Protocol I5T-MC-AACH (b)

Donanemab Follow-On Study: Safety, Tolerability, And Efficacy in Symptomatic Alzheimer's Disease With Validation of Remote Neuropsychological Assessments

NCT04640077

Approval Date: 11-OCT-2021

Title Page

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Protocol Title: Donanemab Follow-On Study: Safety, Tolerability, And Efficacy in Symptomatic Alzheimer's Disease with Validation of Remote Neuropsychological Assessments

Protocol Number: I5T-MC-AACH

Amendment Number: b

Compound: Donanemab (LY3002813)

Study Phase: Phase 2

Short Title: Donanemab Follow-On Study, with Validation of Remote Scale Assessment

Acronym: TRAILBLAZER-EXT

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number

IND: 109157

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

Approval Date: 11-Oct-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	*27-Jan-2021*
Original Protocol	*01-Sep-2020*

Amendment b

Overall Rationale for the Amendment:

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

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Added MRI at V2. Added text to Comment field about MRI at V2, 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 V2 interval tolerance from "±7" days to "–7 to +10" days.	To provide additional time to perform and review MRI prior to infusion.
6.5.1. Standard of Care for Alzheimer's Disease	Added "When medically indicated, initiation, increase, or discontinuation of symptomatic treatments for AD is permitted."	Clarification.
7.1. Discontinuation of Study Intervention	Added cross-reference to the Manual of Operations regarding information about permanent discontinuation guidance.	To provide further guidance.
7.1.1.1. Due to ARIA	Added cross-references to the Manual of Operations regarding information about temporary and permanent discontinuation guidance.	To provide further guidance.
	Modified text regarding considering reinitiating IP.	Recommendation of DMC.
8.2.5. Magnetic Resonance Imaging	Added text, "Unscheduled MRIs may be performed at the discretion of investigator."	Clarification.

Section # and Name	Description of Change	Brief Rationale
8.3.6.2. Dosing Rechallenge and Premedication for Infusions	Added dosing rechallenge details.	Clarification/providing information.
8.3.7. Amyloid-Related Imaging Abnormalities (ARIA-E and ARIA-H)	Added text "While most cases of ARIA-E are asymptomatic, serious cases have been reported. Available data suggest serious cases are most likely to occur early in dosing, after the first, second, or third infusion."	Provided additional information.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: Donanemab Follow-On Study: Safety, Tolerability, And Efficacy in Symptomatic Alzheimer's Disease with Validation of Remote Neuropsychological Assessments

Short Title: Donanemab Follow-On Study, with Validation of Remote Scale Assessment

Rationale:

Part A

Remote assessments of individuals with AD via telemedicine have the potential to reduce burdens associated with clinical care and research participation. Research comparing clinical interviewing conducted through video conferencing and traditional on-site conditions has suggested generally good agreement in a variety of conditions, including dementia and cognitive impairment of various causes. However, limited data is available on the validity of remote web-based assessment of cognitive and functional measures typically implemented in AD research studies. Therefore, the aim of Study I5T-MC-AACH (AACH) Part A is to evaluate the validity of remote (at-home) video assessments of cognitive and functional measures.

Study AACH Part A is a multicenter, randomized, multiple crossover study to validate remote assessment of cognitive and functional scales. Participants will be assessed remotely (through videoconferencing) as well as on-site.

Part B

Part B is a multicenter, open-label study of donanemab treatment for participants with symptomatic AD and naïve to donanemab.

Study AACH Part B will provide additional safety and clinical information as an open-label study. Participants from a sponsor-approved originating donanemab study who were assigned placebo will receive donanemab in the single open-label arm.

Part C

Those who received donanemab in an originating study may participate in a single imaging and cognitive/functional assessment visit.

Study AACH Part C will assess the long-term effect of donanemab on PET imaging biomarkers, cognition, and functioning in participants who have not received IP for at least 52 weeks.

Objectives and Endpoints

Objectives	Endpoints
Primary	
Part A To evaluate the reliability of VTC compared with on-site administered cognitive and functional measures	The intraclass correlation between VTC and on-site assessment for PAIR 1 for • ADAS-Cog$_{13}$ • ADCS-ADL • MMSE • CDR-SB
Part B To evaluate safety and tolerability of donanemab	Standard safety assessments in Part B: • 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
Secondary	
To assess the effect of donanemab on clinical progression in participants with symptomatic AD	Change from baseline up to Week 72 as measured in Part B by: • MMSE score • ADAS-Cog$_{13}$ score • iADRS score • ADCS-iADL score • CDR-SB
To assess the effect of donanemab on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline at Week 36 of Part B as measured by florbetapir F 18 PET scan

To assess the effect of donanemab on brain region volumes	Change in volumetric MRI measures from baseline to Week 72 in Part B
To assess peripheral PK and presence of anti-donanemab antibodies	PK of donanemab in Part B. ADAs against donanemab in Part B including • treatment-emergent ADAs • neutralizing antibodies

Abbreviations: AD = Alzheimer's disease; ADA = antidrug 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; ARIA = amyloid-related imaging abnormality; 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; VTC = video teleconference.

Overall Design

Part A:

The video validation period is a multiple crossover design with participants alternating between in-clinic assessments and at-home assessments of cognitive and functional scales over a minimum of 1 and a maximum of 3 crossovers. Total time in Part A can vary from a minimum of 4 weeks (1 crossover [1 PAIR]) to a maximum of 24 weeks (3 crossovers [3 PAIRS]). Participants do not receive study IP during the video validation period. Participants are randomized 1:1 in regards to order of in-clinic or at-home for the first assessment, either:

- Group 1: Cognitive/functional scale assessment at the study site (on-site), followed by an at-home assessment (VTC), or
- Group 2: Cognitive/functional scale assessment at home (VTC), followed by assessment on-site.

Part B:

Part B is a multicenter, open-label, follow-on study of donanemab in participants with symptomatic AD. Participants who received placebo in the originating trial receive donanemab 700 mg IV Q4W for 3 doses, then 1400 mg intravenously every 4 weeks for up to 36 weeks, (up to 48 weeks total duration in Part B).

Participants may receive donanemab through Week 36 or Week 48. Criteria for scheduled dose discontinuation at 36 weeks are defined by the sponsor and may be based on results of the participant's florbetapir F 18 PET scan at Week 36 or results from external studies such as Study AACG.

Part C:

Participants who received donanemab in the originating trial may participate in an imaging and cognitive/functional assessment visit (Visit 201). Visit 201 occurs anytime at least 52 weeks from the participant's last double-blind visit in the originating study.

Disclosure Statement:
This is a single-arm treatment study with 1 arm that is not blinded.

Number of Participants:

Approximately 200 participants will be enrolled such that approximately 150 participants complete the study.

Intervention Groups and Duration:

Part A: The video validation period is a multiple crossover design with participants alternating between in-clinic assessment and at-home assessment of cognitive and functional scales over a minimum of 1 and a maximum of 3 crossovers. Total time in Part A can vary from a minimum of 4 weeks (1 crossover [1 PAIR]) to a maximum of 24 weeks (3 crossovers [3 PAIRS]). Participants do not receive study IP during the video validation period. Participants are randomized 1:1 in regards to order of in-clinic or at-home for the first assessment, either:

- Group 1: Cognitive/functional scale assessment at the study site (on-site), followed by an at-home assessment (VTC; video teleconference) or
- Group 2: Cognitive/functional scale assessment at home (VTC), followed by assessment on-site.

Part B: Participants who received placebo in the originating trial receive donanemab 700 mg IV Q4W for 3 doses, then 1400 mg IV every 4 weeks for up to 36 weeks (up to 48 weeks total duration in Part B).

Part C: Participants who received donanemab in the originating trial may participate in an imaging and cognitive/functional assessment visit (Visit 201). Visit 201 occurs anytime at least 52 weeks from the participant's last double-blind visit in the originating study.

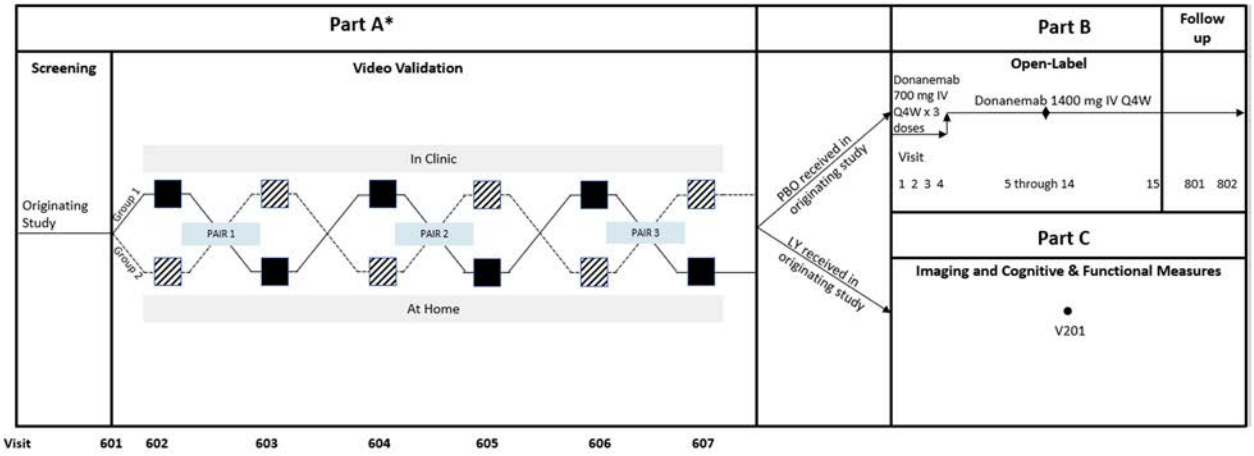
The maximum total duration of study participation for each participant, including screening and the posttreatment follow-up periods, is up to 124 weeks:

- Screening: up to 30 days prior to Visit 602
- Part A, Video assessment: up to 24 weeks
- Part B, Open-label donanemab: up to 72 weeks (treatment received for 36 or 48 weeks)
- Part B, Follow-up: up to 24 weeks

Note: Part C is not added to the maximum total duration of study participation because Part C is a single visit, and Part B participants do not participate in Part C.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: IP = investigational product; IV = intravenous; LY = donanemab; PBO = placebo; Q4W = every 4 weeks; SoA = Schedule of Activities; V = visit.

