COVER PAGE

Official Title:	A Phase 3b/4 Randomized, Double-Blind, Placebo-Controlled, Parallel- Group Study to Verify the Clinical Benefit of Aducanumab (BIIB037) in Participants with Alzheimer's Disease
NCT Number:	NCT05310071
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PROTOCOL NUMBER: 221AD305

PHASE OF DEVELOPMENT: 3b/4

PROTOCOL TITLE: A Phase 3b/4 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Verify the Clinical Benefit of Aducanumab (BIIB037) in Participants with Alzheimer's Disease

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Biogen may transfer any or all of its study-related responsibilities to a contract research organization and other third parties; however, Biogen retains overall accountability for these activities.

SPONSOR SIGNATURE PAGE

Protocol 221AD305 was approved by:

_____ _____

[redacted], PhD Date (*DD MMM YYYY*)

[redacted]

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1. KEY STUDY ELEMENTS

1.1. Synopsis

Protocol Title:	A Phase 3b/4 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Verify the Clinical Benefit of Aducanumab in Participants with Alzheimer's Disease	
Protocol Number:	221AD305	
Version Number:	2.0	
Name of Study Treatment:	Research Name:	BIIB037
	Generic Name:	Aducanumab-avwa
	Trade Names:	Aduhelm™
Study Phase:	3b/4	
Study Indication:	Alzheimer's Disease	
Study Rationale:	The purpose of this Phase 3b/4 confirmatory study is to verify the clinical benefit of aducanumab compared with placebo in participants with Alzheimer's disease, including those with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. In clinical studies, aducanumab demonstrated a dose- and time-dependent reduction in amyloid plaque, one of the pathological hallmarks of Alzheimer's disease. In a Phase 3 study (221AD302), the effect of aducanumab high dose on amyloid plaque was accompanied by statistically significant clinical efficacy as measured on the primary outcome (CDR-SB), all secondary outcomes (MMSE, ADAS-Cog13, ADCS-ADL-MCI), and the tertiary clinical efficacy outcome (NPI-10). The results of Study 221AD302 were supported by sensitivity analyses and analyses of prespecified subgroups as well as data indicating that the reductions in brain amyloid and in clinical decline were correlated. Another Phase 3 study (221AD301) did not confirm the clinical efficacy seen in Study 221AD302. However, the positive biomarker and clinical efficacy results in Study 221AD302 were supported by a third, independently conducted Phase 1b study (221AD103). Aducanumab was approved by the US FDA as a treatment for Alzheimer's disease under the accelerated approval pathway based on aducanumab's reduction in brain amyloid coupled with evidence	

	that reduction in brain amyloid is reasonably likely to predict clinical benefit in Alzheimer's disease. Consistent with the accelerated approval regulations, the present study is being conducted to fulfill a postmarketing requirement from the US FDA to verify the clinical benefit of aducanumab.
Rationale for Dose and Schedule Selection:	Participants will be assigned to 1 of 2 treatment groups in a 2:1 ratio of aducanumab or placebo administered IV Q4W, respectively. Treatment is initiated via titration, which has been demonstrated to result in a lower incidence of ARIA. Titration will start at 1 mg/kg and will escalate to 3, 6 and 10 mg/kg as detailed in Section 3.1.2.

Primary Objective	**Primary Endpoint**
To verify the clinical benefit of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in participants with early Alzheimer's disease.	Change from baseline in CDR-SB score at Week 78
Key Secondary Objectives	**Key Secondary Endpoints**
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the iADRS	Change from baseline in iADRS score at Week 78
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by ADCS-ADL-MCI	Change from baseline in ADCS-ADL-MCI score at Week 78
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by ADAS-Cog13	Change from baseline in ADAS-Cog13 score at Week 78
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the MMSE	Change from baseline in MMSE score at Week 78
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by NPI-10	Change from baseline in NPI-10 score at Week 78

Secondary Objectives	Secondary Endpoints
To assess the effect of aducanumab on cerebral amyloid plaque level as measured by amyloid PET imaging (in a subset of sites and participants)	Change from baseline in amyloid PET signal at Week 78 and Week 104
To assess the effect of aducanumab on cerebral tau levels as measured by tau PET imaging (in a subset of sites and participants)	Change from baseline in tau PET signal at Week 78 and Week 104
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the CDR-SB score	Change from baseline in CDR-SB score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the iADRS	Change from baseline in iADRS score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by ADCS-ADL-MCI	Change from baseline in ADCS-ADL-MCI score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by ADAS-Cog13	Change from baseline in ADAS-Cog13 score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the MMSE	Change from baseline in MMSE score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by NPI-10	Change from baseline in NPI-10 score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the GST composite z-score	Change from baseline in GST composite z-score (based on CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI) at Week 78 and Week 106

[redacted]

Study Design:

Study 221AD305 is a multicenter, randomized, double-blind, placebo-controlled, and parallel group study in participants with early Alzheimer's disease, including those with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. Enrollment will be monitored, via the IRT system, so that the population of participants with mild Alzheimer's disease represents approximately 50% of the total number of participants enrolled in the study. The study will include up to 24 months of treatment as well as screening and post-treatment FU periods. Approximately 1512 participants will be enrolled across an estimated 220 centers globally.

The primary study objective is to verify the clinical benefit of monthly doses of aducanumab on CDR-SB relative to placebo at Week 78. Key secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical decline as compared to placebo at Week 78 as measured by a variety of cognitive and functional scales such as those implemented in the Phase 3 studies (i.e., ADCS-ADL-MCI, ADAS-Cog13, MMSE, and NPI-10), as well as the composite scale, iADRS, which is a linear combination of the ADAS-Cog13 and the ADCS-ADL-MCI. Secondary objectives include assessment of the effect of monthly doses of aducanumab on change in amyloid PET and tau PET signal at Week 78 and 104 as compared to placebo, as well as all clinical endpoints (i.e., CDR-SB, iADRS, ADCS-ADL-MCI, ADAS-Cog13, MMSE, and NPI-10) assessed at the Week 106 timepoint. Secondary objectives also include an assessment of the effect of monthly doses of aducanumab on the GST composite z-score, defined as the average of standardized z scores of the CDR-SB, ADCS-ADL-MCI, and ADAS-Cog13, at Weeks 78 and 106. Tertiary objectives include confirmation of the safety, tolerability, and associated immunogenicity of aducanumab and its PK characteristics, and HEOR and QoL metrics. [redacted]

Substudies

Three optional longitudinal substudies will be completed within this study in subsets of consenting participants: 1) an amyloid PET substudy involving assessments of amyloid by PET scan at

Screening, and Weeks 78 and 104; 2) a tau PET substudy involving assessments of tau by PET scan at Screening, and Weeks 78 and 104 and [redacted]

Study Location: Approximately 220 sites globally are planned.

Study Population: This study will be conducted in participants who meet the following criteria:

- Must be 60 to 85 years old, inclusive, at the time of informed consent.
- Must meet all of the following clinical criteria for MCI due to Alzheimer's disease or mild Alzheimer's disease according to NIA-AA criteria [Albert 2011; McKhann 2011]:
  - Have an MMSE score between 22 and 30 inclusive
  - Have a CDR memory score ≥ 0.5
  - Have a CDR-GS of 0.5 or 1.0
  - Have an RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the DMI score)
- Must consent to ApoE genotyping.
- Must have confirmed amyloid beta pathology by either PET or CSF. (Note: For participants providing only a screening amyloid PET scan, a historical amyloid PET scan obtained within 18 months of Screening Visit 2 is permissible and must be submitted to the central imaging vendor to confirm that study inclusion criteria are met.) In the case of discordant results between CSF and PET, PET scans will be used to assess eligibility.

Detailed criteria are described in Section 6.

Number of Planned Participants: Approximately 1512 participants will be enrolled and randomized.

Treatment Groups: Participants will receive IV infusions of aducanumab or placebo approximately Q4W for 104 weeks. Participants will be randomized to receive aducanumab:placebo in a 2:1 ratio. The

	randomization will be stratified by geographical region, baseline Alzheimer's disease stage status, and ApoE ε4 status (carrier or noncarrier). Randomization will be performed using IRT. Aducanumab will be initiated with a 6-dose titration period prior to reaching the target dose of 10 mg/kg as detailed in Section 3.1.2.
Sample Size Determination:	The sample size is mainly based on results from the primary analysis of Study 221AD302. Results from the post-PV4 population (i.e., the 221AD302 and 221AD301 protocol amendment in which the high dose of aducanumab was increased from 6 mg/kg to 10 mg/kg) in pooled Study 221AD302 and Study 221AD301 data were also considered. A total sample size of 1512 participants is planned to have approximately 90% power to detect a mean difference of 0.48 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation is based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, an SD of 2.33, a dropout rate through Week 78 of 27%, and a randomization ratio of 2:1. The assumed mean difference of 0.48 between the 2 treatment groups represents an approximately 24% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2. A blinded assessment of the pooled SD for the primary efficacy endpoint may be performed approximately 3 months prior to the completion of enrollment and the sample size may be increased as a result. The sample size could also be increased using internal and external clinical study results that become available after the start of this study. In addition, the sample size may be increased if the dropout rate through Week 78 is estimated to exceed 27%. The sample size will not be reduced based on this assessment.
Visit Schedule:	Participants will have approximately 39 scheduled visits, 27 of which are dosing visits, as well as up to 8 telephone safety FU contacts, as follows: • Screening Visits 1 to 3 will occur no more than 60 days before the first dose of study treatment on Day 1. All screening procedures should be completed within 60 days; however, with Sponsor approval, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans (and/or due to other major causes [i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters/disruptions]). These screening visits will include baseline brain MRI, clinical scales of cognition and function,

biological fluid sampling (including CSF), amyloid and tau PET scans (where available), physical and neurological examinations, and all other safety and efficacy assessments.

- Twenty-seven dosing visits (Day 1 and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104).
- Eight telephone safety FU contacts after each of the first 8 doses.
- Four visits separate from dosing for clinical functional and cognitive assessments (Weeks 26, 50, 78, and 106).
- One FU safety visit at Week 122, 18 weeks after last dose at Week 104, or 18 weeks after administration of last dose for those participants who discontinue treatment early.
- A minimum of 6 MRI visits, with 4 during treatment (Week 14 [before escalation to 6 mg/kg, before the fifth dose], Week 22 [before escalation to 10 mg/kg, before the seventh dose], Week 30 [before the third dose at 10 mg/kg], Week 42 [before the sixth dose at 10 mg/kg]. Two additional MRIs will be performed at Week 106, and at the Week 122 safety FU 18 weeks after the final dose [EOS]) or 18 weeks after administration of the last dose for participants who discontinue treatment early.

See the study schematic in Section 1.2.

Duration of Study Participation:	The total duration of the study for each participant will be approximately 130 weeks, including a series of screening visits within 8 weeks before administration of the first dose, and a 104-week placebo-controlled treatment period. Participants will additionally undergo a safety FU Visit 18 weeks after the final dose of aducanumab.
Benefit-Risk Analysis:	Alzheimer's disease is a major public health issue that imposes immense burden on patients and caregivers. The Phase 3 Study 221AD302 met its prespecified primary and secondary endpoints. The statistically significant effect of aducanumab on clinical endpoints was supported by statistically significant dose- and time-dependent reductions of markers of brain amyloid beta plaques, and dose-dependent reductions of relevant markers of downstream Alzheimer's tau pathophysiology and

neurodegeneration. Supportive efficacy data were provided from the Phase 1b Study 221AD103, a smaller randomized, placebo-controlled, dose-finding study that demonstrated a dose-related numerical reduction in decline relative to placebo for CDR-SB and MMSE, as well as dose- and time-dependent reduction of markers of brain amyloid beta plaques. Although Study 221AD301 did not contribute to the evidence of effectiveness on clinical outcomes for aducanumab, the study did further demonstrate that aducanumab reduces amyloid beta plaques, since the PET subset demonstrated statistically significant time- and dose-dependent decreases in amyloid beta plaques. There is also extensive scientific evidence of the role of amyloid in Alzheimer's disease. Collectively, the imaging, fluid biomarker results, the correlation analysis, and the exposure-response modeling are all consistent with a direct effect of aducanumab on lowering brain amyloid beta pathology with a subsequent effect on reducing tau pathology, neurodegeneration and ultimately slowing of clinical decline.

The aducanumab safety database exceeds the minimum ICH guidance, and risk management can be achieved through monitoring for ARIA, as described in the protocol. Most of the safety data from the aducanumab clinical program are derived from Studies 221AD301 and 221AD302. A total of 2757 participants with MCI due to Alzheimer's disease or mild Alzheimer's disease received aducanumab in Studies 221AD301 and 221AD302, accounting for approximately 3983.5 person-years of exposure and 4736.1 total person-years of FU. In the pooled analysis of the placebo-controlled periods of the Phase 3 studies, AEs experienced by participants in the 10 mg/kg IV dose group with an incidence of at least 5% and that were observed at a 2% or greater incidence than in the placebo group were ARIA-E, headache, ARIA-H microhemorrhage, fall, ARIA-H superficial siderosis, and diarrhea. These AEs are ADRs of aducanumab.

ARIA is the most common safety finding observed with aducanumab. ARIA includes ARIA-E, which can be observed on MRI as brain edema or sulcal effusions, and ARIA-H, which includes microhemorrhage and superficial siderosis. ARIA-E was observed in 35.2% of the 10 mg/kg dose group, compared to 2.7% of the placebo group. The incidence of ARIA-E was higher in ApoE ε4 carriers than in ApoE ε4 noncarriers (43.0% and 20.3%, respectively). The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. In the 10 mg/kg group, the majority of ARIA-E events resolved within 12 to 16 weeks of detection (68.9% and 82.8%, respectively) and

98% of ARIA-E resolved radiographically. In the 10 mg/kg group, 10.0% of aducanumab-treated participants experienced symptoms in the setting of ARIA, which included headache, confusion, dizziness, visual disturbances, nausea, and vomiting, with most symptoms being mild or moderate and transient in nature. Seizures, including status epilepticus, can be a severe symptom of ARIA-E.

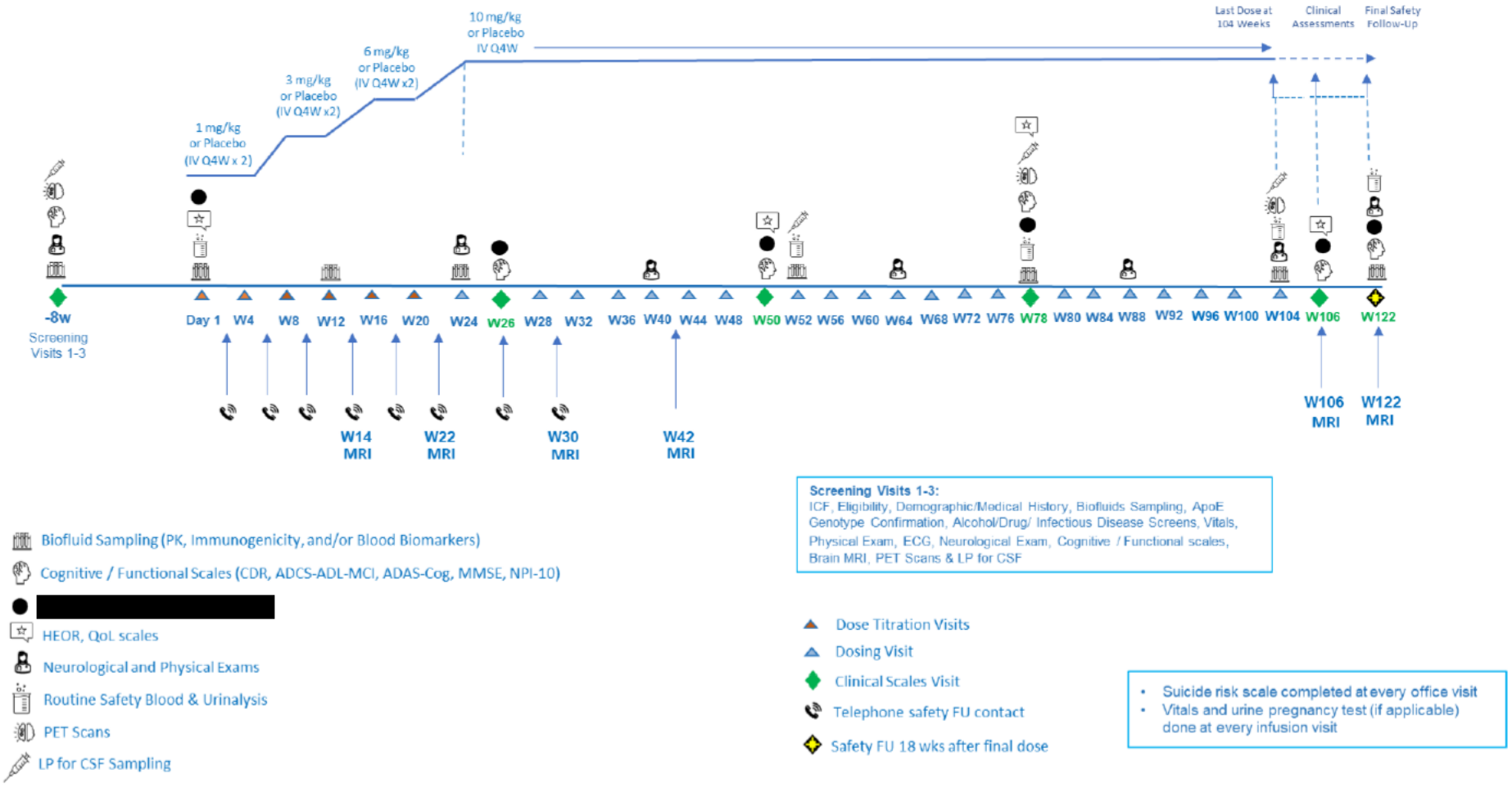
The potential risks related to participation in this study are justified by the anticipated benefit to participants. However, given the partial discrepancies between the 2 pivotal trials, and while acknowledging that this drug has been approved at this time in the US under accelerated approval, the benefit profile of aducanumab at 10 mg/kg IV will be further verified in this study.

General risk mitigation against COVID-19 will be implemented in accordance with the study site's IRB-approved monitoring and prevention control measures. The risk mitigation measures, where applicable, will be amended based on emerging local, regional, and national guidance.

Detailed information about the known and expected benefits and risks and reasonably expected AEs of aducanumab is provided in the Investigator's Brochure and ICF.

