Protocol I5T-MC-AACN(b)

A Phase 3, Open-Label, Parallel-Group, 2-Arm Study to Investigate Amyloid Plaque Clearance with Donanemab Compared with Aducanumab-avwa in Participants with Early Symptomatic Alzheimer's Disease

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Approval Date: 17-May-2022

Title Page

Protocol Title:

A Phase 3, Open-Label, Parallel-Group, 2-Arm Study to Investigate Amyloid Plaque Clearance with Donanemab Compared with Aducanumab-avwa in Participants with Early Symptomatic Alzheimer's Disease

Protocol Number: I5T-MC-AACN

Amendment Number: b

Compound: donanemab (LY3002813)

Brief Title:

A Study to Investigate Amyloid Plaque Clearance with Donanemab Compared with Aducanumab-avwa in Participants with Early Symptomatic Alzheimer's Disease

Study Phase: 3

Acronym: TRAILBLAZER-ALZ 4

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

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Approval Date: Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	*11-Oct-2021*
Original Protocol	*17-Aug-2021*

Amendment b

Overall Rationale for the Amendment:

This amendment adds an MRI at Visit 10 due to a recent label update to aducanumab-avwa.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added an MRI to Visit 10.	Align with label update to aducanumab-avwa
7.1.3 Amyloid-Related Imaging Abnormalities (ARIA)	Clarified the timing of ARIA or donanemab v aducanumab-avwa.	Minor clarification.

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 3, Open-Label, Parallel-Group, 2-Arm Study to Investigate Amyloid Plaque Clearance with Donanemab Compared with Aducanumab-avwa in Participants with Early Symptomatic Alzheimer's Disease

Brief Title:

A Study to Investigate Amyloid Plaque Clearance with Donanemab Compared with Aducanumab-avwa in Participants with Early Symptomatic Alzheimer's Disease

Rationale:

Study I5T-MC-AACN (AACN) is a Phase 3, open-label, head-to-head study to evaluate the superiority of donanemab to aducanumab in participants with Early Symptomatic AD.

The amyloid hypothesis of AD postulates that the production and deposition of Aβ is an early and necessary event in the pathogenesis of AD (Selkoe 2000). Both donanemab and aducanumab have previously demonstrated the ability to reduce brain amyloid plaque burden and potentially slow clinical decline (Sevigny et al 2016; Mintun et al 2021; Aducanumab USPI, 2021). Recently, the FDA approved aducanumab, in the US, under accelerated approval for the treatment of AD based on its ability to reduce amyloid plaque burden (Aducanumab USPI, 2021). The current study aims to evaluate the superiority of donanemab to aducanumab on amyloid plaque clearance in participants with early symptomatic AD.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Co-Primary	
To assess the superiority of donanemab versus aducanumab on complete brain amyloid plaque clearance in participants with early symptomatic AD.	Superiority of percentage of participants who reach complete amyloid plaque clearance on florbetapir F18 PET scan on donanemab versus aducanumab at 6 months.
To assess the superiority of donanemab versus aducanumab on complete brain amyloid plaque clearance in the intermediate tau subpopulation of participants with early symptomatic AD.	Superiority of percentage of participants who reach complete amyloid plaque clearance on florbetapir F18 PET scan in the intermediate tau subpopulation on donanemab versus aducanumab at 6 months.

Key Secondary	
To assess the superiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction.	Superiority of mean absolute change from baseline in brain amyloid plaque on florbetapir F18 PET scan for donanemab versus aducanumab at: • 6 months • 12 months, and • 18 months.
To assess the superiority of donanemab versus aducanumab in time to reach complete amyloid plaque clearance.	Time to reach complete amyloid plaque clearance on donanemab versus aducanumab.
Other Secondary	
To assess the superiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction.	Superiority of mean percent change from baseline in brain amyloid plaque on florbetapir F18 PET scan for donanemab versus aducanumab at: • 6 months • 12 months, and • 18 months.
To assess the non-inferiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction.	Non-inferiority of mean absolute change from baseline in brain amyloid plaque on florbetapir F18 PET scan at: • donanemab 6 months vs aducanumab 12 months, and • donanemab 6 months vs aducanumab 18 months.
To assess the superiority of donanemab versus aducanumab on complete brain amyloid plaque clearance.	Superiority of percentage of participants who reach complete amyloid plaque clearance on florbetapir F18 PET scan on donanemab versus aducanumab at: • 12 months, and • 18 months.

To assess the superiority of donanemab versus aducanumab on complete brain amyloid plaque clearance in the intermediate tau subpopulation.	Superiority of percentage of participants who reach complete amyloid plaque clearance on florbetapir F18 PET scan in the intermediate tau subpopulation on donanemab versus aducanumab at: • 12 months, and • 18 months.
To assess the superiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction in the intermediate tau subpopulation.	Superiority of mean absolute change from baseline in brain amyloid plaque on florbetapir F18 PET scan in the intermediate tau subpopulation for donanemab vs aducanumab at: • 6 months • 12 months, and • 18 months.
To assess the superiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction.	Superiority of change from baseline in brain amyloid plaque reduction on florbetapir F18 PET scan for donanemab 6 months vs aducanumab 12 months.
To evaluate the safety and tolerability of donanemab vs aducanumab	Characterization of standard safety assessments: • Spontaneously reported AEs • Clinical laboratory tests • MRI (ARIA and emergent radiological findings) • Serious hypersensitivity reactions • C-SSRS

Abbreviations: AD = Alzheimer's disease; AE = adverse event; ARIA = amyloid-related imaging abnormalities; C-SSRS = Columbia Suicide-Severity Rating Scale; MRI = magnetic resonance imaging; PET = positron emission tomography.

NOTE: Other pre-specified, non-gated endpoints not listed will be detailed in the SAP.

Overall Design

Study I5T-MC-AACN (AACN) is a Phase 3, open-label, head-to-head study to evaluate the superiority of donanemab to aducanumab in participants with early symptomatic AD.

Brief Summary:

Study AACN is a multicenter, randomized, open-label, head-to-head, Phase 3 study of donanemab compared to aducanumab in participants with early symptomatic AD.

Participants who meet entry criteria will be randomized in a 1:1 ratio to 1 of the following treatment groups:

- donanemab: 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W
- aducanumab: Refer to PI/routine clinical practice

The maximum total duration of study participation for each participant, including screening and the post-treatment follow-up periods, is up to 127 weeks:

- Lead-In: any time prior to complete screening
- Complete Screening: up to 7 weeks
- Open-label study period: 76 weeks
- Follow-Up: up to 44 weeks

The maximum duration of treatment is 72 weeks.

Scheduled Reduction of Donanemab

Participants randomized to donanemab whose amyloid plaque reduction as measured by florbetapir F18 PET scans at Visit 8 (Week 24) or Visit 15 (Week 52) meets criteria will stop donanemab infusions but continue all other assessments for the remaining duration of the open-label period and short-term follow-up period. These dose reduction rules are defined by the sponsor.

Participants randomized to aducanumab will continue monthly infusions throughout the open-label period, regardless of amyloid plaque reduction on florbetapir F18 PET scans.

Participant randomization will be stratified by amyloid burden at baseline and ApoE ε4 status (noncarrier/heterozygous/homozygous).

Number of Participants:

Approximately 200 participants will be randomly assigned to study intervention.

Intervention Groups and Duration:

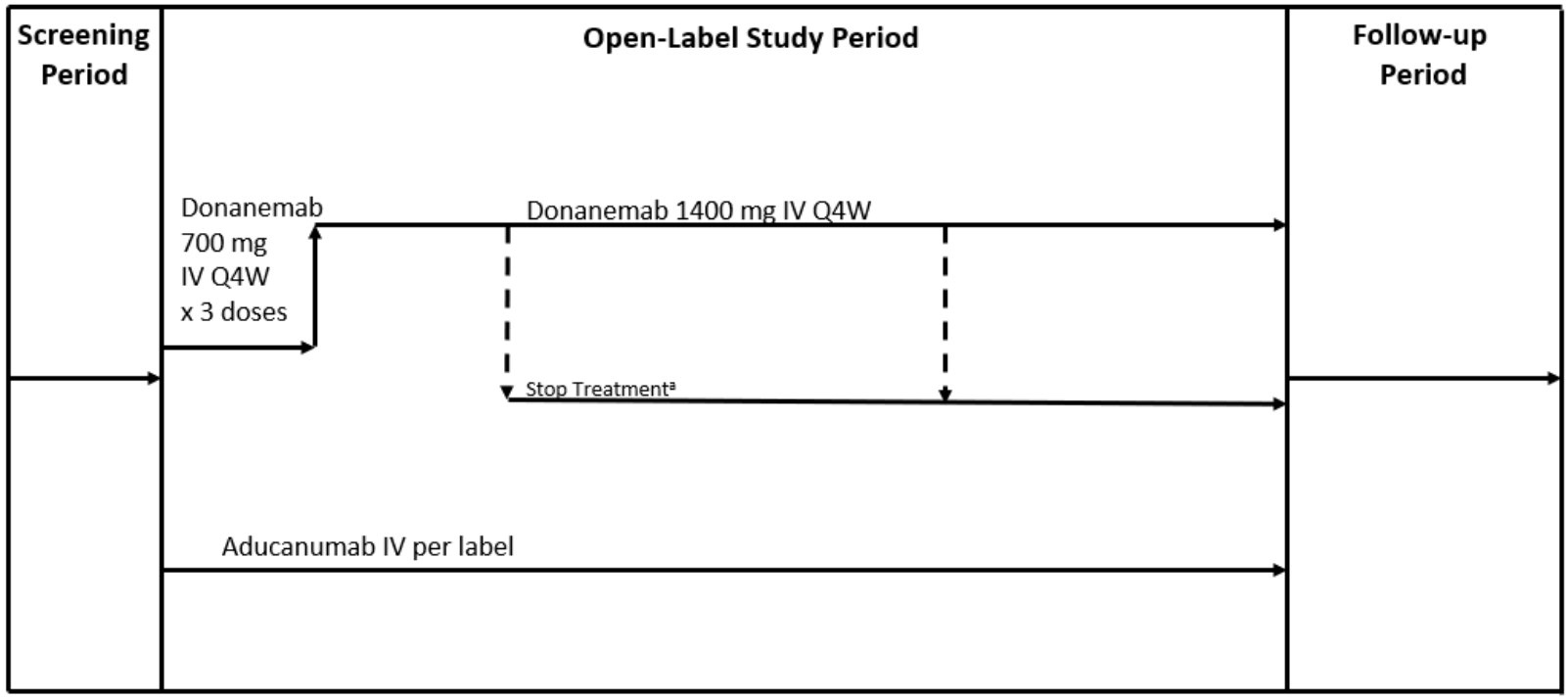
Intervention Name	donanemab	aducanumab
Dosage Level(s)	700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W[a]	Refer to PI/routine clinical practice
Route of Administration	IV infusion	IV infusion
Use	experimental	active-comparator