* Participant should participate in PAIR 1 to proceed to Part B or Part C. V601 occurs up to 30 days prior to V602. Visits in Part A are each separated by 4 weeks. The time between the final visit of Part A and the first visit of Part B or Part C is ≥4 weeks.

♦ IP is administered up to V13 but may be discontinued as early as V10. Visits continue until end of study as indicated in the SoA.

● Imaging and cognitive & functional measures visit occurs any time ≥52 weeks after the participant's last double-blind visit in the originating study. See V201 in the SoA for procedures.

1.3. Schedule of Activities (SoA)

Screening and Part A

	Screening	Part A: Video Validation		Comments
Visit Number	601	602-607		
Weeks Relative to Baseline (V1)	See footnote a.			
Visit Interval Tolerance (days)	–	±4	±4	
Entry and Administrative				
Full informed consent (participant and study partner)	X			
Inclusion and exclusion criteria, review and confirm	X			
Interval medical history, including relevant changes since last visit of originating study	X			
Substance use (alcohol, caffeine, tobacco use)	X			
Concomitant medications	X	X	X	
AEs	X	X	X	
Clinical Assessments				
Physical/neurological examination	X			Complete 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.

	Screening	Part A: Video Validation		Comments
Visit Number	601	602-607		
Weeks Relative to Baseline (V1)	See footnote a.			
Visit Interval Tolerance (days)	–	±4	±4	
Clinician-Administered Assessments (Electronic)				
ADAS-Cog_{13}		X	X	Administer the ADAS-Cog_{13}, ADCS-ADL, CDR-SB, and MMSE prior to medical procedures that could be stressful to the participant (blood draws, etc.; Section 8.1.2). These tests include the audio voice recording of the rater's questions and the participant and study partner responses to assessment questions.
ADCS-ADL		X	X	
CDR-SB		X	X	
MMSE		X	X	
Randomization				
Randomization	X			

Part B

		Part B: Open-Label															Part B: Follow-Up, UV, ED				Comments
Visit Number	UP[b]	1	2	3	4	5	6	7	8	9	10	11[c]	12[c]	13[c]	14[c]	15	801[d]	802[d]	UV	ED	ED only if participant has completed V1 and received IP in Part B.
Weeks Relative to Baseline (V1)		0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96	997		Procedures for some visits may take more than 1 day.
Visit Interval Tolerance (days)		—	-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			
Entry and Administrative																					
Review MRI, clinical labs, and clinical status		X																			Confirm participant does not meet discontinuation criteria (Section 7.2).
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Assessments																					
Height		X																			
Weight		X			X			X			X			X	X			X	X	X	

		Part B: Open-Label															Part B: Follow-Up, UV, ED				Comments
Visit Number	UP[b]	1	2	3	4	5	6	7	8	9	10	11[c]	12[c]	13[c]	14[c]	15	801[d]	802[d]	UV	ED	ED only if participant has completed V1 and received IP in Part B.
Weeks Relative to Baseline (V1)		0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96	997		Procedures for some visits may take more than 1 day.
Visit Interval Tolerance (days)		–	-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sitting BP, pulse, and temperature (with sitting vitals) will be measured at all visits. Sitting BP and pulse will be measured after approximately 5 minutes in the sitting position only. In addition, orthostatic BP and pulse will be measured at V1, V4, V7, V10, V13, V14, ED, and UVs.
Physical/neurological examination		X			X			X			X			X		X		X	X	X	Includes neurological examination V601 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.

		Part B: Open-Label															Part B: Follow-Up, UV, ED				Comments
Visit Number	UP[b]	1	2	3	4	5	6	7	8	9	10	11[c]	12[c]	13[c]	14[c]	15	801[d]	802[d]	UV	ED	ED only if participant has completed V1 and received IP in Part B.
Weeks Relative to Baseline (V1)		0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96	997		Procedures for some visits may take more than 1 day.
Visit Interval Tolerance (days)		–	-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			
12-lead ECG (central or local)		X			X			X			X			X	X					X	Perform prior to administration of IP, when appropriate. ECG at V14 not required for participants who completed dosing at V10.

		Part B: Open-Label															Part B: Follow-Up, UV, ED				Comments
Visit Number	UP[b]	1	2	3	4	5	6	7	8	9	10	11[c]	12[c]	13[c]	14[c]	15	801[d]	802[d]	UV	ED	ED only if participant has completed V1 and received IP in Part B.
Weeks Relative to Baseline (V1)		0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96	997		Procedures for some visits may take more than 1 day.
Visit Interval Tolerance (days)		—	-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			
PET Scans and MRI																					
MRI	X		X		X						X					X				X	Perform prior to V1 at UP if last recorded MRI from originating study occurred >12 months before V1. MRI at V2 is to be performed and reviewed prior to V2 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 V4 is to be performed and reviewed prior to V4 infusion. MRI at V4 may occur 14 days before the scheduled visit date without protocol deviation.

		Part B: Open-Label															Part B: Follow-Up, UV, ED				Comments
Visit Number	UP[b]	1	2	3	4	5	6	7	8	9	10	11[c]	12[c]	13[c]	14[c]	15	801[d]	802[d]	UV	ED	ED only if participant has completed V1 and received IP in Part B.
Weeks Relative to Baseline (V1)		0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96	997		Procedures for some visits may take more than 1 day.
Visit Interval Tolerance (days)		—	-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			
Florbetapir F 18 PET scan											X									X[e]	Florbetapir F 18 PET scan may occur ±14 days from scheduled visit date without protocol deviation.
Clinician-Administered Assessments (Electronic)																					
ADAS-Cog$_{13}$		X			X			X			X			X	X	X	X	X		X	Administer the ADAS-Cog$_{13}$, ADCS-ADL, CDR-SB, and MMSE prior to medical procedures that could be stressful to the participant (blood draws, etc.; Section 8.1.2). These tests include the audio voice recording of the rater's questions and the participant and study partner responses to assessment questions.
ADCS-ADL		X			X			X			X			X	X	X	X	X		X	
CDR-SB (Global Sum of Boxes - CDR)		X			X			X			X			X	X	X	X	X		X	
MMSE		X			X			X			X			X	X	X	X	X		X	
Clinician-Administered Assessments (Paper)																					
C-SSRS Screening/Baseline		X																			

		Part B: Open-Label															Part B: Follow-Up, UV, ED				Comments
Visit Number	UP[b]	1	2	3	4	5	6	7	8	9	10	11[c]	12[c]	13[c]	14[c]	15	801[d]	802[d]	UV	ED	ED only if participant has completed V1 and received IP in Part B.
Weeks Relative to Baseline (V1)		0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96	997		Procedures for some visits may take more than 1 day.
Visit Interval Tolerance (days)		–	-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			
C-SSRS Since Last Visit			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Self-Harm Supplement Form		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Self-Harm Follow-Up Form		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Required if triggered by the Self-Harm Supplement Form per instructions.
Laboratory Tests and Sample Collections[f]																					
Hematology	X	X	X	X	X			X			X			X	X					X	Labs at V14 not required for participants who completed dosing at V10. Perform prior to V1 at UP if last recorded labs from the originating study were collected >6 months before V1.
Clinical Chemistry	X	X	X	X	X			X			X			X	X					X	
P-tau		X			X			X			X			X	X	X	X	X		X	
NfL		X			X			X			X			X	X	X	X	X		X	
Aβ		X			X			X			X			X	X	X	X	X		X	

		Part B: Open-Label															Part B: Follow-Up, UV, ED				Comments
Visit Number	UP[b]	1	2	3	4	5	6	7	8	9	10	11[c]	12[c]	13[c]	14[c]	15	801[d]	802[d]	UV	ED	ED only if participant has completed V1 and received IP in Part B.
Weeks Relative to Baseline (V1)		0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96	997		Procedures for some visits may take more than 1 day.
Visit Interval Tolerance (days)		–	-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			
PK sample (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. Random PK sample collected for participants who do not receive dose at V13.
PK sample (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 administration. Collect from the arm that IP was not administered through.
PK sample (random)															X	X	X	X		X	Do not collect if the last IP infusion was >6 months prior to the scheduled visit.
Immunogenicity (ADA) samples		X	X	X		X		X			X			X	X	X	X	X		X	

		Part B: Open-Label															Part B: Follow-Up, UV, ED				Comments
Visit Number	UP[b]	1	2	3	4	5	6	7	8	9	10	11[c]	12[c]	13[c]	14[c]	15	801[d]	802[d]	UV	ED	ED only if participant has completed V1 and received IP in Part B.
Weeks Relative to Baseline (V1)		0	4	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96	997		Procedures for some visits may take more than 1 day.
Visit Interval Tolerance (days)		–	-7 to +10	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			
Stored Samples																					
Exploratory biomarker samples		X			X			X			X				X			X		X	Collect unless not allowed or unfeasible due to local regulations.
Randomization and Dosing																					
Contact IWRS - dispensation of IP		X	X	X	X	X	X	X	X	X	X	X	X	X							Only contact IWRS at V11, V12, and V13 for participants receiving IP for 48 weeks.
Administer IP		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. Only administer IP at V11, V12, and V13 for participants receiving IP for 48 weeks.