1.2. Study Design Schematic

Figure 1: Study Design Schematic



1.3. Schedule of Activities

Table 1: Schedule of Activities From Screening Through Week 32

Study Week	Screening (≤ 60 days before Day 1)[1]			1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	UV for Change in AD Med[2]	UV for ARIA[3]
Study Day	Visit 1	Visit 2	Visit 3	1	15 ± 3	29 ± 3	43 ± 3	57 ± 3	71 ± 3	85 ± 3	99 ± 3	113 ± 3	127 ± 3	141 ± 3	155 ± 3	169 ± 3	183 ± 3	197 ± 3	211 ± 3	225± 3		
Informed Consent[4]	X																					
Eligibility Criteria	X	X	X	X[5]																		
Demography	X																					
Medical History	X	X	X	X[6]																		
Alcohol/Drug Screen	X																					
HbA1c	X																					
HIV[7]/Hepatitis	X																					
ApoE Genotyping	X																					
[redacted]																						
Height				X																		
Body Weight				X		X		X		X		X		X		X		X		X		
Serum Pregnancy Test[10]	X																					
Urine Pregnancy Test[10]				X		X		X		X		X		X		X		X		X		
FSH[11]	X																					

Study Week	Screening (≤ 60 days before Day 1)[1]			1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	UV for Change in AD Med[2]	UV for ARIA[3]
Study Day	Visit 1	Visit 2	Visit 3	1	15 ± 3	29 ± 3	43 ± 3	57 ± 3	71 ± 3	85 ± 3	99 ± 3	113 ± 3	127 ± 3	141 ± 3	155 ± 3	169 ± 3	183 ± 3	197 ± 3	211 ± 3	225± 3		
Physical Examination	X															X						
Neurological Examination	X															X						
12-Lead ECG[12]	X																					
Vital Signs[13,14]	X			X		X		X		X		X		X		X		X		X		
Hematology, Blood Chemistry, and Urinalysis	X																					
Randomization				X																		
Study Treatment Infusion[15]				X		X		X		X		X		X		X		X		X		
Anti-Aducanumab Ab[16]				X						X						X						
Aducanumab Concentration[17]				X						X						X						X
[redacted]																						
Coagulation Panel[19]	X																					
CSF Collection		X[20]																				
Amyloid PET[21]		X																				
Tau PET[22]			X																			
Brain MRI[23]		X									X				X				X			X
FU Phone Call[24]					X		X		X		X		X		X		X		X			X

Study Week	Screening (≤ 60 days before Day 1)[1]			1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	UV for Change in AD Med[2]	UV for ARIA[3]
Study Day	Visit 1	Visit 2	Visit 3	1	15 ± 3	29 ± 3	43 ± 3	57 ± 3	71 ± 3	85 ± 3	99 ± 3	113 ± 3	127 ± 3	141 ± 3	155 ± 3	169 ± 3	183 ± 3	197 ± 3	211 ± 3	225± 3		
Clinical Scales, Patient-Reported Outcomes, QoL, and HEOR Measures																						
Diagnostic Verification Form[25]	X																X					
RBANS	X																					
MMSE	X																X				X	
CDR	X																X				X	
ADAS-Cog13		X[26]															X				X	
ADCS-ADL-MCI		X[26]															X				X	
NPI-10		X[27]															X				X	
C-SSRS[28]		X		X		X		X		X		X		X		X	X	X		X	X	X
[redacted]																						
RUD-Lite				X																		
EQ-5D-5L[30]				X																		
[redacted]																						
QoL-AD[31]				X																		
Routine Safety Monitoring																						
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																					
SAE Reporting	Monitor and record continuously throughout the study[32]																					
AE Reporting				Monitor and record from Day 1[32]																		

[1] Some examinations required for assessment of participant eligibility must be performed sequentially at Screening Visits 1 through 3, as follows: 1) brain MRI should only be performed once the participant meets eligibility criteria at Screening Visit 1, and 2) the amyloid PET scan should only be performed after confirmation that the participant meets all other eligibility criteria at Screening Visit 1, as well as all MRI-related eligibility criteria at Screening Visit 2. It is

recommended that all screening procedures be completed within 60 days before Day 1; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and/or due to other major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters/disruptions) and is subject to Sponsor approval.

[2] Participants who have a change in Alzheimer's disease medication (other than study treatment) should have a UV. A subset of the clinical efficacy assessments (CDR, MMSE, ADCS-ADL-MCI, and ADAS-Cog13) should be performed prior to the change in medication if the participant alerts the Investigator before the change in medication occurs. If the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments have been performed within 30 days of the change in medication, the assessments do not have to be repeated.

[3] For the frequency of required brain MRI assessments and of PK [redacted] sample collection for participants who develop ARIA-E and/or ARIA-H, see Section 5.3.1. This includes PK [redacted] sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI assessments following resolution of ARIA and resumption of dosing, see Section 5.3.1.6. For management of recurrent ARIA, see Section 5.3.1.7.

[4] This written full informed consent allows for completion of all assessments necessary for screening, treatment, and FU of participants: collection of demographic data (including ethnic and racial data), medical and cognitive status history, sample collection for ApoE genotyping, confirmation of amyloid positivity, and completion of cognitive and functional scales. Additional separate informed consents will be used for the 3 longitudinal substudies involving imaging and CSF sampling over time (see Section 9.4), and for optional future scientific research assessments (see Section 9.6).

[5] All eligibility criteria must be confirmed, and all assessments must be completed, before study treatment infusion.

[6] Medical history should be assessed up until predose on Day 1.

[7] HIV testing is at the Investigator's discretion after consideration of risk factors.

[redacted]

[10] Pregnancy testing will be required for women of childbearing potential only. See Section 11.4.2.

[11] FSH determination will only be required in women at Screening to confirm postmenopausal status. If the participant's status as menopausal is confirmed, no subsequent pregnancy testing of that participant is required.

[12] ECGs will be read locally.

[13] Vital signs will include SBP, DBP, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the participant supine and after the participant has been resting for at least 10 minutes.

[14] If SBP is below 165 mmHg and DBP is below 100 mmHg at Screening, only 1 BP reading needs to be conducted. If either parameter is exceeded, 3 measurements should be taken to determine the average.

[15] The preceding centralized MRI report must have been received and reviewed by the Investigator before continuing with study treatment infusions.

[16] Sample collection for anti-aducanumab Abs will be performed prior to study treatment infusion (where applicable).

[17] Blood sampling for aducanumab concentration will be performed prior to infusion. When collected for ARIA management, a sample will be collected ± 2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified CRF.

[redacted]

[19] Coagulation panels, including PT, PTT, INR, and platelet count, must be performed within 35 days before the LP. If a participant, in the opinion of the Investigator, is at increased bleeding risk, the coagulation panel should be repeated within 7 days before the LP, if necessary. These repeat tests may be

performed locally to facilitate timely review of the results. Before any LP can be performed, the results of the most recent coagulation panel, concomitant medications, and overall general bleeding risk must be reviewed by the Investigator and must indicate that the LP can be performed safely. When the coagulation panel is performed at a visit that includes hematology testing, the platelet count should be done only once.

[20]Screening CSF should only be collected after the participant meets all other eligibility criteria, including MRI criteria, at Screening Visits 1 and 2. An LP should not be performed if the Investigator suspects the presence of intracranial hypertension clinically or radiologically. Before any LP can be performed, the results of the most recent coagulation panel, concomitant medications, and overall general bleeding risk must be reviewed by the Investigator and must indicate that the LP can be performed safely. For participants of the longitudinal CSF substudy, the sample must be taken at Screening using study-specific procedures. If a participant enters the study based on amyloid PET positivity, as determined by a previous amyloid PET scan, and also enters the [redacted] with a negative baseline CSF result, the PET result takes precedence for the purposes of determining eligibility.

[21]Amyloid PET is limited to selected sites with access to the Sponsor-approved amyloid PET radiotracer(s). For participants who are not enrolled in the longitudinal amyloid PET substudy, a historical amyloid PET scan previously obtained within 18 months of Screening Visit 1 is permissible and must be submitted to the central imaging vendor to confirm that study inclusion criteria are met. A historical amyloid PET scan will not be accepted for participants who enroll in the longitudinal amyloid PET substudy. If a participant enters the study based on amyloid PET positivity, as determined by a previous amyloid PET scan, and also enters the [redacted] with a negative baseline CSF result, the PET result takes precedence for purposes of determining eligibility. Screening amyloid PET scan should only be conducted after meeting all other eligibility criteria, including MRI criteria, at Screening Visits 1 and 2. The Screening Period may be extended up to 90 days in the event of logistical issues related to PET scans and/or due to other major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters/disruptions) and is subject to Sponsor approval. For all women of childbearing potential, a pregnancy test must be performed within 24 hours prior to every PET scan.

[22]Tau PET will be performed in a subset of participants at selected sites with access to the Sponsor-approved tau PET radiotracer(s). A Screening tau PET scan is mandatory for all participants at sites with tau PET scanning capabilities; a historical tau PET scan will not be accepted. Screening tau PET will not contribute to eligibility determination. The tau PET scan should only be performed at Screening Visit 3 after the participant has confirmation of a positive amyloid result (either PET or CSF) from Screening Visits 1 or 2, and after meeting all other eligibility criteria, including MRI criteria, at Screening Visits 1 and 2. Screening tau PET scan should be performed prior to randomization. Only in the event of inadequate radiotracer supplies or PET camera availability can the Screening tau PET scan be performed after Day 1, with Sponsor approval; the scan should be performed as close to the first infusion date as possible and must occur prior to the second infusion. The Screening Period may be extended up to 90 days in the event of logistical issues related to PET scans and/or due to other major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters/disruptions) and is subject to Sponsor approval. For all women of childbearing potential, a pregnancy test must be performed within 24 hours prior to every PET scan.

[23]Brain MRI (Screening Visit 2) will not be performed until the participant has met the eligibility criteria and has acceptable laboratory tests from Screening Visit 1.

[24]Safety FU telephone contacts occur during dose escalation. These FU contacts may be performed in person if the participant will be at the site for clinical assessments.

[25]The Research Diagnostic Verification Form is used at Screening Visit 1 for initial diagnosis, and the Diagnostic Staging Form is used at subsequent visits to help standardize diagnostic change across the study. These forms should be completed after the CDR is performed (see the Study Reference Guide).

[26]The baseline ADAS-Cog13 and the ADCS-ADL-MCI must be performed within 20 days of Screening Visit 1, but not on the same day as the screening of CDR or MMSE. These scales can also be performed on Day 1 prior to randomization and study treatment infusion.

[27]The NPI-10 must be performed after the CDR but can be performed at any time during Screening or on Day 1.

[28]At Screening, the Lifetime/Recent C-SSRS will be used. At all postscreening visits, the C-SSRS-SLV version will be used.

[redacted]

[30]Two versions of the EQ-5D-5L questionnaire will be completed only at baseline: the participant's self-reported version and the informant-reported version describing the participant.
[31]Two versions of the QoL-AD questionnaire will be completed: the participant's self-reported version and the informant-reported version describing the participant.
[32]AEs and SAEs related to the PET radiotracer will also be monitored and reported.

Table 2: Schedule of Activities From Week 36 to End of Study

Study Week	**36**	**40**	**42**	**44**	**48**	**50**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**106**	**ET[1]**	**UV AD Meds[2]**	**UV ARIA[3]**	**FU[4] EOS**
Study Day	**253 ± 3**	**281 ± 3**	**295 ± 3**	**309 ± 3**	**337 ± 3**	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**	**561 ± 3**	**589 ± 3**	**617 ± 3**	**645 ± 3**	**673 ± 3**	**701 ± 3**	**729 ± 3**	**743 ± 3**				**855± 3**
Body Weight	X	X		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X		X			X
Urine Pregnancy Test[5]	X	X		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X		X			X
Physical Exam		X								X							X				X		X			X
Neurological Exam		X								X							X				X		X			X
12-Lead ECG							X														X		X			X
Vital Signs[6]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			X
Hematology, Blood Chemistry, and Urinalysis							X														X		X			X
Study Treatment Infusion[7]	X	X		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X					
Anti-Aducanumab Ab[8]							X							X							X		X			X
Aducanumab Concentration[9]							X							X							X		X		X	X
[redacted]																										
CSF Collection[11]							X							X							X		X			
Coagulation Panel[12]							X							X							X		X			
Amyloid PET[13]														X							X		X			
Tau PET[14]														X							X		X			
Brain MRI			X																			X	X		X	X

Study Week	36	40	42	44	48	50	52	56	60	64	68	72	76	78	80	84	88	92	96	100	104	106	ET[1]	UV AD Meds[2]	UV ARIA[3]	FU[4] EOS
Study Day	253 ± 3	281 ± 3	295 ± 3	309 ± 3	337 ± 3	351 ± 3	365 ± 3	393 ± 3	421 ± 3	449 ± 3	477 ± 3	505 ± 3	533 ± 3	547 ± 3	561 ± 3	589 ± 3	617 ± 3	645 ± 3	673 ± 3	701 ± 3	729 ± 3	743 ± 3				122 855± 3
Clinical Scales, Patient-Reported Outcomes, QoL, and HEOR Measures																										
Diagnostic Verification Form						X								X								X	X			
MMSE						X								X								X	X	X		X
CDR						X								X								X	X	X		X
ADAS-Cog13						X								X								X	X	X		X
ADCS-ADL-MCI						X								X								X	X	X		X
NPI-10						X								X								X	X	X		X
C-SSRS-SLV	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																										
RUD-Lite						X								X								X	X			X
[redacted]																										
QoL-AD[16]						X								X								X	X			X
Routine Safety Monitoring																										
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																									
SAE Reporting	Monitor and record continuously throughout the study[17]																									
AE Reporting	Monitor and record continuously throughout the study[17]																									

[1] Participants who withdraw voluntarily from the study prematurely are to return to the site for an ET Visit, unless withdrawal is due to death or withdrawal of consent. If the participant discontinues treatment within 3 months of the previous efficacy assessment visit, and no significant changes in cognitive status are suspected by the Investigator, clinical efficacy assessments are not required. In such cases, the site should notify the Sponsor and the Medical Monitor.

[2] Participants who have a change in Alzheimer's disease medication (other than study treatment) should have a UV. A subset of the clinical efficacy assessments (CDR, MMSE, ADCS-ADL-MCI, and ADAS-Cog13) should be performed prior to the change in medication if the participant alerts the Investigator before the change in medication occurs. If the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments have been performed within 30 days of the change in medication, the assessments do not have to be repeated.

[3] For the frequency of required brain MRI assessments, and of PK [redacted] sample collection for participants who develop ARIA-E and/or ARIA-H, see Section 5.3.1. This includes PK sample collection at the first unscheduled visit for ARIA monitoring per episode only. [redacted] sample collection should

occur at each UV for ARIA management. For the frequency of brain MRI assessments following resolution of ARIA and resumption of dosing, see Section 5.3.1.6. For management of recurrent ARIA, see Section 5.3.1.7.

[4] A safety FU Visit is required 18 weeks after the participant's last dose at 104 weeks. Similarly, participants who discontinue treatment and do not agree to continue in the study (withdrawn participants) should return to sites for a final assessment 18 weeks after their final dose. Participants who discontinue treatment prematurely but agree to remain in the study should continue assessments at a subset of the clinic visits until the end of the study per the Schedule of Activities in Table 3. It is possible that a clinic visit will occur before the FU Visit 18 weeks after the participant's final dose. If the FU Visit occurs within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit.

[5] Pregnancy testing will only be required for women of childbearing potential. Section 11.4.2.

[6] Vital signs will include SBP, DBP, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the participant supine and after the participant has been resting for at least 10 minutes.

[7] The preceding centralized MRI report must have been received and reviewed by the Investigator before continuing with study treatment infusions.

[8] Sample collection for anti-aducanumab Abs will be performed prior to study treatment infusion (where applicable).

[9] Blood sampling for aducanumab concentration will be performed prior to infusion. When collected for ARIA management, a sample will be collected ± 2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified CRF.

[redacted]

[11] Before any LP can be performed, the results of the most recent coagulation panel, concomitant medications, and overall general bleeding risk must be reviewed by the Investigator and must indicate that the LP can be performed safely. An LP should not be performed if the Investigator suspects the presence of intracranial hypertension clinically or radiologically.

[12] Coagulation panels, including PT, PTT, INR, and platelet count, must be performed within 35 days before the LP. If a participant, in the opinion of the Investigator, is at increased bleeding risk, the coagulation panel should be repeated within 7 days before the LP, if necessary. These repeat tests may be performed locally to facilitate a timely review of the results. Before any LP can be performed, the results of the most recent coagulation panel, concomitant medications, and overall general bleeding risk must be reviewed by the Investigator and must indicate that the LP can be performed safely. When the coagulation panel is performed at a visit that includes hematology testing, the platelet count should be done only once.

[13] FU amyloid PET scans at Weeks 78 and 104 will only be conducted at selected sites for participants enrolled in the longitudinal amyloid PET substudy and may be scheduled within a window of -21 to +7 days. Amyloid PET must be conducted using only the Sponsor-approved radiotracer and the same radiotracer used for baseline amyloid PET scan. A QC-passing Screening amyloid PET scan is required to continue in the longitudinal amyloid PET substudy. For participants consenting to both amyloid and tau PET substudies, the amyloid and tau PET scans should be performed on separate days (cannot be performed on the same day). For participants consenting to both CSF and PET substudies, if collected on the same day as a PET scan, CSF should be collected prior to PET. For participants in the amyloid PET longitudinal substudy who withdraw before Week 78, PET assessment will be collected at ET Visit only if withdrawal occurs > 6 months after the previous amyloid PET scan. For all women of childbearing potential, a pregnancy test must be performed within 24 hours prior to every PET scan.

[14] FU tau PET scans at Weeks 78 and 104 should be collected in a subset of participants in the longitudinal tau PET substudy at selected sites and may be scheduled within a window of -21 to +7 days. Tau PET must be conducted using only the Sponsor-approved radiotracer and the same tracer used for baseline tau PET scan. A QC-passing screening tau PET scan is required to continue in the longitudinal tau PET substudy. For participants consenting to both amyloid and tau PET substudies, the amyloid and tau PET scans must be performed on different days (cannot be performed on the same day). For participants consenting to both CSF and PET substudies, if collected on the same day as a PET scan, CSF should be collected prior to PET. For participants in the tau PET longitudinal substudy who withdraw before Week 78, PET assessment will be collected at ET Visit only if withdrawal occurs > 6 months after the previous amyloid PET scan. For all women of childbearing potential, a pregnancy test must be performed within 24 hours prior to every PET scan.

[redacted]

[16] Two versions of the QoL-AD questionnaire will be completed: the participant's self-reported version and the informant-reported version describing the participant.
[17] AEs and SAEs related to the PET radiotracer will also be monitored and reported.

