I5T-MC-AACI Protocol Amendment (e)

Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease

NCT04437511

Approval Date: 10-Nov-2022

Title Page

Protocol Title: Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease

Protocol Number: I5T-MC-AACI

Amendment Number: e

Compound: Donanemab (LY3002813)

Study Phase: Phase 3

Short Title: Donanemab in Early Symptomatic Alzheimer's Disease

Acronym: TRAILBLAZER-ALZ 2

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 (e) Electronically Signed and Approved by Lilly on date provided below.

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment d	*05-Oct-2021*
Amendment c	*03-Sep-2021*
Amendment b	*17-Feb-2021*
Amendment a	*14-Dec-2020*
Original Protocol	*30-Jan-2020*

Amendment [e]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment

The main rationale for the amendment is to remove Cohort 1 and Cohort 2 analyses and to update the analysis method for the primary objective.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Removed reference to amendment (d)	Editorial.
	Removed reference to Cohorts 1 and 2	Cohort analysis was not conducted.
1.2 Schema	Removed reference to Cohorts 1 and 2	Cohort analysis was not conducted.
1.3 Schedule of Activities (SoA)	Added GFAP testing	To evaluate potential disease modification.
	Updated “date” to “window” for MRI	Clarification.
	Added text to extend window for flortaucipir F18 PET scan	Improve feasibility.
	Updated notes for Vital signs and temperature to state that orthostatic BP and pulse will be measured at Visits 35, 38, 41, ED[b] and unscheduled visits	Correction.
	Updated footnote a to clarify the timing to	Improve feasibility.

Section # and Name	Description of Change	Brief Rationale
	collect efficacy assessment	
	Added footnote to extend collection of RUD-Lite and QOL-AD and permit collection by phone.	Improve feasibility.
2.1 Study Rationale	Removed reference to amendment (d)	Editorial.
	Added that the primary analysis will test low-medium (intermediate) tau pathology population	Clarification
3 Objectives and Endpoints	Added GFAP as tertiary/exploratory endpoint	To evaluate potential disease modification.
4.1.2 Double-Blind Period (Visit 2 through 21)	Removed reference to Cohort 1	Cohort analysis was not conducted.
6.3 Measures to Minimize Bias: Randomization and Blinding	Removed reference to Cohorts 1 and 2	Cohort analysis was not conducted.
6.4 Study Intervention Compliance	Added text to clarify situation when a complete infusion can be avoided	Clarification.
7.1 Discontinuation of Study Intervention	Added sentence to allow participants with MRI-incompatible pacemakers who discontinue IP permanently to remain in study but not perform MRI.	Allow continued observation of such participants in the study.
7.2 Participant Discontinuation/Withdrawal from the Study	Removed sentence to allow participants with MRI-incompatible pacemakers who discontinue study intervention permanently to remain in study but not perform MRI.	Allow continued observation of such participants in the study.

Section # and Name	Description of Change	Brief Rationale
8.1 Efficacy Assessments	Added text to clarify the timing for efficacy assessment collection	Improve feasibility.
8.1.1 Primary Efficacy Assessment	Added description about iADRS	Editorial.
8.1.2.1 MMSE	Added description about MMSE	Editorial.
8.1.2.3 CDR	Updated description for CDR	Editorial.
8.6.1 Clearance of Amyloid Deposits	Updated florbetapir F18 PET to amyloid PET	Clarification.
9.1 Statistical Hypotheses	Methodology for primary efficacy data updated from Bayesian Disease Progression Model to Natural Cubic Spline. Removed reference to Cohorts 2.	Change from Bayesian analysis framework to frequentist analysis framework while maintaining high statistical power.
9.2 Sample Size Determination	Removed reference to Cohorts 1 and 2. Updated power to reflect Natural Cubic Spline model.	Cohort analysis was not conducted. Reflected power for methodology.
9.3 Populations for Analyses	Removed Section 9.3.1 related to Cohorts 1 and 2.	Cohort analysis was not conducted.
9.4.1 General Considerations	Removed reference to Cohorts 1 and 2.	Cohort analysis was not conducted.
9.4.3 Primary Endpoint(s)	Methodology for primary efficacy data updated from Bayesian Disease Progression Model to Natural Cubic Spline.	Change from Bayesian analysis framework to frequentist analysis framework while maintaining high statistical power.
9.4.4 Secondary Endpoint(s)	Minor updates.	Editorial.

Section # and Name	Description of Change	Brief Rationale
9.5 Interim Analysis	Removed reference to Cohorts 1 and 2.	Cohort analysis was not conducted.
10.1.6 Dissemination of Clinical Study data	Removed reference to Cohort 1.	Cohort analysis was not conducted
10.2 Clinical Laboratory Tests	Added GFAP testing	To evaluate potential disease modification
10.8 Appendix 8	Update to interim analysis definition.	Clarification.
	Added DSST to the list	

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease

Short Title: Donanemab in Early Symptomatic Alzheimer's Disease

Rationale:

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 Alzheimer's disease (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. The clinical strategy for donanemab identifies early symptomatic AD patients with existing brain amyloid load, as measured using the amyloid plaque biomarker florbetapir F18 positron emission tomography (PET) imaging in conjunction with the presence of tau pathology in the brain. 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 mild cognitive impairment (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.

Study I5T-MC-AACI (AACI) is a Phase 3, double-blind, placebo-controlled study to evaluate the safety and efficacy of N3pG antibody (donanemab) in patients with early symptomatic AD (prodromal AD and mild dementia due to AD) with the presence of brain tau pathology. Study AACI will assess whether removal of existing amyloid plaque can slow the progression of the disease as assessed by clinical outcomes for cognition and function, and by imaging biomarker measures of disease pathology and neurodegeneration over 76 weeks of double-blind observation.

Study AACI expands the patient population compared to the prior Phase 2 study by including participants with high tau pathology. The primary analysis will test the low-medium (intermediate) tau pathology population and the overall population (low-medium and high tau pathology).

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of donanemab versus placebo on clinical progression in participants with early symptomatic AD	iADRS change from baseline through Week 76 in at least one of • the low-medium tau pathology population or • the overall population
Secondary	
To assess the effect of donanemab versus placebo on clinical progression in participants with early symptomatic AD	Change from baseline through Week 76 in at least one of • the low-medium tau pathology population or • the overall population as measured by: • CDR-SB • ADAS-Cog_{13} score • ADCS-iADL score • MMSE score
To assess the effect of donanemab versus placebo on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline through Week 76 as measured by florbetapir F18 PET scan
To assess the effect of donanemab versus placebo on brain tau deposition	Change in brain tau deposition from baseline through Week 76 as measured by flortaucipir F18 PET scan
To assess the effect of donanemab versus placebo on brain region volumes	Change in volumetric MRI measures from baseline through Week 76

Objectives	Endpoints
To evaluate safety and tolerability of donanemab	Standard safety assessments: • Spontaneously reported AEs • Clinical laboratory tests • Vital sign and body weight measurements • 12-lead ECGs • Physical and neurological examinations MRI (ARIA and emergent radiological findings) Infusion related reactions C-SSRS
To assess peripheral PK and presence of anti-donanemab antibodies	Plasma PK of donanemab ADAs against donanemab including • treatment-emergent ADAs • neutralizing antibodies

Abbreviations: AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog_{13} = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living; AE = adverse event; ARIA = amyloid-related imaging abnormalities; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics

Overall Design

Study AACI is a multicenter, randomized, double-blind placebo-controlled, Phase 3 study of donanemab in participants with early symptomatic AD. Participants who meet entry criteria will be randomized in a 1:1 ratio to one of the following treatment groups:

- Donanemab: 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W
- Placebo

After 76 weeks, participants will be assigned to donanemab or placebo based on criteria described in Section 4.1.3.

The maximum total duration of study participation for each participant, including screening and the post-treatment follow-up periods, is up to 205 weeks:

- Lead-In: any time prior to complete screening
- Complete Screening: up to 7 weeks
- Double-Blind: 76 weeks
- Extension: 78 weeks

- Follow-Up: up to 44 weeks

The maximum duration of treatment is 150 weeks.

Scheduled Reduction of Donanemab to Placebo

Participants whose amyloid plaque reduction as measured by florbetapir F18 PET scans at Visit 8 (Week 24), Visit 15 (Week 52), Visit 21 (Week 76), Visit 28 (Week 102), or Visit 35 (Week 130) meets criteria will have a double-blind dose reduction of donanemab to IV placebo for the remaining duration of the study.

These dose reduction rules are defined by the sponsor.

Participant randomization will be stratified by investigative site and tau pathology (low-medium versus high).

Disclosure Statement: This is a parallel, double-blind treatment study with 2 treatment groups.

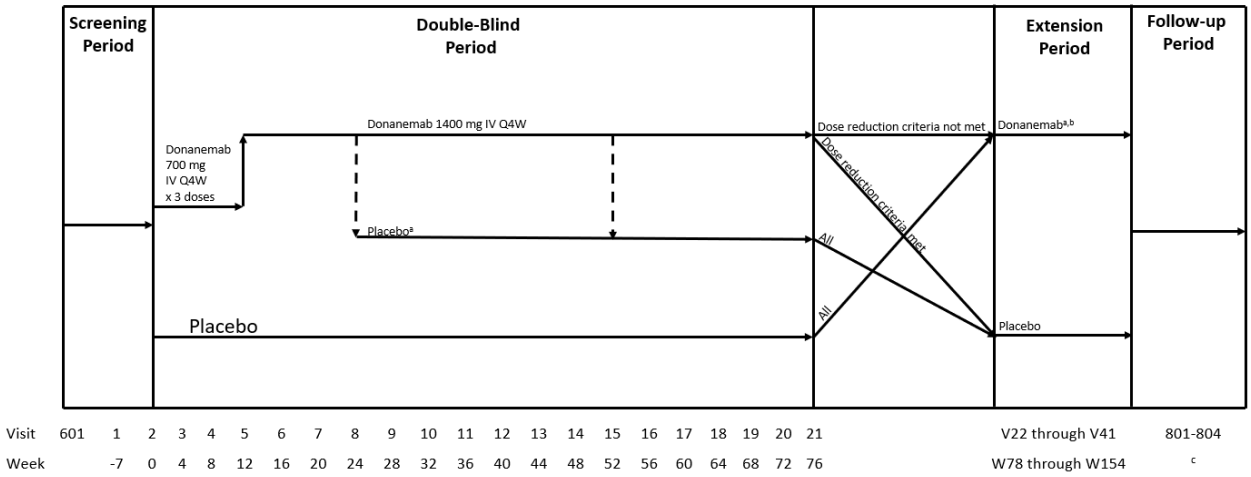
Number of Participants:

Approximately 1800 participants will be randomized in the trial.

It is anticipated that approximately two-third of participants have low-medium tau and approximately one-third of participants have high tau pathology.

External Data Monitoring Committee: Yes

1.2. Schema



Abbreviations: IP = investigational product; IV = intravenous; PET = positron emission tomography; Q4W = every 4 weeks; V = Visit.

[a] Dosing decisions are based on reduction in amyloid burden as determined by the florbetapir F18 PET scan at Weeks 24, 52, 76, 102, and 130.

[b] Donanemab dosing schedule in the extension period is described in Section 4.1.3.

[c] The follow-up period begins 12 weeks after the final administration of IP, and Visits 801 through 804 are scheduled as described in Section 4.1.4. Investigator will be notified if participant is not required to complete all follow-up visits (V801-804).

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

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	Recommend screening to not extend past 63 days. Sponsor may strictly control toward end of study enrollment.
Tolerance Interval for Visit (Days)	Can be done at any time	≤49 before V2	
Entry and Administrative			
Abbreviated (or Full) Informed Consent – participant and study partner	X		The Abbreviated Informed Consent grants consent only for procedures and assessments marked under V601. Study partner(s) are not required to complete the abbreviated Informed Consent.
Full Informed Consent – participant and study partner		X	Do not collect if Full Informed Consent was collected at V601.
Contact IWRS – register visit	X	X	For all visits.
Participant number assigned via IWRS	X		
Demographics	X		
Habits		X	
Inclusion/exclusion review		X	
Physical/neurological examination		X	
Concomitant medications		X	
Preexisting conditions		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	Recommend screening to not extend past 63 days. Sponsor may strictly control toward end of study enrollment.
Tolerance Interval for Visit (Days)	Can be done at any time	≤49 before V2	
Safety Assessments			
Vital signs		X	Sitting BP and pulse will be measured after approximately 5 minutes in the sitting position only. Temperature will also be collected with sitting vitals.
Height and weight		X	
ECG		X	
C-SSRS Baseline and Screening		X	
Self-Harm Supplement Form		X	
Self-Harm Follow-up Form		X	Required if triggered by the Self-Harm Supplement Form per instructions.
Chemistry		X	
Hematology		X	
Entry Diagnostics			
MMSE	X		Participants who do not meet MMSE criteria are not to have any other screening procedures performed. See Section 5.4 for rescreening criteria. See footnote a.
P-tau	X		
ApoE	X		Collect unless not allowed or unfeasible due to local regulations. The ApoE genotype sample may be collected at an alternative visit if it cannot be collected at screening.
Pharmacogenetics sample	X		Collect unless not allowed or unfeasible due to local regulations.

	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	Recommend screening to not extend past 63 days. Sponsor may strictly control toward end of study enrollment.
Tolerance Interval for Visit (Days)	Can be done at any time	≤49 before V2	
Exploratory biomarker sample	X		Collect unless not allowed or unfeasible due to local regulations.
Screening PET Scans and MRI			
Flortaucipir F18 PET scan		X	See footnote b.
MRI		X	See footnote b.
Florbetapir F18 PET scan		X	See footnote b.

Visits 2 through 14

After visit 5, visits without cognitive and functional scales are eligible to be conducted remotely, via mobile healthcare coordinated with and approved by the sponsor, if permitted by local regulations.

Visit No.:	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Notes
Week Relative to Randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	Procedures for some visits may take more than 1 day.
Tolerance Interval for Visit (Days)	0	−7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Inclusion/ exclusion review	X													Confirm that the participant has met all V1 eligibility criteria before proceeding to V2 procedures.
Contact IWRS – register visit	X	X	X	X	X	X	X	X	X	X	X	X	X	For all visits.
Contact IWRS – dispensation of IP	X	X	X	X	X	X	X	X	X	X	X	X	X	For visits where IP will be dispensed.
Physical/ neurological examination	X			X			X			X				V11 is a brief physical and neurological exam, as described in Section 8.2.1. Any clinically significant changes from baseline on physical/neurological examinations should be noted on the AE CRF.
Previous/ concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Preexisting conditions/ adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	
IP administered	X	X	X	X	X	X	X	X	X	X	X	X	X	Administered by IV infusion. The participant should be observed for a minimum of 60 minutes following the end of each infusion.

Visit No.:	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Notes
Week Relative to Randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	Procedures for some visits may take more than 1 day.
Tolerance Interval for Visit (Days)	0	−7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Efficacy Measures														
ADAS-Cog_{13}	X			X			X			X				See footnote a.
ADCS-ADL	X			X			X			X				See footnote a.
CDR	X			X			X			X				See footnote a.
MMSE	X			X			X			X				See footnote a.
DSST medicines version	X			X			X			X				Collect via eCOA only when available.
Safety Assessments														
C-SSRS since last visit	X	X	X	X	X	X	X	X	X	X	X	X	X	If visit is not conducted on site, may collect by phone.
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	X	X	X	If visit is not conducted on site, may collect by phone.
Self-Harm Follow-up Form	X	X	X	X	X	X	X	X	X	X	X	X	X	Required if triggered by Self-Harm Supplement Form per instructions. If visit is not conducted on site, may collect by phone.
Laboratory Tests and Sample Collections[c]														
Hematology	X			X			X			X				
Clinical Chemistry and eGFR (CKD-EPI)	X			X			X			X				eGFR calculated by Lilly-designated lab.
Urinalysis and Urinary protein/creatinine ratio (UPCR)	X						X							UPCR calculated by Lilly-designated lab.