Part C

	Part C	Comments
Visit Number	201	
Timing	Any time ≥52 weeks after participant's last double-blind visit in the originating study.	Procedures may take more than 1 day.
PET Scans		
Flortaucipir F 18 PET scan	X[g]	
Florbetapir F 18 PET scan	X[g]	
Clinician Administered Assessments (Electronic)		
ADAS-Cog_{13}	X	If a PET scan is done on the same day, administer the ADAS-Cog_{13}, ADCS-ADL, CDR-SB, and MMSE prior to PET scan. These tests include the audio voice recording of the rater's questions and the participant and study partner responses to assessment questions.
ADCS-ADL	X	
CDR-SB (Global Sum of Boxes - CDR)	X	
MMSE	X	
P-tau	X	
NfL	X	
Aβ	X	
Exploratory biomarker samples	X	Collect unless not allowed or unfeasible due to local regulations.
AEs	X	
Concomitant medications	X	

Abbreviations: Aβ = amyloid beta; ADA = antidrug antibody; ADAS-Cog_{13} = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; AE = adverse event; BP = blood pressure; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; C-SSRS = Columbia Suicide Severity Rating Scale; CRF = case report form; ECG = electrocardiogram; ED = early discontinuation; IP = investigational product; IV = intravenous; IWRS = interactive web-response system; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; NfL = neurofilament light chain; PET = positron emission tomography; PK = pharmacokinetics; P-tau = phosphorylated tau; UP = unscheduled procedure; UV = unscheduled visit; V = visit.

a V601 occurs up to 30 days prior to V602. V602 cannot occur <30 days from the participant's last double-blind visit of the originating study. V602 through V607 each occur 4 weeks apart. Part A visits may occur up to 24 weeks prior to Part B (V1), for eligible participants. The exact week relative to V1 depends on the number of PAIRs in which the participant elects to participate. The time between the final visit of Part A and the first visit of Part B or Part C is ≥4 weeks.

b UP takes place at the start of Part B (prior to V1), and is only conducted if: participant's last MRI from the originating study is >12 months from V1, or last labs from the originating study were collected >6 months from V1. The investigator confirms continued eligibility as described in Section 7.2.

c V11 and V12 do not occur for participants with a final dose at or before V10. Participants resume the visit schedule with V13 (Week 48). V14 may be optional for some participants, as determined by the sponsor.

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

e For Part B ED visit, collect florbetapir F 18 PET scan only if a florbetapir F 18 PET scan has not yet been performed and participant has received at least 3 doses of donanemab.

f Unscheduled lab tests may be performed at the discretion of the investigator. Collect labs prior to administration of IP, unless otherwise noted.

g Perform the flortaucipir F 18 and florbetapir F 18 PET scans ≥16 hours apart from each other.

2. Introduction

2.1. Study Rationale

Part A

Remote assessments of individuals with AD via telemedicine have the potential to reduce burdens associated with clinical care and research participation. Research comparing clinical interviewing conducted through video conferencing and traditional on-site conditions has suggested generally good agreement in a variety of conditions, including dementia and cognitive impairment of various causes. However, limited data is available on the validity of remote web-based assessment of cognitive and functional measures typically implemented in AD research studies. Therefore, the aim of Study I5T-MC-AACH (AACH) Part A is to evaluate the validity of remote (at-home) video assessments of cognitive and functional measures.

Study AACH Part A is a multicenter, randomized, multiple crossover study to validate remote assessment of cognitive and functional scales. Participants will be assessed remotely (through videoconferencing) as well as on-site.

Part B

Part B is a multicenter, open-label, study of donanemab treatment for participants with symptomatic AD and naïve to donanemab.

Study AACH Part B will provide additional safety and clinical information as an open-label study. Participants from a sponsor-approved originating donanemab study who were assigned placebo will receive donanemab in the single open-label arm.

Part C

Those who received donanemab in an originating study may participate in a single imaging and cognitive/functional assessment visit.

Study AACH Part C will assess the long-term effect of donanemab on PET imaging biomarkers, cognition, and functioning in participants who have not received IP for at least 52 weeks.

2.2. Background

2.2.1. Disease State

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

Converging evidence from both genetic at-risk and age at-risk cohorts suggests that the pathophysiological process of AD begins well more than a decade before the clinical stage now recognized as AD dementia, and that neurodegeneration is already apparent on MRI by the stage of MCI. 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).

2.2.2. Video Assessment

VTC in healthcare settings is common and is used to carry out cognitive assessments, to conduct psychiatric interviews and consultations, and to help with the management of chronic conditions (Cullum et al. 2014; Ignatowicz et al. 2019). Research comparing clinical interviewing conducted through video conferencing and traditional on-site conditions indicates generally good agreement in a variety of conditions, including dementia and cognitive impairment of various causes (Castanho et al. 2017).

A recent systematic review and meta-analysis assessed the effect of VTC administration on adult cognitive tests and investigated whether the scores acquired during a VTC administration were different from those acquired during on-site administration (Brearly 2017). The review concluded that studies including participants with a mean age of 65 to 75, as well as studies that utilized a high-speed network connection, indicated consistent performance across VTC and on-site conditions (studies with slower connections were more variable). Furthermore, subgroup analyses indicated that VTC scores for untimed tasks and those allowing for repetition fell 1/10th of a standard deviation below on-site scores. Test-specific analyses indicated that verbally mediated tasks were not affected by VTC administration but tasks with a motor component yielded more variable data.

With specific regard to instruments that are often used in AD clinical trials, the feasibility of the MMSE by VTC in an older population with dementia has been investigated by several authors (Ciemins et al. 2009; Cullum et al. 2014; Castanho et al 2017) and no differences were reported between video and on-site administrations.

VTC of the ADAS-Cog_{13} has not been investigated as often as the MMSE. Results from 2 studies show no difference in baseline and follow-up scores of the ADAS-Cog_{13} between on-site and VTC testing (Carotenuto et al. 2018; Yoshida et al. 2020). One of these studies reported that in patients with more pronounced cognitive deficits (MMSE <17), the assessment via VTC overestimated the cognitive impairment (Carotenuto et al. 2018).

There are a couple notable limitations of these studies: the remote assessment did not take place at the participant's home or other designated external environment, but rather, on-site, with the participant being located in a different room from the test administrator. Also, in most studies described above, a technician was available to set up the audiovisual and VTC hardware. As such, remote administration in a real-world (at-home) setting needs to be further investigated.

Further, test scores are reliable if the scale is administered in accordance with how that scale has been validated. Any modification to an assessment-validated version can invalidate test scores.

To allow for remote administration, certain scale elements need to be modified as they require physical interaction between study partner and rater for its administration. How these modifications have been operationalized (and thus, to what extent validity has been established) is not clear.

Therefore, this study aims to evaluate the reliability of remote administration, compared to on-site administration, of the specific cognitive and functional measures described.

2.2.3. Donanemab

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

2.2.3.1. Donanemab Clinical Studies

The first human dose study of donanemab was Study I5T-MC-AACC (AACC). Study AACC was a Phase 1, double-blind, randomized within cohort, placebo-controlled, parallel-group, single-dose followed by multiple-dose, dose-escalation study in patients with MCI due to AD or mild-to-moderate AD to assess the safety, tolerability, PD, and PK of single and multiple IV doses of donanemab. After single-dose administration from 0.1 mg/kg to 3.0 mg/kg, the mean terminal elimination half-life was approximately 4 days, increasing to approximately 10 days (243 hours) at the 10-mg/kg dose level. The PK of a single dose of 1.0 mg/kg IV of donanemab in young, healthy subjects was indistinguishable from the PK in AD patients at the same dose level.

In Study AACC, florbetapir F 18 scans were performed at baseline and after the last multiple-ascending dose, separated by approximately 7 months, to assess the PD effects of donanemab. The change from baseline in grey matter Standardized Uptake Value ratio with cerebellum as a reference region was compared across dose cohorts. There was a highly significant reduction from baseline in cerebral amyloid by PET at the highest dose, 10 mg/kg ($p<.0002$). The analysis showed consistent reduction in cortical amyloid among the patients who received 3 to 5 doses of 10 mg/kg of donanemab. The mean observed reduction in florbetapir F 18 PET signal corresponds to a mean 50% reduction in total brain fibrillar amyloid. Meaningful target engagement (amyloid reduction) was likely not achieved at doses smaller than or equal to 3 mg/kg IV Q4W because of the rapid elimination of donanemab and the lack of sustained exposure.

