship between the presence of antibodies and the PK parameters and PD response, including safety and efficacy to donanemab, may be assessed. Additional details may be provided in the SAP.

9.3.8. Handling of Missing Data

For some secondary and exploratory endpoints, participants will be included in the analysis only if baseline and at least 1 postbaseline measurement are available; details will be given in the SAP. If data are missing, sensitivity analyses for endpoints or other imputation-based techniques for handling missing data may be considered and will be detailed in the SAP.

9.3.9. Treatment Group Comparability

9.3.9.1. Participant Disposition

All participants who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. When a participant discontinues from the study, the reason(s) will be collected and will be summarized by treatment group for all randomized participants. The percentage of participants discontinuing from each treatment group will be compared between groups using Fisher's exact test. The comparisons will be done for the overall percentage of participants who discontinue and for select specific reasons for discontinuation.

9.3.9.2. Participant Characteristics

These characteristics will be recorded:

- participant's age
- sex
- race
- height
- body weight
- body mass index (weight (kg)/[height (m)]^2)
- *APOE* ε4 genotype
- MMSE, and
- having 1 or more first degree relatives with AD at baseline.

Baseline characteristics will be summarized by treatment group and the overall population. Summaries will include descriptive statistics for continuous and categorical measures.

For categorical data, Fisher's exact test or Pearson's chi-square test will be used for treatment group comparisons.

For continuous data, analysis of variance, with independent factors for treatment and investigator, will be used.

9.3.9.3. Prior and Concomitant Therapy

Prior medications are defined as those that stop before randomization (Visit 2).

Concomitant medications are defined as those being taken on or after randomization (Visit 2).

Prior and concomitant medications will be listed.

A summary of concomitant medications will be presented as frequencies and percentages for each treatment group. Medications will be coded using the World Health Organization drug dictionary.

9.3.9.4. Treatment Compliance

Summary statistics for treatment compliance will be provided for the

- total number of complete infusions received
- duration of complete infusion, and
- volume of complete infusion by treatment group.

Frequencies and percentages of reasons why infusion was stopped will also be presented.

9.4. Interim Analysis

Interim analyses may be conducted for Study AACQ. Potential interim analyses include safety analyses, futility, early efficacy, and sample size re-estimation. If performed, operational details and a quantitative framework to provide information for these decisions will be prespecified and documented in a separate analysis plan.

9.5. Sample Size Determination

Approximately 800 participants will be randomly assigned to 1 of 4 treatment arms in a 1:1:1:1 ratio. This sample size will provide over 80% power to demonstrate that there is more than 80% probability that at least one of the alternative regimens will reduce the ARIA-E rate by at least 20% compared to the standard regimen by 24 weeks.

The study power was calculated based on an assumed relative benefit of 40% reduction in ARIA-E rate by Week 24 in each of the alternative donanemab regimens compared to the standard regimen. In power calculation, the true ARIA-E rate by Week 24 in the standard donanemab regimen is assumed to be 18.5% and informative prior is elicited from the observed rate in historical data.

In the null scenario where all of the dosing regimens have the same true ARIA-E rate of 18.5% by Week 24, the probability that the CSF is met (i.e., the false positive rate) is controlled at 5% one-sided, or equivalently 10% two-sided.

The power and false-positive rate of the study were determined by simulation using R 4.1.2. Multiple virtual clinical studies were simulated under both null and alternative scenarios, and the Bayesian logistic model was fit in each dataset to obtain the operating characteristics.

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 (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines, and
- 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, 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 potential participant or the potential participant's legally authorized representative, and answer all questions regarding the study.

Potential 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 Code of Federal Regulations 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.

Participants who are rescreened are required to sign a new ICF.

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

10.1.5.1. Data Monitoring Committee

An independent, external DMC will be responsible for reviewing unblinded data during the study.

The committee will include, at a minimum, a physician with appropriate expertise and a statistician.

Access to the unblinded data will be limited to the DMC and the external Statistical Analysis Center statisticians who are providing the analysis of the data. These statisticians will be independent from the study team. The study team will not have access to the unblinded data. Only the DMC is authorized to evaluate unblinded interim analyses.