Table 3: Abbreviated Schedule of Activities for Participants Who Discontinue Study Treatment but Remain in the Study

Study Week[1]	**12**	**24**	**40**	**50/52**	**64**	**78**	**88**	**104**	**106**	**ET**[2]	**UV for ARIA**[3]
Study Day	**85 ± 3**	**169 ± 3**	**281 ± 3**	**351 ± 3**	**449± 3**	**547 ± 3**	**617 ± 3**	**729/743 ± 3**	**743 ± 3**		
Physical Examination		X	X	X	X		X	X		X	
Neurological Examination		X	X	X	X		X	X		X	
12-Lead ECG				X				X		X	
Vital Signs	X	X	X	X	X		X	X		X	X
Hematology, Blood Chemistry, and Urinalysis				X				X		X	
Urine Pregnancy Test[4]	X	X	X	X	X		X	X			
[redacted]											
Coagulation Panel[6]				X		X		X		X	
CSF Collection[7]				X		X		X		X	
Amyloid PET[8]						X					
Tau PET[9]						X					
Brain MRI								X		X	X
Clinical Scales, Patient-Reported Outcomes, QoL, and HEOR Measures											
Diagnostic Verification Form				X		X			X	X	
MMSE				X		X			X	X	
CDR				X		X			X	X	
ADAS-Cog13				X		X			X	X	
ADCS-ADL-MCI				X		X			X	X	
NPI-10				X		X			X	X	
C-SSRS-SLV	X	X	X	X	X	X	X	X	X	X	X
[redacted]											

Study Week[1]	**12**	**24**	**40**	**50/52**	**64**	**78**	**88**	**104**	**106**	**ET**[2]	**UV for ARIA**[3]
Study Day	**85 ± 3**	**169 ± 3**	**281 ± 3**	**351 ± 3**	**449± 3**	**547 ± 3**	**617 ± 3**	**729/743 ± 3**	**743 ± 3**		
[redacted]											
RUD-Lite				X		X			X	X	
[redacted]											
QoL-AD[12]				X		X			X	X	
Routine Safety Monitoring											
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study										
AE Reporting	Monitor and record continuously throughout the study[13]										
SAE Reporting	Monitor and record continuously throughout the study[13]										

[1] Participants who discontinue study treatment and withdraw from the study prematurely will attend an ET visit, and additionally a FU Visit, 18 weeks after their final dose, as noted in Table 2. Participants who discontinue treatment but agree to stay in the study will follow the abbreviated visit schedule outlined here. Participants will begin this Schedule of Activities at the visit that most closely follows study treatment discontinuation.

[2] Participants who withdraw voluntarily from the study prematurely are to return to the site for an ET Visit, unless withdrawal is due to death or withdrawal of consent. If the participant discontinues treatment within 3 months of the previous efficacy assessment visit, and no significant changes in cognitive status are suspected by the Investigator, clinical efficacy assessments are not required. In such cases, the site should notify the Sponsor and the Medical Monitor.

[3] For the frequency of required brain MRI assessments [redacted] sample collection for participants who develop ARIA-E and/or ARIA-H, see Section 5.3.1. This includes PK [redacted] sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI assessments following resolution of ARIA and resumption of dosing, see Section 5.3.1.6. For management of recurrent ARIA, see Section 5.3.1.7.

[4] A urine pregnancy test is required for women of childbearing potential only if the last dose of study treatment was less than 24 weeks before the clinic visit.

[redacted]

[6] Coagulation panels, including PT, PTT, INR, and platelet count, must be performed within 35 days before the LP. If a participant, in the opinion of the Investigator, is at increased bleeding risk, the coagulation panel should be repeated within 7 days before the LP, if necessary. These repeat tests may be performed locally to facilitate a timely review of the results. Before any LP can be performed, the results of the most recent coagulation panel, concomitant medications, and overall general bleeding risk must be reviewed by the Investigator and must indicate that the LP can be performed safely. When the coagulation panel is performed at a visit that includes hematology testing, the platelet count should be done only once.

[7] Before any LP can be performed, the results of the most recent coagulation panel, concomitant medications, and overall general bleeding risk must be reviewed by the Investigator and must indicate that the LP can be performed safely. An LP should not be performed if the Investigator suspects the presence of intracranial hypertension clinically or radiologically.

[8] FU amyloid PET scan at Weeks 78 will only be conducted at selected sites for participants enrolled in the longitudinal amyloid PET substudy and may be scheduled within a window of -21 to +7 days. Amyloid PET must be conducted using only the Sponsor-approved radiotracer and the same radiotracer used for

baseline amyloid PET scan. A QC-passing screening amyloid PET scan is required to continue in the longitudinal amyloid PET substudy. For participants consenting to both amyloid and tau PET substudies, the amyloid and tau PET scans must be performed on different days (cannot be performed on the same day). For participants consenting to both CSF and PET substudies, if collected on the same day as a PET scan, CSF should be collected prior to PET. For participants in the amyloid PET longitudinal substudy who withdraw before Week 78, PET assessment will be collected at ET Visit only if withdrawal occurs > 6 months after the previous amyloid PET scan. For all women of childbearing potential, a pregnancy test must be performed within 24 hours prior to every PET scan.

[9] FU tau PET scan at Weeks 78will only be collected in a subset of participants enrolled in the longitudinal tau PET substudy at selected sites and may be scheduled within a window of -21 to +7 days. Tau PET must be conducted using only the Sponsor-approved radiotracer. A QC-passing Screening tau PET scan is required to continue in the longitudinal tau PET substudy. For participants consenting to both amyloid and tau PET substudies, the amyloid and tau PET scans must be performed on different days (cannot be performed on the same day). For participants consenting to both CSF and PET substudies, if collected on the same day as a PET scan, CSF should be collected prior to PET. For participants in the tau PET longitudinal substudy who withdraw before Week 78, PET assessment will be collected at ET Visit only if withdrawal occurs > 6 months after the previous amyloid PET scan. For all women of childbearing potential, a pregnancy test must be performed within 24 hours prior to every PET scan.

[redacted]

[12]Two versions of the QoL-AD questionnaire will be completed: the participant's self-reported version and the informant-reported version describing the participant.

[13]AEs and SAEs related to the PET radiotracer will also be monitored and reported.

2. LIST OF ABBREVIATIONS

Aβ	amyloid beta
Ab	antibody
AD	Alzheimer's disease
ADAS-Cog13	Alzheimer's Disease Assessment Scale, Cognitive subscale
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study Scale for Activities of Daily Living in Mild Cognitive Impairment
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E ε4
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-hemorrhage
AST	aspartate aminotransferase
CBD	cannabidiol
CDR	Clinical Dementia Rating scale
CDR-GS	Clinical Dementia Rating scale - Global Score
CDR-SB	Clinical Dementia Rating scale - Sum of Boxes
COVID-19	coronavirus disease 2019
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
C-SSRS-SLV	Columbia Suicide Severity Rating Scale - Since Last Visit
DBP	diastolic blood pressure
[redacted]	[redacted]
DMI	delayed memory index on RBANS
[redacted]	[redacted]
DSST	digit symbol substitution test
ECG	electrocardiogram
EMACC	Early Alzheimer's Disease/Mild Cognitive Impairment Alzheimer's Cognitive Composite
EQ-5D-5L	health-related EuroQoL 5-dimension instrument
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FU	follow-up
GST	global statistical test
HbA1c	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEOR	health economic and outcomes research

HIV	human immunodeficiency virus
iADRS	Integrated Alzheimer's Disease Rating Scale
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
IVIG	intravenous immune globulin
LP	lumbar puncture
LS	least squares
MCI	mild cognitive impairment
MMRM	mixed-effect model repeated measure
MMSE	Mini-Mental State Examination
[redacted]	[redacted]
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging and Alzheimer's Association
NPI-10	Neuropsychiatric Inventory-10
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
PV4	protocol version 4
Q4W	every 4 weeks
QoL	quality of life
QoL-AD	Quality of Life in Alzheimer's Disease
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RNA	ribonucleic acid
RUD-Lite	Resource Utilization in Dementia – Lite Version
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SLV	since last visit
THC	tetrahydrocannabinol
US	United States
USPI	United States Prescribing Information
UV	unscheduled visit
[redacted]	[redacted]
[redacted]	[redacted]

3. INTRODUCTION

Aducanumab is a human IgG1 monoclonal antibody targeting soluble and insoluble aggregated forms of amyloid beta. Aducanumab modifies the underlying pathophysiological disease course by removing amyloid plaques, which are considered one of the hallmarks of Alzheimer's disease. Treatment effects observed on both CSF p-tau and tau PET suggest that aducanumab also has a downstream effect on tau pathology, the other major hallmark protein of the disease.

3.1. Study Rationale

The purpose of this confirmatory study is to verify the clinical benefit of aducanumab compared with placebo in participants with Alzheimer's disease, including participants with either MCI due to Alzheimer's disease or mild Alzheimer's disease.

In June 2021, aducanumab was approved by the US FDA under the accelerated approval pathway as a treatment for Alzheimer's disease. Approval was based on evidence that aducanumab reduces brain amyloid, coupled with evidence that the reduction in amyloid identified in aducanumab clinical studies is reasonably likely to predict clinical benefit in Alzheimer's disease.

Consistent with the accelerated approval regulations, this study is being conducted to fulfill a postmarketing requirement from the FDA to verify the clinical benefit of aducanumab. The study is required to be a randomized, controlled trial to evaluate the efficacy of aducanumab compared with an appropriate control for the treatment of Alzheimer's disease and to be of sufficient duration to observe changes on an acceptable endpoint in the enrolled study population.

In accordance with the stated requirements, the study design largely conforms to that of the aducanumab Phase 3 Studies 221AD301 and 221AD302, namely, that it is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

Relevant nonclinical and clinical data (including from the Phase 3 program) are summarized in Section 3.2.3.

3.1.1. Rationale for Study Population

The study population will include participants with MCI due to Alzheimer's disease and participants with mild Alzheimer's disease [Albert 2011; McKhann 2011]. Enrollment will be monitored so that the population of participants with mild Alzheimer's disease represents approximately 50% of the total number of participants enrolled in the study. Aducanumab is expected to provide the most benefit to patients in these early stages of Alzheimer's disease.

3.1.2. Rationale for Dosing Regimen

Participants will be assigned to 1 of 2 treatment groups in a 2:1 ratio of aducanumab to placebo administered IV every 4 weeks. Treatment is initiated via titration, which has been demonstrated to result in a lower incidence of ARIA. Titration will start at 1 mg/kg and will escalate to 3, 6 and 10 mg/kg.

3.2. Background

3.2.1. Overview of Alzheimer's Disease

Alzheimer's disease is an irreversible, progressive neurodegenerative disorder that slowly destroys memory and thinking skills. Initial impairment in memory may be followed by behavioral and neuropsychiatric symptoms and, finally, the inability to perform usual daily life activities. Alzheimer's disease is the most common cause of dementia among older adults and is ultimately fatal.

In the US, more than 5.8 million people are living with Alzheimer's disease. By 2050, this number is projected to more than double [Alzheimer's Association 2020]. Alzheimer's disease was the sixth leading cause of death in the US and the fifth leading cause for people aged 65 years and older in 2018 [Alzheimer's Association 2020].

Life expectancy after an Alzheimer's disease diagnosis depends on various factors, including age at onset and severity at diagnosis [Brodaty 2012; Guehne 2007; Guehne 2005; Xie 2008]. An important distinction for Alzheimer's disease patients is that a significant period of their remaining lives may be spent in the severe disabling disease state, adding to the burden on the health care system [Rizzuto 2012].

In addition to the effect on patients, Alzheimer's disease places a burden on families and caregivers. Informal caregiving for patients with Alzheimer's disease or dementia has been estimated at 18 billion hours per year in the US, valued at $230 billion annually [Alzheimer's Association 2020; Dunbar 2018]. Increased care demands result in increased financial, psychological, and physical stress for the caregiver [Alzheimer's Association 2020; Suehs 2014].

Alzheimer's disease is a pathophysiological and clinical continuum in which specific pathological changes in the brain that occur as a continuous process throughout the course of the disease precede by many years the eventual emergence of clinical symptoms of cognitive decline that also progress continuously over a long period [Jack 2018].

Alzheimer's disease is defined biologically by the presence of 2 abnormal protein deposits: extracellular deposits of brain amyloid plaques (comprising amyloid beta peptides) and neurofibrillary tangles (comprising abnormal tau protein) [Hyman 2012].

Deposition of amyloid beta peptides into amyloid plaques begins decades prior to observable clinical symptoms [Vermunt 2019]. Deposition of amyloid beta is followed sequentially by markers of neurodegeneration [Hardy and Selkoe 2002], accumulation of tau pathology [Hanseeuw 2019], and brain volume loss [Jonsson 2012], all of which initiate prior to the onset of clinical symptoms. This presymptomatic phase of Alzheimer's disease precedes the emergence of clinical symptoms by 10 to 20 years [Villemagne 2013]. At the time of the emergence of the earliest clinical findings, Alzheimer's disease has already been present in the individual for decades, and there is already an advanced pathological disease state in the brain.

The most salient known risk factors for Alzheimer's disease are the unmodifiable contributors of older age, genetics, and family history. Of these, increasing age has the largest known impact on

risk of developing Alzheimer's disease. While several genes have been found to increase the risk of Alzheimer's disease, the ε4 allele of the ApoE gene is the strongest known genetic risk factor [Elias-Sonnenschein 2011; Mattsson 2018]. Compared with the most common ApoE genotype of ε3/ε3, ε4 heterozygosity increases risk of Alzheimer's disease by 3 to 4 times, and ε4 homozygosity increases risk by 8 to 12 times [Alzheimer's Association 2020]. Approximately two-thirds of pathology-confirmed Alzheimer's disease cases are ε4 positive (homozygous or heterozygous), compared with about 15% to 20% of the general population [Mattsson 2018]. Autosomal dominant genetic mutations are estimated to account for fewer than 1% of Alzheimer's disease cases [Bekris 2010].

Developing treatments to halt, slow, or reverse the course of disease is a goal for the scientific community, the clinical health care system, long-term care services, community/support environments serving patients and caregivers, and the federal government [U.S. Department of Health and Human Services 2019].

With pathophysiological changes in the brain starting a decade or more before clinical symptom onset, treatments directed at this goal must begin prior to the development of irreversible neurodegeneration and well before there are advanced clinical symptoms [FDA 2018; U.S. Department of Health and Human Services 2019; Vermunt 2019].

3.2.2. Other Current Therapies for Alzheimer's Disease

Until the approval of aducanumab in 2021 in the US, the only approved Alzheimer's disease treatments included the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine.

None of these other agents address the underlying pathology of the disease. Their effects are reversible and lessen over time due to the continued progression of the disease process [Birks 2006; McShane 2006].

3.2.3. Profile of Previous Experience With Aducanumab

3.2.3.1. Nonclinical Experience

Unlike any other anti-Aβ monoclonal antibody in development, aducanumab was derived from human B cells collected from healthy elderly individuals with no signs of cognitive impairment and from cognitively impaired elderly individuals with unusually slow clinical decline. The screening of libraries of human memory B cells for reactivity against aggregated Aβ led to molecular cloning, sequencing, and recombinant expression of aducanumab [Sevigny 2016].

Aducanumab is a human IgG1 anti-Aβ monoclonal antibody selective for Aβ aggregates, including soluble oligomers and insoluble fibrils, but not monomers, as demonstrated in a variety of biochemical and structural analyses.

Binding of aducanumab to aggregated Aβ promotes the removal of amyloid from the brain, through a microglia-mediated phagocytosis mechanism. Experimental evidence has shown that

removal of amyloid stops or reduces neurotoxicity [Rozkalne 2009; Spires-Jones 2009] that might otherwise lead to neurodegeneration and, ultimately, cognitive impairment.

Nonclinical studies have confirmed in vivo dose-dependent target engagement and dose-dependent reduction in brain amyloid burden for aducanumab [Sevigny 2016].

See the Investigator's Brochure for detailed information on relevant nonclinical and clinical studies.

3.2.3.2. Clinical Experience

The aducanumab clinical development program comprises studies in healthy volunteers and in subjects with Alzheimer's disease. See the Investigator's Brochure for detailed information on the clinical efficacy and safety of aducanumab.

The Phase 3 Study 221AD302 demonstrated a statistically significant treatment benefit (smaller increase in the CDR-SB) for aducanumab 10 mg/kg, compared to placebo (-0.39 [-22%], $p = 0.0120$). Statistically significant treatment effects in favor of aducanumab 10 mg/kg were also observed for all 3 ranked secondary clinical endpoints (MMSE, ADAS-Cog13, and ADCS-ADL-MCI) and the tertiary endpoint (NPI-10). The effect of aducanumab on clinical endpoints was supported by statistically significant dose- and time-dependent reductions of markers of brain amyloid beta plaques, and dose-dependent reductions of relevant markers of downstream Alzheimer's tau pathophysiology and neurodegeneration. The changes on measures of Aβ were correlated with changes on clinical outcomes. The Phase 3 Study 221AD301 did not contribute to the evidence of effectiveness on clinical outcomes for aducanumab; however, the study did further demonstrate that aducanumab reduces amyloid beta plaques, as the PET subset demonstrated statistically significant time- and dose-dependent decreases in amyloid beta plaques. Supportive data were also provided from the Phase 1b Study 221AD103, a smaller randomized, placebo-controlled, dose-finding study conducted in a similar population and using many of the same endpoints that were used in Studies 221AD301 and 221AD302. A dose-related numerical reduction in decline was observed relative to placebo for CDR-SB and MMSE, as well as dose- and time-dependent reduction of markers of brain amyloid beta plaques.

As of March 2022, a total of 3078 participants have been exposed to aducanumab across completed or terminated clinical studies (including 3050 participants with Alzheimer's disease and 28 healthy volunteers). Of those, 2757 participants were enrolled in the Phase 3, placebo-controlled studies (Studies 221AD301 and 221AD302), for approximately 3983.5 person-years of exposure and totaling 4736.1 person-years of FU. The most frequent AE among participants from Studies 221AD301 and 221AD302 with a target dose of 10 mg/kg was ARIA-E (35.2%). Most participants with ARIA-E were asymptomatic, and participants with symptomatic ARIA-E had symptoms that were predominantly mild or moderate in clinical severity. Symptoms reported during ARIA-E episodes included headache, confusional state, dizziness, fatigue, and nausea. In the majority of participants with ARIA-E, the first ARIA-E events were documented to have fully resolved (800 of 815 participants [98.2%]). Similar to ARIA-E, the majority of participants with ARIA-H microhemorrhage and ARIA-H superficial siderosis were asymptomatic and stabilized radiographically. Other AEs observed at an incidence of at least 5% among participants from Studies 221AD301 and 221AD302 with a target dose of 10 mg/kg and at a 2%

or greater incidence than placebo included headache (20.5%), ARIA-H microhemorrhage (19.1%), fall (15.0%), ARIA-H superficial siderosis (14.6%), and diarrhea (8.9%). Seizures, including status epilepticus, occurred more frequently in aducanumab-treated participants who experienced ARIA: 0.4% of all participants in the 10 mg/kg group had a seizure event compared with 0.8% of aducanumab-treated participants who experienced ARIA-E. These events are ADRs of aducanumab.

