Protocol I5T-MC-AACK(a)

A Parallel-group Treatment, Phase 1, Participant- and Investigator-Blind, Randomized, 3 Arm Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Intravenous Dose of Donanemab Compared with Placebo in Healthy Chinese Participants

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Title Page

Protocol Title: A Parallel-group Treatment, Phase 1, Participant- and Investigator-Blind, Randomized, 3 Arm Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Intravenous Dose of Donanemab Compared with Placebo in Healthy Chinese Participants

Protocol Number: I5T-MC-AACK

Amendment Number: AACK(a)

Compound: Donanemab (LY3002813)

Brief Title: A Parallel-group Treatment Phase 1 Study of Single Intravenous Dose of Donanemab in Healthy Chinese Participants

Study Phase: 1

Acronym: AACK

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Number

IND: 109157

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

Document ID: VV-CLIN-062541

Medical Monitor Name and Contact Information will be provided separately

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*11-Jan-2022*

Amendment [a]

Overall Rationale for the Amendment:

The protocol is being amended to

- update the clinical laboratory tests to allow flexibility for testing of blood urea nitrogen or urea
- improve clarity on contraception and barrier guidance, and
- to accommodate changes as per updated protocol template.

A high-level description of the change(s), with a brief rationale, is outlined in the table below. Minor or editorial changes have not been mentioned in the table.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Specified • regulatory agency identifier number • study population, and • ethical considerations of benefit/risk.	Changes were included as per updated protocol template.
5.1 Inclusion Criteria	• Updated language regarding contraceptive requirements for male participants. • Updated examples of surgical sterilization for definition of WNOCBP.	• No contraception is required by male participants participating in this study. • Changes were included as per updated definitions for WNOCBP.
8.2.6.2 Hepatic Safety	Updated the abnormalities that may occur upon close hepatic monitoring or comprehensive hepatic evaluation.	Updated the elevations that may occur if a participant had baseline results more than 1.5× ULN.
8.3.1 Timing and Mechanism for Collecting Events	Updated collection stop timing for pregnancy events.	The overall study period was more than 56-60 days, which is at least 5 terminal half-lives after the last dose of study drug.
10.1 Appendix 1: 10.1.1	Updated the responsibilities of the study investigator.	Changes were included as per updated protocol template.

Section # and Name	Description of Change	Brief Rationale
Regulatory and Ethical Considerations		
10.2 Appendix 2: Clinical Laboratory Tests	• Deleted bicarbonate testing. • Added urea. • Added footnote for BUN or urea testing.	Tests were included or removed depending on feasibility of testing. The footnote was added to allow flexibility for testing of BUN or urea.
10.4 Appendix 4: Contraceptive and Barrier Guidance	The following have been updated: • Section 10.4.1 Definitions o Examples of surgical sterilization for definition of WNOCBP. • Section 10.4.2 Contraception Guidance o Male and female participation in this trial. o Table for contraception guidance for men has been deleted. o examples of highly effective methods of contraception for females, and o ineffective forms of contraception.	• Changes were included as per updated definitions for contraceptive and barrier guidance. • No contraception is required by male participants participating in this study.
10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments	Updated hepatic evaluation testing panel.	Changes were included as per updated liver safety assessments.
10.7 Appendix 7: Abbreviations and Definitions	Updated list of abbreviations and definitions, where applicable.	Only abbreviations and definitions used in this document have been retained.

Abbreviations: BUN = blood urea nitrogen; IP = investigational product; ULN = upper limit of normal; WNOCBP = women not of childbearing potential.

Table of Contents

1. Protocol Summary 8
1.1. Synopsis 8
1.2. Schema 11
1.3. Schedule of Activities (SoA) 12

2. Introduction 15
2.1. Study Rationale 15
2.2. Background 15
2.3. Benefit/Risk Assessment 16

3. Objectives and Endpoints 18

4. Study Design 19
4.1. Overall Design 19
4.1.1. Screening Period 19
4.1.2. Inpatient Period 19
4.1.3. Follow-up Period 19
4.2. Scientific Rationale for Study Design 19
4.3. Justification for Dose 20
4.4. End of Study Definition 20

5. Study Population 21
5.1. Inclusion Criteria 21
5.2. Exclusion Criteria 22
5.3. Lifestyle Considerations 23
5.3.1. Meals and Dietary Restrictions 24
5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco 24
5.3.3. Activity 24
5.4. Screen Failures 24
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant 24

6. Study Intervention(s) and Concomitant Therapy 25
6.1. Study Intervention(s) Administered 25
6.1.1. Administration Details 25
6.2. Preparation, Handling, Storage, and Accountability 26
6.3. Measures to Minimize Bias: Randomization and Blinding 27
6.4. Study Intervention Compliance 28
6.5. Dose Modification 28
6.6. Continued Access to Study Intervention after the End of the Study 28
6.7. Treatment of Overdose 28
6.8. Concomitant Therapy 28

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 30
7.1. Discontinuation of Study Intervention 30

7.2. Participant Discontinuation/Withdrawal from the Study....30
7.2.1. Discontinuation of Inadvertently Enrolled Participants....30
7.3. Lost to Follow-up....31