Study I5T-MC-AACD (AACD) is a Phase 1b single- and multiple-dose study to assess the safety, tolerability, PK, and PD of IV donanemab in patients with MCI due to AD or mild-to-moderate AD. Study AACD has completed clinical activity and patients are no longer being dosed, but the study has not completed database lock. It is evaluating 61 patients in 7 treatment groups receiving single-dose, Q2W or Q4W dosing of either 10 mg/kg, 20 mg/kg, or 40 mg/kg of donanemab. Treatment durations being assessed include single-dose, 6-month dosing Q2W, or up to 72 weeks of Q4W dosing. Safety, PK, and PD data from this ongoing study are used to inform further development of donanemab.

Study I5T-MC-AACG (AACG) is an ongoing Phase 2, double-blind, placebo-controlled study to evaluate the safety and efficacy of donanemab in patients with early symptomatic AD. Study AACG is evaluating approximately 272 patients randomized to donanemab (700 mg Q4W for 3 doses, then 1400 mg Q4W) or placebo.

Study I5T-MC-AACI (AACI) is an ongoing Phase 2, double-blind, placebo-controlled study to evaluate the safety and efficacy of donanemab in patients with early symptomatic AD. Study AACI is evaluating approximately 500 patients randomized to donanemab (700 mg IV Q4W for 3 doses, then 1400 mg IV Q4W) or placebo.

See the IB for detailed nonclinical, 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 AEs of donanemab may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Part A To evaluate the reliability of VTC compared with on-site administered cognitive and functional measures	The intraclass correlation between VTC and on-site assessment for PAIR 1 for • ADAS-Cog$_{13}$ • ADCS-ADL • MMSE • CDR-SB
Part B To evaluate safety and tolerability of donanemab	Standard safety assessments in Part B: • 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
Secondary	
To assess the effect of donanemab on clinical progression in participants with symptomatic AD	Change from baseline up to Week 72 as measured in Part B by: • MMSE score • ADAS-Cog$_{13}$ score • iADRS score • ADCS-iADL score • CDR-SB

To assess the effect of donanemab on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline at Week 36 of Part B as measured by florbetapir F 18 PET scan
To assess the effect of donanemab on brain region volumes	Change in volumetric MRI measures from baseline to Week 72 in Part B
To assess peripheral PK and presence of anti-donanemab antibodies	PK of donanemab in Part B. ADAs against donanemab in Part B including • treatment-emergent ADAs • neutralizing antibodies
Tertiary/Exploratory	
To assess long-term effect of donanemab on brain amyloid deposition, brain tau deposition, blood-based biomarkers, and clinical progression of AD in participants who received donanemab in the originating study	Change in the following endpoints from baseline in the originating study through ≥52 weeks after the participant's last double-blind visit in the originating study, using Part C assessments: • Amyloid plaque deposition as measured by florbetapir F 18 PET scan • Tau deposition as measured by flortaucipir F 18 PET scan • NfL • P-tau • Aβ • MMSE score • ADAS-Cog$_{13}$ score • iADRS score • ADCS-iADL score • CDR-SB
To assess the effect of donanemab on blood-based biomarkers	Change from baseline to Week 72 in the following blood-based biomarkers in Part B: • NfL • P-tau • Aβ

To evaluate the reliability of VTC compared with on-site administered cognitive and functional measures	The intraclass correlation between VTC and on-site assessment for PAIR 2 and PAIR 3 compared with intraclass correlation of PAIR 1 for • ADAS-Cog$_{13}$ • ADCS-ADL • MMSE • CDR-SB
To assess clinical progression as measured by VTC versus F2F-administered cognitive and functional measures	Change from V602 to V608 as measured by • ADAS-Cog$_{13}$ • ADCS-ADL • MMSE • CDR-SB

Abbreviations: Aβ = amyloid beta; AD = Alzheimer's disease; ADA = antidrug 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; ARIA = amyloid-related imaging abnormality; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; F2F = face to face; 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; V = visit; VTC = video teleconference.

4. Study Design

4.1. Overall Design

Part A:

The video validation period is a multiple crossover design with participants alternating between in-clinic assessments and at-home assessments of cognitive and functional scales over a minimum of 1 and a maximum of 3 crossovers. Total time in Part A can vary from a minimum of 4 weeks (1 crossover [1 PAIR]) to a maximum of 24 weeks (3 crossovers [3 PAIRS]). Participants do not receive study IP during the video validation period. Participants are randomized 1:1 in regards to order of in-clinic or at-home for the first assessment, either:

- Group 1: Cognitive/functional scale assessment at the study site (on-site), followed by an at-home assessment (VTC; video teleconference), or
- Group 2: Cognitive/functional scale assessment at home (VTC), followed by assessment on-site.

Part B:

Part B is a multicenter, open-label, follow-on study of donanemab in participants with symptomatic AD. Participants who received placebo in the originating trial receive:

- donanemab 700 mg IV Q4W for 3 doses, then
- donanemab 1400 mg IV Q4W for up to 36 weeks in Part B.

Participants may receive donanemab through Week 36 or Week 48. Criteria for scheduled dose discontinuation at 36 weeks are defined by the sponsor and may be based on results of the participant's florbetapir F 18 PET scan at Week 36 or results from external studies such as Study AACG.

Part C:

Participants who received donanemab in the originating trial may participate in an imaging and cognitive/functional assessment visit (Visit 201). Visit 201 occurs anytime at least 52 weeks from the participant's last double-blind visit in the originating study.

Overall Study:

The maximum total duration of study participation for each participant, including screening and the posttreatment follow-up periods, is up to 124 weeks:

- Screening: up to 30 days prior to Visit 602
- Part A, Video assessment: up to 24 weeks
- Part B, Open-label donanemab: up to 72 weeks (treatment received for 36 or 48 weeks)
- Part B, Follow-up: up to 24 weeks

Note: Part C is not added to the maximum total duration of study participation because Part C is a single visit, and Part B participants do not participate in Part C.

4.1.1. Screening

At or before Visit 601 (randomization for Part A), 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 screening period consists of the visit window of Visit 601. Visit 601 occurs up to 30 days prior to Visit 602.

If the treatment received in the originating study is unknown at the time of screening, participants must meet screening eligibility criteria of Parts A, B, and C to be randomized into the study.

If the treatment received in the originating study is known at the time of screening, participants must meet screening eligibility criteria of

- Part A
  and either
- Part B (if participant received placebo in the originating study) or
- Part C (if participant received donanemab in the originating study and consents to participate in this visit).

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 601. Study assessments are shown in the SoA (Section 1.3).

4.1.2. Part A: Video Assessment

Part A is a multicenter, randomized, multiple crossover study to validate remote assessment of cognitive and functional scales. Part A begins at Visit 601 (randomization), after screening is complete. Participants are randomized to one of 2 groups, as described in the Schema and Overall Design (Sections 1.2 and 4.1, respectively) to be assessed both remotely (through VTC) as well as on-site.

Part A consists of 6 assessments or 3 pairs:

- Pair 1 comprises Visits 602 and 603
- Pair 2 comprises Visits 604 and 605
- Pair 3 comprises Visits 606 and 607

In each pair, each participant is assessed once remotely through VTC and once in person on-site. The participant may elect to proceed to Part B (Visit 1) at any time after participating in Part A Pair 1.

4.1.3. Part B: Open-Label Donanemab

Part B is an open-label donanemab phase beginning at Visit 1. Participants should participate in, at a minimum, Pair 1 of Part A before starting Part B.

At Visit 1, appointments should be made for all remaining visits and should be scheduled as close as possible to the target date, relative to Visit 1.

Assessments and procedures will be performed as indicated in the SoA (Section 1.3). Procedures for some visits may take more than 1 day.

The study investigator and site clinical study team will not have access to florbetapir F 18 PET results during the study to increase objectivity of cognitive assessments.

Participants who meet entry criteria for Part B will be enrolled to receive up to 48 weeks of treatment with donanemab IV Q4W.

4.1.4. Part C: Imaging and Cognitive/Functional Measures

Participants who previously received donanemab in an originating study will be given the option of participating in Visit 201 in Part C. This visit takes place at least 52 weeks after the participant's last double-blind visit in the originating study.

The study investigator and site clinical study team will not have access to florbetapir F 18 PET or flortaucipir F 18 PET results during the study to increase objectivity of cognitive assessments.

Participants in Part C do not participate in Part B, and do not receive IP.

4.2. Scientific Rationale for Study Design

Overall, Study AACH is comprised of 3 parts: A, B, and C (as indicated in Section 4.1).

The objective of **Part A** is to address the scientific need for validating remote clinical outcome assessments, as a methodology that reduces site burden. The study design alternates between in person, on-site clinic assessments with home VTC assessments.

Part B involves treatment with donanemab and is designed to collect data on the safety, tolerability, and other clinical outcome effects of donanemab for up to 48 weeks of treatment in participants with symptomatic AD. The primary objective of Part B is to further accumulate and describe data on the safety and tolerability of donanemab. This study objective is enabled through using a cohort of participants who were randomized to received placebo in an originating study (rather than donanemab), and now have opportunity for access to donanemab treatment. As an open-label study, there will be no placebo group. The potential duration of drug exposure of 36 or 48 weeks was chosen as a duration sufficient to have a significant PD effect on florbetapir amyloid lowering based on Phase 1 data. Safety measures will include the collection of AE reporting (including infusion-related reactions), laboratory assessments, MRI assessments, vital signs and weight, ECG, physical examinations, neurological examinations, and assessments of suicidal ideation and behavior to facilitate a comprehensive safety evaluation. Immunogenicity testing will be performed. In addition to clinical outcomes, imaging biomarkers (florbetapir and volumetric MRI) will also be measured. Florbetapir F 18 PET scans will be used 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. Volumetric MRI will assess the effect of donanemab on brain regional volumes.