3.3. Benefit-Risk Assessment

Alzheimer's disease is a major public health issue that imposes immense burden on patients and caregivers.

The Phase 3 Study 221AD302 met its prespecified primary and secondary endpoints. The statistically significant effect of aducanumab on clinical endpoints was supported by statistically significant dose- and time-dependent reductions of markers of brain amyloid beta plaques, and dose-dependent reductions of relevant markers of downstream Alzheimer's tau pathophysiology and neurodegeneration. Supportive efficacy data were provided from the Phase 1b Study 221AD103, a smaller randomized, placebo-controlled, dose-finding study that demonstrated a dose-related numerical reduction in decline relative to placebo for CDR-SB and MMSE, as well as dose- and time-dependent reduction of markers of brain amyloid beta plaques. Although the Phase 3 Study 221AD301 did not contribute to the evidence of effectiveness on clinical outcomes for aducanumab, the study did further demonstrate that aducanumab reduces amyloid beta plaques, as the PET subset demonstrated statistically significant time- and dose-dependent decreases in amyloid beta plaques. There is also extensive scientific evidence of the role of amyloid in Alzheimer's disease. Collectively, the imaging, fluid biomarker results, the correlation analysis, and the exposure-response modeling are all consistent with a direct effect of aducanumab on lowering brain Aβ pathology with a subsequent effect on reducing tau pathology, neurodegeneration, and ultimately slowing of clinical decline.

The aducanumab safety database exceeds the minimum ICH guidance, and risk management can be achieved through monitoring for ARIA, as described in the protocol. Most of the safety data from the aducanumab clinical program are derived from Studies 221AD301 and 221AD302.

ARIA is the most common safety finding observed with aducanumab. ARIA includes ARIA-E, which can be observed on MRI as brain edema or sulcal effusions, and ARIA-H, which includes microhemorrhage and superficial siderosis. ARIA-E was observed in 35.2% of the 10 mg/kg dose group, compared with 2.7% of the placebo group. The incidence of ARIA-E was higher in ApoE ε4 carriers than in ApoE ε4 noncarriers (43.0% and 20.3%, respectively). The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. In the 10 mg/kg group, the majority of ARIA-E events resolved within 12 to 16 weeks of detection (68.9% and 82.8%, respectively) and 98% of ARIA-E resolved radiographically. In the 10 mg/kg group, 10.0% of aducanumab-treated participants experienced symptoms in the setting of ARIA; these included headache, confusion, dizziness, visual disturbances, nausea, and vomiting, with most symptoms being mild or moderate and transient in nature. Seizures, including status epilepticus, can be a severe symptom of ARIA-E.

The potential risks related to participation in this study are justified by the anticipated benefit to participants. However, given the partial discrepancies between the 2 pivotal trials, and while acknowledging that this drug has been approved at this time in the US via accelerated approval, the benefit profile of aducanumab at 10 mg/kg IV will be further verified in this study.

General risk mitigation against COVID-19 will be implemented in accordance with the study site's IRB-approved monitoring and prevention control measures. The risk mitigation measures, where applicable, will be amended based on emerging local, regional, and national guidance.

Detailed information about the known and expected benefits and risks and reasonably expected AEs of aducanumab is provided in the Investigator's Brochure and ICF.

4. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoints**
To verify the clinical benefit of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in participants with early Alzheimer's disease.	Change from baseline in CDR-SB score at Week 78
Key Secondary Objectives	**Key Secondary Endpoints**
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the iADRS	Change from baseline in iADRS score at Week 78
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by ADCS-ADL-MCI	Change from baseline in ADCS-ADL-MCI score at Week 78
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by ADAS-Cog13	Change from baseline in ADAS-Cog13 score at Week 78
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the MMSE	Change from baseline in MMSE score at Week 78
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by NPI-10	Change from baseline in NPI-10 score at Week 78
Secondary Objectives	**Secondary Endpoints**
To assess the effect of aducanumab on cerebral amyloid plaque level as measured by amyloid PET imaging (where available, in a subset of sites and participants)	Change from baseline in amyloid PET signal at Week 78 and Week 104
To assess the effect of aducanumab on cerebral tau levels as measured by tau PET	Change from baseline in tau PET signal at Week 78 and Week 104

imaging (where available, in a subset of sites and participants)	
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the CDR-SB score	Change from baseline in CDR-SB score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by iADRS	Change from baseline in iADRS score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by ADCS-ADL-MCI	Change from baseline in ADCS-ADL-MCI score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by ADAS-Cog13	Change from baseline in ADAS-Cog13 score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the MMSE	Change from baseline in MMSE score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by NPI-10	Change from baseline in NPI-10 score at Week 106
To assess the effect of monthly doses of aducanumab as compared with placebo on clinical decline as measured by the GST composite z-score	Change from baseline in GST composite z-score (based on CDR-SB, ADAS-Cog13 and ADCS-ADL-MCI) at Week 78 and Week 106
Tertiary Objectives	**Tertiary Endpoints**
To assess the safety and tolerability of monthly doses of aducanumab	• Incidence of AEs and SAEs • Incidence of ARIA-E and ARIA-H • Clinical laboratory shifts in reported values
To assess the immunogenicity of aducanumab	Incidence of anti-aducanumab Abs in serum over time

To collect and characterize the PK parameters of aducanumab in serum	Serum concentrations and PK parameters of aducanumab over time
To assess the effect of aducanumab on participant health status, measured by individual items of the RUD-Lite	• Change from baseline in participant self-reported RUD-Lite items at Weeks 78 and 106 • Change from baseline in informant-rated participant RUD-Lite items at Weeks 78 and 106
To assess the effect of aducanumab on participant health status, measured by the QoL-AD	• Change from baseline in participant self-reported QoL-AD score at Weeks 78 and 106 • Change from baseline in informant-rated participant QoL-AD score at Weeks 78 and 106
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

This clinical study collects samples that, under separate optional consent, may be used for future scientific and genetic research. Objectives related to this future research have not been determined.

5. STUDY DESIGN

5.1. Study Overview

Study 221AD305 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in participants with early Alzheimer's disease, including those with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. Enrollment will be monitored via the IRT system so that the population of participants with mild Alzheimer's disease represents approximately 50% of the total number of participants enrolled in the study. The study will include up to 24 months of treatment as well as screening and post-treatment FU periods. Approximately 1512 participants will be enrolled across an estimated 220 centers globally.

The primary study objective is to verify the clinical benefit of monthly doses of aducanumab on CDR-SB relative to placebo at Week 78. Key secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical decline as compared to placebo at Week 78 as measured by a variety of cognitive and functional scales such as those implemented in the Phase 3 studies (i.e., ADCS-ADL-MCI, ADAS-Cog13, MMSE, and NPI-10), as well as the composite scale iADRS, which is a linear combination of the ADAS-Cog13 and the ADCS-ADL-MCI. Other secondary objectives include assessment of the effect of monthly doses of aducanumab on change in amyloid PET and tau PET signal at Week 78 and 104 as compared with placebo, as well as all clinical endpoints (i.e., CDR-SB, iADRS, ADCS-ADL-MCI, ADAS-Cog13, MMSE, and NPI-10) assessed at the Week 106 timepoint. Secondary objectives also include an assessment of the effect of monthly doses of aducanumab on the GST composite z-score, defined as the average of standardized z scores of the CDR-SB, ADCS-ADL-MCI, and ADAS-Cog13, at Weeks 78 and 106. Tertiary objectives include confirmation of the safety, tolerability, and associated immunogenicity of aducanumab and its PK characteristics, and HEOR and QoL metrics. [redacted]

Participants will receive IV infusions of aducanumab or placebo approximately Q4W for 104 weeks. Participants will be randomized to receive aducanumab:placebo in a 2:1 ratio. The randomization will be stratified by geographical region, baseline disease stage (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), and ApoE ε4 status (carrier or noncarrier). Randomization will be performed using IRT. Aducanumab will be initiated with a 6-dose titration period prior to reaching the target dose of 10 mg/kg, as detailed in Section 3.1.2.

Investigators, outcome assessors, study site staff (except for the designated unblinded pharmacist/technician), study participants, and informants will be blinded to the randomized treatment assignment.

The total duration of the study for each participant will be approximately 130 weeks, including a series of screening visits within 8 weeks before administration of the first dose, and a 104-week placebo-controlled treatment period. Participants will additionally undergo a safety FU Visit 18 weeks after the final dose of aducanumab.

See Figure 1 for schematic of the study design.

Substudies

Three optional longitudinal substudies will be completed within this study in subsets of consenting participants, as follows:

- An amyloid PET substudy involving assessments of amyloid by PET scan at Screening and at Weeks 78 and 104
- A tau PET substudy involving assessments of tau by PET scan at Screening and at Weeks 78 and 104
- [redacted]

For participants of these substudies, study-specific procedures are required for provision of baseline PET scans [redacted]

5.2. Study Duration for Participants

The total duration of the study for each participant will be approximately 130 weeks, including a series of screening visits within 8 weeks before administration of the first dose, and a 104-week placebo-controlled treatment period. Additionally, participants will undergo a safety FU Visit 18 weeks after the final dose of aducanumab.

Participants will have approximately 39 scheduled clinic visits, 27 of which are dosing visits, as well as up to 8 telephone safety FU contacts, as follows:

- Screening Visits 1 to 3 will occur no more than 60 days before the first dose of study treatment on Day 1. Visits will be conducted on multiple days. All screening procedures should be completed within 60 days; however, with Sponsor approval, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans (and/or due to other major causes [i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters/disruptions]). These screening visits will include baseline brain MRI, clinical scales of cognition and function, biological fluid sampling (including CSF), amyloid and tau PET scans (where available), physical and neurological examinations, and all other safety and efficacy assessments. See Section 1.3 for the Schedules of Activities.
- Twenty-seven dosing visits (Day 1 and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104).

- Eight telephone safety FU contacts after each of the first 8 doses.
- Four visits separate from dosing for clinical functional and cognitive assessments (Weeks 26, 50, 78, and 106).
- One safety FU visit at Week 122, 18 weeks after the last dose at Week 104, or 18 weeks after administration of the last dose for participants who discontinue treatment early.
- A minimum of 6 MRI visits, with 4 during treatment (Week 14 [before escalation to 6 mg/kg, before at the fifth dose], Week 22 [before escalation to 10 mg/kg, before the seventh dose], Week 30 [before the third dose at 10mg/kg], and Week 42 [before the sixth dose at 10 mg/kg]. Two additional MRIs will be performed at Week 106 and at Week 122 [EOS] 18 weeks after the final-dose safety FU) or 18 weeks after administration of the last dose for participants who discontinue treatment early.

5.3. Monitoring and Management of ARIA

5.3.1. Dose Suspension or Permanent Discontinuation for ARIA Events

Guidelines on the management and disposition of ARIA cases (including the criteria to be met for the continuation, suspension/resumption, permanent discontinuation of dosing due to ARIA, resumption of dosing after dose suspension due to ARIA [including rules for titrating up to the assigned dose], and management of recurrent ARIA) are provided in the following subsections.

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the Investigator within a specified time after observing the finding on MRI per the imaging manual procedures, with an assessment of severity. All cases of ARIA must be reviewed by the Investigator; decisions on dosing continuation, interruption, or discontinuation will be based on the Investigator's clinical assessment of the participant and the MRI information provided by the central reader. Dosing may also be terminated at the discretion of the Sponsor for medical reasons.

If a participant experiences symptoms that could be suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated.

See Section 8.1 for the full list of criteria for discontinuing study treatment.

5.3.1.1. ARIA-E

Table 4: Disposition of ARIA-E Cases

Clinical Symptom Severity[1]	ARIA-E Severity on MRI (Central Read)		
	Mild	**Moderate**	**Severe**
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing. Once ARIA-E resolves, the participant may resume dosing at the same dose.	
Mild		Suspend dosing. Once ARIA-E and clinical symptoms resolve, the participant may resume dosing at the same dose.	
Moderate	Suspend dosing. Once ARIA-E and clinical symptoms resolve, the participant may resume dosing at the same dose.		
Severe			

[1] Nonserious symptoms only. If serious symptoms of ARIA-E (according to the definition of serious adverse events in Section 11.1.2), treatment should be permanently discontinued.

The following study activities must be followed for participants with ARIA-E:

- Participants with ARIA-E should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI every 4 weeks (± 5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, [redacted] and PK samples will be collected at the first visit, scheduled or unscheduled, following an episode of ARIA-E.

For nonserious ARIA-E and ARIA-E with nonserious symptoms (according to the definition of serious adverse events in Section 11.1.2):

- Participants who develop **ARIA-E that is radiographically mild, per central MRI reading, and who have no symptoms or symptoms that are mild** may continue dosing per protocol. Participants should complete all scheduled clinic visits for assessments and have an unscheduled visit for an MRI Q4W (± 5 days) until the ARIA-E has resolved per the centrally read MRI.

  – If moderate or severe symptoms develop during follow-up of the ARIA-E event, dosing should be suspended.

  – If a follow-up MRI demonstrates radiographically moderate or severe ARIA-E, per central MRI reading, dosing should be suspended.

  If dosing is suspended, once the ARIA-E has resolved per the centrally read MRI and once the clinical symptoms have resolved (in the Investigator's opinion), the participant may resume treatment at the same dose (see Section 5.3.1.6 for dose resumption rules).

- Participants who develop **ARIA-E that is radiographically mild, per central MRI reading, accompanied by moderate or severe clinical symptoms,** should suspend dosing. Once the ARIA-E has resolved per the centrally read MRI and once the clinical

symptoms have resolved (in the Investigator's opinion), the participant may resume treatment at the same dose. See Section 5.3.1.6 for dose resumption rules.

- Participants who develop **ARIA-E that is radiographically moderate or severe, per central MRI reading,** with or without symptoms, should suspend dosing. Dosing may be resumed at the same dose once the ARIA-E has resolved per the centrally read MRI and once the clinical symptoms, if any, have resolved (in the Investigator's opinion). See Section 5.3.1.6 for dose resumption rules.

For serious ARIA-E events or ARIA-E events with serious symptoms (according to the definition of serious adverse events in Section 11.1.2):

- Participants who develop ARIA-E (of any radiographic severity) **that is considered serious or that is accompanied by serious clinical symptoms** (according to the definition of serious adverse events in Section 11.1.2), at any time during the study, should permanently discontinue treatment.

See Section 5.3.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 5.3.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

5.3.1.2. ARIA-H (Microhemorrhage)

Treatment-emergent microhemorrhages are defined as microhemorrhages that occur while the participant is on study treatment and do not include microhemorrhages at baseline.

Table 5: Disposition of ARIA-H (Microhemorrhage) Cases

<table>
<tr><th rowspan="3">Clinical Symptom Severity[1]</th><th colspan="3">Treatment-emergent Microhemorrhages (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><th>≥ 1 and ≤ 4</th><th>≥ 5 and ≤ 9</th><th>≥ 10</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current schedule</td><td>Suspend dosing. Once ARIA-H is stable, the participant may resume dosing at the same dose.</td><td rowspan="2">Permanently discontinue treatment</td></tr>
<tr><td>Symptomatic</td><td colspan="2">Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the participant may resume dosing at the same dose.</td></tr>
</table>

[1] Nonserious symptoms only. If serious symptoms of ARIA-H (according to the definition of serious adverse events in Section 11.1.2), treatment should be permanently discontinued.

The following study activities must be followed for participants with ARIA-H (microhemorrhage):

- Participants with ARIA-H microhemorrhage should complete all scheduled clinic visits for assessments. In addition, if ARIA-H microhemorrhage is radiographically moderate, or if symptoms are present, participants should have an unscheduled visit for an MRI every 4 weeks (± 5 days) until the ARIA-H has stabilized per the centrally read MRI.

ARIA stabilization is defined as no change or a decrease in the number or size of microhemorrhages on 2 consecutive MRIs, including the initial detection MRI. In addition, [redacted] and PK samples will be collected at the first visit, scheduled or unscheduled, following an episode of ARIA. .

For nonserious ARIA-H microhemorrhages and ARIA-H microhemorrhages with nonserious symptoms (according to the definition of serious adverse events in Section 11.1.2):

- Participants who develop between 1 and 4 (**≥ 1 and ≤ 4) treatment-emergent microhemorrhages (mild radiographic per central MRI reading), and who have no symptoms** may continue dosing per protocol.

- Participants who develop between 1 and 4 (**≥ 1 and ≤ 4) treatment-emergent microhemorrhages (mild radiographic per central MRI reading), accompanied by clinical symptoms of any severity,** should suspend dosing. Dosing may be resumed at the same dose once the ARIA-H is radiographically stable on follow-up MRI and clinical symptoms have resolved (in the Investigator's opinion). See Section 5.3.1.6 for dose resumption rules.

- Participants who develop between 5 and 9 (**≥ 5 and ≤ 9) treatment-emergent microhemorrhages (moderate radiographic per central MRI reading), with or without symptoms of any severity,** should suspend dosing. Dosing may be resumed at the same dose once the ARIA-H is radiographically stable on follow-up MRI and clinical symptoms, if any, have resolved (in the Investigator's opinion). See Section 5.3.1.6 for dose resumption rules.

- Participants who develop 10 or more (**≥ 10) treatment-emergent microhemorrhages (severe radiographic per central MRI reading),** should permanently discontinue treatment.

For serious ARIA-H microhemorrhages or ARIA-H microhemorrhages with serious symptoms (according to the definition of serious adverse events in Section 11.1.2):

- Participants who develop ARIA-H microhemorrhage (of any radiographic severity) **that is accompanied by serious clinical symptoms** (according to the definition of serious adverse events in Section 11.1.2) should permanently discontinue treatment.

See Section 5.3.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 5.3.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

5.3.1.3. ARIA-H (Superficial Siderosis)

Table 6: Disposition of ARIA-H (Superficial Siderosis) Cases

Clinical Symptom Severity[1]	Treatment-Emergent Superficial Siderosis (Central Read)		
	Mild	Moderate	Severe
	1	2	> 2
Asymptomatic	Continue dosing at current schedule	Suspend dosing. Once ARIA-H is stable, the participant may resume dosing at the same dose.	Permanently discontinue treatment
Symptomatic	Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the participant may resume dosing at the same dose.		

[1] Nonserious symptoms only. If serious symptoms of ARIA-H (according to the definition of serious adverse events in Section 11.1.2), treatment should be permanently discontinued.