Visit No.:	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Notes
Week Relative to Randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	Procedures for some visits may take more than 1 day.
Tolerance Interval for Visit (Days)	0	−7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
PK Samples (Predose)		X	X	X	X		X			X				Do not collect if the last IP infusion was >6 months prior to the scheduled visit. Predose collections may be collected from the IV site prior to the infusion.
PK Samples (Postdose)	X			X			X							Do not collect if the last IP infusion was >6 months prior to the scheduled visit. Collect within 30 minutes of IP infusion completion. Collect from the arm that IP was not administered through.
Immunogenicity (ADA) Samples	X	X	X	X	X		X			X				
NfL/GFAP	X			X			X			X				
P-tau	X			X			X			X				
Aβ	X			X			X			X				
Exploratory Biomarker Samples	X			X			X			X				Collect unless not allowed or unfeasible due to local regulations.
Other Safety Measures														
Weight	X			X			X			X				
Vital signs and temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	Sitting BP, pulse, and temperature will be measured at all visits. In addition, orthostatic BP and pulse will be measured at V2, V5, V8, V11, and unscheduled visits.
ECG	X						X							Perform prior to administration of IP. Unscheduled ECGs may be performed at the discretion of investigator.

Visit No.:	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Notes
Week Relative to Randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	Procedures for some visits may take more than 1 day.
Tolerance Interval for Visit (Days)	0	−7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
MRI		X		X			X							Perform at least 1 day prior to or after cognitive and functional tests, if applicable. 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. MRI at V5 may occur up to 14 days before the scheduled visit window without protocol deviation. Unscheduled MRIs may be performed at the discretion of investigator, for example if titration is delayed due to temporary suspension of infusions.
Additional Efficacy Measures														
Florbetapir F18 PET scan							X							

Visits 15 through 21 and EDa

Visits without cognitive and functional scales are eligible to be conducted remotely, via mobile healthcare coordinated with and approved by the sponsor, if permitted by local regulations.

Visit No.:	15	16	17	18	19	20	21	EDa	Notes
End of Week Relative to Study Medication Start	52	56	60	64	68	72	76		If a participant discontinues before V21, perform EDa assessments, then the follow-up visits 12 weeks after the last dose received.
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7		
Contact IWRS – register visit	X	X	X	X	X	X	X	X	For all visits.
Contact IWRS – dispensation of IP	X	X	X	X	X	X			For visits where IP will be dispensed.
Physical/neurological examination	X			X			X	X	V18 is a brief physical and neurological exam, as described in Section 8.2.1. Any clinically significant changes from baseline on physical/neurological examinations should be noted on the AE CRF.
Previous/concomitant medications	X	X	X	X	X	X	X	X	
Preexisting conditions/adverse events	X	X	X	X	X	X	X	X	
IP administered	X	X	X	X	X	X			Administered by IV infusion. The participant should be observed for a minimum of 60 minutes following the end of each infusion.
Efficacy Measures									
ADAS-Cog_{13}	X			X			X	X	See footnote a.
ADCS-ADL	X			X			X	X	See footnote a.
CDR	X			X			X	X	See footnote a.
MMSE	X			X			X	X	See footnote a.
DSST medicines version	X			X			X	X	Collect via eCOA only when available.
Safety Assessment									
C-SSRS since last visit	X	X	X	X	X	X	X	X	If visit is not conducted on site, may collect by phone.

Visit No.:	15	16	17	18	19	20	21	EDa	Notes
End of Week Relative to Study Medication Start	52	56	60	64	68	72	76		If a participant discontinues before V21, perform EDa assessments, then the follow-up visits 12 weeks after the last dose received.
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7		
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	If visit is not conducted on site, may collect by phone.
Self-Harm Follow-up Form	X	X	X	X	X	X	X	X	Required if triggered by the Self-Harm Supplement Form per instructions. If visit is not conducted on site, may collect by phone.
Laboratory Tests and Sample Collections[c]									
Hematology	X			X			X	X	
Clinical Chemistry and eGFR (CKD-EPI)	X			X			X	X	eGFR calculated by Lilly-designated lab.
Urinalysis and Urinary protein/creatinine ratio (UPCR)							X	X	UPCR calculated by Lilly-designated lab.
Pharmacokinetic (PK) Samples (Predose)	X			X					Do not collect if the last IP infusion was >6 months prior to the scheduled visit. May be collected from the IV site prior to the infusion.
Pharmacokinetic (PK) Samples (Postdose)	X								Do not collect if the last IP infusion was >6 months prior to the scheduled visit. Collect within 30 minutes of IP infusion completion. Collect from the arm that IP was not administered through.
PK Samples (Random)							X	X	Do not collect if the last IP infusion was >6 months prior to the scheduled visit.
Immunogenicity (ADA) Samples	X						X	X	
NfL/GFAP	X			X			X	X	
P-tau	X			X			X	X	
Aβ	X			X			X	X	
Exploratory Biomarker Samples	X			X			X	X	Collect unless not allowed or infeasible due to local regulation.

Visit No.:	15	16	17	18	19	20	21	EDa	Notes
End of Week Relative to Study Medication Start	52	56	60	64	68	72	76		If a participant discontinues before V21, perform EDa assessments, then the follow-up visits 12 weeks after the last dose received.
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7		
Other Safety Measures									
Weight	X			X			X	X	
Vital signs and temperature	X	X	X	X	X	X	X	X	Sitting BP, pulse, and temperature will be measured at all visits. In addition, orthostatic BP and pulse will be measured at visits 15, 18, 21, EDa, and unscheduled visits.
ECG	X						X	X	Perform prior to administration of IP. Unscheduled ECGs may be performed at the discretion of investigator.
MRI	X						X	X	Perform at least 1 day prior to or after cognitive and functional tests, if applicable. Unscheduled MRIs may be performed at the discretion of investigator, for example if titration is delayed due to temporary suspension of infusions.
Additional Efficacy Measures									
Flortaucipir F18 PET Scan							X	X	Perform ≥16 hours apart from the florbetapir F18 PET scan, if applicable. Collect at EDa only if EDa occurs >36 weeks after randomization. V21 flortaucipir F18 PET scan may be performed at least 1 day after completion of V20 through the end of the V21 window. The flortaucipir F18 PET scan at V21 and EDa may become optional or regionally dependent at sponsor discretion.
Florbetapir F18 PET scan	X						X	X	Perform ≥16 hours apart from the flortaucipir F18 PET scan, if applicable. Collect at EDa only if EDa occurs at ≥3 or more IP infusions after the last florbetapir F18 PET scan.

Extension Period: Visits 22 through 34

After Visit 25, visits without cognitive and functional scales are eligible to be conducted remotely, via mobile healthcare coordinated with and approved by the sponsor, if permitted by local regulations.

Visit No.:	V22	V23	V24	V25	V26	V27	V28	V29	V30	V31	V32	V33	V34	Notes
Week Relative to Randomization	78	82	86	90	94	98	102	106	110	114	118	122	126	Procedures for some visits may take more than 1 day.
Tolerance Interval for Visit (Days)	±7	–7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Contact IWRS – register visit	X	X	X	X	X	X	X	X	X	X	X	X	X	For all visits.
Contact IWRS – dispensation of IP	X	X	X	X	X	X	X	X	X	X	X	X	X	For visits where IP will be dispensed.
Brief physical/neurological examination				X			X			X				As described in Section 8.2.1. Any clinically significant changes from baseline on physical/neurological examinations should be noted on the AE CRF.
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Preexisting conditions/adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	
IP administered	X	X	X	X	X	X	X	X	X	X	X	X	X	Administered by IV at study site. The participant should be observed for a minimum of 60 minutes following the end of each infusion.
Efficacy Measures														
ADAS-Cog_{13}				X			X			X				See footnote a.
ADCS-ADL				X			X			X				See footnote a.
CDR				X			X			X				See footnote a.
MMSE				X			X			X				See footnote a.
DSST medicines version				X			X			X				Collect via eCOA only when available.

Visit No.:	V22	V23	V24	V25	V26	V27	V28	V29	V30	V31	V32	V33	V34	Notes
Week Relative to Randomization	78	82	86	90	94	98	102	106	110	114	118	122	126	Procedures for some visits may take more than 1 day.
Tolerance Interval for Visit (Days)	±7	–7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
RUD-Lite	X						X							Collect RUD-Lite at W78 only if not collected at W76 via AACI Addendum 4. See footnote e.
QOL-AD	X						X							Collect QOL-AD at W78 only if not collected at W76 via AACI Addendum 4. See footnote e.
Safety Assessments														
C-SSRS since last assessment				X			X			X				
Laboratory Tests and Sample Collections														
Hematology				X			X							
Clinical chemistry and eGFR (CKD-EPI)				X			X							eGFR calculated by Lilly-designated lab.
PK Samples (Predose)				X			X							Do not collect if the last IP infusion was >6 months prior to the scheduled visit. Predose collections may be collected from the IV site prior to the infusion.
Immunogenicity (ADA) Samples				X			X							
NfL/GFAP				X			X			X				
P-tau				X			X			X				
Aβ				X			X			X				
Exploratory Biomarker Samples				X			X			X				Collect unless not allowed or unfeasible due to local regulations.
Other Safety Measures														
Weight				X			X			X				

Visit No.:	V22	V23	V24	V25	V26	V27	V28	V29	V30	V31	V32	V33	V34	Notes
Week Relative to Randomization	78	82	86	90	94	98	102	106	110	114	118	122	126	Procedures for some visits may take more than 1 day.
Tolerance Interval for Visit (Days)	±7	–7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Vital signs and temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	Sitting BP, pulse, and temperature will be measured at all visits. In addition, orthostatic BP and pulse will be measured at V22, V25, V28, V31, and unscheduled visits.
MRI		X		X			X							Perform at least 1 day prior to or after cognitive and functional tests, if applicable. MRI at V23 is to be performed and reviewed prior to V23 infusion and may occur no sooner than 21 days after the V22 infusion. If infusions are suspended after the first, second, or third dose of the extension period, an MRI is to be performed and reviewed prior to the fourth infusion. MRI at V25 is to be performed and reviewed prior to V25 infusion. MRI at V25 may occur up to 14 days before the scheduled visit window without protocol deviation. Unscheduled MRIs may be performed at the discretion of investigator, for example if titration is delayed due to temporary suspension of infusions.
Additional Efficacy Measures														
Florbetapir F18 PET scan							X							

Visits 35 through 41, EDb, and follow-up

Visits without cognitive and functional scales are eligible to be conducted remotely, via mobile healthcare coordinated with and approved by the sponsor, if permitted by local regulations.

Visit No.:	V35	V36	V37	V38	V39	V40	V41	EDb	801-804	Notes
Week Relative to Randomization	130	134	138	142	146	150	154		[d]	Procedures for some visits may take more than 1 day. If a participant discontinues after V21 and before V41, perform EDb assessments, then the follow-up visits 12 weeks after the last dose received.
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7		±14	
Contact IWRS – register visit	X	X	X	X	X	X	X	X	X	For all visits.
Contact IWRS – dispensation of IP	X	X	X	X	X	X				For visits where IP will be dispensed.
Brief physical/neurological examination	X			X			X	X		As described in Section 8.2.1. Any clinically significant changes from baseline on physical/neurological examinations should be noted on the AE CRF.
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	
Preexisting conditions/adverse events	X	X	X	X	X	X	X	X	X	
IP administered	X	X	X	X	X	X				Administered by IV at study site. The participant should be observed for a minimum of 60 minutes following the end of each infusion.
Efficacy Measures										
ADAS-Cog_{13}	X			X			X	X		See footnote a.
ADCS-ADL	X			X			X	X		See footnote a.
CDR	X			X			X	X		See footnote a.
MMSE	X			X			X	X		See footnote a.
DSST medicines version	X			X			X	X		Collect via eCOA only when available.
RUD-Lite	X						X	X		Collect at EDb only if EDb occurs at ≥12 weeks after the prior RUD-Lite assessment. See footnote e.
QOL-AD	X						X	X		Collect at EDb only if EDb occurs at ≥12 weeks after the prior QOL-AD assessment. See footnote e.

Visit No.:	V35	V36	V37	V38	V39	V40	V41	EDb	801-804	Notes
Week Relative to Randomization	130	134	138	142	146	150	154		[d]	Procedures for some visits may take more than 1 day. If a participant discontinues after V21 and before V41, perform EDb assessments, then the follow-up visits 12 weeks after the last dose received.
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7		±14	
Safety Assessments										
C-SSRS since last assessment	X			X			X	X	X	
Self-Harm Supplement Form									X	If follow-up visit is not conducted on site, may collect by phone.
Self-Harm Follow-up Form									X	Required if triggered by the Self-Harm Supplement Form per instructions. If follow-up visit is not conducted on site, may collect by phone.
Hematology	X						X	X		
Clinical Chemistry and eGFR (CKD-EPI)	X						X	X		eGFR calculated by Lilly-designated lab.
PK Samples (Predose)	X									Do not collect if the last IP infusion was >6 months prior to the scheduled visit. Predose collections may be collected from the IV site prior to the infusion.
PK (Random)							X	X	X	
Immunogenicity (ADA) Samples	X						X	X	X	
NfL/GFAP	X			X			X	X		
P-tau	X			X			X	X		
Aβ	X			X			X	X		
Exploratory Biomarker Samples	X			X			X	X		Collect unless not allowed or unfeasible due to local regulations.
Other Safety Measures										
Weight	X			X			X	X		
Vital signs and temperature	X	X	X	X	X	X	X	X	X	Sitting BP, pulse, and temperature will be measured at all visits. In addition, orthostatic BP and pulse will be measured at Visits 35, 38, 41, ED[b] and unscheduled visits.

Visit No.:	V35	V36	V37	V38	V39	V40	V41	EDb	801-804	Notes
Week Relative to Randomization	130	134	138	142	146	150	154		[d]	Procedures for some visits may take more than 1 day. If a participant discontinues after V21 and before V41, perform EDb assessments, then the follow-up visits 12 weeks after the last dose received.
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7		±14	
MRI	X						X	X		Perform at least 1 day prior to or after cognitive and functional tests, if applicable. Unscheduled MRIs may be performed at the discretion of investigator, for example if titration is delayed due to temporary suspension of infusions.

Visit No.:	V35	V36	V37	V38	V39	V40	V41	EDb	801-804	Notes
Week Relative to Randomization	130	134	138	142	146	150	154		[d]	Procedures for some visits may take more than 1 day. If a participant discontinues after V21 and before V41, perform EDb assessments, then the follow-up visits 12 weeks after the last dose received.
Tolerance Interval for Visit (Days)	±7	±7	±7	±7	±7	±7	±7		±14	
Flortaucipir F18 PET scan							X	X		Perform ≥16 hours apart from the florbetapir F18 PET scan, if applicable. Collect at EDb only if EDb occurs >36 weeks after V22. V41 flortaucipir F18 PET scan may be performed at least 1 day after completion of V40 through the end of the V41 window. The flortaucipir F18 PET scan at V41 and EDb may become optional or regionally dependent at sponsor discretion.
Florbetapir F18 PET scan	X						X	X		Perform ≥16 hours apart from the flortaucipir F18 PET scan, if applicable. Collect at EDb only if EDb occurs at ≥3 or more IP infusions after the last florbetapir F18 PET scan.