8. Study Assessments and Procedures....32
8.1. Efficacy Assessments....32
8.2. Safety Assessments....32
8.2.1. Physical Examinations....32
8.2.2. Vital Signs....33
8.2.3. Electrocardiograms....33
8.2.4. Clinical Safety Laboratory Tests....34
8.2.5. Pregnancy Testing....34
8.2.6. Safety Monitoring....35
8.3. Adverse Events, Serious Adverse Events, and Product Complaints....37
8.3.1. Timing and Mechanism for Collecting Events....38
8.3.2. Pregnancy....39
8.4. Pharmacokinetics....39
8.4.1. Bioanalysis....40
8.5. Pharmacodynamics....40
8.6. Genetics....40
8.7. Biomarkers....40
8.8. Immunogenicity Assessments....41
8.9. Health Economics OR Medical Resource Utilization and Health Economics....41

9. Statistical Considerations....42
9.1. Statistical Hypotheses....42
9.1.1. Multiplicity Adjustment....42
9.2. Analyses Sets....42
9.3. Statistical Analyses....42
9.3.1. General Considerations....42
9.3.2. Primary Endpoint Analysis....43
9.3.3. Secondary Endpoint Analysis....43
9.3.4. Exploratory Endpoint Analysis....43
9.4. Interim Analysis....43
9.5. Sample Size Determination....44

10. Supporting Documentation and Operational Considerations....45
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations....45
10.1.1. Regulatory and Ethical Considerations....45
10.1.2. Financial Disclosure....46
10.1.3. Informed Consent Process....46
10.1.4. Data Protection....46
10.1.5. Committees Structure....46
10.1.6. Dissemination of Clinical Study Data....47
10.1.7. Data Quality Assurance....47

10.1.8. Source Documents 48
10.1.9. Study and Site Start and Closure 49
10.1.10. Publication Policy 49
10.1.11. Investigator Information 49
10.1.12. Sample Retention 49
10.2. Appendix 2: Clinical Laboratory Tests 50
10.2.1. Blood Sampling Summary 52
10.2.2. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event 52
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 54
10.3.1. Definition of AE 54
10.3.2. Definition of SAE 55
10.3.3. Definition of Product Complaints 56
10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints 56
10.3.5. Reporting of SAEs 58
10.3.6. Regulatory Reporting Requirements 58
10.4. Appendix 4: Contraceptive and Barrier Guidance 60
10.4.1. Definitions 60
10.4.2. Contraception Guidance 61
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 62
10.6. Appendix 6: Provisions for Changes in Study Conduct During Exceptional Circumstances 64
10.7. Appendix 7: Abbreviations and Definitions 67
11. References 70

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Parallel-group Treatment, Phase 1, Participant- and Investigator-Blind, Randomized, 3 Arm Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Intravenous Dose of donanemab Compared with Placebo in Healthy Chinese Participants

Brief Title:

A Parallel-group Treatment Phase 1 Study of Single Intravenous Dose of donanemab in Healthy Chinese Participants

Regulatory Agency Identifier Number:

IND: 109157

Rationale:

Study I5T-MC-AACK will investigate the safety, tolerability, and pharmacokinetics (PK) of single dose intravenous (IV) administration of donanemab in healthy Chinese participants. C [redacted] CI

Objectives, and Endpoints:

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of donanemab versus placebo following single dose IV administration in healthy Chinese participants	• Incidence of treatment-emergent adverse events and serious adverse events
Secondary	
• To characterize the pharmacokinetic profile of donanemab following single dose IV administration in healthy Chinese participants	• C_{max}, and $AUC_{0-\infty}$

Abbreviations: $AUC_{0-\infty}$ = area under the concentration versus time curve from time 0 to infinite time; C_{max} = maximum observed drug concentration; IV = intravenous.

Overall design

This is a parallel treatment, Phase 1, participant- and investigator-blind, placebo-controlled, randomized study to evaluate the safety, tolerability, and PK of a single IV dose of donanemab in healthy Chinese participants. This study will be conducted in China. Up to 36 participants may be enrolled so that approximately 30 participants complete the study.

The study will include 3 cohorts, each with 12 participants randomized in a 5 (donanemab): 1 (placebo) ratio. The planned doses are:

- Cohort 1: 350 mg IV single dose,
- Cohort 2: 700 mg IV single dose, and
- Cohort 3: 1400 mg IV single dose.

Brief summary:

The purpose of this study is to investigate the safety, tolerability, and PK with donanemab compared with placebo in healthy Chinese participants.

Study details include:

- Study duration: approximately 85 days.
- Treatment duration: single dose on Day 1.
- Visit frequency: approximately weekly to once in 2 weeks.

Study Population:

Study AACK will be conducted in young healthy Chinese participants.

Number of participants:

Approximately 36 participants will be enrolled to study intervention.

Intervention groups and duration:

Screening period: 28 days prior to randomization,

Inpatient period: Day -1 to Day 5; Single IV dose of donanemab (350 mg, 700 mg, or 1400 mg) or placebo on Day 1, and

Follow-up period: 12 weeks ± 7 days after completion of dosing or until early discontinuation.