The following study activities must be followed for participants with ARIA-H (superficial siderosis):

- Participants with ARIA-H superficial siderosis should complete all scheduled clinic visits for assessments and should have an unscheduled visit for an MRI every 4 weeks (± 5 days) until the ARIA-H has stabilized per the centrally read MRI. ARIA stabilization is defined as no change or a decrease in the number, size, or location of superficial siderosis on 2 consecutive MRIs, including the initial detection MRI. In addition, [redacted] and PK samples will be collected at the first visit, scheduled or unscheduled, following an episode of ARIA.

For nonserious ARIA-H superficial siderosis or ARIA-H superficial siderosis with nonserious symptoms (according to the definition of serious adverse events in Section 11.1.2):

- Participants who develop **1 treatment-emergent focal area of superficial siderosis (mild radiographic per central MRI reading), and who have no symptoms** may continue dosing per protocol. Participants should complete all scheduled clinic visits for assessments and have an unscheduled visit for an MRI Q4W (± 5 days) until the ARIA-H has stabilized per the centrally read MRI.

- Participants who develop **1 treatment-emergent focal area of superficial siderosis (mild radiographic per central MRI reading), with symptoms of any severity,** should suspend dosing. Dosing may be resumed at the same dose once the ARIA-H is radiographically stable on follow up MRI and once clinical symptoms, if any, have resolved (in the Investigator's opinion). See Section 5.3.1.6 for dose resumption rules.

- Participants who develop **2 treatment-emergent focal areas of superficial siderosis (moderate radiographic per central MRI reading), with or without symptoms of any severity,** should suspend dosing. Dosing may be resumed at the same dose once the ARIA-H is radiographically stable on follow-up MRI and clinical symptoms have resolved (in the Investigator's opinion). See Section 5.3.1.6 for dose resumption rules.

- Participants who develop more than 2 (**> 2) treatment-emergent focal area of superficial siderosis (severe radiographic per central MRI reading), with or without clinical symptoms of any severity,** should permanently discontinue treatment.

For serious ARIA-H superficial siderosis or ARIA-H superficial siderosis with serious symptoms (according to the definition of serious adverse events in Section 11.1.2):

- Participants who develop ARIA-H superficial siderosis (of any radiographic severity) **accompanied by serious clinical symptoms** (according to the definition of serious adverse events in Section 11.1.2), should permanently discontinue treatment.

See Section 5.3.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 5.3.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

5.3.1.4. Cerebral Hemorrhage > 1 cm

Participants who develop any new treatment-emergent cerebral hemorrhage > 1 cm in diameter on T2* sequence, regardless of symptom severity during the study, will permanently discontinue treatment but should be encouraged to remain in the study. Participants should complete a FU Visit 18 weeks after the final dose, protocol-required tests and assessments at a subset of the clinic visits (see Table 3), and in addition, have an unscheduled visit for MRI every 4 weeks (± 5 days) until the cerebral hemorrhage is confirmed stable per centrally read MRI. A cerebral hemorrhage is considered stable if there is no change or a decrease in the size or number of locations between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 4 weeks (± 5 days) later.

5.3.1.5. Coincident (Concurrent) ARIA-H and ARIA-E Cases

Participants who develop ARIA-H coincident with ARIA-E at any time during the study will follow the most restrictive guidelines. For ARIA events, prior to resuming treatment, where applicable, ARIA-E must not be radiographically severe, ARIA-H must be deemed stable, and the participant must be asymptomatic.

5.3.1.6. Resumption of Study Treatment and MRI Monitoring After Suspension Due to ARIA

Participants who suspend treatment due to ARIA may resume treatment if they meet the criteria as described in Sections 5.3.1.1, Section 5.3.1.2, Section 5.3.1.3, Section 5.3.1.4, and Section 5.3.1.5. The preceding centralized MRI report must be received and reviewed by the Investigator before continuing with study treatment infusions.

- Participants who suspend and then resume dosing after having reached the 10 mg/kg dose level (e.g., dose 7 or later) are to resume dosing at the 10 mg/kg dose level.

- If dosing is suspended prior to a participant reaching the 10 mg/kg dose level (e.g., during the first 6 doses), the participant should resume dosing per the titration schedule (e.g., if dosing was suspended after 3 doses, the next dose should be 3 mg/kg).

Routine MRI monitoring should be conducted as follows in the context of dose suspension.

If dosing was suspended prior to completion of the 4 routine monitoring MRIs for asymptomatic ARIA, these should be completed at the same time points in titration, allowing for the number of weeks that dosing was suspended, and any repeated dose during titration.

- If dosing was suspended prior to the fourth dose, the participant should undergo routine MRIs prior to the first dose at 6 mg/kg, and prior to the first, third, and sixth doses at the 10 mg/kg dose level.

- If dosing was suspended prior to the sixth dose, the participant should undergo routine MRIs prior to the first, third, and sixth dose at the 10 mg/kg dose level.

- If dosing was suspended prior to the eighth dose, the participant should undergo routine MRIs prior to the third and sixth doses at the 10 mg/kg dose level.

- If dosing was suspended prior to the eleventh dose, the participant should undergo a routine MRI prior to the sixth dose at 10 mg/kg.

5.3.1.7. Management After Recurrent ARIA

Recurrent ARIA is managed identically to the first ARIA occurrence with respect to dosing and MRI. Consideration should be given to permanent discontinuation in the event of 3 or more recurrent episodes of ARIA.

5.3.2. Infusion Interruption

If any mild or moderate infusion-related reactions (e.g., headache, chills/rigors, and nausea/vomiting) occur during an infusion, the infusion should be slowed or interrupted, and supportive treatment should be instituted at the discretion of the Investigator. After resolution of symptoms, if the infusion had been slowed, the original infusion rate may be resumed; if the infusion had been interrupted, the infusion may be restarted at a rate that does not exceed the original infusion rate. An infusion must be discontinued if not completed within 3 hours.

Refer to the DHA for infusion rate information.

If a severe infusion-related reaction occurs during an infusion, or an allergic reaction such as urticaria or anaphylaxis occurs, the participant will be discontinued from study treatment but may remain in the study. The participant must be appropriately treated in accordance with local practice.

Severity of events is described in Section 11.2.3.

5.4. Study Termination

The Sponsor may terminate this study at any time, after informing Investigators. The Sponsor will notify Investigators when the study is to be placed on hold, completed, or terminated.

5.5. Unscheduled Visits

Data collected during unscheduled visits should be recorded on CRFs only if the data support protocol objectives and/or are required for safety monitoring. Unscheduled visits specifically prompted by a change in Alzheimer's disease medication or ARIA events are specified in Table 1 Table 2, and Table 3.

5.6. End of Study

The end of study is last participant, last visit.

6. STUDY POPULATION

6.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening, or at the timepoint specified in the individual eligibility criterion listed:

1. The participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian, where local regulations and institutional practices permit) must be able, as appropriate and applicable, to understand the purpose and risks of the study, to provide signed and dated informed consent, and to authorize the use of confidential health information in accordance with national and local privacy and ethics regulations.

2. The participant must be 60 to 85 years old, inclusive, at the time of informed consent.

3. All women of childbearing potential must practice effective contraception during the study and for 5 times the half-life or 24 weeks (whichever is longer) after their last dose of study treatment. For further details of contraceptive requirements for this study, refer to Section 11.5.

4. The participant must have a minimum of 9 years of education or vocational training or the equivalent education/vocational training until the age of 15 or, per Investigator judgment, work experience that indicates a lack of mental deficits other than early-stage dementia.

5. The participant must have confirmed amyloid beta pathology by CSF (historical CSF test results not allowed) or amyloid PET. If providing only a screening amyloid PET scan for amyloid positivity, a historical, amyloid PET scan obtained within 18 months of Screening Visit 2 is permissible. Sponsor-approved tracers must be used and scans must be submitted to the central imaging vendor to confirm that study inclusion criteria are met. In the case of discordant results between CSF and PET, PET results will be used to assess eligibility.

6. The participant must have a history of subjective memory decline with gradual onset and slow progression over the last 6 months before Screening, confirmed by study partner.

7. The participant must meet all of the following clinical criteria for MCI due to Alzheimer's disease or mild Alzheimer's disease according to NIA-AA criteria [Albert 2011; McKhann 2011]:

    - Have an MMSE score between 22 and 30 inclusive
    - Have a CDR memory score $\geq$ 0.5
    - Have a CDR-GS of 0.5 or 1.0
    - Have an RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the DMI score)

8. The participant must be in good health, apart from a clinical diagnosis of early Alzheimer's disease, as determined by the Investigator based on medical history and screening assessments.

9. The participant must consent to ApoE genotyping.

10. The participant must have 1 informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the participant (at least 10 hours/week in person or by phone) as to be able to provide accurate information about the participant's cognitive and functional abilities over time. The informant/care partner ideally has known the participant prior to their cognitive decline to have a reference point for change across time. The informant/care partner must be available by phone to provide information to the Investigator and study staff about the participant as well as agree to attend in-person clinic visits that require partner input for scale completion. The informant/care partner must be literate and provide informed consent and should be available for the duration of the study. The same informant/care partner is required to be consistent across all study visits except under rare, unavoidable circumstances (e.g., unexpected informant health crisis) that are approved by the Investigator and Sponsor.

6.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the timepoint specified in the individual criterion listed:

Medical History and Current Health Status

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than Alzheimer's disease) that, in the opinion of the Investigator, might be a contributing cause of the participant's cognitive impairment (e.g., Lewy body dementia, head trauma, substance abuse, frontotemporal dementia, vitamin B_{12} deficiency, abnormal thyroid function, stroke, or other cerebrovascular condition).

2. Clinically significant and/or unstable psychiatric illness within 6 months prior to Screening.

3. Any documented prior history of chronic schizophrenia.

4. History of long-term major depression or bipolar affective disorder with an active episode in the past 5 years.

5. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.

6. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:

    - Acute or subacute hemorrhage

    - Prior cerebral hemorrhage > 1 cm in diameter on T2* sequence or prior subarachnoid hemorrhage unless it can be documented that the finding is not due

to an underlying structural or vascular abnormality (i.e., finding does not suggest participant is at risk of recurrent hemorrhage)

- 4 or more microhemorrhages (defined as ≤ 1 cm in diameter on T2* sequence)
- 1 or more localized superficial siderosis findings
- Cortical infarct (defined as > 1.5 cm in diameter irrespective of anatomic location)
- > 1 lacunar infarct (defined as ≤ 1.5 cm in diameter)
- History of diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scale [Wahlund 2001]
- Any finding that, in the opinion of the Investigator, might be a contributing cause of participant's dementia, might pose a risk to the participant, or might prevent a satisfactory MRI assessment for safety monitoring

7. History of bleeding disorder or predisposing conditions, blood clotting, or clinically significant abnormal results on coagulation profile at Screening as determined by the Investigator.

8. Presence of diabetes mellitus that, in the judgment of the Investigator, cannot be controlled or adequately managed.

9. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year prior to Screening.

10. Clinically significant 12-lead ECG abnormalities as determined by the Investigator.

11. Uncontrolled hypertension defined as: average of 3 SBP/DBP readings > 165 mmHg and/or > 100 mmHg at Screening (blood pressure measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the participant to be eligible for the study); or persistent SBP/DBP readings > 180 mmHg and/or > 100 mmHg 3 months prior to randomization (Day 1) that, in the opinion of the Investigator, are indicative of chronic uncontrolled hypertension.

12. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:

    - Participants with cancers in remission ≥ 5 years prior to Screening Visit 1.
    - Participants with a history of excised or treated basal cell or squamous carcinoma of the skin.

- Participants with localized prostate cancer with treatment cycles that completed at least 6 months prior to Screening Visit 1.

13. History of seizures or new-onset seizures within 10 years prior to Screening.

14. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of AST and ALT ≥ 2 × the upper limit of normal).

15. History or evidence of an autoimmune disorder considered clinically significant by the Investigator.

16. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, or a positive urine drug test (due to a nonprescription drug and without a clear justification of the results according to the Investigator) at Screening.

17. Within 30 days of Screening, clinically significant systemic illness or infection that requires hospitalization or that, in the opinion of the Investigator, is impacting the patient's usual performance in function or cognition.

18. History of or known seropositivity for HIV.

19. Current hepatitis B infection (defined as positive for HBsAg and total anti-HBc). Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive anti-HBs) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

20. Current hepatitis C virus infection (defined as positive HCV antibody and detectable HCV RNA). Participants with positive HCV Ab and undetectable HCV RNA are eligible to participate in the study.

21. History of severe allergic or anaphylactic reactions or of hypersensitivity to any of the inactive ingredients in the drug product. (Refer to the Investigator's Brochure for information on the clinical formulation.)

22. Symptoms consistent with SARS-CoV-2 infection, per the judgment of the Investigator, within 14 days prior to Day 1, including but not limited to fever (temperature > 37.5°C), sore throat, new and persistent cough, shortness of breath, diarrhea, muscle aches, or loss of taste or smell.

23. Any other medical conditions (e.g., renal disease) that are not stable or controlled or, in the opinion of the Investigator, could affect the participant's safety or interfere with the study assessments.

Medications

24. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.

25. Participation in any passive immunotherapy study targeting Aβ within 12 months of Screening unless documentation of receipt of placebo is available.

26. Participation in any study with purported disease-modifying effect in Alzheimer's disease within 12 months prior to Screening unless documentation of receipt of placebo is available.

27. Current use or previous use of medications with a purported disease-modifying effect in Alzheimer's disease, outside of investigational studies.

28. Use of any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the participant at higher risk for AEs, or impair the participant's ability to perform cognitive testing or complete study procedures.

29. Use of allowed chronic concomitant medications (see Section 7.7.1.1) at doses that have not been stable for at least 4 weeks prior to Screening Visit 2 and during Screening up to Day 1, or use of Alzheimer's disease medications (including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine) at doses that have not been stable for at least 8 weeks prior to Screening Visit 2 and during Screening up to Day 1.

30. Use of allowed chronic concomitant medications that affect cognition (e.g., antidepressants, anticonvulsants, atypical and typical antipsychotics, short-/medium-acting benzodiazepines; see Section 7.7.1.2.1) at doses that have not been stable for at least 8 weeks prior to Screening Visit 2 and during Screening up to Day 1.

31. Use of long-acting benzodiazepines (allowed only for sedation prior to MRI/PET scans or LP for participants requiring sedation).

32. Use of medications with antiplatelet or anticoagulant properties (acetylsalicyclic acid [aspirin] is allowed at a dose ≤ 325 mg per day).

33. Use of chemotherapeutic agents and checkpoint inhibitors.

34. Chronic use of systemic immunosuppressive drugs (including systemic corticosteroids) as indicated in Section 7.7.1.2. Local immunosuppressants and local corticosteroids (including inhaled or topical corticosteroids) are allowed; short-term courses of systemic corticosteroids may also be permitted at the Sponsor's discretion.

35. Use of parenteral immunoglobulin (i.e., IVIG), blood products, plasma derivatives, plasma exchange, or plasmapheresis.

36. Use of active or passive immunotherapy agents targeting the CNS.

37. Use of any drug of abuse (prescription or recreational), including but not limited to, amphetamine, cocaine, opiates, methadone, phencyclidine, or barbiturates.

38. Use of THC-containing cannabinoids (products containing only CBD are allowed).

39. Use of opioid medications within 4 weeks prior to Screening Visit 1.

40. Use of anticholinergics, such as benztropine.

41. Use of any investigational drug.

42. Vaccinations (including COVID-19 vaccines and boosters) within 5 days prior to randomization (Day 1).

43. Prior exposure to aducanumab either commercially or by participation in a previous study with aducanumab. (Participants are eligible if they did not receive active aducanumab.)

Study Procedures

44. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; or claustrophobia that cannot be medically managed).

45. Any of the following contraindications to having an amyloid PET scan or LP if CSF testing is used for amyloid confirmation:
    - Contraindications to PET (e.g., inability to lie flat or still for the duration of the scan) or intolerance to previous PET scans (i.e., previous hypersensitivity reactions to any PET ligand or imaging agent or failure to participate in and comply with previous PET scans); the participant has had or plans to have exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.
    - Contraindications to having a LP (e.g., presence of risk for increased or uncontrolled bleeding, anatomical factors at or near the LP site). Any symptoms caused by or related to the optional LP during Screening must be resolved prior to randomization (Day 1).

46. A negative PET scan result with any amyloid-targeting ligand within 12 months prior to Screening.

Other

47. Female participants who are pregnant or currently breastfeeding.

48. Participant currently lives in an organized care facility with extensive intervention and/or support of daily living activities.

49. Blood donation (≥ 1 unit) within 1 month prior to Screening.

50. Inability to comply with study requirements.

51. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the participant unsuitable for enrollment.

6.3. Screening, Rescreening, and Screen Failures

6.3.1. Screening Visits 1 to 3

Participants (or their legally authorized representative where local regulations and institutional practices permit) must provide full written informed consent before any screening tests are performed.

Screening Visits 1 to 3 will be conducted no more than 60 days before receiving the first dose of study treatment. All screening procedures should be completed within 60 days; however, with Sponsor approval, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans (and/or due to other major causes [i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters/disruptions]). A minimum of 2 weeks should separate Screening Visits 1 and 2 to minimize learning effects.

ApoE genotyping may be performed at Visit 1 prior to other screening assessments.

During Screening Visits 1 to 3, participants will complete functional and neurocognitive assessments. These will include the primary clinical scales required for eligibility, CDR, MMSE, RBANS, and may include ADAS-Cog13, ADCS-ADL-MCI, and NPI-10. The clinical scales that are not required for eligibility (i.e., ADAS-Cog13, ADCS-ADL-MCI, and NPI-10), as well as [redacted] and quality-of-life and health economic assessments (RUD-Lite, EQ-5D-5L, [redacted], and QoL-AD) may be completed at Day 1. The C-SSRS will be completed at Screening and at every subsequent visit.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a participant is excluded from the study, the reasons for exclusion will be documented in the participant's source documents and on the screening log.

If a participant fulfills all inclusion and none of the exclusion criteria for study eligibility and the full written ICF is signed, the participant is considered enrolled in the study.

For participants who are not enrolled in the longitudinal amyloid PET substudy, and if providing a historical amyloid PET scan for screening amyloid positivity, the scan obtained within 18 months prior to Screening Visit 2 must be submitted to the central imaging vendor to confirm that study inclusion criteria are met.

6.3.2. Rescreening and Screen Failures

Screen failures are defined as participants who sign the ICF but are not subsequently randomized. Screen failures will be allowed to rescreen under the conditions described below;

however, a minimum of 60 days must pass between the initial and subsequent screening evaluations.