Details about the membership, purpose, responsibilities, and operation will be included in the DMC charter.

10.1.6. Dissemination of Clinical Study Data

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 dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, study 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 provides access to all individual participant data collected during the study, after anonymization, with the exception of pharmacokinetic or genetic data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement.

Data and documents, including the study protocol, SAP, CSR, and blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

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.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the Sponsor. All completed CRFs must be signed prior to archival.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

Quality tolerance limits will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the quality tolerance limits, and remedial actions taken will be summarized in the CSR.

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.

The Sponsor or designee will perform monitoring 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 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 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 electronic data capture 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.

Additionally, clinical outcome assessment data (participant-focused outcome instrument) will be collected by authorized study personnel, via a paper source document, and will be transcribed by the authorized study personnel into the electronic data capture system.

Data collected via the Sponsor-provided data capture system will be stored at a 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.

The first act of recruitment is the first signed ICF.

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, and
- 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.

10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the Sponsor, will participate as investigators in this clinical study.

10.1.12. 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 becomes commercially available for AD.

Sample Type	Custodian	Retention Period after Last Participant Visit[a]
Exploratory biomarkers	Sponsor or Designee	15 years
Pharmacokinetic	Sponsor or Designee	1 year
Immunogenicity	Sponsor or Designee	15 years

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the Lilly-designated laboratory or by the local laboratory.

Local laboratory results are only required if the central laboratory results are not available in time for either study intervention administration or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

In circumstances where the Sponsor approves local laboratory testing in lieu of central laboratory testing, 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.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs – red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs – white blood cells)	
Differential	
Absolute count of:	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin (TBL)	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Albumin	
Calcium	
Glucose	
Cholesterol	
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	

Clinical Laboratory Tests	Comments
Blood	
Urine leukocyte esterase	
Chemistry	
High-sensitivity C-reactive protein (hsCRP)	
PK Samples – donanemab concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Biomarkers **Additional Testing**	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Neurofilament light chain	
Glial fibrillary acidic protein	
sTREM2	
Apolipoprotein E (ApoE)	
Plasma pTau	
Amyloid-Beta 40 and 42	
Genetics Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Exploratory Biomarker Storage Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Serum	
Plasma (EDTA)	
Whole Blood (PAXgene RNA)	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Anti-donanemab antibodies	
Anti-donanemab antibodies neutralization	

Abbreviations: EDTA = ethylenediaminetetraacetic acid; pTau = phosphorylated tau.

10.2.1. 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 test 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 in the table 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 min to 4 hr after the start of the event. ● Note: The optimal collection time is from 1 to 2 hr after the start of event.	Total tryptase
	Complements (C3, C3a, and C5a)
	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. ● Note: If collecting, collect up to 12 hr after the start of the event.	Donanemab antidrug antibodies (ADA)
	Donanemab concentration

Abbreviation: 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 unfavorable 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, and 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.
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- 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.
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, for example, endoscopy, appendectomy: the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting 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 1 or more of the criteria listed:

- Results in death
- 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.
- 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 preexisting condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability or 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.
- Is a congenital anomaly or birth defect
    - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
- 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 PC 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 PCs:
  - deficiencies in labeling information, and
  - use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PCs related to study interventions used in clinical trials are collected 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 they have a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC 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/PC 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/PC 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 PC information is reported on the Product Complaint Form.
- Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC 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 PCs.
- 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 or 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 1 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 an 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 1 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 they have 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 an 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.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor or designee with a copy of any postmortem findings, including histopathology.

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) 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 an SAE paper form (see next section) or to the Sponsor by telephone.
- Contacts for SAE reporting can be found on the SAE paper form.

SAE reporting via paper form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the Sponsor.
- 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 on the SAE paper form.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward 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, IRB/IEC, and investigators.

- An investigator who receives an investigator safety report describing an 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

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly, such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. 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 • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • 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 • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • 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.

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.

