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PROTOCOL NUMBER: 221AD301 / NCT02477800

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000966-72**

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SPONSOR SIGNATURE

Protocol 221AD301 was approved by:

[redacted]

09 APRIL 2015

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Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab , produced in a different Chinese hamster ovary cell line
^{18}F-florbetapir	Also known as florbetapir-fluorine-18 or ^{18}F-AV-45 (amyloid ligand; trade name Amyvid)
Aβ	β-amyloid
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibodies
ADAS-Cog 13	Alzheimer's Disease Assessment Scale - Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
[redacted]	[redacted]
AST	aspartate aminotransferase
CDR	Clinical Dementia Rating
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
ET	Early Termination
FU	follow-up

GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPI-10	Neuropsychiatric Inventory-10
PET	positron emission tomography
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
SABR	Safety and Benefit-Risk
SAE	serious adverse event
SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
UV	unscheduled visit

3. SYNOPSIS

Protocol Number:	221AD301
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	1.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-Sum of Boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy 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 subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78

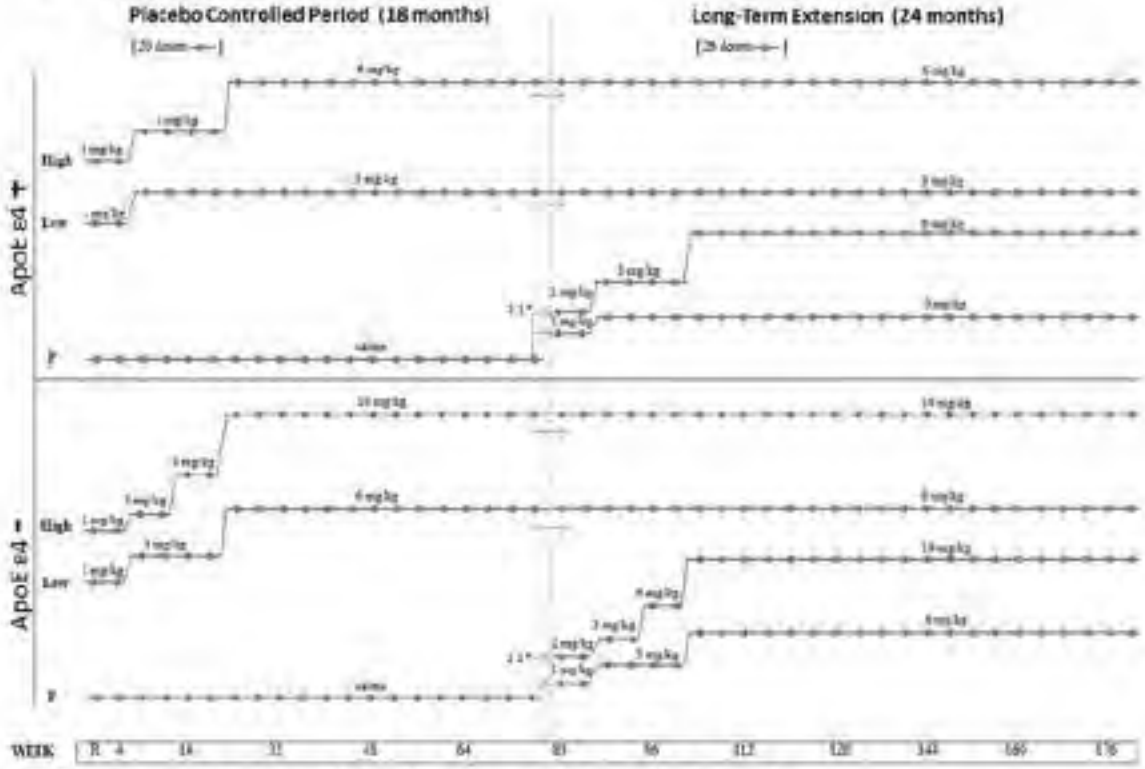
	Secondary objectives and endpoints are as follows: To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by • MMSE – Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13] – Change from baseline in ADAS-Cog 13 at Week 78 • Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] – Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological and additional assessments reported by the subject and informant/care partner. Endpoints for the LTE period of the study are listed in Section 6.4.2.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled period followed by an optional 24-month dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1350 subjects will be enrolled
Study Population:	This study will be conducted in subjects with early AD, including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD according to NIA-AA

	criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator, based on medical history and the Screening assessments. Subject enrollment will be monitored so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (6 mg/kg)** **Placebo** **ApoE ε4 non-carrier** **Low dose (6 mg/kg)** **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a 24-month dose-blind LTE study during which all subjects will receive aducanumab.
Duration of Treatment and Follow-up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8 week Screening Period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow-up). For subjects who enter the optional LTE, the total duration will be approximately 206 weeks or 47 months (up to an 8 week Screening Period, 76 weeks of placebo or aducanumab dosing, 4 weeks of follow-up, 100 weeks of dose-blind aducanumab dosing, and 18 weeks of follow-up).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD301

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; R = randomization date

*Subjects who are assigned to placebo during the placebo-controlled period and are continuing into the LTE will be randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status).

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule

Study Week	Screening (≤ 60 days before Day 1)[1]																											UV for a change in AD medication	FU/ ET[2]
				Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	50	52	56	60	64	68	72	76	78 (ET)		84
Study Day	V1	V2	V3	1	29 ± 3	57 ± 3	85 ±3	113 ±3	141 ±3	169 ±3	183 ±3	197 ±3	225 ±3	253 ±3	281 ±3	309 ±3	337 ±3	351 ±3	365 ±3	393 ±3	421 ±3	449 ±3	477 ±3	505 ±3	533 ±3	547 ±3		650 ±7
Initial Screening Consent[3]	X																												
Full Informed Consent[4]	X																									X[5]			
Eligibility Criteria	X			X																						X[5]			
Medical History	X																												
Alcohol/Drug Screen	X																												
HbA_{1c}	X																												
HIV/Hepatitis/ Coagulation	X																												
ApoE genotyping	X																												
[redacted]																													
Height	X																												
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			X
Serum Pregnancy Test[7]	X																												
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			X
Physical Examination	X						X			X							X							X		X		X

Study Week	Screening (≤ 60 days before Day 1)[1]			Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	50	52	56	60	64	68	72	76	78 (EOT)	UV for a change in AD medication	FU/ET[2]
Study Day	V1	V2	V3	1	29 ± 5	57 ± 3	85 ±3	113 ±3	141 ±3	169 ±3	183 ±3	197 ±3	225 ±3	253 ±3	281 ±3	309 ±3	337 ±3	351 ±3	365 ±3	393 ±3	421 ±3	449 ±3	477 ±3	505 ±3	533 ±3	547 ±3		650 ±7
Neurological Examination	X						X			X							X							X		X		X
12-lead paper ECG	X									X							X							X		X		X
Vital Signs[3]	X			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							X		X		X
Randomization				X																								
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X			
Anti-aducanumab Ab[9]				X						X							X							X		X		X
Aducanumab Concentration[10]				X [11]	X [11]		X [11]	X	X [11]	X [12]		X [11]	X						X [11]	X					X			
[redacted]																												
[redacted]																												
Amyloid PET[13]			X								X															X		
RBANS	X																											
CDR	X										X							X								X	X	X
MMSE	X										X							X								X	X	X
ADCS-ADL-MCI		X [11]									X							X								X	X	X
ADAS-Cog 13		X [11]									X							X								X	X	X

Study Week	Screening (≤ 60 days before Day 1)[1]			Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	50	52	56	60	64	68	72	76	78 (EOT)	UV for a change in AD medication	FU/ ET[2]
Study Day	V1	V2	V3	1	29 ±5	57±7	85 ±3	113 ±3	141 ±3	169 ±3	183 ±3	197 ±3	225 ±3	253 ±3	281 ±3	309 ±3	337 ±3	351 ±3	365 ±3	393 ±3	421 ±3	449 ±3	477 ±3	505 ±3	533 ±3	547 ±3		650 ±7
NPI-10		X [1]									X							X								X		X
EQ-5D (SR)		X [1a]									X							X								X		X
EQ-5D (IR-S)		X [1a]									X							X								X		X
[redacted]																												
mPDQ-20		X [1a]									X							X								X		X
[redacted]																												
C-SSRS				X															X							X		X
AE Reporting				Monitor and record continuously throughout the study																								
Concomitant therapy and procedures				Monitor and record continuously throughout the study																								
SAE reporting				Monitor and record continuously throughout the study																								

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E; CDR = Clinical Dementia Rating scale[redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) =EQ-5D, subject self-reported; EOT = End of Treatment; ET = Early Termination; FU = Follow-up; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory; PET = positron emission tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; [redacted]; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2 and Screening Visit 3

[1] Examinations required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 2) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2.

[2] Visit to be completed in cases of early termination or for subjects who do not enroll in the long-term extension.
[3] Subjects may sign this optional form for an initial screening which allows administration of the RBANS, CDR and MMSE only.
[4] All subjects must sign this informed consent, including subjects who have signed the initial screening consent once they have met the RBANS, CDR and MMSE eligibility criteria.
[5] Only for subjects entering the long-term extension.
[redacted].
[7] Required for women of child bearing potential only (See Section 15.5).
[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.
[9] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study drug infusion
[10] Blood sampling for aducanumab concentration will be performed prior to infusion.
[11] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush
[redacted]
[13] May be collected at any point in time during Screening after eligibility at V1 is confirmed but if collected on the same day as an MRI, it should be collected after the MRI is performed.
[14] Screening PET is required for all subjects, PET at Week 26 and Week 78 will only be conducted in selected sites for subjects who are participating in the PET cohort.
[15] Must be performed within 14 days of V1, but not on the same day as the screening RBANS, CDR or MMSE.
[16] May be performed at any point during screening after the subject has met eligibility criteria on the RBANS, CDR and MMSE.

Table 2: Brain MRI, Aria Management, and Follow-up Phone Call Schedule During the Placebo-Controlled Period

Study Week	Screening[1] (≤ 60 days before Day 1)			Placebo-Controlled Period												Unscheduled Visit for ARIA[2]	FU[3] /ET
				Day 1	2	6	10	14	18	22	26	30	42	54	78		94
Study Day	V1	V2	V3	1	15±3	43±3	71±3	99±3	113±3	155±3	183±3	211±3	295±3	379±3	547±3		826 ±7
Follow-up Phone Call					X	X	X	X	X	X	X	X					
Brain MRI[4]		X						X		X		X	X	X	X	X	X
Aducanumab Concentration[5]										X		X		X			X
MOCA				X												X	

ARIA = amyloid related imaging abnormalities; ET = Early Termination; FU = follow-up; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3

[1] Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1.

[2] Details on ARIA management are in Section 7.2.

[3] Assessments to be completed as part of an ET Visit or for subjects not enrolling into the long-term extension.

[4] Arterial spin labeling MRI and task free functional MRI will be performed only at a subset of sites.

[5] One sample will be collected within 2 days after the MRI visit. Exact collection date and time will be captured for all pharmacokinetic blood samples on a specified case report form.

Table 3: Long-Term Extension Schedule

Study Week	80	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156	160	164	168	172	176	180	182 (EoT)	UV for a change in AD medication	FU ET 198
Study Day	561 ±5	589 ±5	617 ±5	645 ±5	673 ±5	701 ±5	729 ±5	757 ±5	785 ±5	813 ±5	841 ±5	869 ±5	897 ±5	925 ±5	953 ±5	981 ±5	1009 ±5	1037 ±5	1065 ±5	1093 ±5	1121 ±5	1149 ±5	1177 ±5	1205 ±5	1233 ±5	1261 ±5	1275 ±5		1387 ±7
Randomization	X[3]																												
Body Weight	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	X	X		X
Urine Pregnancy Test[2]	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	X	X		X
Physical Examination				X			X						X						X						X		X		X
Neurological Examination				X			X						X						X						X		X		X
12-lead Paper ECG							X						X						X						X				X
Vital Signs	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	X	X		
Hematology, Blood Chemistry and Urinalysis							X						X						X						X				X
Anti-aducanumab Ab[3]	X						X						X						X						X		X		X
[redacted]																													
Aducanumab Concentration[4]	X						X						X						X						X		X		X
Study Drug Infusion	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	X			
[redacted]																													
Amyloid PET[5]														X													X		
CDR[6]							X							X							X						X	X	X
MMSE[6]							X							X							X						X	X	X
ADAS-Cog 13[6]							X							X							X						X	X	X
ADCS-ADL-MCI[6]							X							X							X						X	X	X
NPI-10[6]							X							X							X						X		X

Study Week																											UV for a change in AD medication	FU/ET
	B0	B4	B8	92	96	100	104	108	112	116	120	124	129	132	136	140	144	148	152	154	160	164	168	172	176	180	182 (EOT)		198
Study Day	501 ±5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	953 ± 5	981 ± 5	1009 ±5	1037 ±5	1065 ±5	1093 ±5	1121 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ±5	1275 ± 5		1387 ±7
EQ-5D (IR-S)[1]							X							X							X						X		X
[redacted]																													
C-SSRS														X													X		X
AE Reporting	Monitor and record continuously throughout the study																												
Concomitant Therapy and procedures	Monitor and record continuously throughout the study																												
SAE Reporting	Monitor and record continuously throughout the study																												

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR = Clinical Dementia Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; ET = Early Termination; FU = Follow-up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who were in the placebo group during the placebo-controlled period will be randomized to aducanumab high and low dose (1:1 ratio).
[2] Required for women of childbearing potential only (Section 15.5).
[redacted]
[5] Only for subjects who participate in the PET cohort.
[redacted]

Table 4: Brain MRI, Aria Management, and Follow-Up Phone Call Schedule During the Long-Term Extension

	Long-Term Extension												Unscheduled visit for ARIA[1]	FU/ET
Study Week	82	86	90	94	98	102	106	110	122	134	158	182		198
Study Day	575±5	603±5	631±3	659±5	687±5	715±5	743±5	771±5	855±5	937±5	1107±5	1247±5		1387 ±7
Follow-up Phone Call	X	X	X	X	X	X	X	X						
Brain MRI[2]				X		X		X	X	X	X	X	X	X
MOCA													X	

ARIA = amyloid related imaging abnormalities; ET = Early Termination; FU = follow-up; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging

[1] Details on ARIA management are in Section 7.2.

[2] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites.

4.3. Additional Information

4.3.1. Site Personnel

For each subject, the Principal Investigator (PI) of the site will designate the following investigational site personnel:

- Two independent rating health care professionals (the PI cannot serve as a rating health care professional); one who is responsible for administering the Clinical Dementia Rating (CDR) and a second who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI), and the Mini-Mental State Examination (MMSE)

  The rating health care professionals must not be involved with any other aspect of subject care and management and must remain blinded to adverse events (AEs), concomitant therapy, laboratory data, imaging data or any other data that have the potential of revealing the treatment assignment.

  To ensure consistency across sites, rating health care professionals must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites should attempt to maintain the same rating health care professional throughout the study for specific assessments. Each subject should have the same rating health care professional perform the subject's specific rating assessment throughout the study. If a rating health care professional has to be replaced, the new rating health care professional must undergo the study-specific qualification process prior to administration of the assessment.

- A treating health care professional (the PI may serve as a treating health care professional) who is responsible for the following:
  - Administration of Montreal Cognitive Assessment (MOCA) at Day 1 and during management of ARIA cases.
  - Management of the routine neurological care of the subject.
  - Assessment (including assignment of causality) and treatment of AEs.
  - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.

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

The roles of independent raters and treating health care professional are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject

level. If a rater has administered the CDR to a subject they may not administer the other neurocognitive assessments to that subject 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.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy. Supporting this hypothesis are results from solanezumab and crenezumab studies that have shown a trend in slowing cognitive decline in mild but not moderate AD [Doody 2014; Fagan 2014].

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of

calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne 2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience with Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine immunoglobulin (Ig) G2a chimeric version of the antibody (ch12F6A) with similar properties significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A ≥70 mg/ kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is a randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 6 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab.

  The primary objective of the study is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR- sum of boxes (SB) and MMSE.

  To date, ARIA has been the most frequent AE reported in the study. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. Incidence of ARIA has been observed to be both dose and Apolipoprotein E4 (ApoE ε4) carriage-dependent, especially at the highest doses (refer to the IB for details on events of ARIA).

  Protocol-defined interim analyses have demonstrated a dose- and time-dependent reduction of brain amyloid burden after 6 months of dosing (Week 26), with statistical significance achieved in the 3, 6, and 10 mg/kg groups compared with placebo, and after 1 year of dosing (Week 54), with statistical significance achieved in the 3 and 10 mg/kg groups compared with placebo (6 mg/kg data not yet

available). The results demonstrate target engagement (amyloid plaques) and a pharmacodynamic effect (dose-dependent amyloid reduction). In addition results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE, suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. At Week 54, adjusted mean change (increase) from baseline in CDR-SB score was smaller for both the 3 and 10 mg/kg groups compared with placebo, with statistical significance achieved in the 10 mg/kg group (6 mg/kg data not yet available). At Week 52, adjusted mean changes (decreases) in MMSE score from baseline were statistically significant in the 3 and 10 mg/kg groups (Week 54 6 mg/kg data not yet available). Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment was statistically significant at doses of 3, 6 and 10 mg/kg after 6 months of dosing and at 3 and 10 mg/kg after 12 months of dosing (6 mg/kg data not yet available). The effect on mean decrease from baseline in CDR-SB after 12 months of dosing was observed at both 3 and 10 mg/kg (6 mg/kg data not yet available), with statistical significance achieved at 10 mg/kg. The effect on mean decrease from baseline in MMSE score was statistically significant at 3 and 10 mg/kg. These data indicate that 3 mg/kg could be considered an acceptable dose for Phase 3

studies; however, given the dose-dependent nature of these observations, the use of higher doses (6 and 10 mg/kg) could offer greater benefit at acceptable risk.

ARIA has been identified as an event that may occur with anti-amyloid targeting drug candidates and is considered an event of special interest in the aducanumab program. To date, the incidence of ARIA has been observed to be both dose and ApoE ε4 carriage dependent, especially at the highest doses. In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Slow titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012] which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown to date, the doses to be tested using a titration regimen are 3 and 6 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6 and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows (Table 5 and Figure 1):

ApoE ε4 carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter
- High dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter
- Placebo

  Saline infusion

ApoE ε4 non-carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 5: Dosing Scheme for Aducanumab by Regimen

Dose (Month)		1	2	3	4	5	6	7 to 20
Regimen		Dose (mg/kg)						
ApoE ε4 (+)	Low Dose	1	1	3	3	3	3	3
	High Dose	1	1	3	3	3	3	6
	Placebo	saline						
ApoE ε4 (-)	Low Dose	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If any of the high doses proposed (10 mg/kg in ApoE ε4 non-carriers and 6 mg/kg in ApoE ε4 carriers) is deemed not acceptable, enrollment for the high dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high dose regimens will be revised as described in Section 16.

- Benefit of titration

  A titration schedule has been implemented in this Phase 3 study and in the ongoing multiple-dose Study 221AD103. If, based upon review of the data from

Study 221AD103, titration is not deemed beneficial, it will be eliminated, and subsequently enrolled subjects who are ApoE ε4 carriers will receive a fixed dose of 3 or 6 mg/kg and non-carriers will receive 6 or 10 mg/kg.

5.3.3. Long-Term Extension

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE will continue to receive the same dose of aducanumab that they were on at the end of the placebo-controlled period. Subjects who receive placebo during the placebo-controlled period and who enter the LTE period will be assigned to 1 of 2 treatment groups, based upon their ApoE ε4 carrier status, in a 1:1 ratio (aducanumab low dose: aducanumab high dose). Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 5 and Figure 1).

Any modifications to the dosing scheme (i.e. termination of high dose groups and replacement of titration with fixed dosing, as described in Section 5.3.2) will also be implemented in the LTE.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy 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 subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]

Efficacy

- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory (NPI-10).
- To assess the effect of aducanumab on patient health status, measured by EuroQol health status measures (EQ-5D [informant-rated and patient self-reported]).
- [redacted]
- To assess the effect of aducanumab on patient self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- [redacted]
- To assess the correlation between primary endpoints and key biomarker endpoints.

Pharmacokinetics

- To explore the potential relationships between PK or exposure and response (e.g., clinical and biomarker endpoints) including covariate analysis.
- To explore the potential effect of co-medications on the PK of aducanumab using population PK.

6.3.2. Tertiary Endpoints

Safety and Tolerability:

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers:

- Change from baseline in amyloid PET signal at Week 26 (in a subset of subjects).

- Change from baseline in amyloid PET signal at Week 78 (in a subset of subjects).
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Efficacy

- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject-self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- [redacted]
- Change from baseline in mPDQ-20 at Week 78.
- [redacted]
- Correlation between clinical and biomarker endpoints over time.

Pharmacokinetics

- Serum concentrations of aducanumab, population PK parameters of aducanumab including but not limited to clearance and volumes of central and peripheral compartments.

6.4. Long Term Extension Objectives and Endpoints

6.4.1. Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.
- [redacted]

6.4.2. Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of subjects).
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.
  - [redacted]
  - [redacted]

7. STUDY DESIGN

7.1. Study Overview

Study 221AD301 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional 24-month dose-blind LTE study. Approximately 1350 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose : aducanumab high dose : placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Subject enrollment will be monitored so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a 24-month long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (a total of 26 doses).

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up period of approximately 18 weeks after the final dose. The total duration of study participation for each subject participating in the placebo-controlled period and the LTE will be up to approximately 206 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week follow-up period, a 100-week aducanumab dose-blind treatment period, and a safety follow-up period of approximately 18 weeks after the final dose. The follow-up period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 6 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 5 and Figure 1. Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will receive the

same dose of aducanumab that they received at the end of the placebo-controlled period (up to 6 mg/kg and 10 mg/kg in ApoE ε4 carriers and non-carriers, respectively). Subjects who received placebo during the placebo-controlled period and who enter the LTE period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose: aducanumab high dose); aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented to subjects who develop ARIA. See Section 7.2.1.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE, investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the Principal Investigator within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the Principal Investigator; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Disposition of ARIA-E cases is presented in Table 6 , ARIA-H (microhemorrhage) in Table 7, and ARIA-H (superficial siderosis) in Table 8.

7.2.1.1. Disposition of ARIA-E cases

Table 6: Disposition of ARIA-E Cases

Clinical Symptom Severity	ARIA-E Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing; once ARIA-E resolves the subject may resume dosing at next lower dose	Suspend dosing; once ARIA-E resolves, the subject may resume dosing at next lower dose
Mild	Suspend dosing; once ARIA-E and clinical symptoms resolve, the subject may resume dosing at next lower dose		
Moderate			
Severe or Serious	Discontinue Dosing		

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current

dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.

- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the subjects remain asymptomatic, the subjects may resume treatment but at the next lower dose level. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.
- Subjects who develop **mild, moderate, or severe ARIA-E, as per central MRI reading, accompanied by mild or moderate clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the clinical symptoms have resolved, the subject may resume treatment but at the next lower dose level. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.
- Subjects who develop **mild, moderate, or severe ARIA-E, as per central MRI reading, accompanied by severe or serious clinical symptoms** at any time during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per centrally read MRI.

7.2.1.2. Disposition of ARIA-H cases

Table 7: Disposition of ARIA-H (microhemorrhage) Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">New Incident Microhemorrhages Within 12 Weeks</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 dose and schedule</td><td>Suspend dosing; once ARIA-H is stable the subject may resume dosing at next lower dose</td><td rowspan="4">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="2">Suspend dosing; once ARIA-H stabilizes and clinical symptoms resolve the subject may resume dosing at next lower dose</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe or Serious</td><td colspan="2">Discontinue dosing</td></tr>
</table>

7.2.1.2.1. Asymptomatic ARIA-H (microhemorrhage):

- Subjects who develop a **≥ 1 and ≤ 4 new incident microhemorrhage(s)** within 12 weeks at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥ 5 and ≤ 9 new incident microhemorrhages** occurring within 12 weeks at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the microhemorrhage is confirmed as stable per the centrally read MRI. A microhemorrhage is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the next lower dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.

Table 8: Disposition of ARIA-H (superficial siderosis) Cases

Clinical Symptom Severity	New Incident Areas of Superficial Siderosis Within 12 Weeks		
	1	2	> 2
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing; once ARIA-H is stable the subject may resume dosing at next lower dose	Discontinue dosing
Mild	Suspend dosing; once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at next lower dose		
Moderate			
Severe or Serious	Discontinue dosing		

7.2.1.2.2. Asymptomatic ARIA-H (superficial siderosis):

- Subjects who develop a **single incident focal area of hemosiderosis (also referred to as superficial siderosis)** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the superficial siderosis is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis)** occurring within 12 weeks at any time during the study will temporarily suspend treatment but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later. Once the superficial siderosis is deemed stable, the subjects may resume treatment at the next lower dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.

7.2.1.2.3. Symptomatic ARIA-H (microhemorrhage(s) or superficial siderosis):

- Subjects who develop **≤ 9 new incident microhemorrhages or ≤ 2 new focal area of superficial siderosis** within 12 weeks and mild or moderate clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H (microhemorrhage(s)) is confirmed as stable per the centrally read MRI. Microhemorrhage(s) are considered stable if they are unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks later. Once the ARIA-H is deemed stable and the clinical symptoms have resolved, the subjects may resume treatment but at the next lower dose level. Only subjects who have not missed more than 4 consecutive doses

will be allowed to resume treatment. Guidance for dose reduction is presented in Section 7.2.1.4.

- Subjects who experience **severe clinical symptoms associated with ARIA-H (microhemorrhage(s) or superficial siderosis)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H microhemorrhage(s) or superficial siderosis is confirmed as stable per centrally read MRI.

7.2.1.2.4. ARIA-H (microhemorrhage(s) or superficial siderosis) requiring permanent discontinuation:

- Subjects who develop **≥ 10 new incident microhemorrhages or > 2 new focal areas of superficial siderosis** within 12 weeks regardless of clinical severity will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 2 weeks until the ARIA-H microhemorrhage(s) or superficial siderosis is confirmed as stable per central read MRI.

7.2.1.3. Disposition of Coincident ARIA-H and ARIA-E Cases:

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow ARIA-E guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H be deemed stable, and the subject must be asymptomatic.

7.2.1.4. Dose Reduction for Subjects Developing ARIA:

Dose reduction guidance is presented in the Table 9 below. If further dose reduction is needed, the next lower dose level will be used. If more than 2 dose reductions are needed, Sponsor approval will be required prior to treatment continuation.

Table 9: Dose Reduction for Subjects Experiencing ARIA, Who Resume Treatment After Suspension

Current Dose	Resuming Dose
10 mg/kg	6 mg/kg
6 mg/kg	3 mg/kg
3 mg/kg	1 mg/kg
1 mg/kg	Placebo
Placebo	Placebo

ARIA = amyloid related imaging abnormality
Current dose refers to the dose that the subject was receiving before ARIA was detected

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE and will receive the lowest dose that they

have tolerated during the placebo-controlled period. A subject who is switched to placebo but remains in the study may be titrated to aducanumab 1 mg/kg during the LTE.

7.2.2. 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 Directions for Handling and Administration [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 subject should be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of screening, treatment, and follow-up.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety follow-up period of 18 weeks after the final dose.

Subjects will have approximately 33 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety follow-up contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days).
- 20 outpatient dosing visits.
- 8 telephone safety follow-up contacts approximately 2 weeks after each of the first 8 doses.
- 3 visits for clinical assessments.
- [redacted]
- 2 visits for amyloid PET scan (in a subset of subjects).
- 6 visits for brain MRI.
- 1 follow-up safety visit at Week 94 (only for subjects not entering the LTE).

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE. Subjects who enter the LTE will have approximately 40 additional planned clinic visits, and up to 8 telephone safety follow-up contacts, as follows:

- 26 outpatient dosing visits.

- 8 telephone safety follow-up contacts approximately 2 weeks after each of the first 8 doses.
- 4 visits for clinical assessments.
- [redacted]
- 2 visit for amyloid PET scan (in a subset of subjects).
- 7 visits for brain MRI.
- 1 follow-up safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits as per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, and the Repeatable Battery for Assessment of Neuropsychological Status [RBANS]). This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE and RBANS) must be performed at Screening Visit 1. The ADAS-Cog 13, ADCS-ADL-MCI and NPI-10 will be performed at Screening Visit 2 within 14 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE and RBANS. All other cognitive assessments [redacted] may be performed at any time during screening after eligibility is confirmed during Screening Visit 1. The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. Subjects who fail screening will be permitted to be rescreened once at the Sponsor's discretion. Subjects who fail screening due to PET, MMSE, CDR, hepatitis B or C results, or abnormal MRI findings will not be allowed to re-screen.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE and will receive study treatment every 4 weeks for an additional 100

weeks (26 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE are to return to the study site for a follow-up visit at Week 94 (18 weeks after the last dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A follow-up visit will occur at Week 198 (18 weeks after the last LTE dose). The final study visit for subjects participating in the LTE will be Week 198.

7.4. Study Stopping Rules

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

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

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

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of screening) is permissible for subjects not participating in the PET cohort. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR-Global Score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment.
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and screening assessments.
8. Must consent to apolipoprotein E (Apo E) genotyping.
9. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. Exclusion Criteria

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

Medical History

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, lewy body dementia, fronto-temporal dementia, head trauma)..
2. Clinically significant psychiatric illness (e.g., uncontrolled major depression, schizophrenia, bipolar affective disorder) within 6 months prior to Screening.
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >1 cm in diameter on T2* sequence) unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as > 1.5 cm in diameter).
   - >1 lacunar infarct (defined as ≤ 1.5 cm in diameter).
   - Superficial siderosis.
   - 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 subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Poorly controlled diabetes mellitus as defined (according to the National Glycohemoglobin Standardization Program) by a glycosylated hemoglobin (HbA_{1c}) value of ≥ 7%.

7. 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.
8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings > 165/100 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 subject to be eligible for the study), or persistent SBP/DBP readings > 180/100 mmHg 3 months prior to randomization (Day 1) that in the opinion of the Investigator are indicative of chronic uncontrolled hypertension.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma.
    - Subjects with prostate cancer in situ.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or positive test result for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody IgG, and positive HBcAb) are eligible to participate in the study (US Centers for Disease Control and Prevention's interpretation of the hepatitis B serology panel).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).

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

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 or use of AD 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 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any other passive immunotherapy study targeting Aβ within 48 weeks prior to Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 26 weeks prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures

29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (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, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 24 weeks prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

33. For subjects who consent to lumbar puncture (LP), any contraindications to having a LP (e.g., platelet count <100,000/μL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during screening must be resolved prior to randomization. Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR, hepatitis B or C, or abnormal MRI findings.
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥ 1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension

To be eligible to participate in the LTE, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses. Subjects who do not meet these criteria can enter the LTE only with Sponsor's approval.
2. MMSE score > 15 at the Week 78 Visit.
3. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
4. Female subjects of childbearing potential and male subjects must practice effective contraception during the study and for 24 weeks after their last dose of study treatment.
5. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
6. Must have the ability to comply with procedures for protocol-related tests.
7. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the

subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long Term Extension

Subjects will be excluded from entering the LTE if at Week 78 they have:

any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) to determine study eligibility under a separate initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study.

The following tests should be repeated prior to dosing if they were performed > 60 days prior to Day 1: confirmation of eligibility criteria, abbreviated medical history, physical examination, ECG, hematology, blood chemistry, serum pregnancy test, and all neurocognitive assessments. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier), so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating health care professionals should remain blinded to treatment assignment as well as subject care management and only have access to the information necessary to carry out their responsibilities as detailed in

Section 4.3.1. As a placebo match is not provided for the study, unblinded pharmacy staff are required to manage all aspects of study drug receipt, dispensing and preparation. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

For the LTE, the dose information must remain restricted. The rating and treating health care professional should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by severe or serious clinical symptoms.
  - Symptomatic ARIA-H (microhemorrhages or superficial siderosis) with severe or serious clinical symptoms.
  - ARIA-H with ≥ 10 microhemorrhages and/or ≥ 2 focal areas of superficial siderosis.

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria.
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

Subjects who discontinue treatment should remain in the study and continue protocol-required tests and assessments until the end of the study or until the subjects withdraw consent.

10.2. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

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

Subjects who are withdrawn from the study after receiving ≥1 doses of study treatment should complete the Early Termination (ET) Visit after the reason for withdrawal is identified. Subjects should return to the site as soon as possible to complete assessments as outlined in the Week 94 (Follow-up [FU]/ET) Visit if discontinuing during the double-blind period of the study or as outlined in the Week 198 (FU/ET) Visit if discontinuing from the LTE (see Section 4 for details).

11. STUDY TREATMENT USE

11.1. Regimen

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

Please see Section 4.2 (Schedule of Events) for the study drug infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

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

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.2 (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.

11.3. Precautions

Not applicable.

11.4. Compliance

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

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and the FU/ET Visit (Week 94 or Week 198).

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

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given < 10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤ 325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids and certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended, with the exception of medications used to treat AEs, which would not result in automatic withdrawal. Biogen may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures) performed between the time the subject is enrolled in the study and the FU/ET Visit, unless the subjects is being followed for study-related toxicity.

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

11.6. 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.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

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

Aducanumab is a recombinant human antibody expressed in a Chinese hamster ovary cell line [redacted], 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. [redacted] Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing aducanumab 50 mg/mL, [redacted]. Aducanumab is manufactured in accordance with Good Manufacturing Practices.

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

12.1.1. Aducanumab 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 Biogen.

12.1.2. Aducanumab Storage

Study treatment must be stored in a secure location. Aducanumab is to be stored at 2° 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 2 hours, then it should be kept at 2° to 8°C 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.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (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 personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab 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 (subject-by-subject 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 Biogen. A written explanation must be provided for any discrepancies.

12.2. 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.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

For details on PET imaging ligands, refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

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

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

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

13.2. Pharmacokinetic Assessments

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

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the pharmacodynamic properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in this part of the study.

- [redacted]
- [redacted]
- [redacted]
- [redacted]

13.4. Additional Assessments

[redacted]

13.4.2. ApoE genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

[redacted]

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- [redacted]
- mPDQ-20
- [redacted]

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

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

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

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

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale.

14.2. Laboratory Safety Assessments

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

- Hematology: complete blood count with differential and 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, 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, virology (including HIV if dictated by local law), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier anti-drug antibody (ADA) approach will be used (i.e., screening assay, confirmatory assay,

and titration assay). Confirmed antidrug antibody-positive samples will be tested for the presence of anti-aducanumab neutralizing antibodies using a validated assay.

15. 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 subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 laboratory finding), 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 laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the investigator considers to be clinically significant.

15.1.2. 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 subject 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.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject 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.)

15.1.3. 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 subject is hospitalized. The study site must document all of 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 subject's consent to participate 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 subject's consent to participate 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 subject 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 15.1.2 is met.

15.2. Safety Classifications

15.2.1. 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 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

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.

15.2.3. Severity of Events

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

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the FU/ET visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H 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.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to [redacted].

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the FU/ET visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. Follow-up information regarding an SAE also must be reported with 24 hours.

Events occurring after the FU/ET visit should be reported to Biogen only if the investigator considers the SAE related to study treatment.

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

15.3.4. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the FU/ET Visit must be reported to [redacted]) within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to [redacted] regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject 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 Guide for country-specific [redacted] fax numbers or email [redacted]

15.3.4.1. 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. The Investigator should make every effort to obtain and send death certificates and autopsy reports to [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 24 weeks after their last dose of study drug. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to [redacted] within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to [redacted]

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in 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 to [redacted] within 24 hours of the site becoming aware of the overdose. An overdose must be reported to [redacted] 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 to [redacted]). All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. 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 [redacted] 24-hour emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

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

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the [redacted] 24-hour emergency medical support number at [redacted].

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

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.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of the study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system.
  - Barrier methods of contraception with use of a spermicide: condom or occlusive cap (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.

  - Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at follow-up.
  - Use of condoms with spermicide.
- For males and females of childbearing potential:
  True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, 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, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, 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 and follow up on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor ([redacted]) is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects 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 each aducanumab regimen and placebo. All statistical tests will be 2-sided.

16.2.2.2. Dose Regimens to be Evaluated

The following dose regimens of aducanumab as compared with placebo will be evaluated

- Aducanumab high-dose regimen (6 mg/kg in ApoE ε4 carriers and 10 mg/kg in ApoE ε4 non carriers).
- Aducanumab 6 mg/kg dose regimen (6 mg/kg in ApoE ε4 carriers and ApoE ε4 non-carriers).
- Aducanumab low-dose regimen (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the proposed maximum dose (10mg/kg in ApoE ε4 non-carriers or 6 mg/kg in ApoE ε4 carriers) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose regimen and aducanumab low dose regimen will be modified as shown in Table 10. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of

Type I error rate is thus maintained without a statistical adjustment for such adaptations[Chow and Chang 2011].

Table 10: Dose Group Pooling Strategy in the Event of Treatment Group Termination

Treatment group(s) Terminated	Definitions of Revised Pooled Treatment Groups for Comparison
ApoE ε4 carrier high-dose group(6 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 6 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group(6 mg/kg) AND ApoE ε4 non-carrier high-dose group(10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose regimen versus placebo, aducanumab 6 mg/kg regimen versus placebo, and aducanumab low-dose regimen versus placebo. In the event of a dosing modification (see Table 10), the first comparison is the aducanumab high-dose regimen versus placebo and the second comparison is the aducanumab low-dose regimen versus placebo. If the first comparison is statistically significant ($p \leq 0.05$), then the second comparison will also be made at the 0.05 α level. If the second comparison is statistically significant ($p \leq 0.05$), then the third comparison will also be made at the 0.05 α level. However, all comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for one, two or all three comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1, 2 or all 3 comparisons, respectively.

Due to a current lack of scientific consensus in the AD field on which biomarker(s) might be most appropriate, the selection of the biomarkers and methodology for control of Type I error will be pre-specified in the statistical analysis plan (SAP). Otherwise, there will be no multiple comparison adjustments for the tertiary endpoints.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population with a baseline and at least one post-baseline CDR-SB score. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change from Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population with a baseline and at least one post-baseline MMSE value. A MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction and baseline ApoE ε4 status

16.2.2.5.2. Change from Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADAS-Cog 13 score. A MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction; baseline MMSE and baseline ApoE ε4 status.

16.2.2.5.3. Change from Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADCS-ADL-MCI score. A MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction; baseline MMSE and baseline ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, a MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE and baseline ApoE ε4 status.

Otherwise, an analysis of covariance or its non-parametric equivalent may be used to analyze these exploratory endpoints.

16.2.2.6.2. Long-Term Extension

The additional endpoints for the LTE are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the

placebo-controlled period using the placebo-controlled period baseline. Details of the analyses will be pre-specified in the SAP.

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The population PK characteristics of aducanumab will be determined by nonlinear mixed effects approach. Covariates that might influence the disposition of aducanumab (e.g., body weight, age, sex, immunogenicity, ApoE ε4 status) will be evaluated and the potential exposure-response relationships will be explored.

16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of study treatment (including placebo and aducanumab).

16.4.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.4.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent 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 study treatment for the placebo-controlled period and over the 24-month LTE. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.4.2.2. 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. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized

based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.4.2.3. Vital Signs

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

16.4.2.4. ECG

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

16.4.2.5. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale data will be summarized by treatment group.

16.5. Immunogenicity Data

16.5.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.5.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.6. Interim Analyses

16.6.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.6.2. Interim Superiority Analysis

An interim analysis for superiority will be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The Lan-Demets method with O'Brien-Fleming stopping boundary for efficacy will be used. In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.7. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103 which included 1 year data from 1, 3 and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group will have approximately 90% power to detect a true mean difference of 0.5 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, a SD of 1.92 and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflects a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

The sample size may be reassessed in a blinded manner approximately 3 months before enrollment is complete if at least 15% of the data are available on the primary endpoint. At this interim time-point, the SD for the primary endpoint will be estimated based on the blinded data. The sample size may be increased if the SD is estimated to be more than approximately 2.07. In addition, the sample size could be increased using external clinical trial results that become available after the start of the study.

17. ETHICAL REQUIREMENTS

Biogen, [redacted], and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

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

17.1. Declaration of Helsinki

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

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

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

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

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) as an initial screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed

prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

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

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The 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 (wet signature) and copies of the signed and dated ICFs.

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

17.4. Subject Data Protection

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

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. 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 subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights and a user manual

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by [redacted] and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen 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, [redacted], and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA 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.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen 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 Principal 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 collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen 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 per project-specific plans.

19.2. Study Committees

19.2.1. 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 at least 4 times a year to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The advisory committee will be blinded to subject treatment assignments during the study.

Members of the advisory committee will include external experts in AD medicine and statistics. Biogen will designate one of the participating Investigators to be the chairperson of the advisory committee.

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. 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 subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), 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.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB 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, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. 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 Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. 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 laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen 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.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study 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 subject enrollment, or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early 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)

Biogen MA Inc.
250 Binney Street
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United States

Biogen Idec Research Limited
Innovation House
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SL6 4AY
United Kingdom

PROTOCOL NUMBER: 221AD301/ NCT02477800

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000966-72**

DATE: 26 May 2016
Version 2.0
Final

Supersedes previous (Original) Version 1.0 dated 09 April 2015.

SPONSOR SIGNATURE

Protocol 221AD301 was approved by:

[redacted], PhD

13 June 2016
Date

[redacted]
Biogen MA Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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Chuo-ku
Tokyo
103-0027
Japan

For 24-hour emergency medical support contact

[redacted] at [redacted]

Please refer to the Study Reference Manual for complete contact information.