Part C has an exploration scientific rationale, examining participants who previously received donanemab, but are no longer receiving donanemab following the completion of the originating clinical trial. This exploratory objective is directed toward assessing long-term effect of donanemab on brain amyloid deposition, brain tau deposition, and clinical progression of AD in participants over the interval period when they no longer receive donanemab.

4.3. Justification for Dose

The donanemab target dose of 1400 mg administered IV once Q4W was selected based on current preclinical pharmacology and toxicology data and clinical PK, PD, and safety data. Prior and ongoing exposures include 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, 20 mg/kg, and 40 mg/kg in single- and/or multi-dose dosing schedules. Data from Studies AACC and AACD suggested that PK of donanemab was linear when the dose was ≥10 mg/kg. Mean half-life was about 8 to 10 days when the dose was ≥10 mg/kg, so minimal accumulation in plasma PK was predicted for 1400 mg Q4W IV dosing. High levels of florbetapir F 18 PET signal reductions were seen with a single dose of 20 mg/kg, and were comparable to florbetapir F 18 PET reductions seen with a 10 mg/kg Q2 week dosing schedule at 3 months (see Section 2 and the IB for details).

Based on this as well as decreased patient burden with a Q4W dosing schedule compared with a Q2W dosing schedule and comparable safety (see Section 2), 1400 mg Q4W dosing was selected as the highest dose regimen for robust amyloid plaque lowering. Preliminary 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 ARIA-E; ARIA-H and hypersensitivity reactions; and the overall frequency, severity, and seriousness of AEs at this dose level.

Protocol amendment (a) incorporates a titration schedule of 700 mg IV Q4W for the first 3 doses, then 1400 mg IV Q4W, based on observation of 2 cases of symptomatic ARIA observed within the first 3 doses in an ongoing donanemab 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 parts (as described in Section 4.1) of the study the participant enrolled in, including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of last scheduled assessment shown in the SoA for the last participant in the trial.

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

Part A:

1. Have participated in a double-blind treatment period of a sponsor-approved originating donanemab trial.
2. 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 video/telephone at designated times.
   A second study partner may serve as backup.
3. The study partner(s) is/are required to accompany the participant for signing consent. One study partner is requested to be present on all days the C-SSRS/Self-Harm Supplement Form is administered and 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-SB and the ADCS-ADL assessments. Visits not requiring efficacy assessments 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

   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.
4. Have adequate literacy, vision, and hearing for neuropsychological testing in the opinion of the investigator at the time of screening.
5. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.
6. Stable symptomatic AD medications and other medication that may impact cognition for at least 30 days prior to randomization into Part A (does not apply to as needed or discontinued medications).
7. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Part B:

If the participant's treatment assignment is known at the time of screening, only evaluate Part B inclusion criteria if the participant received placebo in the originating study.

8. Males and females of nonchildbearing potential will be eligible for Part B.

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

Male participants:

i. Men, regardless of their fertility status, with non-pregnant 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 study Part B 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.

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. postmenopausal – 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.

5.2. Exclusion Criteria

Part A:

9. 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 outcome assessments or the analyses in this study.
10. 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.
11. Are Lilly employees or are employees of third-party organizations involved in study which requires exclusion of their employees, or have study partners who are Lilly employees or are employees of third-party organizations involved in a study which requires exclusion of their employees.

Part B:

If the participant's treatment assignment is known at the time of screening, only evaluate Part B exclusion criteria if the participant received placebo in the originating study.

12. Life expectancy <24 months per the investigator's judgment.
13. Known clinically important abnormality, as determined by the investigator, in physical or neurological examination, vital signs, ECG, or clinical laboratory test results from the originating study that could be detrimental to the participant or could compromise the study.
14. Are, in the judgment of the investigator, actively suicidal, and therefore, deemed to be at significant risk for suicide.
15. Poor venous access.
16. Have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants/cardiac pacemaker.
17. Sensitivity to florbetapir F 18, 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, or other contraindication to PET imaging.
18. Have received treatment with a passive anti-amyloid immunotherapy after completion of originating donanemab study.
19. Have received active immunization against Aβ in any other study.

20. Have known allergies to donanemab, related compounds, or any components of the formulation.
21. Discontinuation of administration of IP in the originating study due to an AE if, in the opinion of the investigator, the AE may impact the participant's ability to safely participate in the study.
22. 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.
23. 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).

Part C

If the participant's treatment assignment is known at the time of screening, only evaluate Part C exclusion if the participant received donanemab in the originating study and plans to participate in Part C.

24. For participation in PET assessment: 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, or other contraindication to PET imaging.
    a. For participation in florbetapir PET imaging: Have sensitivity to florbetapir F 18.
    b. For participation in flortaucipir PET imaging: Have sensitivity to flortaucipir F 18.
25. Have received treatment with a passive anti-amyloid immunotherapy after completion of originating donanemab study.
26. Have received active immunization against Aβ in any other study.
27. 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.

5.3. Lifestyle Considerations

Participants participating in Part B should refrain from donating blood or blood products from the time of their entry into Part B 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 CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Participants may rescreen once if screen failure was due to lack of stable symptomatic AD medications or other medication that may impact cognition. The sponsor must be contacted for other exceptional reasons for rescreening.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

The IP used in this study is:

- Donanemab

IP is administered only during the open-label donanemab period (Part B). Participants do not receive IP during Part A or Part C.

The following clinical and imaging assessments are to be performed prior to administration of IP at Part B Visit 1:

- Visit 1 physical and neurological examination, vital signs, and ECG
- If >6 months between the final clinical laboratory assessment from the originating study and Visit 1, clinical laboratory assessment (See SoA; Section 1.3)
- If >12 months between the final centrally read MRI from the originating study and Visit 1, MRI assessment (See SoA; Section 1.3)

See Section 7 for details regarding discontinuation criteria.

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

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

IP is to be administered once Q4W. IP 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.

Sites must have resuscitation equipment available.

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.

IP will be supplied in a vial.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature 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 Part B of the study may receive IP and only authorized site staff may supply 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 site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) 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

Part A

For the video assessment period, participants will be randomized 1:1 to either

- Group 1: Cognitive/functional scale assessment performed on-site, followed by at-home (VTC) assessment, or
- Group 2: Cognitive/functional scale assessment at home (VTC), followed by on-site assessment.

To minimize bias, participants follow a crossover design, alternating between assessment locations, starting with their randomized initial location.

Part B

Part B is an open-label donanemab phase.

Part C

Participants do not receive IP in Part C. Randomization and blinding are not applicable.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive IP directly from the investigator or designee, under medical supervision. The date, time, and volume of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic 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. 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 30 days before Visit 602. Doses of these medications should remain constant when possible through the study. 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 after consultation with a Lilly medical monitor. Concomitant therapy administered to treat an infusion reaction or as premedication for infusions should be documented.

6.5.3. Excluded Medications

Immunoglobulin G therapy (also known as gamma globulin or IV immunoglobulin [IVIG]) is not allowed during the study. Other disease-modifying therapeutic agents may also be excluded medications (see Section 7.2 for additional details).

6.6. Dose Modification

The dosing goal is for the participant to be titrated to the target dose of 1400 mg.

For participants who develop ARIA during the titration period (that is, before the fourth infusion of study drug), the investigator may decide to

- temporarily suspend dosing as described in Section 7.1.1.1, then determine if the participant should remain on 700 mg either temporarily beyond the first 3 doses or throughout the remainder of the treatment period,
- continue the 700 mg 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

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

IP 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
- ARIA
- Systemic hypersensitivity reaction
- Severe noncompliance
- The participant requires an excluded therapeutic agent
- Placement of device incompatible with MRI

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, 1 PK sample should be collected at the soonest scheduled visit regardless if PK 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 collection is required once the participant exceeds 6 months since discontinuation of donanemab infusions.

Clinical Judgment

AE 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 Lilly-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 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 TE ARIA-E and/or ARIA-H at the discretion of the 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 reaction 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).

Placement of Device Incompatible with MRI

Participants who require a ferromagnetic implant or insertion of a cardiac pacemaker that is not MRI-compatible will be permanently discontinued from IP and should have no MRIs. If the participant discontinues from the study, with the exception of an MRI, the participant should have end-of-therapy and/or end-of-study procedures performed as shown in the SoA.

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) are expected events for some participants due to the 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). Reinitiating IP can be considered after resolution of ARIA-E and stabilization of ARIA-H imaging findings and the resolution of any associated symptoms. Both discontinuation and re-initiation decisions may be discussed with the sponsor. Dose modification considerations are described in Section 6.6.

In the event of a finding of ARIA-E on MRI, the investigator is to complete the CRF regarding the presence or absence of symptoms related to the ARIA-E.

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 monitor 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. See the Manual of Operations for temporary and permanent discontinuation guidance.

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 circumstances or to evaluate the IP impact on an uncertain AE.

IP 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 Lilly medical monitor. Temporary treatment discontinuation and restarting should be documented. Restarting treatment after a discontinuation period that is greater than 12 weeks should be discussed between the investigator and Lilly 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 GCP
  - includes findings of exclusory MRI, hematology, or clinical chemistry at an unscheduled procedure prior to the participant starting Part B.

NOTE: If a clinically important abnormality, as determined by the investigator, in physical or neurological examination, vital sign, ECG, or clinical laboratory test results could be detrimental to the participant or could compromise the study, then the participant should not receive IP in Part B.