Abbreviations: IV = intravenous; PI = package insert; Q4W = once every 4 weeks.

[a] Participants randomized to donanemab whose amyloid plaque reduction as measured by florbetapir F18 PET scans at Visit 8 (Week 24) or Visit 15 (Week 52) meets criteria will stop donanemab infusions but continue all other assessments for the remaining duration of the open-label period and short-term follow-up period. These dose reduction rules are defined by the sponsor.

Data Monitoring Committee: Yes

1.2. Schema



Abbreviations: IV = intravenous; mg = milligrams; Q4W = every 4 weeks.

Note: V601 is optional. For participants who do not complete V601, procedures will be included in V1.
Randomization occurs at V2.

[a] Participants whose amyloid plaque reduction as measured by florbetapir F18 PET scans at Visit 8 (Week 24) or Visit 15 (Week 52) meets criteria will stop donanemab infusions but continue all other assessments for the remaining duration of the open-label period and short-term follow-up period. These dose reduction rules are defined by the sponsor.

1.3. Schedule of Activities (SoA)

Screening

	LEAD-IN SCREENING	COMPLETE SCREENING	Notes
Visit No.:	601*	1	V1 may be conducted over more than 1 day. *V601 is optional. If the participant's initial visit is V1, then perform all V601 procedures in addition to V1 procedures.
Day Relative to Randomization	Can be done any time prior to complete screening	-49 to -1	
Tolerance Interval for Visit (Days)	Can be done at any time	≤49 before V2	
Entry and Administrative			
Abbreviated (or Full) Informed Consent – participant	X		The Abbreviated Informed Consent grants consent only for procedures and assessments marked under V601.
Full Informed Consent – participant		X	Do not collect if Full Informed Consent was collected at V601.
Full Informed Consent – study partner	X		Study partner(s) are not required to complete the abbreviated Informed Consent.
Participant number assigned via IWRS	X		
Demographics	X		
Inclusion/exclusion review		X	
Physical/neurological examination		X	As described in the Manual of Operations.
Concomitant medications		X	
Preexisting conditions		X	
Assessments			
Height and weight		X	

	LEAD-IN SCREENING	COMPLETE SCREENING	Notes
Visit No.:	601*	1	V1 may be conducted over more than 1 day. *V601 is optional. If the participant's initial visit is V1, then perform all V601 procedures in addition to V1 procedures.
Day Relative to Randomization	Can be done any time prior to complete screening	-49 to -1	
Tolerance Interval for Visit (Days)	Can be done at any time	≤49 before V2	
ECG		X	Single, locally-read ECG. Unscheduled ECGs may be performed at the discretion of investigator.
Chemistry	X		Blood draw can be performed at either at V601 or V1. Collect all blood draws for screening at the same time.
Hematology	X		
ApoE	X		Blood draw can be performed at either at V601 or V1. Collect all blood draws for screening at the same time.
Entry Diagnostics			
MMSE	X		Participants who do not meet MMSE criteria are not to have any other screening procedures performed. Administer the MMSE prior to medical procedures that could be stressful to the participant (blood draws, etc.).
CDR	X		Administer the CDR prior to medical procedures that could be stressful to the participant (blood draws, etc.).

	LEAD-IN SCREENING	COMPLETE SCREENING	Notes
Visit No.:	601*	1	V1 may be conducted over more than 1 day. *V601 is optional. If the participant's initial visit is V1, then perform all V601 procedures in addition to V1 procedures.
Day Relative to Randomization	Can be done any time prior to complete screening	-49 to -1	
Tolerance Interval for Visit (Days)	Can be done at any time	≤49 before V2	
Screening PET Scans and MRI			
Florbetapir F18 PET scan		X	The participant should meet all other non-imaging eligibility criteria before the screening florbetapir F18 PET scan. Previous florbetapir F18 PET scans within 3 months of randomization may be acceptable. The acceptance of a historical scan is at the discretion of the sponsor.
MRI		X	The participant should meet all other non-imaging eligibility criteria before the screening MRI.

Abbreviations: ApoE = apolipoprotein E; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; IWRS = interactive web response system; MMSE = Mini-Mental State Exam; MRI = magnetic resonance imaging; PET = positron emission tomography; V = visit.

Visits 2 through 11

	Open-Label Study Period										Comments
Visit Number	2	3	4	5	6	7	8	9	10	11	
Weeks relative to first infusion	0	4	8	12	16	20	24	28	32	36	
Visit interval tolerance (days)		-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	
Entry and Administrative											
Inclusion and exclusion criteria, review and confirm	X										Inclusion and exclusion criteria should be confirmed at V2, prior to randomization and administration of the first dose of study intervention.
Randomization	X										
Brief Physical/Neurological Exam	X			X			X			X	As described in the Manual of Operations. Any clinically significant changes from baseline on brief physical/neurological examinations should be noted on the AE CRF.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
AEs	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.
C-SSRS screening/baseline	X										
C-SSRS since last assessment			X		X		X		X		
Administer study intervention	X	X	X	X	X	X	X	X	X	X	See Section 6.1. Administration of study intervention (and treatment-related activities conducted in person) outside of the visit window is not a protocol deviation, unless 2 doses are administered within <21 days of each other. The participant should be observed for a minimum of 30 minutes following the end of each infusion.

	Open-Label Study Period										Comments
Visit Number	2	3	4	5	6	7	8	9	10	11	
Weeks relative to first infusion	0	4	8	12	16	20	24	28	32	36	
Visit interval tolerance (days)		-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	
Vital signs	X	X	X	X	X	X	X	X	X	X	Vital signs include pulse rate, blood pressure, and temperature. Vitals should be measured after participant has been sitting for at least 5 minutes. Vital signs are measured prior to and within 30 minutes after infusion for clinical management, and not recorded in the CRF.
Weight (for aducanumab participants only)	X	X	X	X	X	X	X	X	X	X	Weight is measured prior to dosing with aducanumab only and is not recorded in the CRF.
MRI		X		X			X		X		MRI at V3 is to be performed and reviewed prior to V3 infusion and may occur no sooner than 21 days after the first infusion. If infusions are suspended after the first, second, or third dose, an MRI is to be performed and reviewed prior to the fourth infusion. MRI at V5 is to be performed and reviewed prior to V5 infusion. The MRI should occur at least 14 days after infusion at V4 is administered, and may occur outside of the visit windows. MRI at V8 is to be performed and reviewed prior to V8 infusion. The MRI should occur at least 14 days after infusion at V7 is administered, and may occur outside of the visit windows. MRI at V10 is to be performed and reviewed prior to V10 infusion. The MRI should occur at least 14 days after infusion at V9 is administered, and may occur outside of the visit windows. Unscheduled MRIs may be performed at the discretion of investigator, for example, if titration is delayed due to temporary suspension of infusions.

	Open-Label Study Period										Comments
Visit Number	2	3	4	5	6	7	8	9	10	11	
Weeks relative to first infusion	0	4	8	12	16	20	24	28	32	36	
Visit interval tolerance (days)		-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	
Flortaucipir F18 PET scan	X										Will not be used for eligibility. Participants have +/- 3 months from randomization to obtain flortaucipir results (either from pre-existing scan or new scan). PET scans must be performed ≥16 hours apart from each other. Previous flortaucipir F18 PET scans may be acceptable. The acceptance of a historical scan is at the discretion of the sponsor.
Florbetapir F18 PET scan							X				PET scans must be performed ≥16 hours apart from each other.
Laboratory Tests and Sample Collections	In the event that study intervention is delayed, all laboratory collections should occur on the same day as study intervention infusion – and should be collected prior to infusion.										
Hematology and clinical chemistry							X				Collect prior to infusion.
PK sample							X				Collect prior to infusion. Predose collections may be collected from the IV site prior to the infusion.
Immunogenicity (ADA) samples	X						X				Collect prior to infusion.
Stored Samples											
Genetics sample	X										Collect prior to infusion.
Exploratory biomarker samples	X						X				Collect prior to infusion.