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

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab , produced in a different Chinese hamster ovary cell line
Aβ	β-amyloid
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibodies
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
[redacted]	[redacted]
AST	aspartate aminotransferase
CDR	Clinical Dementia Rating
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
[redacted]	[redacted]
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject
EQ-5D (SR)	EuroQol health status measure, subject self-reported

FU	Follow-up
GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCP	health care professional
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPI-10	Neuropsychiatric Inventory-10
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RNA	ribonucleic acid
SABR	Safety and Benefit-Risk
SAE	serious adverse event
SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

[redacted]	[redacted]
UV	unscheduled visit

3. SYNOPSIS

Protocol Number:	**221AD301**
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	2.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-Sum of Boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy 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 subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78. Secondary objectives and endpoints are as follows: • To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by • MMSE • Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13] • Change from baseline in ADAS-Cog 13 at Week 78

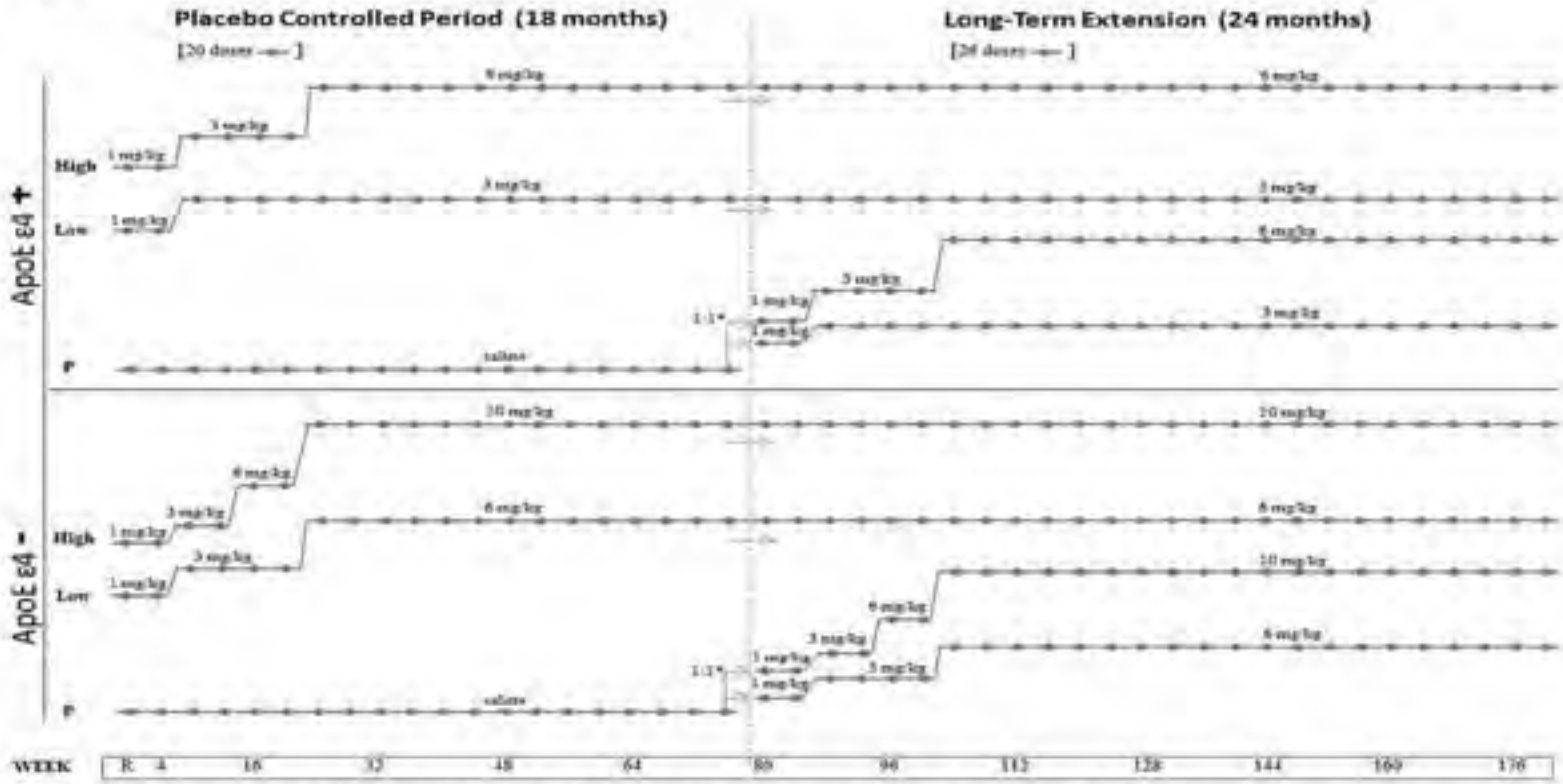
Protocol Number:	**221AD301**
	• Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] • Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension period of the study):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological and additional assessments reported by the subject and informant/care partner. Endpoints for the long-term extension (LTE) period of the study are listed in Section 6.4.2.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled, parallel-group period followed by an optional 24-month dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1350 subjects will be enrolled
Study Population:	This study will be conducted in subjects with early AD, including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD according to NIA-AA criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator, based on medical history and the Screening assessments. Subject enrollment will be monitored so that approximately 60% to 70% apolipoprotein E4 (ApoE ε4) carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (6 mg/kg)** **Placebo**

Protocol Number:	**221AD301**
	ApoE ε4 non-carrier **Low dose (6 mg/kg)** **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a 24-month dose-blind LTE study during which all subjects will receive aducanumab.
Duration of Treatment and Follow Up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow up [FU]). For subjects who enter the optional LTE period, the total duration will be approximately 206 weeks or 47 months (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, 4 weeks of FU, 100 weeks of dose-blind aducanumab dosing, and 18 weeks of FU).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD301

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; LTE = long-term extension; R = randomization date.
*Subjects who are assigned to placebo during the placebo-controlled period and are continuing into the LTE period will be randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status).

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule From Screening Through Week 48

Study Week	Screening (≤60 days before Day 1)[1]			Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Initial Screening Consent[2]	X																	
Full Informed Consent[3]	X																	
Eligibility Criteria	X	X	X	X[4]														
Demography	X																	
Medical History	X	X	X															
Alcohol/Drug Screen	X																	
HbA_{1c}	X																	
HIV[5]/Hepatitis/ Coagulation	X																	
ApoE Genotyping	X																	
[redacted]																		
Height	X																	
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Serum Pregnancy Test[7]	X																	
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X	

Study Week																		
	Screening (≤60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medication**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Physical Examination	X						X			X							X	
Neurological Examination	X						X			X							X	
12-lead Paper ECG	X									X							X	
Vital Signs[2]	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis	X			X						X							X	
Randomization				X														
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X	
Anti-Aducanumab Ab[9]				X						X							X	
Aducanumab Concentration[10]				X[11]	X[11]		X[11]	X	X[11]	X[11]		X[11]	X					
[redacted]																		
[redacted]																		
Amyloid PET[14]			X								X							
[redacted]																		
RBANS	X																	

Study Week																		
	Screening (≤60 days before Day 1)[1]			Wk 1, Day 1	4	8	12	16	20	24	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	V1	V2	V3	1	29 ± 3	57 ± 3	85 ± 3	113 ± 3	141 ± 3	169 ± 3	183 ± 3	197 ± 3	225 ± 3	253 ± 3	281 ± 3	309 ± 3	337 ± 3	
CDR	X										X							X
MMSE	X										X							X
ADCS-ADL-MCI		X[16]									X							X
ADAS-Cog 13		X[16]									X							X
NPI-10		X[17]									X							
EQ-5D (SR)		X[18]									X							
EQ-5D (IR-S)		X[18]									X							
[redacted]																		
mPDQ-20		X[18]									X							
[redacted]																		
C-SSRS				X							X							
AE Reporting				Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																	
SAE Reporting	Monitor and record continuously throughout the study																	

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E; CDR = Clinical Dementia Rating scale; CRO = contract research organization; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted]; ECG = electrocardiogram; [redacted]
EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; HbA_{1c} = glycosylated hemoglobin; HIV = human

immunodeficiency virus; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PET = positron emission tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; [redacted]; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; Wk = Week.

[1] Examinations required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 3) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and subject to Sponsor approval.

[2] Subjects may sign this optional form for an initial screening which allows administration of the RBANS, CDR and MMSE only.

[3] All subjects must sign this informed consent, including subjects who have signed the initial screening consent once they have met the RBANS, CDR, and MMSE eligibility criteria.

[4] All assessments, including the C-SSRS, must be completed before study treatment administration, except the post-dose sample to measure aducanumab concentration.

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

[redacted]

[7] Required for women of childbearing potential only (see Section 15.5).

[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[9] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study treatment infusion.

[10] Blood sampling for aducanumab concentration will be performed prior to infusion.

[11] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[redacted]

[13] May be collected at any point in time during Screening after eligibility at V1 is confirmed but if collected on the same day as an MRI, it should be collected after the MRI is performed.

[14] Screening amyloid PET is required for all subjects; amyloid PET at Week 26 and Week 78 will only be conducted in selected sites for subjects who are participating in the amyloid PET cohort.

[redacted]

[16] Must be performed within 20 days of V1, but not on the same day as the screening RBANS, CDR, or MMSE.

[17] The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1).

[18] May be performed at any point during screening after the subject has met eligibility criteria on the RBANS, CDR, and MMSE.

Table 2: Placebo-Controlled Period Schedule From Week 50 to End of Treatment or Follow-Up

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 weeks after final dose for subjects who terminate treatment early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Informed Consent									X[3]		
Eligibility Criteria									X[3]		
Body Weight		X	X	X	X	X	X	X			X
Urine Pregnancy Test[4]		X	X	X	X	X	X	X			X
Physical Examination							X		X		X
Neurological Examination							X		X		X
12-lead Paper ECG							X		X		X
Vital Signs[5]		X	X	X	X	X	X	X			X
Hematology, Blood Chemistry and Urinalysis							X		X		X
Study Treatment Infusion		X	X	X	X	X	X	X			
Anti-Aducanumab Ab[6]							X		X		X
Aducanumab Concentration[7]		X[8]	X					X			
[redacted]											
Amyloid PET[10]									X		
[redacted]											

Study Week											FU[1]
	50	52	56	60	64	68	72	76	78 (EOT)[2]	UV for a Change in AD Medication	94 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	351 ± 3	365 ± 3	393 ± 3	421 ± 3	449 ± 3	477 ± 3	505 ± 3	533 ± 3	547 ± 3		659 ± 7
CDR	X								X	X	X
MMSE	X								X	X	X
ADCS-ADL-MCI	X								X	X	X
ADAS-Cog 13	X								X	X	X
NPI-10	X								X		
EQ-5D (SR)	X								X		
EQ-5D (IR-S)	X								X		
[redacted]											
mPDQ-20	X								X		
[redacted]											
C-SSRS		X							X		
AE Reporting				Monitor and record continuously throughout the study							
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study										
SAE Reporting	Monitor and record continuously throughout the study										

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR = Clinical Dementia Rating scale; [redacted] C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted] EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; NPI-10 = Neuropsychiatric Inventory-10; PET = positron emission tomography; [redacted] SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study. Subjects who withdraw from study prematurely are to return to the site for the Week 78/EOT Visit; for such subjects, the site is to contact the Sponsor as soon as possible to confirm whether the efficacy assessments specified at the Week 78/EOT Visit are required.

[3] Only for subjects entering the long-term extension period.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[6] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study treatment infusion.

[7] Blood sampling for aducanumab concentration will be performed prior to infusion.

[8] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[9] [redacted]

[10] Amyloid PET at Week 78 will only be conducted in selected sites for subjects who are participating in the amyloid PET cohort.

[redacted]

Table 3: Brain MRI, ARIA Management, and Follow-up Phone Call Schedule During the Placebo-Controlled Period

Study Week	Screening (≤60 days before Day 1)[1]			Placebo-Controlled Period												Unscheduled Visit/ MRI for ARIA[4]	FU[2]
				1	2	6	10	14	18	22	26	30	42	54	78/ EOT[3]		94 (or 18 weeks after final dose for subjects who discontinue treatment early)
Study Day	V1	V2	V3	1	15 ± 3	43 ± 3	71 ± 3	99 ± 3	127 ± 3	155 ± 3	183 ± 3	211 ± 3	295 ± 3	379 ± 3	547 ± 3		659 ± 7
Follow-Up Phone Call[5]					X	X	X	X	X	X	X	X					
Brain MRI[6]		X						X		X		X	X	X	X	X	X
Aducanumab Concentration[7]										X		X		X			X
MOCA				X												X	
[redacted]																	

ARIA = amyloid related imaging abnormalities; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; [redacted]; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3.

[1] Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and subject to Sponsor approval.

[2] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[3] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study. Subjects who withdraw from study prematurely are to return to the site for the Week 78/EOT Visit; for such subjects, the site is to contact the Sponsor as soon as possible to confirm whether the efficacy assessments specified at the Week 78/EOT Visit are required.

[4] If a subject resumes treatment after ARIA, an MRI will be performed 2 weeks (±3 days) after the second administration of study treatment at the restarted dose or each increase in dose if an MRI is not scheduled during this period (see Section 7.2.2.5).

[5] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[6] Arterial spin labeling MRI and task free functional MRI will be performed only at a subset of sites.

[7] One sample will be collected within 2 days after the MRI visit. Exact collection date and time will be captured for all pharmacokinetic blood samples on a specified case report form. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed. For subjects who permanently discontinue treatment and continue in the study, the final aducanumab concentration sample will be collected at the subject's next visit.

Table 4: Long-Term Extension Schedule From Week 80 to Week 134

Study Week																	
	80	84	88	92	96	100	104	106	108	112	116	120	124	128	132	134	UV for a Change in AD Medication
Study Day	561 ± 5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	743 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	939 ± 5	
Randomization	X[1]																
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Urine Pregnancy Test[2]	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Physical Examination				X			X							X			
Neurological Examination				X			X							X			
12-lead Paper ECG							X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Hematology, Blood Chemistry and Urinalysis							X							X			
Anti-Aducanumab Ab[3]	X						X							X			
[redacted]																	
Aducanumab Concentration[5]	X						X							X			

Study Week																	
	80	**84**	**88**	**92**	**96**	**100**	**104**	**106**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**134**	**UV for a Change in AD Medication**
Study Day	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	**743 ± 5**	**757 ± 5**	**785 ± 5**	**813 ± 5**	**841 ± 5**	**869 ± 5**	**897 ± 5**	**925 ± 5**	**939 ± 5**	
Study Treatment Infusion	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
[redacted]																	
CDR							X	X							X	X	X
MMSE							X	X							X	X	X
ADAS-Cog 13							X	X							X	X	X
ADCS-ADL-MCI							X	X							X	X	X
NPI-10							X	X							X	X	
EQ-5D (IR-S)							X	X							X	X	
[redacted]																	
C-SSRS							X								X		
AE Reporting	Monitor and record continuously throughout the study																
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																
SAE Reporting	Monitor and record continuously throughout the study																

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR = Clinical Dementia

Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

1 Subjects who were in the placebo group during the placebo-controlled period will be randomized to aducanumab high and low dose (1:1 ratio).

2 Required for women of childbearing potential only (Section 15.5).

[redacted]

Table 5: Long-Term Extension Schedule From Week 136 to End of Treatment or Follow-Up

Study Week																FU[1]
	136	140	144	148	152	156	160	162	164	168	172	176	180	182 (EOT)[2]	UV for a Change in AD Medication	198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5		1387 ± 7
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Urine Pregnancy Test[3]	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Physical Examination					X							X		X		X
Neurological Examination					X							X		X		X
12-lead Paper ECG					X							X				X
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Hematology, Blood Chemistry and Urinalysis					X							X				X
Anti-aducanumab Ab[4]					X							X		X		X
[redacted]																
Aducanumab Concentration[4]					X							X		X		X

Study Week																**FU**[1]
	136	**140**	**144**	**148**	**152**	**156**	**160**	**162**	**164**	**168**	**172**	**176**	**180**	**182 (EOT)**[2]	**UV for a Change in AD Medication**	**198 (or 18 weeks after final dose for subjects who terminate treatment early)**
Study Day	**953 ± 5**	**981 ± 5**	**1009 ± 5**	**1037 ± 5**	**1065 ± 5**	**1093 ± 5**	**1121 ± 5**	**1135 ± 5**	**1149 ± 5**	**1177 ± 5**	**1205 ± 5**	**1233 ± 5**	**1261 ± 5**	**1275 ± 5**		**1387 ± 7**
Study Drug Infusion	X	X	X	X	X	X	X		X	X	X	X	X			
[redacted]																
Amyloid PET[6]														X		
[redacted]																
CDR							X	X						X	X	X
MMSE							X	X						X	X	X
ADAS-Cog 13							X	X						X	X	X
ADCS-ADL-MCI							X	X						X	X	X
NPI-10							X	X						X		
EQ-5D (IR-S)							X	X						X		
[redacted]																
[redacted]																
C-SSRS							X							X		
AE Reporting	Monitor and record continuously throughout the study															

Study Week																FU[1]
	136	140	144	148	152	156	160	162	164	168	172	176	180	182 (EOT)[2]	UV for a Change in AD Medication	198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5		1387 ± 7
Concomitant Therapy and procedures	Monitor and record continuously throughout the study															
SAE Reporting	Monitor and record continuously throughout the study															

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR = Clinical Dementia Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 198. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study. Subjects who withdraw from the LTE period prematurely are to return to the site for the Week 182/EOT Visit; for such subjects, the site is to contact the Sponsor as soon as possible to confirm whether the efficacy assessments specified at the Week 182/EOT Visit are required.

[redacted] Required for women of childbearing potential only (Section 15.5).

[4] [redacted]

[5] [redacted]

[6] Only for subjects who participate in the amyloid PET cohort.

[redacted]

Table 6: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule During the Long-Term Extension

Study Week	Long-Term Extension												Unscheduled Visit for ARIA[1]	FU[2]
	82	86	90	94	98	102	106	110	122	134	158	182[3]		198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	575 ± 5	603 ± 5	631 ± 5	659 ± 5	687 ± 5	715 ± 5	743 ± 5	771 ± 5	855 ± 5	939 ± 5	1107 ± 5	1275 ± 5		1387 ± 7
Follow-Up Phone Call[4]	X	X	X	X	X	X	X	X						
Brain MRI[5]				X		X		X	X	X	X	X	X	X
MOCA													X	

ARIA = amyloid related imaging abnormalities; EOT = End of Treatment; FU = follow up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging.

[1] If a subject resumes treatment after ARIA, an MRI will be performed 2 weeks (±3 days) after the second administration of study treatment at the restarted dose or each increase in dose if an MRI is not scheduled during this period (see Section 7.2.2.5).

[2] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 198. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[3] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study. Subjects who withdraw from the LTE period prematurely are to return to the site for the Week 182/EOT Visit; for such subjects, the site is to contact the Sponsor as soon as possible to confirm whether the efficacy assessments specified at the Week 182/EOT Visit are required.

[4] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[5] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites

4.3. Additional Information

4.3.1. Site Personnel

A minimum of 3 separate heath care professionals (HCPs) are required:

1. A treating HCP (the Principal Investigator [PI] or Sub-investigator may serve as a treating HCP who is responsible for the following:
   - Administration of Montreal Cognitive Assessment (MOCA) at Day 1 and during management of amyloid-related imaging abnormalities (ARIA) cases.
   - Management of the routine neurological care of the subject.
   - Assessment (including assignment of causality) and treatment of adverse events (AEs).
   - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.
2. An independent rating HCP (designated by the PI of the site) who is responsible for administering the Clinical Dementia Rating (CDR)
3. A second independent rating HCP (designated by the PI of the site) who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI], and the Mini-Mental State Examination (MMSE)

The 2 independent rating HCPs must not be involved with any other aspect of subject 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. PIs cannot serve as rating HCPs. The treating HCPs must not discuss AEs (e.g., ARIA) with the independent rating HCPs.

To ensure consistency across sites, rating HCPs must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites should attempt to maintain the same rating HCP throughout the study for specific assessments. Each subject should have the same rating HCP perform the subject's specific rating assessment throughout the study. If a rating HCP has to be replaced, the new rating HCP 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 subject. As with other laboratory and clinical information, these data should NOT be reviewed by the rating HCPs.

The roles of independent raters and treating HCP are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject level. If a rater has administered the CDR to a subject they may not administer the other neurocognitive assessments to that subject 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.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy. Supporting this hypothesis are results from solanezumab and crenezumab studies that have shown a trend in slowing cognitive decline in mild but not moderate AD [Doody 2014; Fagan 2014].

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of

calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne 2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience With Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine immunoglobulin (Ig) G2a chimeric version of the antibody (ch12F6A) with similar properties significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A ≥70 mg/ kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is an ongoing randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 6 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab.

  The primary objective of Study 221AD103 is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR-sum of boxes (SB) and MMSE.

  To date, ARIA has been the most frequent AE reported in the study. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. Incidence of ARIA has been observed to be both dose and Apolipoprotein E4 (ApoE ε4) carriage-dependent, especially at the highest doses (refer to the IB for details on events of ARIA).

  Protocol-defined interim analyses have demonstrated a dose- and time-dependent reduction of brain amyloid burden after 6 months of dosing (Week 26), with statistical significance achieved in the 3, 6, and 10 mg/kg groups compared with placebo, and after 1 year of dosing (Week 54), with statistical significance achieved

in the 3 and 10 mg/kg groups compared with placebo (see current IB for results of the most recent interim analysis). The results demonstrate target engagement (amyloid plaques) and a pharmacodynamic effect (dose-dependent amyloid reduction). In addition results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE, suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. At Week 54, adjusted mean change (increase) from baseline in CDR-SB score was smaller for both the 3 and 10 mg/kg groups compared with placebo, with statistical significance achieved in the 10 mg/kg group (see current IB for results of the most recent interim analysis). At Week 52, adjusted mean changes (decreases) in MMSE score from baseline were statistically significant in the 3 and 10 mg/kg groups (see current IB for results of the most recent interim analysis). Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment was statistically significant at doses of 3, 6 and 10 mg/kg after 6 months of dosing and at 3 and 10 mg/kg after 12 months of dosing (see current IB for results of the most recent interim analysis). The effect on mean decrease from baseline in CDR-SB after 12 months of dosing was observed at both 3 and 10 mg/kg (see current IB for results of the most recent interim analysis),

with statistical significance achieved at 10 mg/kg. The effect on mean decrease from baseline in MMSE score was statistically significant at 3 and 10 mg/kg. These data indicate that 3 mg/kg could be considered an acceptable dose for Phase 3 studies; however, given the dose-dependent nature of these observations, the use of higher doses (6 and 10 mg/kg) could offer greater benefit at acceptable risk.

ARIA has been identified as an event that may occur with anti-amyloid targeting drug candidates and is considered an event of special interest in the aducanumab program. To date, the incidence of ARIA has been observed to be both dose and ApoE ε4 carriage dependent, especially at the highest doses. In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Slow titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012] which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown to date, the doses to be tested using a titration regimen are 3 and 6 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6 and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows (Table 7 and Figure 1):

ApoE ε4 Carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter
- High dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter
- Placebo

  Saline infusion

ApoE ε4 Non-Carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 7: Dosing Scheme for Aducanumab by Regimen

Dose (Month)		1	2	3	4	5	6	7 to 20
Regimen		Dose (mg/kg)						
ApoE ε4 (+)	Low Dose	1	1	3	3	3	3	3
	High Dose	1	1	3	3	3	3	6
	Placebo	saline						
ApoE ε4 (-)	Low Dose	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If any of the high doses proposed (10 mg/kg in ApoE ε4 non-carriers and 6 mg/kg in ApoE ε4 carriers) is deemed not acceptable, enrollment for the high dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high dose regimens will be revised as described in Section 16.

- Benefit of titration

  A titration schedule has been implemented in this Phase 3 study and in the ongoing multiple-dose Study 221AD103. If, based upon review of the data from Study 221AD103, titration is not deemed beneficial, it will be eliminated, and subsequently enrolled subjects who are ApoE ε4 carriers will receive a fixed dose of 3 or 6 mg/kg and non-carriers will receive 6 or 10 mg/kg.

5.3.3. Long-Term Extension Period

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will continue to receive the same dose of aducanumab that they were on at the end of the placebo-controlled period. Subjects who receive placebo during the placebo-controlled period and who enter the LTE period will be assigned to 1 of 2 treatment groups, based upon their ApoE ε4 carrier status, in a 1:1 ratio (aducanumab low dose: aducanumab high dose). Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 7 and Figure 1).

Any modifications to the dosing scheme (i.e. termination of high dose groups and replacement of titration with fixed dosing, as described in Section 5.3.2) will also be implemented in the LTE period.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy 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 subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Efficacy

- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).
- [redacted]
- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- [redacted]
- To assess the correlation between primary endpoints and key biomarker endpoints.

Pharmacokinetics

- To explore the potential relationships between PK or exposure and response (e.g., clinical and biomarker endpoints) including covariate analysis.
- To explore the potential effect of co-medications on the PK of aducanumab using population PK.

6.3.2. Tertiary Endpoints

Safety and Tolerability:

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers:

- Change from baseline in amyloid PET signal at Week 26 (in a subset of subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of subjects).
- [redacted]

Efficacy

- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject-self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78
- [redacted]
- Change from baseline in mPDQ-20 at Week 78.
- [redacted]
- Correlation between clinical and biomarker endpoints over time.

Pharmacokinetics

- Serum concentrations of aducanumab, population PK parameters of aducanumab including but not limited to clearance and volumes of central and peripheral compartments.

6.4. Long-Term Extension Objectives and Endpoints

6.4.1. Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.
- [redacted]

6.4.2. Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of subjects).
  - [redacted]
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.
  - [redacted]

7. STUDY DESIGN

7.1. Study Overview

Study 221AD301 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional 24-month dose-blind LTE study. Approximately 1350 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Subject enrollment will be monitored so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a 24-month long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (a total of 26 doses).

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of approximately 18 weeks after the final dose.

The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will be up to approximately 206 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 100-week aducanumab dose-blind treatment period, and a safety FU period of approximately 18 weeks after the final dose. The FU period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 6 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 7 and Figure 1. Subjects who received

aducanumab in the placebo-controlled period and who enter the LTE period will receive the same dose of aducanumab that they received at the end of the placebo-controlled period (up to 6 mg/kg and 10 mg/kg in ApoE ε4 carriers and non-carriers, respectively). Subjects who received placebo during the placebo-controlled period and who enter the LTE period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose; aducanumab high dose); aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented to subjects who develop ARIA. See Section 7.2.1.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE period, Investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE period.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification, or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the PI within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the PI; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Guidelines on the management and disposition of ARIA-E and ARIA-H cases (including the criteria to be met for the continuation, suspension/resumption, or permanent discontinuation of dosing due to ARIA) are provided in Sections 7.2.1.1 and 7.2.2. Dosing may also be terminated at the discretion of the Sponsor for medical reasons. See Section 10.1 for the full list of criteria for discontinuing study treatment. In addition, guidelines on reupitration to the subject's assigned dose after ARIA resolves are provided in Section 7.2.2.5.

7.2.1.1. Disposition of ARIA-E Cases

Table 8: Disposition of ARIA-E Cases

Clinical Symptom Severity	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 subject may resume dosing at the same dose.	
Mild	Suspend dosing. Once ARIA-E and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[1]			
Serious, except for "other medically important event"[2]	Discontinue Dosing		

[1] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above and as described in Section 15.3.3.

[2] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.3.3.

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.
- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the subjects remain asymptomatic, the subjects may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.
- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by mild, moderate, severe, or serious ("other medically**

important event" only) clinical symptoms at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the clinical symptoms have resolved, the subject may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.

- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except "other medically important event") clinical symptoms** at any time during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per centrally read MRI.

See Section 7.2.2.5 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.2.6 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.2. Disposition of ARIA-H Cases

7.2.2.1. ARIA-H (Microhemorrhage)

In this study, new incident microhemorrhages are defined as new incident microhemorrhages that occur on treatment and do not include microhemorrhages at baseline.

Table 9: Disposition of ARIA-H (Microhemorrhage) Cases

Clinical Symptom Severity	New Incident Microhemorrhages[1] (Central Read)		
	≥1 and ≤4	≥5 and ≤9	≥10
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing. Once ARIA-H is stable, the subject may resume dosing at the same dose.	Discontinue dosing
Mild	Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[2]			
Serious, except for "other medically important event"[3]	Discontinue dosing		

[1] New incident microhemorrhages = new incident microhemorrhages on treatment; does not include microhemorrhages at baseline.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.3.3.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.3.3.

Asymptomatic ARIA-H (Microhemorrhage)

- Subjects who develop a **≥1 and ≤4 new incident microhemorrhage(s)** at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥5 and ≤9 new incident microhemorrhages** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the microhemorrhage is confirmed as stable per the centrally read MRI. A microhemorrhage is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.
- Subjects who develop **≥ 10 new incident microhemorrhages** during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic

visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the microhemorrhages are deemed stable per centrally read MRI.

Symptomatic ARIA-H (Microhemorrhage)

- Subjects who develop ≤ **9 new incident microhemorrhages and mild, moderate, severe, or serious ("other medically important event" only [Section** 15.3.3]) **clinical symptoms** will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the ARIA-H (microhemorrhage(s)) is confirmed stable per the centrally read MRI. Microhemorrhages are considered stable if they are unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once ARIA-H (microhemorrhage) is deemed stable and the clinical symptoms have resolved, the subject may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.
- Subjects who experience **serious (except "other medically important event" [Section** 15.3.3]) **clinical symptoms associated with microhemorrhage(s)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the microhemorrhage(s) is confirmed stable per centrally read MRI.
- Subjects who develop ≥ **10 new incident microhemorrhages**, regardless of symptom severity, during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the microhemorrhages are deemed stable per centrally read MRI.

See Section 7.2.2.5 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.2.6 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.2.2. ARIA-H (Superficial Siderosis)

Table 10: Disposition of ARIA-H (Superficial Siderosis) Cases

Clinical Symptom Severity	New Incident Areas of Superficial Siderosis[1] (Central Read)		
	1	2	>2
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing. Once ARIA-H is stable the subject may resume dosing at the same dose.	Discontinue dosing
Mild	Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[2]			
Serious, except for "other medically important event"[3]	Discontinue dosing		

[1] New incident superficial siderosis = new incident superficial siderosis on treatment.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.3.3.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.3.3.

Asymptomatic ARIA-H (Superficial Siderosis)

- Subjects who develop a **single incident focal area of hemosiderosis (also referred to as superficial siderosis)** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the superficial siderosis is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 2 weeks (±3 days) later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis)** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later.

Once the superficial siderosis is deemed stable, the subjects may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.

- Subjects who develop >**2 focal areas of hemosiderosis (superficial siderosis)** occurring at any time during the study must permanently discontinue treatment and should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later.

Symptomatic ARIA-H (superficial siderosis)

- Subjects who develop ≤**2 new focal areas of superficial siderosis** and **mild, moderate, severe, or serious ("other medically important event" only)** clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the ARIA-H superficial siderosis is confirmed stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the ARIA-H (superficial siderosis) is deemed stable and the clinical symptoms have resolved, the subjects may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.
- Subjects who experience **serious (except "other medically important event" [Section 15.3.3]) clinical symptoms associated with ARIA-H (superficial siderosis)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the superficial siderosis is confirmed stable per centrally read MRI.
- Subjects who develop >**2 new focal areas of superficial siderosis** regardless of clinical symptom severity will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the superficial siderosis is confirmed stable per centrally read MRI.

See Section 7.2.2.5 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.2.6 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.2.3. ARIA-H (Macrohemorrhage)

- Subjects who develop any new incident macrohemorrhage, regardless of symptom severity during the study, will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an

unscheduled visit for MRI and MOCA every 2 weeks (±3 days) until the macrohemorrhage is confirmed stable per centrally read MRI.

7.2.2.4. Disposition of Coincident ARIA-H and ARIA-E Cases

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow the most restrictive guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H be deemed stable, and the subject must be asymptomatic. For example, if a subject experiences asymptomatic ARIA-H (1-4 microhemorrhages) coincident with ARIA-E assessed as moderate on MRI and accompanied by mild clinical symptoms, the dose should be suspended per the ARIA-E guidelines summarized in Table 11.

7.2.2.5. Resumption of Study Treatment After Suspension due to ARIA

7.2.2.5.1. MRI Monitoring

When treatment resumes after a dose suspension due to ARIA, an MRI and MOCA will be performed 2 weeks (±3 days) after the second administration of the restarted dose if they do not have a scheduled MRI occurring during this period. In addition, if treatment was suspended during the dose titration prior to the subject reaching the maximum assigned dose, an MRI and MOCA will be performed 2 weeks (±3 days) after the second administration of each increase in dose. MRIs will otherwise be performed as indicated in the Schedules of Events (Section 4.2).

7.2.2.5.2. Dosing Upon Resumption of Study Treatment

Subjects who suspend treatment due to ARIA for the first time may resume treatment at the same dose if they meet the criteria as described in Sections 7.2.1.1, 7.2.2, and 7.2.2.4. Subjects who suspend and then resume dosing after having already reached their assigned top dose level are to continue dosing at that dose level. However, if dosing is suspended during the dose titration period, the subject (1) must receive at least 2 doses at the restart dose before titrating up to the next dose level and (2) must complete at least the required number of doses at that dose level per their assigned dosing regimen, as outlined in Table 11.

Table 11: Resumption of Study Treatment Following Dose Suspension Due to ARIA During Titration

Assigned Dosing Regimen (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses Needed Before Going to the Next Higher Dose
ApoE ε4 (+)			
Low Dose (3 mg/kg)	1 mg/kg	1	2
High Dose (6 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	3

Assigned Dosing Regimen (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses Needed Before Going to the Next Higher Dose
	3 mg/kg	2	2
	3 mg/kg	3	2
	3 mg/kg	4	2
ApoE ε4 (-)			
Low Dose (6 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	3
	3 mg/kg	2	2
	3 mg/kg	3	2
	3 mg/kg	4	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2
	6 mg/kg	1	2
	6 mg/kg	2	2

7.2.2.6. Management After Recurrent ARIA (Dosing and MRI)

If the subject has a second occurrence of ARIA (i.e., a second occurrence of ARIA-E or of ARIA-H, or ARIA-E and ARIA-H) that requires dose suspension, after the ARIA-E resolves or stabilizes, the subject is to resume dosing at the next lower dose and is to receive 2 doses at that dose level (i.e., the restart dose) before titrating up to the next higher dose. Once dosing has resumed, the guidelines outlined in Table 11 apply, unless the subject has reduced from 1 mg/kg to placebo. In this case, the subject will remain on placebo for the duration of the placebo-controlled portion of the study. If a subject resumes treatment after ARIA, an MRI and MOCA will be performed 2 weeks (±3 days) after the second administration of the restarted dose, and 2 weeks (±3 days) after the second administration of each increase in dose unless the subject has a scheduled MRI during this period. MRIs will otherwise be performed as indicated in the Schedules of Events (Section 4.2).

If the subject experiences a third episode of ARIA that requires dose suspension, the subject must discontinue study treatment. Subjects who discontinue treatment are to remain in the study and continue all protocol-required tests and assessments.

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE period and will receive the lowest dose that they have tolerated during the placebo-controlled period. A subject who is switched to placebo but remains in the study may be titrated to aducanumab 1 mg/kg during the LTE period.

7.2.3. 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 Directions for Handling and Administration (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 subject will be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of screening, treatment, and FU.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety FU period of 18 weeks after the final dose.

Subjects will have approximately 33 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety FU contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days). It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and subject to Sponsor approval.
- 20 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses
- 3 visits for clinical assessments.
- [redacted]
- 2 visits for amyloid PET scan (in a subset of subjects).
- [redacted]
- 6 visits for brain MRI.
- 1 FU safety visit at Week 94 (only for subjects not entering the LTE period) or 18 weeks after last administration of study treatment for those subjects who withdraw from study.

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period. Subjects who enter the LTE period will have approximately 40 additional planned clinic visits, and up to 8 telephone safety FU contacts, as follows:

- 26 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses
- 4 visits for clinical assessments.
- [redacted]
- 2 visits for amyloid PET scan (in a subset of subjects).
- [redacted]
- 7 visits for brain MRI.
- 1 FU safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, and the Repeatable Battery for Assessment of Neuropsychological Status [RBANS]). This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE and RBANS) must be performed at Screening Visit 1. The ADAS-Cog 13, and ADCS-ADL-MCI will be performed at Screening Visit 2 within 20 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE and RBANS. The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1). All other cognitive assessments [redacted] may be performed at any time during Screening after eligibility is confirmed during Screening Visit 1. The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and subject to Sponsor approval.

Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion. Subjects who fail Screening due to PET, MMSE, CDR, hepatitis B or C results, or abnormal MRI findings will not be allowed to rescreen.

Subjects who fail Screening because allowed chronic medications have not been at stable doses for at least 4 weeks prior to Screening Visit 1 or whose use of AD medications has not been at stable doses for at least 8 weeks prior to Screening Visit 1 may return for rescreening after use of these medications has been stabilized for the required period.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period and will receive study treatment every 4 weeks for an additional 100 weeks (26 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE period are to return to the study site for an FU Visit at Week 94 (18 weeks after the last dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE period are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A FU Visit will occur at Week 198 (18 weeks after the last LTE dose). The final study visit for subjects participating in the LTE period will be Week 198.

Subjects who discontinue treatment are to remain in the study and continue all protocol-required tests and assessments until the end of the study or until withdrawal of consent. Subjects are encouraged to return for FU assessments approximately 18 weeks after their last dose of study treatment, as are subjects who withdraw from the study.

7.4. Study Stopping Rules

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

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

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

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of Screening) is permissible for subjects not participating in the amyloid PET cohort. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR-Global Score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index (DMI) score).
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and Screening assessments.
8. Must consent to apolipoprotein E (Apo E) genotyping.
9. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. Exclusion Criteria

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

Medical History

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, lewy body dementia, fronto-temporal dementia, head trauma).
2. Clinically significant psychiatric illness (e.g., uncontrolled major depression, schizophrenia, bipolar affective disorder) within 6 months prior to Screening.
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >1 cm in diameter on T2* sequence) unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as >1.5 cm in diameter).
   - >1 lacunar infarct (defined as ≤1.5 cm in diameter).
   - Superficial siderosis.
   - 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 subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Presence of diabetes mellitus that, in the judgment of the Investigator, cannot be controlled or adequately managed.
7. 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.

8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings >165/100 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 subject to be eligible for the study), or persistent SBP/DBP readings >180/100 mmHg 3 months prior to randomization (Day 1) that in the opinion of the Investigator are indicative of chronic uncontrolled hypertension.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma.
    - Subjects with prostate cancer in situ.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or known seropositivity for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody IgG, and positive HBcAb) are eligible to participate in the study (US Centers for Disease Control and Prevention's interpretation of the hepatitis B serology panel).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).
19. Any other medical conditions (e.g., renal disease) that are not stable or controlled, or, which in the opinion of the Investigator, could affect the subject's safety or interfere with the study assessments.

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 or use of AD 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 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any passive immunotherapy study targeting Aβ within 12 months of Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 12 months prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures

29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (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, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 6 months prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.
33. For subjects who consent to lumbar puncture (LP), any contraindications to having a LP (e.g., platelet count <100,000/μL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during Screening must be resolved prior to randomization.

Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR, hepatitis B or C, or abnormal MRI findings.
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension Period

To be eligible to participate in the LTE period, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses. Subjects who do not meet these criteria can enter the LTE period only with Sponsor's approval.
2. MMSE score >15 at the Week 78 Visit.
3. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
4. Female subjects of childbearing potential and male subjects must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment.
5. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
6. Must have the ability to comply with procedures for protocol-related tests.
7. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study,

and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long-Term Extension Period

Subjects will be excluded from entering the LTE period if at Week 78 they have:

1. Any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any Screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) to determine study eligibility under a separate initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further Screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all Screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scan issues and subject to Sponsor approval. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the Screening log. The total study duration for each subject participating only in the placebo-controlled period will be approximately 102 weeks (approximately an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of FU).

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier), so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE period with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating HCPs should

remain blinded to treatment assignment as well as subject care management and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. As 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 subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

For the LTE period, the dose information must remain restricted. The rating and treating HCP should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by serious clinical symptoms except for "other medically important event" as defined in Table 8.
  - Symptomatic ARIA-H (microhemorrhages) with serious clinical symptoms except for "other medically important event" as defined in Table 9.
  - Symptomatic ARIA-H (superficial siderosis) with or serious clinical symptoms except for "other medically important event" as defined in Table 10.
  - ARIA-H with ≥10 microhemorrhages and/or >2 focal areas of superficial siderosis.
  - Any new incident macrohemorrhage.
  - A third recurrence of ARIA after rechallenge that requires dose suspension

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria.
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

A subject who discontinues treatment is to remain in the study and continue protocol-required tests and assessments until the end of the study or until the subject withdraws consent. The site

is to contact the Sponsor as soon as possible after discontinuation to confirm whether the efficacy assessments outlined for the EOT Visit in Section 4.2 need to be performed.

10.2. Withdrawal of Subjects From Study

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

- Death.
- Withdrawal of consent.
- Lost to follow-up.

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

Subjects who are withdrawn from the study after receiving ≥1 doses of study treatment should complete the EOT Visit after the reason for withdrawal is identified. For such subjects, the site is to contact the Sponsor as soon as possible after withdrawal to confirm whether the efficacy assessments outlined for this visit in Section 4.2 need to be performed. These subjects are also to return to the site for a FU Visit 18 weeks after receiving their last dose of study treatment.

11. STUDY TREATMENT USE

11.1. Regimen

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

Please see Section 4.2 (Schedule of Events) for the study treatment infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

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

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.3 (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.

11.3. Precautions

Not applicable.

11.4. Compliance

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

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to Screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and the FU Visit (Week 94 or Week 198) or EOT 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.

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given <10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids (including inhaled and topical corticosteroids) are allowed; certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended, with the exception of medications used to treat AEs, which would not result in automatic withdrawal. The Sponsor may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures) performed between the time the subject is enrolled in the study and the FU or EOT Visit, unless the subjects is being followed for study-related toxicity.

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

11.6. 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.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

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

Aducanumab is a recombinant human antibody expressed in a Chinese hamster ovary cell line [redacted], 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. [redacted]. Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing aducanumab 50 mg/mL, [redacted] Aducanumab is manufactured in accordance with Good Manufacturing Practices.

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

12.1.1. Aducanumab 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 Biogen.

12.1.2. Aducanumab Storage

Study treatment must be stored in a secure location. Aducanumab is to be stored at 2° 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 2 hours, then it should be kept at 2° to 8°C 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.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (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 personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab 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 (subject-by-subject 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 Biogen. A written explanation must be provided for any discrepancies.

12.2. 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.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

To confirm amyloid pathology at Screening, PET scans will be performed using Amyvid™ (^{18}F-florbetapir), Vizamyl™ (^{18}F-flutemetomol), or Neuraceq™ (^{18}F-florbetaben). For those subjects participating in the amyloid PET substudy, Screening and FU scans must be performed using Amyvid. For subjects participating in the PET substudy in Japan, Vizamyl (^{18}F-flutemetomol) will be used. For details on PET imaging ligands, [redacted] refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

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

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

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

13.2. Pharmacokinetic Assessments

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

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the pharmacodynamic properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the amyloid PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in the amyloid PET substudy.

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

13.4. Additional Assessments

[redacted]

13.4.2. ApoE Genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

[redacted] upport discovery and verification of biomarkers related to AD or aducanumab pharmacology.

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- [redacted]
- mPDQ-20
- [redacted]

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

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

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

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

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale.

14.2. Laboratory Safety Assessments

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

- Hematology: complete blood count with differential and 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, virology (including HIV at the Investigator's discretion after consideration of risk factors), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier anti-drug antibody (ADA) approach will be used (i.e., Screening assay, confirmatory assay, and titration assay). Confirmed antidrug antibody-positive samples will be tested for the presence of anti-aducanumab neutralizing antibodies using a validated assay.

15. 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 subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 laboratory finding), 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 laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the Investigator considers to be clinically significant.

Pre-treatment nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.1.2. 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 subject 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.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject 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.)

15.1.3. 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 subject is hospitalized. The study site must document all of 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 subject's consent to participate 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 subject's consent to participate 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 subject 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 15.1.2 is met.

15.2. Safety Classifications

15.2.1. 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 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

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.

15.2.3. Severity of Events

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

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the FU or EOT Visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H 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.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to [redacted].

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the FU or EOT Visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. This also applies to SAEs that occur after administration of the ligand. FU information regarding an SAE also must be reported with 24 hours.

Events occurring after the FU or EOT Visit should be reported to Biogen only if the Investigator considers the SAE related to study treatment.

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

15.3.4. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the FU or EOT Visit must be reported to [redacted]) within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to [redacted] regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event

- The relationship of the event to study treatment

To report initial or FU information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Guide for country-specific [redacted] fax numbers or email [redacted]

15.3.4.1. 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. The Investigator should make every effort to obtain and send death certificates and autopsy reports to [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

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

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to [redacted] within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to [redacted]

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in 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 to [redacted] within 24 hours of the site becoming aware of the overdose. An overdose must be reported to [redacted] 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 to [redacted]. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. 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 [redacted] 24-hour emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

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

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the [redacted] 24-hour emergency medical support number at [redacted]

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

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.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of this study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.