Abbreviations: Aβ = amyloid beta; ADA = anti-drug antibody; ADAS-Cog_{13} = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; AE CRF = adverse event case report form; ApoE = Apolipoprotein E; BP = blood pressure; CDR = Clinical Dementia Rating Scale; CKD-EPI = chronic kidney disease epidemiology collaboration; C-SSRS = Columbia Suicide Severity Rating Scale; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; eCOA = electronic Clinical Outcome Assessment; EDa = early discontinuation a; EDb = early discontinuation b; eGFR = estimated glomerular filtration rate; GFAP = glial fibrillary acidic protein; IP = investigational product; IWRS = interactive web-response system; IV = intravenous; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; NfL = neurofilament light chain; No. = Number; PET = positron emission tomography; PK = pharmacokinetics; P-tau = phosphorylated tau; QOL-AD = Quality of Life in Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia – Lite Version; UPCR = urinary protein/creatinine ratio; V = Visit.

a Administer the ADAS-Cog_{13}, ADCS-ADL, CDR, MMSE and DSST medicines version prior to medical procedures that could be stressful to the participant (blood draws, etc.). These tests include the audio voice recording of the rater's questions and the participant and study partner responses to assessment questions. If an efficacy assessment (ADAS-Cog13, ADCS-ADL, CDR, MMSE, or DSST medicines version) cannot be collected at the scheduled visit, it may be collected at the next opportunity, if within 30 days of the scheduled assessment.

b The participant should meet MMSE eligibility criteria before the screening flortaucipir F18 PET scan, MRI, and florbetapir F18 PET scan. Perform the flortaucipir F18 and florbetapir F18 PET scans ≥16 hours apart from each other. If results are received after the screening window, the participant remains eligible contingent on meeting the other eligibility criteria. If the investigator feels it is necessary, a repeat of screening labs may be performed. A historical florbetapir and/or flortaucipir PET scan may be submitted to be considered for eligibility if performed within 6 months of randomization. The acceptance of a historical scan is at the discretion of the sponsor.

c Unscheduled lab tests may be performed at the discretion of the investigator. Collect labs prior to administration of IP, unless otherwise noted. Record the date and times of sample collection on the Lab Requisition Form.

d The follow-up period begins 12 weeks after the final administration of IP, and Visits 801 through 804 are scheduled as described in Section 4.1.4.

e If RUD-Lite or QOL-AD cannot be collected at the scheduled visit, it may be collected at the next opportunity. If visit is not conducted on site, it maybe collected by phone.

2. Introduction

2.1. Study Rationale

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 Alzheimer's disease (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. The clinical strategy for donanemab identifies early symptomatic AD patients with existing brain amyloid load, as measured using the amyloid plaque biomarker florbetapir F18 positron emission tomography (PET) imaging in conjunction with the presence of tau pathology in the brain. 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 mild cognitive impairment (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.

Study I5T-MC-AACI (AACI) is a Phase 3, double-blind, placebo-controlled study to evaluate the safety and efficacy of N3pG antibody (donanemab) in Participants with early symptomatic AD (prodromal AD and mild dementia due to AD) with the presence of brain tau pathology. Study AACI will assess whether removal of existing amyloid plaque can slow the progression of the disease as assessed by clinical outcomes for cognition and function, and by imaging biomarker measures of disease pathology and neurodegeneration over 76 weeks of double-blind observation.

Study AACI expands the Participant population compared to the prior Phase 2 study by including participants with high tau pathology. The primary analysis will test low-medium (intermediate) tau pathology population and the overall population.

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 magnetic resonance imaging (MRI) by the stage of MCI. 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).

2.2.1. Donanemab Nonclinical Studies

The safety of donanemab, a plaque-specific monoclonal antibody, was assessed in a 6-week toxicity study in cynomolgus monkeys, including evaluations of safety pharmacology and toxicokinetics. The administration of donanemab in monkeys of up to a maximum dose of 100 mg/kg/week (bolus intravenous [IV]) for 6 weeks resulted in no drug-related findings. Repeat-dose hazard identification studies of up to 6 months' duration were conducted in the aged PDAPP (APPV717F) transgenic mouse model of Aβ deposition to investigate potential effects related to clearance of Aβ from the brain. In addition, a specialized 3-month study to investigate the potential for cerebral amyloid angiopathy-associated microhemorrhages was conducted in aged PDAPP transgenic mice. These studies in the PDAPP mouse were conducted with mE8c (LSN3026818), a murine analog antibody of donanemab, to avoid limitations due to potential immunogenicity from repeated administration of the humanized antibody to the mouse.

No drug-related findings occurred in the hazard identification studies in PDAPP mice at mE8c doses of up to 100 mg/kg/week (the highest dose tested). Treatment of PDAPP mice with mE8c at 12.5 mg/kg/week for 3 months did not exacerbate cerebral amyloid angiopathy-associated microhemorrhages at a dose that produced a maximum pharmacological response (reduction in deposited brain Aβ) in these animals.

See the Investigator's Brochure (IB) for additional details regarding nonclinical donanemab studies.

2.2.2. Donanemab Clinical Studies

Two Phase 1 studies (Study I5T-MC-AACC [AACC] and Study I5T-MC-AACD [AACD]) have been conducted in participants with MCI and mild-to-moderate AD. In both studies, rapid and sustained reduction in cerebral amyloid plaques were observed with donanemab doses ≥10 mg/kg.

One Phase 2 study (Study I5T-MC-AACG [AACG]) has been conducted in participants with early symptomatic AD and intermediate (low to medium) cerebral tau burden. Treatment with donanemab compared with placebo resulted in a significant slowing of disease progression, as measured by the integrated Alzheimer's Disease Rating Scale (iADRS; Wessels et al. 2015) as well as deep and rapid reduction in amyloid plaque level. Safety findings observed in clinical development include ARIAs, IRRs, and the presence of ADAs (Mintun et al. 2021).

See the IB for detailed safety and PK information regarding donanemab.

2.3. Benefit/Risk Assessment

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of donanemab versus placebo on clinical progression in participants with early symptomatic AD	iADRS change from baseline through Week 76 in at least one of • the low-medium tau pathology population or • the overall population
Secondary	
To assess the effect of donanemab versus placebo on clinical progression in participants with early symptomatic AD	Change from baseline through Week 76 in at least one of • the low-medium tau pathology population or • the overall population as measured by: • CDR-SB • ADAS-Cog$_{13}$ score • ADCS-iADL score • MMSE score
To assess the effect of donanemab versus placebo on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline through Week 76 as measured by florbetapir F18 PET scan
To assess the effect of donanemab versus placebo on brain tau deposition	Change in brain tau deposition from baseline through Week 76 as measured by flortaucipir F18 PET scan
To assess the effect of donanemab versus placebo on brain region volumes	Change in volumetric MRI measures from baseline through Week 76
To evaluate safety and tolerability of donanemab	Standard safety assessments: • Spontaneously reported AEs • Clinical laboratory tests • Vital sign and body weight measurements • 12-lead ECGs

Objectives	Endpoints
	• Physical and neurological examinations MRI (ARIA and emergent radiological findings) Infusion related reactions C-SSRS
To assess peripheral PK and presence of anti-donanemab antibodies	Plasma PK of donanemab ADAs against donanemab including • treatment-emergent ADAs • neutralizing antibodies
Tertiary/Exploratory	
To assess the effect of donanemab versus placebo on blood-based biomarkers	Plasma • NfL • GFAP • P-tau • Aβ levels
To assess the effect of donanemab versus placebo on cognition	Change in DSST - Medicines Version from baseline through Week 76.
To assess the efficacy of donanemab to prolong time in the current disease state	CDR global score CDR-SB
Extension Period	
To evaluate the clinical efficacy between early start participants versus delayed start participants treated with donanemab	iADRS, CDR-SB, ADAS-Cog$_{13}$, ADCS-iADL, and MMSE score endpoint will be evaluated for the extension period following the approach outlined in Liu-Seifert et al. (2015)
To evaluate if continued treatment with donanemab beyond 72 weeks results in amyloid clearance in participants who had not met dose reduction criteria during the double-blind period	Change in brain amyloid plaque deposition from baseline through Week 154 as measured by florbetapir F18 PET scan

To evaluate amyloid plaque re-accumulation in participants who met dose reduction criteria during double-blind and extension periods	Change in brain amyloid plaque deposition from time of meeting dose reduction criteria through Week 154 as measured by florbetapir F18 PET scan
To evaluate the quality of life, dependency level, healthcare resource utilization, and level of formal and informal care attributable to AD between early start participants versus delayed start participants treated with donanemab	QOL-AD, dependency level (derived from ADCS-ADL), and RUD-Lite will be evaluated for the extension period following the approach outlined in Liu-Seifert et al. (2015)

Abbreviations: Aβ = amyloid beta; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog_{13} = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study - Activities of Daily Living; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living; AE = adverse event; ARIA = amyloid-related imaging abnormalities; CDR = Clinical Dementia Rating Scale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; C-SSRS = Columbia Suicide Severity Rating Scale; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; GFAP = glial fibrillary acidic protein; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; NfL = neurofilament light chain; PET = positron emission tomography; PK = pharmacokinetics; P-tau = phosphorylated tau; QOL-AD = Quality of Life in Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia – Lite Version.

4. Study Design

4.1. Overall Design

Study AACI is a multicenter, randomized, double-blind placebo-controlled, Phase 3 study of donanemab in participants with early symptomatic AD. Participants who meet entry criteria will be randomized in a 1:1 ratio to one of the following treatment groups:

- Donanemab: 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W
- Placebo

After 76 weeks, participants will be assigned to donanemab or placebo based on criteria described in Section 4.1.3.

The maximum total duration of study participation for each participant, including screening and the post-treatment follow-up periods, is up to 205 weeks:

- Lead-In: any time prior to complete screening
- Complete Screening: up to 7 weeks
- Double-Blind: 76 weeks
- Extension: 78 weeks
- Follow-Up: up to 44 weeks

The maximum duration of treatment is 150 weeks.

Scheduled Reduction of Donanemab to Placebo

Participants whose amyloid plaque reduction as measured by florbetapir F18 PET scans at Visit 8 (Week 24),Visit 15 (Week 52), Visit 21 (Week 76), Visit 28 (Week 102), or Visit 35 (Week 130) meets dose reduction criteria will have a double-blind dose reduction of donanemab to IV placebo for the remaining duration of the study.

These dose reduction rules are defined by the sponsor.

4.1.1. Lead-In and Screening Period (Visits 601 and 1)

At or before Visit 1, the study will be explained to the participant (and his or her legal representative, if applicable) and study partner. Informed consent must be obtained before any study procedures are conducted. The lead-in period (V601) is optional and may occur any time prior to Visit 1. The screening period spans the time between Visit 1 to Visit 2.

4.1.1.1. Visit 601

For those who participate in V601, a preliminary screening informed consent may be obtained to conduct lead-in screening to collect demographics data, administer the Mini Mental State Examination (MMSE) and collect laboratory samples.

Participants who do not meet the MMSE screening criteria are not to have imaging screening procedures performed. For rescreening instructions, see Section 5.4. All participants must sign the full informed consent to participate in Visit 1.

4.1.1.2. Visit 1

Once the full informed consent is signed, 49 days are allowed for completion of the remaining Visit 1 screening assessments and procedures, as described in the SoA (Section 1.3).

Participants who meet MMSE screening criteria may proceed to the remaining screening procedures.

Although imaging may be the last screening procedures of the study, it is expected that the centrally read results will be available within the screening window. However, it will not be a protocol deviation should the screening results not be available within the screening window.

Participants whose screening imaging results are not available until after the screening window will remain eligible within Visit 1 until these results become available.

Visit 1 is not considered complete until all screening procedures have been completed, results have been reviewed by the investigator or qualified designee, and the investigator or qualified designee has confirmed that the participant is eligible to be randomized. Only then can the participant proceed to Visit 2.

Current or planned use of concomitant medications, the effects of vacations or absences on protocol compliance, and general compliance with the protocol will be discussed at Visit 1. Participants must meet all eligibility criteria (Sections 5.1 and 5.2) to continue to Visit 2.

NOTE: The screening tolerance window is extended to 180 days at Visit 1 for participants in screening at the time of a temporary randomization pause. If such participants remain in screening for >90 days, chemistry, hematology, and ECG must be repeated to reassess eligibility criteria prior to Visit 2 (randomization).

4.1.2. Double-Blind Period (Visits 2 through 21)

The treatment period is a double-blind treatment phase beginning at Visit 2 (randomization). At Visit 2, appointments should be made for all remaining visits and should be scheduled as close as possible to the target date, relative to Visit 2. Participants who meet entry criteria will be enrolled and randomized to receive up to 72 weeks of treatment with donanemab or placebo during the double-blind period.

During this double-blind period, participants will receive IV donanemab or IV placebo Q4W. Assessments and procedures will be performed as indicated in the SoA (Section 1.3). Procedures for some visits may take more than 1 day.

Final endpoint measures and safety assessments for the double-blind period will be performed at visit 21 (week 76) 4 weeks following the participant's last dose of investigational product (IP).

The study investigator and site clinical study team will not have access to any florbetapir F18 and flortaucipir F18 follow-up PET results in order to maintain blinding to any potential changes in amyloid and tau deposition.

4.1.3. Extension Period (Visits 22 through 41)

Participants will be evaluated for amyloid plaque reduction by PET scan at V21. Dose reduction criteria for donanemab are defined by the sponsor.

- Participants randomized to donanemab during the double-blind period who do not meet dose reduction criteria by V21 will continue receiving donanemab.
    - Participants who remained on 700 mg during the double-blind period will have the opportunity to dose escalate to 1400 mg at V25 or after.
- Participants randomized to donanemab during the double-blind period who meet dose reduction criteria by V21 will be assigned to receive placebo starting at V22.
- Participants randomized to placebo during the double-blind period will be assigned to receive donanemab starting at V22, and will follow the same dose titration as participants during the double-blind period.

All participants, by design, may have the opportunity to receive donanemab at some point in the study; however, assignment in the extension period is double-blind.

After the extension period, participants will attend follow-up visits (V801 through V804) as described in Section 4.1.4.

4.1.4. Follow-Up (Visits 801 through 804)

Participants will have immunogenicity and safety follow-up visits (Visit 801 through Visit 804) beginning 12 weeks after their last dose of IP.

Participants will continue to have quarterly immunogenicity and safety follow-up visits until the participant completes V804 or the site is notified that the participant is not required to complete all follow-up visits, whichever occurs first. See the SoA (Section 1.3) for the timing of events and the measures to be assessed.

Follow-up visits are not required if the participant meets release requirements determined by the sponsor.

4.2. Scientific Rationale for Study Design

Study AACI is a multicenter, randomized, double-blind, placebo-controlled, study of donanemab in patients with early symptomatic AD (where early symptomatic AD refers to the combination of 2 stages: MCI-AD and mild AD dementia), MMSE 20-28, and with cerebral tau pathology that is elevated, as measured by flortaucipir. The study is intended to further characterize the benefits and risks of treatment with donanemab versus placebo in participants with early symptomatic AD.

Study AACI includes a placebo treatment arm and allows all participants to continue their symptomatic AD standard of care concomitant medications. Inclusion of a placebo treatment arm is acceptable because there are no confirmed clinically effective disease modifying treatments for AD; this approach is in agreement with the use of placebo described in the Declaration of Helsinki (WMA 2013). The use of a placebo comparator in Study AACI is needed to determine the efficacy and safety of donanemab therapy.

The study includes a screening visit, which can last up to 49 days (see exception in Section 4.1.1), at which participants are required to have flortaucipir F 18 PET imaging results consistent with elevated tau in order to be randomized to the double-blind period. The duration of the double-blind period of the study is 76 weeks and includes up to 72 weeks of treatment with endpoint

measures at the end of the double-blind period (Week 76), to assess the safety, tolerability, and efficacy of donanemab versus placebo.

In addition to AE reporting, safety measures such as laboratory assessments, immunogenicity testing, vital signs and weight monitoring, electrocardiogram (ECG) monitoring, physical examinations, neurological examinations, MRI assessments, and assessments of suicidal ideation and behavior are included to facilitate a comprehensive safety evaluation.

Amendment d adds a long-term extension period designed to further evaluate donanemab efficacy and safety over time.

See Section 8.1 for descriptions of outcome measures. In addition to clinical outcomes, imaging biomarkers will also be measured to assess the direct effect of donanemab on amyloid plaque removal, which is a known hallmark pathology of AD, and hypothesized to contribute to the cognitive and functional decline in people with AD. Amyloid pathology is theorized to be a mediator for clinical decline and therefore it is hypothesized that the removal of amyloid may slow clinical decline.