Ethical Considerations of Benefit/Risk:

The following are the risks and discomforts associated with donanemab:

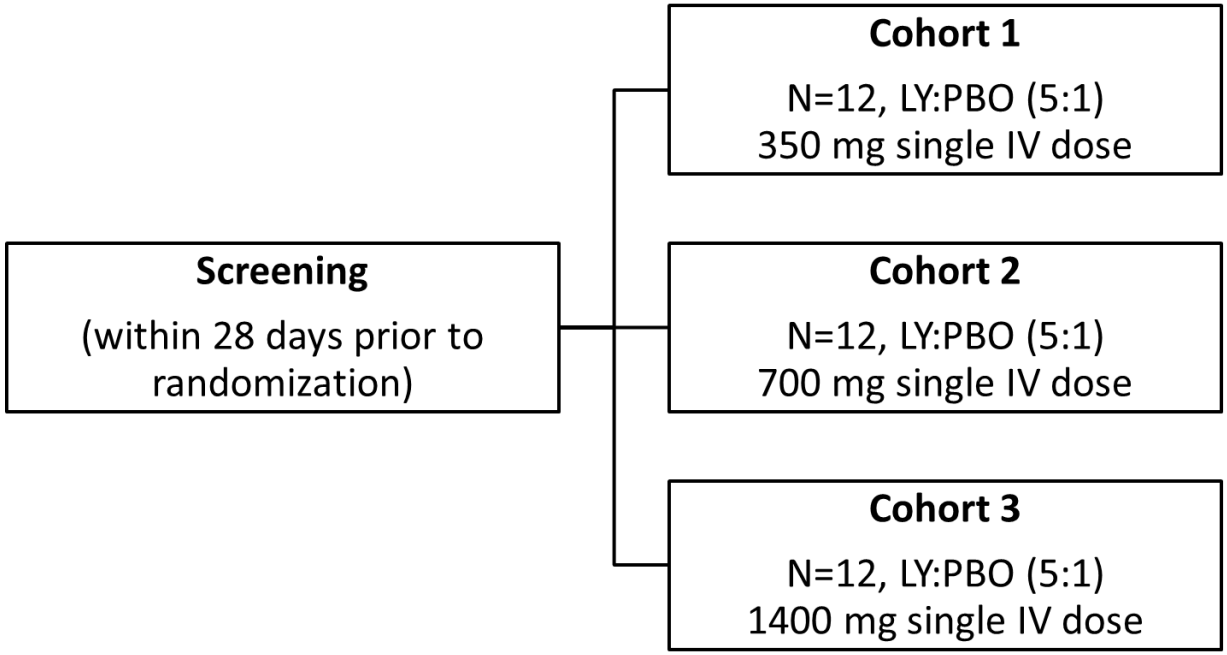
- amyloid-related imaging abnormalities (ARIA)
- treatment-emergent anti-drug antibodies (TE-ADAs), and
- infusion-related reactions (IRRs) and hypersensitivity.

- In Study AACK, amyloid-related imaging abnormality–edema/effusions (ARIA-E) and amyloid-related imaging abnormality–hemorrhage/hemosiderin deposition (ARIA-H) events are not expected given the young healthy population being enrolled. These participants are expected to not have amyloid deposits in their brain and thus the risk of ARIA-E and ARIA-H is considered low.
- TE-ADAs have been observed after a single dose of donanemab across all dose levels assessed, including the single cohort of healthy participants in Study I5T-MC-AACC (AACC). Therefore, TE-ADAs will be carefully monitored in this study.

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

Data Monitoring Committee: No

1.2. Schema



Abbreviations: IV = intravenous; LY = LY3009813; N = number of participants; PBO = placebo.

1.3. Schedule of Activities (SoA)

Study Schedule Protocol I5T-MC-AACK

Procedure	Screening	Inpatient period						Follow-up								Comments
Study Day (D)	-28 to -2	-1	1	2	3	4	5	8 ±1d	15 ±1d	22 ±1d	29 ±1d	43 ±4d	57 ±4d	71 ±4d	85/ED ±7d	
Informed consent	X															
I/E criteria	X	X														
Admit to CRU		X														
Discharge from CRU							X									
Outpatient visit	X							X	X	X	X	X	X	X	X	
Randomization			X													
Donanemab/placebo administration			X													
Medical history, demographics	X															
Weight, height, BMI	X															
Physical examination	X	X	X	X			X	X	X	X	X	X	X	X	X	Full physical exam at screening and symptom-directed physical assessment at other timepoints and as deemed necessary by investigator

Procedure	Screening	Inpatient period						Follow-up								Comments
Study Day (D)	-28 to -2	-1	1	2	3	4	5	8 ±1d	15 ±1d	22 ±1d	29 ±1d	43 ±4d	57 ±4d	71 ±4d	85/ED ±7d	
Neurological exam	X	X	X	X			X				X				X	
Vital signs (supine): blood pressure, pulse rate, temperature (hour)[a]	X	X	0, 6	24	X	X	X	X	X	X	X	X	X	X	X	Time points may be added if warranted and agreed upon between Lilly and the investigator.
12-lead ECG (hour)[a]	X		0, 6	24			X				X				X	Single ECG
AE and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical lab tests	X	X		X			X		X		X				X	Includes hematology, clinical chemistry, urinalysis
Serology[b]	X															Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody
Ethanol and urine drug screen	X	X														
Pregnancy test[c]	X	X													X	
FSH	X															For postmenopausal females only
Pharmacokinetic sampling (hours)[d]			P, end of infus-ion, 3	24	48	72	96	X	X	X	X	X	X		X	Sampling times are relative to the time of study treatment administration (0 min).