- Placement of an intrauterine device or intrauterine system
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (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.
- Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at FU.
  - Use of condoms with spermicide.
  - Female sexual partners who underwent surgical sterilization (e.g., bilateral tubal ligation), are postmenopausal, are post-hysterectomy, or are using highly effective contraception as listed above for female subjects.

For males and females of childbearing potential:

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, 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, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, 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 and FU on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of the event.

- Pursue SAE FU information actively and persistently. FU information must be reported to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE FU information, if possible, until the event has resolved or become stable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor [redacted] is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects 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 each aducanumab regimen and placebo. All statistical tests will be 2-sided.

16.2.2.2. Dose Regimens to be Evaluated

The following dose regimens of aducanumab as compared with placebo will be evaluated:

- Aducanumab high-dose regimen (6 mg/kg in ApoE ε4 carriers and 10 mg/kg in ApoE ε4 non carriers).
- Aducanumab 6 mg/kg dose regimen (6 mg/kg in ApoE ε4 carriers and ApoE ε4 non-carriers).
- Aducanumab low-dose regimen (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the proposed maximum dose (10mg/kg in ApoE ε4 non-carriers or 6 mg/kg in ApoE ε4 carriers) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose regimen and aducanumab low dose regimen will be modified as shown in Table 12. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of

Type I error rate is thus maintained without a statistical adjustment for such adaptations[Chow and Chang 2011].

Table 12: Dose Group Pooling Strategy in the Event of Treatment Group Termination

Treatment group(s) Terminated	Definitions of Revised Pooled Treatment Groups for Comparison
ApoE ε4 carrier high-dose group (6 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 6 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group (6 mg/kg) AND ApoE ε4 non-carrier high-dose group (10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose regimen versus placebo, aducanumab 6 mg/kg regimen versus placebo, and aducanumab low-dose regimen versus placebo. In the event of a dosing modification (see Table 12), the first comparison is the aducanumab high-dose regimen versus placebo and the second comparison is the aducanumab low-dose regimen versus placebo. If the first comparison is statistically significant ($p \leq 0.05$), then the second comparison will also be made at the 0.05 α level. If the second comparison is statistically significant ($p \leq 0.05$), then the third comparison will also be made at the 0.05 α level. However, all comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for one, two or all three comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1, 2, or all 3 comparisons, respectively.

Due to a current lack of scientific consensus in the AD field on which biomarker(s) might be most appropriate, the selection of the biomarkers and methodology for control of Type I error will be pre-specified in the statistical analysis plan (SAP). Otherwise, there will be no multiple comparison adjustments for the tertiary endpoints.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population with a baseline and at least one post-baseline CDR-SB score. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change From Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population with a baseline and at least one post-baseline MMSE value. A MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction and baseline ApoE ε4 status

16.2.2.5.2. Change From Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADAS-Cog 13 score. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction; baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5.3. Change From Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADCS-ADL-MCI score. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction; baseline MMSE, and baseline ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, a MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE and baseline ApoE ε4 status.

Otherwise, an analysis of covariance or its non-parametric equivalent may be used to analyze these exploratory endpoints.

16.2.2.6.2. Long-Term Extension Period

The additional endpoints for the LTE period are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the placebo-controlled period using the placebo-controlled period baseline. Details of the analyses will be pre-specified in the SAP.

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The population PK characteristics of aducanumab will be determined by nonlinear mixed effects approach. Covariates that might influence the disposition of aducanumab (e.g., body weight, age, sex, immunogenicity, ApoE ε4 status) will be evaluated and the potential exposure-response relationships will be explored.

16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of study treatment (including placebo and aducanumab).

16.4.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.4.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent 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 study treatment for the placebo-controlled period and over the 24-month LTE period. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.4.2.2. 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. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.4.2.3. Vital Signs

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

16.4.2.4. ECG

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

16.4.2.5. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale data will be summarized by treatment group.

16.5. Immunogenicity Data

16.5.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.5.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.6. Interim Analyses

16.6.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.6.2. Interim Superiority Analysis

An interim analysis for superiority may be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The Lan-DeMets method with O'Brien-Fleming stopping boundary for efficacy will be used. In order to maintain the treatment blind in the event of this interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.7. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103 which included 1 year data from 1, 3 and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group will have approximately 90% power to detect a true mean difference of 0.5 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, a SD of 1.92 and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflects a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

The sample size may be reassessed in a blinded manner approximately 3 months before enrollment is complete if at least 15% of the data are available on the primary endpoint. At this interim time-point, the SD for the primary endpoint will be estimated based on the blinded data. The sample size may be increased if the SD is estimated to be more than approximately 2.07. In addition, the sample size could be increased using external clinical trial results that become available after the start of the study.

17. ETHICAL REQUIREMENTS

Biogen, [redacted] and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

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.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

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

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

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) as an initial screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed

prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

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

Subjects will be informed that their race and ethnicity will be collected and will be used during analysis of study results.

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The 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 (wet signature) and copies of the signed and dated ICFs.

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

17.4. Subject Data Protection

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

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

During the study, subjects' race and ethnicity will be collected. These data may be used in the analysis of the safety, efficacy, and/or pharmacokinetic profile of the study treatment. It is unknown if the potency or effects of the study treatment are influenced by race or ethnicity.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. 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 subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights and a user manual.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by [redacted] and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen 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, [redacted], and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA 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.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen 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 PI 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 collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen 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 per project-specific plans.

19.2. Study Committees

19.2.1. 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 subject accrual and oversee study conduct, including advising on study design and execution. The advisory committee will be blinded to subject treatment assignments during the study.

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

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. 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 subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), 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.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB 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, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. 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 Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. 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 laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen 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.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study 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 subject enrollment, or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early 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)

Biogen MA Inc.
250 Binney Street
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United States

Biogen Idec Research Limited
Innovation House
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SL6 4AY
United Kingdom

PROTOCOL NUMBER: 221AD301/NCT02477800

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000966-72**

DATE: 21 July 2016
Version 3.0
Final

Supersedes previous (Original) Version 1.0 dated 09 April 2015 and Version 2.0 dated 26 May 2016.

SPONSOR SIGNATURE

Protocol 221AD301 was approved by:

[redacted]

28 July 2016
Date

[redacted], PhD

[redacted]

Biogen MA Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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Japan

For 24-hour emergency medical support contact

[redacted] at [redacted]

Please refer to the Study Reference Manual for complete contact information.

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

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab , produced in a different Chinese hamster ovary cell line
Aβ	β-amyloid
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibodies
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
[redacted]	[redacted]
AST	aspartate aminotransferase
[redacted]	[redacted]
CDR	Clinical Dementia Rating
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
[redacted]	[redacted]
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject

EQ-5D (SR)	EuroQol health status measure, subject self-reported
FU	Follow-up
GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCP	health care professional
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPI-10	Neuropsychiatric Inventory-10
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RNA	ribonucleic acid
SABR	Safety and Benefit-Risk
SAE	serious adverse event
SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction

TEAE	treatment-emergent adverse event
[redacted]	[redacted]
UV	unscheduled visit

3. SYNOPSIS

Protocol Number:	**221AD301**
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	3.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-Sum of Boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy 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 subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78. Secondary objectives and endpoints are as follows: To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by • MMSE - Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13]

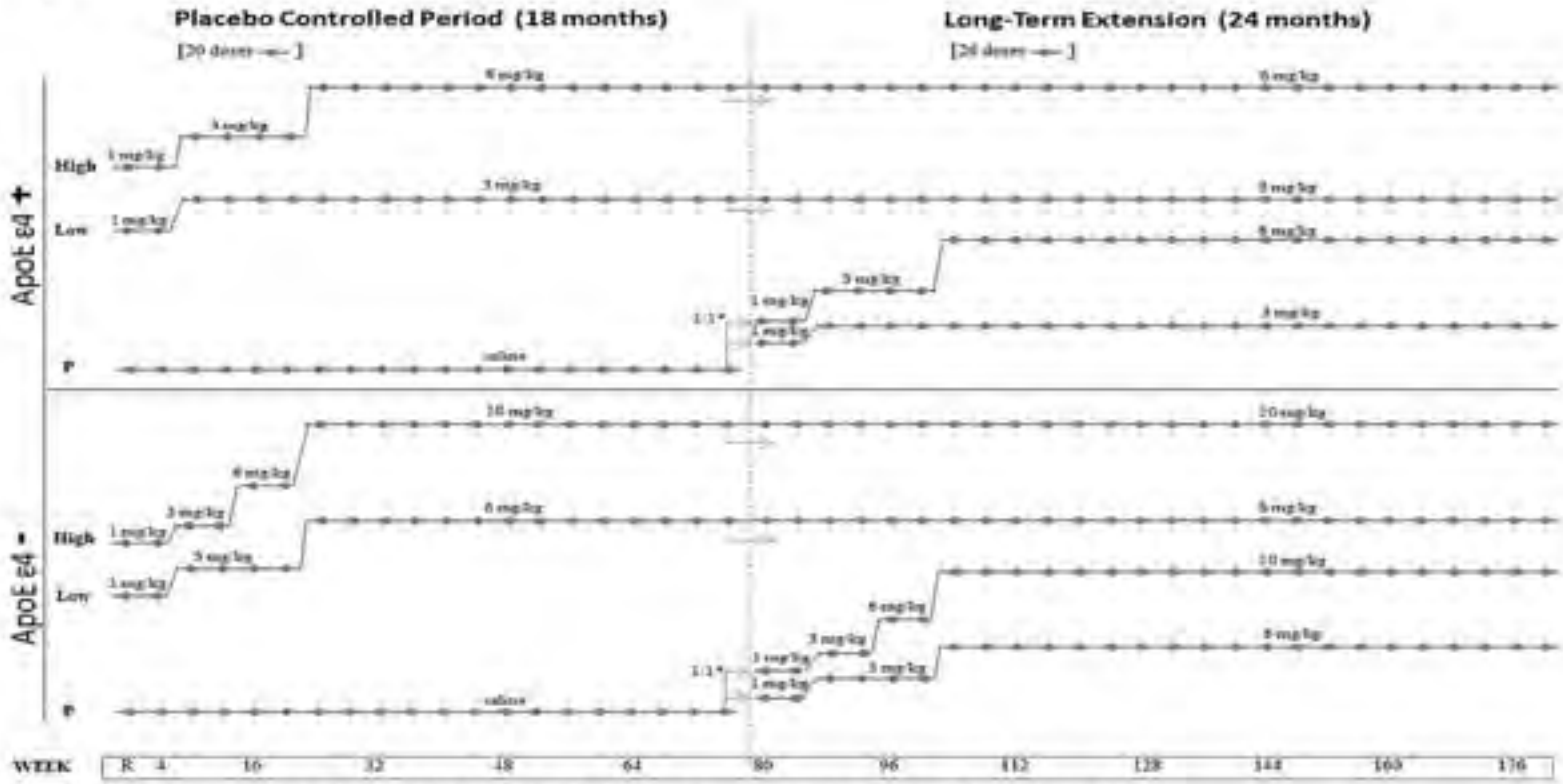
Protocol Number:	**221AD301**
	- Change from baseline in ADAS-Cog 13 at Week 78 • Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] - Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension period of the study):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological and additional assessments reported by the subject and informant/care partner. Endpoints for the long-term extension (LTE) period of the study are listed in Section 6.4.2.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled, parallel-group period followed by an optional 24-month dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1350 subjects will be enrolled
Study Population:	This study will be conducted in subjects with early AD, including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD according to NIA-AA criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator, based on medical history and the Screening assessments. Subject enrollment will be monitored so that approximately 60% to 70% apolipoprotein E4 (ApoE ε4) carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (6 mg/kg)**

Protocol Number:	**221AD301**
	Placebo **ApoE ε4 non-carrier** **Low dose (6 mg/kg)** **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a 24-month dose-blind LTE study during which all subjects will receive aducanumab.
Duration of Treatment and Follow Up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow up [FU]). For subjects who enter the optional LTE period, the total duration will be approximately 206 weeks or 47 months (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, 4 weeks of FU, 100 weeks of dose-blind aducanumab dosing, and 18 weeks of FU).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD301

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; LTE = long-term extension; R = randomization date.
*Subjects who are assigned to placebo during the placebo-controlled period and are continuing into the LTE period will be randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status).

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule From Screening Through Week 48

Study Week	Screening (≤60 days before Day 1)[1]			Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	V1	V2	V3	1	29 ± 3	57 ± 3	85 ± 3	113 ± 3	141 ± 3	169 ± 3	183 ± 3	197 ± 3	225 ± 3	253 ± 3	281 ± 3	309 ± 3	337 ± 3	
Initial Screening Consent[2] (optional)	X																	
Full Informed Consent[3]	X																	
Eligibility Criteria	X	X	X	X[4]														
Demography	X																	
Medical History	X	X	X															
Alcohol/Drug Screen	X																	
HbA_{1c}	X																	
HIV[5]/Hepatitis/ Coagulation	X																	
ApoE Genotyping	X																	
[redacted]																		
Height	X																	
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Serum Pregnancy Test[7]	X																	
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X	

Study Week																		
	Screening (≤60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medication**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Physical Examination	X						X			X							X	
Neurological Examination	X						X			X							X	
12-lead Paper ECG	X									X							X	
Vital Signs[8]	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis	X			X						X							X	
Randomization				X														
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X	
Anti-Aducanumab Ab[9]				X						X							X	
Aducanumab Concentration[10]				X[11]	X[11]		X[11]	X	X[11]	X[12]		X[13]	X					
[redacted]																		
[redacted]																		
Amyloid PET[14]			X								X							
[redacted]																		
RBANS	X																	

Study Week																		
	Screening (≤60 days before Day 1[1])			Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	V1	V2	V3	1	29 ± 3	57 ± 3	85 ± 3	113 ± 3	141 ± 3	169 ± 3	183 ± 3	197 ± 3	225 ± 3	253 ± 3	281 ± 3	309 ± 3	337 ± 3	
CDR	X										X							X
MMSE	X										X							X
ADCS-ADL-MCI		X[16]									X							X
ADAS-Cog 13		X[16]									X							X
NPI-10		X[17]									X							
EQ-5D (SR)		X[18]									X							
EQ-5D (IR-S)		X[18]									X							
[redacted]																		
mPDQ-20		X[18]									X							
[redacted]																		
C-SSRS				X							X							
AE Reporting				Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																	
SAE Reporting	Monitor and record continuously throughout the study																	

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E [redacted]; CDR = Clinical Dementia Rating scale; CRO = contract research organization; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject;

EQ-5D (SR) = EQ-5D, subject self-reported; HbA_{1c} = glycosylated hemoglobin; HIV = human immunodeficiency virus; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PET = positron emission tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; [redacted]; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; Wk = Week.

[1] Examinations required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 3) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and subject to Sponsor approval.

[2] Subjects may sign this optional form for an initial screening which allows administration of the RBANS, CDR and MMSE only.

[3] All subjects must sign this informed consent, including subjects who have signed the optional initial screening consent once they have met the RBANS, CDR, and MMSE eligibility criteria.

[4] All assessments, including the C-SSRS, must be completed before study treatment administration, except the post-dose sample to measure aducanumab concentration.

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

[redacted]

[7] Required for women of childbearing potential only (see Section 15.5).

[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[9] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study treatment infusion.

[10] Blood sampling for aducanumab concentration will be performed prior to infusion. Note: For subjects who permanently discontinue treatment and continue in the study, the final aducanumab concentration sample will be collected at the subject's next visit.

[11] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[redacted]

[13] May be collected at any point in time during Screening after eligibility at V1 is confirmed but if collected on the same day as an MRI, it should be collected after the MRI is performed.

[redacted]

[16] Must be performed within 20 days of V1, but not on the same day as the screening RBANS, CDR, or MMSE.

[17] The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1).

[18] May be performed at any point during screening after the subject has met eligibility criteria on the RBANS, CDR, and MMSE.

Table 2: Placebo-Controlled Period Schedule From Week 50 to End of Treatment or Follow-Up

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 weeks after final dose for subjects who terminate treatment early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Informed Consent									X[3]		
Eligibility Criteria									X[3]		
Body Weight		X	X	X	X	X	X	X			X
Urine Pregnancy Test[4]		X	X	X	X	X	X	X			X
Physical Examination							X		X		X
Neurological Examination							X		X		X
12-lead Paper ECG							X		X		X
Vital Signs[5]		X	X	X	X	X	X	X			X
Hematology, Blood Chemistry and Urinalysis							X		X		X
Study Treatment Infusion		X	X	X	X	X	X	X			
Anti-Aducanumab Ab[6]							X		X		X
Aducanumab Concentration[7]		X[8]	X					X			
[redacted]											
[redacted]											
Amyloid PET[10]									X		
[redacted]											

Study Week											FU[1]
	50	52	56	60	64	68	72	76	78 (EOT)[2]	UV for a Change in AD Medication	94 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	351 ± 3	365 ± 3	393 ± 3	421 ± 3	449 ± 3	477 ± 3	505 ± 3	533 ± 3	547 ± 3		659 ± 7
CDR	X								X	X	X
MMSE	X								X	X	X
ADCS-ADL-MCI	X								X	X	X
ADAS-Cog 13	X								X	X	X
NPI-10	X								X		
EQ-5D (SR)	X								X		
EQ-5D (IR-S)	X								X		
[redacted]											
mPDQ-20	X								X		
[redacted]											
C-SSRS		X							X		
AE Reporting				Monitor and record continuously throughout the study							
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study										
SAE Reporting	Monitor and record continuously throughout the study										

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); [redacted]; CDR = Clinical Dementia Rating scale; [redacted] C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted] EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; NPI-10 = Neuropsychiatric Inventory-10; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study. Subjects who withdraw from study prematurely are to return to the site for the Week 78/EOT Visit; for such subjects, the site is to contact the Sponsor as soon as possible to confirm whether the efficacy assessments specified at the Week 78/EOT Visit are required.

[3] Only for subjects entering the long-term extension period.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[6] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study treatment infusion.

[7] Blood sampling for aducanumab concentration will be performed prior to infusion. Note: For subjects who permanently discontinue treatment and continue in the study, the final aducanumab concentration sample will be collected at the subject's next visit.

[8] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[redacted]

[10] Amyloid PET at Week 78 will only be conducted in selected sites for subjects who are participating in the amyloid PET cohort.

[redacted]

Table 3: Brain MRI, ARIA Management, and Follow-up Phone Call Schedule During the Placebo-Controlled Period

Study Week	Screening (≤60 days before Day 1)[1]			Placebo-Controlled Period												Unscheduled Visit/ MRI for ARIA[4]	FU[2] 94 (or 18 weeks after final dose for subjects who discontinue treatment early)
				1	2	6	10	14	18	22	26	30	42	54	78/ EOT[3]		
Study Day	V1	V2	V3	1	15 ± 3	43 ± 3	71 ± 3	99 ± 3	127 ± 3	155 ± 3	183 ± 3	211 ± 3	295 ± 3	379 ± 3	547 ± 3		659 ± 7
Follow-Up Phone Call[5]					X	X	X	X	X	X	X	X					
Brain MRI[6]		X						X		X		X	X	X	X	X	X
Aducanumab Concentration[7]										X		X		X		X	X
MOCA				X												X	
[redacted]																	

ARIA = amyloid related imaging abnormalities; ARIA-E = amyloid related imaging abnormality-edema; ARIA-H = amyloid related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PK = pharmacokinetic [redacted]; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3.

1. Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and subject to Sponsor approval.
2. Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[3] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study. Subjects who withdraw from study prematurely are to return to the site for the Week 78/EOT Visit; for such subjects, the site is to contact the Sponsor as soon as possible to confirm whether the efficacy assessments specified at the Week 78/EOT Visit are required.

[4] For the frequency of required brain MRI, MOCA, PK, and biomarker assessments for subjects who develop ARIA-E and/or ARIA-H, see Sections 7.2.1.1 to 7.2.1.5. For the frequency of brain MRI, MOCA, PK, and biomarker assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[5] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[6] Arterial spin labeling MRI and task free functional MRI will be performed only at a subset of sites.

[7] One sample will be collected within 2 days after the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

Table 4: Long-Term Extension Schedule From Week 80 to Week 134

Study Week																	
	80	84	88	92	96	100	104	106	108	112	116	120	124	128	132	134	UV for a Change in AD Medication
Study Day	561 ± 5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	743 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	939 ± 5	
Randomization	X[1]																
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Urine Pregnancy Test[2]	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Physical Examination				X			X							X			
Neurological Examination				X			X							X			
12-lead Paper ECG							X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Hematology, Blood Chemistry and Urinalysis							X							X			
Anti-Aducanumab Ab[3]	X						X							X			
[redacted]																	
Aducanumab Concentration[4]	X						X							X			

Study Week																	
	80	**84**	**88**	**92**	**96**	**100**	**104**	**106**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**134**	**UV for a Change in AD Medication**
Study Day	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	**743 ± 5**	**757 ± 5**	**785 ± 5**	**813 ± 5**	**841 ± 5**	**869 ± 5**	**897 ± 5**	**925 ± 5**	**939 ± 5**	
Study Treatment Infusion	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
[redacted]																	
Amyloid PET[3]															X		
[redacted]																	
CDR								X								X	X
MMSE								X								X	X
ADAS-Cog 13								X								X	X
ADCS-ADL-MCI								X								X	X
NPI-10								X								X	
EQ-5D (IR-S)								X								X	
[redacted]																	
[redacted]																	
C-SSRS								X								X	
AE Reporting	Monitor and record continuously throughout the study																
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																
SAE Reporting	Monitor and record continuously throughout the study																

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [redacted] [redacted] CDR = Clinical Dementia Rating; [redacted] C-SSRS = Columbia Suicide Severity Rating Scale;

ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[redacted]

[redacted]

[redacted]

[redacted]

Table 5: Long-Term Extension Schedule From Week 136 to End of Treatment or Follow-Up

Study Week																FU[1]
	136	140	144	148	152	156	160	162	164	168	172	176	180	182 (EOT)[2]	UV for a Change in AD Medication	198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5		1387 ± 7
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Urine Pregnancy Test[3]	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Physical Examination					X							X		X		X
Neurological Examination					X							X		X		X
12-lead Paper ECG					X							X				X
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Hematology, Blood Chemistry and Urinalysis					X							X				X
Anti-aducanumab Ab[4]					X							X		X		X
[redacted]																
Aducanumab Concentration[5]					X							X		X		X

Study Week																**PT**[1]
	136	**140**	**144**	**148**	**152**	**156**	**160**	**162**	**164**	**168**	**172**	**176**	**180**	**182 (EOT)**[2]	**UV for a Change in AD Medication**	**198 (or 18 weeks after final dose for subjects who terminate treatment early)**
Study Day	**953 ± 5**	**981 ± 5**	**1009 ± 5**	**1037 ± 5**	**1065 ± 5**	**1093 ± 5**	**1121 ± 5**	**1135 ± 5**	**1149 ± 5**	**1177 ± 5**	**1205 ± 5**	**1233 ± 5**	**1261 ± 5**	**1275 ± 5**		**1387 ± 7**
Study Drug Infusion	X	X	X	X	X	X	X		X	X	X	X	X			
[redacted]																
Amyloid PET[5]														X		
[redacted]																
CDR								X						X	X	X
MMSE								X						X	X	X
ADAS-Cog 13								X						X	X	X
ADCS-ADL-MCI								X						X	X	X
NPI-10								X						X		
EQ-5D (IR-S)								X						X		
[redacted]																
[redacted]																
C-SSRS								X						X		
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy and procedures	Monitor and record continuously throughout the study															

Study Week																FU[1]
	136	140	144	148	152	156	160	162	164	168	172	176	180	182 (EOT)[2]	UV for a Change in AD Medication	198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5		1387 ± 7
SAE Reporting	Monitor and record continuously throughout the study															

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); [redacted]; CDR = Clinical Dementia Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PET = positron emission tomography; [redacted] SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 198. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study. Subjects who withdraw from the LTE period prematurely are to return to the site for the Week 182/EOT Visit; for such subjects, the site is to contact the Sponsor as soon as possible to confirm whether the efficacy assessments specified at the Week 182/EOT Visit are required.

[3] Required for women of childbearing potential only (Section 15.5).

[redacted]

[6] Only for subjects who participate in the amyloid PET cohort.

[redacted]

Table 6: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule During the Long-Term Extension

Study Week	Long-Term Extension												Unscheduled Visit for ARIA[1]	FU[2]
	82	86	90	94	98	102	106	110	122	134	158	182[3]		198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	575 ± 5	603 ± 5	631 ± 5	659 ± 5	687 ± 5	715 ± 5	743 ± 5	771 ± 5	855 ± 5	939 ± 5	1107 ± 5	1275 ± 5		1387 ± 7
Follow-Up Phone Call[4]	X	X	X	X	X	X	X	X						
Brain MRI[5]				X		X		X	X	X	X	X	X	X
Aducanumab Concentration[6]													X	
MOCA													X	
[redacted]														

ARIA = amyloid related imaging abnormalities; ARIA-E = amyloid related imaging abnormality-edema; ARIA-H = amyloid related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; FU = follow up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PK = pharmacokinetic.

1 For the frequency of required brain MRI, MOCA, PK, and biomarker assessments for subjects who develop ARIA-E and/or ARIA-H, see Sections 7.2.1.1 to 7.2.1.5. For the frequency of brain MRI, MOCA, PK, and biomarker assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

2 Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 198. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[3] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study. Subjects who withdraw from the LTE period prematurely are to return to the site for the Week 182/EOT Visit; for such subjects, the site is to contact the Sponsor as soon as possible to confirm whether the efficacy assessments specified at the Week 182/EOT Visit are required.

[4] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[5] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites

[6] One sample will be collected within 2 days after the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

4.3. Additional Information

4.3.1. Site Personnel

A minimum of 3 separate heath care professionals (HCPs) are required:

1. A treating HCP (the Principal Investigator [PI] or Sub-investigator may serve as a treating HCP) who is responsible for the following:
   - Administration of Montreal Cognitive Assessment (MOCA) at Day 1 and during management of amyloid-related imaging abnormalities (ARIA) cases.
   - Management of the routine neurological care of the subject.
   - Assessment (including assignment of causality) and treatment of adverse events (AEs).
   - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.
2. An independent rating HCP (designated by the PI of the site) who is responsible for administering the Clinical Dementia Rating (CDR)
3. A second independent rating HCP (designated by the PI of the site) who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI], and the Mini-Mental State Examination (MMSE)

The 2 independent rating HCPs must not be involved with any other aspect of subject 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 2 independent rating HCPs must not share any information about subjects. PIs cannot serve as rating HCPs. The treating HCPs must not discuss AEs (e.g., ARIA) with the independent rating HCPs.

To ensure consistency across sites, rating HCPs must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites should attempt to maintain the same rating HCP throughout the study for specific assessments. Each subject should have the same rating HCP perform the subject's specific rating assessment throughout the study. If a rating HCP has to be replaced, the new rating HCP 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 subject. As with other laboratory and clinical information, these data should NOT be reviewed by the rating HCPs.

The roles of independent raters and treating HCP are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject level. If a rater has administered the CDR to a subject they may not administer the other neurocognitive assessments to that subject 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.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy. Supporting this hypothesis are results from solanezumab and crenezumab studies that have shown a trend in slowing cognitive decline in mild but not moderate AD [Doody 2014; Fagan 2014].

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of

calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne 2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience With Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine immunoglobulin (Ig) G2a chimeric version of the antibody (ch12F6A) with similar properties significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A ≥70 mg/ kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is an ongoing randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 6 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab.

  The primary objective of Study 221AD103 is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR-sum of boxes (SB) and MMSE.

  To date, ARIA has been the most frequent AE reported in the study. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. Incidence of ARIA has been observed to be both dose and Apolipoprotein E4 (ApoE ε4) carriage-dependent, especially at the highest doses (refer to the IB for details on events of ARIA).

  Protocol-defined interim analyses have demonstrated a dose- and time-dependent reduction of brain amyloid burden after 6 months of dosing (Week 26), with statistical significance achieved in the 3, 6, and 10 mg/kg groups compared with placebo, and after 1 year of dosing (Week 54), with statistical significance achieved

in the 3 and 10 mg/kg groups compared with placebo (see current IB for results of the most recent interim analysis). The results demonstrate target engagement (amyloid plaques) and a pharmacodynamic effect (dose-dependent amyloid reduction). In addition results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE, suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. At Week 54, adjusted mean change (increase) from baseline in CDR-SB score was smaller for both the 3 and 10 mg/kg groups compared with placebo, with statistical significance achieved in the 10 mg/kg group (see current IB for results of the most recent interim analysis). At Week 52, adjusted mean changes (decreases) in MMSE score from baseline were statistically significant in the 3 and 10 mg/kg groups (see current IB for results of the most recent interim analysis). Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment was statistically significant at doses of 3, 6 and 10 mg/kg after 6 months of dosing and at 3 and 10 mg/kg after 12 months of dosing (see current IB for results of the most recent interim analysis). The effect on mean decrease from baseline in CDR-SB after 12 months of dosing was observed at both 3 and 10 mg/kg (see current IB for results of the most recent interim analysis),

with statistical significance achieved at 10 mg/kg. The effect on mean decrease from baseline in MMSE score was statistically significant at 3 and 10 mg/kg. These data indicate that 3 mg/kg could be considered an acceptable dose for Phase 3 studies; however, given the dose-dependent nature of these observations, the use of higher doses (6 and 10 mg/kg) could offer greater benefit at acceptable risk.

ARIA has been identified as an event that may occur with anti-amyloid targeting drug candidates and is considered an event of special interest in the aducanumab program. To date, the incidence of ARIA has been observed to be both dose and ApoE ε4 carriage dependent, especially at the highest doses. In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Slow titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012] which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown to date, the doses to be tested using a titration regimen are 3 and 6 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6 and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows (Table 7 and Figure 1):

ApoE ε4 Carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter
- High dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter
- Placebo

  Saline infusion

ApoE ε4 Non-Carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 7: Dosing Scheme for Aducanumab by Regimen

Dose (Month)		1	2	3	4	5	6	7 to 20
Regimen		Dose (mg/kg)						
ApoE ε4 (+)	Low Dose	1	1	3	3	3	3	3
	High Dose	1	1	3	3	3	3	6
	Placebo	saline						
ApoE ε4 (-)	Low Dose	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If any of the high doses proposed (10 mg/kg in ApoE ε4 non-carriers and 6 mg/kg in ApoE ε4 carriers) is deemed not acceptable, enrollment for the high dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high dose regimens will be revised as described in Section 16.

- Benefit of titration

  A titration schedule has been implemented in this Phase 3 study and in the ongoing multiple-dose Study 221AD103. If, based upon review of the data from Study 221AD103, titration is not deemed beneficial, it will be eliminated, and subsequently enrolled subjects who are ApoE ε4 carriers will receive a fixed dose of 3 or 6 mg/kg and non-carriers will receive 6 or 10 mg/kg.

5.3.3. Long-Term Extension Period

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will continue to receive the same dose of aducanumab that they were on at the end of the placebo-controlled period. Subjects who receive placebo during the placebo-controlled period and who enter the LTE period will be assigned to 1 of 2 treatment groups, based upon their ApoE ε4 carrier status, in a 1:1 ratio (aducanumab low dose: aducanumab high dose). Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 7 and Figure 1).

Any modifications to the dosing scheme (i.e. termination of high dose groups and replacement of titration with fixed dosing, as described in Section 5.3.2) will also be implemented in the LTE period.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy 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 subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Efficacy

- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).
- [redacted]
- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- [redacted]
- To assess the correlation between primary endpoints and key biomarker endpoints.

Pharmacokinetics

- To explore the potential relationships between PK or exposure and response (e.g., clinical and biomarker endpoints) including covariate analysis.
- To explore the potential effect of co-medications on the PK of aducanumab using population PK.

6.3.2. Tertiary Endpoints

Safety and Tolerability:

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers:

- Change from baseline in amyloid PET signal at Week 26 (in a subset of subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of subjects).
- [redacted]

Efficacy:

- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject-self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78
- [redacted]
- Change from baseline in mPDQ-20 at Week 78.
- [redacted]
- Correlation between clinical and biomarker endpoints over time.

Pharmacokinetics

- Serum concentrations of aducanumab, population PK parameters of aducanumab including but not limited to clearance and volumes of central and peripheral compartments.

6.4. Long-Term Extension Objectives and Endpoints

6.4.1. Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.
- [redacted]

6.4.2. Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of subjects).
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.
  - [redacted]
  - [redacted]
  - [redacted]

7. STUDY DESIGN

7.1. Study Overview

Study 221AD301 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional 24-month dose-blind LTE study. Approximately 1350 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Subject enrollment will be monitored so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a 24-month long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (a total of 26 doses).

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of approximately 18 weeks after the final dose.

The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will be up to approximately 206 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 100-week aducanumab dose-blind treatment period, and a safety FU period of approximately 18 weeks after the final dose. The FU period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 6 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 7 and Figure 1. Subjects who received

aducanumab in the placebo-controlled period and who enter the LTE period will receive the same dose of aducanumab that they received at the end of the placebo-controlled period (up to 6 mg/kg and 10 mg/kg in ApoE ε4 carriers and non-carriers, respectively). Subjects who received placebo during the placebo-controlled period and who enter the LTE period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose; aducanumab high dose); aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented to subjects who develop ARIA. See Section 7.2.1.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE period, Investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE period.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification, or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the PI within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the PI; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Guidelines on the management and disposition of ARIA-E and ARIA-H 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. Dosing may also be terminated at the discretion of the Sponsor for medical reasons. See Section 10.1 for the full list of criteria for discontinuing study treatment.

7.2.1.1. Disposition of ARIA-E Cases

Table 8: Disposition of ARIA-E Cases

Clinical Symptom Severity	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 subject may resume dosing at the same dose.	
Mild	Suspend dosing. Once ARIA-E and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[1]			
Serious, except for "other medically important event"[2]	Discontinue Dosing		

[1] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above and as described in Section 15.3.3.

[2] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.3.3.

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.
- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the subjects remain asymptomatic, the subjects may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.

- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by mild, moderate, severe, or serious ("other medically important event" only) clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the clinical symptoms have resolved, the subject may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.
- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except "other medically important event") clinical symptoms** at any time during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection approximately every 4 weeks until the ARIA-E has resolved per centrally read MRI.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.2. ARIA-H (Microhemorrhage)

In this study, new incident microhemorrhages are defined as new incident microhemorrhages that occur on treatment and do not include microhemorrhages at baseline.

Table 9: Disposition of ARIA-H (Microhemorrhage) Cases

Clinical Symptom Severity	New Incident Microhemorrhages[1] (Central Read)		
	≥1 and ≤4	≥5 and ≤9	≥10
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing. Once ARIA-H is stable, the subject may resume dosing at the same dose.	Discontinue dosing
Mild	Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[2]			
Serious, except for "other medically important event"[3]	Discontinue dosing		

[1] New incident microhemorrhages = new incident microhemorrhages on treatment; does not include microhemorrhages at baseline.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.3.3.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.3.3.

Asymptomatic ARIA-H (Microhemorrhage)

- Subjects who develop a **≥1 and ≤4 new incident microhemorrhage(s)** at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥5 and ≤9 new incident microhemorrhages** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the microhemorrhage is confirmed as stable per the centrally read MRI. A microhemorrhage is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.

- Subjects who develop ≥ **10 new incident microhemorrhages** during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the microhemorrhages are deemed stable per centrally read MRI.

Symptomatic ARIA-H (Microhemorrhage)

- Subjects who develop ≤ **9 new incident microhemorrhages and mild, moderate, severe, or serious ("other medically important event" only [Section 15.3.3]) clinical symptoms** will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the ARIA-H (microhemorrhage(s)) is confirmed stable per the centrally read MRI. Microhemorrhages are considered stable if they are unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once ARIA-H (microhemorrhage) is deemed stable and the clinical symptoms have resolved, the subject may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.
- Subjects who experience **serious (except "other medically important event" [Section 15.3.3]) clinical symptoms associated with microhemorrhage(s)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the microhemorrhage(s) is confirmed stable per centrally read MRI.
- Subjects who develop ≥ **10 new incident microhemorrhages**, regardless of symptom severity, during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the microhemorrhages are deemed stable per centrally read MRI.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.3. ARIA-H (Superficial Siderosis)

Table 10: Disposition of ARIA-H (Superficial Siderosis) Cases

Clinical Symptom Severity	New Incident Areas of Superficial Siderosis[1] (Central Read)		
	1	2	>2
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing. Once ARIA-H is stable the subject may resume dosing at the same dose.	Discontinue dosing
Mild	Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[2]			
Serious, except for "other medically important event"[3]	Discontinue dosing		

[1] New incident superficial siderosis = new incident superficial siderosis on treatment.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.3.3.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.3.3.

Asymptomatic ARIA-H (Superficial Siderosis)

- Subjects who develop a **single incident focal area of hemosiderosis (also referred to as superficial siderosis)** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the superficial siderosis is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 2 weeks (±3 days) later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis)** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Superficial siderosis is considered

stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the superficial siderosis is deemed stable, the subjects may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.

- Subjects who develop >**2 focal areas of hemosiderosis (superficial siderosis)** occurring at any time during the study must permanently discontinue treatment and should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later.

Symptomatic ARIA-H (superficial siderosis)

- Subjects who develop ≤**2 new focal areas of superficial siderosis** and **mild, moderate, severe, or serious ("other medically important event" only)** clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the ARIA-H superficial siderosis is confirmed stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the ARIA-H (superficial siderosis) is deemed stable and the clinical symptoms have resolved, the subjects may resume treatment at the same dose. Only subjects who have not missed more than 4 consecutive doses will be allowed to resume treatment.
- Subjects who experience **serious (except "other medically important event" [Section 15.3.3]) clinical symptoms associated with ARIA-H (superficial siderosis)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the superficial siderosis is confirmed stable per centrally read MRI.

- Subjects who develop **>2 new focal areas of superficial siderosis** regardless of clinical symptom severity will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the superficial siderosis is confirmed stable per centrally read MRI.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.4. ARIA-H (Macrohemorrhage)

- Subjects who develop any new incident macrohemorrhage, regardless of symptom severity during the study, will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the macrohemorrhage is confirmed stable per centrally read MRI.

7.2.1.5. Disposition of Coincident ARIA-H and ARIA-E Cases

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow the most restrictive guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H must be deemed stable, and the subject must be asymptomatic. For example, if a subject experiences asymptomatic ARIA-H (1–4 microhemorrhages) coincident with ARIA-E assessed as moderate on MRI and accompanied by mild clinical symptoms, the dose should be suspended per the ARIA-E guidelines summarized in Table 11.

7.2.1.6. Resumption of Study Treatment After Suspension due to ARIA

7.2.1.6.1. MRI Monitoring

When treatment resumes after a dose suspension due to ARIA, an MRI and MOCA will be performed as well as biomarker and PK sample collection 2 weeks (±3 days) after the second administration of the restarted dose if they do not have a scheduled MRI occurring during this period. In addition, if treatment was suspended during the dose titration prior to the subject reaching the maximum assigned dose, an MRI and MOCA will be performed as well as biomarker and PK sample collected 2 weeks (±3 days) after the second administration of each increase in dose. MRIs will otherwise be performed as indicated in the Schedules of Events (Section 4.2).

7.2.1.6.2. Dosing Upon Resumption of Study Treatment

Subjects who suspend treatment due to ARIA for the first time may resume treatment at the same dose if they meet the criteria as described in Sections 7.2.1.1 to 7.2.1.5. Subjects who suspend and then resume dosing after having already reached their assigned top dose level are to continue dosing at that dose level. However, if dosing is suspended during the dose titration period, the

subject (1) must receive at least 2 doses at the restart dose before titrating up to the next dose level and (2) must complete at least the required number of doses at that dose level per their assigned dosing regimen, as outlined in Table 11.

Table 11: Resumption of Study Treatment Following Dose Suspension Due to ARIA During Titration

Assigned Dosing Regimen (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses Needed Before Going to the Next Higher Dose
ApoE ε4 (+)			
Low Dose (3 mg/kg)	1 mg/kg	1	2
High Dose (6 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	3
	3 mg/kg	2	2
	3 mg/kg	3	2
	3 mg/kg	4	2
ApoE ε4 (-)			
Low Dose (6 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	3
	3 mg/kg	2	2
	3 mg/kg	3	2
	3 mg/kg	4	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2
	6 mg/kg	1	2
	6 mg/kg	2	2

7.2.1.7. Management After Recurrent ARIA (Dosing and MRI)

If the subject has a second occurrence of ARIA (i.e., a second occurrence of ARIA-E or of ARIA-H, or ARIA-E and ARIA-H) that requires dose suspension, after the ARIA-E resolves or stabilizes, the subject is to resume dosing at the next lower dose and is to receive 2 doses at that

dose level (i.e., the restart dose) before titrating up to the next higher dose. Once dosing has resumed, the guidelines outlined in Table 11 apply, unless the subject has reduced from 1 mg/kg to placebo. In this case, the subject will remain on placebo for the duration of the placebo-controlled portion of the study. If a subject resumes treatment after ARIA, an MRI and MOCA will be performed as well as biomarker and PK sample collection 2 weeks (±3 days) after the second administration of the restarted dose, and 2 weeks (±3 days) after the second administration of each increase in dose unless the subject has a scheduled MRI during this period. MRIs will otherwise be performed as indicated in the Schedules of Events (Section 4.2).

If the subject experiences a third episode of ARIA that requires dose suspension, the subject must discontinue study treatment. Subjects who discontinue treatment are to remain in the study and continue all protocol-required tests and assessments.

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE period and will receive the lowest dose that they have tolerated during the placebo-controlled period. A subject who is switched to placebo but remains in the study may be titrated to aducanumab 1 mg/kg during the LTE period.

7.2.2. 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 Directions for Handling and Administration (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 subject will be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of screening, treatment, and FU.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety FU period of 18 weeks after the final dose.

Subjects will have approximately 32 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety FU contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days). It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and subject to Sponsor approval.

- 20 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 3 visits for clinical assessments.
- [redacted]
- 3 visits (including Screening) for amyloid PET scan (in a subset of subjects).
- [redacted]
- 6 visits for brain MRI.
- 1 FU safety visit at Week 94 (only for subjects not entering the LTE period) or 18 weeks after last administration of study treatment for those subjects who withdraw from study.

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period. Subjects who enter the LTE period will have approximately 36 additional planned clinic visits, and up to 8 telephone safety FU contacts, as follows:

- 26 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 4 visits for clinical assessments.
- [redacted]
- 2 visits for amyloid PET scan (in a subset of subjects).
- [redacted]
- 7 visits for brain MRI.
- 1 FU safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate (optional) initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, and the Repeatable Battery for Assessment of Neuropsychological Status [RBANS]). This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments.

Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE and RBANS) must be performed at Screening Visit 1. The ADAS-Cog 13 and ADCS-ADL-MCI will be performed at Screening Visit 2 within 20 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE and RBANS. The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1). All other cognitive assessments [redacted] may be performed at any time during Screening after eligibility is confirmed during Screening Visit 1. The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and subject to Sponsor approval.

Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion. Subjects who fail Screening due to PET, MMSE, CDR, hepatitis B or C results, or abnormal MRI findings will not be allowed to rescreen.

Subjects who fail Screening because allowed chronic medications have not been at stable doses for at least 4 weeks prior to Screening Visit 1 or whose use of AD medications has not been at stable doses for at least 8 weeks prior to Screening Visit 1 may return for rescreening after use of these medications has been stabilized for the required period.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period and will receive study treatment every 4 weeks for an additional 100 weeks (26 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE period are to return to the study site for an FU Visit at Week 94 (18 weeks after the last dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE period are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A FU Visit will occur at Week 198 (18 weeks after the last LTE dose). The final study visit for subjects participating in the LTE period will be Week 198.

Subjects who discontinue treatment are to remain in the study and continue all protocol-required tests and assessments until the end of the study or until withdrawal of consent. Subjects are encouraged to return for FU assessments approximately 18 weeks after their last dose of study treatment, as are subjects who withdraw from the study.

7.4. Study Stopping Rules

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

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

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

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of Screening) is permissible for subjects not participating in the amyloid PET cohort. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR-Global Score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index (DMI) score).
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and Screening assessments.
8. Must consent to apolipoprotein E (Apo E) genotyping.
9. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. Exclusion Criteria

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

Medical History

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, lewy body dementia, fronto-temporal dementia, head trauma).
2. Clinically significant psychiatric illness (e.g., uncontrolled major depression, schizophrenia, bipolar affective disorder) within 6 months prior to Screening.
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >1 cm in diameter on T2* sequence) unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as >1.5 cm in diameter).
   - >1 lacunar infarct (defined as ≤1.5 cm in diameter).
   - Superficial siderosis.
   - 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 subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Presence of diabetes mellitus that, in the judgment of the Investigator, cannot be controlled or adequately managed.
7. 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.

8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings >165/100 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 subject to be eligible for the study), or persistent SBP/DBP readings >180/100 mmHg 3 months prior to randomization (Day 1) that in the opinion of the Investigator are indicative of chronic uncontrolled hypertension.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma.
    - Subjects with prostate cancer in situ.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or known seropositivity for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody IgG, and positive HBcAb) are eligible to participate in the study (US Centers for Disease Control and Prevention's interpretation of the hepatitis B serology panel).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).
19. Any other medical conditions (e.g., renal disease) that are not stable or controlled, or, which in the opinion of the Investigator, could affect the subject's safety or interfere with the study assessments.

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 or use of AD 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 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any passive immunotherapy study targeting Aβ within 12 months of Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 12 months prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures

29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (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, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 6 months prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

33. For subjects who consent to lumbar puncture (LP), any contraindications to having a LP (e.g., platelet count <100,000/μL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during Screening must be resolved prior to randomization. Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR, hepatitis B or C, or abnormal MRI findings.
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension Period

To be eligible to participate in the LTE period, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses. Subjects who do not meet these criteria can enter the LTE period only with Sponsor's approval.
2. MMSE score >15 at the Week 78 Visit.
3. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
4. Female subjects of childbearing potential and male subjects must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment.
5. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
6. Must have the ability to comply with procedures for protocol-related tests.
7. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally

be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long-Term Extension Period

Subjects will be excluded from entering the LTE period if at Week 78 they have:

1. Any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any Screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) to determine study eligibility under a separate, optional initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further Screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all Screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scan issues and subject to Sponsor approval. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the Screening log. The total study duration for each subject participating only in the placebo-controlled period will be approximately 102 weeks (approximately an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of FU).

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier), so that approximately 60% to 70% ApoE ε4 carriers are enrolled. Enrollment will also be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE period with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating HCPs should

remain blinded to treatment assignment as well as subject care management and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. As 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 subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

For the LTE period, the dose information must remain restricted. The rating and treating HCP should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by serious clinical symptoms except for "other medically important event" as defined in Table 8.
  - Symptomatic ARIA-H (microhemorrhages) with serious clinical symptoms except for "other medically important event" as defined in Table 9.
  - Symptomatic ARIA-H (superficial siderosis) with or serious clinical symptoms except for "other medically important event" as defined in Table 10.
  - ARIA-H with ≥10 microhemorrhages and/or >2 focal areas of superficial siderosis.
  - Any new incident macrohemorrhage.
  - A third recurrence of ARIA after rechallenge that requires dose suspension

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria.
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

A subject who discontinues treatment is to remain in the study and continue protocol-required tests and assessments until the end of the study or until the subject withdraws consent. The site

is to contact the Sponsor as soon as possible after discontinuation to confirm whether the efficacy assessments outlined for the EOT Visit in Section 4.2 need to be performed.

10.2. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

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

Subjects who are withdrawn from the study after receiving ≥1 doses of study treatment should complete the EOT Visit after the reason for withdrawal is identified. For such subjects, the site is to contact the Sponsor as soon as possible after withdrawal to confirm whether the efficacy assessments outlined for this visit in Section 4.2 need to be performed. These subjects are also to return to the site for a FU Visit 18 weeks after receiving their last dose of study treatment.

11. STUDY TREATMENT USE

11.1. Regimen

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

Please see Section 4.2 (Schedule of Events) for the study treatment infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

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

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.2 (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.

11.3. Precautions

Not applicable.

11.4. Compliance

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

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to Screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and until the subject'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.

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given <10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids (including inhaled and topical corticosteroids) are allowed; certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended, with the exception of medications used to treat AEs, which would not result in automatic withdrawal. The Sponsor may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures) performed between the time the subject is enrolled in the study and until the subject's final clinic visit (including FU visit), unless the subjects is being followed for study-related toxicity.

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

11.6. 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.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

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

Aducanumab is a recombinant human antibody expressed in a Chinese hamster ovary cell line [redacted], 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. [redacted] Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing aducanumab 50 mg/mL, [redacted] Aducanumab is manufactured in accordance with Good Manufacturing Practices.

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

12.1.1. Aducanumab 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 Biogen.

12.1.2. Aducanumab Storage

Study treatment must be stored in a secure location. Aducanumab is to be stored at 2° 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 2 hours, then it should be kept at 2° to 8°C 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.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (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 personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab 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 (subject-by-subject 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 Biogen. A written explanation must be provided for any discrepancies.

12.2. 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.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

To confirm amyloid pathology at Screening, PET scans will be performed using Amyvid™ (^{18}F-florbetapir), Vizamyl™ (^{18}F-flutemetomol), or Neuraceq™ (^{18}F-florbetaben). For those subjects participating in the amyloid PET substudy, Screening and FU scans must be performed using Amyvid. For subjects participating in the PET substudy in Japan, Vizamyl (^{18}F-flutemetomol) will be used. For details on PET imaging ligands, [redacted] refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

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

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

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

13.2. Pharmacokinetic Assessments

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

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the pharmacodynamic properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the amyloid PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in the amyloid PET substudy.

- [redacted] for MRI.
- [redacted]
- [redacted]
- [redacted]
- [redacted]

13.4. Additional Assessments

[redacted]

13.4.2. ApoE Genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

[redacted]

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- [redacted]
- mPDQ-20
- [redacted]

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

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

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

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

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale.

14.2. Laboratory Safety Assessments

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

- Hematology: complete blood count with differential and 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, virology (including HIV at the Investigator's discretion after consideration of risk factors), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier anti-drug antibody (ADA) approach will be used (i.e., Screening assay, confirmatory assay, and titration assay). Confirmed antidrug antibody-positive samples will be tested for the presence of anti-aducanumab neutralizing antibodies using a validated assay.

15. 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 subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 laboratory finding), 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 laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the Investigator considers to be clinically significant.

Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.1.2. 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 subject 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.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject 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.)

15.1.3. 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 subject is hospitalized. The study site must document all of 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 subject's consent to participate 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 subject's consent to participate 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 subject 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 15.1.2 is met.

15.2. Safety Classifications

15.2.1. 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 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

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.

15.2.3. Severity of Events

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

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the subject's final clinic visit (including FU visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H 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.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to [redacted].

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between signing of the ICF and the subject's final clinic visit (including FU visit) will be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. This also applies to SAEs that occur after administration of the ligand. FU information regarding an SAE also must be reported with 24 hours.

Events occurring after the subject's final clinic visit (including FU visit) should be reported to Biogen only if the Investigator considers the SAE related to study treatment.

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

15.3.4. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the subject's final clinic visit (including FU visit) must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to [redacted] regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event

- The relationship of the event to study treatment

To report initial or FU information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Guide for country-specific [redacted] fax numbers or email [redacted]

15.3.4.1. 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. The Investigator should make every effort to obtain and send death certificates and autopsy reports to [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

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

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to [redacted] within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to [redacted].

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in 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 to [redacted] within 24 hours of the site becoming aware of the overdose. An overdose must be reported to [redacted] 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 to [redacted] All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. 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 [redacted] 24-hour emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

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

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the [redacted] 24-hour emergency medical support number at [redacted].

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

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.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of this study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.

- Placement of an intrauterine device or intrauterine system
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (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.
- Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at FU.
  - Use of condoms with spermicide.
  - Female sexual partners who underwent surgical sterilization (e.g., bilateral tubal ligation), are postmenopausal, are post-hysterectomy, or are using highly effective contraception as listed above for female subjects.

  For males and females of childbearing potential:

  True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, 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, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, 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 and FU on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of the event.

- Pursue SAE FU information actively and persistently. FU information must be reported to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE FU information, if possible, until the event has resolved or become stable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor ([redacted]) is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects 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 each aducanumab regimen and placebo. All statistical tests will be 2-sided.

16.2.2.2. Dose Regimens to be Evaluated

The following dose regimens of aducanumab as compared with placebo will be evaluated:

- Aducanumab high-dose regimen (6 mg/kg in ApoE ε4 carriers and 10 mg/kg in ApoE ε4 non carriers).
- Aducanumab 6 mg/kg dose regimen (6 mg/kg in ApoE ε4 carriers and ApoE ε4 non-carriers).
- Aducanumab low-dose regimen (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the proposed maximum dose (10mg/kg in ApoE ε4 non-carriers or 6 mg/kg in ApoE ε4 carriers) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose regimen and aducanumab low dose regimen will be modified as shown in Table 12. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of

Type I error rate is thus maintained without a statistical adjustment for such adaptations[Chow and Chang 2011].

Table 12: Dose Group Pooling Strategy in the Event of Treatment Group Termination

Treatment group(s) Terminated	Definitions of Revised Pooled Treatment Groups for Comparison
ApoE ε4 carrier high-dose group (6 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 6 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group (6 mg/kg) AND ApoE ε4 non-carrier high-dose group (10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose regimen versus placebo, aducanumab 6 mg/kg regimen versus placebo, and aducanumab low-dose regimen versus placebo. In the event of a dosing modification (see Table 12), the first comparison is the aducanumab high-dose regimen versus placebo and the second comparison is the aducanumab low-dose regimen versus placebo. If the first comparison is statistically significant ($p \leq 0.05$), then the second comparison will also be made at the 0.05 α level. If the second comparison is statistically significant ($p \leq 0.05$), then the third comparison will also be made at the 0.05 α level. However, all comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for one, two or all three comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1, 2, or all 3 comparisons, respectively.

Due to a current lack of scientific consensus in the AD field on which biomarker(s) might be most appropriate, the selection of the biomarkers and methodology for control of Type I error will be pre-specified in the statistical analysis plan (SAP). Otherwise, there will be no multiple comparison adjustments for the tertiary endpoints.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population with a baseline and at least one post-baseline CDR-SB score. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change From Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population with a baseline and at least one post-baseline MMSE value. A MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction and baseline ApoE ε4 status

16.2.2.5.2. Change From Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADAS-Cog 13 score. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction; baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5.3. Change From Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADCS-ADL-MCI score. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction; baseline MMSE, and baseline ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, a MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE and baseline ApoE ε4 status.

Otherwise, an analysis of covariance or its non-parametric equivalent may be used to analyze these exploratory endpoints.

16.2.2.6.2. Long-Term Extension Period

The additional endpoints for the LTE period are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the placebo-controlled period using the placebo-controlled period baseline. Details of the analyses will be pre-specified in the SAP.

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The population PK characteristics of aducanumab will be determined by nonlinear mixed effects approach. Covariates that might influence the disposition of aducanumab (e.g., body weight, age, sex, immunogenicity, ApoE ε4 status) will be evaluated and the potential exposure-response relationships will be explored.

16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of study treatment (including placebo and aducanumab).

16.4.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.4.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent 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 study treatment for the placebo-controlled period and over the 24-month LTE period. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.4.2.2. 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. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.4.2.3. Vital Signs

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

16.4.2.4. ECG

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

16.4.2.5. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale data will be summarized by treatment group.

16.5. Immunogenicity Data

16.5.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.5.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.6. Interim Analyses

16.6.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.6.2. Interim Superiority Analysis

An interim analysis for superiority may be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The Lan-DeMets method with O'Brien-Fleming stopping boundary for efficacy will be used. In order to maintain the treatment blind in the event of this interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.7. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103 which included 1 year data from 1, 3 and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group will have approximately 90% power to detect a true mean difference of 0.5 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, a SD of 1.92 and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflects a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

The sample size may be reassessed in a blinded manner approximately 3 months before enrollment is complete if at least 15% of the data are available on the primary endpoint. At this interim time-point, the SD for the primary endpoint will be estimated based on the blinded data. The sample size may be increased if the SD is estimated to be more than approximately 2.07. In addition, the sample size could be increased using external clinical trial results that become available after the start of the study.

17. ETHICAL REQUIREMENTS

Biogen[redacted], and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

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.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

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

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

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) as an initial optional screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed

prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

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

Subjects will be informed that their race and/or ethnicity will be collected and will be used during analysis of study results (only in countries where permitted by local law/regulation).

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The 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 (wet signature) and copies of the signed and dated ICFs.

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

17.4. Subject Data Protection

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

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

During the study, subjects' race and/or ethnicity will be collected (only in countries where permitted by local law/regulation). These data may be used in the analysis of the safety, efficacy, and/or pharmacokinetic profile of the study treatment. It is unknown if the potency or effects of the study treatment are influenced by race or ethnicity.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. 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 subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights and a user manual.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by [redacted] and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen 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, [redacted], and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA 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.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen 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 PI 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 collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen 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 per project-specific plans.

19.2. Study Committees

19.2.1. 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 subject accrual and oversee study conduct, including advising on study design and execution. The advisory committee will be blinded to subject treatment assignments during the study.

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

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. 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 subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), 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.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB 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, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. 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 Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. 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 laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen 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.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study 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 subject enrollment, or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early 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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PROTOCOL NUMBER: 221AD301/NCT02477800

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000966-72**

DATE: 24 March 2017
Version 4.0
Final

Supersedes previous Version 3.0 dated 21 July 2016.

SPONSOR SIGNATURE

Protocol 221AD301 was approved by:

[redacted]

[redacted], PhD

[redacted]

Biogen MA Inc.

27 March 2017

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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Please refer to the Study Reference Manual for complete contact information.

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

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab, produced in a different Chinese hamster ovary cell line
Aβ	β-amyloid
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibodies
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
[redacted]	[redacted]
AST	aspartate aminotransferase
[redacted]	[redacted]
CDR	Clinical Dementia Rating
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
[redacted]	[redacted]
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject
EQ-5D (SR)	EuroQol health status measure, subject self-reported

FU	Follow-up
GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCP	health care professional
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPI-10	Neuropsychiatric Inventory-10
PBMC	Peripheral blood mononuclear cells
PD	pharmacodynamic
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RNA	ribonucleic acid
SABR	Safety and Benefit-Risk
SAE	serious adverse event
SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction

TEAE	treatment-emergent adverse event
[redacted]	[redacted]

3. SYNOPSIS

Protocol Number:	**221AD301**
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	4.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-Sum of Boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy 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 subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78. Secondary objectives and endpoints are as follows: To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by • MMSE - Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13] - Change from baseline in ADAS-Cog 13 at Week 78

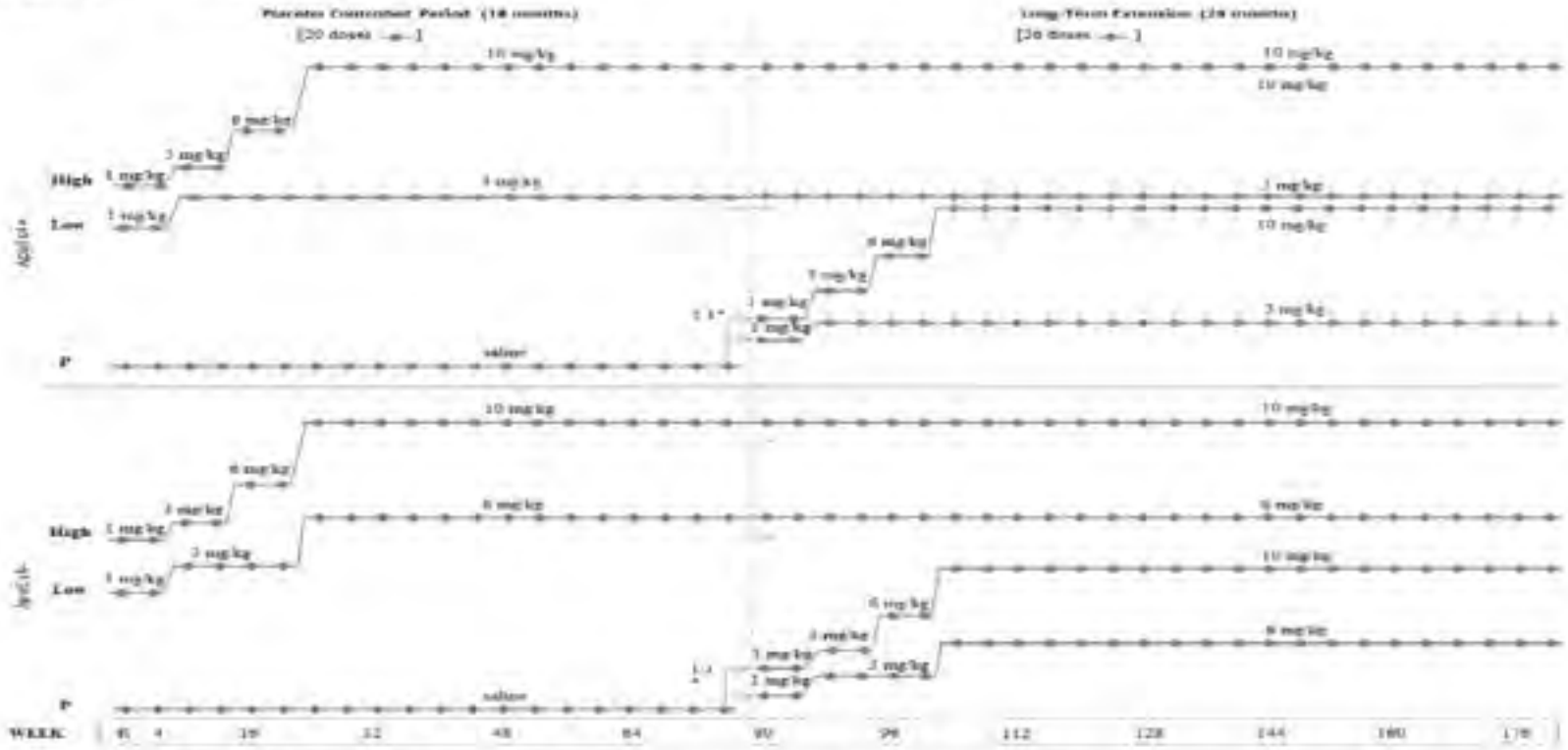
Protocol Number:	**221AD301**
	• Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] - Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension period of the study):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological and additional assessments reported by the subject and informant/care partner. Endpoints for the long-term extension (LTE) period of the study are listed in Section 6.4.2.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled, parallel-group period followed by an optional 24-month dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1350 subjects will be enrolled
Study Population:	This study will be conducted in subjects with early AD, including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD according to NIA-AA criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator, based on medical history and the Screening assessments. The ratio of apolipoprotein ε4 (ApoE ε4) carriers to non-carriers in the study population will reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (10 mg/kg)** **Placebo** **ApoE ε4 non-carrier**

Protocol Number:	221AD301
	Low dose (6 mg/kg) **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a 24-month dose-blind LTE study during which all subjects will receive aducanumab.
Duration of Treatment and Follow Up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow up [FU]). For subjects who enter the optional LTE period, the total duration will be approximately 206 weeks or 47 months (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, 4 weeks of FU, 100 weeks of dose-blind aducanumab dosing, and 18 weeks of FU).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD301

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; LTE = long-term extension; R = randomization date.
*Subjects who are assigned to placebo during the placebo-controlled period and are continuing into the LTE period will be randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status).

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule From Screening Through Week 48

Study Week	Screening (≤ 60 days before Day 1)[1]			Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	V1	V2	V3	1	29 ± 3	57 ± 3	85 ± 3	113 ± 3	141 ± 3	169 ± 3	183 ± 3	197 ± 3	225 ± 3	253 ± 3	281 ± 3	309 ± 3	337 ± 3	
Initial Screening Consent[2] (optional)	X																	
Full Informed Consent[2]	X																	
Eligibility Criteria	X	X	X	X[4]														
Demography	X																	
Medical History	X	X	X															
Alcohol/Drug Screen	X																	
HbA_{1c}	X																	
HIV[5]/Hepatitis/ Coagulation	X																	
ApoE Genotyping	X																	
[redacted]																		
Height	X																	
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Serum Pregnancy Test[7]	X																	
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X	
Physical Examination	X						X			X							X	

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medication**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Neurological Examination	X						X			X							X	
12-lead Paper ECG	X									X							X	
Vital Signs[8]	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis	X			X						X							X	
Randomization				X														
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X	
Anti-Aducanmab Ab[9]				X						X			X					
Aducanmab Concentration[10]				X[11]	X[11]		X[11]	X	X[11]	X[11]		X[11]	X					
[redacted]																		
PBMC Collection	X						X	X		X			X					
[redacted]																		
Amyloid PET[14]			X								X							
[redacted]																		
RBANS	X																	
CDR	X										X							X
MMSE	X										X							X

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	V1	V2	V3	1	29 ± 3	57 ± 3	85 ± 3	113 ± 3	141 ± 3	169 ± 3	183 ± 3	197 ± 3	225 ± 3	253 ± 3	281 ± 3	309 ± 3	337 ± 3	
ADCS-ADL-MCI		X[16]									X							X
ADAS-Cog 13		X[16]									X							X
NPI-10		X[17]									X							
EQ-5D (SR)		X[18]									X							
EQ-5D (IR-S)		X[18]									X							
[redacted]																		
mPDQ-20		X[19]									X							
[redacted]																		
C-SSRS				X							X							
AE Reporting				Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																	
SAE Reporting	Monitor and record continuously throughout the study																	

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E; [redacted]; CDR = Clinical Dementia Rating scale; CRO = contract research organization; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted]; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; HbA_{1c} = glycosylated hemoglobin; HIV = human immunodeficiency virus; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; [redacted]; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; Wk = Week.

[1] Examinations required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 3) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.
[2] Subjects may sign this optional form for an initial screening which allows administration of the RBANS, CDR and MMSE only.
[3] All subjects must sign this informed consent, including subjects who have signed the optional initial screening consent once they have met the RBANS, CDR, and MMSE eligibility criteria.
[4] All assessments, including the C-SSRS, must be completed before study treatment administration, except the post-dose sample to measure aducanumab concentration.
[5] HIV testing is at the Investigator's discretion after consideration of risk factors.
[redacted]
[7] Required for women of childbearing potential only (see Section 15.5).
[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.
[9] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study treatment infusion.
[10] Blood sampling for aducanumab concentration will be performed prior to infusion. Note: For subjects who permanently discontinue treatment and continue in the study, the final aducanumab concentration sample will be collected at the subject's next visit.
[11] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.
[redacted]
May be collected at any point in time during Screening after eligibility at V1 is confirmed but if collected on the same day as an MRI, it should be collected after the MRI is performed.
[14] Screening amyloid PET is required for all subjects; amyloid PET at Week 26 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy. The amyloid PET at Week 26 may be scheduled within a window of ±7 days.
[redacted]
[16] Must be performed within 20 days of V1, but not on the same day as the screening RBANS, CDR, or MMSE.
[17] The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1).
[18] May be performed at any point during screening after the subject has met eligibility criteria on the RBANS, CDR, and MMSE.

Table 2: Placebo-Controlled Period Schedule From Week 50 to End of Treatment or Follow-Up

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 weeks after final dose for subjects who terminate treatment early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Informed Consent									X[3]		
Eligibility Criteria									X[3]		
Body Weight		X	X	X	X	X	X	X			X
Urine Pregnancy Test[4]		X	X	X	X	X	X	X			X
Physical Examination							X		X		X
Neurological Examination							X		X		X
12-lead Paper ECG							X		X		X
Vital Signs[5]		X	X	X	X	X	X	X			X
Hematology, Blood Chemistry and Urinalysis							X		X		X
Study Treatment Infusion		X	X	X	X	X	X	X			
Anti-Aducanumab Ab[6]			X						X		X
Aducanumab Concentration[7]		X[8]	X						X		X
[redacted]											
PBMC Collection			X						X		X
[redacted]											
Amyloid PET[10]									X		
[redacted]											

Study Week											FU[1]
	50	52	56	60	64	68	72	76	78 (EOT)[2]	UV for a Change in AD Medication	94 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	351 ± 3	365 ± 3	393 ± 3	421 ± 3	449 ± 3	477 ± 3	505 ± 3	533 ± 3	547 ± 3		659 ± 7
CDR	X								X	X	X
MMSE	X								X	X	X
ADCS-ADL-MCI	X								X	X	X
ADAS-Cog 13	X								X	X	X
NPI-10	X								X		
EQ-5D (SR)	X								X		
EQ-5D (IR-S)	X								X		
[redacted]											
mPDQ-20	X								X		
[redacted]											
C-SSRS		X							X		
AE Reporting				Monitor and record continuously throughout the study							
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study										
SAE Reporting	Monitor and record continuously throughout the study										

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); [redacted] CDR = Clinical Dementia Rating scale; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events. Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases.

[3] Only for subjects entering the long-term extension period.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[6] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study treatment infusion.

[7] Blood sampling for aducanumab concentration will be performed prior to infusion. Note: For subjects who permanently discontinue treatment and continue in the study, the final aducanumab concentration sample will be collected at the subject's next visit.

[8] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[9] [redacted]

[10] Amyloid PET at Week 78 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy and may be scheduled within a window of ±7 days.

[redacted]

Table 3: Brain MRI, ARIA Management, and Follow-up Phone Call Schedule During the Placebo-Controlled Period

Study Week	Screening (≤ 60 days before Day 1)[1]			Placebo-Controlled Period													Unscheduled Visit/ MRI for ARIA[4]	FU[2]
				1	2	6	10	14	18	22	26	30	42	54	66	78/ EOT[3]		94 (or 18 weeks after final dose for subjects who discontinue treatment early)
Study Day	V1	V2	V3	1	15 ± 3	43 ± 3	71 ± 3	99 ± 3	127 ± 3	155 ± 3	183 ± 3	211 ± 3	295 ± 3	379 ± 3	463± 3	547 ± 3		659 ± 7
Follow-Up Phone Call[5]					X	X	X	X	X	X	X	X						
Brain MRI[6]		X						X		X		X	X	X	X	X	X	X
Aducanumab Concentration[7]										X		X		X			X[8]	X
MOCA				X													X	
[redacted]																		
PBMC collection[9]																	X[8]	

ARIA = amyloid related imaging abnormalities; ARIA-E = amyloid related imaging abnormality-edema; ARIA-H = amyloid related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; [redacted]; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3.

[1] Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

[2] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[3] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events. Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases.

[4] For the frequency of required brain MRI, MOCA, PK, and biomarker assessments for subjects who develop ARIA-E and/or ARIA-H, see Sections 7.2.1.1 to 7.2.1.5. For the frequency of brain MRI, MOCA, PK, and biomarker assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[5] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[6] Arterial spin labeling MRI and task free functional MRI will be performed only at a subset of sites.

[7] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[8] Only at the first unscheduled visit for ARIA monitoring per episode

[9] [redacted]

Table 4: Long-Term Extension Schedule From Week 80 to Week 134

Study Week																	
	80	84	88	92	96	100	104	106	108	112	116	120	124	128	132	134	UV for a Change in AD Medication
Study Day	561 ± 5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	743 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	939 ± 5	
Randomization	X[1]																
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Urine Pregnancy Test[2]	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Physical Examination				X			X							X			
Neurological Examination				X			X							X			
12-lead Paper ECG							X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Hematology, Blood Chemistry and Urinalysis							X							X			
Anti-Aducanumab Ab[3]	X						X							X			
[redacted]																	
PBMC collection							X							X			
Aducanumab Concentration[5]	X						X							X			
Study Treatment Infusion	X	X	X	X	X	X	X		X	X	X	X	X	X	X		

Study Week																	
	80	84	88	92	96	100	104	106	108	112	116	120	124	128	132	134	UV for a Change in AD Medication
Study Day	561 ± 5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	743 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	939 ± 5	
[redacted]																	
Amyloid PET[1]															X		
[redacted]																	
CDR								X								X	X
MMSE								X								X	X
ADAS-Cog 13								X								X	X
ADCS-ADL-MCI								X								X	X
NPI-10								X								X	
EQ-5D (IR-S)								X								X	
[redacted]																	
C-SSRS								X								X	
AE Reporting	Monitor and record continuously throughout the study																
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																
SAE Reporting	Monitor and record continuously throughout the study																

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); [redacted]; CDR = Clinical Dementia Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit

[1] Subjects who were in the placebo group during the placebo-controlled period will be randomized to aducanumab high and low dose (1:1 ratio).

[2] Required for women of childbearing potential only (Section 15.5).

[3] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

Table 5: Long-Term Extension Schedule From Week 136 to End of Treatment or Follow-Up

Study Week																FU[1]
	136	140	144	148	152	156	160	162	164	168	172	176	180	182 (EOT)[2]	UV for a Change in AD Medication	198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5		1387 ± 7
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Urine Pregnancy Test[3]	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Physical Examination					X							X		X		X
Neurological Examination					X							X		X		X
12-lead Paper ECG					X							X				X
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Hematology, Blood Chemistry and Urinalysis					X							X				X
Anti-aducanumab Ab[4]					X									X		X
[redacted]																
PBMC collection					X									X		X
Aducanumab Concentration[5]					X							X		X		X
Study Drug Infusion	X	X	X	X	X	X	X		X	X	X	X	X			

Study Week																FU[1]
	136	140	144	148	152	156	160	162	164	168	172	176	180	182 (EOT)[2]	UV for a Change in AD Medication	198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5		1387 ± 7
[redacted]																
Amyloid PET[5]														X		
[redacted]																
CDR								X						X	X	X
MMSE								X						X	X	X
ADAS-Cog 13								X						X	X	X
ADCS-ADL-MCI								X						X	X	X
NPI-10								X						X		
EQ-5D (IR-S)								X						X		
[redacted]																
[redacted]																
C-SSRS								X						X		
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy and procedures	Monitor and record continuously throughout the study															
SAE Reporting	Monitor and record continuously throughout the study															

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); [redacted]; CDR = Clinical Dementia Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale;

ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 198. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events. Subjects who withdraw from the LTE period prematurely are to return to the site for the EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases.

[3] Required for women of childbearing potential only (Section 15.5).

[redacted]

[6] Only for subjects who participate in the amyloid PET substudy Amyloid PET may be scheduled within a window of ±7 days.

[redacted]

Table 6: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule During the Long-Term Extension

Study Week	Long-Term Extension												Unscheduled Visit for ARIA[1]	FU[2]
	82	86	90	94	98	102	106	110	122	134	158	182[3]		198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	575 ± 5	603 ± 5	631 ± 5	659 ± 5	687 ± 5	715 ± 5	743 ± 5	771 ± 5	855 ± 5	939 ± 5	1107 ± 5	1275 ± 5		1387 ± 7
Follow-Up Phone Call[4]	X	X	X	X	X	X	X	X						
Brain MRI[5]				X		X		X	X	X	X	X	X	X
Aducanumab Concentration[6]													X[7]	
MOCA													X	
[redacted]														
PBMC collection[8]													X[7]	

ARIA = amyloid related imaging abnormalities; ARIA-E = amyloid related imaging abnormality-edema; ARIA-H = amyloid related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; FU = follow up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; [redacted].

[1] For the frequency of required brain MRI, MOCA, PK, and biomarker assessments for subjects who develop ARIA-E and/or ARIA-H, see Sections 7.2.1.1 to 7.2.1.5. For the frequency of brain MRI, MOCA, PK, and biomarker assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 198. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[3] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events. Subjects who withdraw from the LTE period prematurely are to return to the site for the Week EOT Visit; for such subjects, efficacy

assessments specified at the EOT visit are not required if the subject 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 in such cases.

[4] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[5] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites

[6] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[7] Only at the first unscheduled visit for ARIA monitoring per episode

[8] [redacted]

4.3. Additional Information

4.3.1. Site Personnel

A minimum of 3 separate heath care professionals (HCPs) are required:

1. A treating HCP (the Principal Investigator [PI] or Sub-investigator may serve as a treating HCP) who is responsible for the following:
   - Administration of Montreal Cognitive Assessment (MOCA) at Day 1 and during management of amyloid-related imaging abnormalities (ARIA) cases.
   - Management of routine neurological care of the subject.
   - Assessment (including assignment of causality) and treatment of adverse events (AEs).
   - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.
2. An independent rating HCP (designated by the PI of the site) who is responsible for administering the Clinical Dementia Rating (CDR)
3. A second independent rating HCP (designated by the PI of the site) who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI], and the Mini-Mental State Examination (MMSE)

The 2 independent rating HCPs must not be involved with any other aspect of subject 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 2 independent rating HCPs must not share any information about subjects. PIs cannot serve as rating HCPs. The treating HCPs must not discuss AEs (e.g., ARIA) with the independent rating HCPs.

To ensure consistency across sites, rating HCPs must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites must attempt to maintain the same rating HCP throughout the study for specific assessments in an attempt to remain consistent. Each subject should have the same rating HCP perform the subject's specific rating assessment throughout the study. A qualified approved back-up rater should only conduct assessments in place of the primary rater due to extenuating circumstances resulting in unavailability (e.g. due to illness, vacation, or travel). If a rating HCP has to be replaced, the new rating HCP 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 subject. As with other laboratory and clinical information, these data should NOT be reviewed by the rating HCPs.

The roles of independent raters and treating HCP are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject level. If a rater has administered the CDR to a subject they may not administer the other neurocognitive assessments to that subject 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.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy.

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne 2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after

active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience With Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine immunoglobulin (Ig) G2a chimeric version of the antibody (ch12F6A) with similar properties significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A $\geq$ 70 mg/ kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is an ongoing randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 10 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab. Note: The fixed-dose cohorts enrolled both ApoE ε4 carriers and non-carriers while the titration cohort is comprised of ApoE ε4 carriers only.

  The primary objective of Study 221AD103 is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR-sum of boxes (SB) and MMSE.

  To date, the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. Incidence of ARIA has been observed to be both dose and Apolipoprotein E4 (ApoE ε4) carriage-dependent, especially at the highest doses. The incidence of ARIA-E appeared to be lower in the group receiving titration to 10 mg/kg (comprising ApoE ε4 carriers only; 8/23[35%]) than in carriers in the 6 mg/kg and 10 mg/kg fixed-dose groups (9/21 [43%] and 11/20 [55%], respectively). The incidence of ARIA in ApoE ε4 carriers who were titrated up to 6 mg/kg(2 doses of 3 mg/kg, then 6 mg/kg) was 15% (2/13), with an overall rate of 11% (2/19) as no

ApoE ε4 non-carriers (0/6) experienced ARIA. Of note, among the subjects receiving titration to 10 mg/kg who had ARIA-E, the abnormalities were observed at the 3 and 6 mg/kg doses, before they reached 10 mg/kg. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these 12 continued treatment and received at least 10 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H. Furthermore, ARIA-E events when they occurred (in the titration group) have been either asymptomatic or associated with mild symptoms that resolved, and most subjects who had ARIA-E continued treatment (6/8; 75%) compared with only 36% (4/11) of carriers in the fixed-dose 10 mg/kg arm (refer to the IB for details on events of ARIA).

Protocol-specified interim analyses of the ongoing multiple-ascending dose Study 221AD103 have demonstrated engagement of aducanumab with amyloid plaques, a pharmacodynamic (PD) effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a slowing of clinical decline in aducanumab-treated subjects. The dose- and time-dependent reduction of brain Aβ burden observed with aducanumab treatment was statistically significant at doses of 3, 6, and 10 mg/kg after 6 and 12 months of dosing, as well as with 1 mg/kg and titration from 1 to 10 mg/kg after 12 months of dosing. Over the first year of the LTE (24 months of dosing), further dose-dependent reductions in cerebral Aβ were observed. The results demonstrate target engagement (amyloid plaques) and a PD effect (dose-dependent amyloid reduction).

In addition results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE (at fixed doses of 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg compared with placebo), suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. In the most recent interim analysis, generally consistent treatment differences were seen for the fixed-dose cohorts, and in the titration group, effects on the CDR-SB and MMSE after 1 year were generally consistent with the fixed-dose results. Compared with placebo, adjusted mean changes from baseline to Week 54 in CDR-SB scores favored all aducanumab dose regimens tested, with treatment differences of 0.5 points or greater favoring aducanumab at doses of 3, 6, and 10 mg/kg and titration to 10 mg/kg, and statistical significance seen in the 10 mg/kg and the titration groups. On the MMSE, adjusted mean decreases from baseline to Week 52 were suggested a clinically meaningful benefit in the 3 and 10 mg/kg groups and the titration group and were significantly lower in the 10 mg/kg group. Furthermore, results from the LTE for the fixed-dose regimens have demonstrated continued slowing of clinical decline in subjects continuing on aducanumab compared with subjects who switched from placebo to aducanumab in the LTE. Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes

aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results along with the observed safety and tolerability profile warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment in Study 221AD103 was statistically significant at doses of 3, 6 and 10 mg/kg after 6 months of dosing, and at 3, 6, and 10 mg/kg as well as with titration to 10 mg/kg after 12 months of dosing. On the exploratory endpoints of CDR-SB and MMSE changes from baseline, a dose-dependent slowing of clinical decline was observed for aducanumab versus placebo after 1 year of treatment. Compared with placebo, adjusted mean changes from baseline to Week 54 for CDR-SB favored all the aducanumab dose groups tested, with treatment differences of 0.5 points or greater at fixed doses of aducanumab 3, 6, and 10 mg/kg and also with titration to 10 mg/kg. On the MMSE, adjusted mean decreases from baseline to Week 52 were smaller in all dose groups than in the placebo group. Of note, on the CDR-SB, the point estimate for the titration group (comprising ApoE ε4 carriers only) was generally similar to that for the 10 mg/kg group and significantly lower than placebo in both those groups; on the MMSE, the point estimate for the titration group is generally similar to that in the 10 mg/kg group (which showed significantly less decline than placebo) and the 3 mg/kg group.

To date, the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. However, the incidence of ARIA-E, as well as discontinuations from treatment due to ARIA-E, in subjects receiving aducanumab titrated to 10 mg/kg (ApoE ε4 carriers only) appear to be reduced (8/23 [35%]) compared with fixed doses of aducanumab at 6 mg/kg (9/21[43%]) and 10 mg/kg (11/20[55%]). Furthermore, among those subjects randomized to receive aducanumab titrated to 10 mg/kg, ARIA-E occurred only at the 3 mg/kg and 6 mg/kg dose levels. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these 12 continued treatment and received at least 10 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H..

In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored in this study. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012] which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown to date, the doses to be tested using a titration regimen are 3 and 10 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6 and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (450 subjects each) in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose: placebo) as follows (Table 7 and Figure 1):

ApoE ε4 Carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

ApoE ε4 Non-Carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 7: Dosing Scheme for Aducanumab by Regimen

Dose (Month)		1	2	3	4	5	6	7 to 20
Regimen		Dose (mg/kg)						
ApoE ε4 (+)	Low Dose	1	1	3	3	3	3	3
	High Dose	1	1	3	3	6	6	10[1]
	Placebo	saline						
ApoE ε4 (-)	Low Dose	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

[1] 10 mg/kg is the target dose for all ApoE ε4 carriers assigned to the aducanumab high-dose regimen. Subjects enrolled under previous versions of the protocol and assigned to the previous high-dose regimen of 6 mg/kg will be titrated to 10 mg/kg upon receipt of at least 2 doses at 6 mg/kg.

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If the high dose (10 mg/kg) is deemed not acceptable, enrollment for the high dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high-dose regimens will be revised as described in Section 16.

5.3.3. Long-Term Extension Period

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will maintain the dosing scheme outlined in the protocol at the time of transition from the PC period to the LTE period (e.g. subjects who are on stable dosing in the PC period will continue on the same dose, subjects who are on a titration regimenduring the transition will continue to titrate into the LTE period and subjects who complete the PC period under protocol versions 1-3 and are assigned to the high dose aducanumab treatment group may up titrate to 10 mg/kg in the LTE). Subjects who receive placebo during the placebo-controlled period and who enter the LTE period will be assigned to 1 of 2 treatment groups, based upon their ApoE ε4 carrier status, in a 1:1 ratio (aducanumab low dose: aducanumab high dose). Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 7 and Figure 1).

ApoE ε4 carrier subjects who are enrolled in the LTE and randomized to the high-dose group prior to implementation of version 4 of the protocol will be allowed to titrate to 10 mg/kg. Any modifications to the dosing scheme (i.e. termination of high-dose group, as described in Section 5.3.2) will also be implemented in the LTE period.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy 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 subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Efficacy

- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).
- [redacted]
- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- [redacted]
- To assess the correlation between primary endpoints and key biomarker endpoints.

Pharmacokinetics

- To explore the potential relationships between PK or exposure and response (e.g., clinical and biomarker endpoints) including covariate analysis.
- To explore the potential effect of co-medications on the PK of aducanumab using population PK.

6.3.2. Tertiary Endpoints

Safety and Tolerability:

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers:

- Change from baseline in amyloid PET signal at Week 26 (in a subset of subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of subjects).
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Efficacy

- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject-self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78
- [redacted]
- Change from baseline in mPDQ-20 at Week 78.
- [redacted]
- Correlation between clinical and biomarker endpoints over time.

Pharmacokinetics

- Serum concentrations of aducanumab, population PK parameters of aducanumab including but not limited to clearance and volumes of central and peripheral compartments.

6.4. Long-Term Extension Objectives and Endpoints

6.4.1. Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.

- [redacted]

6.4.2. Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of subjects).
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.
  - [redacted]
  - [redacted]
  - [redacted]

7. STUDY DESIGN

7.1. Study Overview

Study 221AD301 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional 24-month dose-blind LTE study. Approximately 1350 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). The ratio of ApoE ε4 carriers to non-carriers in the study population will reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a 24-month long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (a total of 26 doses).

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of approximately 18 weeks after the final dose.

The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will be up to approximately 206 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 100-week aducanumab dose-blind treatment period, and a safety FU period of approximately 18 weeks after the final dose. The FU period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 10 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 7 and Figure 1. Note: 10 mg/kg is the target dose for all ApoE ε4 carriers in the high dose group. ApoE ε4 carriers who are enrolled in

the high dose group receiving 6 mg/kg must have received 2 or more doses at 6 mg/kg prior to being titrated up to 10 mg/kg. Subjects who received placebo during the placebo-controlled period and who enter the LTE period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose: aducanumab high dose); aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented in subjects who develop ARIA. See Section 7.2.1. .