Participants must not enter Part B if the final centrally read MRI from the originating study or unscheduled MRI performed in Study AACH prior to Part B demonstrate presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage, severe white matter disease, 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.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted if participant completed Visit 1 and received IP (Part B only), 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 Lilly medical monitor agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly 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 10.1.8.

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

8.1.1. Cognitive and Functional Measures

The following cognitive and functional measures will be included in this study:

- ADAS-Cog$_{13}$
- ADCS-ADL
- MMSE
- CDR-SB

These measures are utilized in Parts A, B, and C. For differences in administration of the measures, see Section 8.1.2.

8.1.1.1. CDR-SB

The CDR-SB (Hughes et al. 1982; Morris 1993) is a global assessment tool that can be used to effectively evaluate both cognition and function. The tool was initially developed to measure dementia severity and covers 6 categories or "boxes": Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care.

The CDR global ratings, calculated using an algorithm, range from 0 (no dementia) to 3 (severe dementia) while CDR-SB scores, calculated by adding the box scores, range from 0 to 18 (with higher scores indicative of more impairment). Scoring is determined by a clinician through a semistructured and in-depth interview with both the affected individual and their study partner. The study partner and participant must be interviewed separately.

This scale demonstrates acceptable psychometric characteristics (Coley et al. 2011; Cedarbaum et al. 2013) and has been shown to be sensitive enough to detect disease progression, even in populations with less advanced clinical disease (Williams et al. 2013; Wessels et al. 2015).

8.1.1.2. MMSE

The MMSE is a brief instrument used to assess cognitive function in patients (Folstein et al. 1975).

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

8.1.1.3. ADAS-Cog$_{13}$

The 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 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.

8.1.1.4. iADRS

The iADRS (Wessels et al. 2015) represents a composite that was developed using both a theory-driven approach (incorporating measures of both cognition and function) and a data-mining approach (identifying the most sensitive combination of scales through analysis of data from the AD Neuroimaging Initiative and the EXPEDITION, EXPEDITION2, and EXPEDITION3 studies).

The iADRS is a simple linear combination of scores from 2 well-established, therapeutically sensitive, widely accepted measures in AD, the ADAS-Cog$_{13}$ and the ADCS-iADL, measuring the core domains of AD. All items of these 2 scales are included without additional weighting of items, yielding face validity and ease of interpretation of the composite relative to its components.

The iADRS score will be derived from the ADAS-Cog$_{13}$ and the ADCS-iADL. The ADAS-Cog$_{13}$ and the ADCS-ADL will be the actual scales administered to participants.

8.1.1.5. ADCS-ADL

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire that is to be answered by the participants study partner (Galasko et al. 1997, 2004).

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 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 (Galasko et al. 1997, 2004).

8.1.2. Order of Assessments and Rater Roles

Assessments administered to the participant are the MMSE, ADAS-Cog13, CDR, and C-SSRS (C-SSRS is in Part B only). Assessments administered to the study partner are the CDR and ADCS-ADL.

Refer to the table below for the sequence of tests for both participant and study partner.

Psychometric Rater	Global Rater
Participant	**Study Partner**
1: MMSE 2: ADAS-Cog$_{13}$	1: ADCS-ADL 2: CDR[a]
	Participant
4: C-SSRS (Part B only)	3: CDR[a]

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; CDR = Clinical Dementia Rating Scale; C-SSRS = Columbia Suicide Severity Rating Scale; MMSE = Mini Mental State Examination; VTC = video teleconference.

a The CDR must always be administered to the study partner first and then to the participant. It is recommended that both sections are administered on the same day. For VTC assessment; the participant and the study partner cannot be present during the other party's interview.

Note that, in Parts B and C, the ADAS-Cog$_{13}$ and MMSE should be administered by a different rater than the ADCS-ADL and CDR.

In Part A, for Pair 1 within each subject, the VTC assessment and the on-site assessment must be conducted by 2 separate raters. In subsequent pairs, every effort should be made to have separate raters conduct the VTC assessment and the on-site assessment.

In Part B, the global and psychometric raters should administer the same scale to the same participant throughout the study whenever possible. 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 (e.g., blood draws). Note that some procedures (MRI, flortaucipir F 18 PET tau imaging, florbetapir F 18 PET amyloid imaging) can be conducted on other days within the visit window. The CDR rater should be blinded to AEs to avoid bias in the CDR assessment.

Cognitive and functional testing will be administered using an 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. Cognitive and functional testing for each participant should be performed at approximately the same time on each day, whenever possible, to reduce potential variability.

8.1.3. Biomarker Efficacy Measures

Biomarker efficacy measures collected in this study are described in the respective sections below:

- Florbetapir F 18 PET scan – Section 8.6.1
- Flortaucipir F 18 PET scan – Section 8.8
- Volumetric MRI – Section 8.8

8.2. Safety Assessments

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

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 an 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 as indicated in the SoA (Section 1.3).

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

12-lead digital ECGs will be collected 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.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (replicates) than expected at a time point is allowed when needed to ensure high-quality records.

ECGs 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/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 report, document this review, and record 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 laboratory manual and the SoA.
3. If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's 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.

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

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

This technology will be used to check for evidence of ARIA-H or ARIA-E and safety findings (volumetric MRI will also be used to calculate brain volumes, as noted in Section 8.8).

The MRI scans will be reviewed by the investigator or qualified designee for immediate participant management. Any clinically significant findings noted that result in a new or updated diagnosis should be recorded as an AE. After the MRI scan is read locally, the MRI scans will be sent for analysis to a centralized MRI vendor designated by Lilly. The centralized MRI vendor's interpretation of the participant's final MRI from the originating study or unscheduled MRI performed in Study AACH prior to Part B will determine final MRI eligibility for Part B.

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, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 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 CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and 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 being treated with donanemab 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 being treated with donanemab should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

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

C-SSRS

The C-SSRS 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 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

AEs 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 AE and SAE 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, IRBs/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

WOCBP are excluded from Study AACH. 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 symptom should be provided to the sponsor in the CRF.

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

In the case of generalized urticaria or suspected anaphylaxis, additional blood and urine samples should be collected as described in Section 10.2. 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.

However, if an infusion reaction occurs, appropriate medication may be used for the acute event as determined by the study investigators (see Section 6.5.2). The medications used should be documented.

The participant may be premedicated for subsequent infusions. If infusion reactions are observed, but review of the data suggests that dosing may continue, administration of medicines managing the reaction may be administered before starting subsequent infusions at the discretion of the investigator, according to local practice guidelines.

Dosing rechallenge is contraindicated in participants that have experienced a suspected or possible anaphylactic reaction (e.g., reaction involving 2 or more organ systems [for example, mucocutaneous, respiratory, cardiovascular, or gastrointestinal systems] occurring in close proximity to dosing), in a prior dose (Sampson et al. 2006). For infusion-related reactions which are not suspicious for anaphylaxis, 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's discretion and according to local practice guidelines.

Prior to initiating premedication, the investigator must 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-E are asymptomatic, serious cases have been reported. Available data suggest serious cases are most likely to occur early in dosing, after the first, second, or third infusion.

When symptoms do occur, they are reported to be most commonly:

- headache,
- worsening of cognitive function,
- alteration of consciousness,
- seizures,
- unsteadiness, and
- vomiting.

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 an 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.

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

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 SAP.

8.3.9. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.

Sponsor collects product complaints on IPs used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Section 10.3 of the protocol.

8.3.9.1. Time Period for Detecting Product Complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug provided for the study, the investigator will promptly notify the sponsor.

8.3.9.2. Prompt Reporting of Product Complaints to Sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.

8.3.9.3. Follow-Up of Product Complaints

Follow-up applies to all participants, including those who discontinue IP.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

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.

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 assessment is on the SoA at that visit. Dosing dates and times should be collected. Subsequent PK sample collection should follow the protocol SoA for serum donanemab collection unless the scheduled visit exceeds 6 months since discontinuation of infusions. No additional collection for donanemab is required once the participant exceeds 6 months since discontinuation of donanemab 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

Florbetapir F 18 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 F 18 PET signal) will be assessed at time points described in Part B and C of the SoA (Section 1.3).

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Blood-Based 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 RNA, proteins, lipids, and other cellular elements.

Serum, plasma, and whole blood RNA samples for exploratory 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.

Accumulation of Tau Deposits

Flortaucipir F 18 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 F 18 PET signal) will be assessed at the time point described in Part C of the SoA (Section 1.3).

Volumetric MRI

Effects on regional brain volumes, as assessed by volumetric MRI, will be performed according to the SoA (Section 1.3). Donanemab effects on volumetric MRI will be assessed to evaluate the loss of brain volume that occurs in AD patients.

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.

TE ADAs are defined in Section 9.4.6.1. If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE ADA positive, additional samples may be taken for up to 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

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

Part A:

The ICC comparing VTC administration of the ADAS-Cog_{13}, the ADCS-ADL, the MMSE, and the CDR-SB will show at a minimum 'acceptable' agreement with the on-site assessment of the same scales. Acceptable agreement is defined as an ICC value of 0.70 or greater (Koo and Li 2016; Coons 2009).

The ICC will remain consistent across multiple pairs of VTC and on-site assessments.

Disease progression measured by VTC administration will be no different than disease progression measured by on-site assessments.

Part B:

No statistical hypotheses for Part B of the study.