Procedure	Screening	Inpatient period						Follow-up								Comments
Study Day (D)	-28 to -2	-1	1	2	3	4	5	8 ±1d	15 ±1d	22 ±1d	29 ±1d	43 ±4d	57 ±4d	71 ±4d	85/ED ±7d	
Immunogenicity sampling[d]			P						X		X		X		X	
Pharmacogenetic sample[e] – apolipoprotein E genotype ε4			P													

Abbreviations: AE = adverse event; BMI = body mass index; CRU = clinical research unit; D = day; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle stimulating hormone; I/E = inclusion/exclusion criteria; P = predose.

[a] Times with respect to start of dosing. ECGs, blood pressure, and pulse rate after 5 minutes supine. Zero-hour collection within 2 hours before dosing. Time allowances (minutes): 6 hour (±30), 24 hour (±90).

[b] These tests may be waived if performed within 6 months prior to screening, and if test results are available for "review" for Hepatitis B, C and HIV

[c] Females only. Serum pregnancy test at screening and urine pregnancy test at other timepoints as indicated or when performed at investigator's discretion

[d] Assayed by Lilly-designated laboratory.

[e] Pharmacogenetic sampling for apolipoprotein E genotype ε4 carrier status will be collected as allowed by local regulations.

2. Introduction

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

2.1. Study Rationale

Study I5T-MC-AACK (AACK) will investigate the safety, tolerability, and pharmacokinetics (PK) of single dose intravenous (IV) administration of donanemab in healthy Chinese participants. CCI

2.2. Background

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

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

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

Two Phase 1 studies (Study I5T-MC-AACC [AACC] and Study I5T-MC-AACD [AACD]) have been conducted in participants with MCI due to AD and mild to moderate AD. In Study AACC, single IV dose of donanemab from 0.1 mg/kg to 10 mg/kg was administered in single-ascending dose phase, and IV doses from 0.3 mg/kg to 10 mg/kg once per month for a total of 4 doses were administered in multiple-ascending dose phase. In addition, a single IV dose of 1 mg/kg donanemab was administered to a single cohort of healthy participants. In Study AACD, single and multiple doses from 10 mg/kg to 40mg/kg were administered. In both studies, rapid and

sustained reduction in cerebral amyloid plaques were observed with donanemab doses ≥10 mg/kg.

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

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

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

CCI [redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of donanemab is provided in the investigator's brochure (IB).

2.3. Benefit/Risk Assessment

The following are the risks and discomforts associated with donanemab:

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

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

Incidences of ARIA-E occur spontaneously at rates of 0.1-1%. Incidences of ARIA-H occur spontaneously at rates of 10-20% (Ketter et al. 2017). Both spontaneously occur more frequently in apolipoprotein E genotype ε4 (ApoE4) carriers than noncarriers, and ARIA-E is a risk factor for the occurrence of ARIA-H. Both ARIA-E and ARIA-H occur more frequently with antibody

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

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

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

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

- Skin rash,
- Pruritus (itching),
- Dyspnea,
- Urticaria (hives),
- Angioedema (for example, swelling of the lips and/or tongue),
- Hypotension, and
- Anaphylactic reaction.

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

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

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of donanemab versus placebo following single dose IV administration in healthy Chinese participants	• Incidence of treatment-emergent adverse events and serious adverse events
Secondary	
• To characterize the pharmacokinetic profile of donanemab following single dose IV administration in healthy Chinese participants	• C_{max}, and $AUC_{0-\infty}$
Exploratory	
• To characterize immunogenicity of donanemab following single dose IV administration in healthy Chinese participants	• Incidence of TE-ADA

Abbreviations: $AUC_{0-\infty}$ = area under the concentration versus time curve from time 0 to infinite time; C_{max} = maximum observed drug concentration; IV = intravenous; TE-ADA = treatment-emergent anti-drug antibodies.

4. Study Design

4.1. Overall Design

This is a parallel treatment, Phase 1, participant- and investigator-blind, placebo-controlled, randomized study to evaluate the safety, tolerability, and PK of a single IV dose of donanemab in healthy Chinese participants. This study will be conducted in China. Up to 36 participants may be enrolled so that approximately 30 participants complete the study.

The study will include 3 cohorts, each with 12 participants randomized in a 5 (donanemab): 1 (placebo) ratio. The planned doses are:

- Cohort 1: 350 mg IV single dose,
- Cohort 2: 700 mg IV single dose, and
- Cohort 3: 1400 mg IV single dose.

4.1.1. Screening Period

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

Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. In such instances, the following screening tests and procedures may be repeated: vital signs and clinical laboratory tests.

4.1.2. Inpatient Period

Eligible participants will be admitted to the clinical research unit (CRU) on Day -1 prior to dosing with study intervention. On Day 1, participants will be dosed with single IV dose of donanemab or placebo. Participant will be discharged on Day 5 at the discretion of the investigator and after completion of all assessments as mentioned in SoA (Section 1.3). Participants will be monitored for safety and PK, and immunogenicity samples will be collected as mentioned in SoA (Section 1.3).

4.1.3. Follow-up Period

After discharge from CRU, participants will be required to visit the CRU on an outpatient basis at the timepoints indicated in SoA (Section 1.3). The follow-up period will be 12 weeks ± 7 days after completion of dosing or until early discontinuation.