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE period, Investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE period.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification, or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the PI within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the PI; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Guidelines on the management and disposition of ARIA-E and ARIA-H 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. Dosing may also be terminated at the discretion of the Sponsor for medical reasons. See Section 10.1 for the full list of criteria for discontinuing study treatment.

7.2.1.1. ARIA-E Cases

Table 8: Disposition of ARIA-E Cases

Clinical Symptom Severity	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 subject may resume dosing at the same dose.	
Mild	Suspend dosing. Once ARIA-E and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[1]			
Serious, except for "other medically important event"[2]	Discontinue Dosing		

[1] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above and as described in Section 15.1.2.

[2] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.
- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the subjects remain asymptomatic, the subjects may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.
- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by mild, moderate, severe, or serious ("other medically**

important event" only) clinical symptoms at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E has resolved and the clinical symptoms have resolved, the subject may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.

- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except "other medically important event") clinical symptoms** at any time during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection approximately every 4 weeks until the ARIA-E has resolved per centrally read MRI.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.2. ARIA-H (Microhemorrhage)

In this study, new incident microhemorrhages are defined as new incident microhemorrhages that occur on treatment and do not include microhemorrhages at baseline.

Table 9: Disposition of ARIA-H (Microhemorrhage) Cases

Clinical Symptom Severity	New Incident Microhemorrhages[1] (Central Read)		
	Mild	Moderate	Severe
	≥ 1 and ≤ 4	≥ 5 and ≤ 9	≥ 10
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing. Once ARIA-H is stable, the subject may resume dosing at the same dose.	Discontinue dosing
Mild	Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[2]			
Serious, except for "other medically important event"[3]	Discontinue dosing		

[1] New incident microhemorrhages = new incident microhemorrhages on treatment; does not include microhemorrhages at baseline.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Microhemorrhage)

- Subjects who develop a **≥ 1 and ≤ 4 new incident microhemorrhage(s) [mild]** at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥ 5 and ≤ 9 new incident microhemorrhages [moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the microhemorrhage is confirmed as stable per the centrally read MRI. A microhemorrhage is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.

- Subjects who develop ≥ **10 new incident microhemorrhages [severe]** during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the microhemorrhages are deemed stable per centrally read MRI.

Symptomatic ARIA-H (Microhemorrhage)

- Subjects who develop ≤ **9 new incident microhemorrhages (mild or moderate) and mild, moderate, severe, or serious ("other medically important event" only [Section** 15.1.2**]) clinical symptoms** will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the ARIA-H (microhemorrhage(s) is confirmed stable per the centrally read MRI. Microhemorrhages are considered stable if they are unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once ARIA-H (microhemorrhage) is deemed stable and the clinical symptoms have resolved, the subject may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.
- Subjects who experience **serious (except "other medically important event" [Section** 15.1.2**]) clinical symptoms associated with microhemorrhage(s)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the microhemorrhage(s) is confirmed stable per centrally read MRI.
- Subjects who develop ≥ **10 new incident microhemorrhages (severe)**, regardless of symptom severity, during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the microhemorrhages are deemed stable per centrally read MRI.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.3. ARIA-H (Superficial Siderosis)

Table 10: Disposition of ARIA-H (Superficial Siderosis) Cases

<table>
<tr><th rowspan="3">Clinical Symptom Severity</th><th colspan="3">New Incident Areas of Superficial Siderosis[1] (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><th>1</th><th>2</th><th>> 2</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing. Once ARIA-H is stable the subject may resume dosing at the same dose.</td><td rowspan="6">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="4">Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[2]</td></tr>
<tr><td>Serious, except for "other medically important event"[3]</td><td colspan="2">Discontinue dosing</td></tr>
</table>

[1] New incident superficial siderosis = new incident superficial siderosis on treatment.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Superficial Siderosis)

- Subjects who develop a **single incident focal area of hemosiderosis (also referred to as superficial siderosis)[mild]** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the superficial siderosis is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 2 weeks (±3 days) later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis)[moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Superficial siderosis is

considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the superficial siderosis is deemed stable, the subjects may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.

- Subjects who develop > **2 focal areas of hemosiderosis (superficial siderosis)[severe]** occurring at any time during the study must permanently discontinue treatment and should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later.

Symptomatic ARIA-H (superficial siderosis)

- Subjects who develop ≤ **2 new focal areas of superficial siderosis (mild or moderate)** and **mild, moderate, severe, or serious ("other medically important event" only)** clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the ARIA-H superficial siderosis is confirmed stable per the centrally read MRI. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the ARIA-H (superficial siderosis) is deemed stable and the clinical symptoms have resolved, the subjects may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.
- Subjects who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with ARIA-H (superficial siderosis)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the superficial siderosis is confirmed stable per centrally read MRI.

- Subjects who develop > **2 new focal areas of superficial siderosis (severe)** regardless of clinical symptom severity will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the superficial siderosis is confirmed stable per centrally read MRI.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.4. ARIA-H (Macrohemorrhage)

- Subjects who develop any new incident macrohemorrhage, regardless of symptom severity during the study, will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for MRI and MOCA as well as biomarker and PK sample collection every 2 weeks (±3 days) until the macrohemorrhage is confirmed stable per centrally read MRI.

7.2.1.5. Coincident ARIA-H and ARIA-E Cases

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow the most restrictive guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H must be deemed stable, and the subject must be asymptomatic. For example, if a subject experiences asymptomatic ARIA-H (1-4 microhemorrhages) coincident with ARIA-E assessed as moderate on MRI and accompanied by mild clinical symptoms, the dose should be suspended per the ARIA-E guidelines summarized in Table 8.

7.2.1.6. Resumption of Study Treatment After Suspension due to ARIA

7.2.1.6.1. MRI Monitoring

When treatment resumes after a dose suspension due to ARIA, an MRI and MOCA will be performed as well as biomarker and PK sample collection 2 weeks (±3 days) after the second administration of the restarted dose. In addition, if treatment was suspended during the dose titration prior to the subject reaching the maximum assigned dose, an MRI and MOCA will be performed as well as biomarker and PK sample collected 2 weeks (±3 days) after every second dose until completion of the titration period, with subjects assumed to be titrating to 10 mg/kg (titration period of 6 doses and a final MRI after the second dose at 10 mg/kg) to maintain study blinding, not counting unscheduled MRI visits for monitoring of ARIA. MRIs will otherwise be performed as indicated in the Schedules of Events (Section 4.2).

7.2.1.6.2. Dosing Upon Resumption of Study Treatment

Subjects who suspend treatment due to ARIA for the first time may resume treatment at the same dose if they meet the criteria as described in Sections 7.2.1.1 to 7.2.1.5. Subjects who suspend and then resume dosing after having already reached their assigned top dose level are to continue dosing at that dose level. However, if dosing is suspended prior to a subject reaching their

assigned top dose level, the subject (1) must receive at least 2 doses at the restart dose before titrating up to the next dose level and (2) must complete at least the required number of doses at that dose level per their assigned dosing regimen, as outlined in the right column of Table 11.

Table 11: Resumption of Study Treatment Following Dose Suspension Due to ARIA During Titration

Assigned Dosing Regimen (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses at Current Dose Level Needed Before Going to the Next Higher Dose
ApoE ε4 (+)			
Low Dose (3 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2
	6 mg/kg	1	2
	6 mg/kg	2	2
ApoE ε4 (-)			
Low Dose (6 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	3
	3 mg/kg	2	2
	3 mg/kg	3	2
	3 mg/kg	4	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2
	6 mg/kg	1	2
	6 mg/kg	2	2

7.2.1.7. Management After Recurrent ARIA (Dosing and MRI)

If the subject has a second occurrence of ARIA (i.e., a second occurrence of ARIA-E or of ARIA-H, or ARIA-E and ARIA-H) that requires dose suspension, after the ARIA-E resolves or stabilizes, the subject is to resume dosing at the next lower dose and is to receive 2 doses at that dose level (i.e., the restart dose) before titrating up to the next higher dose. Once dosing has resumed, the guidelines outlined in Table 11 apply, unless the subject has reduced from 1 mg/kg to placebo. In this case, the subject will remain on placebo for the duration of the placebo-controlled portion of the study. If a subject resumes treatment after ARIA, an MRI and MOCA will be performed as well as biomarker and PK sample collection 2 weeks (±3 days) after the second administration of the restarted dose, and 2 weeks (±3 days) after every second dose until the completion of titration, with all subjects assumed to be titrating to 10 mg/kg (6 doses) to maintain study blinding. MRIs will otherwise be performed as indicated in the Schedules of Events (Section 4.2).

If the subject experiences a third episode of ARIA that requires dose suspension, the subject must discontinue study treatment. Subjects who discontinue treatment are to remain in the study and continue all protocol-required tests and assessments.

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE period and will maintain the dosing scheme from the placebo-controlled period into the LTE, which may include a continuation on the same dose or completion of titration into the LTE period. A subject who is dose-reduced to placebo but remains in the study may be titrated to aducanumab 1 mg/kg during the LTE period.

7.2.2. 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 Directions for Handling and Administration (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 subject will be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of screening, treatment, and FU.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety FU period of 18 weeks after the final dose.

Subjects will have approximately 32 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety FU contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days). It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.
- 20 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 3 visits for clinical assessments.
- [redacted]
- 3 visits (including Screening) for amyloid PET scan (in a subset of subjects).
- [redacted]
- 7 visits for brain MRI.
- 1 FU safety visit at Week 94 (only for subjects not entering the LTE period) or 18 weeks after last administration of study treatment for those subjects who withdraw from study.

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period. Subjects who enter the LTE period will have approximately 36 additional planned clinic visits, and up to 8 telephone safety FU contacts, as follows:

- 26 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 4 visits for clinical assessments.
- [redacted]
- 2 visits for amyloid PET scan (in a subset of subjects).
- [redacted]
- 7 visits for brain MRI.
- 1 FU safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate (optional) initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, the Repeatable Battery for Assessment of

Neuropsychological Status [RBANS]) and ApoE genotyping. This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE and RBANS) must be performed at Screening Visit 1. To ensure the study population is reflective of the broader AD population, with both ApoE ε4 carriers and non-carriers enrolled, ApoE genotyping may be performed at Visit 1 prior to other screening assessments. The ADAS-Cog 13 and ADCS-ADL-MCI will be performed at Screening Visit 2 within 20 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE and RBANS. The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1). All other cognitive assessments [redacted] may be performed at any time during Screening after eligibility is confirmed during Screening Visit 1. The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion. Subjects who fail Screening due to PET, MMSE, CDR, hepatitis B or C results, or abnormal MRI findings will not be allowed to rescreen.

Subjects who fail Screening because allowed chronic medications have not been at stable doses for at least 4 weeks prior to Screening Visit 1 or whose use of AD medications has not been at stable doses for at least 8 weeks prior to Screening Visit 1 may return for rescreening after use of these medications has been stabilized for the required period.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period and will receive study treatment every 4 weeks for an additional 100 weeks (26 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE period are to return to the study site for an FU Visit at Week 94 (18 weeks after the last dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE period are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A FU Visit will occur at Week 198 (18 weeks after the last LTE dose). The final study visit for subjects participating in the LTE period will be Week 198.

Subjects who discontinue treatment are to remain in the study and continue all protocol-required tests and assessments until the end of the study or until withdrawal of consent. Subjects who withdraw from the study are encouraged to return for FU assessments approximately 18 weeks after their last dose of study treatment.

7.4. Study Stopping Rules

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

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

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

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of Screening) is permissible for subjects not participating in the amyloid PET substudy. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR-Global Score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index (DMI) score).
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and Screening assessments.
8. Must consent to ApoE genotyping.
9. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. Exclusion Criteria

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

Medical History

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, lewy body dementia, fronto-temporal dementia, head trauma).
2. Clinically significant unstable psychiatric illness (e.g., uncontrolled major depression, uncontrolled schizophrenia, uncontrolled bipolar affective disorder) within 6 months prior to Screening.
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >1 cm in diameter on T2* sequence) unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as > 1.5 cm in diameter).
   - >1 lacunar infarct (defined as ≤1.5 cm in diameter).
   - Superficial siderosis.
   - 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 subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Presence of diabetes mellitus that, in the judgment of the Investigator, cannot be controlled or adequately managed.
7. 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.

8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings > 165/100 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 subject to be eligible for the study), or persistent SBP/DBP readings > 180/100 mmHg 3 months prior to randomization (Day 1) that in the opinion of the Investigator are indicative of chronic uncontrolled hypertension.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma of the skin.
    - Subjects with localized prostate cancer with treatment cycles that completed at least 6 months prior to Screening.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or known seropositivity for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for both hepatitis B surface antigen AND hepatitis B core antibody).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).
19. Any other medical conditions (e.g., renal disease) that are not stable or controlled, or, which in the opinion of the Investigator, could affect the subject's safety or interfere with the study assessments.

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 or use of AD 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 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any passive immunotherapy study targeting Aβ within 12 months of Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 12 months prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures

29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (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, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 6 months prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.
33. For subjects who consent to lumbar puncture (LP), any contraindications to having a LP (e.g., platelet count < 100,000/μL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during Screening must be resolved prior to randomization. Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR, hepatitis B or C, or abnormal MRI findings.
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥ 1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension Period

To be eligible to participate in the LTE period, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses, regardless of the reason. Subjects who do not meet these criteria can enter the LTE period only with Sponsor's approval.
2. MMSE score > 10 at the Week 78 Visit.
3. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
4. Female subjects of childbearing potential and male subjects must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment.
5. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
6. Must have the ability to comply with procedures for protocol-related tests.
7. Has one informant/care partner who, in the Investigator's judgment, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long-Term Extension Period

Subjects will be excluded from entering the LTE period if at Week 78 they have:

1. Any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any Screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) and ApoE genotyping to determine study eligibility under a separate, optional initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further Screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all Screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study. To ensure the study population is reflective of the broader AD population, with both ApoE ε4 carriers and non-carriers enrolled, ApoE genotyping may be performed at Visit 1 prior to other screening assessments.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the Screening log. The total study duration for each subject participating only in the placebo-controlled period will be approximately 102 weeks (approximately an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of FU).

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Enrollment will be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE period with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating HCPs should remain blinded to treatment assignment as well as subject care management and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. As 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 subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

For the LTE period, the dose information must remain restricted. The rating and treating HCP should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by serious clinical symptoms except for "other medically important event" as defined in Table 8.
  - Symptomatic ARIA-H (microhemorrhages) with serious clinical symptoms except for "other medically important event" as defined in Table 9.
  - Symptomatic ARIA-H (superficial siderosis) with or serious clinical symptoms except for "other medically important event" as defined in Table 10.
  - ARIA-H with ≥ 10 microhemorrhages and/or > 2 focal areas of superficial siderosis.
  - Any new incident macrohemorrhage.
  - A third recurrence of ARIA after rechallenge that requires dose suspension

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria.
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

A subject who discontinues treatment is to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events or until the subject withdraws consent.

10.2. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

Note: A subject who discontinues study treatment will not be automatically withdrawn from the study, regardless of the number of doses missed, if they continue to attend clinic visits and complete all assessments.

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

Subjects who are withdrawn from the study after receiving ≥ 1 doses of study treatment should complete the EOT Visit after the reason for withdrawal is identified. For such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases. Subjects 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.

11. STUDY TREATMENT USE

11.1. Regimen

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

Please see Section 4.2 (Schedule of Events) for the study treatment infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

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

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.2 (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.

11.3. Precautions

Not applicable.

11.4. Compliance

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

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to Screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and until the subject'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.

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given < 10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤ 325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids (including inhaled and topical corticosteroids) are allowed; certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended. Medications used to treat AEs would not result in automatic withdrawal. The Sponsor may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures) performed between the time the subject is enrolled in the study and until the subject's final clinic visit (including FU visit), unless the subjects is being followed for study-related toxicity.

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

11.6. 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.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

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

Aducanumab is a recombinant human antibody expressed in a Chinese hamster ovary cell line [redacted], 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. [redacted] Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing aducanumab 50 mg/mL, [redacted] Aducanumab is manufactured in accordance with Good Manufacturing Practices.

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

12.1.1. Aducanumab 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 Biogen.

12.1.2. Aducanumab Storage

Study treatment must be stored in a secure location. Aducanumab is to be stored at 2° 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 2 hours, then it should be kept at 2° to 8°C 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.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (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 personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab 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 (subject-by-subject 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 Biogen. A written explanation must be provided for any discrepancies.

12.2. 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.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

To confirm amyloid pathology at Screening, PET scans will be performed using Amyvid™ (^{18}F-florbetapir), Vizamyl™ (^{18}F-flutemetomol), or Neuraceq™ (^{18}F-florbetaben). For those subjects participating in the amyloid PET substudy, Screening and FU scans must be performed using Amyvid and for subjects participating in the PET substudy in Japan, Vizamyl (^{18}F-flutemetomol) may also be used. For details on PET imaging ligands, [redacted] refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

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

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

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

13.2. Pharmacokinetic Assessments

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

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the PD properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the amyloid PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in the amyloid PET substudy.

[redacted]

13.4. Additional Assessments

[redacted]

13.4.2. ApoE Genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

[redacted]

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- [redacted]
- mPDQ-20
- [redacted]

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

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

13.5. Future Scientific Research Assessments

[redacted]

[redacted]

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

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

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale.

14.2. Laboratory Safety Assessments

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

- Hematology: complete blood count with differential and 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, virology (including HIV at the Investigator's discretion after consideration of risk factors), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier anti-drug antibody (ADA) approach will be used (i.e., Screening assay, confirmatory assay, and titration assay). Confirmed antidrug antibody-positive samples will be tested for the presence of anti-aducanumab neutralizing antibodies using a validated assay.

15. 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 subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 laboratory finding), 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 laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the Investigator considers to be clinically significant.

Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.1.2. 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 subject 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.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject 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.)

15.1.3. 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 subject is hospitalized. The study site must document all of 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 subject's consent to participate 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 subject's consent to participate 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 subject 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 15.1.2 is met.

15.2. Safety Classifications

15.2.1. 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 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

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.

15.2.3. Severity of Events

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

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the subject's final clinic visit (including FU visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H 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.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to [redacted]

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between signing of the ICF and the subject's final clinic visit (including FU visit) will be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. This also applies to SAEs that occur after administration of the ligand. FU information regarding an SAE also must be reported with 24 hours.

Events occurring after the subject's final clinic visit (including FU visit) should be reported to Biogen only if the Investigator considers the SAE related to study treatment.

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

15.3.4. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the subject's final clinic visit (including FU visit) must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to [redacted] regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or FU information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Guide for country-specific [redacted] fax numbers or email [redacted]

15.3.4.1. 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. The Investigator should make every effort to obtain and send death certificates and autopsy reports to [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

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

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to [redacted] within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to [redacted]

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in 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 to [redacted] within 24 hours of the site becoming aware of the overdose. An overdose must be reported to [redacted] 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 to [redacted]

[redacted]). All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. 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 [redacted] 24-hour emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

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

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the [redacted] 24-hour emergency medical support number at [redacted].

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

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.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of this study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system
  - Barrier methods of contraception with use of a spermicide: condom or occlusive cap (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.

- Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at FU.
  - Use of condoms with spermicide.
  - Female sexual partners who underwent surgical sterilization (e.g., bilateral tubal ligation), are postmenopausal, are post-hysterectomy, or are using highly effective contraception as listed above for female subjects.

For males and females of childbearing potential:

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, 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, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, 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 and FU on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE FU information actively and persistently. FU information must be reported to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE FU information, if possible, until the event has resolved or become stable.

- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor ([redacted]) is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects 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 each aducanumab regimen and placebo. All statistical tests will be 2-sided.

16.2.2.2. Dose Regimens to be Evaluated

The following dose regimens of aducanumab as compared with placebo will be evaluated:

- Aducanumab high-dose regimen (10 mg/kg in ApoE ε4 [including 6 mg/kg for subjects enrolled under protocol version 1-3 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study] and 10 mg/kg in ApoE ε4 non carriers).
- Aducanumab low-dose regimen (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the maximum dose (10mg/kg) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose regimen and aducanumab low dose regimen will be modified as shown in Table 12. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of Type I error rate is thus maintained without a statistical adjustment for such adaptations[Chow and Chang 2011].

Table 12: Dose Group Pooling Strategy in the Event of Treatment Group Termination

Treatment Group(s) Terminated	Definitions of Revised Pooled Treatment Groups for Comparison
ApoE ε4 carrier high-dose group (10 mg/kg) [including 6 mg/kg for subjects enrolled under protocol version 1-3 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study]	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 10 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group (10 mg/kg) AND ApoE ε4 non-carrier high-dose group (10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose regimen versus placebo and aducanumab low-dose regimen versus placebo. All comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for 1 or 2 comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1 or 2, respectively.

Due to a current lack of scientific consensus in the AD field on which biomarker(s) might be most appropriate, the selection of the biomarkers and methodology for control of Type I error will be pre-specified in the statistical analysis plan (SAP). Otherwise, there will be no multiple comparison adjustments for the tertiary endpoints.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population with a baseline and at least one post-baseline CDR-SB score. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change From Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population with a baseline and at least one post-baseline MMSE value. A MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction and baseline ApoE ε4 status

16.2.2.5.2. Change From Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADAS-Cog 13 score. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction; baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5.3. Change From Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADCS-ADL-MCI score. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction; baseline MMSE, and baseline ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, a MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE and baseline ApoE ε4 status.

Otherwise, an analysis of covariance or its non-parametric equivalent may be used to analyze these exploratory endpoints.

16.2.2.6.2. Long-Term Extension Period

The additional endpoints for the LTE period are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the placebo-controlled period using the placebo-controlled period baseline. Details of the analyses will be pre-specified in the SAP.

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The population PK characteristics of aducanumab will be determined by nonlinear mixed effects approach. Covariates that might influence the disposition of aducanumab (e.g., body weight, age, sex, immunogenicity, ApoE ε4 status) will be evaluated and the potential exposure-response relationships will be explored.

16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of study treatment (including placebo and aducanumab).

16.4.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.4.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent 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 study treatment for the placebo-controlled period and over the 24-month LTE period. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.4.2.2. 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. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.4.2.3. Vital Signs

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

16.4.2.4. ECG

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

16.4.2.5. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale data will be summarized by treatment group.

16.5. Immunogenicity Data

16.5.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.5.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.6. Interim Analyses

16.6.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.6.2. Interim Superiority Analysis

An interim analysis for superiority may be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The O'Brien-Fleming boundary approach will be used for the analysis. In order to maintain the treatment blind in the event of this interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.7. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103 which included 1 year data from 1, 3 and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group will have approximately 90% power to detect a true mean difference of 0.5 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, a SD of 1.92 and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflects a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

The sample size may be reassessed in a blinded manner approximately 3 months before enrollment is complete if at least 15% of the data are available on the primary endpoint. At this interim time-point, the SD for the primary endpoint will be estimated based on the blinded data. The sample size may be increased if the SD is estimated to be more than approximately 2.07. In addition, the sample size could be increased using external clinical trial results that become available after the start of the study.

17. ETHICAL REQUIREMENTS

Biogen, [redacted] and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

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.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

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

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

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) as an initial optional screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

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

Subjects will be informed that their race and/or ethnicity will be collected and will be used during analysis of study results (only in countries where permitted by local law/regulation).

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The 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 (wet signature) and copies of the signed and dated ICFs.

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

17.4. Subject Data Protection

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

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

During the study, subjects' race and/or ethnicity will be collected (only in countries where permitted by local law/regulation). These data may be used in the analysis of the safety, efficacy, and/or pharmacokinetic profile of the study treatment. It is unknown if the potency or effects of the study treatment are influenced by race or ethnicity.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. 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 subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights and a user manual.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by [redacted] and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen 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, [redacted], and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA 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.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen 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 PI 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 collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen 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 per project-specific plans.

19.2. Study Committees

19.2.1. 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 subject accrual and oversee study conduct, including advising on study design and execution. The advisory committee will be blinded to subject treatment assignments during the study.

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

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. 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 subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), 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.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB 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, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. 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 Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. 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 laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen 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.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study 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 subject enrollment, or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early 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)

Biogen MA Inc.
225 Binney Street
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United States

Biogen Idec Research Limited
Innovation House
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SL6 4AY
United Kingdom

PROTOCOL NUMBER: 221AD301/NCT02477800

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000966-72**

DATE: 18 September 2017
Version 5.0
Final

Supersedes previous Version 4.0 dated 24 March 2017.

SPONSOR SIGNATURE

Protocol 221AD301 was approved by:

[redacted]

[redacted] PhD

21 September 2017
Date

[redacted]

Biogen MA Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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Chuo-ku
Tokyo
103-0027
Japan

For 24-hour emergency medical support contact

[redacted] at [redacted]

Please refer to the Study Reference Manual for complete contact information.

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

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab, produced in a different Chinese hamster ovary cell line
Aβ	β-amyloid (peptide derived from membrane bound amyloid precursor protein)
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibody
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-hemorrhage or superficial siderosis
[redacted]	[redacted]
AST	aspartate aminotransferase
[redacted]	[redacted]
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating sum of boxes
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
[redacted]	[redacted]
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
[redacted]	[redacted]

	[redacted]
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject
EQ-5D (SR)	EuroQol health status measure, subject self-reported
FU	follow-up
GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCP	health care professional
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NIA-AA	National Institute on Aging (NIA) at National Institutes of Health (NIH) and the Alzheimer's Association (AA)
NPI-10	Neuropsychiatric Inventory-10
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RNA	ribonucleic acid
SABR	Safety and Benefit-Risk
SAE	serious adverse event

SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
[redacted]	[redacted]

3. SYNOPSIS

Protocol Number:	**221AD301**
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	5.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-sum of boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results, along with the observed safety and tolerability profile, warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy 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 subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78. Secondary objectives and endpoints are as follows: To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by

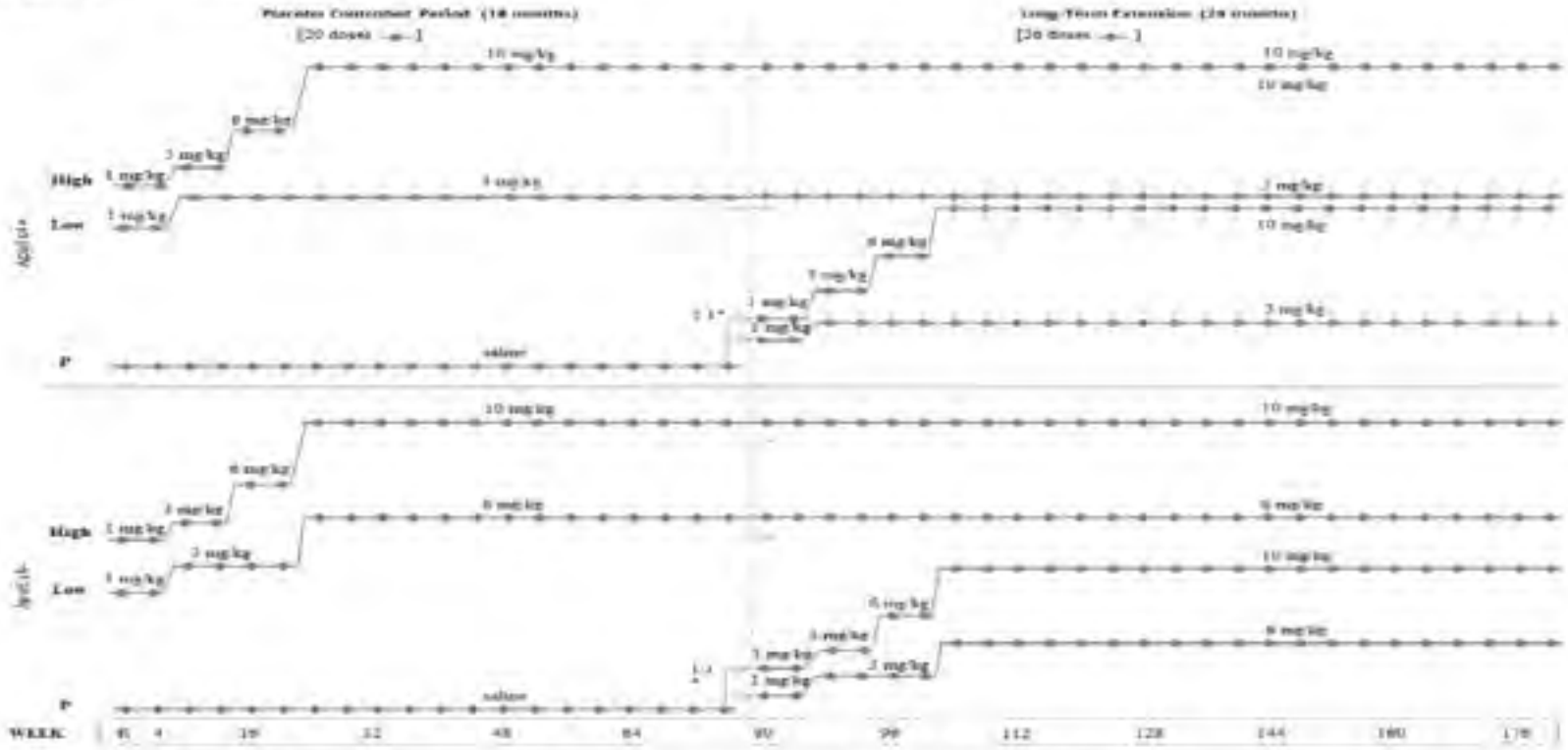
Protocol Number:	**221AD301**
	• MMSE - Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13] - Change from baseline in ADAS-Cog 13 at Week 78 • Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] - Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2. Additional exploratory objectives and endpoints are listed in Section 6.4.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension period of the study):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health-outcomes assessments. Endpoints for the long-term extension (LTE) period of the study are listed in Section 6.5.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled, parallel-group period followed by an optional 24-month dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1350 subjects will be enrolled Note: In the event that a prespecified, blinded sample size re-estimation is performed, the sample size may be increased but will not exceed 1764 subjects.
Study Population:	This study will be conducted in subjects with early AD, including subjects with MCI due to AD and a subset of mild AD according to National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer's Association (NIA-AA) criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator.

Protocol Number:	**221AD301**
	based on medical history and the screening assessments. The ratio of apolipoprotein E4 (ApoE ε4) carriers to non-carriers in the study population will generally reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology, such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose:placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (10 mg/kg)** **Placebo** **ApoE ε4 non-carrier** **Low dose (6 mg/kg)** **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a 24-month dose-blind LTE study during which all subjects will receive aducanumab.
Duration of Treatment and Follow Up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow-up [FU]). For subjects who enter the optional LTE period, the total study duration will be approximately 206 weeks or 47 months (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 4 weeks of FU, plus an optional LTE period including 100 weeks of dose-blind aducanumab dosing and 18 weeks of FU).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD301

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; LTE = long-term extension; P = placebo; R = randomization date.
*Subjects who are assigned to placebo during the placebo-controlled period and are continuing into the LTE period will be randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status).

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule From Screening Through Week 48

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	V1	V2	V3	1	29 ± 3	57 ± 3	85 ± 3	113 ± 3	141 ± 3	169 ± 3	183 ± 3	197 ± 3	225 ± 3	253 ± 3	281 ± 3	309 ± 3	337 ± 3	
Initial Screening Consent[2] (optional)	X																	
Full Informed Consent[3]	X																	
Eligibility Criteria	X	X	X	X[4]														
Demography	X																	
Medical History	X	X	X															
Alcohol/Drug Screen	X																	
HbA_{1c}	X																	
HIV[5]/Hepatitis/ Coagulation	X																	
ApoE Genotyping	X																	
[redacted]																		
Height	X																	
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Serum Pregnancy Test[7]	X																	
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X	

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medication**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Physical Examination	X						X			X							X	
Neurological Examination	X						X			X							X	
12-lead Paper ECG	X									X							X	
Vital Signs[8]	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis	X			X						X							X	
Randomization				X														
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X	
Anti-Aducanumab Ab[9]				X						X			X					
Aducanumab Concentration[10]				X[11]	X[11]		X[11]	X	X[13]	X[11]		X[11]	X					
[redacted]																		
PBMC Collection	X						X	X		X			X					
[redacted]																		
Amyloid PET[14]			X								X							
[redacted]																		
RBANS	X																	

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	V1	V2	V3	1	29 ± 3	57 ± 3	85 ± 3	113 ± 3	141 ± 3	169 ± 3	183 ± 3	197 ± 3	225 ± 3	253 ± 3	281 ± 3	309 ± 3	337 ± 3	
CDR	X										X							X
MMSE	X										X							X
ADCS-ADL-MCI		X[10]									X							X
ADAS-Cog 13		X[10]									X							X
NPI-10		X[17]									X							
EQ-5D (SR)		X[18]									X							
EQ-5D (IR-S)		X[19]									X							
[redacted]																		
mPDQ-20		X[16]									X							
[redacted]																		
C-SSRS				X							X							
AE Reporting				Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																	
SAE Reporting	Monitor and record continuously throughout the study																	

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E; [redacted]; CDR = Clinical Dementia Rating scale; CRO = contract research organization; [redacted] d; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted] ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; HbA_{1c} = glycosylated hemoglobin; HIV = human immunodeficiency virus; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC

= peripheral blood mononuclear cells; PET = positron emission tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; [redacted]; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; Wk = Week.

[1] Examination required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 3) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

[2] Subjects may sign this optional form for an initial Screening which allows administration of the RBANS, CDR, and MMSE only, as well as ApoE genotyping.

[3] All subjects must sign this informed consent, including subjects who have signed the optional initial screening consent, once they have met the RBANS, CDR, and MMSE eligibility criteria.

[4] All assessments, including the C-SSRS, must be completed before study treatment administration, except the post-dose sample to measure aducanumab concentration.

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

[6] [redacted].

[7] Required for women of childbearing potential only (see Section 15.5).

[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[9] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study treatment infusion.

[10] Blood sampling for aducanumab concentration will be performed prior to infusion. Note: For subjects who permanently discontinue treatment and continue in the study, the final aducanumab concentration sample will be collected at the subject's next visit.

[11] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[redacted]

[14] Screening amyloid PET is required for all subjects; amyloid PET at Week 26 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy. The amyloid PET at Week 26 may be scheduled within a window of ±7 days.

[redacted]

[16] Must be performed within 20 days of V1, but not on the same day as the screening RBANS, CDR, or MMSE.

[17] The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening V1).

[18] May be performed at any point during Screening after the subject has met eligibility criteria on the RBANS, CDR, and MMSE.

Table 2: Placebo-Controlled Period Schedule From Week 50 to End of Treatment or Follow-Up

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 weeks after final dose for subjects who terminate treatment early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Informed Consent									X[3]		
Eligibility Criteria									X[3]		
Body Weight		X	X	X	X	X	X	X			X
Urine Pregnancy Test[4]		X	X	X	X	X	X	X			X
Physical Examination							X		X		X
Neurological Examination							X		X		X
12-lead Paper ECG							X		X		X
Vital Signs[5]		X	X	X	X	X	X	X			X
Hematology, Blood Chemistry and Urinalysis							X		X		X
Study Treatment Infusion		X	X	X	X	X	X	X			
Anti-Aducanumab Ab[6]			X						X		X
Aducanumab Concentration[7]		X[8]	X						X		X
[redacted]											
PBMC Collection			X						X		X
[redacted]											

Study Week											**FU**[1]
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78 (EOT)**[2]	**UV for a Change in AD Medication**	**94 (or 18 weeks after final dose for subjects who terminate treatment early)**
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Amyloid PET[10]									X		
[redacted]											
CDR	X								X	X	X
MMSE	X								X	X	X
ADCS-ADL-MCI	X								X	X	X
ADAS-Cog 13	X								X	X	X
NPI-10	X								X		
EQ-5D (SR)	X								X		
EQ-5D (IR-S)	X								X		
[redacted]											
mPDQ-20	X								X		
[redacted]											
C-SSRS		X							X		
AE Reporting				Monitor and record continuously throughout the study							
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study										
SAE Reporting	Monitor and record continuously throughout the study										

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); [redacted]; CDR = Clinical Dementia Rating scale; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events. Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases.

[3] Only for subjects entering the long-term extension period.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[6] Sample collection for anti-aducanumab antibody will be performed prior to blood collection for aducanumab concentration or study treatment infusion.

[7] Blood sampling for aducanumab concentration will be performed prior to infusion. Note: For subjects who permanently discontinue treatment and continue in the study, the final aducanumab concentration sample will be collected at the subject's next visit.

[8] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[redacted]

[10] Amyloid PET at Week 78 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy and may be scheduled within a window of ±7 days.

[redacted]

Table 3: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule During the Placebo-Controlled Period

Study Week	Screening (≤ 60 days before Day 1)[1]			Placebo-Controlled Period														FU[2]
				1	2	6	10	14	18	22	26	30	42	54	66	78/ EOT[3]	Unscheduled Visit/ MRI for ARIA[4]	94 (or 18 weeks after final dose for subjects who discontinue treatment early)
Study Day	V1	V2	V3	1	15 ± 3	43 ± 3	71 ± 3	99 ± 3	127 ± 3	155 ± 3	183 ± 3	211 ± 3	295 ± 3	379 ± 3	463± 3	547 ± 3		659 ± 7
Follow-Up Phone Call[5]					X	X	X	X	X	X	X	X						
Brain MRI[6]		X						X		X		X	X	X	X	X	X	X
Aducanumab Concentration[7]										X		X		X			X	X
MOCA				X													X	
[redacted]																		
PBMC collection[8]																	X	

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; [redacted]; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3.

[1] Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

[2] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[3] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events. Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases.

[4] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Sections 7.2.1.1 to 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[5] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[6] Arterial spin labeling MRI and task free functional MRI will be performed only at a subset of sites.

[7] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[redacted]

Table 4: Long-Term Extension Schedule From Week 80 to Week 134

Study Week																	
	80	84	88	92	96	100	104	106	108	112	116	120	124	128	132	134	UV for a Change in AD Medication
Study Day	561 ± 5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	743 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	939 ± 5	
Randomization	X[1]																
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Urine Pregnancy Test[2]	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Physical Examination				X			X							X			
Neurological Examination				X			X							X			
12-lead Paper ECG							X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Hematology, Blood Chemistry and Urinalysis							X							X			
Anti-Aducanumab Ab[3]	X						X							X			
[redacted]																	
PBMC collection							X							X			
Aducanumab Concentration[3]	X						X							X			

Study Week																	
	80	**84**	**88**	**92**	**96**	**100**	**104**	**106**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**134**	**UV for a Change in AD Medication**
Study Day	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**729 ± 5**	**743 ± 5**	**757 ± 5**	**785 ± 5**	**813 ± 5**	**841 ± 5**	**869 ± 5**	**897 ± 5**	**925 ± 5**	**939 ± 5**	
Study Treatment Infusion	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
[redacted]																	
Amyloid PET[5]															X		
[redacted]																	
CDR								X								X	X
MMSE								X								X	X
ADAS-Cog 13								X								X	X
ADCS-ADL-MCI								X								X	X
NPI-10								X								X	
EQ-5D (IR-S)								X								X	
[redacted]																	
[redacted]																	
C-SSRS								X								X	
AE Reporting	Monitor and record continuously throughout the study																
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																
SAE Reporting	Monitor and record continuously throughout the study																

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); [redacted] CDR = Clinical Dementia Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted] EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit

[1] Subjects who were in the placebo group during the placebo-controlled period will be randomized to aducanumab high and low dose (1:1 ratio).

[2] Required for women of childbearing potential only (Section 15.5).

[redacted]

[5] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[redacted]

Table 5: Long-Term Extension Schedule From Week 136 to End of Treatment or Follow-Up

Study Week																FU[1]
	136	140	144	148	152	156	160	162	164	168	172	176	180	182 (EOT)[2]	UV for a Change in AD Medication	198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5		1387 ± 7
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Urine Pregnancy Test[3]	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Physical Examination					X							X		X		X
Neurological Examination					X							X		X		X
12-lead Paper ECG					X							X				X
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Hematology, Blood Chemistry and Urinalysis					X							X				X
Anti-aducanumab Ab[4]					X									X		X
[redacted]																
PBMC collection					X									X		X

Study Week																FU[1]
	136	140	144	148	152	156	160	162	164	168	172	176	180	182 (EOT)[2]	UV for a Change in AD Medication	198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5		1387 ± 7
Aducanumab Concentration[3]					X							X		X		X
Study Drug Infusion	X	X	X	X	X	X	X		X	X	X	X	X			
[redacted]																
Amyloid PET[5]														X		
[redacted]																
CDR								X						X	X	X
MMSE								X						X	X	X
ADAS-Cog 13								X						X	X	X
ADCS-ADL-MCI								X						X	X	X
NPI-10								X						X		
EQ-5D (IR-S)								X						X		
[redacted]																
[redacted]																
C-SSRS								X						X		

Study Week																FU[1]
	136	140	144	148	152	156	160	162	164	168	172	176	180	182 (EOT)[2]	UV for a Change in AD Medication	198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5		1387 ± 7
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy and procedures	Monitor and record continuously throughout the study															
SAE Reporting	Monitor and record continuously throughout the study															

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment Version); [redacted]; CDR = Clinical Dementia Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted] EQ-5D (IR-S) = EQ-5D, informant reported on subject; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; [redacted] SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 198. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events. Subjects who withdraw from the LTE period prematurely are to return to the site for the EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases.

[3] Required for women of childbearing potential only (Section 15.5).

[redacted]

[6] Only for subjects who participate in the amyloid PET substudy Amyloid PET may be scheduled within a window of ±7 days.

[redacted]

Table 6: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule During the Long-Term Extension

Study Week	Long-Term Extension													Unscheduled Visit for ARIA [1]	FU[2]
	80	82	86	90	94	98	102	106	110	122	134	158	182[3]		198 (or 18 weeks after final dose for subjects who terminate treatment early)
Study Day	561 ± 5	575 ± 5	603 ± 5	631 ± 5	659 ± 5	687 ± 5	715 ± 5	743 ± 5	771 ± 5	855 ± 5	939 ± 5	1107 ± 5	1275 ± 5		1387 ± 7
Follow-Up Phone Call[4]		X	X	X	X	X	X	X	X						
Brain MRI[5]					X		X		X	X	X	X	X	X	X
Aducanumab Concentration[6]														X	
MOCA	X													X	
[redacted]															
PBMC collection[7]														X	

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; [redacted].

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Sections 7.2.1.1 to 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 198. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose. The only exception is a subject who discontinues treatment prematurely and continues on study for at least 18 weeks after receiving the final dose.

[3] Subjects who discontinue treatment prematurely are to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events. Subjects who withdraw from the LTE period prematurely are to return to the site for the Week EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases.