Abbreviations: ADA = anti-drug antibody; AEs = adverse events; CRF = case reporting form; C-SSRS = Columbia-Suicide Severity Rating Scale; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; V = visit.

Visits 12 through 21 and Follow-Up

	Open-Label Treatment											Short-term Follow-up	Comments
Visit Number	12	13	14	15	16	17	18	19	20	21	ET	801-804^	^Visit 801 to 804 may be used for return to baseline ADA monitoring and other safety assessments at discretion of the sponsor and may be requested within the time period listed.
Weeks relative to first infusion	40	44	48	52	56	60	64	68	72	76	-	84-120	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-	±14	
Entry and Administrative													
Brief Physical/Neurological Exam				X			X			X	X	X	As described in the Manual of Operations. Any clinically significant changes from baseline on brief physical/neurological examinations should be noted on the AE CRF.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
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.
C-SSRS since last assessment	X		X		X		X		X		X	X	

	Open-Label Treatment											Short-term Follow-up	Comments
Visit Number	12	13	14	15	16	17	18	19	20	21	ET	801-804^	^Visit 801 to 804 may be used for return to baseline ADA monitoring and other safety assessments at discretion of the sponsor and may be requested within the time period listed.
Weeks relative to first infusion	40	44	48	52	56	60	64	68	72	76	-	84-120	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-	±14	
Administer study intervention	X	X	X	X	X	X	X	X	X				See Section 6.1. Administration of study intervention (and treatment-related activities conducted in person) outside of the visit window is not a protocol deviation, unless 2 doses are administered within <21 days of each other. The participant should be observed for a minimum of 30 minutes following the end of each infusion.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	Vital signs include pulse rate, blood pressure, and temperature. Vitals should be measured after participant has been sitting for at least 5 minutes. Vital signs are measured prior to and within 30 minutes after infusion for clinical management, and not recorded in the CRF.
Weight (for aducanumab participants only)	X	X	X	X	X	X	X	X	X				Weight is measured prior to dosing with aducanumab only and is not recorded in the CRF.

	Open-Label Treatment											Short-term Follow-up	Comments
Visit Number	12	13	14	15	16	17	18	19	20	21	ET	801-804^	^Visit 801 to 804 may be used for return to baseline ADA monitoring and other safety assessments at discretion of the sponsor and may be requested within the time period listed.
Weeks relative to first infusion	40	44	48	52	56	60	64	68	72	76	-	84-120	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-	±14	
MRI		X											MRI at V13 is to be performed and reviewed prior to V13 infusion. The MRI should occur at least 14 days after infusion at V12 is administered, and may occur outside of the visit windows. Unscheduled MRIs may be performed at the discretion of investigator, for example, if titration is delayed due to temporary suspension of infusions.
Florbetapir F18 PET scan				X						X	X		Collect at ET only if ET occurs at 3 or more IP infusions after the last florbetapir F18 PET scan.
Laboratory Tests and Sample Collections	In the event that study intervention is delayed, all laboratory collections should occur on the same day as study intervention infusion - and should be collected prior to infusion.												
Hematology and clinical chemistry				X						X	X		Collect prior to infusion.
PK sample				X						X	X	X	Collect prior to infusion. Predose collections may be collected from the IV site prior to the infusion.
Immunogenicity (ADA) samples				X						X	X	X	Collect prior to infusion.

	Open-Label Treatment											Short-term Follow-up	Comments
Visit Number	12	13	14	15	16	17	18	19	20	21	ET	801-804^	^Visit 801 to 804 may be used for return to baseline ADA monitoring and other safety assessments at discretion of the sponsor and may be requested within the time period listed.
Weeks relative to first infusion	40	44	48	52	56	60	64	68	72	76	-	84-120	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-	±14	
Stored Samples													
Exploratory biomarker samples				X						X	X		Collect prior to infusion.

Abbreviations: ADA = anti-drug antibody; AEs = adverse events; CRF = electronic case reporting form; C-SSRS = Columbia-Suicide Severity Rating Scale; ET = early termination; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; V = visit.

2. Introduction

Donanemab is an antibody directed at the pyroglutamate modification of the third amino acid of amyloid beta (N3pG Aβ) epitope that is present only in brain amyloid plaques. It is being studied for the treatment of AD. The mechanism of action of donanemab antibody is to target and remove deposited amyloid plaque, a key pathological hallmark of AD, via microglial-mediated clearance.

Aducanumab is a human anti-Aβ monoclonal antibody that selectively targets aggregated forms of Aβ, including soluble oligomers and insoluble fibrils (Ferrero et al 2016). It was recently approved, in the US, under accelerated approval for the treatment of AD (Aducanumab USPI, 2021).

2.1. Study Rationale

Study I5T-MC-AACN (AACN) is a Phase 3, open-label, head-to-head study to evaluate the superiority of donanemab to aducanumab in reaching amyloid plaque clearance in participants with early symptomatic AD.

This strategy is based on the amyloid hypothesis of AD, which postulates that the production and deposition of Aβ is an early and necessary event in the pathogenesis of AD (Selkoe 2000). Clinical data supporting this hypothesis comes from the observation that parenchymal Aβ levels are elevated prior to the manifestation of AD symptoms, and further supported by genetic variants of AD that overproduce brain Aβ and genetic variants that protect against Aβ production (Jonsson et al. 2012; Fleisher et al. 2015). Furthermore, early in the disease, the presence of brain amyloid appears to increase the risk of conversion from MCI to AD dementia (Doraiswamy et al. 2012). These data suggest that removal of deposited amyloid and clearance of Aβ can result in the slowing of AD progression. Both donanemab and aducanumab have previously demonstrated the ability to reduce brain amyloid plaque burden and potentially slow clinical decline (Sevigny et al 2016; Mintun et al 2021; Aducanumab USPI, 2021). Recently, the FDA approved aducanumab for clinical use based on its ability to reduce amyloid plaque burden (Aducanumab USPI, 2021). The current study aims to evaluate the superiority of donanemab to aducanumab in reaching amyloid plaque clearance.

2.2. Background

Alzheimer's disease is an age-related neurodegenerative disorder characterized by progressive decline in cognitive function and the ability to perform activities of daily living. The amyloid hypothesis of AD postulates that the accumulation of Aβ is an early and necessary event in the pathogenesis of AD. This hypothesis suggests that interventions that slow the accumulation of Aβ plaque in the brain or increase clearance of Aβ may be able to slow the progression of the AD clinical syndrome. Another hallmark neuropathological lesion of AD is comprised of intraneuronal, neurofibrillary tangles consisting of tau proteins, which spread through the brain and mark disease progression (Braak and Braak 1996). The relationship between these 2 pathologies is still unclear, although the presence of both is necessary for the diagnosis of definite AD.

Converging evidence from both genetic at-risk and age at-risk cohorts suggests that the pathophysiological process of AD begins well more than a decade before the clinical stage now recognized as AD dementia, and that neurodegeneration is already apparent on MRI by the stage of MCI (Jack et al 2010). Like many disorders, AD occurs on a continuum from asymptomatic (preclinical) to MCI, and then to dementia in mild, moderate, and severe stages. Recent clinical trial results in mild-to-moderate AD dementia, as well as evidence from transgenic animal experiments, suggest that treating AD during the earlier stages could have the greatest potential benefit on the disease and inhibiting progression, particularly when considering therapies targeted at Aβ reduction (Doody et al. 2014; Fleisher et al. 2015; Siemers et al. 2016).

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, Participant Information Leaflet, Package Insert, or Development Safety Update Report or Summary of Product Characteristics.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of aducanumab may be found in the Participant Information Leaflet, Package Insert, or Summary of Product Characteristics.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Co-Primary	
To assess the superiority of donanemab versus aducanumab on complete brain amyloid plaque clearance in participants with early symptomatic AD.	Superiority of percentage of participants who reach complete amyloid plaque clearance on florbetapir F18 PET scan on donanemab versus aducanumab at 6 months.
To assess the superiority of donanemab versus aducanumab on complete brain amyloid plaque clearance in the intermediate tau subpopulation of participants with early symptomatic AD.	Superiority of percentage of participants who reach complete amyloid plaque clearance on florbetapir F18 PET scan in the intermediate tau subpopulation on donanemab versus aducanumab at 6 months.
Key Secondary	
To assess the superiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction.	Superiority of mean absolute change from baseline in brain amyloid plaque on florbetapir F18 PET scan for donanemab versus aducanumab at: • 6 months • 12 months, and • 18 months.
To assess the superiority of donanemab versus aducanumab in time to reach complete amyloid plaque clearance.	Time to reach complete amyloid plaque clearance on donanemab versus aducanumab.
Other Secondary	
To assess the superiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction.	Superiority of mean percent change from baseline in brain amyloid plaque on florbetapir F18 PET scan for donanemab versus aducanumab at: • 6 months • 12 months, and • 18 months.