4.3. Justification for Dose

Based on data presented in Section 2.2.2 as well as decreased participant burden with a Q4W dosing schedule compared with a Q2W dosing schedule and comparable safety (see Section 2), 1400 mg Q4 week dosing was selected as the highest dose regimen for robust amyloid plaque lowering. Safety data from AACD 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 amyloid-related imaging abnormalities (ARIA)-E, ARIA-H and hypersensitivity reactions, and the overall frequency, severity, and seriousness of AEs at this dose level.

Protocol amendment (a) incorporated a titration schedule of 700 mg IV Q4W for the first 3 doses and then 1400 mg IV Q4W based on observation of two cases of symptomatic ARIA observed within their first 3 doses in this study.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study, including the last visit or the last scheduled procedure shown in the SoA.

The end of the study for the primary outcome is defined as the date of the last visit of the double-blind period in the study.

End of the study is the date of the last visit or last scheduled procedure shown in the SoA for the last patient.

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:

Type of Participant and Disease Characteristics

1. 60 to 85 years of age inclusive, at the time of signing the informed consent.
2. Gradual and progressive change in memory function reported by the participant or informant for ≥6 months.
3. An MMSE score of 20 to 28 (inclusive) at Visit 601 or 1.
4. Inclusion criterion 4 is removed.
5. Meet flortaucipir F18 scan (central read) criteria (Section 8.1.2.5).
6. Meet florbetapir F18 scan (central read) criteria (Section 8.1.2.5).
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 or available by phone on all days the C-SSRS/Self-Harm Supplement Form is administered. The study partner must be present on all days the cognitive and functional scales are administered. If a participant has a second study partner, it is preferred that 1 study partner be primarily responsible for the CDR and the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL) assessments. Visits requiring the following assessments and scales 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/Self-Harm Supplement Forms
   - CDR, and
   - ADCS-ADL.

   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.
10. Stable concomitant symptomatic AD medications and other medication that may impact cognition for at least approximately 30 days prior to randomization (does not apply to topical, as needed [prn], or discontinued medications).

Sex

11. 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. Male participants:
        i. Men, regardless of their fertility status, with non-pregnant women of childbearing potential (WOCBP) partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following last dose of IP.
            A. Men and their partners may choose to use a double–barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined).
            B. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
        ii. Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in WOCBP (90 days).
        iii. Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following last dose of IP.
        iv. Men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.
    c. Female participants:
        i. Women not of childbearing potential may participate and include those who are:
            A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis; or
            B. post-menopausal – defined as either

a. A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL; or
b. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
c. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Informed Consent

12. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

13. Significant neurological disease affecting the central nervous system other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures (except febrile childhood seizures).
14. Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, 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 <24 months.
15. History of cancer within the last 5 years, with the exception of non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, nonprogressive prostate cancer, or other cancers with low risk of recurrence or spread.
16. Participants with any current primary psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the participant's ability to complete the study. Participants with history of schizophrenia or other chronic psychosis are excluded.
17. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
18. History of alcohol or drug use disorder (except tobacco use disorder) within 2 years before the screening visit.
19. History of clinically significant multiple or severe drug allergies, significant atopy, or severe posttreatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and/or exfoliative dermatitis).

Imaging, Vital Signs, Electrocardiograms, Laboratory Tests, and Physical Examination

20. Have any clinically important abnormality at screening, as determined by investigator, in physical or neurological examination, vital signs, ECG, or clinical laboratory test results that could be detrimental to the participant, could compromise the study, or show evidence of other etiologies for dementia.
21. Screening MRI which shows evidence of significant abnormality that would suggest another potential etiology for progressive dementia or a clinically significant finding that may impact the participant's ability to safely participate in the study.
22. Have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants/cardiac pacemaker.
23. 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.
24. Sensitivity to florbetapir F18 or flortaucipir F18.
25. Poor venous access.
26. Contraindication to PET.
27. 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.
28. Alanine aminotransaminase (ALT) ≥2.5X the upper limit of normal (ULN) of the performing laboratory, aspartate aminotransferase (AST) ≥2.5X ULN, total bilirubin level (TBL) ≥1.5X ULN, or alkaline phosphatase (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 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

29. Have had prior treatment with a passive anti-amyloid immunotherapy <5 half-lives prior to randomization.
30. Have received active immunization against Aβ in any other study.
31. Have known allergies to donanemab, related compounds, or any components of the formulation.

Prior/Concurrent Clinical Study Experience

32. Are currently enrolled in any other interventional clinical trial involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.

33. Have participated, within the last 30 days (4 months for studies conducted in Japan; 3 months for studies conducted in the United Kingdom), in a clinical trial involving an IP. If the previous IP is scientifically or medically incompatible with this study and has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening (participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor).
34. Have previously completed or withdrawn from this study or received donanemab in any prior investigational study. (This exclusion criterion does not apply to participants who are allowed to rescreen before randomization in this study).

Other Exclusions

35. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
36. Are Lilly employees or are employees of third-party organizations (TPOs) involved in 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 IP.

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

Screen failures are defined as participants who consent to participate in the clinical study but are 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 serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened if the screen failure is due to non-eligible imaging results.

If the screen failure is due to an MMSE score >28, then 1 rescreen will be allowed after 24 weeks.

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

6. Study Intervention

Study intervention and IP are defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the trial protocol.

6.1. Study Intervention(s) Administered

Investigational products used in this study are:

- Donanemab
- Placebo

Investigational product 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 preparation instructions.

Note that at visits which require cognitive assessments be performed, all cognitive scales are to be administered before study medication is administered.

Investigational product is to be administered once Q4W. Investigational product must not be administered at a dosing interval of <21 days at any time in the study. Based on permitted visit windows, it would appear that study medication could theoretically be administered at a 2-week interval. However, administration of 2 doses within <21 days of each other will be a protocol deviation.

See Section 6.5.2 for infusion-related reactions and premedication instructions, if applicable.

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

Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Clinical trial materials are manufactured in accordance with current Good Manufacturing Practices (GMP).

IP will be supplied in a vial. Placebo will be provided as a solution.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.
2. Only participants enrolled in the study may receive IP. Only authorized study personnel may supply, prepare, or administer IP. All IP 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 is responsible for IP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

4. Further guidance and information for the final disposition of unused IPs are provided by the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study, with design to maintain blinding to treatment. To preserve the blinding of the study, a minimal number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

The independent external data monitoring committee (DMC) is unblinded to randomization.

Investigational product will be prepared by an unblinded pharmacist or other qualified unblinded personnel and will be administered by a blinded nurse or other qualified blinded personnel, as described in the pharmacy preparation instructions. Authorized study personnel will confirm that they have located the correct packages by entering a confirmation number found on the label into the interactive web-response system (IWRS).

Emergency unblinding at a participant level for AEs may be performed through the IWRS. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All unblinding events are recorded and reported by the IWRS.

If an investigator, authorized study personnel performing assessments, or participant/partner is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a Lilly Medical Monitor for the participant to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Participants who meet all criteria for enrollment will be assigned a study (participant) number at Visit 601 or Visit 1 and randomized to double-blind treatment at Visit 2. Participants will be randomized to donanemab or Placebo in a 1:1 ratio.

Participants who continue into the extension period will be assigned to placebo or donanemab, as described in Section 4.1.3. Assignment will be double-blind.

For between-group comparability, participant randomization will be stratified by investigative site and tau pathology (low-medium versus high). Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. Randomization into 1 stratum may be discontinued at the discretion of the sponsor.

6.4. Study Intervention Compliance

IP will be administered under medical supervision by the investigator or designee. The dose of IP 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% (approximately 105 mL) 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 (e.g., due to technical complications), every effort should be made to complete the infusion within 24 hours if possible except if an infusion reaction occurs that prevents rechallenge. If less than 75% of the infusion solution is given, this must be recorded as an incomplete infusion on the CRF.

Missed infusions should be recorded on the CRF.

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

6.5. 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 in the CRF, along with any changes to dose.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants and their study partners will be instructed to consult the investigator or other appropriate study personnel at the site before initiation of any new medications or supplements and before changing dose of any current concomitant medications or supplements.

6.5.1. Standard of Care for Alzheimer's Disease

To ensure standard of care for AD, use of approved symptomatic treatments for AD is permitted in this study. The section below provides additional guidance on managing concomitant medication use.

Use of approved or standard of care symptomatic treatments for AD is permitted during the study, provided that the dose has been unchanged for at least approximately 30 days before Visit 2. Doses of these medications should remain constant when possible throughout the double-blind period and extension period (Visit 2 to Visit 41). When medically indicated, initiation, increase or discontinuation of symptomatic treatments for AD is permitted.

Nonmedication treatments for AD such as behavioral management are permitted but are subject to the same restrictions as medication treatment taken for AD.

6.5.2. Medications for Infusion Reactions

If an infusion reaction occurs, medications managing the reaction may be administered at the discretion of the investigator, 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 . 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. Also see Sections 8.3.6.1 and 8.3.6.2.

6.5.3. Excluded Medications

Immunoglobulin G (IgG) therapy (also known as gamma globulin or intravenous immunoglobulin [IVIG]) is not allowed during the study. See Section 7.2 for additional exclusions.

Note: Concurrent use of passive anti-amyloid immunotherapies other than donanemab, such as gantenerumab, lecanemab, or aducanumab, is not permitted during the study.

6.6. Dose Modification

Dose modification of IP is not permitted in this study, except for participants whose amyloid plaque reduction meets dose reduction criteria, as described in Section 4.1, or as described below.

The goal of the study is for the participant to be titrated to the target dose. For participants who develop ARIA during the titration period (that is, before the fourth infusion of study drug of the double-blind or of the extension period), the investigator may decide to

- temporarily suspend dosing as described in Section 7.1.1.1, then determine if the participant should remain on the pre-suspension dose either temporarily beyond the first 3 doses or throughout the remainder of the treatment period,
- continue the same dose either temporarily beyond the first 3 doses or throughout the remainder of the treatment period, or
- continue the dosing schedule as outlined in Section 4.1.

6.7. Intervention after the End of the Study

Amendment d adds an extension period to Study AACI.

No intervention will be provided after the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Investigational product may be discontinued for a participant for the following reasons (details given below):

- By request of the participant or participant's designee (for example, legal guardian)
- Clinical judgment
- A hepatic event or liver test abnormality
- C-SSRS results
- ECG finding
- ARIA
- Systemic hypersensitivity reaction
- Severe noncompliance
- The participant requires an excluded therapeutic agent

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) IP. If IP is definitively discontinued, the participant will remain in the study (following the SoA, except as noted below) to be evaluated for safety and efficacy.

If IP infusion is permanently discontinued and the participant remains in the study. See Section 8.5 for PK sampling instructions. Participants who require a ferromagnetic implant or insertion of a cardiac pacemaker that is not MRI compatible will be permanently discontinued from IP and are not to have further MRIs.

Clinical Judgment

Adverse event or clinically significant laboratory value, ECG result, physical examination finding, MRI finding (such as symptomatic ischemic stroke), C-SSRS result, or vital sign measurement of such severity that, in the opinion of the investigator or sponsor-designated medical monitor, continued treatment is not in the best interest of the participant.

Hepatic Event or Liver Test Abnormality

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

Discontinuation of the IP 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 international normalized ratio (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%)

C-SSRS

In addition, IP may be discontinued if participants:

- Answer "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or
- Answer "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.

ECG

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.

ARIA

Treatment with IP may be permanently discontinued in participants with treatment-emergent (TE) ARIA-E and/or ARIA-H at the discretion of the principal investigator (PI) depending on severity of clinical and radiologic findings (see Manual of Operations for permanent discontinuation guidance). For temporary discontinuation for ARIA-related reasons, see Section 7.1.1.1.

Systemic Hypersensitivity Reaction

If the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity suspicious for an anaphylactic reaction (see Section 8.3.6) has occurred related to IP administration, the participant should be permanently discontinued from the investigational drug.

Severe Noncompliance

Severe noncompliance to the study protocol, that results in a safety concern, in the judgment of the investigator, may be reason for discontinuing IP.

Excluded Therapeutic Agent

The participant, for any reason, requires a treatment with an excluded therapeutic agent (Section 6.5.3) and temporary discontinuation criteria cannot be met (see Section 7.1.1.2).

7.1.1. Temporary Discontinuation

7.1.1.1. Due to ARIA

The development of ARIA-E and/or ARIA-H (microhemorrhages and/or cortical superficial siderosis [cSS]) are expected events and occur more commonly on treatment with donanemab. The site PI may temporarily discontinue IP if the participant develops TE ARIA-H or ARIA-E to an extent deemed clinically significant by the site PI (see Manual of Operations for temporary discontinuation guidance). Dose modification considerations are described in Section 6.6.

Reinitiating IP can be considered after resolution of ARIA-E and stabilization of ARIA-H imaging findings and the resolution of any associated symptoms.

See Section 8.3.7 for details on adverse event reporting for ARIA-E and ARIA-H.

In cases of new ARIA-E or ARIA-H, given the context of the severity of the imaging findings and symptoms, the site PI, at his/her clinical discretion, can elect to recommend discontinuing IP and then follow the participant with serial MRIs every 4 to 6 weeks (fluid attenuation inversion recovery [FLAIR] and T2* gradient-recall echo) and symptoms, to monitor stabilization or resolution. Upon resolution of ARIA-E and stabilization of ARIA-H and the resolution of any associated symptoms, the participant can be considered for re-initiating IP. There is no defined time duration for this monitoring period while off IP, and will be based on clinical judgment.

Both the decision to stop and restart IP may be discussed with the sponsor-designated medical monitor (refer to Manual of Operations).

7.1.1.2. Due to Reasons Other than ARIA

Temporary discontinuation from IP treatment is allowed if a short-term treatment with an excluded medication is necessary, secondary to hospitalization, personal or exceptional circumstances or to evaluate the IP impact on an uncertain AE.

Investigational product may be restarted at the next scheduled visit, 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 his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study

- if the participant enrolls in any other clinical study involving an investigational medicinal product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another disease-modifying 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
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

At the time of discontinuing from the study, if possible, an early discontinuation (ED) 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 both from the IP and from 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.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, discussion should occur between the sponsor and investigator. If the investigator and the sponsor-designated medical monitor agree it is medically appropriate to continue, the investigator must obtain documented approval from sponsor-designated medical monitor to allow the inadvertently enrolled participant to continue in the study with or without treatment with IP. Safety follow up is as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (AEs and SAEs) of the protocol.

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 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 IP. 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.

Discontinuation of specific sites or of the study as a whole are handled as part of regulatory, ethical, and trial oversight considerations in Section 10.1.9.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue IP.

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

Cognitive and functional testing will be administered using an electronic Clinical Outcome Assessment (eCOA) tablet. The audio voice recordings of the rater's questions and the participant's and study partner's responses will also be collected via the eCOA tablet during administration of the cognitive and functional testing for central monitoring of rater scale administration, where local guidelines permit. Cognitive and functional testing for each participant should be performed at approximately the same time on each day, whenever possible, to reduce potential variability.

Note that the CDR must be administered by a different rater than the ADAS-Cog$_{13}$, MMSE, RUD-Lite, QOL-AD, and DSST medicines version. The ADCS-ADL should be administered by the same rater as the CDR.

The CDR rater should be blinded to AEs to avoid bias in the CDR assessment.

These 2 raters should continue administering the same scale whenever possible to the same participant throughout the study. The PI has the responsibility of selecting the raters who will administer the instruments at the site and ensuring all training requirements have been met by those raters.

When administered, cognitive and functional testing should be performed before medical procedures that could be stressful for the participant (for example, blood draws). Note that procedures (for example, MRI, flortaucipir F18 PET tau imaging, florbetapir F18 PET amyloid imaging) can be conducted on other days within the visit window. If an efficacy assessment (ADAS-Cog13, ADCS-ADL, CDR, MMSE, or DSST medicines version) cannot be collected at the scheduled visit, it may be collected at the next opportunity, if within 30 days of the scheduled assessment.