[4] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[5] Arterial-spin labeling MRI and taskfree functional MRI will be performed only at a subset of sites

[6] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[redacted]

4.3. Additional Information

4.3.1. Site Personnel

A minimum of 3 separate heath care professionals (HCPs) are required:

1. A treating HCP (the Principal Investigator [PI] or Sub-investigator may serve as a treating HCP) who is responsible for the following:
   - Administration of Montreal Cognitive Assessment (MOCA) at Day 1, Week 80, and during management of amyloid-related imaging abnormalities (ARIA) cases.
   - Management of routine neurological care of the subject.
   - Assessment (including assignment of causality) and treatment of adverse events (AEs).
   - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.
2. An independent rating HCP (designated by the PI of the site) who is responsible for administering the Clinical Dementia Rating (CDR)
3. A second independent rating HCP (designated by the PI of the site) who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI], and the Mini-Mental State Examination (MMSE)

The 2 independent rating HCPs must not be involved with any other aspect of subject 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 2 independent rating HCPs must not share any information about subjects. PIs cannot serve as rating HCPs. The treating HCPs must not discuss AEs (e.g., ARIA) with the independent rating HCPs.

To ensure consistency across sites, rating HCPs must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites must attempt to maintain the same rating HCP throughout the study for specific assessments in an attempt to remain consistent. Each subject should have the same rating HCP perform the subject's specific rating assessment throughout the study. A qualified approved back-up rater should only conduct assessments in place of the primary rater due to extenuating circumstances resulting in unavailability (e.g. due to illness, vacation, or travel). If a rating HCP has to be replaced, the new rating HCP 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 subject. As with other laboratory and clinical information, these data should NOT be reviewed by the rating HCPs.

The roles of independent raters and treating HCP are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject level. If a rater has administered the CDR to a subject, they may not administer the other neurocognitive assessments to that subject 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.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy.

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne 2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after

active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience With Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ immunoglobulin (Ig) G1 monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine IgG2a chimeric version of the antibody (ch12F6A) with similar properties to aducanumab (BIIB037) significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A $\geq$ 70 mg/ kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is an ongoing randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 10 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab. Note: The fixed-dose cohorts enrolled both apolipoprotein E4 (ApoE ε4) carriers and non-carriers while the titration cohort is comprised of ApoE ε4 carriers only.

  The primary objective of Study 221AD103 is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR-sum of boxes (SB) and MMSE.

  To date, the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. The incidence of ARIA-E appeared to be lower in the group receiving titration to 10 mg/kg (comprising ApoE ε4 carriers only; 8/23 [35%]) than in carriers in the 6 mg/kg and 10 mg/kg fixed-dose groups (9/21 [43%] and 11/20 [55%], respectively). The incidence of ARIA in ApoE ε4 carriers who were titrated up to 6 mg/kg (2 doses of 3 mg/kg, then 6 mg/kg) was 15% (2/13), with an overall rate of 11% (2/19) as no ApoE ε4 non-carriers (0/6) experienced ARIA. Of note, among the subjects receiving titration to 10 mg/kg who had ARIA-E, the abnormalities were

observed at the 3 and 6 mg/kg doses, before they reached 10 mg/kg. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these, 12 continued treatment and received at least 10 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H. Furthermore, ARIA-E events when they occurred (in the titration group) have been either asymptomatic or associated with mild symptoms that resolved, and most subjects who had ARIA-E continued treatment (6/8; 75%) compared with only 36% (4/11) of carriers in the fixed-dose 10 mg/kg arm (refer to the IB for details on events of ARIA).

Protocol-specified interim analyses of the ongoing multiple-ascending dose Study 221AD103 have demonstrated engagement of aducanumab with amyloid plaques, a pharmacodynamic (PD) effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a slowing of clinical decline in aducanumab-treated subjects. The dose- and time-dependent reduction of brain Aβ burden observed with aducanumab treatment was statistically significant at doses of 3, 6, and 10 mg/kg after 6 and 12 months of dosing, as well as with 1 mg/kg and titration from 1 to 10 mg/kg after 12 months of dosing. Over the first year of the LTE (24 months of dosing), further dose-dependent reductions in cerebral Aβ were observed. The results demonstrate target engagement (amyloid plaques) and a PD effect (dose-dependent amyloid reduction).

In addition, results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE (at fixed doses of 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg compared with placebo), suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. In the most recent interim analysis, generally consistent treatment differences were seen for the fixed-dose cohorts, and in the titration group, effects on the CDR-SB and MMSE after 1 year were generally consistent with the fixed-dose results. Compared with placebo, adjusted mean changes from baseline to Week 54 in CDR-SB scores favored all aducanumab dose regimens tested, with treatment differences of 0.5 points or greater favoring aducanumab at doses of 3, 6, and 10 mg/kg and titration to 10 mg/kg, and statistical significance seen in the 10 mg/kg and the titration groups. On the MMSE, adjusted mean decreases from baseline to Week 52 suggested a clinically meaningful benefit in the 3 and 10 mg/kg groups and the titration group and were significantly lower in the 10 mg/kg group. Furthermore, results from the LTE for the fixed-dose regimens have demonstrated continued slowing of the clinical decline in subjects continuing on aducanumab compared with subjects who switched from placebo to aducanumab in the LTE. Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human IgG1 monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are

neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results, along with the observed safety and tolerability profile, warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment in Study 221AD103 was statistically significant at doses of 3, 6, and 10 mg/kg after 6 months of dosing, and at 3, 6, and 10 mg/kg as well as with titration to 10 mg/kg after 12 months of dosing. On the exploratory endpoints of CDR-SB and MMSE changes from baseline, a dose-dependent slowing of clinical decline was observed for aducanumab versus placebo after 1 year of treatment. Compared with placebo, adjusted mean changes from baseline to Week 54 for CDR-SB favored all the aducanumab dose groups tested, with treatment differences of 0.5 points or greater at fixed doses of aducanumab 3, 6, and 10 mg/kg and also with titration to 10 mg/kg. On the MMSE, adjusted mean decreases from baseline to Week 52 were smaller in all dose groups than in the placebo group. Of note, on the CDR-SB, the point estimate for the titration group (comprising ApoE ε4 carriers only) was generally similar to that for the 10 mg/kg group and significantly lower than placebo in both those groups; on the MMSE, the point estimate for the titration group is generally similar to that in the 10 mg/kg group (which showed significantly less decline than placebo) and the 3 mg/kg group.

To date, the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. However, the incidence of ARIA-E, as well as discontinuations from treatment due to ARIA-E, in subjects receiving aducanumab titrated to 10 mg/kg (ApoE ε4 carriers only) appear to be reduced (8/23 [35%]) compared with fixed doses of aducanumab at 6 mg/kg (9/21 [43%]) and 10 mg/kg (11/20 [55%]). Furthermore, among those subjects randomized to receive aducanumab titrated to 10 mg/kg, ARIA-E occurred only at the 3 mg/kg and 6 mg/kg dose levels. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these, 12 continued treatment and received at least 10 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H.

In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA

incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored in this study. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012], which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown to date, the doses to be tested using a titration regimen are 3 and 10 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6, and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (approximately 450 subjects each [Note: In the event a prespecified blinded, sample size re-estimation is performed, the sample size may be increased but will not exceed 588 subjects per treatment group]) in a 1:1:1 ratio (aducanumab low dose:aducanumab high dose:placebo) as follows (Table 7 and Figure 1):

ApoE ε4 Carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

ApoE ε4 Non-Carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 7: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status

Dose (Month)		1	2	3	4	5	6	7 to 20
Treatment Group		Dose (mg/kg)						
ApoE ε4 (+)	Low Dose	1	1	3	3	3	3	3
	High Dose	1	1	3	3	6	6	10[1]
	Placebo	saline						
ApoE ε4 (-)	Low Dose	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

[1] 10 mg/kg is the target dose for all ApoE ε4 carriers assigned to the aducanumab high-dose group. Subjects enrolled under previous versions of the protocol and assigned to the previous high-dose of 6 mg/kg will be titrated to 10 mg/kg upon receipt of at least 2 doses at 6 mg/kg.

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If the high dose (10 mg/kg) is deemed not acceptable, enrollment for the high-dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high-dose groups will be revised as described in Section 16.

5.3.3. Long-Term Extension Period

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will maintain the dosing scheme outlined in the protocol at the time of transition from the placebo-controlled period to the LTE period (e.g. subjects who are on stable dosing in the placebo-controlled period will continue on the same dose, subjects who are on a titration regimen during the transition will continue to titrate into the LTE period and subjects who complete the placebo-controlled period under protocol versions 1 to 3 and are assigned to the high dose aducanumab treatment group may up titrate to 10 mg/kg in the LTE). Subjects who receive placebo during the placebo-controlled period and who enter the LTE period will be assigned to 1 of 2 treatment groups, based upon their ApoE ε4 carrier status, in a 1:1 ratio (aducanumab low

dose: aducanumab high dose). Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 7 and Figure 1).

ApoE ε4 carrier subjects who are enrolled in the LTE and randomized to the high-dose group prior to implementation of version 4 of the protocol will be allowed to titrate to 10 mg/kg. Any modifications to the dosing scheme (i.e. termination of high-dose group, as described in Section 5.3.2) will also be implemented in the LTE period.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy 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 subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker/Efficacy/Health Outcomes

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).

- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- To assess the correlation between primary endpoint and cerebral amyloid plaque content as measured by PET imaging.

Pharmacokinetics

- To collect and characterize the PK parameters of aducanumab in serum.

6.3.2. Tertiary Endpoints

Safety and Tolerability

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers/Efficacy/Health Outcomes

- Change from baseline in amyloid PET signal at Week 26 (in a subset of subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of subjects).
- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- Change from baseline in mPDQ-20 at Week 78.
- Correlation between the primary endpoint and cerebral amyloid plaque content as measured by PET imaging over time.

Pharmacokinetics

- Serum concentrations and PK parameters of aducanumab.

6.4. Additional Exploratory Objectives and Endpoints

6.4.1. Additional Exploratory Objectives

[redacted]

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

6.4.2. Additional Exploratory Endpoints

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

6.5. Long-Term Extension Objectives and Endpoints

6.5.1. Tertiary LTE Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.
- To evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health outcomes assessments.

6.5.2. Tertiary LTE Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of subjects).
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.

6.5.3. Additional Exploratory LTE Objective

- [redacted]

6.5.4. Additional Exploratory LTE Endpoints

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

7. STUDY DESIGN

7.1. Study Overview

Study 221AD301 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional 24-month dose-blind LTE study. Approximately 1350 subjects (or, in the event that a prespecified, blinded sample size re-estimation is performed, may be increased but will not exceed 1764 subjects, see Section 16.8) will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). The ratio of ApoE ε4 carriers to non-carriers in the study population will generally reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a 24-month long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (a total of 26 doses).

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of 18 weeks after the final dose.

The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will be up to approximately 206 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 100-week aducanumab dose-blind treatment period, and a safety FU period of 18 weeks after the final dose. The FU period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 10 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 7 and Figure 1. Note: 10 mg/kg is the

target dose for all ApoE ε4 carriers in the high-dose group. ApoE ε4 carriers who are enrolled in the high-dose group receiving 6 mg/kg must have received 2 or more doses at 6 mg/kg prior to being titrated up to 10 mg/kg. Subjects who received placebo during the placebo-controlled period and who enter the LTE period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose: aducanumab high dose); aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented in subjects who develop ARIA. See Section 7.2.1.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE period, Investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE period.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification, or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the PI within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the PI; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Guidelines on the management and disposition of ARIA-E and ARIA-H 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. Dosing may also be terminated at the discretion of the Sponsor for medical reasons. See Section 10.1 for the full list of criteria for discontinuing study treatment.

7.2.1.1. ARIA-E Cases

Table 8: Disposition of ARIA-E Cases

Clinical Symptom Severity	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 subject may resume dosing at the same dose.	
Mild	Suspend dosing. Once ARIA-E and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[1]			
Serious, except for "other medically important event"[2]	Discontinue Dosing		

[1] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above and as described in Section 15.1.2.

[2] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.
- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. If the ARIA-E has resolved and the subjects remain asymptomatic (in the Investigator's opinion), the subjects may resume treatment at

the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.

- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by mild, moderate, severe, or serious ("other medically important event" only) clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. If the ARIA-E has resolved and the clinical symptoms have resolved (in the Investigator's opinion), the subject may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.
- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except "other medically important event") clinical symptoms** at any time during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA approximately every 4 weeks until the ARIA-E has resolved per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.2. ARIA-H (Microhemorrhage)

In this study, new incident microhemorrhages are defined as new incident microhemorrhages that occur on treatment and do not include microhemorrhages at baseline.

Table 9: Disposition of ARIA-H (Microhemorrhage) Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">New Incident Microhemorrhages[1] (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><th></th><th>≥ 1 and ≤ 4</th><th>≥ 5 and ≤ 9</th><th>≥ 10</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing. Once ARIA-H is stable, the subject may resume dosing at the same dose.</td><td rowspan="5">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="4">Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[2]</td></tr>
<tr><td>Serious, except for "other medically important event"[3]</td><td colspan="2">Discontinue dosing</td></tr>
</table>

[1] New incident microhemorrhages = new incident microhemorrhages on treatment; does not include microhemorrhages at baseline.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Microhemorrhage)

- Subjects who develop a **≥ 1 and ≤ 4 new incident microhemorrhage(s) [mild]** at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥ 5 and ≤ 9 new incident microhemorrhages [moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the microhemorrhage is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. A microhemorrhage is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.

- Subjects who develop ≥ **10 new incident microhemorrhages [severe]** during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the microhemorrhages are deemed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

Symptomatic ARIA-H (Microhemorrhage)

- Subjects who develop ≤ **9 new incident microhemorrhages (mild or moderate) and mild, moderate, severe, or serious ("other medically important event" only [Section** 15.1.2**]) clinical symptoms** will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the ARIA-H (microhemorrhage(s) is confirmed stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Microhemorrhages are considered stable if they are unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once ARIA-H (microhemorrhage) is deemed stable and the clinical symptoms have resolved (in the Investigator's opinion), the subject may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.
- Subjects who experience **serious (except "other medically important event" [Section** 15.1.2**]) clinical symptoms associated with microhemorrhage(s)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the microhemorrhage(s) is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.
- Subjects who develop ≥ **10 new incident microhemorrhages (severe)**, regardless of symptom severity, during the study will permanently discontinue treatment. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the microhemorrhages are deemed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.3. ARIA-H (Superficial Siderosis)

Table 10: Disposition of ARIA-H (Superficial Siderosis) Cases

<table>
<tr><td rowspan="2">Clinical Symptom Severity</td><td colspan="3">New Incident Areas of Superficial Siderosis[1] (Central Read)</td></tr>
<tr><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td></td><td>1</td><td>2</td><td>>2</td></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing. Once ARIA-H is stable the subject may resume dosing at the same dose.</td><td rowspan="5">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="4">Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[2]</td></tr>
<tr><td>Serious, except for "other medically important event"[3]</td><td colspan="2">Discontinue dosing</td></tr>
</table>

[1] New incident superficial siderosis = new incident superficial siderosis on treatment.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Superficial Siderosis)

- Subjects who develop a **single incident focal area of hemosiderosis (also referred to as superficial siderosis) [mild]** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the superficial siderosis is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 2 weeks (±3 days) later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis) [moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read

MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the superficial siderosis is deemed stable, the subjects may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.

- Subjects who develop **>2 focal areas of hemosiderosis (superficial siderosis) [severe]** occurring at any time during the study must permanently discontinue treatment and should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later.

Symptomatic ARIA-H (superficial siderosis)

- Subjects who develop **≤ 2 new focal areas of superficial siderosis (mild or moderate)** and **mild, moderate, severe, or serious ("other medically important event" only)** clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the ARIA-H superficial siderosis is confirmed stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if it is unchanged between 2 consecutive MRIs including the initial detection MRI and the MRI performed 2 weeks (±3 days) later. Once the ARIA-H (superficial siderosis) is deemed stable and the clinical symptoms have resolved (in the Investigator's opinion), the subjects may resume treatment at the same dose. Subjects who have missed more than 4 consecutive doses due to ARIA will not be allowed to resume treatment.
- Subjects who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with ARIA-H (superficial siderosis)** will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the superficial siderosis is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.
- Subjects who develop **>2 new focal areas of superficial siderosis (severe)** regardless of clinical symptom severity will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 2 weeks (±3 days) until the superficial siderosis is confirmed stable per centrally read MRI. In addition,

biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.4. ARIA-H (Macrohemorrhage)

- Subjects who develop any new incident macrohemorrhage, regardless of symptom severity during the study, will permanently discontinue treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for MRI and MOCA every 2 weeks (±3 days) until the macrohemorrhage is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA-H (macrohemorrhage).

7.2.1.5. Coincident ARIA-H and ARIA-E Cases

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow the most restrictive guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H must be deemed stable, and the subject must be asymptomatic. For example, if a subject experiences asymptomatic ARIA-H (1-4 microhemorrhages) coincident with ARIA-E assessed as moderate on MRI and accompanied by mild clinical symptoms, the dose should be suspended per the ARIA-E guidelines summarized in Table 8. In addition, unscheduled visits should occur as described in Section 7.2.1.1 through Section 7.2.1.4.

7.2.1.6. Resumption of Study Treatment After Suspension due to ARIA

7.2.1.6.1. MRI Monitoring

When treatment resumes after a dose suspension due to ARIA, an MRI and MOCA will be performed 2 weeks (±3 days) after the second administration of the restarted dose. In addition, if treatment was suspended during the dose titration prior to the subject reaching the maximum assigned dose, an MRI and MOCA will be performed 2 weeks (±3 days) after every second dose until completion of the titration period, with subjects assumed to be titrating to 10 mg/kg (titration period of 6 doses and a final MRI after the second dose at 10 mg/kg) to maintain study blinding, not counting unscheduled MRI visits for monitoring of ARIA. MRIs will otherwise be performed as indicated in the Schedule of Events (Section 4.2).

7.2.1.6.2. Dosing Upon Resumption of Study Treatment

Subjects who suspend treatment due to ARIA for the first time may resume treatment at the same dose if they meet the criteria as described in Sections 7.2.1.1 to 7.2.1.5. Subjects who suspend and then resume dosing after having already reached their assigned top dose level are to continue dosing at that dose level. However, if dosing is suspended prior to a subject reaching their assigned top dose level, the subject (1) must receive at least 2 doses at the restart dose before titrating up to the next dose level and (2) must complete at least the required number of doses at that dose level per their assigned treatment group, as outlined in the right column of Table 11.

Table 11: Resumption of Study Treatment Following Dose Suspension Due to ARIA During Titration

Assigned Treatment Group (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses at Current Dose Level Needed Before Going to the Next Higher Dose
ApoE ε4 (+)			
Low Dose (3 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2
	6 mg/kg	1	2
	6 mg/kg	2	2
ApoE ε4 (-)			
Low Dose (6 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	3
	3 mg/kg	2	2
	3 mg/kg	3	2
	3 mg/kg	4	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2
	6 mg/kg	1	2
	6 mg/kg	2	2

7.2.1.7. Management After Recurrent ARIA (Dosing and MRI)

If the subject has a second occurrence of ARIA (i.e., a second occurrence of ARIA-E or of ARIA-H, or ARIA-E and ARIA-H) that requires dose suspension (per criteria in Section 7.2.1.1, Section 7.2.1.2, and Section 7.2.1.3), after the ARIA-E resolves or stabilizes, the subject is to resume dosing at the next lower dose and is to receive 2 doses at that dose level (i.e., the restart dose) before titrating up to the next higher dose. Once dosing has resumed, the guidelines

outlined in Table 11 apply, unless the subject has reduced from 1 mg/kg to placebo. In this case, the subject will remain on placebo for the duration of the placebo-controlled portion of the study. If a subject resumes treatment after ARIA, an MRI and MOCA will be performed 2 weeks (±3 days) after the second administration of the restarted dose, and 2 weeks (±3 days) after every second dose until the completion of titration, with all subjects assumed to be titrating to 10 mg/kg (6 doses) to maintain study blinding. MRIs will otherwise be performed as indicated in the Schedule of Events (Section 4.2).

If the subject experiences a third episode of ARIA that requires dose suspension (i.e., after experiencing 2 prior episodes of ARIA meeting the criteria for dose suspension [see Section 7.2.1.1, Section 7.2.1.2, and Section 7.2.1.3]), the subject must discontinue study treatment. Subjects who discontinue treatment are to remain in the study and continue all protocol-required tests and assessments.

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE period and will maintain the dosing scheme from the placebo-controlled period into the LTE, which may include a continuation on the same dose or completion of titration into the LTE period. A subject who is dose-reduced to placebo but remains in the study may be titrated to aducanumab 1 mg/kg during the LTE period.

7.2.2. 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 Directions for Handling and Administration (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 subject will be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of Screening, treatment, and FU.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety FU period of 18 weeks after the final dose.

Subjects will have approximately 32 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety FU contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days). It is recommended that all screening procedures be completed within 60 days; however, the overall screening

period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

- 20 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 3 visits for clinical assessments.
- [redacted]
- 3 visits (including Screening) for amyloid PET scan (in a subset of subjects).
- [redacted]
- 7 visits for brain MRI.
- 1 FU safety visit at Week 94 (only for subjects not entering the LTE period) or 18 weeks after last administration of study treatment for those subjects who withdraw from study.

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period. Subjects who enter the LTE period will have approximately 36 additional planned clinic visits, and up to 8 telephone safety FU contacts, as follows:

- 26 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 4 visits for clinical assessments.
- [redacted]
- 2 visits for amyloid PET scan (in a subset of subjects).
- [redacted]
- 7 visits for brain MRI.
- 1 FU safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate (optional) initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, the Repeatable Battery for Assessment of

Neuropsychological Status [RBANS]) and ApoE genotyping. This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE, and RBANS) and ApoE genotyping must be performed at Screening Visit 1. ApoE genotyping may be performed at Visit 1 prior to other screening assessments. The ADAS-Cog 13 and ADCS-ADL-MCI will be performed at Screening Visit 2 within 20 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE, and RBANS. The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1). All other cognitive assessments [redacted] may be performed at any time during Screening after eligibility is confirmed during Screening Visit 1. [redacted]

The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion. Subjects who fail Screening due to not meeting entry criteria for PET, MMSE, hepatitis B or C results, having a CDR global score >0.5, or having abnormal MRI findings will not be allowed to rescreen. Note: Subjects with a CDR global score of 0 but who meet the other entry criteria may repeat the screening CDR evaluation after 6 months of the initial evaluation.

Subjects who fail Screening because allowed chronic medications have not been at stable doses for at least 4 weeks prior to Screening Visit 1 or whose use of AD medications has not been at stable doses for at least 8 weeks prior to Screening Visit 1 may return for rescreening after use of these medications has been stabilized for the required period.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period and will receive study treatment every 4 weeks for an additional 100 weeks (26 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE period are to return to the study site for an FU Visit at Week 94 (18 weeks after the last dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE period are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A FU Visit will occur at Week 198 (18 weeks after the last LTE dose). The final study visit for subjects participating in the LTE period will be Week 198.

Subjects who discontinue treatment are to remain in the study and continue all protocol-required tests and assessments until the end of the study or until withdrawal of consent. Subjects who withdraw from the study are encouraged to return for FU assessments 18 weeks after their last dose of study treatment.

7.4. Study Stopping Rules

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

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore, there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. 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. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of Screening) is permissible for subjects not participating in the amyloid PET substudy. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR global score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index score).
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and screening assessments.
8. Must consent to ApoE genotyping.
9. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. 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

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, Lewy body dementia, fronto-temporal dementia, head trauma).
2. Clinically significant unstable psychiatric illness (e.g., uncontrolled major depression, uncontrolled schizophrenia, uncontrolled bipolar affective disorder) within 6 months prior to Screening.
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >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 subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as >1.5 cm in diameter).
   - >1 lacunar infarct (defined as ≤1.5 cm in diameter).
   - Superficial siderosis.
   - 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 subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Presence of diabetes mellitus that, in the judgment of the Investigator, cannot be controlled or adequately managed.

7. 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.
8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [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 subject 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.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma of the skin.
    - Subjects with localized prostate cancer with treatment cycles that completed at least 6 months prior to Screening.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or known seropositivity for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for both hepatitis B surface antigen AND hepatitis B core antibody).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).

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

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 or use of AD 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 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any passive immunotherapy study targeting Aβ within 12 months of Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 12 months prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures

29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (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, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 6 months prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

33. For subjects who consent to LP, any contraindications to having a LP (e.g., platelet count < 100,000/μL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during Screening must be resolved prior to randomization. Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR global score >0.5, hepatitis B or C, or abnormal MRI findings. (Subjects who fail Screening due to a CDR global score of 0 may be rescreened; such subjects will be allowed to repeat the screening CDR assessment after 6 months.)
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥ 1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension Period

To be eligible to participate in the LTE period, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses, regardless of the reason. Subjects who do not meet these criteria can enter the LTE period only with Sponsor's approval.
2. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
3. Female subjects of childbearing potential and male subjects must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment.
4. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
5. Must have the ability to comply with procedures for protocol-related tests.
6. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally

be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long-Term Extension Period

Subjects will be excluded from entering the LTE period if at Week 78 they have:

1. Any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) and ApoE genotyping to determine study eligibility under a separate, optional initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study. ApoE genotyping may be performed at Visit 1 prior to other screening assessments.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log. The total study duration for each subject participating only in the placebo-controlled period will be approximately 102 weeks (approximately an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of FU).

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose: aducanumab high dose: placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Enrollment will be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE period with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating HCPs should remain blinded to treatment assignment as well as subject care management and only have access

to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. As 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 subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

For the LTE period, the dose information must remain restricted. The rating and treating HCP should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by serious clinical symptoms except for "other medically important event" as defined in Table 8.
  - Symptomatic ARIA-H (microhemorrhages) with serious clinical symptoms except for "other medically important event" as defined in Table 9.
  - Symptomatic ARIA-H (superficial siderosis) with or serious clinical symptoms except for "other medically important event" as defined in Table 10.
  - ARIA-H with ≥ 10 microhemorrhages and/or >2 focal areas of superficial siderosis.
  - Any new incident macrohemorrhage.
  - A third episode of ARIA after rechallenge that requires suspension (i.e., after experiencing 2 prior episodes of ARIA meeting the criteria for dose suspension (see Section 7.2.1.1, Section 7.2.1.2, and Section 7.2.1.3).

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria.
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

A subject who discontinues treatment is to remain in the study and continue protocol-required tests and assessments until the end of the study per the schedule of events or until the subject withdraws consent.

10.2. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

Note: A subject who discontinues study treatment will not be automatically withdrawn from the study, regardless of the number of doses missed, if they continue to attend clinic visits and complete all assessments.

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

Subjects who are withdrawn from the study after receiving ≥ 1 doses of study treatment should complete the EOT Visit after the reason for withdrawal is identified. For such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases. Subjects 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.

11. STUDY TREATMENT USE

11.1. Regimen

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

Please see Section 4.2 (Schedule of Events) for the study treatment infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

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

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.2 (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.

11.3. Precautions

Not applicable.

11.4. Compliance

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

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to Screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and until the subject'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.

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given < 10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤ 325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids (including inhaled and topical corticosteroids) are allowed; certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended. Medications used to treat AEs would not result in automatic withdrawal. The Sponsor may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures) performed between the time the subject is enrolled in the study and until the subject's final clinic visit (including FU visit), unless the subjects is being followed for study-related toxicity.

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

11.6. 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.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

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

Aducanumab is a recombinant human antibody expressed in a Chinese hamster ovary cell line [redacted], 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. [redacted]. Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing either:

- aducanumab 50 mg/mL [redacted]

  or

- aducanumab 100 mg/mL [redacted]

The concentration for each vial (either 50 or 100 mg/mL) appears on the label. Aducanumab is manufactured in accordance with Good Manufacturing Practices.

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

12.1.1. Aducanumab 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 Biogen.

12.1.2. Aducanumab 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 2 hours, then it should be kept at 2°C to 8°C 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.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (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 personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab 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 (subject-by-subject 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 Biogen. A written explanation must be provided for any discrepancies.

12.2. 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.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

To confirm amyloid pathology at Screening, PET scans will be performed using Amyvid™ (^{18}F-florbetapir), Vizamyl™ (^{18}F-flutemetomol), or Neuraceq™ (^{18}F-florbetaben). For those subjects participating in the amyloid PET substudy, Screening and FU scans must be performed using Amyvid and for subjects participating in the PET substudy in Japan, Vizamyl

(^{18}F-flutemetomol) may also be used. For details on PET imaging ligands, [redacted] refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

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

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

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

13.2. Pharmacokinetic Assessments

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

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the PD properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the amyloid PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in the amyloid PET substudy.

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

13.4. Additional Assessments

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

13.4.2. ApoE Genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

[redacted]

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- [redacted]
- mPDQ-20
- [redacted]

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

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

13.5. Future Scientific Research Assessments

[redacted]

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

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

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy, and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale (C-SSRS).

14.2. Laboratory Safety Assessments

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

- Hematology: complete blood count with differential and 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, virology (including HIV at the Investigator's discretion after consideration of risk factors), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

Presence of serum anti-aducanumab will be determined using a validated assay. A standard 3-tier antidrug antibody (ADA) approach will be used (i.e., screening assay, confirmatory assay, and titration assay). It is planned that confirmed ADA-positive samples may be evaluated for the presence of anti-aducanumab neutralizing antibodies using a validated assay.

15. 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 subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 laboratory finding), 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 laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the Investigator considers to be clinically significant.

Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.1.2. 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 subject 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.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject 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.)

15.1.3. 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 subject is hospitalized. The study site must document all of 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 subject's consent to participate 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 subject's consent to participate 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 subject 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 15.1.2 is met.

15.2. Safety Classifications

15.2.1. 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 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

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.

15.2.3. Severity of Events

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

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the subject's final clinic visit (including FU visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H 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.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to [redacted]

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between signing of the ICF and the subject's final clinic visit (including FU visit) will be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. This also applies to SAEs that occur after administration of the ligand. FU information regarding an SAE also must be reported with 24 hours.

Events occurring after the subject's final clinic visit (including FU visit) should be reported to Biogen only if the Investigator considers the SAE related to study treatment.

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

15.3.4. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the subject's final clinic visit (including FU visit) must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to [redacted] regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event

- The relationship of the event to study treatment

To report initial or FU information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Guide for country-specific [redacted] fax numbers or email [redacted]

15.3.4.1. 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. The Investigator should make every effort to obtain and send death certificates and autopsy reports to [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

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

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to [redacted] within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to [redacted].

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in 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 to [redacted] within 24 hours of the site becoming aware of the overdose. An overdose must be reported to [redacted] 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 to [redacted]). All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. 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 [redacted] emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

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

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the [redacted] 24-hour emergency medical support number at [redacted].

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

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.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of this study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system

- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (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.
- Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at FU.
  - Use of condoms with spermicide.
  - Female sexual partners who underwent surgical sterilization (e.g., bilateral tubal ligation), are postmenopausal, are post-hysterectomy, or are using highly effective contraception as listed above for female subjects.

  For males and females of childbearing potential:

  True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, 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, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, 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 and FU on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE FU information actively and persistently. FU information must be reported to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of new information.

- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE FU information, if possible, until the event has resolved or become stable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor ([redacted]) is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects 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 each aducanumab dose (high and low) and placebo. All statistical tests will be 2-sided.

16.2.2.2. Aducanumab Doses to be Evaluated

The following aducanumab doses as compared with placebo will be evaluated:

- Aducanumab high-dose (10 mg/kg in ApoE ε4 [including 6 mg/kg for subjects enrolled under protocol version 1-3 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study] and 10 mg/kg in ApoE ε4 non-carriers).
- Aducanumab low-dose (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the maximum dose (10 mg/kg) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose and aducanumab low dose will be modified as shown in Table 12. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of Type I error rate is thus maintained without a statistical adjustment for such adaptations [Chow and Chang 2011].

Table 12: Treatment Groups in the Event of High Dose Group Termination

High Dose Group(s) Terminated	Definitions of Revised Treatment (Low/High Dose) Groups for Comparison
ApoE ε4 carrier high-dose group (10 mg/kg) [including 6 mg/kg for subjects enrolled under protocol version 1-3 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study]	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 10 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group (10 mg/kg) AND ApoE ε4 non-carrier high-dose group (10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose versus placebo and aducanumab low-dose versus placebo. All comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for 1 or 2 comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1 or 2, respectively.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population with a baseline and at least one post-baseline CDR-SB score. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change From Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population with a baseline and at least one post-baseline MMSE value. A MMRM model will be used as the primary analysis to

analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction and baseline ApoE ε4 status

16.2.2.5.2. Change From Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADAS-Cog 13 score. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction, baseline MMSE, and baseline ApoE ε4 status.

16.2.2.5.3. Change From Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population with a baseline and at least one post-baseline ADCS-ADL-MCI score. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction, baseline MMSE, and baseline ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, an MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE and baseline ApoE ε4 status.

Otherwise, an analysis of covariance may be used to analyze these exploratory endpoints or descriptive summary statistics may be presented.

16.2.2.6.2. Long-Term Extension Period

The endpoints for the LTE period are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the placebo-controlled period using the placebo-controlled period baseline. Details of the analyses will be prespecified in the statistical analysis plan (SAP).

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The serum concentrations and PK parameters of aducanumab will be summarized descriptively.

16.4. Additional Exploratory Analyses

[redacted]

16.5. Safety

16.5.1. Analysis Population

The safety population is defined as all subjects who received at least 1 dose of study treatment (including placebo and aducanumab).

16.5.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.5.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent 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 study treatment for the placebo-controlled period and over the 24-month LTE period. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.5.2.2. 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. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.5.2.3. Vital Signs

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

16.5.2.4. ECG

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

16.5.2.5. Columbia Suicide Severity Rating Scale

The C-SSRS data will be summarized by treatment group.

16.6. Immunogenicity Data

16.6.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.6.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.7. Interim Analyses

16.7.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.7.2. Interim Superiority Analysis

An interim analysis for superiority may be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The O'Brien-Fleming boundary approach will be used for the analysis. In order to maintain the treatment blind in the event of this interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.8. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103, which included 1-year data from 1, 3, and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group will have approximately 90% power to detect a true mean difference of 0.5 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 1.92, and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflects a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

The sample size for this study (and for the identically designed Study 221AD302) may be reassessed in a blinded manner approximately 3 months before enrollment is complete if at least 10% of the data are available on the primary endpoint from each study. At this interim timepoint, the SD for the primary endpoint will be estimated based on the pooled blinded data (i.e., treatment groups combined) from Studies 221AD301 and 221AD302. The sample size may be increased if the SD is estimated to be more than approximately 2.07 to assure adequate power for detecting a treatment effect. In addition, the sample size could be increased using external clinical trial results that become available after the start of the study. Based on this reassessment, the sample size may be increased by up to approximately 30% and the revised sample size for each study will not exceed 1764 subjects (or 588 subjects per group).

17. ETHICAL REQUIREMENTS

Biogen, [redacted], and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

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.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

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

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

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE, and RBANS) as well as ApoE genotyping as an initial optional screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed prior to the administration of further screening assessments.

Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

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

Subjects will be informed that their race and/or ethnicity will be collected and will be used during analysis of study results (only in countries where permitted by local law/regulation).

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The 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 (wet signature) and copies of the signed and dated ICFs.

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

17.4. Subject Data Protection

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

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

During the study, subjects' race and/or ethnicity will be collected (only in countries where permitted by local law/regulation). These data may be used in the analysis of the safety, efficacy, and/or pharmacokinetic profile of the study treatment. It is unknown if the potency or effects of the study treatment are influenced by race or ethnicity.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. 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 subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights, and a user manual.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by [redacted] and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen 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, [redacted], and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA 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.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen 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 PI 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 collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen 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 per project-specific plans.

19.2. Study Committees

19.2.1. 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 subject accrual and oversee study conduct, including advising on study design and execution. The advisory committee will be blinded to subject treatment assignments during the study.

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

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. 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 subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), 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.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB 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, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. 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 Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. 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 laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen 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.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study 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 subject enrollment, or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early 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)

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

PROTOCOL NUMBER: 221AD301 / NCT02477800

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

PHASE OF DEVELOPMENT: 3

PROTOCOL TITLE: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease

EUDRA CT NO: **2015-000966-72**

DATE: 28 June 2018
Version 6.0
FINAL

Supersedes previous Version 5.0 dated 18 September 2017.

SPONSOR SIGNATURE

Protocol 221AD301 was approved by:

[redacted]

2 July 2018

[redacted], PhD

Date

Biogen MA Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SPONSOR INFORMATION

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Chuo-ku
Tokyo
103-0027
Japan

For 24-hour emergency medical support contact

[redacted] at [redacted]

Please refer to the Study Reference Manual for complete contact information.

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

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-β-amyloid immunoglobulin G_1 monoclonal antibody with an amino acid sequence identical to aducanumab, produced in a different Chinese hamster ovary cell line
Aβ	β-amyloid (peptide derived from membrane bound amyloid precursor protein)
AA	Alzheimer's Association
AD	Alzheimer's disease
ADA	antidrug antibody
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-hemorrhage or superficial siderosis
[redacted]	[redacted]
AST	aspartate aminotransferase
[redacted]	[redacted]
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating sum of boxes
ch12F6A	murine IgG_{2a} chimeric version of 12F6A or aducanumab
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment
EQ-5D	EuroQol health status measure
[redacted]	[redacted]

	[redacted]
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject
EQ-5D (SR)	EuroQol health status measure, subject self-reported
FU	follow-up
GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCP	health care professional
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IR	informant rated
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LTE	long-term extension
LP	lumbar puncture
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NIA-AA	National Institute on Aging (NIA) at National Institutes of Health (NIH) and the Alzheimer's Association (AA)
NPI-10	Neuropsychiatric Inventory-10
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RNA	ribonucleic acid
SABR	Safety and Benefit-Risk

SAE	serious adverse event
SAP	statistical analysis plan
SB	sum of boxes
SBP	systolic blood pressure
SD	standard deviation
SR	subject rated
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
[redacted]	[redacted]

3. SYNOPSIS

Protocol Number:	**221AD301**
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Version Number:	6.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's Disease
Study Rationale:	The purpose of this Phase 3 study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early Alzheimer's Disease (AD), including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human monoclonal antibody that recognizes aggregated forms of β-amyloid (Aβ), including soluble Aβ oligomers and deposited fibrillar Aβ. Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a pharmacodynamic effect on amyloid reduction, and an effect on the Clinical Dementia Rating (CDR)-sum of boxes (SB) and Mini-Mental State Examination (MMSE) suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results, along with the observed safety and tolerability profile, warrant further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.
Phase of Development:	3
Study Objectives and Endpoints (placebo-controlled period of the study):	The primary objective of the study is to evaluate the efficacy 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 subjects with early AD. The primary endpoint that relates to this objective is the change from baseline in CDR-SB score at Week 78. Secondary objectives and endpoints are as follows: To assess the effect of monthly doses of aducanumab as

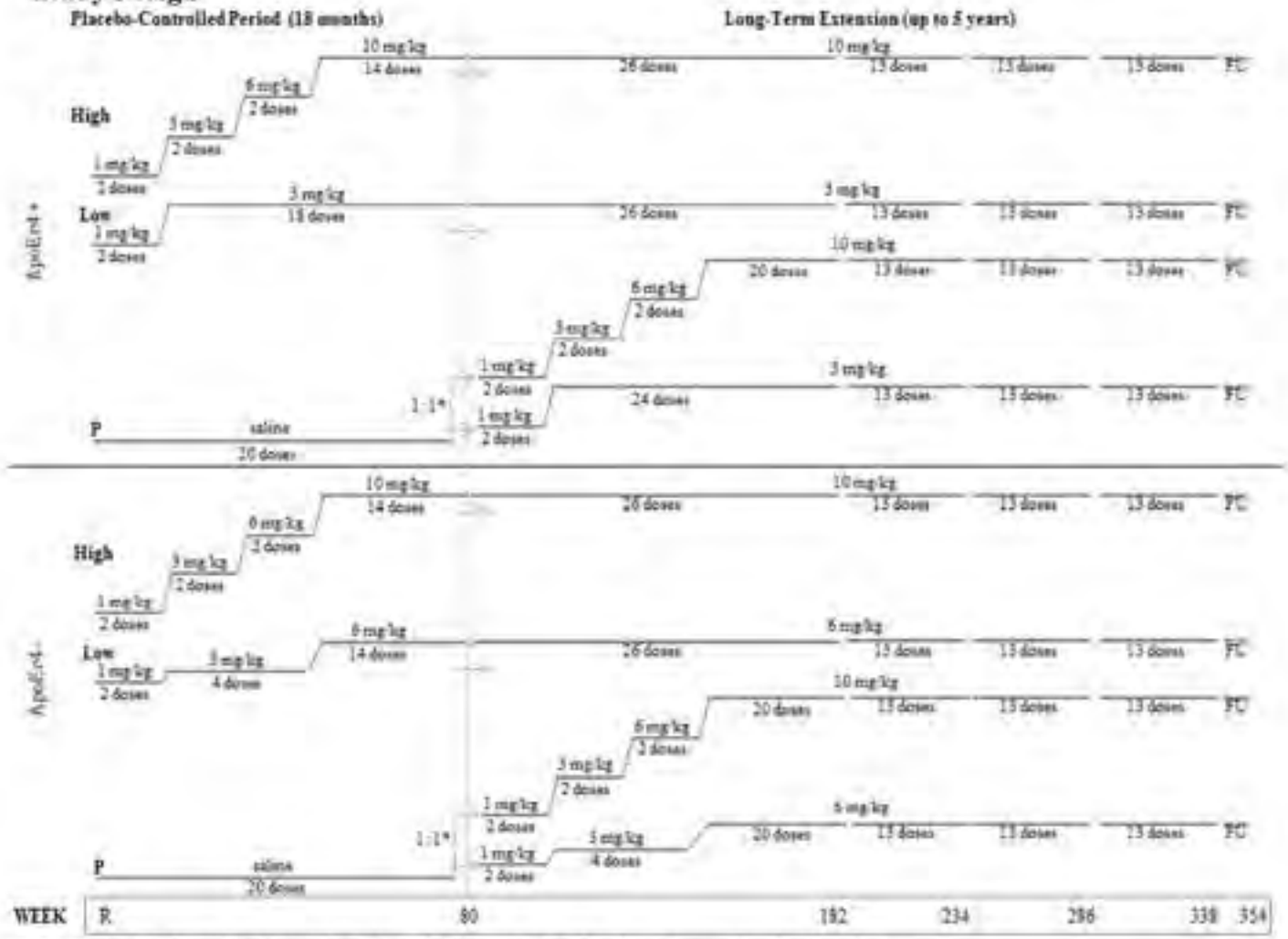
Protocol Number:	**221AD301**
	compared with placebo on clinical progression as measured by • MMSE - Change from baseline in MMSE score at Week 78 • Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13] - Change from baseline in ADAS-Cog 13 at Week 78 • Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI] - Change from baseline in ADCS-ADL-MCI score at Week 78 Tertiary objectives of this study are listed in Section 6.3.1. Tertiary endpoints of this study are listed in Section 6.3.2. Additional exploratory objectives and endpoints are listed in Section 6.4.
Study Objectives and Endpoints (Dose-Blind Long-Term Extension period of the study):	The objectives are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health-outcomes assessments. Endpoints for the long-term extension (LTE) period of the study are listed in Section 6.5.
Study Design:	Multicenter, randomized study with an 18-month double-blind, placebo-controlled, parallel-group period followed by an optional up to 5-year, dose-blind, LTE period
Study Location:	Approximately 150 sites globally
Number of Planned Subjects:	Approximately 1605 subjects are planned to be enrolled.
Study Population:	This study will be conducted in subjects with early AD, including subjects with MCI due to AD and a subset of mild AD according to National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer's Association (NIA-AA) criteria. Subjects must be positive for amyloid pathology as measured by amyloid positron emission tomography scan. Subjects must be 50 to 85 years old, and apart from the clinical diagnosis of early AD, they must be in good health as determined by the Investigator, based on medical history and the screening assessments. The

Protocol Number:	**221AD301**
	ratio of apolipoprotein E4 (ApoE ε4) carriers to non-carriers in the study population will generally reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology, such that subjects with mild AD represent a small percentage of the total enrolled in the trial. Detailed criteria are described in Section 8.
Treatment Groups:	For the 18-month placebo-controlled period of the study and based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups in a 1:1:1 ratio (aducanumab low dose: aducanumab high dose:placebo) as follows: **ApoE ε4 carrier** **Low dose (3 mg/kg)** **High dose (10 mg/kg)** **Placebo** **ApoE ε4 non-carrier** **Low dose (6 mg/kg)** **High dose (10 mg/kg)** **Placebo** After completion of the placebo-controlled period, subjects may enter a dose-blind LTE study during which all subjects will receive aducanumab for up to 5 years.
Duration of Treatment and Follow Up:	Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of follow-up [FU]). For subjects who enter the optional LTE period, the total study duration will vary and be up to approximately 362 weeks or 83 months (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 4 weeks of FU, plus an optional LTE period including 256 weeks of dose-blind aducanumab dosing and 18 weeks of FU).