Objectives	Endpoints
To assess the non-inferiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction.	Non-inferiority of mean absolute change from baseline in brain amyloid plaque on florbetapir F18 PET scan at: • donanemab 6 months vs aducanumab 12 months, and • donanemab 6 months vs aducanumab 18 months.
To assess the superiority of donanemab versus aducanumab on complete brain amyloid plaque clearance.	Superiority of percentage of participants who reach complete amyloid plaque clearance on florbetapir F18 PET scan on donanemab versus aducanumab at: • 12 months, and • 18 months.
To assess the superiority of donanemab versus aducanumab on complete brain amyloid plaque clearance in the intermediate tau subpopulation.	Superiority of percentage of participants who reach complete amyloid plaque clearance on florbetapir F18 PET scan in the intermediate tau subpopulation on donanemab versus aducanumab at: • 12 months, and • 18 months.
To assess the superiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction in the intermediate tau subpopulation.	Superiority of mean absolute change from baseline in brain amyloid plaque on florbetapir F18 PET scan in the intermediate tau subpopulation for donanemab vs aducanumab at: • 6 months • 12 months, and • 18 months.
To assess the superiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction.	Superiority of change from baseline in brain amyloid plaque reduction on florbetapir F18 PET scan for donanemab 6 months vs aducanumab 12 months.

Objectives	Endpoints
To evaluate the safety and tolerability of donanemab vs aducanumab.	Characterization of standard safety assessments: • Spontaneously reported AEs • Clinical laboratory tests • MRI (ARIA and emergent radiological findings) • Serious hypersensitivity reactions • C-SSRS

Abbreviations: AD = Alzheimer's disease; AE = adverse event; ARIA = amyloid-related imaging abnormalities; C-SSRS = Columbia Suicide-Severity Rating Scale; PET = positron emission tomography; SAP = Statistical Analysis Plan.

NOTE: Other pre-specified, non-gated endpoints not listed will be detailed in the SAP.

Estimands

Estimands are described in the SAP.

4. Study Design

4.1. Overall Design

Study AACN is a multicenter, randomized, open-label, head-to-head, Phase 3 study of donanemab compared to aducanumab in participants with early symptomatic AD.

Participants who meet entry criteria will be randomized in a 1:1 ratio to 1 of the following treatment groups:

- donanemab: 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W
- aducanumab: refer to PI/routine clinical practice

The maximum total duration of study participation for each participant, including screening and the post-treatment follow-up periods, is up to 127 weeks:

- Lead-In: any time prior to complete screening
- Complete Screening: up to 7 weeks
- Open-label study period: 76 weeks
- Follow-Up: up to 44 weeks

The maximum duration of treatment is 72 weeks.

Scheduled Reduction of Donanemab

Participants randomized to donanemab whose amyloid plaque reduction as measured by florbetapir F18 PET scans at Visit 8 (Week 24) or Visit 15 (Week 52) meets criteria will stop donanemab infusions but continue all other assessments for the remaining duration of the open-label period and short-term follow-up period. These dose reduction rules are defined by the sponsor.

Participants randomized to aducanumab will continue monthly infusions throughout the open-label period, regardless of amyloid plaque reduction on florbetapir F18 PET scans.

Change in amyloid burden (as assessed with florbetapir F18 PET by personnel blinded to treatment allocation) will be compared in donanemab and aducanumab-treated participants.

Participant randomization will be stratified by amyloid burden and ApoE ε4 status (noncarrier/heterozygous/homozygous).

4.2. Scientific Rationale for Study Design

Study AACN is a Phase 3, open-label, head-to-head study to evaluate the superiority of donanemab to aducanumab in reaching amyloid plaque clearance in participants with early symptomatic AD.

Amyloid plaque is a known hallmark pathology of AD, and is hypothesized to contribute to the cognitive and functional decline in people with AD. Therefore, it is hypothesized that the removal of amyloid by donanemab may slow clinical progression.

The study includes a screening visit, which can last up to 49 days, at which participants are required to have florbetapir F18 PET imaging results in order to be randomized to donanemab or aducanumab. The duration of the open-label treatment period of the study is 76 weeks and

includes up to 72 weeks of treatment with primary endpoint measure at 6 months, to assess the superiority of donanemab versus aducanumab in reaching amyloid plaque clearance.

In addition to AE reporting, safety measures such as laboratory assessments, MRI assessments (ARIA and emergent radiological findings), serious hypersensitivity reactions, and assessments of suicidal ideation and behavior are included to facilitate a comprehensive safety evaluation.

4.3. Justification for Dose

Decreased participant burden with a Q4W dosing schedule compared with a Q2W dosing schedule and comparable safety (see IB), 1400 mg Q4W dosing was selected as the highest dose regimen for robust amyloid plaque lowering. Safety data from Study AACG showed that the 1400-mg dose of donanemab had an acceptable safety profile based on the ability to monitor and manage AEs and AEs of special interest including ARIA-E, ARIA-H and hypersensitivity reactions, and the overall frequency, severity, and seriousness of AEs at this dose level.

A titration schedule of 700 mg IV Q4W for the first 3 doses and then 1400 mg IV Q4W was chosen to decrease the risk of ARIA-E.

Participants randomized to the aducanumab arm will receive approved-label dosing for aducanumab.

4.4. End of Study Definition

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

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

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 50 to 85 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Gradual and progressive change in memory function reported by the participant or informant for ≥6 months.
3. Meet florbetapir F18 PET scan criteria.
4. A Clinical Dementia Rating (CDR)-Global Score of 0.5 or 1.
5. An MMSE score between 20 and 30 (inclusive).
6. Must consent to apolipoprotein E (ApoE) genotyping.
7. Have a study partner who will provide written informed consent to participate, is in frequent contact with the participant (defined as at least 10 hours per week), and will accompany the participant to study visits or be available by telephone at designated times.

   A second study partner may serve as backup. The study partner(s) is/are required to accompany the participant for signing consent. One study partner is requested to be present on all days the C-SSRS is administered and must be present at screening for the completion of the CDR. Other visits must have a study partner available by telephone if not accompanying participant at a visit for the following assessments:
   - AEs and concomitant medications
   - Relevant portions of the C-SSRS

   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 he or she accompanies the participant.
8. Have adequate literacy, vision, and hearing for neuropsychological testing in the opinion of the investigator at the time of screening.
9. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

Sex and Contraceptive/Barrier Requirements

10. Males and females will be eligible for this study.

    a. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

b. Female participants.
    a. Women not of childbearing potential (defined in Appendix 4, Section 10.4) may participate.

Informed Consent

11. 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.

5.2. Exclusion Criteria

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

Medical Conditions

12. 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, history of transient ischemic attack or stroke, or epilepsy or recurrent seizures (except febrile childhood seizures).
13. Current serious or unstable medical illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, psychiatric (including actively suicidal or deemed at risk of suicide, or current alcohol or substance abuse), immunologic, infectious, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses in this study; or has a life expectancy of approximately ≤24 months.
14. History of clinically significant multiple or severe drug allergies, or severe posttreatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and/or exfoliative dermatitis).
15. History of bleeding disorder or use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤325 mg daily).

Imaging, Electrocardiograms, Laboratory Tests, and Physical Examination

16. Have any clinically important abnormality at screening, as determined by the investigator, on physical or neurological examination, ECG, MRI, or clinical laboratory test results that could be detrimental to the participant, compromise study integrity, or show evidence of other etiologies for dementia.
17. Have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants/cardiac pacemaker.
18. Have a centrally read MRI demonstrating presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease at screening.
19. Contraindications to having a PET scan.
20. Sensitivity to florbetapir F18 or flortaucipir F18.
21. Poor venous access.

22. 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.
23. ALT ≥2.5X ULN of the performing laboratory, AST ≥2.5X ULN, TBL ≥1.5X ULN, or ALP ≥2X ULN at screening.
    Note: Participants with TBL ≥1.5X ULN are not excluded if they meet all of the following criteria for Gilbert's syndrome:
    - Bilirubin is predominately indirect (unconjugated) at screening (direct bilirubin within normal limits).
    - Absence of liver disease.
    - ALT, AST, and ALP ≤1X ULN at screening.
    - Hemoglobin is not significantly decreased at screening.

Prior/Concomitant Therapy

24. Have known allergies to donanemab or aducanumab, related compounds, or any components of the formulation.
25. Have had prior or current treatment with donanemab or aducanumab.

Prior/Concurrent Clinical Study Experience

26. Prior or current participation in any active or passive immunotherapy study targeting Aβ, unless documentation of receipt of placebo.
27. Are currently enrolled in any other interventional clinical trial involving a study intervention or any other type of medical research judged not to be scientifically or medically compatible with this study.
28. Have participated, within the last 30 days, in any clinical trial involving a study intervention. Participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor.

Other Exclusions

29. Are study personnel directly involved with the execution of this study, and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
30. Are Lilly employees or are employees of TPOs directly involved in the study which requires exclusion of their employees, or have study partners who are Lilly employees or are employees of TPOs involved in a study which requires exclusion of their employees.