8.1.1. Primary Efficacy Assessment

The integrated Alzheimer's Disease Rating Scale (iADRS) assesses the impact of cognitive loss on the ability to conduct everyday activities and provides a measure of global AD severity as a single summary score. The iADRS comprises 2 underlying domains ("cognitive ability" and "functional ability"), with each representing related but separate concepts. The iADRS integrates the items that make up both domains into a single overall score that is conceptually distinct from

either domain assessed individually. The combination score of the iADRS captures commonalities across its domains, minimizing noise that exists within each domain individually. The iADRS captures clinical progression from MCI due to AD through moderate dementia due to AD, and treatment effects have been demonstrated across MCI and mild dementia due to AD (Honig et al. 2018; Wessels et al. 2020; Mintun et al. 2021). The iADRS has been validated (Wessels et al. 2015, 2018) and its statistical properties have been described. Minimal clinically important change estimates for the iADRS have been defined (Wessels et al. 2022b) and associations with meaningful outcomes of disease such as caregiver burden and quality of life have been demonstrated (Wessels et al. 2022a).

The ADAS-Cog13 and the ADCS-ADL will be the actual scales administered to participants.

8.1.2. Secondary Efficacy Assessments

8.1.2.1. MMSE

The Mini-Mental State Examination (MMSE) is a brief instrument used to assess cognitive function in participants (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. The MMSE should whenever possible be administered by the same rater from visit to visit to reduce potential variability.

8.1.2.2. ADAS-Cog$_{13}$

The Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog$_{13}$) is a rater-administered instrument that was designed to assess the severity of dysfunction in the cognitive and noncognitive behaviors characteristic of persons with AD (Rosen et al. 1984). The ADAS-Cog$_{13}$ should, whenever possible, be administered by the same rater from visit to visit to reduce potential variability.

The cognitive subscale of the ADAS, the ADAS-Cog$_{13}$, consists of 13 items assessing areas of cognitive function that are the most typically impaired in AD: orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures (Mohs et al. 1997). The ADAS-Cog$_{13}$ scale ranges from 0 to 85, with higher scores indicating greater disease severity.

8.1.2.3. CDR

The CDR (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 semi-structured and in-depth interview with both the affected individual and their study partner. 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).

The CDR should be administered whenever possible by the same rater from visit to visit to reduce potential variability. The participant's memory, orientation, judgment, and problem-solving ability are assessed. The study partner and participant must be interviewed separately.

Note: The CDR may be administered to the participant and/or study partner by phone. Regardless of administration method, the CDR must be administered to the study partner prior to the participant. While the participant may complete the CDR by phone, other procedures and assessments may be required in person, as described in the SoA (Section 1.3).

8.1.2.4. ADCS-ADL

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire that is to be answered by the participant's study partner (Galasko et al. 1997, 2004). The ADCS-ADL should be administered by the same rater from visit to visit to reduce potential variability.

The ADCS-ADL subset of items (items 6a and 7 to 23) for iADLs will be used as a secondary efficacy measure. The focus in the early symptomatic AD population is on the iADLs rather than the basic Activities of Daily Living (bADLs), which are thought to be affected in more severe stages of the disease. The range for the iADL score is 0 to 59, with lower scores indicating greater disease severity.

For each of the specific items, the study partner is first asked if the participant attempted the ADL during the past 4 weeks. If the participant did attempt the ADL, the study partner is asked to rate the participant's performance level based on a set of performance descriptions. Scores for each item and the overall score for the tool are calculated. The range for the total ADCS-ADL score is 0 to 78, with lower scores indicating greater level of impairment. Separate scores for the bADLs (0 to 19) will also be computed.

8.1.2.5. Biomarker Efficacy Measures

Florbetapir F18 PET scan

Change in amyloid burden (as assessed by florbetapir F18 PET) will be compared in donanemab- and placebo-treated participants.

Flortaucipir F18 PET scan

Change in tau pathology (as assessed by flortaucipir F18 PET) will be compared in donanemab- and placebo-treated participants.

Volumetric MRI

Volumetric magnetic resonance imaging (vMRI) of the brain will be performed according to the SoA (Section 1.3). Donanemab- and placebo-treatment effects on vMRI will be assessed and compared to evaluate the loss of brain volume that occurs in AD participants.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical and Neurological Examinations

Complete and brief physical examinations will be performed as indicated in the SoA (Section 1.3).

The complete physical examination will include assessment of the following:

- general appearance;
- skin, head, and neck;
- lymph nodes;
- thyroid;
- abdomen (bowel sounds, liver and spleen palpation);
- back (costovertebral angle tenderness); and
- musculoskeletal, cardiovascular, and respiratory systems.

The brief physical examination will include assessments of the following:

- skin,
- lungs,
- cardiovascular system, and
- abdomen (bowel sounds, liver and spleen palpation).

Complete neurological examinations will be performed as indicated in the SoA (Section 1.3).

The examinations will include a thorough assessment of the following:

- gait,
- balance,
- coordination,
- cranial nerves,
- sensory and motor systems, and
- reflexes.

If necessary, given the training of the PI, a neurologist may be consulted in the event of significant new findings.

If a clinically meaningful change in a MRI is noted during the study, an additional full neurological exam should be performed as soon as possible, along with any other medical follow-up deemed necessary by the investigator.

8.2.2. Vital Signs

Vital signs, including temperature, will be measured at all visits.

Vital signs should be taken before administration of IP. Vital signs may be repeated as needed.

8.2.2.1. Blood Pressure

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

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

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

Any clinically significant findings from vital sign measurements that result in a diagnosis and that occur after the participant receives the first dose of study treatment should be reported to Lilly or its designee as an AE via CRF/electronic data entry.

8.2.2.2. Height, Weight, and Body Temperature

Height and body weight will be measured. Measurements should be taken, when possible, with the same scale for all measurements. Body mass index will be calculated from the height and body weight.

Temperature will be recorded using an oral or tympanic (or other acceptable route) thermometer.

Any body weight data entered into the CRF will be used for the overall data analysis

8.2.3. Electrocardiograms

For each participant, 12-lead digital ECGs will be collected during the double-blind period, according to the SoA (Section 1.3). 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. Collection of more ECGs (replicates) than expected at a timepoint is allowed when needed to ensure high-quality records.

Electrocardiograms will initially 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 subject 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/corrected 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 evaluation.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread. A report based on

data from this overread will be issued to the investigative site. These data are not routinely reported back to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate participant management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of collection, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and to 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 in the AE section of the CRF. The laboratory reports must be filed with the source documents. 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 IP, should be repeated until the values return to normal, baseline, or are no longer considered clinically significant by the investigator or medical monitor.

1. 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.
2. All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA and laboratory manual (or standard collection requirements, if applicable).
3. If laboratory values from non-protocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE, AE, or dose modification), then the results must be recorded in the CRF. Laboratory results from this laboratory must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a new diagnosis and that occur after the participant receives the first dose of IP should be reported to Lilly or its designee as an AE via CRF/electronic data entry.

8.2.5. Magnetic Resonance Imaging

Magnetic resonance imaging 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 (vMRI will also be used to calculate brain volumes, as noted in Section 9.4.4).

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. After the MRI scan is read locally, the MRI scans will be sent for analysis to a centralized MRI vendor 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 site as "does" or "does not" meet MRI eligibility criteria.

Specific analyses of the scans, including assessments of ARIA-H and ARIA-E and calculations of brain volumes, 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 sites.

8.2.6. Hepatic Safety Monitoring

Close Hepatic Monitoring

Laboratory tests (Section 10.4), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of 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 ≥2x baseline (except for participants with Gilbert's syndrome)

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

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

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 laboratory 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 1 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*, 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*, or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert's syndrome)

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for Prothrombin time and INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography [CT] scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the sponsor-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 serum 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.

8.2.7. Suicidal Ideation and Behavior Risk Monitoring

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior 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. Consideration should be given to discontinuing the study medication in subjects who experience signs of suicidal ideation or behavior, following a risk assessment.

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

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

C-SSRS

Columbia Suicide-Severity Rating Scale is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events.

8.3. Adverse Events and Serious Adverse Events

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

- Adverse events (AEs)
- Serious adverse events (SAEs)

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and remain responsible for following up on AEs that are serious, considered related to the IP or study procedures, or that caused the participant to discontinue the IP (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF through the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF through the time points specified in the SoA.

Medical occurrences that begin before the start of IP but after signing of the ICF will be recorded on the AE CRF.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to sponsor begins after the participant has signed the ICF and has received IP or PET tracer. However, if an SAE occurs after signing the ICF, but prior to receiving IP or PET

tracer, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

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

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

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-Up of AEs and SAEs

After the initial AE/SAE 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 8.3.8), 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). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IP 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 an IP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), 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.

8.3.5. Pregnancy

Women of childbearing potential are excluded from Study AACI. Therefore, pregnancy is not expected to occur. However, if pregnancy does occur, follow the instructions below.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of IP and until 90 days after the last dose of IP received.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

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

8.3.6. Hypersensitivity, Including Infusion-Related Reactions

8.3.6.1. Management of Infusion-Related Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each sign or symptom should be provided to the sponsor in the Hypersensitivity, Anaphylactic, and Infusion Related Reactions CRF.

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

If a participant experiences a systemic hypersensitivity reaction or infusion related reaction either involving two or more organ systems (e.g. 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 (IRR kit). Tryptase and when applicable urine N-methylhistamine should be repeated in approximately 4 weeks to obtain post-event baseline. Laboratory results are provided to the sponsor via the central laboratory.

8.3.6.2. Dosing rechallenge and premedication for infusions

Premedication for dosing is not planned.

Dosing rechallenge is contraindicated in participants that have experienced a suspected or possible anaphylactic reaction (e.g. reaction involving two 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, after review of the data, and at the investigator's discretion, the participant may be rechallenged. If rechallenge is planned, the participant may be premedicated for subsequent doses at the investigator discretion and according to local practice guidelines.

Prior to initiating premedication, the investigator may consult with the sponsor.

Any premedication given will be documented as a concomitant therapy (Section 6.5.2).

8.3.7. Amyloid-Related Imaging Abnormalities (ARIA-E and ARIA-H)

While most cases of ARIA are asymptomatic, serious cases have been reported. Available data suggests serious cases are most likely to occur early in dosing, after the first, second, or third infusion.

When symptoms are present in association with these imaging abnormalities, they have been reported to include, but may not be limited to, headache, vomiting, unsteadiness, dizziness, tremor, confusion, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures (Ostrowitzki et al. 2012; Sperling et al. 2012; VandeVrede et al. 2020; Mintun et al. 2021; Swanson et al. 2021).

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

If the above-mentioned symptoms are reported, and:

- ARIA-E is suspected, then the abnormality is best detected by FLAIR sequences on MRI, while
- ARIA-H is best detected with the T2* gradient-recalled echo on MRI.

An unscheduled MRI with these imaging sequences should be obtained upon suspicion of ARIA. If ARIA is present, it is recommended to repeat MRIs with these sequences every 4 to 6 weeks until resolution of ARIA-E or stabilization of ARIA-H is documented. For asymptomatic or mild symptoms, the participant can be observed; for moderate symptoms associated with ARIA-E, the use of oral or IV steroids can be considered. In the case of severe symptoms associated with ARIA-E, it is recommended to hospitalize the participant for close observation and consider the use of IV steroids such as high-dose dexamethasone or a similar agent (see Manual of Operations for more detail).

The unscheduled MRI should be performed in the same manner as the currently scheduled MRIs in the protocol, which includes sending the images for central review (Section 8.2.5).

For procedure to follow in the event of ARIA-E or ARIA-H, see Section 7.1.1.1.

In the event of a finding of ARIA-E on MRI, the investigator is to complete the ARIA-E Related Events CRF regarding the presence or absence of symptoms related to the ARIA-E, and ARIA-E should be reported as an adverse event in the Adverse Events CRF.

8.3.8. 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 Study SAP.

8.3.9. Complaint Handling

Lilly collects product complaints on investigational medicinal products or investigational devices used in clinical trials in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Study participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the investigational medicinal product so that the situation can be assessed.

8.4. Treatment of Overdose

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis of IP 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.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the serum concentrations of donanemab. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

A maximum of 3 blood samples per participant may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

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

Bioanalytical samples collected to measure donanemab concentrations will be retained for a maximum of 1 year following last subject 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.

8.6. Pharmacodynamics

8.6.1. Clearance of Amyloid Deposits

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

Clearance of amyloid deposits (as assessed by florbetapir F18 PET and/or florbetaben F18 PET signal) will be compared in donanemab- and placebo-treated participants for those participants who undergo amyloid PET scans as described in the SoA (Section 1.3).

8.6.2. Accumulation of Tau Deposits

Flortaucipir F18 PET provides quantitative assessment of tau deposition in the brain and can serve as a PD biomarker of accumulation of tau deposits as AD progresses.

Accumulation of tau deposits (as assessed by flortaucipir F18 PET signal) will be compared in donanemab- and placebo-treated participants for those participants who undergo flortaucipir F18 PET scans as described in the SoA (Section 1.3).

8.7. Genetics

8.7.1. Apolipoprotein E Genotyping

Apolipoprotein E (ApoE) genotyping is a mandatory part of this study, unless country-specific laws and regulations prohibit this type of testing. Blood sampling for ApoE genotyping will be performed as shown in the SoA (Section 1.3). Neither participants nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results.

Failure to collect samples for ApoE will not be considered a protocol deviation if country-specific regulations prohibit the testing of genetic material or transportation of such material outside of the country.

8.7.2. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to donanemab and to investigate genetic variants thought to play a role in AD or other neurological conditions. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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 at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards (IRBs) impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable

response that may not be observed until later in the development of donanemab or after donanemab becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

8.8. 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 deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Serum, plasma, and whole blood RNA 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 donanemab, pathways associated with AD, mechanism of action of donanemab, 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 at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of donanemab or after donanemab becomes commercially available.

8.9. Immunogenicity Assessments

Where local regulations and ERBs allow, at the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against donanemab. To interpret the results of immunogenicity, a venous blood sample will be collected, if warranted, 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. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of donanemab. The testing paradigm is outlined in Section 9.4.7.1.

Treatment-emergent ADAs are defined in Section 9.4.7.1. 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 for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to donanemab. Any samples remaining after 15 years will be destroyed.

8.10. Medical Resource Utilization and Health Economics

8.10.1. Dependency Level (derived from ADCS-ADL)

Dependence, or the level of assistance required by a participant, has been suggested as a construct for assessing the effect of AD treatment. The process of increasing dependence on others is intended as a complementary measure to existing clinical measures in order to help explain the impact of AD on economic issues such as the risk of institutionalization and caregiver burden (McLaughlin et al. 2010; Spackman et al. 2013).

The ADCS-ADL scores were used to map individuals into 1 of 6 dependence levels (0 to 5):

- Level 0 – No iADL/bADL impairment;
- Level 1 – Some supervision needed on isolated iADLs;
- Level 2 – Supervision on multiple iADLs or loss of at least 1 household activity;
- Level 3 – Supervision on all types of iADLs or homebound;
- Level 4 – Supervision on some bADLs; and
- Level 5 – Impaired transfer or complete incontinence (Kahle-Wrobleski et al. 2015).

An approach to transforming continuous functional scale scores into discrete levels of dependence was examined previously in a longitudinal observational study, with preliminary results suggesting acceptable validity and progression in dependence level over time (Kahle-Wrobleski et al. 2017). At baseline, 49.6% of those with mild AD dementia were dependence level 2 and 42.7% were at levels 3 or 4. At 18 months, the proportion of participants at level 2 declined to 31.2% while that at levels 3 and 4 rose to 58.8%.

Analyses will be conducted to examine changes in dependence levels across the trial population as well as potential differences on dependence level by treatment group assignment.