This table provides examples of highly effective, effective, and unacceptable methods of contraception.

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • 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 or AD and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to donanemab or other amyloid targeting interventions and AD. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analyzed for pharmacogenetic research.
- 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 CSR 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 AD diagnosis, progression, treatment, and monitoring 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 8.2.6 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

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

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HbsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA[a]
Basophils	**Hepatitis C virus (HCV) testing**
Eosinophils	HCV antibody
Platelets	HCV RNA[a]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	**Hepatitis E virus (HEV) testing**
Direct bilirubin	HEV IgG antibody
Alkaline phosphatase (ALP)	HEV IgM antibody
Alanine aminotransferase (ALT)	HEV RNA[a]
Aspartate aminotransferase (AST)	**Anti-nuclear antibody (ANA)**
Gamma-glutamyl transferase (GGT)	**Anti-smooth muscle antibody (ASMA)**[b]
Creatine kinase (CK)	**Anti-actin antibody**[c]
Hepatic Coagulation Panel	**Immunoglobulin IgA (quantitative)**
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgG (quantitative)**
Urine Chemistry	**Immunoglobulin IgM (quantitative)**
Drug screen	**Epstein-Barr virus (EBV) testing**
Haptoglobin	EBV antibody

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

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

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

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[a]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA[a]
Phosphatidylethanol (Peth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology**
Ethyl glucuronide (EtG)	Culture
Epstein-Barr virus (EBV) testing	Blood
EBV DNA[a]	Urine

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

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 and study partner(s) will be obtained for the below items, as required by ERB's and local regulations.

Additional consent from the participant and study partner(s) will be obtained, if required, for

- participation in remote visits, as defined in Section "Remote Visits"
- a change in the method of study intervention administration
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, 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

- AE collection
- concomitant medication review, or
- administration of the C-SSRS.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations 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

- AE collection
- concomitant medication review
- administration of study intervention
- blood sample collection, and
- safety assessments.

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 AEs, SAEs, and PCs 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.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the Sponsor to determine appropriate actions. These actions may include working with the Sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit or at an alternate location such as an infusion center.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site, the investigator, Sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, these additional requirements must be met:

- Only authorized study personnel may supply, prepare, or administer study intervention.
- The main protocol safety requirements related to study intervention administration must be followed, for example
  - postinfusion observations
  - infusion duration
  - storage
  - preparation and handling of study intervention, and
  - resuscitation equipment.
- Mobile healthcare personnel will be licensed healthcare providers with advanced life support training to manage emergency situations, for example, Advanced Cardiovascular Life Support certification.

Screening period guidance

To ensure safety of study participants, the site should follow the rules described in the protocol.

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 or 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
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
AD	Alzheimer's disease
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ARIA-E	amyloid-related imaging abnormalities that show cerebral edema
ARIA-H	amyloid-related imaging abnormalities that show cerebral microhemorrhages
AST	aspartate aminotransferase
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product
authorized AxMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product
AxMP	auxiliary medicinal product. See also NIMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the Sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or Sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
C-SSRS	Columbia-Suicide Severity Rating Scale
CIOMS	Council for International Organizations of Medical Sciences

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
CONSORT	Consolidated Standards of Reporting Trials
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 study participant
CSF	critical success factor
CSR	clinical study report
CT	computerized tomography
DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for efficacy, or for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
ECG	Electrocardiogram
ED	early discontinuation
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.
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical study.
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.

Interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the complete reporting database for the primary outcome is created/locked.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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 Boards
IRR	Infusion-related reactions
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant assigned to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment
IV	intravenous
IWRS	interactive web-response system
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both
Misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging

NIMP	Non-investigational Medicinal Product See AxMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment.
Participant	Equivalent to CDISC term "subject": an individual who participates in a clinical study, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PET	positron emission tomography
PK/PD	pharmacokinetics/pharmacodynamics
SAE	serious adverse event
SAP	statistical analysis plan
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
sTREM2	soluble triggering receptor expressed on myeloid cells 2
TE	treatment-emergent
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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