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD301

4.1. Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; FU = follow-up; P = placebo; R = randomization date.

*Subjects who are assigned to placebo during the placebo-controlled period are randomized in a 1:1 ratio to high and low dose aducanumab treatment (based upon their ApoE ε4 carrier status) for the long-term extension period on Study Day 1.

4.2. Schedule of Events

Table 1: Placebo-Controlled Period Schedule From Screening Through Week 48

Study Week	Screening (≤ 60 days before Day 1)[1]			Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Initial Screening Consent[2] (optional)	X																	
Full Informed Consent[3]	X																	
Eligibility Criteria	X	X	X	X[4]														
Demography	X																	
Medical History	X	X	X															
Alcohol/Drug Screen	X																	
HbA_{1c}	X																	
HIV[5]/Hepatitis/ Coagulation	X																	
ApoE Genotyping	X																	
[redacted]																		
Height	X																	
Body Weight	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Serum Pregnancy Test[7]	X																	
Urine Pregnancy Test[7]				X	X	X	X	X	X	X		X	X	X	X	X	X	
Physical Examination	X						X			X							X	

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			**Wk 1, Day 1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**UV for a Change in AD Medication**
Study Day	**V1**	**V2**	**V3**	**1**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**197 ± 3**	**225 ± 3**	**253 ± 3**	**281 ± 3**	**309 ± 3**	**337 ± 3**	
Neurological Examination	X						X			X							X	
12-lead Paper ECG	X									X							X	
Vital Signs[8]	X			X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis	X			X						X							X	
Randomization				X[9]														
Study Drug Infusion				X	X	X	X	X	X	X		X	X	X	X	X	X	
Anti-Aducanumab Ab[10]				X						X			X					
Aducanumab Concentration[11]				X[12]	X[13]		X[12]	X	X[12]	X[12]		X[12]	X					
[redacted]																		
PBMC Collection	X						X	X		X			X					
[redacted]																		
Amyloid PET[15]			X								X							
[redacted]																		
RBANS	X																	
CDR	X										X							X

Study Week																		
	Screening (≤ 60 days before Day 1)[1]			Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	UV for a Change in AD Medication
Study Day	V1	V2	V3	1	29 ± 3	57 ± 3	85 ± 3	113 ± 3	141 ± 3	169 ± 3	183 ± 3	197 ± 3	225 ± 3	253 ± 3	281 ± 3	309 ± 3	337 ± 3	
MMSE	X										X							X
ADCS-ADL-MCI		X[17]									X							X
ADAS-Cog 13		X[17]									X							X
NPI-10		X[18]									X							
EQ-5D (SR)		X[19]									X							
EQ-5D (IR-S)		X[19]									X							
[redacted]																		
mPDQ-20		X[19]									X							
[redacted]																		
C-SSRS				X							X							
AE Reporting				Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																	
SAE Reporting	Monitor and record continuously throughout the study																	

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ApoE = apolipoprotein E; ARIA = amyloid-related imaging abnormalities; [redacted]; CDR = Clinical Dementia Rating scale; CRO = contract research organization; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; [redacted] EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; LTE = long-term extension; MMSE = Mini Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; RBANS = Repeatable

Battery for the Assessment of Neuropsychological Status; SAE = serious adverse event; UV = unscheduled visit; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; Wk = Week.

[1] Examination required for assessment of subject eligibility must be performed at V1. Brain MRI (Table 3) should only be performed once the subject meets eligibility criteria at V1. Amyloid PET should only be performed if the subject meets eligibility criteria at V1 and V2. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

[2] Subjects may sign this optional form for an initial Screening which allows administration of the RBANS, CDR, and MMSE only, as well as ApoE genotyping.

[3] All subjects must sign this informed consent, including subjects who have signed the optional initial screening consent, once they have met the RBANS, CDR, and MMSE eligibility criteria.

[4] All assessments, including the C-SSRS, must be completed before study treatment administration, except the post-dose sample to measure aducanumab concentration.

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

[7] Required for women of childbearing potential only (see Section 15.5).

[8] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

[9] Randomization for both the placebo-controlled period and LTE period will occur on Study Day 1 (see Section 9.2).

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

[11] Blood sampling for aducanumab concentration will be performed prior to infusion.

[12] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[13] Samples will be collected prior to infusion (where applicable).

[15] Screening amyloid PET is required for all subjects; amyloid PET at Week 26 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy. The amyloid PET at Week 26 may be scheduled within a window of ±7 days.

[17] Must be performed within 20 days of V1, but not on the same day as the screening RBANS, CDR, or MMSE.

[18] The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening V1).

[19] May be performed at any point during Screening after the subject has met eligibility criteria on the RBANS, CDR, and MMSE.

Table 2: Placebo-Controlled Period Schedule From Week 50 to End of Treatment or Follow-Up

Study Week											FU[1]
	50	52	56	60	64	68	72	76	78 (EOT)[2]	UV for a Change in AD Medication	94 (or 18 wks after final dose for subjects who DCT early)
Study Day	**351 ± 3**	**365 ± 3**	**393 ± 3**	**421 ± 3**	**449 ± 3**	**477 ± 3**	**505 ± 3**	**533 ± 3**	**547 ± 3**		**659 ± 7**
Informed Consent									X[3]		
Eligibility Criteria									X[3]		
Body Weight		X	X	X	X	X	X	X			X
Urine Pregnancy Test[4]		X	X	X	X	X	X	X			X
Physical Examination							X		X		X
Neurological Examination							X		X		X
12-lead Paper ECG							X		X		X
Vital Signs[5]		X	X	X	X	X	X	X			X
Hematology, Blood Chemistry and Urinalysis							X		X		X
Study Treatment Infusion		X	X	X	X	X	X	X			

Study Week											FU[1]
	50	52	56	60	64	68	72	76	78 (EOT)[2]	UV for a Change in AD Medication	94 (or 18 wks after final dose for subjects who DCT early)
Study Day	351 ± 3	365 ± 3	393 ± 3	421 ± 3	449 ± 3	477 ± 3	505 ± 3	533 ± 3	547 ± 3		659 ± 7
Anti-Aducanumab Ab[6]			X						X		X
Aducanumab Concentration[7]		X[8]	X						X		X
[redacted]											
PBMC Collection			X						X		X
[redacted]											
Amyloid PET[10]									X		
[redacted]											
CDR	X								X	X	X
MMSE	X								X	X	X
ADCS-ADL MCI	X								X	X	X
ADAS-Cog 13	X								X	X	X
NPI-10	X								X		
EQ-5D (SR)	X								X		

Study Week											FU[1]
	50	52	56	60	64	68	72	76	78 (EOT)[2]	UV for a Change in AD Medication	94 (or 18 wks after final dose for subjects who DCT early)
Study Day	351 ± 3	365 ± 3	393 ± 3	421 ± 3	449 ± 3	477 ± 3	505 ± 3	533 ± 3	547 ± 3		659 ± 7
EQ-5D (IR-S)	X								X		
[redacted]											
mPDQ-20	X								X		
[redacted]											
C-SSRS		X							X		
AE Reporting	Monitor and record continuously throughout the study										
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study										
SAE Reporting	Monitor and record continuously throughout the study										

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; [redacted]; CDR = Clinical Dementia Rating scale; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; DCT = discontinue treatment; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit; wks = weeks.

[1] Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10. and Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur 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. Note: Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject

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 in such cases.

[3] Only for subjects entering the long-term extension period.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.

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

[7] Blood sampling for aducanumab concentration will be performed prior to infusion.

[8] One additional blood sample for aducanumab concentration will be collected between 10 and 60 minutes after completion of the infusion and line flush. Note: For subjects who suspend treatment due to ARIA, only 1 blood sample is required to be collected at each specified visit during the period of dose suspension; all other visits/assessments are required to be performed.

[9] Sample will be collected prior to infusion (where applicable).

[10] Amyloid PET at Week 78 will only be conducted in selected sites for subjects who are participating in the amyloid PET substudy and may be scheduled within a window of ±7 days.

[redacted]

Table 3: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule During the Placebo-Controlled Period

Study Week	Screening (≤ 60 days before Day 1)[1]			Placebo-Controlled Period													FU[2]
				1	2	6	10	14	18	22	26	30	42	54	66	78/ EOT[3]	Unscheduled Visit/ MRI for ARIA[4]	94 (or 18 wks after final dose for subjects who DCT early)
Study Day	V1	V2	V3	1	15 ± 3	43 ± 3	71 ± 3	99 ± 3	127 ± 3	155 ± 3	183 ± 3	211 ± 3	295 ± 3	379 ± 3	463 ± 3	547 ± 3		659 ± 7
Follow-Up Phone Call[5]					X	X	X	X	X	X	X	X						
Brain MRI[6]		X						X		X		X	X	X	X	X	X	X
Aducanumab Concentration[7]										X		X		X			X	X
MOCA				X													X	
[redacted]																		
PBMC Collection[8]																	X	

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality-hemorrhage or superficial siderosis; DCT = discontinue treatment; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; [redacted]; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3; wks = weeks.

1 Brain MRI (V2) will not be performed until the subject has met the eligibility criteria and has acceptable laboratory tests from V1. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

2 Subjects who complete the placebo-controlled period and do not enter the LTE are to return to the site for a safety FU Visit at Week 94. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose.

3 Subjects who discontinue treatment prematurely are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur 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. Subjects who withdraw from study prematurely are

to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases.

[4] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[5] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[6] Arterial spin labeling MRI and task-free functional MRI will be performed only at a subset of sites.

[7] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[8] Sample may be collected ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

Table 4: Long-Term Extension Period Schedule From Week 80 to Week 134

Study Week	80	84	88	92	96	100	104	106	108	112	116	120	124	128	132	134	UV for a Change in AD Medication
Study Day	561 ± 5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	743 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	939 ± 5	
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Urine Pregnancy Test[1]	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Physical Examination				X			X							X			
Neurological Examination				X			X							X			
12-lead Paper ECG							X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
Hematology, Blood Chemistry and Urinalysis							X							X			
Anti-Aducanumab Ab[2]	X						X							X			
[redacted]																	
PBMC Collection							X							X			
Aducanumab Concentration[2]	X						X							X			

Study Week	80	84	88	92	96	100	104	106	108	112	116	120	124	128	132	134	UV for a Change in AD Medication
Study Day	561 ± 5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	729 ± 5	743 ± 5	757 ± 5	785 ± 5	813 ± 5	841 ± 5	869 ± 5	897 ± 5	925 ± 5	939 ± 5	
Study Treatment Infusion	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
[redacted]																	
Amyloid PET[4]															X		
[redacted]																	
CDR								X								X	X
MMSE								X								X	X
ADAS-Cog 13								X								X	X
ADCS-ADL-MCI								X								X	X
NPI-10								X								X	
EQ-5D (IR-S)								X								X	
[redacted]																	
[redacted]																	
C-SSRS								X								X	
AE Reporting	Monitor and record continuously throughout the study																
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																
SAE Reporting	Monitor and record continuously throughout the study																

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); [redacted] CDR = Clinical Dementia Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] Required for women of childbearing potential only (see Section 15.5).

[2] Sample will be collected prior to infusion (where applicable).

[redacted]

[4] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[redacted]

Table 5: Long-Term Extension Period Schedule From Week 136 to Week 182

Study Week	136	140	144	148	152	156	160	162	164	168	172	176	180	182	UV for a Change in AD Medication
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5	
Body Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	
Urine Pregnancy Test[3]	X	X	X	X	X	X	X		X	X	X	X	X	X	
Physical Examination					X							X		X	
Neurological Examination					X							X		X	
12-lead Paper ECG					X							X			
Vital Signs	X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis					X							X			
Anti-Aducanumab Ab[2]					X									X	
[redacted]															
PBMC Collection					X									X	
Aducanumab Concentration[2]					X							X		X	
Study Drug Infusion	X	X	X	X	X	X	X		X	X	X	X	X		
[redacted]															
Amyloid PET[4]														X	

Study Week	136	140	144	148	152	156	160	162	164	168	172	176	180	182	UV for a Change in AD Medication
Study Day	953 ± 5	981 ± 5	1009 ± 5	1037 ± 5	1065 ± 5	1093 ± 5	1121 ± 5	1135 ± 5	1149 ± 5	1177 ± 5	1205 ± 5	1233 ± 5	1261 ± 5	1275 ± 5	
[redacted]															
CDR								X						X	X
MMSE								X						X	X
ADAS-Cog 13								X						X	X
ADCS-ADL-MCI								X						X	X
NPI-10								X						X	
EQ-5D (IR-S)								X						X	
[redacted]															
C-SSRS								X						X	
AE Reporting	Monitor and record continuously throughout the study														
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study														
SAE Reporting	Monitor and record continuously throughout the study														

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); [redacted]; CDR = Clinical Dementia Rating; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MMSE = Mini-Mental State Examination; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] Required for women of childbearing potential only (Section 15.5).

[2] Sample will be collected prior to infusion (where applicable).

[redacted]

[4] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[redacted]

Table 6: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule From Weeks 80 to 182 of the Long-Term Extension Period

Study Week	Long-Term Extension													Unscheduled Visit for ARIA[1]
	80	82	86	90	94	98	102	106	110	122	134	158	182	
Study Day	561 ± 5	575 ± 5	603 ± 5	631 ± 5	659 ± 5	687 ± 5	715 ± 5	743 ± 5	771 ± 5	855 ± 5	939 ± 5	1107 ± 5	1275 ± 5	
Follow-Up Phone Call[2]		X	X	X	X	X	X	X	X					
Brain MRI[3]					X		X		X	X	X	X	X	X[4]
Aducanumab Concentration[4]														X
MOCA	X													X
[redacted]														
PBMC Collection[5]														X

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; [redacted].

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Phone visit may be performed in person if the subject will be at the study site for clinical assessments.

[3] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites, and will not be performed at any visit after Week 182.

[4] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[5] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

Table 7: Long-Term Extension Period Schedule From Week 184 to Week 234

Study Week	184	188	192	196	200	204	208	212	216	220	224	228	232	UV for ARIA[1]
Study Day	1289 ± 5	1317 ± 5	1345 ± 5	1373 ± 5	1401 ± 5	1429 ± 5	1457 ± 5	1485 ± 5	1513 ± 5	1541 ± 5	1569 ± 5	1597 ± 5	1625 ± 5	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination							X						X	
Neurological Examination							X						X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis													X	
PBMC Collection														X[3]
Aducanumab Concentration														X[4]
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	
Brain MRI													X	X
CDR													X	
MMSE													X	
ADAS-Cog 13													X	
ADCS-ADL-MCI													X	
EQ-5D-(IR-S)													X	

Study Week														
	184	**188**	**192**	**196**	**200**	**204**	**208**	**212**	**216**	**220**	**224**	**228**	**232**	**UV for ARIA**[1]
Study Day	**1289 ± 5**	**1317 ± 5**	**1345 ± 5**	**1373 ± 5**	**1401 ± 5**	**1429 ± 5**	**1457 ± 5**	**1485 ± 5**	**1513 ± 5**	**1541 ± 5**	**1569 ± 5**	**1597 ± 5**	**1625 ± 5**	
MOCA														X
C-SSRS													X	
AE Reporting	Monitor and record continuously throughout the study													
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study													
SAE Reporting	Monitor and record continuously throughout the study													

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CDR = Clinical Dementia Rating scale; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Required for women of childbearing potential only (Section 15.5).

[3] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[4] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

Table 8: Long-Term Extension Period Schedule From Week 236 to Week 286

Study Week	236	240	244	248	252	256	260	264	268	272	276	280	284	UV for ARIA[1]
Study Day	1653 ± 5	1681 ± 5	1709 ± 5	1737 ± 5	1765 ± 5	1793 ± 5	1821 ± 5	1849 ± 5	1877 ± 5	1905 ± 5	1933 ± 5	1961 ± 5	1989 ± 5	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination							X						X	
Neurological Examination							X						X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis													X	
PBMC Collection														X[3]
Aducanumab Concentration														X[4]
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	
Brain MRI													X	X
Amyloid PET[5]							X							
CDR													X	
MMSE													X	
ADAS-Cog 13													X	
ADCS-ADL-MCI													X	
EQ-5D-(IR-S)													X	

Study Week														
	236	240	244	248	252	256	260	264	268	272	276	280	284	UV for ARIA[1]
Study Day	1653 ± 5	1681 ± 5	1709 ± 5	1737 ± 5	1765 ± 5	1793 ± 5	1821 ± 5	1849 ± 5	1877 ± 5	1905 ± 5	1933 ± 5	1961 ± 5	1989 ± 5	
[redacted]														
MOCA														X
C-SSRS													X	
AE Reporting	Monitor and record continuously throughout the study													
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study													
SAE Reporting	Monitor and record continuously throughout the study													

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; CDR = Clinical Dementia Rating scale; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted] EQ-5D (IR-S) = EQ-5D, informant reported on subject; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[2] Required for women of childbearing potential only (Section 15.5).

[3] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[4] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[5] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

Table 9: Long-Term Extension Period Schedule From Week 288 to the End of Treatment or Follow-Up

Study Week																FU[1]
	288	292	296	300	304	308	312	316	320	324	328	332	336	338 EOT[2]	UV for ARIA[3]	354 (or 18 wks after final dose for subjects who DCT early)
Study Day	2017 ± 5	2045 ± 5	2073 ± 5	2101 ± 5	2129 ± 5	2157 ± 5	2185 ± 5	2213 ± 5	2241 ± 5	2269 ± 5	2297 ± 5	2325 ± 5	2353 ± 5	2367 ± 5		2479 ± 7
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine Pregnancy Test[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination							X							X		X
Neurological Examination							X							X		X
12-lead Paper ECG																X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology, Blood Chemistry and Urinalysis													X			X
Anti-Aducanumab Ab														X		X
PBMC Collection														X[5]	X[6]	X
Aducanumab Concentration														X	X[7]	X
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X			

Study Week																**PV**[1]
	288	**292**	**296**	**300**	**304**	**308**	**312**	**316**	**320**	**324**	**328**	**332**	**336**	**338 EOT**[2]	**UV for ARIA**[3]	**354 (or 18 wks after final dose for subjects who DCT early)**
Study Day	**2017 ± 5**	**2045 ± 5**	**2073 ± 5**	**2101 ± 5**	**2129 ± 5**	**2157 ± 5**	**2185 ± 5**	**2213 ± 5**	**2241 ± 5**	**2269 ± 5**	**2297 ± 5**	**2325 ± 5**	**2353 ± 5**	**2367 ± 5**		**2479 ± 7**
[redacted]																
Brain MRI														X[9]	X	X[9]
Amyloid PET[10]														X		
[redacted]																
CDR														X		X
MMSE														X		X
ADAS-Cog 13														X		X
ADCS-ADL-MCI														X		X
NPI-10														X[3]		
EQ-5D-(IR-S)														X		
[redacted]																
MOCA															X	
C-SSRS														X		
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study															

Study Week																FU[1]
	288	292	296	300	304	308	312	316	320	324	328	332	336	338 EOT[2]	UV for ARIA[3]	354 (or 18 wks after final dose for subjects who DCT early)
Study Day	2017 ± 5	2045 ± 5	2073 ± 5	2101 ± 5	2129 ± 5	2157 ± 5	2185 ± 5	2213 ± 5	2241 ± 5	2269 ± 5	2297 ± 5	2325 ± 5	2353 ± 5	2367 ± 5		2479 ± 7
SAE Reporting	Monitor and record continuously throughout the study															

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; [redacted]; CDR = Clinical Dementia Rating scale; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; DCT = discontinue treatment; ECG = electrocardiogram; EOT = end of treatment; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; FU = follow-up ; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; [redacted]; SAE = serious adverse event; UV = unscheduled visit; wks = weeks.

[1] Subjects who complete the LTE period are to return to the site for a safety FU Visit at Week 354. Subjects who discontinue treatment or withdraw from the study early are to have a safety FU Visit at 18 weeks after their final dose.

[2] Subjects who discontinue treatment prematurely are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments continue protocol-required tests and assessments at a subset of the clinic visits (see Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur 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. Subjects who withdraw from study prematurely are to return to the site for an EOT Visit. For subjects who discontinue treatment early, efficacy assessments specified at the EOT visit are not required if the subject 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 in such cases.

[3] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[4] Required for women of childbearing potential only (see Section 15.5).

[5] This assessment is only to be performed if the EOT Visit is at or before Week 182.

[6] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[7] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[redacted]

[9] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites, and will not be performed at any visit after Week 182.

[10] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[redacted]

Table 10: Subjects Who Discontinue Study Treatment but Remain in the Study – Placebo-Controlled Period

Study Week	Placebo-Controlled Period[1]							
	12	24	26	48	50	72	78 (EOT)[2]	UV for ARIA[3]
Study Day	85 ± 3	169 ± 3	183 ± 3	337 ± 3	351 ± 3	505± 3	547 ± 3	
Informed Consent							X[4]	
Body Weight	X	X		X		X		
Eligibility Criteria							X[4]	
Physical Examination	X	X		X		X	X	
Neurological Examination	X	X		X		X	X	
12-lead Paper ECG		X		X		X	X	
Vital Signs	X	X		X		X		
Hematology, Blood Chemistry and Urinalysis		X		X		X	X	
[redacted]								
PBMC Collection								X[5]
Aducanumab Concentration								X[6]
[redacted]								
Brain MRI[7]							X	X
Amyloid PET[8]			X				X	
[redacted]								
CDR			X		X		X	
MMSE			X		X		X	
ADAS-Cog 13			X		X		X	
ADCS-ADL-MCI			X		X		X	

Study Week	Placebo-Controlled Period[1]							
	12	24	26	48	50	72	78 (EOT)[2]	UV for ARIA[3]
Study Day	85 ± 3	169 ± 3	183 ± 3	337 ± 3	351 ± 3	505± 3	547 ± 3	
NPI-10			X		X		X	
EQ-5D (SR)			X		X		X	
EQ-5D (IR-S)			X		X		X	
[redacted]								
mPDQ-20			X		X		X	
[redacted]								
MOCA								X
C-SSRS			X				X	
AE Reporting	Monitor and record continuously throughout the study							
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study							
SAE Reporting	Monitor and record continuously throughout the study							

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; [redacted] CDR = Clinical Dementia Rating scale; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOT = end of treatment; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; EQ-5D (SR) = EQ-5D, subject self-reported; FU = follow-up; LTE = long-term extension; MMSE = Mini Mental State Examination; mPDQ-20 = modified Perceived Deficits Questionnaire-20; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI-10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; [redacted]; SAE = serious adverse event; SoE = schedule of events; UV = unscheduled visit.

[1] Subjects who discontinue study treatment prematurely during the placebo-controlled period are to remain in the study, attend a FU Visit 18 weeks after their final dose as listed in Table 2 and Table 3, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10, and Table 11) until the end of the study per the schedule of events. (It is possible that a clinic visit will occur before the FU Visit.) If the FU Visit will occur 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. If the subject who discontinued treatment but remained in the study chooses to enroll in the LTE period, he or she will follow the SoE in Table 11.

[2] Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT Visit are not required if the subject 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 in such cases.

[3] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[4] Only for subjects entering the long-term extension period.

[5] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[6] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.

[7] Arterial spin labeling MRI and task-free functional MRI will be performed only at a subset of sites.

[8] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.

[redacted]

Table 11: Subjects Who Discontinue Study Treatment but Remain in the Study – Long-Term Extension Period

Study Week	LTE Period[1]															
	92	104	106	128	134	152	162	176	182	208	232	260	284	312	338 (EOT)[2]	UV for ARIA[3]
Study Day	645 ± 5	729 ± 5	743 ± 5	897 ± 5	939 ± 5	1065 ± 5	1135 ± 5	1233 ± 5	1275 ± 5	1457 ± 5	1625 ± 5	1821 ± 5	1989 ± 5	2185 ± 5	2367 ± 5	
Body Weight	X	X		X		X		X	X	X	X	X	X	X	X	
Physical Examination	X	X		X		X		X	X	X	X	X	X	X	X	
Neurological Examination	X	X		X		X		X	X	X	X	X	X	X	X	
12-lead Paper ECG		X		X		X		X								
Vital Signs	X	X		X		X		X	X	X	X	X	X	X	X	
Hematology, Blood Chemistry and Urinalysis		X		X		X		X			X		X			
[redacted]																
PBMC Collection																X[5]
Aducanumab Concentration																X[6]
[redacted]																
Brain MRI[7]					X				X		X		X		X[7]	X
Amyloid PET[8]									X			X			X	
[redacted]																
CDR			X		X		X		X		X		X		X	
MMSE			X		X		X		X		X		X		X	
ADAS-Cog 13			X		X		X		X		X		X		X	
ADCS-ADL-MCI			X		X		X		X		X		X		X	
NPI-10			X		X		X		X						X[4]	

Study Week	LTE Period[1]															
	92	104	106	128	134	152	162	176	182	208	232	260	284	312	338 (EOT)[2]	UV for ARIA[3]
Study Day	645 ± 5	729 ± 5	743 ± 5	897 ± 5	939 ± 5	1065 ± 5	1135 ± 5	1233 ± 5	1275 ± 5	1457 ± 5	1625 ± 5	1821 ± 5	1989 ± 5	2185 ± 5	2367 ± 5	
EQ-5D-(IR-S)			X		X		X		X		X		X		X	
[redacted]																
MOCA																X
C-SSRS			X		X		X		X		X		X		X	
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study															
SAE Reporting	Monitor and record continuously throughout the study															

AD = Alzheimer's disease; AE = adverse event; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version).ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality hemorrhage or superficial siderosis; [redacted]; CDR = Clinical Dementia Rating scale; [redacted]; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOT = end of treatment; [redacted]; EQ-5D (IR-S) = EQ-5D, informant reported on subject; FU = follow-up; LTE = long-term extension; MMSE = Mini Mental State Examination; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NPI 10 = Neuropsychiatric Inventory-10; PBMC = peripheral blood mononuclear cells; PET = positron emission tomography; PK = pharmacokinetic; [redacted]; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects who discontinue study treatment during the LTE period are to remain in the study, attend a FU Visit as listed in Table 9, and then will continue protocol-required tests and assessments at a subset of the clinic visits.

[2] Subjects who withdraw from study prematurely are to return to the site for an EOT Visit; for such subjects, efficacy assessments specified at the EOT Visit are not required if the subject 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 in such cases.

[3] For the frequency of required brain MRI and MOCA assessments, and PK, biomarker, and PBMC sample collection for subjects who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1 to Section 7.2.1.5. This includes PK, biomarker, and PBMC sample collection at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and MOCA assessments following resolution of ARIA and resumption of dosing, see Section 7.2.1.6. For management of recurrent ARIA, see Section 7.2.1.7.

[4] This assessment is only to be performed if the EOT Visit is at or before Week 182.

[5] Sample may be collected within ±2 days of the MRI visit at the same time as sample collection for aducanumab concentration.

[6] One sample will be collected within ±2 days of the MRI visit. Exact collection date and time will be captured for all PK blood samples on a specified case report form.
[7] Arterial-spin labeling MRI and task-free functional MRI will be performed only at a subset of sites, and will not be performed at any visit after Week 182.
[8] Only for subjects who participate in the amyloid PET substudy. Amyloid PET may be scheduled within a window of ±7 days.
[redacted]

4.3. Additional Information

4.3.1. Site Personnel

A minimum of 3 separate heath care professionals (HCPs) are required:

1. A treating HCP (the Principal Investigator [PI] or Sub-investigator may serve as a treating HCP) who is responsible for the following:
   - Administration of Montreal Cognitive Assessment (MOCA) at Day 1, Week 80, and during management of amyloid-related imaging abnormalities (ARIA) cases.
   - Management of routine neurological care of the subject.
   - Assessment (including assignment of causality) and treatment of adverse events (AEs).
   - Review of selected hematology and blood chemistry results from the central laboratory to assess if the subject's study treatment should be temporarily withheld or permanently discontinued according to the criteria detailed in Section 10.1.
2. An independent rating HCP (designated by the PI of the site) who is responsible for administering the Clinical Dementia Rating (CDR)
3. A second independent rating HCP (designated by the PI of the site) who will administer the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI], and the Mini-Mental State Examination (MMSE)

The 2 independent rating HCPs must not be involved with any other aspect of subject 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 2 independent rating HCPs must not share any information about subjects. PIs cannot serve as rating HCPs. The treating HCPs must not discuss AEs (e.g., ARIA) with the independent rating HCPs.

To ensure consistency across sites, rating HCPs must complete the standardized study-specific qualification process on clinical efficacy assessment scoring prior to administration of the specific assessment at their site. All sites must attempt to maintain the same rating HCP throughout the study for specific assessments in an attempt to remain consistent. Each subject should have the same rating HCP perform the subject's specific rating assessment throughout the study. A qualified approved back-up rater should only conduct assessments in place of the primary rater due to extenuating circumstances resulting in unavailability (e.g., due to illness, vacation, or travel). If a rating HCP has to be replaced, the new rating HCP 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 subject. As with other laboratory and clinical information, these data should NOT be reviewed by the rating HCPs.

The roles of independent raters and treating HCP are NOT interchangeable at the subject level. In addition, the 2 independent raters are not interchangeable at the subject level. If a rater has administered the CDR to a subject, they may not administer the other neurocognitive assessments to that subject 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.

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2013, there were 44.4 million people living with dementia worldwide and that this figure will increase to 135.5 million by 2050 [Alzheimer's Disease International 2014].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack 2013].

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum rather than having categorical stages. Evidence suggests the pathophysiological changes begin years before clinical onset and as the disease progresses, cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Revised criteria for the clinical diagnosis of AD were published by the National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer's Association (AA) [Albert 2011; McKhann 2011; Sperling 2011] and the International Working Group (IWG) [Dubois 2010; Dubois 2014], and a group that included members from both NIA-AA and IWG published recommendations to harmonize the criteria [Morris 2014]. These criteria base the diagnosis of AD on both clinical and biological elements, recognizing the existence of a nonclinical stage of the disease by accepting AD diagnoses prior to signs of dementia using AD biomarkers.

The scientific community has shifted its focus to target patients in the earlier course of the disease continuum with the belief that those patients are more likely to benefit from anti-amyloid therapy.

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). Aducanumab is a human monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have reported on results that demonstrated in the brain of an animal model of AD that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress [Rozkalne

2009; Spires-Jones 2009]. Similarly, patients with AD who generated anti-Aβ antibodies after active immunization with aggregated Aβ(42) showed slower rates of decline of cognitive function and activities of daily living [Hock 2003].

5.1. Profile of Previous Experience With Aducanumab

5.1.1. Nonclinical Experience

Aducanumab is a unique human, anti-Aβ immunoglobulin (Ig) G1 monoclonal antibody identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ.

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine IgG2a chimeric version of the antibody (ch12F6A) with similar properties to aducanumab (BIIB037) significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD, through a microglia-mediated phagocytic mechanism. These data suggest aducanumab could provide benefit by reducing plaque burden.

The toxicokinetic profile of aducanumab was evaluated in Tg2576 mice in 13-week and 6-month studies and in cynomolgus monkeys in a 4-week study. Of the 2 species, the Tg2576 mouse is considered the primary pharmacologically relevant species given that these mice accumulate amyloid plaques in the cerebral parenchyma and vasculature. In addition to the standard histopathological evaluation in mice, Perls' staining of hemosiderin (a breakdown product of hemoglobin) was performed to quantify microhemorrhage. Microhemorrhage has been observed both as a background finding in transgenic mouse models of AD [Winkler 2001], including Tg2576 mice [Kumar-Singh 2005], and as a drug-related finding in transgenic mice treated with some anti-Aβ antibodies [Pfeifer 2002; Racke 2005; Wilcock and Colton 2009].

Findings consistent with amyloid plaques and vascular amyloid were identified in the brain sections of animals in all groups, including the control group, as expected with this model. In both studies, repeated administration of ch12F6A or aducanumab was well tolerated with no treatment-related deaths observed during the dosing period. In the 13-week toxicology study, meningeal/cerebral vascular inflammation and/or vascular thickening were observed in mice dosed with ch12F6A $\geq$ 70 mg/kg compared with the control group. In the 6-month study, although slight differences were observed between ch12F6A-treated groups and the control group, animals treated with aducanumab were comparable to the control animals. The evaluation of microhemorrhage, characterized by quantification of hemosiderin in Perls stained brain sections of each main study and recovery animal, demonstrated no significant increase in scores with ch12F6A or aducanumab treatment in either study. The incidence and severity of hemorrhage or cerebral vascular inflammation were comparable in the 13-week and 6-month mouse studies.

See the Investigator's Brochure (IB) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

Aducanumab has been evaluated in one completed single ascending dose study (221AD101) and one ongoing multiple ascending dose study (221AD103):

- Study 221AD101 was a Phase 1, randomized, double-blind, placebo-controlled, study of aducanumab in subjects with mild or moderate AD.

  The primary objective was to evaluate the safety and tolerability of a range of aducanumab doses (0.3 to 60 mg/kg) when administered as single intravenous (IV) infusions. The secondary objectives were to assess the pharmacokinetic (PK) and immunogenicity of aducanumab after single-dose administration.

  A single dose of aducanumab up to 30 mg/kg was demonstrated to be well tolerated. Dose-limiting ARIA (2 subjects with ARIA-E [edema] and 1 subject with ARIA-E and ARIA-H [microhemorrhage]) was observed in the 60 mg/kg dose group resulting in termination of further dosing in that cohort; no cases of ARIA were observed at single doses below 60 mg/kg. The PK profile was dose linear.

- Study 221AD103 is an ongoing randomized, double-blind, placebo-controlled multiple dose study of aducanumab in subjects with prodromal or mild AD who are amyloid positive. The study comprises a placebo-controlled period with subjects receiving monthly doses of aducanumab (fixed doses of 1, 3, 6, or 10 mg/kg, or titration up to 10 mg/kg) or placebo for a year followed by a dose-blind long-term extension (LTE) period with subjects receiving monthly doses of aducanumab. Note: The fixed-dose cohorts enrolled both apolipoprotein E4 (ApoE ε4) carriers and non-carriers while the titration cohort is comprised of ApoE ε4 carriers only.

  The primary objective of Study 221AD103 is to evaluate the safety and tolerability of multiple doses of aducanumab administered monthly as single IV infusions. The secondary objectives are to assess the effect of aducanumab on cerebral amyloid plaque content as measured by ^{18}F-florbetapir positron emission tomography (PET), and to evaluate the PK and immunogenicity of aducanumab after multiple-dose administration. Exploratory objectives include assessment of the effect of aducanumab on the clinical progression of AD as measured by CDR-sum of boxes (SB) and MMSE.

  In the most recent interim analysis (25 May 2017), the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. ARIA-E was radiographically monitored by magnetic resonance imaging (MRI) and typically observed early in treatment (between 2 to 5 doses). In most cases, ARIA-E resolved 4 to 12 weeks after onset and ARIA-H was typically stable 2 to 4 weeks after onset. In the placebo-controlled period, the incidence of ARIA-E appeared to be lower in the group receiving titration to 10 mg/kg (comprising ApoE ε4 carriers only; 8/23 [35%]) than in carriers in the 6 mg/kg and 10 mg/kg fixed-dose groups (9/21 [43%] and 11/20 [55%], respectively). Of note, among the subjects receiving titration to 10 mg/kg who had ARIA-E, the abnormalities were observed at the 3 and 6 mg/kg dose levels, before they reached

10 mg/kg. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these, 12 continued treatment and received at least 17 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H. Furthermore, ARIA-E events when they occurred (in the titration group) have been either asymptomatic or associated with mild symptoms that resolved, and most subjects who had ARIA-E continued treatment (6/8; 75%) compared with only 36% (4/11) of carriers in the fixed-dose 10 mg/kg arm (refer to the IB for details on events of ARIA). In the LTE period, the incidence of ARIA-E in ApoE ε4 carriers who were titrated up to 6 mg/kg (2 doses of 3 mg/kg, then 6 mg/kg) was 23% (3/13), with an overall rate of 16% (3/19) as no ApoE ε4 non-carriers (0/6) experienced ARIA-E.

Protocol-specified interim analyses of the ongoing multiple-ascending dose Study 221AD103 have demonstrated engagement of aducanumab with amyloid plaques, a pharmacodynamic (PD) effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a slowing of clinical decline in aducanumab-treated subjects. The dose- and time-dependent reduction of brain Aβ burden observed with aducanumab treatment was statistically significant at doses of 3, 6, and 10 mg/kg after 6 and 12 months of dosing, as well as with 1 mg/kg and titration from 1 to 10 mg/kg after 12 months of dosing. Further dose-dependent reductions in brain Aβ were observed for up to 36 months. Subjects who switched from placebo to aducanumab in the LTE period saw a reduction in brain Aβ similar to that seen by subjects who received aducanumab in the placebo-controlled period. The results demonstrate target engagement (amyloid plaques) and a PD effect (dose-dependent amyloid reduction).

In addition, results from the interim analyses showed an effect at 1 year on the exploratory endpoints CDR-SB and MMSE (at fixed doses of 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg compared with placebo), suggesting a reduction in the progression of clinical impairment for aducanumab-treated versus placebo-treated subjects. Furthermore, generally consistent treatment differences were seen for the fixed-dose cohorts, and in the titration group, effects on the CDR-SB and MMSE after 1 year were generally consistent with the fixed-dose results. Compared with placebo, adjusted mean changes from baseline to Week 54 in CDR-SB scores favored all aducanumab dose regimens tested, with treatment differences of 0.5 points or greater favoring aducanumab at doses of 3, 6, and 10 mg/kg and titration to 10 mg/kg, and statistical significance seen in the 10 mg/kg and titration groups. On the MMSE, adjusted mean decreases from baseline to Week 52 suggested a clinically meaningful benefit in the 3 and 10 mg/kg groups and the titration group and were significantly lower than placebo in the 10 mg/kg group. Furthermore, CDR-SB and MMSE data suggested a clinical benefit in those continuing on aducanumab up to 3 years compared with those who switched from placebo to aducanumab in the LTE period. Refer to the IB for details on interim analyses results.

5.2. Study Rationale

The purpose of this study is to assess the efficacy and safety of aducanumab compared with placebo in subjects with early AD including subjects with mild cognitive impairment (MCI) due to AD and a subset of mild AD. Aducanumab is a human IgG1 monoclonal antibody that recognizes aggregated forms of Aβ, including soluble Aβ oligomers and deposited fibrillar Aβ. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008] and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. For this reason, treatment with aducanumab is expected to slow progression of AD, while preserving global function longer, when compared with untreated subjects.

Interim analyses of the ongoing multiple dose study (Study 221AD103) have demonstrated target engagement, a PD effect on amyloid reduction, and an effect on CDR-SB and MMSE suggestive of a reduction in the progression of clinical impairment for aducanumab-treated subjects. These results, along with the observed safety and tolerability profile, warrant the further Phase 3 investigation of aducanumab in a patient population spanning the early stages of the AD continuum.

5.3. Rationale for Dose and Schedule Selection

The dosing regimen selected for this study was based on the PK and PD relationship for removal of brain amyloid and effect on CDR-SB and MMSE observed in Study 221AD103 interim analyses and on safety, tolerability, and PK data from studies 221AD101 (complete) and 221AD103 (ongoing).

The dose- and time-dependent reduction of brain amyloid burden observed with aducanumab treatment in Study 221AD103 was statistically significant at doses of 3, 6, and 10 mg/kg after 6 months of dosing, and at 3, 6, and 10 mg/kg as well as with titration to 10 mg/kg after 12 months of dosing. On the exploratory endpoints of CDR-SB and MMSE changes from baseline, a dose-dependent slowing of clinical decline was observed for aducanumab versus placebo after 1 year of treatment. Compared with placebo, adjusted mean changes from baseline to Week 54 for CDR-SB favored all the aducanumab dose groups tested, with treatment differences of 0.5 points or greater at fixed doses of aducanumab 3, 6, and 10 mg/kg and also with titration to 10 mg/kg. On the MMSE, adjusted mean decreases from baseline to Week 52 were smaller in all dose groups than in the placebo group. Of note, on the CDR-SB, the point estimate for the titration group (comprising ApoE ε4 carriers only) was generally similar to that for the 10 mg/kg group and significantly lower than placebo in both those groups; on the MMSE, the point estimate for the titration group is generally similar to that in the 10 mg/kg group (which showed significantly less decline than placebo) and the 3 mg/kg group.

In the most recent interim analysis (25 May 2017), the incidence of ARIA has been observed to be both dose- and ApoE ε4 carriage-dependent, especially at the highest doses when administered as a fixed dose. However, the incidence of ARIA-E, as well as discontinuations from treatment due to ARIA-E, in subjects receiving aducanumab titrated to 10 mg/kg (ApoE ε4 carriers only) appear to be reduced (8/23 [35%]) compared with fixed doses of aducanumab at

6 mg/kg (9/21 [43%]) and 10 mg/kg (11/20 [55%]). Furthermore, among those subjects randomized to receive aducanumab titrated to 10 mg/kg, ARIA-E occurred only at the 3 mg/kg and 6 mg/kg dose levels. Also, 13 (of 23, 57%) subjects in the titration arm have been titrated to 10 mg/kg, and of these, 12 continued treatment and received at least 17 doses of 10 mg/kg; none of these subjects experienced ARIA-E or ARIA-H.

In an effort to maximize the dose-dependent amyloid reduction and effect on CDR-SB and MMSE that have been observed with doses of 3 mg/kg and higher while maintaining ARIA incidence, severity, and related discontinuation rate within acceptable levels, a titration regimen will be explored in this study. It has been suggested that the ARIA observed following treatment with amyloid targeting agents may be due, in part, to the initial large removal of amyloid and subsequent saturation of perivascular brain amyloid clearance mechanisms [Weller 2008]. Titration to the target dose is expected to result in slower initial amyloid removal, yet trigger alternative mechanisms of amyloid clearance including monoclonal antibody-dependent Fc-mediated microglial clearance [Ostrowitzki 2012], which would prevent saturation of amyloid clearance and subsequent ARIA during titration and once the target dose is reached. Since aducanumab-induced ARIA has been demonstrated to occur early during treatment, with most cases occurring within the first 5 doses, titration of aducanumab for up to 6 doses prior to reaching the target dose may result in reduction of ARIA incidence and severity.