8.10.2. Resource Utilization in Dementia – Lite Version (RUD-Lite)

The RUD-Lite is designed to assess the healthcare resource utilization of patients and their caregivers and to determine the level of formal and informal care attributable to AD (Wimo et al. 2013). The data are collected through a structured interview with the study partner. Information on both caregivers (caregiving time and work status) and participants (accommodation and healthcare resource utilization) is gathered from the baseline and follow-up interviews. Caregivers will be asked to provide data on time spent assisting participants' basic Activities of Daily Living (ADLs), such as using the toilet, eating, dressing, grooming, walking, and bathing; assisting participants' instrumental ADLs, such as shopping, cooking, housekeeping, laundry, transportation, taking medication, and managing finances; and providing supervision. The resource utilization quantified by the RUD-Lite can be used for calculating cost offsets and in cost-effectiveness models.

8.10.3. Quality of Life in Alzheimer's Disease (QOL-AD)

The QoL-AD is a valid, reliable, and disease-specific measure of quality of life for an AD population (Logsdon et al. 1999, 2002; Thorgrimsen et al. 2003). It includes 13 items, each rated on a 4-point scale. Summing the items provides an overall score to index the participant's quality of life. The QoL-AD is administered to the participant by a rater and asks the participant to provide ratings on mood, relationships, memory, finances, etc. The participant's primary caregiver also is asked to complete the same measure.

9. Statistical Considerations

The primary efficacy objective of Study AACI is to demonstrate donanemab slows the cognitive and/or functional decline in AD versus placebo as measured by the iADRS through 76 weeks in the population of participants with low-medium tau pathology or the overall population. This study includes high tau participants, a population not studied in Study AACG. The overall population will include all enrolled early symptomatic AD participants with a low-medium (intermediate) or high tau pathology at baseline.

9.1. Statistical Hypotheses

The primary efficacy objective will be assessed using a Natural Cubic Spline (NCS) model with 2 degrees of freedom of the primary outcome iADRS at Month 18.

The primary efficacy analysis will be conducted on two populations: the intermediate tau population at baseline and the overall population. The hypothesis will be tested with a control of family wise 2-sided type I error rate of 5% following the chain procedure (Millen and Dmitrienko 2011).

The testing scheme, and a graphic testing procedure that will be used to control the overall false positive rate for the primary endpoint and major secondary endpoints will be described in the Study SAP.

Major secondary hypotheses defined in a similar manner are that donanemab is superior to placebo with regard to:

- Clinical progression in participants with early symptomatic AD through Week 76, as measured by MMSE, ADAS-Cog_{13}, CDR-SB, and ADCS-iADL
- Brain amyloid deposition at Week 76 measured by florbetapir F18 PET scan
- Brain tau deposition at Week 76 measured by flortaucipir F18 PET scan
- Brain region volumes at Week 76 measured by vMRI

9.2. Sample Size Determination

Approximately 1800 participants will be randomly assigned in the study. It is anticipated that approximately two-third of participants have low-medium tau and approximately one-third of participants have high tau pathology.

The powering and sample size determination of the trial is based on the low-medium tau pathology population. The assumptions for the power calculation were based on the results of the Study AACG data. The mean progression levels in the placebo and donanemab arms from the MMRM analysis on iADRS were -10.06 and -6.86 points (approximately 32% slowing) over 18 months, respectively, with a standard deviation of 11.06. The assumed discontinuation rate of AACI is 30%. Multiple longitudinal datasets were simulated, and the NCS model with 2 degrees of freedom was fit to each sample to determine the power. With a sample size of approximately 1000 randomized participants in the low-medium tau pathology population, the NCS model with 2 degrees of freedom provides greater than 95% power to achieve statistical significance at a 1-sided 0.025 level for the treatment difference relative to placebo, as measured by iADRS at Month 18. If both treatment arms are placebo-like with no efficacy, the type I error is 2.5%.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF.
Enrolled/Intent-to-Treat	All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.
Efficacy Evaluable	All participants with a complete baseline assessment and at least 1 complete post-baseline assessment.* Participants will be grouped according to randomized treatment assignment (donanemab or placebo), even if the participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.
Safety	All participants randomly assigned to IP and who take at least 1 dose of IP.

Abbreviations: ICF = informed consent form; IP = investigational product.

* For each assessment, the efficacy evaluable population will be defined as all participants with a baseline measurement and at least 1 complete post-baseline measurement for that respective assessment.

9.4. Statistical Analyses

9.4.1. General Considerations

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

Unless otherwise noted, all pairwise 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.

Details on the testing strategy for the primary and key secondary analyses will be specified in the Study SAP.

All efficacy analyses will follow the intent-to-treat (ITT) principle unless otherwise specified. An ITT analysis is an analysis of data by the groups to which subjects are assigned by random allocation, even if the subject 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, subjects 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.

For MMRM models, observations collected at nonscheduled visits will not be included in the analyses.

A database lock for the double-blinded phase primary efficacy analysis is expected to occur after all randomized subjects have had a chance to complete the double-blind period of the study. Efficacy and safety analyses will be conducted based on data collected during the double-blind period. Additional database lock(s) may occur. Additional efficacy and safety analyses will be conducted based on data collected during the extension period. Data collected during the immunogenicity and safety follow-up period will be summarized and analyzed separately.

The study will include several separate SAPs: a main study SAP (referred to as Study SAP) which will detail the analyses for the objectives for double-blinded, placebo-controlled phase, and a long-term extension (LTE) SAP which will detail analyses for the objectives of LTE phase. The analyses for any addenda such as analyses for open-label safety cohort will be included in a separate addendum-specific SAP.

The main Study SAP will be finalized prior to unblinding of all participants in the placebo-controlled phase. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints and a more technical and detailed description of the statistical analyses will be described in the SAPs.

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

9.4.1.1. Handling of Missing Items for Scales

If any of the individual items for ADAS-Cog_{13} or ADCS-ADL are missing or unknown, every effort will be made to obtain the score for the missing item or items. For ADAS-Cog_{13}, if 4 or fewer of a total of 13 items are missing, the total score (maximum = 85) will be imputed as follows: the total from remaining items will be multiplied by a factor that includes the maximum score for the missing items. For example, if the first item, "Word-Recall Task," which ranges from a score of 0 through 10 (maximum = 10), is missing, and the second item "Commands," which ranges from a score of 0 to 5 (maximum = 5), is missing, then the multiplication factor = 85/(85 - [10 + 5]) = 85/70 = 1.21. Thus, the total score for this example will be the sum of the remaining 11 items multiplied by 1.21. The imputed number will be rounded up to the nearest integer. If more than 4 items are missing, the total score for ADAS-Cog_{13} at that visit will be considered missing.

For the ADCS-iADL, if <30% of the items are missing, the total score will be imputed. The sum of the nonmissing items will be prorated to the sum of total items. The imputed number will be rounded up to the nearest integer. If the nearest integer is greater than the maximum possible score, the imputed score will be equal to the maximum score. If >30% of the items are missing, the total score for ADCS-iADL at that visit will be considered missing. The same imputation technique will be applied to the ADCS-ADL total score. Note that, depending on the specific item responses that are missing, it is possible to have an imputed total score for both the

DCS-iADL and the ADCS-ADL, an imputed total score for 1 but not the other, or both total scores missing.

The same imputation technique will be applied to the CDR-SB. If only 1 box (of 6) of the CDR is missing, the sum of the boxes will be imputed by prorating the sum from the other 5 boxes. If the score from more than 1 box is not available, the CDR-SB at that visit will be considered missing.

The iADRS score is calculated as:

ADCS-iADL score-ADAS-Cog_{13} score + 85.

If either ADAS-Cog_{13} or ADCS-iADL is missing, iADRS score will be considered missing.

For all other scales, if any item is missing, any total or sum involving that item will be considered missing.

9.4.2. Treatment Group Comparability

9.4.2.1. 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.

The reasons for discontinuation will be collected when the participant's participation in the study ends and will be summarized by treatment group for all randomized subjects. The percentage of subjects 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.

9.4.2.2. Participant Characteristics

The participant's age, sex, race, height, body weight, body mass index (weight (kg) / [height (m)]2), tobacco use, alcohol use, caffeine use, years of education, work status, time since onset of first AD symptoms, time since diagnosis, baseline MMSE, ApoE genotype (E4 carrier versus non-carrier), having 1 or more first degree relatives with AD, and acetylcholinesterase inhibitor (AChEI) and/or memantine use at baseline will be recorded.

Baseline characteristics will be summarized by treatment group and overall. 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 (ANOVA), with independent factors for treatment and investigator, will be used.

9.4.2.3. 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 AChEI/memantine medications.

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

9.4.2.4. 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.

9.4.3. Primary Endpoint(s)

The primary objective of this study is to test the hypothesis that IV infusion of donanemab will slow the cognitive and/or functional decline of AD as measured by iADRS score compared with placebo in the population of participants with intermediate tau pathology at baseline and the overall population.

A NCS analysis (Chambers and Hastie 1992) with 2 degrees of freedom (DF) will be used to assess the difference between treatment groups in iADRS score at Week 76. The NCS model provides a type of smoothing function to the data and can adequately estimate longitudinal trajectories under a variety of shapes (for example, linear and quadratic) for each treatment group. The degrees of freedom of the model can be prespecified to establish the level of smoothing of the data. The number and location of the "knots" is utilized to parse out different time periods where the data may transition from one shape to another to provide an adequate fit and the location of the knots will be provided in the SAP.

The iADRS score at baseline and at each of the postbaseline visits will be included in model as a dependent variable. Study visit will be treated as a continuous variable with values equal to weeks between baseline and postbaseline exam dates. The model will include these fixed effects: NCS basis expansion terms (2 terms), NCS basis expansion term-by-treatment interaction (2 terms), baseline age, concomitant AChEI and/or memantine use at baseline (yes/no), and potentially other covariates will be included in the model and specified in the Study SAP. An unstructured variance-covariance structure matrix will be used to adjust for intra-subject correlation. If the unstructured variance-covariance structure matrix results in a lack of convergence, the following structures will be used in sequence:

- Heterogeneous Toeplitz covariance structure
- Heterogeneous autoregressive order 1 covariance structure
- Heterogeneous compound symmetry covariance structure, and
- Compound symmetry covariance structure.

The primary time point for treatment comparison will be at Week 76.

The primary efficacy analysis may be modified to use an alternative statistical model based on interactions with regulatory agencies and/or internal decision making, and if modified, the model will be outlined in the Study SAP prior to unblinding of the placebo-controlled phase.

As a sensitivity analysis, a Bayesian Disease Progression Model (DPM) on the iADRS will evaluate possible slowing of disease progression with treatment of donanemab relative to placebo. The primary purpose of the DPM is to estimate a quantity known as the disease progression ratio (DPR), which measures the proportion of disease progression in donanemab-treated participants relative to placebo-treated participants.

The MMRM analysis will also be assessed for the iADRS. The change from baseline score on the iADRS at each scheduled postbaseline visit (according to the SoA) during the treatment period will be the dependent variable. The model for the fixed effects will include the following terms: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. Visit will be considered a categorical variable. The null hypothesis is that the contrast between the donanemab group versus placebo at the last visit equals 0. An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence:

- heterogeneous Toeplitz covariance structure
- heterogeneous autoregressive covariance structure
- heterogeneous compound symmetry covariance structure
- compound symmetry covariance structure

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

The primary time point for treatment comparison will be at Week 76. The treatment group contrast in least-squares mean progression and its associated p-value and 95% CI will be calculated for the treatment comparison of donanemab versus placebo using the MMRM model specified above.

All analyses as described above, including the NCS with 2 DF, DPM, and MMRM models on iADRS will be assessed in the intermediate tau population and overall population.

Details about these analyses, as well as other sensitivity analyses including NCS with 3 degree of freedom, and quadratic models will be described in the SAP.

9.4.4. Secondary Endpoint(s)

Similar to the primary endpoint of iADRS, each of the secondary efficacy outcomes will be assessed using NCS with 2 DF, DPM, and MMRM analyses for the intermediate tau population and overall population. These secondary efficacy outcomes include ADAS-Cog_{13}, ADCS-iADL, CDR-SB, and MMSE.

Longitudinal changes from baseline in amyloid plaque (as measured by florbetapir F18 PET scan) will be analyzed using MMRM including the following terms in the model: baseline biomarker value, treatment, visit, treatment-by-visit interaction, and baseline-by-visit interaction.

The change from baseline to endpoint in tau deposition (as measured by flortaucipir PET scan) will be analyzed using an analysis of covariance (ANCOVA) model with terms of baseline value and treatment. Atrophy in vMRI parameters will be analyzed using MMRM including the following terms in the model: treatment, visit, treatment-by-visit interaction, baseline vMRI, intracranial volume, and age at baseline.

Any additional analyses of secondary efficacy outcomes and biomarkers will be specified in the Study SAP.

9.4.5. Tertiary/Exploratory Endpoint(s)

Efficacy analyses will be conducted to evaluate the hypotheses of delayed start disease modification by donanemab on clinical progression as measured by iADRS, CDR-SB, ADCS-iADL, ADAS-Cog_{13}, and MMSE. The statistical method outlined in Liu-Seifert et al. (2015) will be used to analyze each clinical endpoint to compare the treatment efficacy between the early start participants (randomized to donanemab at the beginning of AACI) and delayed start participants (receiving donanemab for the first time in the extension period). The analysis will follow the intent-to-treat (ITT) principle unless otherwise specified. The details of the analyses will be described in the SAP.

Change in brain amyloid plaque deposition (as measured by florbetapir F18 PET) will be evaluated through Week 154 for the participants who had not met dose reduction criteria during the double-blind period. The brain amyloid plaque deposition (as measured by florbetapir F18 PET) will also be assessed in participants who met dose reduction criteria during double-blind and extension period to evaluate amyloid plaque re-accumulation.

Additional exploratory and extension period endpoints and their respective analyses will be described in the Study SAP.

9.4.6. Other Safety Analyses

All safety analyses will be made on the Safety Population. Refer to the Study SAP for additional details.

9.4.7. Other Analyses

9.4.7.1. Evaluation of Immunogenicity

Subject samples will be analyzed using a 4-tiered approach. All samples will be assessed in Tier 1 (screening) for the possible presence of ADAs. Samples found to produce a signal above or equal to the screening cut point will be assessed in Tier 2 to confirm specificity to donanemab (confirmation). Any samples confirmed as specific for anti-donanemab antibodies will be reported as “detected.” All samples below the screening cut point (Tier 1) or not confirmed (Tier 2) will be reported as “not detected.” Any “detected” sample in Tier 2 will be assessed in Tier 3 (titer assessment) and Tier 4 (neutralizing antibodies). Anti-drug antibody titer values will be reported from Tier 3 titer assessment. Any samples above the Tier 4 assay cut point will be reported as “detected for neutralizing antibodies”; samples below the assay cut point in Tier 4 will be reported as “not detected for neutralizing antibodies.”

The frequency and percentage of subjects with preexisting (baseline) ADAs, ADAs at any time after baseline, and TE ADAs to donanemab will be tabulated. If no ADAs are detected at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimal required dilution of the assay. For samples with ADAs detected at baseline, TE ADAs are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For the TE ADA subjects, the distribution of maximum titers will be described. The frequency of neutralizing antibodies may also be tabulated. The relationship between the presence of antibodies to donanemab and PK, PD, safety, and/or efficacy assessment may be assessed.

9.4.7.2. Pharmacokinetic/Pharmacodynamic Analyses

Compartmental modeling of donanemab PK data using nonlinear mixed effects modeling or other appropriate software may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported. Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. If appropriate, data from other studies of donanemab may be used in this analysis.

The PK/PD relationships between plasma donanemab concentration and SUVr, cognitive endpoints, ARIA incidence rate, or other markers of PD activity may be explored graphically. The relationship between the presence of antibodies to donanemab and PK, PD, safety, and/or efficacy may be assessed graphically.

To facilitate this modeling, and to ensure that exposure estimates from this study are available at the end of the trial, it is intended that the PK data will be locked after all participants complete Visit 18 (64 weeks of treatment), to allow PK modeling to begin before the end of the trial. No safety or efficacy data will be included in the 64-week PK lock.

An Early PK Lock Plan will be developed and implemented prior to this lock, which will specify the safeguards to be taken to ensure the integrity of the study. It is intended that the results of the PK analysis will be provided in a separate report.