4.2. Scientific Rationale for Study Design

CCI [redacted]

CCI

[redacted]

4.3. Justification for Dose

CCI

[redacted]

4.4. End of Study Definition

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

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

5. Study Population

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

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

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

5.1. Inclusion Criteria

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

Age

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

Type of participant and disease characteristics

2. Participants who are overtly healthy as determined by medical evaluation, including medical history, physical examination, laboratory tests, and ECG.
3. Are native Chinese participants. To qualify as a native Chinese, the participant, the participant's biological parents, and all four of the participant's biological grandparents must be of Chinese origin.
4. Have clinical laboratory test results within the normal reference range for the population or investigative site or results with acceptable deviations that are judged to be not clinically significant by the investigator.
5. Have venous access sufficient to allow for blood sampling and administration of investigational product for IV administration as per the protocol.
6. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

Weight

7. Have a body mass index (BMI) of 18.0 and 28.0, kg/m^2, inclusive.

Sex and contraceptive/barrier requirements

8. Male and/or female

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Appendix 4 (Section 10.4).

a. Male participants:
   No male contraception is required except in compliance with specific local government study requirements .

b. Female participants:
Women not of child-bearing potential may participate in the study. Females are considered women not of child-bearing potential if:

- they have a congenital anomaly such as mullerian agenesis,
- they are infertile due to surgical sterilization (examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.), or
- they are post-menopausal.

Refer to Appendix 4 (Section 10.4) for other definitions.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

10. Are lactating.
11. Are women of childbearing potential.
12. Have known allergies to donanemab, related compounds or any components of the formulation or history of significant atopy.
13. Have a clinically significant ECG abnormality as determined by the investigator.
14. Have an abnormal blood pressure and/or pulse rate as determined by the investigator.
15. Have significant previous or current history of comorbidities capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study intervention; or of interfering with the interpretation of data.
16. Have history of intracranial hemorrhage, cerebrovascular aneurysm or arteriovenous malformation, or carotid artery occlusion, stroke or epilepsy.
17. Have a history or presence of psychiatric disorders considered clinically significant in the opinion of the investigator that may compromise the safety of the participant or compliance to study procedures.
18. Regularly use known drugs of abuse and/or show positive findings on drug screening.
19. Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
20. Show evidence of hepatitis C and/or positive hepatitis C antibody.
21. Show evidence of hepatitis B and/or hepatitis B surface antigen.
22. Have donated blood of more than 400 mL within the previous 8 weeks of study screening.

23. Have had leukemia, lymphoma, or any malignancy within the past five years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for three years.
24. Have had breast cancer within the past 10 years.

Prior/Concomitant Therapy

25. Have used or intend to use over-the-counter or prescription medication (including herbal medications and traditional medications) within 14 days prior to dosing. Specific medications listed in Section 6.8, concomitant medications, may be allowed.
26. Have had gamma globulin therapy within the last six months.
27. Have received treatment with biologic agents (such as monoclonal antibodies, including marketed drugs) within three months or five half-lives (whichever is longer) prior to dosing.
28. Have significant allergies to humanized monoclonal antibodies
29. Have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).

Prior/Concurrent Clinical Study Experience

30. Have participated, within the last 30 days, in a clinical study involving an investigational product; at least five half-lives or 30 days (whichever is longer) should have passed.
31. Have previously completed or withdrawn from this study or any other study investigating donanemab.

Other Exclusions

32. Have an average weekly alcohol intake that exceeds 21 units per week (males ≤65 years old) and 14 units per week (females), or are unwilling to stop alcohol consumption from 48 hours prior to admission, until the participant has been discharged from the CRU
33. Smoke more than 10 cigarettes, or cigarette equivalent per day or are unable to abide by CRU smoking restrictions.
34. Are unwilling to comply with the dietary restrictions required for this study.
35. Are CRU personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
36. Are employees of Eli Lilly and Company (Lilly) or the CRU.
37. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study.

5.3.1. Meals and Dietary Restrictions

Standard meals will be provided at all times while participants are resident at the CRU.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

- Participants should avoid caffeinated beverages while at the CRU, and for 12 hours prior to admission to the CRU. At other times during the outpatient period, participants are permitted to maintain their regular caffeine consumption. Decaffeinated beverages are permitted.
- Alcohol consumption is not permitted while at the CRU, and for 48 hours prior to admission and outpatient visits until leaving the CRU. At other times, participants are permitted to have an average weekly alcohol intake not exceeding 21 units per week (males ≤65 years old) and 14 units per week (females). One unit is equal to:
    - 12 oz or 360 mL of beer,
    - 5 oz or 150 mL of wine, or
    - 1.5 oz or 45 mL of distilled spirits.
- Participants who smoke will be advised to not smoke more than 10 cigarettes per day during the study. Participants will be asked to refrain from smoking for approximately one hour prior to each ECG and vital sign measurement, and to abide by the CRU smoking restrictions.

5.3.3. Activity

- Participants will be advised to maintain their regular levels of physical activity or exercise during the study but to refrain from vigorous exercise.
- Strenuous activity should be avoided from 24 hours prior to admission until discharge from the CRU.
- While certain study procedures are in progress at the CRU, participants may be required to remain recumbent or sitting.