5.3. Lifestyle Considerations

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.

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 Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

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

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

Intervention Name	donanemab	aducanumab
Dosage Level(s)	700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W[a]	refer to PI/routine clinical practice
Route of Administration	IV infusion	IV infusion
Use	experimental	active-comparator

Abbreviations: IV = intravenous; PET = positron emission tomography; PI = package insert; Q4W = once every 4 weeks.

[a] Participants randomized to donanemab whose amyloid plaque reduction as measured by florbetapir F18 PET scans at Visit 8 (Week 24) or Visit 15 (Week 52) meets criteria will stop donanemab infusions but continue all other assessments for the remaining duration of the open-label period and short-term follow-up period. These dose reduction rules are defined by the sponsor.

Donanemab is administered by IV infusion over a minimum of 30 minutes. Detailed instructions for administration, including reconstitution and infusion rate, can be found in the pharmacy manual.

Donanemab is to be administered once Q4W. Donanemab must not be administered at a dosing interval of <21 days at any time in the study.

See Section 8.3.3.1 for infusion-related reactions.

For aducanumab, it is expected that the investigator review appropriate product label/institutional guidelines for confirmation dosing (i.e., need for pre-medication, dose, schedule, toxicity management and dose modifications).

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

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study

intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study in which participants will be randomized in a 1:1 ratio to donanemab:aducanumab.

For between-group comparability, participant randomization will be stratified by amyloid burden and ApoE ε4 status (noncarrier/heterozygous/homozygous). Any further stratification variables will be stated in the SAP. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. Randomization into 1 stratum may be discontinued or overenrolled at the discretion of the sponsor to manage between-group comparability.

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

In order to maintain the scientific integrity of this trial, access to certain aspects of the study data will be strictly controlled prior to the potential interim analysis and testing of the primary and key secondary objectives. Access to the EDC system will be limited to those who require this information for their role and all access will be documented.

For the primary efficacy analysis database, that is, the database to which study statisticians (Lilly and/or its designee) have access, measurements from post-baseline florbetapir F18 PET scans will be scrambled or masked to preclude the ability to conduct the primary efficacy analysis. Scrambled or masked florbetapir F18 PET measurements will be used in the reporting database until the interim analysis or the 6-month database lock, and the same procedures will also be utilized for the testing of the objectives associated with 12- and 18-month outcomes.

In the event of an interim efficacy analysis assigned to the DMC, only the designated SAC, which is independent of the sponsor, will perform analyses on unblinded data, that is, the primary efficacy analysis database with correct treatment assignments.

Further details are included in the study blinding plan.

6.4. 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. 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.

6.5. Dose Modification

Dose modification of donanemab is not permitted in this study except for participants whose amyloid plaque reduction meets criteria, as described in Section 4.1, and some instances of ARIA; if ARIA occurs during the titration period (that is, before the fourth infusion of donanemab), dose modification can be considered at the discretion of the investigator or designee as described in the Manual of Operations. If an ARIA-E and/or symptomatic ARIA-H event occurs, additional data should be provided to the sponsor in the ARIA Related Events CRF.

Investigators should consult the aducanumab appropriate product label/institutional guidelines toxicity management and dose modifications.

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

Not applicable.

6.7. Treatment of Overdose

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

1. Contact the medical monitor immediately.
2. Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
3. Closely monitor the participant for any AE/SAE.
4. Obtain a plasma sample for analysis of study intervention if requested by the medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/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.

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

6.8.1. Medications for Alzheimer's Disease

Use of approved or standard of care symptomatic treatments for AD is permitted during the study. When medically indicated, initiation, increase, or discontinuation of symptomatic treatments for AD is permitted.

Disease-modifying prescription medications are not allowed at any time during the study.

Nonmedication treatments for AD, such as behavioral management, are permitted.

6.8.2. 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.

6.8.3. Excluded Medications

IgG therapy (also known as gamma globulin or IVIG) is not allowed during the study. Use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤325 mg daily) are not allowed during the study.

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

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety and biomarker collection. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- by request of the participant or participant's designee (for example, legal guardian)
- based on a specific AE profile, the Medical Monitor, or the study sponsor physician/scientist, in discussions with the Principal Investigator
- incorrect enrollment
- severe noncompliance to the study protocol in the judgment of the investigator
- systemic hypersensitivity reaction suspicious for an anaphylactic reaction or angioedema
- participant requires an excluded therapeutic agent
- based on investigator clinical judgment
- participants answered 'yes' to Question 4 or 5 on the 'Suicidal Ideation' portion of the C-SSRS, or
- participants 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 for C-SSRS responses.

7.1.1. Liver Chemistry Stopping Criteria

Participants who are discontinued from study intervention due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the CRF.

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

- ALT or AST >8X ULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and TBL >2X ULN or INR >1.5
- 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

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

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using QTcF after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Amyloid-Related Imaging Abnormalities (ARIA)

The development of ARIA-E and/or ARIA-H (microhemorrhages and/or cSS) are expected events and occur more commonly on treatment with donanemab and aducanumab.

While most cases of ARIA-E are asymptomatic, serious cases have been reported. Available data for donanemab suggest serious cases are most likely to occur early in dosing, after the first, second, or third infusion. For aducanumab, enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment, particularly during titration.

ARIA-E

For asymptomatic mild-to-moderate ARIA-E, study intervention may be continued and participants may be monitored with unscheduled MRIs at the investigator's discretion.

If a participant develops ARIA-E to an extent deemed clinically significant by the investigator or designee, such as symptomatic ARIA-E or severe ARIA-E on imaging, then the investigator or designee may consider withholding study intervention (see Manual of Operations for temporary discontinuation guidance). The participant should be monitored for improvement by MRI(s) (fluid attenuation inversion recovery and T2* gradient-recall echo). Symptoms should be monitored in participants with symptomatic ARIA-E. Upon resolution of ARIA-E on imaging and resolution of associated symptoms, reinitiating study intervention can be considered by the investigator or designee. If resolution is not observed, participants should be permanently discontinued from study intervention, but continue other study activities (see Manual of Operations for permanent discontinuation guidance).

If ARIA-E occurs during the titration period, dose modifications may be considered (see Manual of Operations).

In the event of a finding of ARIA-E on MRI, the investigator is to complete the ARIA Related Events CRF regarding the presence or absence of symptoms related to the ARIA-E, and ARIA-E should be reported as an AE in the AE CRF. Information regarding symptoms attributed to the ARIA-E event should be entered in the ARIA Related Events CRF and should not be reported as AEs.

ARIA-H

See Manual of Operations for temporary and permanent discontinuation guidance. For new or increased number or severity of asymptomatic ARIA-H, in some circumstances, study intervention may be temporarily discontinued and participants monitored for related symptoms

and with unscheduled MRIs at the investigator's discretion. In the case of symptomatic ARIA-H, the investigator or designee should monitor for changes in symptoms and may consider withholding study intervention. Upon stabilization of ARIA-H and resolution of associated symptoms, reinitiating study intervention can be considered. If stabilization of imaging findings and resolution of associated symptoms is not observed, participants should be permanently discontinued from study intervention, but continue other study activities.

In the event of symptomatic ARIA-H, the investigator is to complete the ARIA Related Events CRF regarding the symptoms related to the ARIA-H, and ARIA-H should be reported as an AE in the AE CRF. Information regarding symptoms attributed to the ARIA-H event should be entered in the ARIA Related Events CRF and should not be reported as AEs.

7.1.4. Temporary Discontinuation

Temporary discontinuation from study intervention treatment is allowed secondary to hospitalization, personal or exceptional circumstances, or to evaluate the study intervention impact on an uncertain AE.

Study intervention may be restarted at the investigator's discretion.

If temporary discontinuation is due to an AE, it should be reported to the sponsor-designated medical monitor. Temporary treatment discontinuation and re-starting should be documented. Restarting treatment after a discontinuation period that is greater than 12 weeks should be discussed between the investigator and sponsor-designated medical monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

- at any time at the participant's own request
- 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 enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, or
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and the study at that time.

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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

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

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Biomarker Efficacy Measures

Florbetapir F18 PET scan

Change in amyloid burden (as assessed with florbetapir F18 PET by personnel blinded to treatment allocation) will be compared in donanemab and aducanumab-treated participants.

8.2. Safety Assessments

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

8.2.1. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3) and following the study-specific recommendations included in Manual of Operations for the study.

8.2.2. Electrocardiograms

For each participant, single 12-lead digital ECGs will be collected during the screening period, according to the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the 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 entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the participant will be assessed by the investigator for symptoms (e.g., palpitations, near syncope, syncope) and to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in participant management is needed.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of collection and any alert reports.

8.2.3. Clinical Safety Laboratory Tests

- See Appendix 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 after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, 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 (e.g., SAE or AE or dose modification), then report the information as an AE.

8.2.4. Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with study intervention 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.

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

C-SSRS

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 NIMH trial group for the purpose of being counterpart to the C-CASA categorization of suicidal events.

8.2.5. Magnetic Resonance Imaging

MRI of the brain will be performed according to the SoA (Section 1.3) and as clinically indicated. Unscheduled MRIs may be performed at the discretion of investigator.