Additional modeling may be performed based on the results of the graphical analyses.

9.4.7.3. 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 (CIUMC 2016).

9.5. Interim Analyses

Interim analyses may be conducted for Study AACI. Interims potentially executed include futility, early efficacy, and sample size re-estimation. Operational details and a quantitative framework to provide information for these decisions will be documented in the SAP prior to execution of interim(s).

Unblinded interims will be executed through the external DMC. Study sites will receive information about interim results only if they need to know for the safety of their participants or changes to the protocol. For interims that stop the trial early, subjects will proceed to their early discontinuation visit.

Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

The SAP will describe the interim analyses in greater detail, if any are planned.

9.6. Data Monitoring Committee

For details on the DMC, refer to Section 10.1.5.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - applicable International Council for Harmonisation (ICH) GCP Guidelines, and
  - applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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.
- 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, and
  - 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.

10.1.2. Financial Disclosure

Investigators and subinvestigators 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 his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed

consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- As used in this protocol, the term "informed consent" includes all consent and assent given by the participant or their legal representatives and by study partners.
- 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 must be kept on file.

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

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her 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 his/her 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.

10.1.5. Committees Structure

A DMC consisting of members external to Lilly will be established. The purpose of the DMC is to conduct periodic monitoring of clinical trial data for Study AACI. 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 statistical analysis center (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 studies. The timing and frequency of the periodic clinical trial data review by the DMC will be detailed in a DMC charter.

The DMC is authorized to evaluate unblinded interim and safety analyses. In addition, the DMC may request key efficacy data to put safety observations into context and to assess a reasonable benefit/risk profile for ongoing participants in the study. The DMC will make recommendation to the Lilly Research Laboratories Senior Management Designee, who may order the immediate implementation of the DMC recommendation, or may convene an internal review committee, which is independent from the study team, to review the recommendation according to standard Lilly policy. Study sites will receive information about interim results ONLY if it is required for the safety of their participants or change in protocol.

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, and Study SAPs, 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.clinicalstudydatarequest.com.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on a printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., 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.
- Monitoring details describing strategy (e.g., 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 15 years after study completion 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, the 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 the sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

An electronic data capture (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) will be collected by the participant/partner and/or authorized study personnel via a paper source document and will be transcribed by authorized study personnel into the EDC system.

Additionally, eCOA data (participant-focused outcome instrument) will be directly recorded by authorized study personnel into an instrument (for example, tablet). The eCOA data will serve as the source documentation and the investigator will not maintain a separate, written or electronic, record of these data.

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

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

and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that 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.

10.1.9. Study and Site Start and Closure

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 site open and will be the study start date.

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:

- 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 of participants by the investigator, and
- discontinuation of further IP development.

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

The publication policy for Study AACI is described in the Clinical Trial Agreement.

10.1.11. Investigator Information

Physicians with a specialty in neurology, geriatrics, or psychiatry will participate as investigators in this clinical trial. In addition, licensed clinicians who have clearly documented experience in AD may participate as investigators in this clinical study.

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).
- 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 as required by local regulations.
- In circumstances where the sponsor approves local laboratory testing in lieu of central testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulation.

Investigators must document their review of the laboratory safety results.

Laboratory analyte results denoted below that could unblind the study will not be reported to investigative sites or other blinded personnel.

Clinical Laboratory Tests	**Comments**
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs)	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBC and WBC)	
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
ALP	

ALT	
AST	
GGT	
BUN	
Creatinine	
CK	
Uric acid	
Albumin	
Calcium	
Glucose	
Cholesterol	
Urinalysis	
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Blood	
Urine leukocyte esterase	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)	
Urinary protein/creatinine ratio (UPCR)	
PK Samples – donanemab concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Biomarkers	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
ApoE	
NfL/GFAP	
P-tau	
Aβ	
Pharmacogenetics sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory storage samples:	All samples will be collected at all visits except for the Lead-In Screening. Plasma only will be collected at the Lead-In Screening Visit.
Serum	

Plasma (EDTA)	
Paxgene RNA tube	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-donanemab antibodies	
Anti-donanemab antibodies neutralization	
Hypersensitivity Tests (IRR kit)	Selected tests may be obtained in the event of infusion related reaction, anaphylaxis or systemic allergic/hypersensitivity reactions. These should be collected as soon after the event as possible (optimally 30 minutes to 2 hours after the start of the event and after participant has been stabilized as necessary). Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-donanemab antibodies (Immunogenicity)	
Donanemab Concentrations (PK)	
Tryptase	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. Collect and repeat in approximately 4 weeks for post event baseline
Urine N-methylhistamine (NMH)	Obtain only if tryptase sample was collected >2 hours after the hypersensitivity event. Collect and repeat in approximately 4 weeks for a post event baseline.
IgE	
Basophil Activation Test	Will be performed if a validated assay is available.
Complement (C3a and C5a)	
Cytokine Panel	

Abbreviations: Aβ = amyloid beta; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoE = apolipoprotein E; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; EDTA = Ethylenediaminetetraacetic acid; GFAP = glial fibrillary acidic protein; GGT = gamma-glutamyl transferase; IgE = immunoglobulin E; NfL = neurofilament light chain; NMH = N-methylhistamine; RBC = red blood cell; PK = pharmacokinetics; P-tau = phosphorylated tau; RNA = ribonucleic acid; WBC = white blood cells.

10.3. Appendix 3: 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 or clinical study participant, temporally associated with the use of IP, whether or not considered related to the IP. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IP.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, or vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition. • New condition(s) detected or diagnosed after IP 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 IP 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/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 an AE/SAE if they fulfill the definition of an AE/SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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 (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that at any dose:

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 the hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

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 (e.g., 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

f. Other situations:

- Medical or scientific judgment should be exercised 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. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the 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 the 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: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 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 IP and each occurrence of each AE/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her 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 the 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 the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the 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 the sponsor or designee with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. 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 paper SAE data collection tool (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 paper SAE form (see next section) or to the medical monitor by telephone.
- SAE reporting is done through the eCRF.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found on the paper CRF.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-Up Assessments

Selected tests may be obtained in the event of a TE hepatic abnormality and may be required in follow-up with participants in consultation with the sponsor-designated medical Monitor.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Antinuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by the sponsor-designated laboratory.

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

10.5. Appendix 5: Flortaucipir F18 Tau PET Imaging

Flortaucipir F18 PET scans will be performed as part of the study eligibility criteria and as indicated in the SoA (Section 1.3).

For inclusion and exclusion criteria related to the flortaucipir F18 PET scans, refer to Sections 5.1 and 5.2.

Site investigators, participants, and study partners will only be informed of the eligibility results of PET scans obtained prior to randomization, as they relate to the study, and will not be informed of scan results obtained post randomization. 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 F18 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 AACI's PET scans.

	Effective Dose (mSv) per Scan*	Number of Scans in First Year**	Effective Dose (mSv) for Scans in First Year	Number of Scans in Second Year**	Effective Dose (mSv) for Scans in Second Year	Number of Scans in Third Year**	Effective Dose (mSv) for Scans in Third Year	Number of Scans in Fourth Year**	Effective Dose (mSv) for Scans in Fourth Year	Sum of Effective Dose (mSv) for Years 1, 2, 3, and 4
Flortaucipir F18 Scan (10 mCi IV)	9.10	1	9.10	1	9.10	0	0	1	9.10	27.30
Florbetapir F18 Scan (10 mCi IV)	7.43	2	14.86	2	14.86	2	14.86	1	7.43	52.01
Total		3	23.96	3	23.96	2	14.86	2	16.53	79.31

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

*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.

** In the event of an ED scan, up to 1 additional flortaucipir F18 and/or 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.

10.6. Appendix 6: Florbetapir F18 Amyloid PET Imaging

Florbetapir F18 PET scans will be performed as part of the study eligibility criteria to determine participant eligibility for participation in Study AACI. Additional florbetapir F18 PET scans will be performed as indicated in the SoA (Section 1.3). Specific instructions for the florbetapir F18 PET scan itself will be provided in the PET Imaging Manual.

For inclusion and exclusion criteria related to florbetapir F18 PET imaging, see Sections 5.1 and 5.2.

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 above (Section 10.5) 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.

10.7. Appendix 7: Removed

Appendix 7 is removed.

10.8. Appendix 8: Abbreviations

Term	Definition
Aβ	amyloid beta
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog$_{13}$	Alzheimer's Disease Assessment Scale – Cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
ADCS-iADL	Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	analysis of variance
ApoE	apolipoprotein E
ARIA	amyloid-related imaging abnormalities
AST	aspartate aminotransferase
bADL	basic Activities of Daily Living
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment, but the participant is not, or vice versa, or when the sponsor is aware of the treatment, but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CK	Creatine kinase
CIOMS	Council for International Organizations of Medical Sciences

Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
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, GCP, and applicable regulatory requirements.
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
cSS	cortical superficial siderosis
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
Device Deficiencies	Equivalent to product complaint
DMC	data monitoring committee
DSST	Digit symbol substitution test
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
ED	early discontinuation
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 ICF directly or through their legally acceptable representatives.
FLAIR	fluid attenuation inversion recovery
GCP	good clinical practice
GGT	Gamma-glutamyl transferase
iADRS	integrated Alzheimer's Disease Rating Scale
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 his or her 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 ICF.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the complete reporting database for the primary outcome is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical 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.
IP	investigational product
IRR	infusion-related reaction
ITT	intent-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
IVIG	Intravenous immunoglobulin
IWRS	interactive web-response system
MAD	Multiple-ascending dose
MCI	mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NCS	Natural Cubic Spline
N3pG Aβ	Pyroglutamate modification of the third amino acid of amyloid beta
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
PD	pharmacodynamics
PET	positron emission tomography
PI	principal investigator
PK	pharmacokinetics
PRN	As needed
PRO	patient-reported outcomes
P-tau	phosphorylated tau
Q2W	every 2 weeks
Q4W	every 4 weeks
QTc	corrected QT interval
QTcF	Fridericia's formula
RNA	ribonucleic acid
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.
SUSARs	suspected unexpected serious adverse reactions
SUVr	Standardized Uptake Value ratio
TBL	total bilirubin level
TE	treatment-emergent
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TPO	third-party organization
ULN	upper limit of normal
vMRI	volumetric magnetic resonance imaging
WOCBP	women of childbearing potential

10.9. Appendix 9: Protocol Amendment History

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

The amendment is considered to be substantial because it is likely to have a significant impact on the scientific value of the trial.

Overall Rationale for the Amendment:

This amendment adds a long-term extension phase to Study AACI. The extension period is designed to further evaluate donanemab efficacy and safety over time.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Aligned to changes in text of the body.	Rationale for each change described below.
1.2. Schema	Added extension period to figure.	Alignment with addition of extension period.
1.3. Schedule of Activities	Added "Contact IWRS – register visit" procedure for all visits.	Clarification. All visits must be registered with IWRS regardless of IP dispensation.
	Added note for "Contact IWRS – dispensation of IP" that this procedure is for visits where IP will be dispensed.	Clarification.
	Added eGFR (CKD-EPI) to clinical chemistry.	Clarification.
	Added UPCR to urinalysis.	Clarification.
	Modified note for postdose PK: "Collect within 30 minutes of IP ~~administration~~ infusion completion."	Clarification.
	Added MRI at V3. Added text to Comment 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.
	Changed V3 tolerance interval from "±7" days to "–7 to +10" days.	To provide additional time to perform and review MRI prior to infusion.

Section # and Name	Description of Change	Brief Rationale
	Added MRI at V23. Added text to Comment field about MRI at V23, including text about MRI timings relative to V22 infusion and fourth extension period infusion.	To allow for better characterization of the incidence and severity of ARIA at an earlier time point.
	Changed V23 tolerance interval from "±7" days to "–7 to +10" days.	To provide additional time to perform and review MRI prior to infusion.
	Moved follow-up column (V801-804) to extension phase table.	Organization.
	Added footnote describing follow-up visits as occurring 12 weeks after the last dose of IP.	Clarification.
	Renamed ED visit as EDa.	Clarification. The extension phase has a separate ED visit, named EDb.
	Added SoA table for extension period.	Extension period added to study.
	Modified footnote b: "The participant should meet ~~all other~~ MMSE eligibility criteria before the screening flortaucipir F18 PET scan, MRI, and florbetapir F18 PET scan."	Correction.
	Added footnote d, which describes follow-up visits 801 through 804.	Clarification.
2.1. Study Rationale	Modified description of primary endpoint.	Alignment with change to primary endpoint.
	Added rationale for addition of long-term extension period.	Extension period added to study.
2.2.2. Donanemab Clinical Studies	Updated section.	Update to reflect new information.
3. Objectives and Endpoints	Modified the primary endpoint to include the overall population.	Opportunity to test the overall population.

Section # and Name	Description of Change	Brief Rationale
	Combined 2 of the secondary objective/endpoints. (High tau population will be described in the SAP as an exploratory objective.)	Organization.
	Added objectives and endpoints for the extension period.	Extension period added to study.
4.1. Overall Design 4.1.3. Extension Period (Visits 22 through 41)	Added design details for the extension period.	Extension period added to study.
4.1.2. Double-Blind Period (Visits 2 through 21)	Modified text: Participants who meet entry criteria will be enrolled and randomized to … donanemab or placebo during the double-blind period."	Clarification.
4.1.4. Follow-Up (Visits 801 through 804)	Moved from 4.1.3. to 4.1.4. Removed references to week numbers for the follow-up period. Removed text related to an extension protocol. Added a note that follow-up may not be required for some participants.	Organization. Clarification. Follow-up will occur 12 weeks after the final dose of IP is administered. Extension period added to study. Clarification.
4.2. Scientific Rationale for Study Design	Modified text: "Inclusion of a placebo treatment arm is acceptable because there are no confirmed clinically ~~currently~~ effective disease modifying treatments for AD;…".	Clarification.
	Added rationale for the long-term extension period.	Extension period added to study.
4.4. End of Study Definition	Added definition for end of the study.	Extension period added to study. Added definition for clarity.

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Modified Inclusion Criterion 7: added CDR and ADCS-ADL to the list of study partner assessments that may be conducted by phone.	Add flexibility.
6.3. Measures to Minimize Bias: Randomization and Blinding	Added assignment and blinding information for the extension period.	Extension period added to study.
6.5.1. Standard of Care for Alzheimer's Disease	Added clarification that standard of care medications "should remain constant when possible throughout the double-blind period and extension period (Visit 2 to Visit ~~21~~41).	Extension period added to study.
6.5.3. Excluded Medications	Added note concerning concurrent use of passive anti-amyloid immunotherapies.	Clarification.
6.6. Dose Modification	Added text: "For participants who develop ARIA during the titration period (that is, before the fourth infusion of study drug of the double-blind or of the extension period), the investigator may decide to…".	Extension period added to study. Added text for clarity.
	Modified text: "continue the same ~~pre-suspension~~ dose…".	Clarification.
	Added "or as described below" in first sentence.	Clarification.
6.7. Intervention after the End of the Study	Updated subsection to reflect addition of the extension period.	Extension period added to study.
7.1. Discontinuation of Study Intervention	Added cross-reference to the Manual of Operations regarding information about permanent discontinuation guidance.	To provide further guidance.

Section # and Name	Description of Change	Brief Rationale
7.1.1.1. Due to ARIA	Added 2 cross-references to the Manual of Operations regarding information about temporary discontinuation guidance. Modified text (2 instances) regarding considering reinitiating IP.	To provide further guidance. Recommendation of DMC
8.1. Efficacy Assessments	Specified that RUD-Lite and QOL-AD must be administered by a different rater than the CDR.	Addition of RUD-Lite and QOL-AD as described below for Section 8.10.
8.1.2.3. CDR	Added note regarding administering the CDR by phone.	Clarification.
8.2.5. Magnetic Resonance Imaging	Added text to allow performance of unscheduled MRIs	Clarification.
8.3.1. Time Period and Frequency for Collecting AE and SAE Information	Added text: "but prior to receiving IP or PET tracer…".	Clarification.
8.3.7. Amyloid-Related Imaging Abnormalities (ARIA-E and ARIA-H)	Added text regarding the likely timing of serious ARIA cases based on available data. Added cross-reference to the Manual of Operations regarding management of participants. Updated symptoms and citations.	To provide additional insight into timing of ARIA. To provide further guidance. Update to align with IB.
8.10. Medical Resource Utilization and Health Economics	Added subheader 8.10.1. Added subheader 8.10.2 and description of RUD-Lite. Added subheader 8.10.3 and description of QOL-AD.	Organization. Text not modified. RUD-Lite and QOL-AD are assessments of interest for the extension period.
9. Statistical Considerations	Added text, "…or the overall population."	Alignment with change to primary endpoint.