5.4. Screen Failures

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

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

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

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

CCI [redacted]

CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

6.1.1. Administration Details

CCI [redacted]

6.1.1.1. Premedication for Infusions

CCI [redacted]

6.1.1.2. Management of Infusion Reactions

CCI
CCI

6.2. Preparation, Handling, Storage, and Accountability

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

Note: In some cases, CRU may destroy the material if, during the CRU selection, the evaluator has verified and documented that the CRU has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a participant- and investigator-blind study. The sponsor and site monitors are not blinded.

On Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the 2 arms of the study (randomization ratio 5:1), according to the randomization schedule generated prior to the study by the statistics department at sponsor/designee. Each participant will be dispensed a blinded study intervention, labeled with the participant's unique randomization number, throughout the study.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study interventions and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

In the event of a Quality Assurance audit, the auditors will be allowed access to unblinded study intervention records at the sites to verify that randomization or dispensing has been done accurately.

To preserve the blinding of the study, a minimum number of Lilly personnel and staff at the CRU (namely, CRU pharmacy staff) will see the randomization table before the study is complete. Individuals involved in study drug preparation will not be involved in any of the clinical aspects of the study, including study drug administration and AE assessments.

Blinding will be maintained throughout the conduct of the study as described in the blinding and unblinding plan section of the statistical analysis plan (SAP) or in a separate document.

Emergency codes will be available to the investigator. A code, which reveals the study intervention for a specific study participant, may be opened during the study only if the participant's well-being requires knowledge of the participant's treatment assignment.

If a participant's study treatment assignment is unblinded, the participant must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or CRP for the study participant to continue in the study. If a participant is discontinued, safety assessments will be collected per protocol for the remainder of the inpatient period. See early discontinuation procedures provided in SoA (Section 1.3). During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. Where feasible and when timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a participant's treatment assignment. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Upon completion of the study, all codes must be returned to Lilly or its designee.

6.4. Study Intervention Compliance

Study intervention will be administered under medical supervision by designated CRU staff. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of the dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

6.5. Dose Modification

This is a parallel treatment, single dose study. Dose adjustments are not permitted in this study.

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

Not applicable.

6.7. Treatment of Overdose

For this study, any dose of study intervention greater than dose of study intervention assigned through randomization will be considered an overdose.

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

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

6.8. Concomitant Therapy

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

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency for concomitant therapy of special interest.

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

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

Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use in a 24-hour period at the discretion of the investigator. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

Not applicable since this is single dose study.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request,
- at the request of the participant's designee (for example, parents or legal guardian),
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons,
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, and
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

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

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request the 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 identifies a participant who did not meet enrolment criteria and was inadvertently enrolled, discussion must occur between the Lilly clinical pharmacologist or CRP and the investigator to determine if the participant may continue in the study. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist or CRP to allow the inadvertently enrolled participant to continue in the study.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designees 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.

8. Study Assessments and Procedures

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

Section 1.3 lists the SoA, detailing the study procedures and their timing (including tolerance limits for timing).

The specifications in this protocol for the timings of safety and sample collections are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the case report form (CRF).

Appendix 2 (Section 10.2) lists the clinical laboratory tests that will be performed for this study.

Appendix 2 (Section 10.2.1) provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

Efficacy is not evaluated in the study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height, weight, and BMI will also be measured and recorded.
- Symptom-directed physical assessment may be conducted at other visits as mentioned in SoA and as determined by the investigator.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.1.1. Neurological Examination

A directed neurological examination will be performed by the investigator (or designee) at the time points specified in the SoA (Section 1.3). If clinically significant abnormalities are noted at these time points, additional examinations should be performed as clinically necessary. The examiner should be familiar with the participant's baseline examination. Elements of the examination may include inspection for tremors, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign.

Table AACK.8.1 presents the scoring of the neurological examination findings.

Table AACK.8.1. Scoring of Neurological Examinations Surveys

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

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the Schedule of Activities (Section 1.3) and following the study-specific recommendations included in Manual of Operations for the study.
- Additional vital signs may be measured during the study if warranted.
- Blood pressure and pulse rate should be measured after at least five minutes supine.
- Unscheduled orthostatic vital signs should be assessed if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participants should be supine for at least five minutes and stand for at least three minutes. If the participant feels unable to stand, only the supine vital signs will be recorded.

8.2.2.1. Body Temperature

Body temperature should be measured as indicated in Section 1.3, or any time that it is clinically indicated.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT intervals.

For each participant, a single 12-lead ECG will be collected according to the SoA (see Section 1.3). ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary by the investigator. All ECGs recorded should be stored at the CRU.

Electrocardiograms will be interpreted by the investigator or qualified designee at the CRU:

- as soon as possible after the time of ECG collection, and
- ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visits and for immediate management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT interval from baseline), the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed and must document his or her review of the ECG printed at the time of collection.

Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Tests

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

8.2.5. Pregnancy Testing

Pregnancy testing will be carried out as mentioned in SoA.

8.2.6. Safety Monitoring

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

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

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

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

8.2.6.1. Hypersensitivity Reactions

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

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

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Appendix 2 (Section 10.2.2). Laboratory results are provided to the sponsor via the central laboratory.