If a participant fails screening due to exclusion criteria that are not indicative of uncontrolled disease, the participant may be allowed to rescreen on 2 occasions if the disease is controlled at a later date, at the discretion of the Investigator and approval of the Medical Monitor.

- If ineligibility is due to unstable medications, rescreening is allowed when permitted chronic medications are at stable doses for at least 4 weeks prior to Screening Visit 2.

- When Alzheimer's disease medications are at stable doses for at least 8 weeks prior to Screening Visit 2 (see Section 7.7.1.1).

Participants are also allowed to rescreen if ineligibility is due to unforeseen nonclinical reasons, such as weather or public health directives.

Participants who fail Screening due to meeting the following exclusionary criteria will not be allowed to rescreen:

- Amyloid negative PET scan or amyloid negative CSF sample

- Exclusionary MRI findings

- Outside of the MMSE score requirements of 22 to 30 inclusive

- Current hepatitis B or C (as described in Section 6.2, exclusion criteria 19 and 20)

Note: Participants who meet all other entry criteria but fail Screening due to not meeting the threshold inclusion criteria for early Alzheimer's disease as assessed by CDR (i.e., with a global score of 0) or RBANs (i.e., with an RBANs DMI score > 85) may be allowed to rescreen once only after at least 6 months from the initial screening evaluation and after review and approval of the Medical Monitor. Participants who fail screening due to a CDR global score > 1 will not be permitted to rescreen.

At rescreening, all assessments should be repeated with the following exceptions:

- Amyloid PET if done < 12 months since last assessment for participants consenting to the longitudinal substudy (amyloid PET for eligibility is acceptable within 18 months)

- Amyloid CSF if done < 6 months from last assessment

- Tau PET if done < 6 months from last assessment

- MRI if done < 3 months from last assessment

[redacted]

If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

7. STUDY TREATMENT

7.1. Regimen

Following titration, participants will receive either aducanumab 10 mg/kg or placebo IV every 4 weeks.

At each applicable visit, the preceding centralized MRI report must have been received and reviewed by the Investigator before continuing with dose administration.

Refer to and follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Aducanumab is to be administered by IV infusion following dilution into saline.

There are no fasting or food intake requirements/restrictions associated with this intravenously administered treatment.

See Section 1.3 for the study treatment infusion schedule during the study. See Section 7.3 for details about aducanumab study treatment.

7.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

7.1.2. Placebo

Placebo (0.9% sterile sodium chloride for injection) will be supplied by the study site.

7.2. Modification of Dose and/or Treatment Schedule

Refer to Section 5.3.1 (dose suspension) and Section 5.3.2 (infusion interruption). Doses should be administered at least 21 days apart. If the dosing interval cannot be met, the dose administration should be assessed by the study Medical Monitor.

7.3. Study Treatment Management

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA aligns with all other references, including the protocol.

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff and ensuring blinding is maintained. Study treatment is to be dispensed only to participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to

that participant. Study treatment are for one-time use only; do not use any study treatment remaining in the vial for another participant.

7.3.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab-avwa

Trade Names: Aduhelm™

Synonyms: Fully human, IgG_1, anti-Aβ monoclonal antibody

Aducanumab is a human antibody expressed in a Chinese hamster ovary cell line, purified to a high degree of purity, and formulated as a liquid. Aducanumab is an IgG_1 consisting of 2 heavy and 2 kappa light chains connected by inter-chain disulfide bonds. Aducanumab has 1 carbohydrate moiety linked to Asn-304. Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing aducanumab 100 mg/mL as well as the excipients L-histidine hydrochloride, L-histidine free base, L-arginine hydrochloride, L-methionine, and polysorbate 80.

The concentration appears on the label. Aducanumab is manufactured in accordance with Good Manufacturing Practice.

The contents of the label will be in accordance with all applicable regulatory requirements. Aducanumab should not be used after the expiration date.

At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site staff.

7.3.1.1. Preparation

The individual preparing aducanumab should carefully review the instructions provided in the DHA.

Aducanumab is to be administered by IV infusion following dilution into saline.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or drug, it should not be used. The vial in question should be saved at the study site, and the problem immediately reported to the Sponsor.

Contact information for reporting a problem is provided in the Official Study Contact List in the Study Reference Manual.

7.3.1.2. Storage

Study treatment must be stored in a secure location. Aducanumab is to be stored at 2°C to 8°C (36°F to 46°F), in a locked storage container with limited access. Aducanumab should be protected from light, protected from freezing, and should not be shaken. If administration of the prepared aducanumab is delayed for more than 4 hours, then it should be kept at 2°C to 8ºC until use. If administration of the prepared aducanumab is delayed for more than 24 hours, it must be discarded. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

7.3.1.3. Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by the Sponsor (or its designee) unless approved for onsite destruction.

If any aducanumab supplies are to be destroyed at the study site, the institution or appropriate site staff must obtain prior approval from the Sponsor, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers and quantities), the date of destruction, and proof of destruction.

7.3.1.4. Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (participant-by-participant accounting), and accounts of any study treatment accidentally or deliberately destroyed.

Unless otherwise notified, all vials both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of aducanumab supplied, dispensed, and subsequently destroyed or returned to the Sponsor. A written explanation must be provided for any discrepancies.

7.3.2. Placebo

The placebo (0.9% sterile sodium chloride for injection) will be provided by the site in the form of 100 mL saline IV bags.

7.4. Blinding Procedures

This is a multicenter, randomized study with a 24-month double-blind, placebo-controlled, parallel-group treatment period.

All study staff who conduct participant assessments will be blinded to the participant treatment assignments. See Section 14.1 for details. The rating HCPs should remain blinded to treatment assignment as well as participant care management and only have access to the information necessary to carry out their responsibilities as detailed in Section 14.1. Since a placebo match is not provided for the study, unblinded pharmacy staff are required to manage all aspects of study

treatment receipt, dispensing, and preparation. To maintain the study blind, it is imperative that participant treatment assignments are not shared with the participants, their families, or any member of the blinded study team, either at the study site or at the Sponsor or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded CRO or Sponsor safety staff.

The CDR Raters and the Independent Non-CDR Raters must remain blinded to knowledge of a participant's AEs and SAEs.

To maintain rater blinding, it is imperative that participant treatment assignments, dosing dates, and laboratory data are not shared with the CDR Rater or Independent Non-CDR rater.

Post-baseline medical imaging (including MRI, ARIA findings, and PET) should not be shared with participants or raters. Local reads of post-baseline amyloid or tau PET scans should not be conducted. Details will be specified in the blinding charter. See Section 14.1 for further details.

At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, the Sponsor will provide the randomization codes to Investigators, who then can inform their participants about the treatment received.

In the event of a medical emergency that requires unblinding of a participant's treatment assignment, refer to Section 11.4.4.

7.5. Precautions

Not applicable.

7.6. Compliance

Compliance with treatment dosing is to be monitored and recorded by unblinded site staff.

Study treatment will be administered by the site staff.

7.7. Concomitant Therapy and Procedures

7.7.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the informed consent and until the participant's final clinic visit (including the FU Visit).

No premedication (e.g., anti-allergy drugs, antipyretic analgesics) should be used prior to the start of study treatment infusion unless discussed with the study Medical Monitor in advance.

Participants should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations.

7.7.1.1. Allowed Concomitant Therapy

The following medications are allowed:

- With the exceptions described below, under Section 7.7.1.2, medications for chronic conditions are allowed at a stable dose during the study as long as the participant has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 2 and during the screening period.

- Symptomatic therapies for Alzheimer's disease, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that participants are receiving a stable dose for at least 8 weeks prior to Screening Visit 2 and during the screening period and that they stay on a stable dose while in the study.

- Vaccinations are allowed during the study. Administration of any vaccination/booster should not be given < 5 days prior to any dosing visit and for 10 days after a dosing visit.

7.7.1.2. Disallowed Concomitant Therapy

The following medications are not allowed for the duration of the study:

- Medications with antiplatelet or anticoagulant properties (acetylsalicylic acid [aspirin] at a dose ≤ 325 mg per day is allowed)

- Chemotherapeutic agents and checkpoint inhibitors

- Chronic use of immunosuppressive drugs (including systemic corticosteroids). Local immunosuppressants and local corticosteroids (including inhaled or topical corticosteroids) are allowed; short-term courses of systemic corticosteroids may also be permitted at the Sponsor's discretion.

- Parenteral immunoglobulin (e.g., IVIG), blood products, plasma derivatives, plasma exchange, and plasmapheresis

- Active or passive immunotherapy agents targeting the CNS

- Any drug of abuse (prescription or recreational), including but not limited to amphetamine, cocaine, opiates, propoxyphene, methadone, methaqualone, phencyclidine, or barbiturates

- THC-containing cannabinoids (products containing CBD only are allowed)

- Anticholinergics such as benztropine; anticholinergics for bladder control with limited cognitive effects are permitted but should be avoided if possible.

- Any investigational drug

7.7.1.2.1. Medications with Limitations of Use

- Benzodiazepines:
  - Long-acting benzodiazepines are only permitted for sedation prior to MRI or PET scans or LP for those participants requiring sedation. These medications should not be taken within 12 hours before cognitive testing.
  - Short- and medium-acting benzodiazepines (e.g., alprazolam, lorazepam, oxazepam, temazepam) are allowed if used chronically on a stable dose for 8 weeks prior to Screening Visit 1 and during the Screening Period up to Day 1. If they are newly prescribed after randomization on Day 1, it is recommended that the medication is stable for at least 1 week before a cognitive testing visit. If used intermittently, these medications should not be taken within 12 hours before cognitive testing.
- Chronic use of sedating antihistamines is allowed on a stable dose for 8 weeks prior to Screening Visit 1 and during the Screening Period up to Day 1 is allowed. If used intermittently, these medications should not be taken within 12 hours before cognitive testing. Nonsedating antihistamines (e.g., fexofenadine, cetirizine) are allowed.
- Opioid medications are not allowed within 4 weeks prior to Screening Visit 1. After randomization on Day 1, short-term, intermittent use of prescription narcotics are allowed only in specific situations (e.g., after surgical procedures) and should not be taken within 12 hours before cognitive testing.
- Antidepressants with known effects on cognition (e.g., tricyclic antidepressants) are not allowed. Mild depression or depressive mood arising in the context of Alzheimer's disease is not a criterion for study withdrawal. Use of other antidepressants that do not affect cognition is allowed if at stable doses for 8 weeks prior to Screening Visit 1 and during the Screening Period up to Day 1. If participants are newly prescribed acceptable antidepressants after randomization on Day 1, it is recommended that the medication is stable for at least 1 week before a cognitive testing visit.
- Anticonvulsants that have significant effects on cognition are not allowed. Anticonvulsants with limited cognitive effects, such as lamotrigine, pregabalin, and levetiracetam are allowed if, in the opinion of the Investigator, they are not producing sedation or contributing to cognitive impairment. The participant must be on a stable dose for 8 weeks prior to Screening Visit 1 and during the Screening Period up to Day 1. If participants are newly prescribed acceptable anticonvulsants after randomization on Day 1, it is recommended that the medication is stable for at least 1 week before a cognitive testing visit and that, in the opinion of the Investigator, they are not producing sedation or contributing to cognitive impairment.
- Atypical and typical antipsychotics that have significant effects on cognition are not allowed. Behavioral symptoms arising during the course of the study in the context of Alzheimer's disease are not criteria for study withdrawal. Per the Investigator's opinion,

use of atypical and typical antipsychotics is allowed if at stable doses for 8 weeks prior to Screening Visit 1 and during the Screening Period up to Day 1 or used on an as-needed basis. If participants are newly prescribed acceptable atypical and typical antipsychotics after randomization on Day 1, or if used intermittently during the study, it is recommended that the medication is stable for at least 1 week before a cognitive testing visit.

- Intermittent or occasional use of any other sedating medications (e.g., melatonin, zolpidem, eszopiclone) is not allowed within 12 hours before cognitive testing.

Participants should be instructed to continue the medications that they were receiving at enrollment without any changes (see allowed concomitant therapy, Section 7.7.1.1) and avoid starting any new medications or herbal preparations during the study period, since these may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Participants should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and, if needed, by the Medical Monitor to determine whether the participant's study treatment should be suspended. Medications used to treat AEs would not result in automatic permanent study treatment discontinuation. However, if a participant requires continued use of a disallowed therapy, the participant must permanently discontinue study treatment. The Sponsor may be consulted if required.

Participants who have a change in Alzheimer's disease medication (other than study treatment) should have an unscheduled visit. A subset of the clinical efficacy assessments (CDR-SB, MMSE, ADCS-ADL-MCI, and ADAS-Cog13) should be performed prior to the change in medication if the participant alerts the Investigator before the change in medication occurs. If the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If an unscheduled visit for a change in Alzheimer's disease medication occurs within 30 days of the previous efficacy assessment visit and the Investigator suspects no significant changes in cognitive status, efficacy assessments specified at this visit are not required.

7.7.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy, nocturnal-assisted breathing device) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the participant is enrolled in the study and the participant's final clinic visit (including FU Visit), unless the participant is being monitored for study-related toxicity.

The use of concomitant therapies or procedures defined above must be recorded on the participant's CRF. AEs related to administration of these therapies or procedures must be documented on the appropriate AE CRF.

7.8. Continuation of Treatment

No further provisions are made for access to the study treatment. If aducanumab is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

8. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

8.1. Discontinuation of Study Treatment

A participant *must* permanently discontinue aducanumab for any of the following reasons:

- The participant develops any new acute or subacute hemorrhage.
- The participant develops any treatment-emergent incident of cerebral hemorrhage > 1 cm in diameter on T2* sequence.
- The participant develops a radiographically severe ARIA-H (10 or more treatment-emergent microhemorrhage or more than 2 treatment-emergent superficial siderosis)
- The participant develops any radiographic type of ARIA- E or ARIA-H accompanied by serious symptoms (according to the definition of serious adverse events in Section 11.1.2).
- The participant develops a cortical infarct (defined as > 1.5 cm in diameter irrespective of anatomic location).
- The participant develops more than 1 (> 1) lacunar infarct (defined as ≤ 1.5 cm in diameter).
- The participant withdraws consent to continue study treatment.
- The participant experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the participant's treatment assignment.
- The participant experiences an AE that necessitates treatment discontinuation or requires continued treatment that meets exclusionary criteria.
- The participant experiences a severe infusion reaction.
- The participant initiates treatment of Alzheimer's disease with a commercially available disease-modifying drug.
- At the discretion of the Investigator for medical reasons, including treatment-emergent ARIA events.
- At the discretion of the Sponsor for safety or other reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.
- The participant becomes pregnant; study treatment must be discontinued immediately, and pregnancy must be reported according to protocol instructions.

The primary reason for discontinuation of study treatment must be recorded in the participant's CRF.

Participants who discontinue treatment are encouraged to remain in the study, attend a safety FU Visit 18 weeks after the last dose of study treatment, and immediately continue protocol required tests and assessments at a subset of the clinic visits (see Table 3) until the end of the study per the Schedule of Activities or until the participant withdraws consent.

8.2. Lost to Follow-Up

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- In cases in which the participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.3. Withdrawal of Participants From Study

Participants must be withdrawn from the study for any one of the following reasons:

- The participant withdraws consent for participation in the study.
- The participant enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The participant is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

Note: A participant who discontinues study treatment will not be automatically withdrawn from the study, regardless of the number of doses missed. The participant is to remain in the study, and continue with a FU Visit 18 weeks after the participant's last dose of study treatment, and protocol-required tests and assessments at a subset of the clinic visits (see Table 3) until the end of the study or until the participant withdraws consent.

The primary reason for the participant's withdrawal from the study must be recorded in the participant's CRF.

Participants who are withdrawn from the study after receiving ≥ 1 doses of study treatment should complete the ET Visit after the reason for withdrawal is identified. For such participants, efficacy assessments specified at the ET Visit are not required if the participant discontinues treatment within 3 months of the previous efficacy assessment visit, and no significant changes in cognitive status are suspected by the Investigator; the site should notify the Sponsor and Medical Monitor in such cases. Participants who are withdrawn from the study are also to return to the site for a FU Visit 18 weeks after receiving their last dose of study treatment.

Participants should undergo an ET visit unless withdrawal is due to death or withdrawal of consent.

Participants who withdraw from the study may be replaced if enrollment is still open.

9. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

See Section 1.3 for the timing of all assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the study site to have the evaluations repeated.

Where available, and with permission from the Sponsor, home visits may be permitted, with limitations. For visits that involve cognitive assessments, such as the CDR and ADAS-Cog13, the same in-person site rater must also perform the home visit. Note: The Week 78 visit is never permitted to be a home assessment. Refer to the Study Reference Manual for details.

9.1. Clinical Efficacy Assessments

The following clinical scales will be assessed to verify the clinical benefit of aducanumab:

Clinical Assessments

- CDR

  The CDR is a 5-point scale used to stage Alzheimer's disease by characterization of the 6 domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. This information is collected through a semistructured interview of the participant and the informant. Scores range from 0 to 3, with a higher score indicating greater impairment. The CDR-SB score is obtained by summing each of the CDR domain box scores, with scores ranging from 0 to 18. The CDR-SB is a more detailed quantitative index than the global score, providing more precise information on participants with MCI and early Alzheimer's disease, as well as improved tracking of changes over time.

- ADCS-ADL-MCI

  The ADCS-MCI-ADL is a functional evaluation scale for MCI participants, based on the information provided by an informant who rates 18 areas of daily living. Higher scores indicate greater independent and healthy functioning, with total score ranging from 0 to 53.

- ADAS-Cog13

  The ADAS-Cog13 is a brief objective cognitive assessment of the severity of cognitive symptoms of Alzheimer's disease. The composite scale was developed to include both participant-completed tests and informant-based assessments that measure the cognitive domains of memory, language, and praxis. The original ADAS-Cog11 version of the scale included the specific tasks of word recall, naming objects and fingers, commands, constructional praxis, ideational praxis, orientation, word recognition, and language. The

ADAS-Cog13 revised version was adapted to include delayed memory and number cancellation tasks to more sensitively capture the memory and executive functioning deficits seen in early-stage Alzheimer's disease. The ADAS-Cog13 scores range from 0 to 85, with higher scores indicating worse performance.

- MMSE

The MMSE is a brief cognitive screening tool that provides clinicians the ability to rapidly assess cognitive ability in less than 10 minutes. It is an 11-question measure that tests orientation, registration, attention and calculation, recall, language, and visuospatial skills. The MMSE scores range from 0 to 30, with higher scores indicating better performance.

- NPI-10

The NPI-10 is a questionnaire administered to the informant and is designed to obtain information on the presence of neuropsychiatric symptoms and behaviors in a patient with Alzheimer's disease. The presence and severity of 10 areas are assessed: delusions, hallucinations, agitation/aggression, depression, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, and aberrant motor behavior. Higher scores indicate greater impairment.