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

The MRI scans will be reviewed by the investigator or qualified designee for immediate participant management. Any clinically significant findings noted at baseline that result in a diagnosis should be recorded as a preexisting condition or AE. MRI scans are read locally and will be sent for analysis to a centralized MRI vendor (blinded to treatment allocation) designated by Lilly. Final MRI eligibility at screening will be determined by the centralized MRI vendor designated by Lilly and the MRI results will be reported to the investigator as “does” or “does not” meet MRI eligibility criteria.

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/safety will be reported back to the investigator.

8.2.6. Hepatic Safety Monitoring

Close hepatic monitoring

Laboratory tests (Appendix 6, Section 10.6), including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5x 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)

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

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

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

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/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/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/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for 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

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

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

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

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

The definitions of the following events can be found in Appendix 3:

- AEs
- SAEs
- 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 or study (see Section 6.8.3).

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.4) 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 Appendix 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event					
AE	Signing of the 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 with study procedures or occurring after receiving PET tracer	Signing of the ICF	Start of intervention	Within 24 hours 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 hours of awareness	SAE CRF	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	90 days after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	N/A
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC 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	PC form	

Abbreviations: AE = adverse event; CRF = case reporting form; ICF = informed consent form; N/A = not applicable; PC = product complaint; PET = positron emission tomography; SAE = serious adverse event.

[a] SAEs after study participation 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

a. 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.

b. After learning of a pregnancy in the female partner of a study participant, the investigator will

    a. obtain a consent to release information from the pregnant female partner directly, and

    b. within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

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

Female participants who become pregnant

a. The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

b. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

c. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

d. A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

e. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

8.3.3. Hypersensitivity Including Infusion-Related Reactions

8.3.3.1. Management of Infusion-Related Reactions

If a systemic hypersensitivity reaction occurs, additional data describing each sign or symptom should be provided to the sponsor in the Hypersensitivity, Anaphylactic, and Infusion-Related Reactions CRF. Participants who experience a systemic hypersensitivity, should have vital signs collected.

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

If a participant experiences a systemic hypersensitivity reaction or infusion-related reaction either involving 2 or more organ systems (for example, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems), or that is severe, additional blood and urine samples should be collected as close to the event as possible, as described in Section 10.2.1. Tryptase and when applicable urine *N*-methylhistamine should be repeated in approximately 4 weeks (and prior to the next infusion, if applicable) to obtain post-event baseline. Laboratory results are provided to the sponsor via the central laboratory and are not needed for clinical management of the participant.

8.3.3.2. Dosing Rechallenge and Premedication for Infusions

Donanemab

Premedication for dosing is not planned. Dosing rechallenge is contraindicated in participants that have experienced a suspected or possible anaphylactic reaction (for example, reaction involving 2 or more organ systems [for example, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems] occurring in close proximity to dosing), in a prior dose (Sampson et al. 2006). For infusion-related reactions which are not suspicious for anaphylaxis, at the investigator's discretion, the participant may continue to receive study intervention. The participant may be premedicated for subsequent doses at investigator's discretion and according to local practice guidelines. Any premedication given will be documented as a concomitant therapy (Section 6.8).

Aducanumab

Investigators should consult the product label and follow local practice.

8.3.4. Adverse Events of Special Interest

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

- ARIA-E
- ARIA-H
- Hypersensitivity, immediate and non-immediate, including infusion-related reactions and anaphylaxis

The topics listed above, as well as other topics which may be subsequently determined by the sponsor, will be subject to enhanced surveillance activities. Additionally, the topics above will be analyzed for presentation in the Clinical Study Report in accordance with the SAP.

8.4. Pharmacokinetics

a. Serum samples will be collected for measurement of serum concentrations of study intervention as specified in the SoA.
b. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
c. 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.
d. Bioanalytical samples collected to measure study intervention will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism, protein binding, or bioanalytical method development/validation work.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

8.6.1. Apolipoprotein E Genotyping

ApoE genotyping is a mandatory part of this study. Blood sampling for ApoE genotyping will be performed 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.

8.6.2. Whole Blood Samples for Pharmacogenetic Research

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

See Appendix 5, Section 10.5 for information regarding genetic research and Appendix 1, Section 10.1.12 for details about sample retention and custody.

8.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including proteins, lipids, and other cellular elements.

Serum and plasma, samples for biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow.

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 study intervention, and/or research method 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 (Section 1.3), venous blood samples will be collected to determine antibody production against donanemab. Antibodies may be further characterized and/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 9.3.6.2. 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 or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

The primary objectives of this study are to demonstrate that donanemab is superior to aducanumab in achieving complete brain amyloid plaque clearance at 6 months in the overall population and the intermediate tau subpopulation. These two objectives will be considered as co-primary, with the 6-month test occurring when all participants have had a chance to receive their 6-month amyloid PET scan.

The parameters of interest for the primary analyses (for both ITT and the intermediate tau subpopulation) are:

- $p_{dona,6m}$: the probability that a participant will achieve complete brain amyloid clearance at 6 months under the donanemab treatment regimen.
- $p_{adu,6m}$: the probability that a participant will achieve complete brain amyloid clearance at 6 months under the aducanumab treatment regimen.

Odds ratio: $OR_{6m} = [(p_{dona,6m})/(1- p_{dona,6m})]/[(p_{adu,6m})/(1- p_{adu,6m})]$

The null and alternative (1-sided) hypotheses to be tested are:

- H_0: $OR_{6m} = 1$
- H_A: $OR_{6m} > 1$

The odds ratio for the overall population and for the intermediate tau subpopulation will be estimated using logistic regression models as described in Section 9.3. The analyses of the two primary end points and the key secondary endpoints will be controlled to be under a 2-sided Type 1 error rate of 5%, or equivalently, a 1-sided rate of 2.5%. The details regarding the testing scheme for these analyses will be described in the SAP.

9.2. Analyses Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set / ITT analysis set	All randomized participants with baseline and at least one post-baseline amyloid PET scan. Participants will be included in the analyses according to the planned intervention.
Intermediate tau set	All randomized participants with baseline and at least one post-baseline amyloid PET scan and a baseline flortaucipir F18 PET scan meeting the intermediate tau criteria.

Participant Analysis Set	Description
Safety analysis set	All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.

The full analysis and intermediate tau sets are used to analyze endpoints related to the amyloid plaque objectives and the safety analysis set is used to analyze the endpoints and assessments related to safety.

9.3. Statistical Analyses

9.3.1. General Considerations

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

Unless otherwise noted, tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 (or equivalently, a 1-sided 0.025 alpha level); 2-sided CIs will be displayed with a 95% confidence level. All tests of interactions between treatment and other factors will be conducted at an alpha level of 0.05.

A suitable approach such as Bretz's graphical approach may be utilized to provide strong control of the study wise Type I error rate for the primary and key secondary hypotheses at an alpha level of 0.05 (Bretz et al. 2009; Bretz et al. 2011). Details on the graphical approach and testing strategy will be specified in the SAP prior to the first participant visit.

All amyloid plaque analyses will follow the ITT principle unless otherwise specified. An ITT analysis is an analysis of data by the groups to which participants are assigned by random allocation, even if the participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.

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 nonmissing observation collected prior to the first administration of study medications. Endpoint is the last nonmissing postbaseline measurement.

To allow for sequential testing, database locks and the testing of corresponding primary and key secondary objectives are expected to occur after all randomized participants have had a chance to complete the scheduled 24-week PET scan, the scheduled 52-week PET scan, and the scheduled 76-week PET scan. Data collected during the immunogenicity and safety follow-up period will be summarized and analyzed separately.

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 clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to first participant visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary

of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.3.1.1. Handling of Missing Data for Efficacy Endpoints

For most efficacy endpoints, participants will be included in the analysis only if baseline and at least one post-baseline measurement are available. For most endpoints analyzed after the 6 month database lock, participants will be included only if both baseline and post-baseline measurements are available. For analyses on endpoints at 12 or 18 months, only participants with baseline and at least one post-baseline measurements will be included and will be analyzed within the framework of the repeated measures models as detailed in the analyses. Sensitivity analyses for endpoints including last observation carried forward or other imputation-based techniques for handling missing data may be considered and will be detailed in the SAP.

9.3.2. Treatment Group Comparability

9.3.2.1. 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.

9.3.2.2. Participant Characteristics

The participant's age, sex, race, height, body weight, body mass index (weight (kg)/[height (m)]2), ApoE ε4 genotype, MMSE, CDR-global score, and having 1 or more first degree relatives with AD at baseline will be recorded.

Baseline characteristics will be summarized by treatment group and the overall population. Summaries will include descriptive statistics for continuous and categorical measures. Fisher's exact test or Pearson's chi-square test will be used for treatment group comparisons of categorical data. For continuous data, analysis of variance, with independent factors for treatment and investigator, will be used.

9.3.2.3. 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). A summary of concomitant medications will be presented as frequencies and percentages for each treatment group. Fisher's exact test will be used to test for treatment differences between groups.

If the start or stop dates of therapies are missing or partial to the degree that determination cannot be made of whether the therapy is prior or concomitant, the therapy will be deemed concomitant.

Prior and concomitant medications will be listed.