8.2.6.2. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 5 [Section 10.5]), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin, gamma-glutamyl transferase, and creatine kinase should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

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

TBL ≥1.5× ULN	TBL ≥1.5× baseline (except for patients with Gilbert's syndrome)

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

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

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

Comprehensive hepatic evaluation

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

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

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

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

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

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

hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

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

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

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

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

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

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

- AEs
- SAEs
- Product complaints (PCs)

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

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

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

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

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

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

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	signing of the ICF	participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention and deemed reasonably possibly related to study procedures	signing of the ICF	start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE# and SAE updates – after start of study intervention	start of intervention	participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant's study participation has ended and the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in [female participants and female partners of male participants]	After the start of study intervention	participation in study has ended	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

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

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant:

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

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

8.4. Pharmacokinetics

Venous blood samples of approximately 4 mL will be collected for measurement of serum concentrations of donanemab as specified in the SoA. The actual date and time (24-hour clock time) of each sampling will be recorded. On the day of dosing, every attempt should be made to

collect samples at the specified time. However, failure to do so will not constitute a protocol violation.

A maximum of three samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of donanemab. Samples collected for analyses of donanemab serum concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.

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

8.4.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of donanemab will be assayed using a validated enzyme-linked immunosorbent assay (ELISA) method. Analyses of samples collected from placebo-treated participants are not planned.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of one year following the last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample for deoxyribonucleic acid isolation will be collected from participants as per local regulations. Samples will be assessed for ApoE4 carrier status as allowed by local regulations. Previous studies have suggested that ApoE4 carriers may be at increased risk of ARIA-E. Assessment of ApoE4 carrier status may help better define the risk of ARIA-E in participants administered donanemab.

Samples will be stored as per local regulations or ethics committee requirements. Samples will be immediately destroyed once donanemab is launched or there is no further request for testing the samples from Chinese authority.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against donanemab. Antibodies may be further characterized for their ability to neutralize the activity of donanemab. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of donanemab. All samples for immunogenicity should be taken predose when applicable and possible. Treatment-emergent ADAs are defined in Section 9.3.4.1.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of donanemab at a laboratory approved by the sponsor. Antidrug antibody samples will be stored as per local regulation or ethics committee requirements. Samples will be immediately destroyed once donanemab is launched or there is no further request on testing the samples from China authority. Samples may also be used for development and control of an immunogenicity assay.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

Not applicable.

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Analyses Sets

The following populations are defined:

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

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Pharmacokinetic analysis may be conducted on data from participants who receive at least one dose of the study intervention and have evaluable PK data. Safety analyses will be conducted for all enrolled participants who receive study intervention, whether or not they completed all protocol requirements.

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

Additional exploratory analyses of the data may be conducted as deemed appropriate. Details of analyses will be fully documented in the SAP.

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

9.3.2. Primary Endpoint Analysis

The primary endpoint is the incidence of TEAEs and SAEs events to investigate the safety and tolerability of donanemab versus placebo following IV administration of single dose in Chinese healthy participants.

The statistical evaluation of safety will be listed and/or summarized by treatment group.

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

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. Safety parameters will be listed and summarized using standard descriptive statistics as appropriate.

The incidence of symptoms for each treatment will be presented by severity and by association with the study intervention as perceived by the investigator. Symptoms reported to have occured prior to randomization will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of TEAEs and SAEs will be reported.

9.3.3. Secondary Endpoint Analysis

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

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

9.3.4. Exploratory Endpoint Analysis

9.3.4.1. Evaluation of immunogenicity

The frequency and percentage of participants with preexisting ADA and with TE-ADA to donanemab will be tabulated by treatment. Treatment emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).

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

9.4. Interim Analysis

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

9.5. Sample Size Determination

Approximately 36 participants may be enrolled in three dosing cohorts. The sample sizes described are customary for Phase 1 studies evaluating safety and PK parameters and is not powered on the basis of statistical hypothesis testing. Each cohort will comprise approximately 12 participants with a randomization ratio of 5:1 between donanemab and placebo. Participants who discontinue the study before completing may be replaced at the discretion of the sponsor and investigator. The replacement participant can complete the entire study period.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.3. Informed Consent Process

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

10.1.4. Data Protection

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

10.1.5. Committees Structure

Not applicable.

10.1.6. Dissemination of Clinical Study Data

Communication of suspended or terminated dosing

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

Reports

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

Data

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

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source data may include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC reviews, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

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

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

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

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

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in 10.1.7.

10.1.9. Study and Site Start and Closure

First act of recruitment

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

Study or site termination

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

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

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

Not applicable.

10.1.12. Sample Retention

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

10.2. Appendix 2: Clinical Laboratory Tests

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

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

Clinical Laboratory Tests

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

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

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered a protocol violation.

[a] Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities

[b] Performed at screening only

[c] If clinically indicated, per the investigator's discretion.

[d] These tests may be waived if performed within 6 months prior to screening, and if test results are available for "review" for Hepatitis B, C and HIV.

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

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

10.2.1. Blood Sampling Summary

This table summarize the maximum number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may occur, but this will not require a protocol amendment.

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	26	1	26
Clinical laboratory tests[a]	8	6	48
Pharmacokinetics sampling[b]	4	14 (+3)	68
Blood discard for cannula patency[c]	3	15	45
Immunogenicity sampling[a]	10	5	50
Pharmacogenetics	10	1	10
Total			247
Total for clinical purposes (rounded to the nearest 10 mL)			250

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

[b] A maximum of 3 blood samples per patient may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor.