[redacted]

[redacted]

It is recommended that clinical assessments be performed at the same time of day for participants during their study visits.

Some tests will require the informant to participate and answer questions regarding the participant's daily activities and cognitive capabilities. Some scales will be audio recorded for training and evaluation purposes.

The recommended order of administration of the clinical assessments is described in the Study Reference Manual.

The key secondary endpoint, the modified iADRS, is a composite endpoint that combines the ADAS-Cog13 and ADCS-ADL-MCI to capture decline of both cognition and daily function. The [redacted] cognitive functioning tests include the following neuropsychological tests: word retrieval from the ADAS-Cog13, [redacted]. These are calculated to form the EMACC composite [Jaeger 2021; Jaeger 2017]. The GST composite z-score is calculated by averaging the standardized z-scores for the CDR-SB, ADCS-ADL-MCI, and ADAS-Cog13.

9.2. Laboratory Efficacy Assessments

Samples will be analyzed using Good Laboratory Practice validated assays.

9.3. Pharmacokinetic Assessments

The following parameters will be calculated to assess the PK of aducanumab:

- Serum concentrations of aducanumab will be measured using a validated assay.

9.4. Pharmacodynamic Assessments

Serial measurements of disease- or treatment-related [redacted] will be assessed in all participants.

The pharmacodynamic properties of aducanumab will be confirmed through analyses of blood samples that will include, but are not limited to, [redacted]

Optional Substudies

The following substudies will be conducted in a subset of sites and participants, where available. Investigator participation in these substudies is optional and contingent upon approval by the ethics committee or IRB. If the Investigator is not participating in a substudy, or if the tests described below are not approved by the Investigator's ethics committee and/or IRB, the relevant section of the ICF will not be applicable to that site. Informed consents must be recorded in the CRF. Approximately 400 participants are expected to enroll in each of the 3 [redacted]. Participating in multiple substudies (where available) is highly encouraged. Historical CSF samples or PET scans are not acceptable for participants in the longitudinal [redacted].

The pharmacodynamic properties of aducanumab will be confirmed through the following longitudinal substudies:

1. Measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET

   Participants who consent to this optional longitudinal PET substudy will undergo 3 PET scans (Screening, Week 78, and Week 104). Only sites with capabilities to perform amyloid PET with Sponsor-approved tracer will be allowed to perform this assessment. Detailed PET scanning protocols will be described in a separate procedural manual for PET.

2. Measurement of neurofibrillary tangle burden in certain areas of the brain as measured by tau PET

   Participants who consent to this optional longitudinal PET substudy will undergo 3 PET scans (Screening, Week 78, and Week 104). Only sites with capabilities to perform tau PET with Sponsor-approved tracer will be allowed to perform this assessment. Detailed PET scanning protocols will be described in a separate procedural manual for PET.

[redacted]

[redacted]

9.6. Future Scientific Research Assessments

[redacted]

Participants will sign a separate, written ICF if they agree to their samples being used in this way.

The residual samples may be utilized to identify or verify putative, prognostic, and predictive markers associated with disease and markers of therapeutic response to treatment, and/or to develop diagnostic and analytical tests. Background and dynamic clinical disease characteristics and associated [redacted] data may be utilized to predict subsequent disease worsening (severity), identify high-risk patient subgroups, and identify predictors of response to treatment.

9.7. Additional Assessments

The following assessments will be performed to evaluate the effect of aducanumab in participants and informants:

- EQ-5D-5L (for both participant and informant)
- QoL-AD (for both participant and informant)
- [redacted]
- RUD-Lite (for informant only)

Some tests will require the informant/care partner to participate and answer questions regarding the participant's daily activities and cognitive capabilities.

The recommended order of administration of the clinical assessments is described in the Study Reference Manual.

10. SAFETY ASSESSMENTS

See Section 1.3 for the timing of all safety assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the study site to have the evaluations repeated.

If in-clinic visits are not able to occur, a remote visit via telephone or video call may be used to collect safety assessments as deemed appropriate by the Sponsor (refer to the Study Reference Manual for details).

10.1. Clinical Safety Assessments

The following clinical assessments will be performed to confirm the safety profile of aducanumab:

- AE and SAE monitoring
- Physical examination, including height and body weight
- Neurological examination
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate)
- 12-lead ECG
- Brain MRI
- Concomitant therapy and procedures
- C-SSRS Lifetime/Recent at screening and the C-SSRS-SLV for postscreening visits

  The C-SSRS assesses the patient's risk of suicide and aids in stratifying patients into categories of low, moderate, or high risk. The C-SSRS separates ideation and behavior by using 4 constructs (severity of ideation, intensity of ideation, behavior, and lethality), based on factors identified in previous studies as predictive of suicide attempts and completed suicide. Higher scores indicate greater risk of suicide. The Lifetime/Recent version allows practitioners to gather lifetime history of suicidality, as well as any recent suicidal ideation/behavior. The Since Last Visit (C-SSRS-SLV) version of the scale assesses suicidality since the patient's last visit.

10.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice validated assays.

The following laboratory assessments will be performed to evaluate the safety profile of aducanumab:

- Hematology: complete blood count with platelet count, and absolute neutrophil count.
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, lactate dehydrogenase, gamma glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium.
- Urinalysis: color, specific gravity, pH, protein, glucose, blood, ketones, and microscopic examination (if abnormal).
- Serum and urine pregnancy test for women of childbearing potential only.
- Coagulation (panel [PT, aPTT, INR, platelet count] also conducted prior to LP), virology (including hepatitis B, hepatitis C, and HIV [the latter at the Investigator's discretion after consideration of risk factors]), HbA1c, and alcohol/drug screen at Screening.

10.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier antidrug antibody approach will be used (i.e., screening assay, confirmatory assay, and titration assay). Additional characterization of the immune response may be performed.

11. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the participant. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each participant or his/her legally authorized representative (where local regulations and institutional practices permit) must be given the names and telephone numbers of site staff for reporting SAEs, pregnancies, overdoses, and medical emergencies. Throughout the protocol, the Sponsor is named, but reporting may be done through a CRO.

11.1. Definitions

11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal assessment such as an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal assessment (e.g., laboratory value, vital sign, and ECG) result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless 1 or more of the following criteria are met:

- The result meets the criteria for an SAE.
- The result requires the participant to receive specific corrective therapy.
- The result is considered by the Investigator to be clinically significant.

11.1.2. Serious Adverse Event

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

- Results in death.
- In the view of the Investigator, places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.

- Results in a congenital anomaly/birth defect.
- Is a medically important event.

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

11.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the participant is hospitalized. The study site must document all the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the participant's consent to be in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the participant's consent to be in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
  - If a participant is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 11.1.2 is met.

11.2. Safety Classifications

11.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 11.1.2.
- The relationship of the event to study treatment as defined in Section 11.2.2.
- The severity of the event as defined in Section 11.2.3.

11.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment and, if applicable, the PET radioligand(s).

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational drug if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational drug if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.
Relationship of Event to PET Radioligand(s)	
Not related	An AE will be considered "not related" to the use of the radioligand if there is not a reasonable possibility that the event has been caused by the radioligand. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the radioligand and the AE, the presence of a biologically implausible relationship between the radioligand and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the radioligand if there is a reasonable possibility that the event may have been caused by the radioligand. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the radioligand and the AE, a known response pattern of the suspected radioligand, improvement following discontinuation or dose reduction, a biologically plausible relationship between the radioligand and the AE, or a lack of an alternative explanation for the AE.

11.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given at the request of participant.
Moderate	Symptoms of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptoms may be needed.

Severity of Event	
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or participant hospitalized.

11.2.4. Expectedness of Events

Expectedness of all SAEs will be determined by the Sponsor according to the Investigator's Brochure for aducanumab.

11.3. Monitoring and Recording Events

11.3.1. Adverse Events

Any AE experienced by the participant between the time of first dose of study treatment and the participant's final clinical visit (including FU Visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the participant for AEs and will record any new AEs or updates to previously reported AEs on the CRF. Pretreatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

AEs that are ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcomes that occur following study completion or discontinuation will not be recorded on the CRF.

11.3.2. Adverse Events of Special Interest

An AE of special interest is an AE of scientific and medical concern specific to this study, for which ongoing monitoring and reporting are required.

Radiographic ARIA (ARIA-E and ARIA-H), as well as any symptoms of ARIA, are considered AEs of special interest and will be entered on the Adverse Event of Special Interest CRF within 72 hours following the receipt of abnormal MRI findings from the central MRI reader.

AE reporting for ARIA-E and ARIA-H will be based on the following centrally read MRI sequences: fluid attenuated inversion recovery/T2 for ARIA-E and T2*/gradient echo for ARIA-H.

TEAEs associated with ARIA or suspected to be associated with ARIA must be reported as separate TEAEs as well as being grouped with ARIA to ensure accurate reporting of events possibly related to ARIA.

Seizures, falls, and hypersensitivity reactions are also considered AEs of special interest.

If the event qualifies as an SAE, an SAE form should be submitted per the guidelines in Section 11.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to the Sponsor.

11.3.3. Serious Adverse Events

Any SAE experienced by the participant between the time of the signing of the ICF and the participant's final clinical visit (including FU Visit) is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. After the participant completes the study, newly occurring SAEs should be reported to the Sponsor on an SAE Form only if the Investigator considers the SAE to be related to study treatment.

SAEs must be reported to the Sponsor (or designee) within 24 hours (as described in Section 11.3.4 or according to national law. This also applies to SAEs that occur after administration of the radioligand. Follow-up information regarding an SAE also must be reported within 24 hours.

Any SAE that is ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

11.3.4. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify the Sponsor within 24 hours of the study site staff becoming aware of the SAE or according to national law. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs
A report ***must be submitted*** to the Sponsor regardless of the following: • Whether or not the participant has undergone study-related procedures • Whether or not the participant has received study treatment • The severity of the event • The relationship of the event to study treatment To report initial or follow-up information on an SAE, fax or email a completed SAE form; refer to the Study Reference Manual for country-specific contact information.

11.3.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event or according to national law. The Investigator should make every

effort to obtain and send death certificates and autopsy reports to the Sponsor. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

11.3.5. Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Appropriate Sponsor personnel will unblind SUSARs for the purpose of regulatory reporting. The Sponsor will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

11.4. Procedures for Handling Special Situations

11.4.1. Public Health Emergencies

In the event of a public health emergency that results in site closure, travel restrictions, and/or the study being deprioritized at the site such that clinic visit(s) cannot occur, a protocol deviation would be incurred for any deviation from the protocol-specified visits and assessments, with additional notation that this protocol deviation is due to the public health emergency.

If a protocol-specified clinical visit cannot occur due to a public health emergency, the following mitigating options should be pursued, in order of preference (in which the highest preference option that is feasible should be done): 1) transfer to another active study site that is open, 2) home visit, 3) telemedicine visit (e.g., by telephone or web conference), and 4) local laboratory visit. These mitigating options only apply in the setting of a public health emergency in which a protocol-specified clinic visit cannot occur and should not be pursued solely due to participant's preference. If the participant does not participate in one of these options, a Safety Telephone call must be conducted within 14 days of the last dosing visit.

Details on which visits and procedures are eligible to be performed at alternative medical facilities will be provided by the Sponsor in writing. All procedures performed at alternative medical facilities will need to be performed as described in this protocol and medical staff will need to be trained accordingly. If a participant cannot attend the study site visit for administration of study drug, a home visit or a visit to an alternative medical facility may be appropriate. Study treatment administration outside of the study site may require appropriately delegated study site staff or a home healthcare service with Sponsor approval.

The Sponsor will determine appropriate start and end dates for each contingency measure, where the duration of the mitigations may begin at the onset of site restrictions for a specific site and/or country and may end once those restrictions are lifted and in accordance with local laws and regulations. The adaptations to the visits and procedures described are alternatives or deviations to the main protocol procedures.

These contingency measures will only be implemented in exceptional cases and after the site has received written notification from the Sponsor. The Sponsor will have the final authority to decide what mitigations can be implemented, in accordance with local laws and regulations.

The Sponsor will communicate decisions to the Principal Investigator(s) and study site(s) via protocol clarification letters. The protocol clarification letter will include details such as which visits are eligible to be conducted via televisits. Study sites will be responsible for notifying any required boards or committees.

11.4.2. Pregnancy

Participants should not become pregnant during the study and for 24 weeks after their last dose of study treatment. If a female participant becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female participant from first dose of study drug to 24 weeks after her last dose by faxing or emailing the appropriate form to the Sponsor within 24 hours of the study site staff's becoming aware of the pregnancy. Refer to the Official Study Contact List in the Study Reference Manual for complete contact information. The Investigator or site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female participants should be reported as an SAE if conception occurred during the study treatment period or within 24 weeks after last dose of study treatment.

11.4.3. Overdose

An overdose is any dose of study treatment administered to a participant that exceeds the dose assigned to the participant according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to the Sponsor within 24 hours of the site staff becoming aware of the overdose. An overdose must be reported to the Sponsor even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and overdose forms must be completed and faxed or emailed to the Sponsor. All study treatment-related dosing information must be recorded on the dosing CRF.

11.4.4. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention according to current standards of care. The Investigator (or designee) should contact the Sponsor-designated Medical Services. Refer to the Official Study Contact List in the Study Reference Manual for complete contact information.

11.4.4.1. Unblinding for Medical Emergency

In this study, emergency decoding will be made available to the Investigator and designated personnel at the Sponsor through IRT.

In a medical emergency, when knowledge of the participant's treatment assignment may possibly influence the participant's clinical care, the Investigator may access the participant's treatment assignment by IRT. However, prior to unblinding, the Investigator can refer to the Official Study Contact List in the Study Reference Manual for complete contact information.

The Investigator must document the reasons for unblinding in the participant's source documents. The Investigator is strongly advised not to divulge the participant's treatment assignment to any individual not directly involved in managing the medical emergency or to personnel involved with the analysis and conduct of the study.

11.5. Contraception Requirements

All women of childbearing potential must ensure that effective contraceptive methods are used during the study and for 5 times the half-life or 24 weeks (whichever is longer) after their last dose of study treatment. For all women of childbearing potential, a pregnancy test must be performed 24 hours prior to every PET scan. In addition, participants should not donate sperm or eggs for the duration of the study and for at least 24 weeks after their last dose of study treatment.

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant UNLESS they meet one of the following conditions:

- Postmenopausal
  - 12 months of natural (spontaneous) amenorrhea without an alternative medical cause or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
  - 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle-stimulating hormone level ≥ 40 mIU/mL, or at least 5 continuous years of natural (spontaneous) amenorrhea without an alternative medical cause
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of this study, effective contraception is defined as use of one of the following:

For females:

- Progesterone-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
- Placement of an intrauterine device or intrauterine hormone-releasing system.

- The following barrier methods of contraception with use of a spermicide: condom or occlusive cap (i.e., diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository; the use of barrier contraceptives should always be supplemented with the use of a spermicide (where applicable).

- Male sexual partners who underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate. If documentation is not available, the participant must use contraception.

For males:

- Vasectomy with negative semen analysis at follow-up. If documentation is not available, the participant must use contraception.

- Intercourse with a woman who uses the methods described for females if she is of childbearing potential.

For males or females:

- True abstinence, when this is consistent with the preferred and usual lifestyle of the participant, can be considered an acceptable method of contraception based on the evaluation of the Investigator, who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 11.4.2 .

11.6. Safety Responsibilities

11.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the CRF regardless of the severity or relationship to study treatment.

- Determine the seriousness, relationship, and severity of each event.

- Determine the onset and resolution dates of each event.

- Monitor and record all pregnancies in female participants and follow up on the outcome of all pregnancies.

- Complete an SAE form for each SAE and report it to the Sponsor (or designee) within 24 hours of the site staff becoming aware of the event or according to national law.

- Pursue SAE FU information actively and persistently. FU information must be reported to the Sponsor (or designee) within 24 hours of the site staff becoming aware of new information or according to national law.

- Ensure all AE and SAE reports are supported by documentation in the participants' medical records.

- Pursue AE FU information, if possible, until the event has resolved or become stable. Record AE FU information, including resolution, on the CRF as applicable.

- Report SAEs to local ethics committees as required by local law.

11.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a study site activation and participant enrollment, the Clinical Monitor is responsible for reviewing with site staff the definitions of AE and SAE as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

- The Sponsor (or designee) is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required timeframes.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 4.

12.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized with summary statistics (mean, SD, median, and range) or with frequency distributions.

12.2. Efficacy and Pharmacodynamics

12.2.1. Analysis Sets

The FAS includes all participants who are randomized and received at least 1 dose of study treatment (aducanumab or placebo). The FAS will be used for efficacy analyses.

12.2.2. Methods of Analysis

12.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include the following: number of participants with data, mean, SD, median, and range. For categorical endpoints, these will generally include number of participants randomized or dosed, number with data, and the percent of those with data in each category. Statistical testing for efficacy endpoints will be made between aducanumab and placebo. All statistical tests will be 2-sided.

12.2.2.2. General Considerations for Analyses of Week 78 Endpoints

Analyses of Week 78 endpoints will only include data up to the Week 78 visit. See Section 12.7 for additional information.

12.2.2.3. Considerations for Multiple Comparison Adjustments

The primary endpoint will be tested at a 2-sided alpha level of 0.05. If the primary endpoint is statistically significant, then the key secondary endpoints will be tested in the following order.

- iADRS
- ADCS-ADL-MCI
- ADAS-Cog13
- MMSE
- NPI-10

Each test will be performed at a 2-sided alpha level of 0.05 and will only be performed if the preceding test is statistically significant.

12.2.2.4. Considerations for Efficacy Endpoint Analysis

In analyses performed on the FAS, participants will be analyzed based on the intent-to-treat principle according to their randomized treatment assignment regardless of treatment received. The primary estimand on the treatment effect of aducanumab is for the primary endpoint based on the continuous variable of change from baseline scores in CDR-SB. This analysis is conducted for an estimand with a treatment policy strategy to handle all ICEs, with the following attributes as outlined by ICH E9 (R1):

- Analysis set: all participants in the FAS
- Variable: the change from baseline scores in CDR-SB at Week 78 regardless of ICEs
- Analysis set level summary: LS mean difference from MMRM model in change from baseline between aducanumab dose and placebo
- ICEs and strategies for addressing ICEs: all observed data to be included regardless of ICEs

The ICEs include treatment discontinuation or a change in concomitant use of Alzheimer's disease symptomatic medication.