Summary tables will also be provided for concomitant anticholinergics that affect cognitive function and acetyl-cholinesterase-inhibitor/memantine medications.

Medications will be coded using the World Health Organization drug dictionary.

9.3.2.4. 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.

9.3.3. Primary Analyses

Proportion of Participants with Amyloid Plaque Clearance at 6 months

The primary objective of this study is to test the hypothesis that participants treated with donanemab will have a significantly greater proportion of participants who reach amyloid plaque clearance compared to participants treated with aducanumab at the 6-month timepoint in both the ITT population and the intermediate tau subpopulation.

As the 6-month timepoint is the first scheduled opportunity to collect a post-baseline florbetapir F18 PET scan, the comparison of donanemab to aducanumab in complete brain amyloid clearance at 6 months will be performed using logistic regression. The logistic regression model will include fixed effect for treatment, ApoE ε4 genotype, and baseline amyloid level. The test for this endpoint will be based on the contrast for the main effect of treatment from this logistic regression model. Treatment effects will be presented using odds ratios and 95% confidence intervals. This analysis will be conducted on the full ITT population and the intermediate tau subpopulation.

9.3.4. Secondary Analyses

The mean change from baseline in amyloid plaque levels at months 6, 12, and 18, and the time to amyloid plaque clearance are the four key secondary endpoints. It is expected that these endpoints will be analyzed sequentially as data for them are available. That is, for any efficacy analyses for 6-month/12-month/18-months endpoints, data will be available at baseline and for all timepoints up to and including the time point in question.

9.3.4.1. Mean Change from Baseline in Amyloid Plaque

Consequently, mean change from baseline in amyloid plaque levels at Month 6 will be analyzed using an analysis of covariance method with the treatment group as fixed effect variable of interest, and APOE e4 genotype, and baseline amyloid levels as the covariates. For the analysis of mean change from baseline at 12 and 18 months, a separate mixed model repeated measures (MMRM) analysis with data up to that specific time point will be used. This model will include the fixed effects of treatment, time, and treatment by time interaction, and APOE e4 genotype, and baseline amyloid level as covariates. Correlation among repeated measures on the same subject will be accounted for by enforcing an unstructured variance covariance matrix among the residuals. If the unstructured covariance structure matrix results in a lack of convergence, the following structures will be used in sequence until convergence is reached: heterogeneous

Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

9.3.4.2. Time to Amyloid Plaque Clearance

Time to amyloid plaque clearance between the two treatment groups will be analyzed and compared using a log-rank test for survival data. Time to amyloid plaque clearance is defined as the earliest time (6/12/18 months) at which the participant reaches plaque levels below a certain pre-defined threshold. Subjects who do not have their plaque cleared by the end of the study period or those who drop out prior to the end of the study without achieving amyloid plaque clearance will be censored at their last available time point. Kaplan-Meier estimates of percent of patients reaching amyloid plaque clearance and p-value from the log-rank test will be used to determine the superiority of donanemab vs aducanumab in lowering time to plaque clearance. Additionally, time to plaque clearance may also be analyzed using a Cox proportional-hazards model. More details on these analyses will be provided in the SAP as appropriate.

9.3.4.3. Proportion of Participants with Amyloid Plaque Clearance

The 12-month and 18-month comparison of proportion of participants with amyloid plaque clearance for donanemab versus aducanumab will include repeated post-baseline amyloid plaque clearance status (Yes/No) measurements and will be analyzed using separate generalized linear mixed model (PROC GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis assuming binomial distribution with a logit link. These models will be analyzed using data for outcomes up to and including the time point in question. The GLIMMIX model will include fixed effects for treatment, month, treatment-by-month interaction, APOE e4 genotype, and baseline amyloid level as covariates. An unstructured variance-covariance matrix will be used to model the correlation among repeated measures on the same individual. If model convergence is not reached, as planned for the MMRM analyses, lesser restrictive variance-covariance structures will be employed until model convergence is attained.

9.3.4.4. Other Outcomes

Analyses of other secondary outcomes such as mean percent change in amyloid levels from baseline at 6, 12, and 18 months, non-inferiority of donanemab at 6 months versus aducanumab at 12 and 18 months with respect to mean change from baseline in amyloid levels, superiority of donanemab at 6 months vs aducanumab at 12 months, will be done using the appropriate models for continuous and binary outcomes for repeated or non-repeated data as specified above. Treatment effects will be estimated using least squares mean differences or odds ratios along with 95% confidence intervals using appropriate contrasts for the treatment main effect or the treatment by time interaction effects from statistical models described above. Further details on analyses for other secondary or exploratory outcomes including defining margins for non-inferiority analyses will be described in the SAP.

9.3.5. Other Safety Analyses

All safety analyses will be made on the safety population. Refer to the SAP for additional details.

9.3.6. Other Analyses

9.3.6.1. Pharmacokinetics Analyses

Data from this study may be combined with data from other studies to better characterize the PK of donanemab, as well as to explore the relationship between exposure and efficacy and/or safety outcomes. In this case, a separate PK analysis plan will be developed, and the results of these analyses will be described in a separate PK report.

9.3.6.2. Evaluation of Immunogenicity

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

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

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

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

9.3.6.3. 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).

9.4. Interim Analysis

An interim analysis may occur for an early efficacy assessment of the primary objective. The timing of the interim analysis may occur when a sufficient number of participants (for example, approximately 75-125) have had a chance to receive their 6-month amyloid PET scan. Regardless of the result of the interim analysis, the study will continue in order to assess the 12- and 18-month objectives.

If the interim analysis is deemed not necessary to be conducted by the sponsor, the primary efficacy analysis will be conducted when all participants have had a chance to receive their 6-month amyloid PET scan. The SAP and blinding plan will describe the potential to conduct an interim analysis in greater detail as well as the testing scheme and alpha spending function to control the Type-I error should the interim be performed. If the interim analysis is conducted, the analysis will be executed through an external DMC.

9.5. Sample Size Determination

Approximately 200 participants will be enrolled and randomized in a 1:1 ratio to the 2 treatment regimens (donanemab and aducanumab). It is expected that approximately 180 participants will complete 6-month florbetapir F18 PET scans (approximately 90 per treatment regimen). It is

further anticipated that approximately 50% of participants randomized will belong to the intermediate tau subpopulation.

This sample size will provide at least 98% power to demonstrate that donanemab is superior to aducanumab in achieving complete amyloid brain plaque clearance individually at 6 months in the overall population and the intermediate tau subpopulation. Power estimates were obtained using specific contrasts for the 6-month time point of treatment by time interaction effect within the framework of generalized linear mixed effect model assuming a logit link.

The assumptions for this power calculation are that 35.7%, 50.1%, and 54.6% of donanemab treated participants reach complete brain amyloid clearance at 6 months, 12 months, and 18 months, respectively. The corresponding complete brain amyloid clearance percentages for aducanumab treated participants are assumed to be 3.0%, 22.8%, and 27.8%, respectively. The simulation for the power calculation and sample size determination was carried out in SAS Enterprise Guide Version 7.15 and all sample size estimates were obtained assuming a 2-sided significance level of 0.05.

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 CIOMS International Ethical Guidelines
    - Applicable ICH GCP Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

10.1.4. Data Protection

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

10.1.5. Committees Structure

A DMC consisting of members external to Lilly will be established. The purpose of the establishment of the DMC is for the potential to conduct an early efficacy analysis for Study AACN. If the interim analysis is not deemed necessary to be conducted by the sponsor, the DMC will not be convened to review study data. The DMC will consist of a minimum of 3 members,

including a physician with expertise in AD and a statistician. No member of the DMC will influence study sites. A SAC will prepare and provide unblinded data to the DMC. The SAC members will not be Lilly employees, but will come from TPOs designated by Lilly. The SAC members will have no contact with sites and no privileges to influence changes to the ongoing study. Further details of the DMC will be described in a 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.

Data

The sponsor provides access to all individual participant data collected during the trial and after anonymization, with the exception of PK, images, or genetic data. Data are available for 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, clinical study report, and blank or annotated CRFs, 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 permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.
- 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 (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered 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 CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

An EDC 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 EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, COA data (participant-focused outcome instrument) and other data will be collected by the participant/caregiver/authorized study personnel, via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

Data collected via the sponsor-provided data capture system(s) will be stored (at third parties). 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/electronic transfers 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 and will be the study start date.

Study or Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

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

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 the study intervention.

Sample Type	**Custodian**	**Retention Period After Last Participant Visit[a]**
Biomarkers	Sponsor or Designee	15 years
PK	Sponsor or Designee	1 year
Genetics	Sponsor or Designee	15 years
Immunogenicity (ADA)	Sponsor or Designee	15 years

Abbreviations: ADA = anti-drug antibody; PK = pharmacokinetic.

[a] Max potential retention unless local requirements differ.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the central laboratory (unless specified otherwise below).
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/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 (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

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	
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	

Clinical Laboratory Tests	Comments
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	
PK Samples – donanemab and aducanumab concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Biomarkers **Additional Testing**	Assayed by Lilly-designated laboratory.
Apolipoprotein E (ApoE)	Results will not be provided to the investigators.
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)	
Immunogenicity (ADA) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Anti-donanemab antibodies	
Anti-donanemab antibodies neutralization	

10.2.1. Clinical Laboratory Tests for Hypersensitivity Events

- Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis or angioedema is suspected.