9.2. Sample Size Determination

Approximately 200 participants will be enrolled and randomized in a 1:1 ratio to the 2 groups (Group 1: Cognitive/functional scale assessment on-site, followed by VTC assessment; or Group 2: Cognitive/functional scale assessment by VTC, followed by assessment on-site). It is expected that approximately 180 participants will complete Pair 1 of Part A. Approximately 150 participants are expected to complete the study.

A correlation coefficient of 0.80 between on-site and VTC assessment is assumed.

Furthermore, it is assumed that the 2 modalities will yield similar means but different standard deviations. A mean ADAS-Cog_{13} total score of 27.2 and a SD of 8 and 9 were used for the power calculation. These estimates were derived from Studies I8D-MC-AZES, I8D-MC-AZET, and H8A-MC-LZAX, all reflecting an early or mild AD population.

This sample size will provide approximately 81% power to demonstrate 'acceptable' reliability, defined as the lower limit of the 95% confidence interval for ICC above 0.70.

This power calculation is based on the ADAS-Cog_{13}, as this is the scale anticipated to have most scale adaptations and most variability from on-site to VTC assessment. Other scales should therefore demonstrate equal or greater power for these comparisons.

Simulations (carried out in R) with 1000 iterations, utilizing above described assumption, yields an average ICC of 0.793 and average 95% confidence interval of 0.732 to 0.841.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	Part A: All participants randomized. Participants will be analyzed according to the assessment order actually completed. Part B: All participants given IP during Part B. Part C: All participants participating in a Part C follow-up assessment.
Efficacy Evaluable (scale-dependent)	Part A: All participants with at least 1 complete pair of assessments for the considered scale. Part B: All participants with any Part B efficacy assessment. Part C: All participants with any Part C efficacy assessment.
Safety	All participants who receive at least 1 dose of IP during Part B.
Pharmacokinetic Analysis	All enrolled participants who received at least 1 dose of IP during Part B and have at least 1 evaluable PK sample.

Abbreviations: IP = investigational product; PK = pharmacokinetics.

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, statistical tests will be conducted at a 2-sided alpha level of 0.05 and 95% confidence intervals will be displayed as 2-sided.

No adjustments for multiple comparisons are planned.

All analyses involving calculation of ICCs will be limited to the Efficacy Evaluable population, requiring participants to contribute complete pairs of on-site and remote clinical assessments to be included. The ICC will be calculated as 2-way mixed-effect model looking for absolute agreement across multiple raters, with raters defined as on-site assessment and VTC assessment. See Section 9.4.2 below and the SAP for further specification of the analysis.

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

Baseline definitions are dependent on the quantity being assessed. For TE safety analyses, only participants who have both a baseline observation and a postbaseline observation will be included in the analysis for each analyte or parameter, respectively. The SAP will define baselines where needed.

A database lock is expected to occur after all randomized participants have completed participation in Part A of the study. Analyses related to the validation of remote assessments compared to on-site assessments will be conducted. As no IP is administered during Part A, safety analyses will be limited.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principle feature of the protocol. Any other change made to the data analysis methods described in the protocol, and the justification for making the change, will be described

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

The SAP will be finalized prior to first participant visit and will include a more technical and detailed description of the statistical analyses described in these sections.

Handling of missing items for scales

Because the ICC computation requires each item in its calculation, no imputation will occur in ICC analyses. If any of the individual items for any scale are missing or unknown, the total score for that scale for that visit will be considered missing.

Whether virtual administration of the clinical assessments will result in more missing item scores relative to the on-site assessment is also of interest. To address this question, the number of missing items across the administration of each of the clinical scales will summarized by modality.

For the MMRM objective in Part A and all analyses in Part B related to ADAS-Cog_{13} and ADCS-ADL, if a limited number of individual test items are missing, imputation using prorating will be implemented to obtain a total score. Details of this prorating and the circumstances in which it will be used are included in the SAP.

Whether virtual administration of the clinical assessments will result in more missing item scores relative to the on-site assessment is also of interest. To address this question, the number of missing items across the administration of each of the clinical scales will summarized by modality.

9.4.2. Primary Endpoint(s)

Part A

The primary objective for Part A of this study is to evaluate the reliability of VTC compared with on-site administered cognitive and functional measures. This will be assessed by estimating the ICC and the associated 95% confidence interval for the first pair of observations from participants and comparing the lower bound of the confidence interval to 0.70, the ICC cut-off for acceptable reliability.

Using the guidelines and notation for defining ICCs published by McGraw and Wong (1996), the ICC of primary interest for this study is a 2-way mixed model, interaction absent, with single measurements from each modality on participants, looking at absolute agreement – ICC(A,1). In the present study, the 'raters' are the 2 modalities by which the clinical scales are assessed, on-site and VTC. As we are interested in comparing these specific modalities, modality is considered a fixed effect.

An ANOVA model will be fit to the data with fixed effects of modality, time effect, age, years of education, and presence/absence of anti-dementia drugs. To estimate the ICC and the associated confidence interval, the appropriate mean squares from this model will be used for these estimates. Refer to the SAP for more details.

Part B

The primary objective for Part B of the study is to characterize the safety and tolerability of donanemab. For Part B of the study, safety will be assessed by summarizing spontaneously reported AEs (including infusion-related reactions), laboratory analytes, vital signs and body weight measurements, ECGs, physical and neurological examinations, MRI scans, and C-SSRS assessments.

9.4.3. Secondary Endpoint(s)

To assess the effect of donanemab on clinical progression in participants with symptomatic AD, MMRMs will be fit to the Part B data up to Week 72 for ADAS-Cog_{13}, ADCS-ADL, iADRS, MMSE, and CDR-SB. The models will include terms for visit, age, years of education, and presence/absence of anti-dementia drugs. Visit will be considered a categorical variable. Observed case analyses will also be conducted for each scale. Additionally, if participant numbers are adequate, AD progression from these models can be compared to anticipated progression had the patient remained untreated. Details of such a comparison are contained in the SAP.

Change from baseline in brain amyloid deposition at Week 36 and Week 72 of Part B will be assessed using an MMRM. The model will include terms for visit, age, years of education, and presence/absence of anti-dementia drugs. Visit will be considered a categorical variable. An observed case analysis will also be conducted.

Change from baseline in brain region volumes at Week 72 for Part B will be assessed using an ANCOVA model. The model will include terms for age, years of education, and presence/absence of anti-dementia drugs. An observed case analysis will also be conducted. The brain regions of interest will be defined in the SAP.

PK analyses will be defined by the PK scientist and will be specified in the PK analysis plan.

Categorical displays of ADAs against donanemab and neutralizing antibodies will be presented.

9.4.4. Tertiary/Exploratory Endpoint(s)

As a sensitivity analysis for the primary endpoint of Part A, to assess whether the VTC clinical assessment includes any bias relative to the on-site clinical assessment, an ICC looking at the consistency of the 2 measures will be calculated – ICC(C,1) per McGraw and Wong (1996). By definition, the consistency ICC will be equal to or larger than the ICC for absolute agreement. Large differences between the absolute agreement and consistency ICCs suggest a shift (upward or downward) in the VTC relative to the on-site assessment.

Using the same ANOVA model specified in Section 9.4.2, the ICCs and 95% confidence intervals for the second pair and third pair of on-site and remote clinical assessments will be estimated. Comparisons between the ICCs from the first pair of assessments and the second and third pairs of assessments will be made to measure consistency across measures. If fewer than 50 pairs of clinical assessments are collected for Pairs 2 or 3, only descriptive statistics will be reported. See the SAP for further details.

To compare disease progression as measured by VTC versus on-site, an MMRM will be fit to the clinical assessment measures. Observations will be grouped by test modality (VTC and on-site).

The MMRM will include terms for modality, visit, visit-by-modality interaction, age, years of education, and presence/absence of anti-dementia drugs. Visit will be considered a categorical variable. The null hypothesis is that the contrast between the VTC modality versus the on-site modality at each 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.

Changes in the blood-based biomarkers of NfL, P-tau, and Aβ during Part B will be summarized with observed case analyses.

For participants in Part C of the study, the interest is whether the changes in brain amyloid deposition, brain tau deposition, and clinical progression of AD for participants who received donanemab in the originating study are maintained after donanemab treatment is removed. For each of these endpoints, change from the last observation of the originating study will be fit using an ANCOVA model including terms for age, years of education, and presence/absence of anti-dementia drugs. Observed case analyses will also be presented.

9.4.5. Other Safety Analyse(s)

Additional safety summaries will be performed if warranted upon review of the data.

9.4.6. Other Analyse(s)

9.4.6.1. Evaluation of Immunogenicity

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.

Other analyses are described in the SAP.

9.5. Interim Analyses

No interim analyses are planned for this study. All data is unblinded for sponsor use on a continual basis.

9.6. Data Monitoring Committee (DMC)

Not applicable.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, 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.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Investigator sites are compensated for participation in the study as detailed in the CTA.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or 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, 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 re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

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

10.1.4. Data Protection

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

The participant must be informed that 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.

The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

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

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

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

For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on 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 the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

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

Additionally, eCOA data (participant-focused outcome instrument) will be directly recorded by the investigator site 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.

10.1.7. 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.

10.1.8. 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
- 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 assures appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

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

10.1.10. 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.

Investigators must document their review of each laboratory safety report.