12.2.2.5. Analysis of the Primary Endpoint

The primary analysis of the primary endpoint is based on a rank ANCOVA and an MMRM model. Non-normality of data is a key analytic consideration. A rank ANCOVA model of the change from baseline CDR-SB at Week 78 adjusting for treatment group, baseline CDR-SB, baseline MMSE, baseline disease stage, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status will be used to test the statistical significance of the difference between aducanumab and placebo-treated groups at Week 78. Missing data will be imputed using multiple imputation assuming missing at random before performing the rank ANCOVA. The following covariates will be included in the imputation model: treatment group, baseline CDR-SB, baseline MMSE, baseline disease stage, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/noncarrier). An MMRM model will be used to estimate the difference in change from baseline CDR-SB between treatment groups using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, baseline disease stage, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. An unstructured covariance matrix will be used to model the within-participant variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. In the primary analysis, missing data are assumed to be missing at random [Rubin 1976].

A sensitivity analysis will be performed to assess the robustness of the primary analysis to deviations from the missing-at-random assumption. Imputation for missing data will be conducted to have outcomes that enable an estimand with a treatment policy strategy. The sensitivity analysis will be conducted for the FAS population. The copy increment from reference method will be applied to impute the postwithdrawal data for any aducanumab-treated participant who withdraws from study early based on data from the placebo group rather than the participant's own randomized treatment group [Carpenter 2013]. This method assumes that any benefit gained from previous treatment will be retained, but participants progress as if they were on placebo after withdrawal from study. For any participant on placebo who withdraws early, their postwithdrawal profile will be imputed following the missing-at-random principle.

Supplementary analyses will include repeating the primary analysis twice with the data censored after each of the following intercurrent events:

- premature discontinuation of the study treatment
- any change to concomitant AD symptomatic medications during the study (if multiple events occur to the same participant, data after the earliest event will be censored)

12.2.2.6. Key Secondary Endpoints

The key secondary endpoints are described in Section 4. An MMRM model will be used as the primary analysis to analyze change from baseline in all key secondary endpoints using fixed effects of treatment, time, treatment-by-time interaction, a given key secondary endpoint score at baseline, a baseline key secondary endpoint score by time interaction, baseline MMSE, baseline disease stage, Alzheimer's disease symptomatic medication use at Baseline, region, and laboratory ApoE ε4 status.

12.2.2.7. Secondary Endpoints

The secondary endpoints are described in Section 4.

An MMRM model will be used also as the primary analysis to analyze change from baseline in all secondary endpoints using fixed effects of treatment, time, treatment-by-time interaction, a given secondary endpoint score at baseline, a baseline secondary endpoint score by time interaction, baseline MMSE, baseline disease stage, Alzheimer's disease symptomatic medication use at Baseline, region, and laboratory ApoE ε4 status.

12.2.2.8. Tertiary and [redacted] Endpoints

Analyses of the tertiary and [redacted] endpoints regarding quality-of-life questionnaires, health economic metrics, as well as the [redacted], if performed, will be prespecified in the SAP.

12.3. Methods of Analysis for Pharmacokinetic Endpoints

12.3.1. Analysis Set

The PK analysis set is defined as all participants who are dosed with aducanumab and had at least 1 measurable aducanumab concentration in serum.

[redacted]

12.5. Analysis of Safety Endpoints

12.5.1. Analysis Set

The safety analysis set is defined as all participants who are randomized and received at least 1 dose of study treatment (aducanumab or placebo).

12.5.2. Methods of Analysis

All AEs, laboratory data, and vital signs will be evaluated for safety.

12.5.3. Adverse Events

AEs will be coded using MedDRA.

Only TEAEs will be presented in the summary tables. Treatment emergence is defined as having an onset date that is on or after the start of study treatment or as worsening after the start of study treatment.

Incidence of TEAEs will be summarized by treatment groups, overall, by severity and by relationship to aducanumab. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class.

Incidence, severity, and symptomatology of ARIA will be summarized by treatment group. The analysis of ARIA incidence will also be performed for all different types of ARIA (e.g., ARIA-E and ARIA-H).

12.5.4. Clinical Laboratory Results

Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters and shifts from baseline to high/positive status for urinalysis will be presented. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

12.5.5. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities.

12.5.6. ECGs

The number and percentage of participants with shifts to categorical values (abnormal not AE, or abnormal AE) will be summarized by treatment groups.

12.5.7. C-SSRS

Baseline C-SSRS and postbaseline C-SSRS-SLV data will be summarized using descriptive statistics (i.e., number of participants, mean, SD, median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables.

12.6. Methods of Analysis for Immunogenicity Data

12.6.1. Analysis Set

The immunogenicity analysis set is defined as all participants in the safety analysis set who have at least 1 postdose sample evaluated for immunogenicity.

12.6.2. Methods of Analysis

Treatment-emergent ADAs in serum will be summarized.

12.7. Interim Analyses

Interim analyses for superiority may be performed after approximately 60% of the participants have completed the 18-month visit (or discontinued). The alpha level at the interim analysis will be determined using the O'Brien-Fleming boundary approach. The alpha level for the final analysis will be adjusted to achieve an overall type I error of 0.05.

If an interim analysis is performed, the interim analysis will be performed by an independent group external to the Sponsor that will not be involved in the conduct of the study after unblinding. A potential role for the IDMC in this interim analysis will be fully described in the IDMC charter. The aim of this interim analysis is to allow the possibility to verify the clinical treatment benefit of aducanumab early. The analysis will be discussed in detail in the SAP.

After all participants have had an opportunity to complete the Week 78 visit, the Sponsor will perform an unblinded analysis. This unblinded analysis will performed by a small internal independent team (separate from the study team). Analyses of Week 78 endpoints will only include data up to the Week 78 visit (see Section 12.2.2.2).

12.8. Sample Size Considerations

The sample size is mainly based on results from the primary analysis of Study 221AD302. Results from the post-PV4 population (i.e., the 221AD302 and 221AD301 protocol amendment in which the high dose of aducanumab was increased from 6 mg/kg to 10 mg/kg) in pooled data from Studies 221AD302 and 221AD301 were also considered. A total sample size of 1512 participants is planned to have approximately 90% power to detect a mean difference of 0.48 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation is based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, an SD of 2.33, a dropout rate through Week 78 of 27%, and a randomization ratio of 2:1. The assumed mean difference of 0.48 between the 2 treatment groups represents an approximately 24% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

A blinded assessment of the pooled SD for the primary efficacy endpoint may be performed approximately 3 months prior to the completion of enrollment and the sample size may be increased as a result. The sample size could also be increased using internal and external clinical study results that become available after the start of this study. In addition, the sample size may be increased if the dropout rate through Week 78 is estimated to exceed 27%. The sample size will not be reduced based on this assessment.

13. ETHICAL AND REGULATORY REQUIREMENTS

The Sponsor, any contracted third party, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and GCP guidelines and conduct the study according to local regulations.

The Investigators are responsible for demonstrating timely oversight of all clinical trial data from their site, including data external to the EDC system, such as laboratory, imaging, and electronic clinical outcomes assessment data. Investigators must approve all their data on completed CRFs by signing electronically, at the participant, visit, or casebook level, at any time prior to an interim lock or database lock as well as before any subsequent relock. The EDC system does not prohibit Investigator approval or signing in any way.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

13.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

13.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor or designated CRO will submit documents on behalf of the study sites in countries other than the US.

If the Investigator makes any changes to the ICF, the Sponsor must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to the Sponsor. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

The Sponsor must receive a letter documenting ethics committee approval that specifically identifies the protocol, protocol number, and ICF prior to the initiation of the study. Protocol amendments will be participant to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

13.3. Changes to Final Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a participant. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 13.4).

13.4. Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent must be obtained with the approved ICFs.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the participant must be explained to the participant and/or the participant's legally authorized representative (where local regulations and institutional practices permit). The participant and/or the participant's legally authorized representative must be given sufficient time to consider whether to participate in the study.

The Investigator must reassess the participant's capacity to provide informed consent periodically over the course of the study. In the event the participant is no longer cognitively intact and loses capacity to provide informed consent, the Investigator must obtain participant consent by the participant's legally authorized representative (in accordance with local laws and regulations) or withdraw the participant from the study.

A separate informed consent will be used for the 3 longitudinal substudies involving imaging and CSF sampling over time.

The level of information provided to participants should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF must be given to the participant and/or the participant's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the participant's medical record.

When additional information that may affect participants' willingness to continue in the study becomes available, the Investigators will be notified in a timely manner, according to all local and applicable law. An updated ICF may be required.

13.5. Participant Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by applicable national and local privacy regulations (e.g., Protected Health Information authorization in North America).

During the study, participants' race and ethnicity and year of birth will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or PK profile of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity.

In the US only, where permitted by applicable law and governing ethics committees, a code for environmental health will be obtained using the participant's address. The address will not be stored on source documents, study records or CRFs, nor stored in the University of Wisconsin website where the code is obtained (see Study Reference Manual for more information). These data will be used in the [redacted] of the impacts of social determinants of health on treatment efficacy. It is unknown whether the effects of the study treatment are influenced by social determinants of health, but they are believed to be important to our scientific understanding of Alzheimer's disease.

In the US only, where permitted by applicable law and governing ethics committees, participants will have the option to report gender identity and sexual orientation information. These data will be used in an [redacted] of the disease course and treatment impacts of gender identity, which are currently unknown but are believed to be important to our scientific understanding of Alzheimer's disease.

Biogen will not disclose the result of ApoE testing to the participants. The investigator is responsible to ensure participant's full understanding of the potential safety risks associated with genotyping, cognizant of the ethical and legal issues of disclosing results without appropriate genetic counselling.

Study reports will be used for research purposes only. The participant will not be identified by name in CRFs, study-related forms, study reports, or any related publications. The Sponsor, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the participant's personal medical data confidential.

13.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

13.7. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor with the participant before the participant makes a decision to participate in the study).

13.8. Study Report Signatory

The Sponsor will designate one of the participating Investigators as a signatory for the study report. This determination will be made by several factors including but not limited to the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or participant enrollment; or by other factors determined to be relevant by the Sponsor.

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

13.9. Registration of Study and Disclosure of Study Results

The Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

The Sponsor also will notify, when required, the regulatory authorities and ethics committees about the completion or termination of this study and send a copy of the study synopsis in accordance with necessary timelines.

13.10. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

14. KEY ROLES AND STUDY GOVERNANCE COMMITTEES

14.1. Site Staff

Refer to the Study Reference Manual for further details regarding site staff responsibilities, including key blinding procedures for the 3 study roles.

A minimum of 3 separate HCPs are required:

1. A treating Investigator or Subinvestigator who is responsible for the following:
   - Management of routine neurological care of the participant.
   - Assessment (including assignment of causality) and treatment of AEs.
   - Review of selected hematology and blood chemistry results from the central laboratory to assess whether the participant's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 8.1.
2. The CDR Rater (designated by the Investigator of the site) who is an independent rater responsible for administering the CDR.
3. The Independent Non-CDR Rater (designated by the Investigator of the site) who will administer the remainder of the clinical scales of cognition and function as well as the QoL questionnaires and health economic metrics.

The CDR Rater and the Independent Non-CDR Rater must not be involved with any other aspect of participant care and management and must remain blinded to AEs, concomitant therapy, laboratory data, imaging data, or any other data that have the potential of revealing the treatment assignment. The CDR Rater and Independent Non-CDR Rater must not share any information about participants. Treating Investigators should not serve as raters, with the exception of the Research Diagnostic Verification and subsequent Disease Staging Forms. Treating Investigators must not discuss AEs (e.g., ARIA) or ARIA-related MRI-monitoring scheduling matters with the CDR Rater or Independent Non-CDR Rater.

To ensure consistency across sites, all study raters must complete the standardized study-specific qualification and training process prior to administering clinical efficacy assessments. All sites must attempt to maintain the same rater for a given participant throughout the study. A qualified, approved back-up rater should conduct assessments in place of the primary rater only if extenuating circumstances (e.g., illness, vacation, or travel) result in unavailability of the primary rater. If a rater has to be replaced, the new rater must undergo the study-specific qualification process prior to administration of the assessment.

Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the participant. As with other laboratory and clinical information, these data should NOT be reviewed by the raters.

The roles of the CDR Rater, the Independent Non-CDR Rater, and treating Investigator are not interchangeable. In addition, the CDR Rater is not interchangeable with the Independent Non-CDR Rater at the participant level. For example, if a rater has administered the CDR to a participant, they may not administer the other neurocognitive assessments to that participant at any point during the study.

An unblinded pharmacist (or authorized designee) will be responsible for the storage, distribution, preparation, and accountability of study treatment. The unblinded pharmacist will also be responsible for maintaining the unblinded pharmacy record separate from the main study file in order to support the study blind.

14.2. Vendors

The Sponsor will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

14.2.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study, including but not limited to study initiation, monitoring, and management of SAE reports. Before participants are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

14.2.2. Interactive Response Technology

IRT will be used in this study. Before participants are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

14.2.3. Electronic or Remote Data Capture

Participant information will be captured and managed by study sites on electronic CRFs by a Web-based EDC tool configured by the EDC vendor. Electronic Clinical Outcome Assessment will be entered by site staff on a Web-based tool. The site staff will monitor data via a secure Web portal.

14.2.4. Central Laboratories for Laboratory Assessments

The Sponsor has selected a central laboratory service to perform all standard hematology, blood chemistry, and urinalysis testing for the study. This central laboratory will also receive, track, and ship all urine, blood, CSF samples, and [redacted], PK, [redacted], and antidrug antibody testing, including aliquots from these samples retained as backup in case original samples are lost or not evaluable. [redacted]

Laboratories performing specialized testing will be identified in regulatory documentation. These laboratories will use appropriately validated or qualified assays to test study samples.

14.2.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by the Sponsor to read and interpret all MRIs for this study within the timeframe specified in the procedural manual for MRI. In cases of ARIA-E and ARIA-H, the central imaging laboratory must expedite notification to the Investigator and the Sponsor. For the purposes of study conduct, the MRI interpretations from the central reader will prevail over those from the local radiologist.

The central imaging laboratory will also be utilized to facilitate collection and analysis of PET scans.

14.2.6. Central Review of Raters

The Sponsor has selected a rater management group to establish rater qualifications, provide studyspecific training about the rater process, and provide oversight. As part of the oversight process, the rater management group will incorporate a central review of the raters to ensure that data are consistently rated across sites.

14.2.7. Neurocognitive Assessments

The Sponsor has selected a rater management group to establish rater qualification, study-specific training, and oversight. The study raters are required to complete qualifications steps and required training prior to administering study assessments. The rater management group will oversee the assessments in accordance with project-specific plans.

14.3. Study Committees

14.3.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will meet periodically to monitor participant accrual and oversee study conduct, including advising on study design and execution.

Members of the advisory committee will include external experts in Alzheimer's disease. The Sponsor will designate one of the participating external experts to be the chairperson of the advisory committee.

14.3.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. The IDMC may also participate in a review of efficacy data only during interim analysis. Members of the IDMC will not be allowed to participate as Investigators in this study. The IDMC will review safety data on an ongoing basis to ensure safe and proper treatment of participants. The IDMC, based on the nature, frequency, and/or severity of AEs, may recommend protocol modifications, dose suspension, dose termination, or study termination. An IDMC charter will provide full guidance on the function and practices to be followed by the IDMC.

15. ADMINISTRATIVE PROCEDURES

15.1. Study Site Initiation

The Investigator must not screen any participants prior to the Sponsor completing a study initiation visit. This initiation visit with the Investigator and other site staff, as appropriate, will include a detailed review of the protocol, study procedures, and study responsibilities.

15.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate. The Investigator is responsible for endorsing all CRF data prior to any interim or final database lock.

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

15.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the participants' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on participant safety, data integrity, and critical data and processes.

During these visits, CRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Documentation of results will be provided to the Sponsor in a timely fashion to allow FU and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of participant rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

15.4. Study Funding

The Sponsor is responsible for setting up the funding of the study. All financial details are provided in the separate contracts between the institution, Investigator, and the Sponsor organization.

15.5. Publications

Details are included in the clinical trial agreement for this study.

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17. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3b/4 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Verify the Clinical Benefit of Aducanumab (BIIB037) in Participants with Alzheimer's Disease," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

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AMENDMENT SUMMARY

Biogen Protocol 221AD305

A Phase 3b/4 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Verify the Clinical Benefit of Aducanumab (BIIB037) in Participants with Alzheimer's Disease

For Global Protocol Amendment: Version 2

Date: 15 April 2022

Version 2.0 of the protocol has been prepared for this amendment, which supersedes Version 1.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 221AD305 is to correct typographical errors in Table 1 and Table 2, the Schedule of Assessments. Correction of these errors was requested by FDA, thereby requiring a global protocol amendment.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Table 1, Schedule of Activities From Screening Through Week 32

Study Week 2 (~~14~~ ±3 days)

Study Week 28 (~~225~~ ±3 days)

Study Week 30 (~~239~~ ±3 days)

Study Week 32 (~~239~~ ±3 days)

Now reads:

Study Week 2 (**15** ±3 days)

Study Week 28 (**197** ±3 days)

Study Week 30 (**211** ±3 days)

Study Week 32 (**225** ±3 days)

Study Week	Screening (≤ 60 days before Day 1)[1]			1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Study Day	Visit 1	Visit 2	Visit 3	1	~~14~~ **15** ± 3	29 ± 3	43 ± 3	57 ± 3	71 ± 3	85 ± 3	99 ± 3	113 ± 3	127 ± 3	141 ± 3	155 ± 3	169 ± 3	183 ± 3	~~225~~ **197** ± 3	~~239~~ **211** ± 3	~~239~~ **225** ± 3

Rationale: This change was requested by FDA and therefore constituted a protocol amendment.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Table 2, Schedule of Activities From Week 36 to End of Study

Change: Aducanumab autoantibody assessment was included in Version 1 of the protocol as assessed at the unscheduled visit for ARIA and not at the End-of-Study visit. This was a transpositional error. Autoantibody assessment is now removed from this visit and added to the End-of-Study visit.

Now reads:

Study Week	36	40	42	44	48	50	52	56	60	64	68	72	76	78	80	84	88	92	96	100	104	106	ET[1]	UV AD Meds[2]	UV ARIA[3]	FU[4] EOS 122
Study Day	253 ± 3	281 ± 3	295 ± 3	309 ± 3	337 ± 3	351 ± 3	365 ± 3	393 ± 3	421 ± 3	449 ± 3	477 ± 3	505 ± 3	533 ± 3	547 ± 3	561 ± 3	589 ± 3	617 ± 3	645 ± 3	673 ± 3	701 ± 3	729 ± 3	743 ± 3				**855± 3**
Anti-Aducanumab Ab[5]							X							X							X		X		~~X~~	**X**

Rationale: In light of the amendment being triggered for correction of typographical errors, this error was also corrected.