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Hypotheses	Modified subsection to add changes to primary endpoint and add description of primary endpoint analysis.	
9.2 Sample Size Determination	Added clarifying text regarding the number of participants in Cohort 1.	Clarification.
9.4.1. General Considerations	Added, "Additional efficacy and safety analyses will be conducted based on data collected during the extension period." Also added, "The analyses for any addenda will be included in the Study SAP or an additional addendum-specific SAP.	Clarification.
9.4.1.1. Handling of Missing Items for Scales	Modified text: "Thus, the total score for this example will be the sum of the remaining 11~~2~~ items multiplied by 1.21."	Correction.
9.4.3. Primary Endpoint(s)	Added population description to description of the primary endpoint.	Alignment with change to primary endpoint.
	Added details related to the quadratic model.	Clarification.
	Modified text, "…the mean for each treatment group over the ~~entire~~ double-blind ~~duration~~ period of the study…".	Clarification.
9.4.4. Secondary Endpoint(s)	Added details related to the quadratic model.	Clarification.
9.4.5. Tertiary/Exploratory Endpoint(s)	Added details related to the objectives and endpoints for the extension period.	Extension period added to study.
10.2. Appendix 2: Clinical Laboratory Tests	Arranged CKD-EPI and UPCR under "Calculations" group.	Organization.

Section # and Name	Description of Change	Brief Rationale
10.5. Appendix 5: Flortaucipir F18 Tau PET Imaging	Updated effective radiation dose table.	Extension period added to study.
Throughout	Minor editorial changes.	Minor, therefore, not described.
	Corrected instances of CDR-SB to CDR.	Correction. CDR is the assessment. CDR-SB is a calculation based on the assessment.

Amendment: c (03-Sep-2021)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the conduct or management of the trial.

Overall Rationale for the Amendment:

This amendment increases the sample size by approximately 300 participants and defines an approximately equivalent number of early enrolled participants as Cohort 1. Cohort 1 will be unblinded to the sponsor, but remain blinded at site, participant, and study partner level, at a prespecified timepoint and analyzed prior to the end of the study. Cohort 1 data will be utilized to inform analyses of safety and efficacy of donanemab and planning future studies in Alzheimer's disease. Cohort 2 will remain double-blinded for the duration of the study.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Modified Number of Participants	Alignment with changes made in Section 9.2.
1.2. Schema	Added note related to Cohorts 1 and 2.	Clarification.
4.1.2. Double-Blind Period (Visits 2 through 21)	Added note that Cohort 1 will be sponsor unblinded, as described in Section 9.3.1.	Amendment defines Cohort 1.
6.3. Measures to Minimize Bias: Randomization and Blinding	Added description of blinding for Cohorts 1 and 2.	Amendment defines Cohort 1, which will be unblinded to the sponsor.
	Moved sentence about the DMC being unblinded to randomization.	Organization.
9.2. Sample Size Determination	Increased total study sample size to 1800 (from 1500).	Amendment defines Cohort 1 of 300 randomized participants.
	Added and defined Cohorts 1 and 2.	Regulatory feedback.
	Specified that the power of the study is based on Cohort 2.	The primary analysis will be composed of Cohort 2 only; it will not include Cohort 1.

Section # and Name	Description of Change	Brief Rationale
9.3.1. Cohorts 1 and 2	Added subsection. Provided details related to Cohorts 1 and 2.	To clarify the purpose of Cohort 1, and how the data from Cohort 1 will be used.
9.4.1. General Considerations	Added "Additional database lock(s) may occur."	To accommodate analyses of Cohort 1.
	Added details related to the Cohort 1 SAP and Study SAP.	Clarification.
	Moved paragraph related to change in the data analysis methods.	Organization.
9.5. Interim Analyses	Added safety as a potential reason for conducting an interim analysis.	Cohort 1 analysis will include, but not be limited to, safety.
	Added "Interim analyses of Cohort 1 will be conducted by Lilly." Specified that other interim analyses involving Cohort 2 will be executed through the external DMC.	Only Cohort 1 will be unblinded to sponsor. Cohort 2 will *not* be unblinded to sponsor prior to data lock.
Throughout	Minor editorial corrections. Minor clarifying changes (for example, clarify between Cohort 1 SAP and Study SAP).	Minor, therefore, not described.

Amendment: b (17-Feb-2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment adapts Protocol AACI as a Phase 3 study. The goal of the study is to confirm Phase 2 results.

Section # and Name	Description of Change	Brief Rationale
Title page 2.1 Study Rationale	Updated study to Phase 3	To reproduce and confirm Study I5T-MC-AACG (TRAILBLAZER-ALZ) data.
1.1 Synopsis	Updated to reflect changes in body of protocol.	Rationale described per section.
	Removed text under "Intervention Groups and Duration".	Text repeats information under "Overall Design" in synopsis.
1.2 Schema 1.3 Schedule of Activities	Updated screening window and follow up.	Removed P-tau as an eligibility criterion and step in screening. Follow up timing corrected to align with timing described in Section 4.1.3.
1.3 Schedule of Activities	Removed notes for P-tau assay.	P-tau no longer required for inclusion, therefore notes were no longer applicable.
	Added note for pharmacogenetics and exploratory biomarker sample: "collect unless not allowed or unfeasible due to local regulations.	Clarification.
	Added language to allow for some visits to be conducted remotely.	Add flexibility and decrease participant burden.
	Removed DSST.	Decrease participant burden.
	Added note for C-SSRS-related assessments collection for remote visits.	Add flexibility.
	Removed hematology and clinical chemistry collection at V3 and V4.	Decrease participant burden. Phase 2 data supports collecting less frequently.

Section # and Name	Description of Change	Brief Rationale
	Removed urinalysis at V15.	Decrease participant burden.
	Added PK Sample collection (predose) at V5 and V8.	Predose concentration necessary to interpret results of ADA sample.
	Removed PK Sample collection (postdose) at V20.	Decrease participant burden. Phase 2 data supports not collecting at this visit.
	Removed ECG at V3, V4, V5, V11. Added note that ECG may be collected at the discretion of the investigator.	Decrease participant burden. Adequate sampling at this timepoint.
	Added notes for MRI	Reminder/clarification.
	Added note for Flortaucipir F18 PET scan regarding V21.	Clarification/flexibility depending on regional availability and sponsor discretion.
	Updated footnote a to include DSST medicines version.	Reminder/clarification.
2.1 Study Rationale	Updated assessment and analysis population.	Aligned with changes in Section 9 Statistical Considerations.
2.2.2 Donanemab Clinical Studies	Updated description of Study AACG.	Update.
3. Objectives and Endpoints	Changed primary analysis from CDR-SB in overall population or low-medium tau population to iADRS in the low-medium tau population.	Adapting as a Phase 3 study, therefore updating primary endpoint to confirm Phase 2 results.
	Added CDR-SB, removed iADRS as secondary endpoints in low-medium tau population.	Update per change to primary endpoint.
	Defined populations for secondary endpoints: iADRS, CDR-SB-ADAS-Cog_{13}, ADCS-iADL, and MMSE.	Adding specificity.
	Removed DSST from exploratory endpoints.	DSST no longer collected

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Updated total duration of study, screening duration, and follow up.	Alignment with Section 1.2 Schema and Section 1.3 Schedule of Activities. See rationale above.
4.1.1 Lead-In and Screening Period (Visits 601 and 1)	Removed the P-tau assay as a screening assessment for eligibility.	P-tau assay removed as a step in screening and eligibility criterion.
4.1.1.1 Visit 601 4.1.1.2 Visit 1	Created subsections. Reorganized text to discuss Visits 1 and 601 separately.	Clarity and organization.
4.1.3 Follow-Up (Visits 801 through 804)	Removed list of specific assessments.	Detailed in the Schedule of Activities.
	Added statement describing when follow up visits may not be necessary.	Follow up visits may not be necessary for participants who enroll in an extension study that includes these assessments.
4.2 Scientific Rationale for Study Design	"…there are no currently effective ~~available~~ disease modifying treatments for AD…"	Clarification.
	Removed sentence describing provision for if donanemab meets success factors for late-stage clinical development.	Scenario described in Section 6.7.
	Removed description of CDR-SB	Alignment with updated primary endpoint.
4.3 Justification for Dose	Removed text related to clinical data described in Section 2.2.2.	Text was redundant with prior section.
	Changed description of safety data from Study AACD.	Safety data no longer preliminary.
4.4 End of Study Definition	Added definition for end of the study.	Clarification.
5.1 Inclusion Criteria	Criterion 4 removed, which required P-tau assay results for screening.	P-tau results or historical positive AD pathology is no longer required for progression to imaging assessments.
	Criterion 7: added 'or available by phone' for study partner.	Added flexibility. Clarification.

Section # and Name	Description of Change	Brief Rationale
	Modified language related to assessments requiring a study partner be available by telephone.	
	Criterion 10: modified criterion to specify concomitant medications for symptomatic AD or medications that may impact cognition. Changed time point from 1 month to approximately 30 days.	Add flexibility.
6.1 Study Intervention(s) Administered	Updated where detailed instructions for administration is found.	Clarification.
	Added requirement for resuscitation equipment and rescue medications to be available wherever the IP is administered.	Added instructions for safety.
6.4 Study Intervention Compliance	Updated language to be inclusive of visits not at the site.	Clarification and added flexibility.
6.5.1 Standard of Care for Alzheimer's Disease	Modified time point for unchanged dose of symptomatic treatments for AD.	Alignment with Inclusion Criterion 10.
	Added statement describing that modification of symptomatic treatments for AD is permitted when medically indicated.	Clarification.
6.5.2 Medications for Infusion Reactions	Removed 'after consultation with a Lilly Medical Monitor'.	Inclusion or continuation of the participant is at the discretion of the investigator.
	Added reminder for completing the related CRF.	Reminder/Clarification.
6.6 Dose Modification	Updated language to more clearly outline investigator options for participants who	Clarification.

Section # and Name	Description of Change	Brief Rationale
	develop ARIA during the titration period.	
6.7 Intervention after the End of the Study	Modified language describing potential for participants to enroll in an extension protocol.	Added details.
7.1 Discontinuation of Study Intervention	Removed redundant text related to PK sampling.	Redundant with text in Section 8.5.
	Added language related to systemic hypersensitivity reaction.	Safety: added details.
7.1.1.1 Due to ARIA	Updated language describing ARIA events.	Alignment with current safety data.
	Removed requirement that discontinuation and re-initiation must be discussed with the sponsor.	These decisions are at the discretion of the investigator. Investigator may discuss decision with sponsor if desired.
	Moved text related to AE reporting to 8.3.7. Added cross reference.	Organization of information within document.
7.1.1.2. Due to Reasons Other than ARIA	Added 'exceptional circumstances' as a potential reason to temporarily discontinue IP.	Allowance for exceptional circumstances.
8.1 Efficacy Assessments	Added 'where local guidelines permit' for audio voice recordings.	Clarification.
	Modified note language concerning which assessments must or should be administered by a different rater.	Clarification.
	Minor edit to describe that any procedure can be conducted on other days within the visit window.	Clarification.
8.1.1 Primary Efficacy Assessment 8.1.2.3 CDR-SB	Switched text between the subsections.	Alignment with change of primary efficacy assessment.

Section # and Name	Description of Change	Brief Rationale
8.1.2.5 Biomarker Efficacy Measures	Removed scheduling language.	Not relevant to section. Scheduling described in Section 1.3.
8.2.4 Clinical Safety Laboratory Assessments	Modified language to instructions.	Clarification of instructions.
8.2.7 Suicidal Ideation and Behavior Risk Monitoring	Modified language, "Participants ~~being treated with donanemab~~ should be…"	Study is double blinded. Therefore, all participants should be monitored appropriately.
8.3 Adverse Events and Serious Adverse Events	Removed language related to experimental devices.	The P-tau assay is no longer being used as a screening step.
8.3.6.1 Management of Infusion-Related Reactions 8.3.6.2. Dosing rechallenge and Premedication for Infusions	Updated language and instructions based on current safety data.	Safety: updated to expand reasons for sample collection.
8.3.7 Amyloid-Related Imaging Abnormalities (ARIA-E and ARIA-H)	Moved text related to AE reporting from Section 7.1.1.1.	Clarification. Organization of information in document.
8.3.9 Medical Device Deficiencies	Removed section and related subsections.	The P-tau assay is no longer being used as a screening step.
8.5 Pharmacokinetics	Modified language to be inclusive of placebo.	Clarification.
9 Statistical Considerations	Updated section and associated subsections to reflect changes to study phase and endpoints.	Alignment with study design changes detailed above.
9.1 Statistical Hypotheses	Removed examples and calculations better described in the SAP to reflect low-medium tau as the primary population.	Clarity, organization of information across documents.
9.2 Sample Size Determination	Increased sample size to 1500 participants. Updated	To confirm results from Study AACG, and to reflect the phase 3 sample size.

Section # and Name	Description of Change	Brief Rationale
	associated calculations to reflect a change to the iADRS.	
9.4.7.2 Pharmacokinetic/ Pharmacodynamic Analyses	Added information regarding PK data lock (no safety or efficacy data included).	To facilitate PK modeling.
9.5 Interim Analyses	Modified language describing interim analyses.	Clarification.
10.1.5 Committees Structure	Modified DMC members description.	Correction.
10.2 Appendix 2: Clinical Laboratory Tests	Added requirements for when the sponsor approves local lab testing in lieu of central testing.	Clarification of requirements.
	Added eGFR (CKD-EPI) and spot urine protein/creatinine.	Safety: proactively monitoring of renal parameters.
	Updated language and instructions for Hypersensitivity Tests (IRR kit) based on current safety data.	Safety: updated to expand reasons and timing of sample collection.
10.5 Appendix 5: Flortaucipir F18 Tau PET Imaging	Updated language related to the safety profile of flortaucipir.	Updated to reflect data available.
10.7 Appendix 7: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting	Removed appendix.	P-tau is no longer a step in the screening process.
Throughout document	Minor editorial changes.	Minor, therefore, not described.

Amendment: a (14-Dec-2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment adds a titration period in response to safety concerns.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 4.1 Overall Design	Added titration period of 700 mg for first 3 doses.	Safety.
1.3 Schedule of Activities 4.1.1 Lead-In and Screening Period (Visits 601 and 1)	Changed extra days added to the tolerance interval when P-tau results are needed from V1 from 7 to 10.	Operational considerations: result turnaround time longer than initially anticipated.
1.3 Schedule of Activities 3 Objectives and Endpoints	Corrected abbreviation for DSST.	Correction.
4.1.1 Lead-In and Screening Period (Visits 601 and 1)	Added exception for the screening tolerance window for temporary randomization pauses.	Operational considerations.
4.3 Justification for Dose	Added justification for titration doses.	Addition of titration schedule.
6.4 Study Intervention Compliance	Added instructions for when a participant does not complete the titration phase.	Safety.
6.6 Dose Modification	Added instructions for when a participant develops ARIA.	Safety.
8.1.2.4 ADCS-ADL	Corrected description of scores, "…~~higher~~ lower scores indicating greater level of impairment."	Correction.
9.4.1.1 Handling of Missing Items for Scales	Corrected iADRS score calculation.	Correction.
Throughout	Editorial changes	Minor editorial changes, therefore, not described.

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