[c] Site may choose to use a cannula for blood collection as per site procedure.

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

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

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

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

Abbreviations: IL = interleukin.

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

10.3.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

c. Results in death

d. 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.

e. Requires inpatient hospitalization or prolongation of existing hospitalization

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

f. Results in persistent disability/incapacity

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

g. Is a congenital anomaly/birth defect

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

h. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical

events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

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

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

AE, SAE, and Product Complaint Recording

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via SAE Report

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

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of child bearing potential	Females are considered a woman of child bearing potential if: • they have had at least one cycle of menses, or • they have Tanner 4 breast development. Any amount of spotting should be considered menarche. If Tanner Staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trial regarding Tanner staging.
Women not of child bearing potential	Females are considered women not of child bearing potential if: • they have a congenital anomaly such as Mullerian agenesis, • they are infertile due to surgical sterilization, or • they are post-menopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Post-menopausal state	The post-menopausal state should be defined as: 1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or 2. A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND With a follicle-stimulating hormone >40 mIU/mL; or 3. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy * Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.
Reproductive toxicology studies	Embryo-fetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses that could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.

10.4.2. Contraception Guidance

For male participants:

Males may participate in this trial.

No male contraception is required except in compliance with specific local government study requirements.

For female participants:

1. Women of childbearing potential (WOCBP) are excluded from the trial.

2. Women not of childbearing potential (WNOCBP) may participate in this trial.

See Appendix 4, Section 10.4.1 for definitions.

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

Methods	Examples
Highly effective contraception	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: The barrier method must include use of a spermicide (i.e, condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.
Ineffective forms of contraception	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal, • post coital douche • lactational amenorrhea

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

See Section 8.2.6.2 for guidance on appropriate test selection.

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

Local testing may be performed in addition to central testing when necessary for immediate participant management. The local laboratory must be qualified in accordance with applicable local regulations.

Hepatic evaluation testing

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatic Clinical Chemistry Panel**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Alkaline phosphatase isoenzymes
Eosinophils	Ceruloplasmin
Platelets	Ethyl alcohol (EtOH)
Cell morphology (RBC and WBC)	Haptoglobin
Hepatic Coagulation Panel	Immunoglobulin IgA (quantitative)
Prothrombin time, International Normalized ratio (PT-INR)	Immunoglobulin IgG (quantitative)
Serology	Immunoglobulin IgM (quantitative)
Hepatitis A virus (HAV) testing:	**Urine Chemistry**
HAV total antibody	Drug screen
HAV IgM antibody	**Other Serology**

Tests assayed by Lilly-designated central laboratory	
Hepatis B virus (HBV) testing:	Anti-nuclear antibody (ANA)
Hepatitis B surface antigen (HBsAg)	Anti-smooth muscle antibody (ASMA)[a]
Hepatitis B surface antibody (anti-HBs)	Anti-actin antibody[c]
Hepatitis B core total antibody (anti-HBc)	Epstein-Barr virus (EBV) testing:
Hepatitis B core IgM antibody	EBV antibody
HBV DNA[b]	EBV DNA[b]
Hepatis C virus (HCV) testing:	Cytomegalovirus (CMV) testing:
HCV antibody	CMV antibody
HCV RNA[b]	CMV DNA[b]
Hepatitis D virus (HDV) testing:	Herpes simplex virus (HSV) testing:
HDV antibody	HSV (Type 1 and 2) antibody
Hepatitis E virus (HEV) testing:	HSV (Type 1 and 2) DNA[b]
HEV IgG antibody	Liver kidney microsomal type 1 (LKM-1) antibody
HEV IgM antibody	
HEV RNA[b]	
Tests assayed ONLY by investigator-designated local laboratory	
Microbiology	**Other Chemistry**
Culture:	Acetaminophen
Blood	Acetaminophen protein adducts
Urine	Copper
Urine Chemistry	Phosphatidylethanol (PEth)
Ethyl glucuronide (EtG)	

Abbreviations: DNA = deoxyribonucleic acid; Ig = immunoglobulin; INR = international normalized ratio.

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

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

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

10.6. Appendix 6: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

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

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

Data capture

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

Safety reporting

Regardless of the type of remote visit implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to on-site visits

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

Screening period guidance

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

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

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as

on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.7. Appendix 7: Abbreviations and Definitions

Term	Definition
Aβ	amyloid beta
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AD	Alzheimer's disease
ADA	anti-drug antibody
AE	adverse event
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ApoE4	apolipoprotein E genotype ε4
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormality–edema/effusions
ARIA-H	amyloid-related imaging abnormality–hemorrhage/hemosiderin deposition
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
CFR	Code of Federal Regulations
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.

CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
ECG	electrocardiogram
EDC	electronic data capture system
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
HIV	Human immunodeficiency virus
I5T-MC-AACC	AACC
I5T-MC-AACD	AACD
I5T-MC-AACG	AACG
I5T-MC-AACK	AACK
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
IRR	infusion-related reactions
IV	intravenous
Lilly	Eli Lilly and Company
MCI	mild cognitive impairment
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK	pharmacokinetics\
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
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TE-ADA	treatment-emergent anti-drug antibodies

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