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	

Clinical Laboratory Tests	**Comments**
CK	
Uric acid	
Albumin	
Calcium	
Glucose	
Cholesterol	
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.
NfL	
P-tau	
Aβ	
Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory storage samples:	
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	Selected tests may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions. These should be collected as soon after the event as possible. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-donanemab antibodies (Immunogenicity)	
Donanemab concentrations (PK)	
Tryptase	Do not collect if >12 hours have passed since the hypersensitivity event.
NMH	Obtain only if tryptase sample was collected >2 hours after the hypersensitivity event. Obtain a follow-up sample at the next scheduled visit or after 4 weeks, whichever is later.
Drug-specific IgE	Will be performed if a validated assay is available.
Basophil Activation Test	Will be performed if a validated assay is available.
Complement (C3, C3a, and C5a)	
Cytokine Panel	

Abbreviations: Aβ = amyloid beta; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; EDTA = Ethylenediaminetetraacetic acid; 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 cell.

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 Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, 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 conditions 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 overdose should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT 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 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 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 sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 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 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between 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 sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change 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 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 healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to 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.
- Contacts for SAE reporting can be found in 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.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in eCRF.

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

Hepatic Evaluation Testing

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

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

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

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

Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [b]	EBV DNA [b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [b]	HSV (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	

Abbreviations: INR = international normalized ratio; RNA = ribonucleic acid.

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

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

[c] Not required if ASMA is tested.

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

10.5. Appendix 5: Florbetapir F 18 Amyloid PET Imaging

Florbetapir F 18 PET scans will be performed as part of the study as indicated in the SoA (Section 1.3).

Site investigators, participants, and study partners will not be informed of scan results obtained. 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.

PET Scan Safety

The primary risk related to florbetapir F 18 PET is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion and cumulatively are presented in the tables below and will be provided in the ICF. Details on the clinical information to date regarding florbetapir F 18 exposure will be provided in the ICF. More detailed information about the known and expected benefits and risks of florbetapir F 18 can be found in the US Package Insert for florbetapir F 18 Injection (Amyvid™ package insert, 2012).

Participants must minimize movement during each PET procedure, which can last 20 to 30 minutes for each scan. Most state-of-the-art imaging systems are designed to reduce head motion and participant discomfort.

PART B: The table below shows the effective radiation dose of the Study AACH'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	Sum of Effective Dose (mSv) for Years 1 and 2
Florbetapir F 18 Scan (10 mCi IV)	7.43	1	7.43	0	0	7.43
Totals		1	7.43	0	0	7.43

Abbreviations: CT = computed tomography; ED = early discontinuation; IV = intravenous; 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.

Note: In the event a repeat scan is required (for example., the scan is not analyzable), 1 additional florbetapir F 18 scan may be received. If an ED visit is performed, collect florbetapir F 18 PET scan only if a florbetapir F 18 PET scan has not yet been performed and participant has received at least 3 doses of donanemab.

PART C: The table below shows the effective radiation dose of the Study AACH's PET scans.

	Effective Dose (mSv) per Scan*	Number of Scans in Part C	Effective Dose (mSv) for Part C
Flortaucipir F 18 Scan (10 mCi IV)	9.10	1	9.10
Florbetapir F 18 Scan (10 mCi IV)	7.43	1	7.43
Totals		2	16.53

Abbreviations: CT = computed tomography; IV = intravenous; PET = positron emission tomography.

*Dose shown includes radiation exposure from the radiotracer and assumes a non-clinical 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.

Note: In the event a repeat scan is required (for example, the scan is not analyzable), 1 additional florbetapir F 18 scan may be received.

10.6. Appendix 6: Flortaucipir F 18 Tau PET Imaging

Flortaucipir F 18 PET scans will be performed as part of the study as indicated in the SoA (Section 1.3).

Site investigators, participants, and study partners will not be informed of scan results obtained. 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 F 18 PET is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion and cumulatively are shown in the table above (Section 10.5) and will be provided in the ICF. Details on the clinical information to date regarding flortaucipir F 18 exposure will be provided in the ICF. More detailed information about the known and expected benefits and risks of flortaucipir F 18 can be found in the IB.

Participants must minimize movement during each PET procedure, which can last 20 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: Abbreviations

Term	Definition
Aβ	amyloid beta
AD	Alzheimer's disease
ADA	antidrug 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
ARIA	amyloid-related imaging abnormality
AST	aspartate aminotransferase
CDISC	Clinical Data Interchange Standards Consortium
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CK	creatine kinase
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
CTA	clinical trial agreement

DMC	data monitoring committee
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board
FLAIR	fluid attenuation inversion recovery
GCP	good clinical practice
GGT	gamma glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act
iADRS	integrated Alzheimer's Disease Rating Scale
IB	Investigator's Brochure
ICC	intraclass correlation
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
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 informed consent form.
INR	international normalized ratio
IP	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.
IRB	Institutional Review Board
IV	intravenous(ly)

IWRS	interactive web-response system
MCI	mild cognitive impairment
MMRM	mixed-effect model for repeated measurements
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NfL	neurofilament light chain
NIMH	National Institute of Mental Health
PAIR	A complete crossover comprising an at home assessment and an on-site assessment. • Pair 1 comprises Visits 602 and 603 • Pair 2 comprises Visits 604 and 605 • Pair 3 comprises Visits 606 and 607
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
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
Q2W	every 2 weeks
Q4W	every 4 weeks
QTc	corrected QT interval
QTcF	Fridericia's formula
RNA	ribonucleic acid
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.
SoA	Schedule of Activities
SUVr	Standardized uptake value ratio

TBL	total bilirubin level
TE	treatment-emergent
ULN	upper limit of normal
VTC	video teleconference
WOCBP	women of childbearing potential

10.8. Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances

Exceptional circumstances, such as pandemics or natural disasters, may cause disruptions to the conduct of the study. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations. Such changes are intended to mitigate risks of participants missing visits, allow participants to continue safely in the study, and maintain the data integrity of the study. GCP compliance and minimization of risk to study integrity are important considerations. Ensuring the safety of study participants is the prevailing consideration.

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

Additional written guidance, if needed, will be provided by the sponsor in the event written approval is granted for changes in study conduct.

ERBs, regulatory bodies, and any other relevant local authorities, as required, will be notified as early as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation. If approval of ERBs, regulatory bodies, or both is required per local regulations, confirmation of this approval will be retained in the study records.

Informed Consent

Additional consent from the participant will be obtained, as applicable, for:

- participation in remote visits, as defined in the Remote Visit section,
- a change of the method, location, or both, of IP administration,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct

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

The following changes in study conduct will not be considered protocol deviations. Missing data will be captured as protocol deviations.

Remote Visits

Mobile healthcare

In Part B, healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to: review of concomitant medications, collection of blood samples, physical assessments, administration of PROs, administration of IP, and collection of health information.

Other alternate locations

Other procedures that may be done at an alternate location in exceptional circumstances are infusion, laboratory draws, etc.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Investigational Product and Ancillary Supplies

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit;
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf;
- arranging delivery of study supplies; and
- working with the sponsor to determine how IP is to be administered to the participant. Examples: Administration of IP to the participant during a mobile healthcare visit or at an alternate infusion center. The first 3 infusions must be administered in the clinic.

These requirements must be met before action is taken:

- Alternate delivery of IP should be performed in a manner that does not compromise patient confidentiality and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (e.g., participant's home), investigator, sponsor, or both should ensure oversight of the shipping

process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions should be provided to the participant on how to return any unused or completed study supplies.

In addition, if IP is to be administered to the participant during a mobile healthcare visit or at an alternate location, these additional requirements must be met:

- Only authorized study personnel may supply, prepare, or administer IP; and
- Follow infusion instructions described in Section 6.1.

Adjustments to Visit Windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, thereby minimizing missing data and preserving the intended conduct of the study, the windows for visits may be adjusted, upon further specific guidance from the sponsor, but within this range:

Visit Number	Tolerance
Part B Visits 2 through 15, and Visits 801 and 802	In extenuating circumstances, the visit window for visits in Part B may be extended to ±10 days. Note: IP cannot be administered twice within 21 days (Section 6.1).

Abbreviation: IP = investigational product.

Documentation

Documentation of Changes in Study Conduct

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of IP and relevant communications, including delegation, should be filed with site study records. Also, investigator should document when study conduct returns to normal.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Missing Data and Other Protocol Deviations

The study site should document specific explanations for any missing data and other protocol deviations. This information will also be captured by the monitors in the monitoring system. Although protocol deviations may be unavoidable in an exceptional circumstance, documentation of protocol deviations and missing data will be important for data analysis and reporting.

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)

Amendment a (27 Jan 2021)

Overall Rationale for the Amendment

This amendment adds a titration period to Part B in response to 2 cases of symptomatic ARIA in an ongoing donanemab study.

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 (SoA)	Added tolerance for MRI at Visit 4. Corrected footnote a. "V602 cannot occur ≤30 days..."	To allow MRI review prior to planned dose escalation. Correction.
2.2.3.1 Donanemab Clinical Studies	Added information for Study AACI.	Updated to reflect AACI amendment.
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 Order of Assessments and Rater Roles	Clarified note for ADAS-Cog_{13} and MMSE.	Clarification.
10.6 Appendix 6: Flortaucipir F 18 Tau PET Imaging	Removed sentence related to flortaucipir F 18 being in clinical evaluation.	US FDA approval of flortaucipir F 18 tracer established a known safety profile.
Throughout	Editorial changes	Minor editorial changes, therefore, not described.

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