- Collect sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Sample should be repeated in approximately 4 weeks (and prior to the next infusion, if applicable) to obtain post-event baseline.

The table below summarizes the laboratory parameters that will be evaluated. These laboratory tests are bundled in the hypersensitivity laboratory testing kit.

Hypersensitivity Tests	**Notes** Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
donanemab ADAs (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
donanemab concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators. ***Note*:** Optimally collected between 30 minutes to 2 hours after the start of the event. Do not collect if >12 hours have passed since the hypersensitivity event. If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine sample for *N*-methylhistamine testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine *N*-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine sample following the event. Tryptase and when applicable urine *N*-methylhistamine should be repeated in approximately 4 weeks (and prior to the next infusion, if applicable) to obtain post-event baseline.
N-methylhistamine	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Drug-specific IgE	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Basophil activation test	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigators. ***Note:*** The basophil activation test is an in vitro cell-based assay that only requires a serum sample. It is a surrogate assay for drug-specific IgE but is not specific for IgE.

Complement (C3, C3a, and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.
Cytokine panel (IL-6, IL-1β, and IL-10)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigators.

Abbreviations: ADA = antidrug antibody; IgE = immunoglobulin E; IL = interleukin; PK = pharmacokinetic.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing 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. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/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 PC 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 product complaint and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the PC 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/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 post-mortem 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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in site training material.

SAE Reporting via Paper Form

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

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, 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
WOCBP	Females are considered a WOCBP if • they have had at least one cycle of menses, or • they have Tanner 4 breast development. Any amount of spotting should be considered menarche. If Tanner Staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trial regarding Tanner staging.
Women not of child bearing potential	Females are considered women not of child bearing potential if • they have a congenital anomaly such as Mullerian agenesis, • they are infertile due to surgical sterilization, or • they are post-menopausal. Examples of surgical sterilization include: hysterectomy, bilateral oophorectomy, tubal ligation.
Post-menopausal state	The post-menopausal state should be defined as: 1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or 2. A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, 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 3. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy * Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.
Reproductive Toxicology Studies	Embryo-fetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses, which could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.

10.4.2. Contraception Guidance

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

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/assays including diagnostic tests related to donanemab or other amyloid targeting interventions and AD. Genetic research may consist of the analysis of one 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 clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on donanemab or other amyloid targeting interventions 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

10.6.1. Hepatic Evaluation Testing

See Section 8.2.6 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

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

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)

Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[d]	Anti-actin antibody[b]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

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

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

[c] Assayed ONLY by investigator-designated local laboratory; no central testing available.

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

10.7. Appendix 7: Flortaucipir F18 PET Imaging

Flortaucipir F18 PET scan will be performed after eligibility is established (Section 1.3).

No results will be provided to site investigators, participants, and study partners for the flortaucipir F18 scans. Any significant findings that may be of potential medical concern will be provided for appropriate follow-up

PET Scan-Specific Information

PET Scan Procedures

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

Scan Safety

The primary risk related to flortaucipir F18 PET is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion and cumulatively are shown in the table below and will be provided in the ICF. The safety profile of flortaucipir has been well-characterized in clinical studies and is considered acceptable for a diagnostic radiopharmaceutical. Details on the clinical information to date regarding flortaucipir F18 exposure will be provided in the ICF. More detailed information about the known and expected benefits and risks of flortaucipir F18 can be found in the IB.

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.

The table below shows the effective radiation dose of the Study AACN's PET scans.

	Effective Dose (mSv) per Scan[a]	Number of Scans in First Year[b]	Effective Dose (mSv) for Scans in First Year	Number of Scans in Second Year[b]	Effective Dose (mSv) for Scans in Second Year	Sum of Effective Dose (mSv) for Years 1 and 2
Flortaucipir F18 Scan (10 mCi IV)	9.10	1	9.10	0	0	9.10
Florbetapir F18 Scan (10 mCi IV)	7.43	2	14.86	2	14.86	29.72
Totals		3	23.96	2	14.86	38.82

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.

[b] In the event of an ED scan, up to 1 additional florbetapir F18 scan may be received in 1 year.

Note: In the event a repeat scan is required (for example, the scan is not analyzable), 1 additional flortaucipir F18 and/or 1 additional florbetapir F18 scan may be received in 1 year.

10.8. Appendix 8: Florbetapir F18 PET Imaging

Florbetapir F18 PET scans will be performed as part of the study eligibility criteria to determine participant eligibility for participation in Study AACN. Additional florbetapir F18 PET scans will be performed as indicated in the SoA (Section 1.3).

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-Specific Information

PET Scan Procedures

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

PET Scan Safety

The primary risk related to florbetapir F18 PET is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion and cumulatively are presented in the table in Appendix 7 and will be provided in the ICF. Details on the clinical information to date regarding florbetapir F18 exposure will be provided in the ICF. More detailed information about the known and expected benefits and risks of florbetapir F18 can be found in the United States Package Insert for florbetapir F18 Injection (Amyvid™ package insert, 2012).

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.

10.9. Appendix 9: CDR and MMSE

10.9.1. CDR

The CDR-SB (Hughes et al. 1982; Morris 1993) is a global assessment tool that can be used to effectively evaluate both cognition and function. The tool was initially developed to measure dementia severity and covers 6 categories or "boxes": Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. The CDR global ratings, calculated using an algorithm, range from 0 (no dementia) to 3 (severe dementia) while CDR-SB scores, calculated by adding the box scores, range from 0 to 18 (with higher scores indicative of more impairment). Scoring is determined by a clinician through a semistructured and in-depth interview with both the affected individual and their study partner. The study partner and participant must be interviewed separately. This scale demonstrates acceptable psychometric characteristics (Coley et al. 2011; Cedarbaum et al. 2013) and has been shown to be sensitive enough to detect disease progression, even in populations with less advanced clinical disease (Williams et al. 2013; Wessels et al. 2015).

10.9.2. MMSE

The MMSE is a brief instrument used to assess cognitive function in patients (Folstein et al. 1975). The instrument measures orientation, memory, and attention; 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.

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
Aβ	Amyloid beta
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ApoE	Apolipoprotein E
ARIA	Amyloid-related imaging abnormalities
AST	aspartate aminotransferase
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDR	Clinical Dementia Rating
CDR-SB	CDR-Sum of Boxes
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
COA	clinical outcome assessment
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.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
cSS	cortical superficial siderosis
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography

CTA	Clinical Trial Agreement
D. Bil	direct bilirubin
DNA	deoxyribonucleic acid
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 harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
ECG	Electrocardiogram
EDC	Electronic data capture
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.
EU	European Union
FDA	Food and Drug Administration
GCP	good clinical practice
GGT	Gamma-glutamyl transferase
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

IVIG	intravenous immunoglobulin
IRB	Institutional Review Board
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 allocated 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
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NIMH	National Institute of Mental Health
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PD	pharmacodynamics
PET	positron emission tomography
PI	package insert
PK	pharmacokinetics
PT-INR	Prothrombin time – INR
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
QTL	Quality tolerance limit
SAC	Statistical Analysis Center
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
SoA	Schedule of activities
TBL	Total bilirubin level
TE	Treatment-emergent
TPOs	Third-party organizations
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
WOCBP	Women of childbearing potential

10.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment a: (11-Oct-2021)

Overall Rationale for the Amendment:

This amendment allows for better characterization of the incidence and severity of ARIA at an earlier time point.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Modified "Weeks relative to ~~randomization~~ first infusion".	Clarification. Visits should be scheduled in relation to the first IP infusion.
	Changed V3 interval tolerance from "±7" days to "–7 to +10" days.	To provide additional time to perform and review MRI prior to infusion.
	Added line to collect weight for aducanumab participants.	Aducanumab uses weight-based dosing. Weight is not recorded in the CRF.
	Added MRI at V3. Added text to the Comments field about MRI at V3, including text about MRI timings relative to the first and fourth infusions.	To allow for better characterization of the incidence and severity of ARIA at an earlier time point.
6.5. Dose Modification	Modified description of ARIA events in relation to dose modification and providing data for the ARIA Related Events CRF.	Clarification.
6.8.1. Medications for Alzheimer's Disease	Added "When medically indicated, initiation, increase, or discontinuation of symptomatic treatments for AD is permitted."	Clarification.
7.1.3. Amyloid-Related Imaging Abnormalities (ARIA)	Added note "While most cases of ARIA-E are asymptomatic, serious cases have been reported. Available data suggest serious cases are most likely to occur early in	To provide additional information.

Section # and Name	Description of Change	Brief Rationale
	dosing, after the first, second, or third infusion."	
	Added cross-references to the Manual of Operations regarding information about temporary and permanent discontinuation guidance.	To provide further guidance.
	Modified text regarding considerations related to reinitiating study intervention..	Recommendation of DMC.
	Added instructions to complete the ARIA Related Events CRF in the event of symptomatic ARIA-H.	To provide instructions.
8.2.5. Magnetic Resonance Imaging	Added text to allow performance of unscheduled MRIs.	Clarification.

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