Given the tolerability and apparent efficacy of aducanumab shown, the doses to be tested using a titration regimen are 3 and 10 mg/kg for ApoE ε4 carriers, and 6 and 10 mg/kg for ApoE ε4 non-carriers. Titration will start at 1 mg/kg and will escalate to 3, 6, and 10 mg/kg as detailed below.

5.3.1. Dosing Scheme

5.3.1.1. Placebo-Controlled Period

Doses will be administered approximately 4 weeks apart, over approximately 76 weeks (a total of 20 doses). Based upon their ApoE ε4 carrier status, subjects will be assigned to 1 of 3 treatment groups (approximately 535 subjects each [see Section 16.8]) in a 1:1:1 ratio (aducanumab low dose:aducanumab high dose:placebo) as follows (Table 12 and Figure 1):

ApoE ε4 Carrier

- Low dose (3 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg thereafter
- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter
- Placebo

  Saline infusion

ApoE ε4 Non-Carrier

- Low dose (6 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter

- High dose (10 mg/kg)

  1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter

- Placebo

  Saline infusion

Table 12: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status

Dose (Month)		1	2	3	4	5	6	7 to 20
Treatment Group		Dose (mg/kg)						
ApoE ε4 (+)	Low Dose	1	1	3	3	3	3	3
	High Dose	1	1	3	3	6	6	10[1]
	Placebo	saline						
ApoE ε4 (-)	Low Dose	1	1	3	3	3	3	6
	High Dose	1	1	3	3	6	6	10
	Placebo	saline						

[1] 10 mg/kg is the target dose for all ApoE ε4 carriers assigned to the aducanumab high-dose group. Subjects enrolled under protocol versions prior to Version 4 and assigned to the previous high-dose of 6 mg/kg will be titrated to 10 mg/kg upon receipt of at least 2 doses at 6 mg/kg.

5.3.2. Dosing Scheme Modification

An independent data monitoring committee (IDMC) will review unblinded safety data, including serious AEs (SAEs) and incident cases of ARIA, from all ongoing aducanumab studies (e.g., Studies 221AD103, 221AD104, 221AD301, and 221AD302) as described in the IDMC charter.

The dosing scheme can be modified in the following circumstances:

- Safety and tolerability of the high dose

  If the high dose (10 mg/kg) is deemed not acceptable, enrollment for the high-dose group(s) will be terminated and subjects will not be replaced. Subjects who have already been randomized to the discontinued dose will be down-dosed to the next available dose according to their ApoE ε4 carrier status. Definition of low and high-dose groups will be revised as described in Section 16.

5.3.3. Long-Term Extension Period

Subjects who received aducanumab in the placebo-controlled period and who enter the LTE period will maintain the dosing scheme outlined in the protocol at the time of transition from the placebo-controlled period to the LTE period (e.g., subjects who are on stable dosing in the placebo-controlled period will continue on the same dose, subjects who are on a titration regimen during the transition will continue to titrate into the LTE period and subjects who complete the placebo-controlled period under protocol versions prior to Version 4 and are assigned to the high dose aducanumab treatment group may up titrate to 10 mg/kg in the LTE). Subjects randomized to placebo at the start of the placebo-controlled period (Study Day 1) will also be randomized to receive dose-blinded aducanumab (low dose:high dose, 1:1 ratio) for the LTE period. Randomization will be stratified by subject ApoE ε4 carrier status. Subjects will be dosed using the same regimen described for the placebo-controlled period (see Table 12 and Figure 1).

Any modifications to the dosing scheme (i.e., termination of high-dose group, as described in Section 5.3.2) will also be implemented in the LTE period.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the efficacy 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 subjects with early AD.

The primary endpoint that relates to this objective is change from baseline in CDR-SB score at Week 78.

6.2. Secondary Objectives and Endpoints

A secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the MMSE.

- The endpoint that relates to this objective is change from baseline in MMSE score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADAS-Cog 13.

- The endpoint that relates to this objective is change from baseline in ADAS-Cog 13 score at Week 78.

Another secondary objective is to assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by ADCS-ADL-MCI.

- The endpoint that relates to this objective is change from baseline in ADCS-ADL-MCI score at Week 78.

6.3. Tertiary Objectives and Endpoints

6.3.1. Tertiary Objectives

Safety and Tolerability

- To assess the safety and tolerability of monthly doses of aducanumab.
- To assess the immunogenicity of aducanumab.

Biomarker/Efficacy/Health Outcomes

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid PET imaging (in a subset of approximately 400 subjects).
- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).

- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20) [Lenderking 2014].
- To assess the correlation between primary endpoint and cerebral amyloid plaque content as measured by PET imaging.

Pharmacokinetics

- To collect and characterize the PK parameters of aducanumab in serum.

6.3.2. Tertiary Endpoints

Safety and Tolerability

- Incidence of all AEs and SAEs.
- Brain MRI findings including incidence of ARIA-E and ARIA-H.
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers/Efficacy/Health Outcomes

- Change from baseline in amyloid PET signal at Week 26 (in a subset of sites and subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of sites and subjects).
- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- Change from baseline in mPDQ-20 at Week 78.
- Correlation between the primary endpoint and cerebral amyloid plaque content as measured by PET imaging over time.

Pharmacokinetics

- Serum concentrations and PK parameters of aducanumab.

6.4. Additional Exploratory Objectives and Endpoints

6.4.1. Additional Exploratory Objectives

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

6.4.2. Additional Exploratory Endpoints

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

- [redacted]

6.5. Long-Term Extension Objectives and Endpoints

6.5.1. Tertiary LTE Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD.
- To evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health outcomes assessments.

6.5.2. Tertiary LTE Endpoints

- The incidence of AEs and/SAEs; brain MRI findings (including the incidence of ARIA-E and ARIA-H); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - CDR-SB score.
  - MMSE score.
  - ADAS-Cog 13 score.
  - ADCS-ADL-MCI score.
  - Amyloid PET signal (in a subset of sites and subjects).
  - NPI-10 total score.
  - Informant-rated EQ-5D index score.

6.5.3. Additional Exploratory LTE Objective

- [redacted]

6.5.4. Additional Exploratory LTE Endpoints

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

7. STUDY DESIGN

7.1. Study Overview

Study 221AD301 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study in subjects with early AD, including MCI due to AD and a subset of mild AD, followed by an optional dose-blinded LTE period of up to 5 years. Approximately 1605 subjects (see Section 16.8) will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Subjects will be randomized to receive aducanumab low dose:aducanumab high dose:placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). The ratio of ApoE ε4 carriers to non-carriers in the study population will generally reflect the distribution in the broader AD population. Enrollment will also be monitored, via interactive response technology (IRT), such that subjects with mild AD represent a small percentage of the total enrolled in the trial.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (up to a total of 65 doses over 5 years). The EOT Visit will occur at Week 338, or when the last subject has had his or her Week 182 Visit, whichever occurs first.

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of 18 weeks after the final dose.

The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will vary and be up to approximately 362 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 256-week aducanumab dose-blind treatment period, and a safety FU period of 18 weeks after the final dose. The FU period of 18 weeks is based on an estimated mean elimination half-life in humans of 16 to 24 days (mean approximately 20 days, based on results from the single ascending dose study [Study 221AD101]) and anticipated brain concentrations of aducanumab of less than one-third the EC_{50} (inhibitory concentration at 50% of the maximum observed biologic effect) for binding fibrillar amyloid at 8 weeks after the last dose.

During the placebo-controlled period, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 10 mg/kg whereas ApoE ε4 non-carriers will receive

placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 12 and Figure 1. Note: As of Protocol Version 4, 10 mg/kg is the target dose for all ApoE ε4 carriers in the high-dose group. ApoE ε4 carriers who were randomly assigned to the high-dose group when the target dose was 6 mg/kg (under protocol versions prior to Version 4) must have received 2 or more doses at 6 mg/kg prior to being titrated up to 10 mg/kg. Subjects who received placebo during the placebo-controlled period will be assigned to treatment based upon their ApoE ε4 carrier status in a 1:1 ratio (aducanumab low dose:aducanumab high dose) for the LTE period, and aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period.

See Section 5.3.2 for details of dosing scheme modification.

Individual dose adjustments may also be implemented in subjects who develop ARIA. See Section 7.2.1.

Investigators, study site staff (except for the designated unblinded pharmacist/technician), and study subjects will be blinded to the subjects' randomized treatment assignment for the placebo-controlled period. During the LTE period, Investigators and subjects will remain blinded to the treatment assignment in the placebo-controlled period and the aducanumab dose for the LTE period.

7.2. Study Specifics

7.2.1. Dose Suspension, Modification, or Termination for ARIA Events

Discontinuation of Dosing for a Given Subject

The central MRI reading center will report incident cases of ARIA-E and ARIA-H to both the Sponsor and the PI within a specified time after observing the finding on MRI per the imaging manual procedures. All cases of ARIA will be reviewed by the Sponsor and the PI; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the MRI information provided by the central reader. IDMC notification rules will be outlined in the IDMC charter. Guidelines on the management and disposition of ARIA-E and ARIA-H 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. Dosing may also be terminated at the discretion of the Sponsor for medical reasons. See Section 10.1 for the full list of criteria for discontinuing study treatment.

7.2.1.1. ARIA-E Cases

Table 13: Disposition of ARIA-E Cases

Clinical Symptom Severity	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 subject may resume dosing at the same dose.	
Mild	Suspend dosing. Once ARIA-E and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[1]			
Serious, except for "other medically important event"[2]	Discontinue Dosing		

[1] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above and as described in Section 15.1.2.

[2] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

- Subjects who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study may continue in the study at their current dose. Subjects should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. The Sponsor may require that the subjects discontinue dosing or continue dosing at a lower dose level based on review of safety and MRI data.
- Subjects who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. If the ARIA-E has resolved and the subjects remain asymptomatic (in the Investigator's opinion), the subjects may resume treatment at the same dose.

- Subjects who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by mild, moderate, severe, or serious ("other medically important event" only) clinical symptoms** at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. If the ARIA-E has resolved and the clinical symptoms have resolved (in the Investigator's opinion), the subject may resume treatment at the same dose.
- Subjects who develop mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except "other medically important event") clinical symptoms at any time during the study will permanently discontinue treatment but remain in study. Subjects 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 10, and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-E has resolved per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.2. ARIA-H (Microhemorrhage)

In this study, new incident microhemorrhages are defined as new incident microhemorrhages that occur on treatment and do not include microhemorrhages at baseline.

Table 14: Disposition of ARIA-H (Microhemorrhage) Cases

Clinical Symptom Severity	New Incident Microhemorrhages[1] (Central Read)		
	Mild	Moderate	Severe
	≥ 1 and ≤ 4	≥ 5 and ≤ 9	≥ 10
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing. Once ARIA-H is stable, the subject may resume dosing at the same dose.	Discontinue dosing
Mild	Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.		
Moderate			
Severe			
Serious "other medically important event" only[2]			
Serious, except for "other medically important event"[3]	Discontinue dosing		

[1] New incident microhemorrhages = new incident microhemorrhages on treatment; does not include microhemorrhages at baseline.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Microhemorrhage)

- Subjects who develop a **≥ 1 and ≤ 4 new incident microhemorrhage(s) [mild]** at any time during the study may continue treatment at the current dose.
- Subjects who develop **≥ 5 and ≤ 9 new incident microhemorrhages [moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhage is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. A microhemorrhage is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. Once the microhemorrhage is deemed stable, subjects may resume treatment at the same dose.

- Subjects who develop ≥ **10 new incident microhemorrhages [severe]** during the study will permanently discontinue treatment but remain in study. Subjects 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 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhages are deemed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

Symptomatic ARIA-H (Microhemorrhage)

- Subjects who develop ≤ **9 new incident microhemorrhages (mild or moderate) and mild, moderate, severe, or serious ("other medically important event" only [Section 15.1.2]) clinical symptoms** will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H (microhemorrhage(s) is confirmed stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Microhemorrhages are considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. Once ARIA-H (microhemorrhage) is deemed stable and the clinical symptoms have resolved (in the Investigator's opinion), the subject may resume treatment at the same dose.
- Subjects who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with microhemorrhage(s)** will permanently discontinue treatment but remain in study. Subjects 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 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhage(s) is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.
- Subjects who develop ≥ **10 new incident microhemorrhages (severe)**, regardless of symptom severity, during the study will permanently discontinue treatment but remain in study. Subjects 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 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the microhemorrhages are deemed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.3. ARIA-H (Superficial Siderosis)

Table 15: Disposition of ARIA-H (Superficial Siderosis) Cases

<table>
<tr><th rowspan="2">Clinical Symptom Severity</th><th colspan="3">New Incident Areas of Superficial Siderosis[1] (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><th></th><th>1</th><th>2</th><th>>2</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing. Once ARIA-H is stable the subject may resume dosing at the same dose.</td><td rowspan="5">Discontinue dosing</td></tr>
<tr><td>Mild</td><td colspan="2" rowspan="4">Suspend dosing. Once ARIA-H stabilizes and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious "other medically important event" only[2]</td></tr>
<tr><td>Serious, except for "other medically important event"[3]</td><td colspan="2">Discontinue dosing</td></tr>
</table>

[1] New incident superficial siderosis = new incident superficial siderosis on treatment.

[2] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above as described in Section 15.1.2.

[3] SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator), require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect as described in Section 15.1.2.

Asymptomatic ARIA-H (Superficial Siderosis)

- Subjects who develop a **single incident focal area of hemosiderosis (also referred to as superficial siderosis) [mild]** may continue treatment at the current dose, but must have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the superficial siderosis is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 4 weeks (±5 days) later.
- Subjects who develop **2 focal areas of hemosiderosis (superficial siderosis) [moderate]** occurring at any time during the study will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in

addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Once the superficial siderosis is deemed stable, the subjects may resume treatment at the same dose.

- Subjects who develop >**2 focal areas of hemosiderosis (superficial siderosis) [severe]** occurring at any time during the study must permanently discontinue treatment but remain in study. Subjects 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 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

Symptomatic ARIA-H (superficial siderosis)

- Subjects who develop ≤ **2 new focal areas of superficial siderosis (mild or moderate)** and **mild, moderate, severe, or serious ("other medically important event" only)** clinical symptoms will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the ARIA-H superficial siderosis is confirmed stable per the centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Superficial siderosis is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. Once the ARIA-H (superficial siderosis) is deemed stable and the clinical symptoms have resolved (in the Investigator's opinion), the subjects may resume treatment at the same dose.
- Subjects who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with ARIA-H (superficial siderosis)** will permanently discontinue treatment but remain in study. Subjects 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 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA every 4 weeks (±5 days) until the superficial siderosis is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.
- Subjects who develop >**2 new focal areas of superficial siderosis (severe)** regardless of clinical symptom severity will permanently discontinue treatment but remain in study. Subjects 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 10 and Table 11), and, in addition, have an unscheduled visit for an MRI and MOCA

every 4 weeks (±5 days) until the superficial siderosis is confirmed stable per centrally read MRI. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA.

See Section 7.2.1.6 for details on resumption of dosing when suspension occurs during the titration period and Section 7.2.1.7 for guidelines on resuming dosing after a recurrence of ARIA.

7.2.1.4. ARIA-H (Macrohemorrhage)

Subjects who develop any new incident macrohemorrhage (defined as >1 cm in diameter on T2* sequence), regardless of symptom severity during the study, will permanently discontinue treatment, but remain in study. Subjects 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 10 and Table 11) and, in addition, have an unscheduled visit for MRI and MOCA every 4 weeks (±5 days) until the macrohemorrhage is confirmed stable per centrally read MRI. A macrohemorrhage is considered stable if there is no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs, including the initial detection MRI and the MRI performed 4 weeks (±5 days) later. In addition, biomarker, PK, and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA-H (macrohemorrhage).

7.2.1.5. Coincident ARIA-H and ARIA-E Cases

Subjects who develop ARIA-H coincident with ARIA-E at any time during the study will follow the most restrictive guidelines. Prior to resuming treatment, where applicable, ARIA-E must resolve, ARIA-H must be deemed stable, and the subject must be asymptomatic. For example, if a subject experiences asymptomatic ARIA-H (1-4 microhemorrhages) coincident with ARIA-E assessed as moderate on MRI and accompanied by mild clinical symptoms, the dose should be suspended per the ARIA-E guidelines summarized in Table 13. In addition, unscheduled visits should occur as described in Section 7.2.1.1 through Section 7.2.1.4.

7.2.1.6. Resumption of Study Treatment After Suspension due to ARIA

7.2.1.6.1. MRI Monitoring

When treatment resumes after a dose suspension due to ARIA, an MRI and MOCA will be performed 2 weeks (±5 days) after the second administration of the restarted dose. In addition, if treatment was suspended during the dose titration prior to the subject reaching the maximum assigned dose, an MRI and MOCA will be performed 2 weeks (±5 days) after every second dose until completion of the titration period, with subjects assumed to be titrating to 10 mg/kg (titration period of 6 doses and a final MRI after the second dose at 10 mg/kg) to maintain study blinding, not counting unscheduled MRI visits for monitoring of ARIA. MRIs will otherwise be performed as indicated in the Schedule of Events (Section 4.2).

7.2.1.6.2. Dosing Upon Resumption of Study Treatment

Subjects who suspend treatment due to ARIA may resume treatment at the same dose if they meet the criteria as described in Sections 7.2.1.1 to 7.2.1.5. Subjects who suspend and then resume dosing after having already reached their assigned top dose level are to continue dosing at that dose level. However, if dosing is suspended prior to a subject reaching their assigned top dose level, the subject (1) must receive at least 2 doses at the restart dose before titrating up to the next dose level and (2) must complete at least the required number of doses at that dose level per their assigned treatment group, as outlined in the right column of Table 16.

Table 16: Resumption of Study Treatment Following Dose Suspension Due to ARIA During Titration

Assigned Treatment Group (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses at Current Dose Level Needed Before Going to the Next Higher Dose
ApoE ε4 (+)			
Low Dose (3 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2
	6 mg/kg	1	2
	6 mg/kg	2	2
ApoE ε4 (-)			
Low Dose (6 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	3
	3 mg/kg	2	2
	3 mg/kg	3	2
	3 mg/kg	4	2
High Dose (10 mg/kg)	1 mg/kg	1	2
	1 mg/kg	2	2
	3 mg/kg	1	2
	3 mg/kg	2	2

Assigned Treatment Group (Maximum Dose)	Dose Level at Which ARIA Occurred	Number of Doses Prior to ARIA	Number of Doses at Current Dose Level Needed Before Going to the Next Higher Dose
	6 mg/kg	1	2
	6 mg/kg	2	2

7.2.1.7. Management After Recurrent ARIA (Dosing and MRI)

If the subject has more than one occurrence of ARIA (i.e., a second or any additional occurrences of ARIA-E or of ARIA-H, or ARIA-E and ARIA-H) that requires dose suspension (per criteria in Section 7.2.1.1, Section 7.2.1.2, and Section 7.2.1.3), after the ARIA resolves or stabilizes, the subject is to resume dosing at the same dose as that described in Section 7.2.1.6.2. Once dosing has resumed, the guidelines outlined in Table 16 apply. If a subject resumes treatment after ARIA, an MRI and MOCA will be performed 2 weeks (±5 days) after the second administration of the restarted dose, and 2 weeks (±5 days) after every second dose until the completion of titration, with all subjects assumed to be titrating to 10 mg/kg (6 doses) to maintain study blinding. MRIs will otherwise be performed as indicated in the Schedule of Events (Section 4.2).

Subjects who develop ARIA during the placebo-controlled period but continue or resume treatment at an active dose are eligible to enter the LTE period and will maintain the dosing scheme from the placebo-controlled period into the LTE, which may include a continuation on the same dose or completion of titration into the LTE period.

For subjects who discontinued treatment due to a third ARIA event that required dose suspension under a previous version of the protocol and remained on the study: these subjects will not resume dosing.

For subjects who resumed dosing at the next lower dose after recurrent ARIA under a previous version of the protocol and have not titrated to their target dose: these subjects will continue dosing (i.e., receive 2 doses at that dose level before titrating up to the next higher dose).

For subjects who dose-reduced to placebo after recurrent ARIA under a previous version of the protocol and remained in the study: these subjects can resume dosing during the LTE period and will be titrated up to his or her randomly assigned dose using the same regimen as that described for the placebo-controlled period (see Table 12 and Figure 1).

For subjects who dose-reduced to placebo after recurrent ARIA and then resumed dosing at aducanumab 1 mg/kg during the LTE period under a previous version of the protocol: these subjects can be titrated up to his or her randomly assigned dose using the same regimen as that described for the placebo-controlled period (see Table 12 and Figure 1).

For subjects who had dose suspension due to a recurrent ARIA event prior to the implementation of Protocol Version 6.0 that did not resolve or stabilize until after the implementation of Protocol Version 6.0: these subjects are to resume dosing at the same dose as that described in Section 7.2.1.6.2.

7.2.2. 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 Directions for Handling and Administration (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 subject will be discontinued from study treatment but may remain in the study. The subject must be appropriately treated in accordance with local practice.

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study period will consist of Screening, treatment, and FU.

The double-blind, placebo-controlled period of the study will consist of an 8-week screening period, a 76-week treatment period, and a safety FU period of 18 weeks after the final dose.

Subjects will have approximately 32 scheduled clinic visits during the placebo-controlled period, and up to 8 telephone safety FU contacts, as follows:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days). It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.
- 20 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 3 visits for clinical assessments.
- [redacted]
- 3 visits (including Screening) for amyloid PET scan (in a subset of subjects).
- [redacted]
- 7 visits for brain MRI.

- 1 FU safety visit at Week 94 (only for subjects not entering the LTE period) or 18 weeks after last administration of study treatment for those subjects who withdraw from study.

Subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period. Subjects who enter the LTE period will have approximately up to 76 additional planned clinic visits, and up to 8 telephone safety FU contacts, as follows:

- 65 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 7 visits for clinical assessments.
- [redacted]
- 4 visits for amyloid PET scan (in a subset of subjects).
- [redacted]
- 10 visits for brain MRI.
- 1 FU safety visit.

Subjects who have a change in AD medication (other than study treatment) during the placebo-controlled or LTE period should have an unscheduled visit; all clinical assessments for the primary and secondary endpoints should be performed prior to the change in medication.

Subjects who experience ARIA during the placebo-controlled or LTE period should have unscheduled visits per the guidelines in Section 7.2.1.

7.3.1. Screening

During the Screening Visit, under a separate (optional) initial consent process, subjects can complete the neurocognitive scales (CDR, MMSE, the Repeatable Battery for Assessment of Neuropsychological Status [RBANS]) and ApoE genotyping. This initial neurocognitive screening is intended to reduce the burden on subjects and sites by avoiding unnecessary testing if subjects do not meet key inclusion criteria. If the subject meets inclusion criteria for these 3 scales, then the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which would allow the administration of all screening assessments.

The neurocognitive assessments that have exclusion cut points (CDR, MMSE, and RBANS) and ApoE genotyping must be performed at Screening Visit 1. ApoE genotyping may be performed at Visit 1 prior to other screening assessments. The ADAS-Cog 13 and ADCS-ADL-MCI will be performed at Screening Visit 2 within 20 days after Visit 1 and must NOT be performed on the same day as the CDR, MMSE, and RBANS. The NPI-10 can be performed at any time during Screening as long as it is performed after the CDR (e.g., including at Screening Visit 1). All other cognitive assessments [redacted] may be performed at any time during Screening after eligibility is confirmed during Screening Visit 1. [redacted]

[redacted]

The MRI at Screening Visit 2 should be done only after the subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met.

Subject eligibility for the study will be determined no more than 60 days prior to study entry. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval.

Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion. Subjects who fail Screening due to not meeting entry criteria for PET, MMSE, hepatitis B or C results, having a CDR global score >0.5, or having abnormal MRI findings will not be allowed to rescreen. Note: Subjects with a CDR global score of 0 but who meet the other entry criteria may repeat the screening CDR evaluation after 6 months of the initial evaluation.

Subjects who fail Screening because allowed chronic medications have not been at stable doses for at least 4 weeks prior to Screening Visit 1 or whose use of AD medications has not been at stable doses for at least 8 weeks prior to Screening Visit 1 may return for rescreening after use of these medications has been stabilized for the required period.

7.3.2. Treatment

Eligible subjects will report to the study site to receive study treatment every 4 weeks for 76 weeks (20 doses). All subjects who meet the LTE inclusion and exclusion criteria will be eligible to enter the LTE period and will receive study treatment every 4 weeks for up to an additional 256 weeks (65 doses), with the first dose administered approximately 4 weeks after the final dose in the placebo-controlled period of the study. Subjects will continue treatment once every 4 weeks, until Week 336, or until the last subject has had his or her Week 182 Visit, whichever occurs first.

7.3.3. Follow-Up

All subjects participating in the placebo-controlled period are to return to the study site approximately 2 weeks after the final dose for clinical assessments.

Subjects participating in the placebo-controlled period and not entering the LTE period are to return to the study site for a FU Visit at Week 94 (18 weeks after the last placebo-controlled period dose). The final study visit for these subjects will be Week 94.

Subjects who participate in the LTE period are to return to the study site to receive their first LTE dose approximately 4 weeks after their last dose in the placebo-controlled period of the study. A FU Visit will occur 18 weeks after the last LTE period dose. The timing of the final study visit for subjects participating in the LTE period will vary, since the EOT Visit for a subject who participates in the LTE period will occur at Week 338, or when the last subject has had his or her Week 182 Visit, whichever occurs first.

Subjects who discontinue treatment are to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of

the clinic visits (see Table 10 and Table 11) until the end of the study or until withdrawal of consent. Subjects who withdraw from the study are encouraged to return for FU assessments 18 weeks after their last dose of study treatment.

7.4. Study Stopping Rules

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

Dosing may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety and tolerability data or following the futility analysis, or at the discretion of the Sponsor; therefore, there are no study-specific stopping rules defined in this protocol.

7.5. End of Study

The end of study is last subject, last visit. The EOT Visit for a subject who continues in the study will occur at Week 338, or when the last subject has had his or her Week 182 Visit, whichever occurs first.

8. SELECTION OF SUBJECTS

8.1. 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. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 50 to 85 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.
5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of Screening) is permissible for subjects not participating in the amyloid PET substudy. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.
6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
   - A CDR global score of 0.5.
   - An RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index score).
   - An MMSE score between 24 and 30 (inclusive).
7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and screening assessments.
8. Must consent to ApoE genotyping.
9. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.2. 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

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's cognitive impairment (e.g., substance abuse, vitamin B_{12} deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, Lewy body dementia, fronto-temporal dementia, head trauma).
2. Clinically significant unstable psychiatric illness (e.g., uncontrolled major depression, uncontrolled schizophrenia, uncontrolled bipolar affective disorder) within 6 months prior to Screening.
3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
   - Acute or sub-acute hemorrhage.
   - Prior macrohemorrhage (defined as >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 subject is at risk of recurrent hemorrhage).
   - Greater than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as >1.5 cm in diameter; irrespective of anatomic location).
   - >1 lacunar infarct (defined as ≤1.5 cm in diameter).
   - Superficial siderosis.
   - 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 subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.
5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the Investigator.
6. Presence of diabetes mellitus that, in the judgment of the Investigator, cannot be controlled or adequately managed.

7. 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.
8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.
9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [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 subject 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.
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:
    - Subjects with cancers in remission more than 5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma of the skin.
    - Subjects with localized prostate cancer with treatment cycles that completed at least 6 months prior to Screening.
11. History of seizure within 10 years prior to Screening.
12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\geq 2 \times$ the upper limit of normal).
13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).
15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.
16. History of or known seropositivity for human immunodeficiency virus (HIV).
17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for both hepatitis B surface antigen AND hepatitis B core antibody).
18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).

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

Medications

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or complete study procedures.
21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 and during Screening up to Study Day 1, or use of AD 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 1 and during Screening up to Study Day 1.
22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).
23. Use of illicit narcotic medication.
24. Vaccinations within 10 days prior to randomization (Day 1).
25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.
26. Participation in any passive immunotherapy study targeting Aβ within 12 months of Screening unless documentation of receipt of placebo is available.
27. Participation in any study with purported disease-modifying effect in AD within 12 months prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.
28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures

29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).
30. Contraindication to having a PET scan (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, failure to participate in and comply with previous PET scans).
31. A negative PET scan result with any amyloid-targeting ligand within 6 months prior to Screening.
32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

33. For subjects who consent to LP, any contraindications to having a LP (e.g., platelet count <100,000/μL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during Screening must be resolved prior to randomization (Day 1). Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.
35. Previous participation in this study. Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR global score >0.5, hepatitis B or C, or abnormal MRI findings. (Subjects who fail Screening due to a CDR global score of 0 may be rescreened; such subjects will be allowed to repeat the screening CDR assessment after 6 months.)
36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥ 1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

8.3. Inclusion Criteria for Long-Term Extension Period

To be eligible to participate in the LTE period, subjects must meet the following eligibility criteria at Week 78:

1. Subject must have completed the placebo-controlled period of the study including the Week 78 Visit. Subject must have taken at least 14 doses and not have missed more than 4 consecutive doses, except for subjects whose dose was suspended due to ARIA (See Section 7.2.1). Subjects who do not meet these criteria may enter the LTE period only with Sponsor's approval.
2. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and provide signed and dated informed consent (or assent) and authorization to use confidential health information in accordance with national and local subject privacy regulations.
3. Female subjects of childbearing potential and male subjects must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment.
4. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.
5. Must have the ability to comply with procedures for protocol-related tests.

6. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

8.4. Exclusion Criteria for Long-Term Extension Period

Subjects will be excluded from entering the LTE period if at Week 78 they have:

1. Any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the subject's participation in and completion of the study.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative, where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). During Screening, subjects can complete the neurocognitive scales (CDR, MMSE and RBANS) and ApoE genotyping to determine study eligibility under a separate, optional initial consent process. If the subject meets inclusion criteria for these 3 scales the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process which would allow the administration of all screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study. ApoE genotyping may be performed at Visit 1 prior to other screening assessments.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues related to PET scans and is subject to Sponsor approval. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log. The total study duration for each subject participating only in the placebo-controlled period will be approximately 102 weeks (approximately an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 18 weeks of FU).

9.2. Randomization and Registration of Subjects

Subjects will be registered at the Screening Visit and randomized only after all baseline assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive aducanumab low dose:aducanumab high dose:placebo in a 1:1:1 ratio. The randomization will be stratified by site and ApoE ε4 status (carrier or non-carrier). Subjects randomized to placebo at the start of the placebo-controlled period will also be randomized to receive dose-blinded aducanumab (low dose:high dose, 1:1 ratio) for the LTE period and randomization will be stratified by subject ApoE ε4 carrier status. Treatment group assignments for the placebo-controlled period and the LTE period will be assigned at Study Day 1. Enrollment will be monitored, via the IRT, such that the population of subjects with mild AD represents a small percentage of the total enrolled in the trial. Subjects who withdraw from the study may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This study consists of a randomized, double-blind, placebo-controlled period, followed by a dose-blinded LTE period with all subjects receiving aducanumab.

For the double-blinded placebo-controlled period, all study staff who conduct subject assessments will be blinded to the subject treatment assignments. The rating HCPs should remain blinded to treatment assignment as well as subject care management and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. As 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 subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

For the LTE period, the dose information must remain restricted. The rating and treating HCP should remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities as detailed in Section 4.3.1. To maintain the study blind, it is imperative that dose information is not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Biogen or its representatives, except the unblinded pharmacist (or designee), the unblinded pharmacy monitor, and the unblinded [redacted] or Biogen safety staff.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject develops any of the following:
  - ARIA-E accompanied by serious clinical symptoms except for "other medically important event" as defined in Table 13.
  - Symptomatic ARIA-H (microhemorrhages) with serious clinical symptoms except for "other medically important event" as defined in Table 14.
  - Symptomatic ARIA-H (superficial siderosis) with or serious clinical symptoms except for "other medically important event" as defined in Table 15.
  - ARIA-H with ≥ 10 microhemorrhages and/or >2 focal areas of superficial siderosis.
  - Any new incident macrohemorrhage (defined as >1 cm in diameter on T2* sequence).

  See Section 7.2.1 for full details regarding discontinuation and dose reduction due to ARIA-E or ARIA-H.
- The subject becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria (see Section 11.5.1.2).
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

A subject who discontinues treatment is to remain in the study, attend a FU Visit 18 weeks after the final dose, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11) until the end of the study per the schedule of events or until the subject withdraws consent.

10.2. Withdrawal of Subjects From Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.

Note: A subject who discontinues study treatment will not be automatically withdrawn from the study, regardless of the number of doses missed. The subject is to remain in the study, and continue with a FU Visit 18 weeks after the final dose, and protocol-required tests and assessments at a subset of the clinic visits (see Table 10 and Table 11) until the end of the study or until the subject withdraws consent.

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

Subjects who are withdrawn from the study after receiving ≥ 1 doses of study treatment should complete the EOT Visit after the reason for withdrawal is identified. For such subjects, efficacy assessments specified at the EOT Visit are not required if the subject 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 in such cases. Subjects 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.

11. STUDY TREATMENT USE

11.1. Regimen

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

Please see Section 4.2 (Schedule of Events) for the study treatment infusion schedule during the placebo-controlled and LTE periods of the study.

Aducanumab is to be administered by IV infusion following dilution into saline. See Section 12 for details of aducanumab study treatment.

11.1.1. Aducanumab

The Sponsor will provide aducanumab to study sites.

11.1.2. Placebo

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

11.2. Modification of Dose and/or Treatment Schedule

Refer to Section 7.2.1 (dose suspension) and Section 7.2.2 (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.

11.3. Precautions

Not applicable.

11.4. Compliance

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

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior AD medication use within the 12 months prior to Screening will be captured.

A concomitant therapy is any drug or substance administered between the informed consent and until the subject'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.

11.5.1.1. Allowed Concomitant Therapy

- Medications for chronic conditions are allowed at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1 and during the screening period.
- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and during the screening period and that they stay on a stable dose while in the study.
- Vaccinations with live or attenuated vaccines are allowed during the study. Administration of any vaccination/booster should not be given < 10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anti-coagulant properties, except the use of aspirin at a dose of ≤ 325 mg per day.
- Non-prescription narcotic medication.
- Immunosuppressive drugs (including systemic corticosteroids). Local corticosteroids (including inhaled and topical corticosteroids) are allowed; certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Subjects should be instructed to continue the medications that they were receiving at enrollment without any changes (see allowed concomitant therapy above) and avoid starting any new medications or herbal preparations during the study period, as it may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended. Medications used to treat AEs would not result in automatic permanent study treatment discontinuation. However, as noted in Section 10.1, if a subject requires continued use of a disallowed therapy, the subject must permanently discontinue study treatment. The Sponsor may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication, and all clinical assessments for the primary and secondary objectives should be performed prior to the change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures)

performed between the time the subject is enrolled in the study and until the subject's final clinic visit (including FU Visit), unless the subjects is being followed for study-related toxicity.

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

11.6. 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.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another subject.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

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

Aducanumab is a recombinant 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. [redacted] Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing either:

- aducanumab 50 mg/mL [redacted]

  or

- aducanumab 100 mg/mL [redacted]

The concentration for each vial (either 50 or 100 mg/mL) appears on the label. Aducanumab is manufactured in accordance with Good Manufacturing Practices.

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

12.1.1. Aducanumab 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 Biogen.

12.1.2. Aducanumab 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 8°C 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.

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen (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 personnel must obtain prior approval from Biogen by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified in writing of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Aducanumab 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 (subject-by-subject 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 Biogen. A written explanation must be provided for any discrepancies.

12.2. 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.

12.3. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

To confirm amyloid pathology at Screening, PET scans will be performed using Amyvid™ (^{18}F-florbetapir), Vizamyl™ (^{18}F-flutemetomol), or Neuraceq™ (^{18}F-florbetaben). For those subjects participating in the amyloid PET substudy, Screening and FU scans must be performed

using Amyvid and for subjects participating in the PET substudy in Japan, Vizamyl (^{18}F-flutemetomol) may also be used. For details on PET imaging ligands, [redacted] refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

Refer to Section 4.2 for the timing of assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of aducanumab:

- CDR
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

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

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

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

13.2. Pharmacokinetic Assessments

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

13.3. Pharmacodynamic Assessments

The following tests will be performed to assess the PD properties of aducanumab:

- Serial measurement of amyloid plaque burden in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 subjects participating in the amyloid PET cohort).

  Only sites with capabilities of performing ^{18}F-florbetapir PET will be allowed to perform this assessment. Investigator participation in this part of the study is optional and contingent upon approval by his/her ethics committee (EC) or institutional review board (IRB). If the Investigator is not participating or the test is not approved by his/her EC/IRB, the relevant section of the ICF will not be applicable to that site.

  Subject participation in this part of the study is optional at participating sites. Informed consent must be recorded in the CRF. Detailed PET scanning protocols will be described in a separate procedural manual for PET. Approximately 400 subjects are expected to participate in the amyloid PET substudy.

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

13.4. Additional Assessments

[redacted]

13.4.2. ApoE Genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit.

[redacted]

13.4.4. Health Outcomes Assessments

The following assessments will be performed to evaluate the effect of aducanumab in subjects and caregivers:

- EQ-5D (SR)
- EQ-5D (IR-S)
- [redacted]
- mPDQ-20
- [redacted]

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

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

13.5. Future Scientific Research Assessments

[redacted]

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

14.1. Clinical Safety Assessments

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

- AE and SAE monitoring.
- Physical examination, including height and weight.
- Neurological examination.
- Vital signs (body temperature, heart rate, SBP, DBP, and respiratory rate).
- 12-lead ECG.
- Brain MRI.
- Concomitant medication, therapy, and procedure monitoring.
- MOCA (for ARIA monitoring and management).
- Columbia Suicide Severity Rating Scale (C-SSRS).

14.2. Laboratory Safety Assessments

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

- Hematology: complete blood count with differential and 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, virology (including HIV at the Investigator's discretion after consideration of risk factors), HbA_{1c}, and alcohol/drug screen at Screening.

14.3. Immunogenicity Assessments

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

15. 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 subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 laboratory finding), 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 laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the Investigator considers to be clinically significant.

Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.1.2. 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 subject 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.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject 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.)

15.1.3. 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 subject is hospitalized. The study site must document all of 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 subject's consent to participate 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 subject's consent to participate 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 subject 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 15.1.2 is met.

15.2. Safety Classifications

15.2.1. 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 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

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.

15.2.3. Severity of Events

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

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the IB for aducanumab.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the subject's final clinic visit (including FU Visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. Pre-treatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form.

15.3.2. Adverse Events of Special Interest

ARIA-E and ARIA-H 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.

If the event qualifies as an SAE an SAE form should be submitted per the guidelines in Section 15.3.4. Investigators should include a copy of the centrally read MRI report when submitting the SAE form to [redacted].

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between signing of the ICF and the subject's final clinic visit (including FU Visit) will be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen (or designee) within 24 hours as described in Section 15.3.4. This also applies to SAEs that occur after administration of the ligand. FU information regarding an SAE also must be reported with 24 hours.

Events occurring after the subject's final clinic visit (including FU Visit) should be reported to Biogen only if the Investigator considers the SAE related to study treatment.

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

15.3.4. 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 [redacted] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and the subject's final clinic visit (including FU Visit) must be reported to [redacted] within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to [redacted] regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event

- The relationship of the event to study treatment

To report initial or FU information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Guide for country-specific [redacted] fax numbers or email [redacted]

15.3.4.1. 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. The Investigator should make every effort to obtain and send death certificates and autopsy reports to [redacted]. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit Risk (SABR) will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

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

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to [redacted] within 24 hours of the study site staff becoming aware of the pregnancy at the SAE reporting fax number provided in the study reference manual. The Investigator or study site staff must report the outcome of the pregnancy to [redacted].

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in 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 to [redacted] within 24 hours of the site becoming aware of the overdose. An overdose must be reported to [redacted] 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 to [redacted]. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. 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 [redacted] 24-hour emergency medical support number. Refer to the Study Reference Guide's Official Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

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

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. However, prior to unblinding, the Investigator can contact the [redacted] 24-hour emergency medical support number at [redacted]

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.5. Contraception Requirements

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.
- Post hysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

For the purposes of this study, highly effective contraception is defined as use of 1 of the following:

- For females of childbearing potential:
  - Established use of oral, injected, or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system

- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (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.
- Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.

- For males:
  - Vasectomy with negative semen analysis at FU.
  - Use of condoms with spermicide.
  - Female sexual partners who underwent surgical sterilization (e.g., bilateral tubal ligation), are postmenopausal, are post-hysterectomy, or are using highly effective contraception as listed above for female subjects.

  For males and females of childbearing potential:

  True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, 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, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, 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 and FU on the outcome of the pregnancy in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen (or designee) within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE FU information actively and persistently. FU information must be reported to Biogen (or designee) within 24 hours of the study site staff becoming aware of new information.

- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE FU information, if possible, until the event has resolved or become stable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor ([redacted]) is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen (or designee) is to notify all appropriate regulatory authorities, central EC/IRBs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy and Pharmacodynamics

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), will be used for the efficacy analyses. Subjects will be analyzed in the groups to which they were randomized.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of subjects 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 each aducanumab dose (high and low) and placebo. All statistical tests will be 2-sided.

16.2.2.2. Aducanumab Doses to be Evaluated

The following aducanumab doses as compared with placebo will be evaluated:

- Aducanumab high-dose (10 mg/kg in ApoE ε4 [including 6 mg/kg for subjects enrolled under protocol versions prior to Version 4 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study] and 10 mg/kg in ApoE ε4 non-carriers).
- Aducanumab low-dose (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

In the event that the maximum dose (10 mg/kg) is terminated after the start of the study (Section 5.3.2) the definition of aducanumab high dose and aducanumab low dose will be modified as shown in Table 17. The dosing modification will be entirely based on interim analysis of outcomes that are independent of, and uninformative about, the treatment-related efficacy effect. Control of Type I error rate is thus maintained without a statistical adjustment for such adaptations [Chow and Chang 2011].

Table 17: Treatment Groups in the Event of High Dose Group Termination

High Dose Group(s) Terminated	Definitions of Revised Treatment (Low/High Dose) Groups for Comparison
ApoE ε4 carrier high-dose group (10 mg/kg) [including 6 mg/kg for subjects enrolled under versions prior to Version 4 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study]	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 3 mg/kg and non-carrier 10 mg/kg
ApoE ε4 non-carrier high-dose group (10 mg/kg)	Low: ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg High: ApoE ε4 carrier 10 mg/kg and non-carrier 6 mg/kg
ApoE ε4 carrier high-dose group (10 mg/kg) AND ApoE ε4 non-carrier high-dose group (10 mg/kg)	ApoE ε4 carrier 3 mg/kg and non-carrier 6 mg/kg

16.2.2.3. Considerations for Multiple Comparison Adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose versus placebo and aducanumab low-dose versus placebo. All comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 6. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for 1 or 2 comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for 1 or 2, respectively.

16.2.2.4. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment, time, treatment-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

16.2.2.5. Analysis of the Secondary Endpoints

16.2.2.5.1. Change From Baseline to Week 78 in MMSE

The population for the analysis will be subjects in the ITT population. A MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment, time, treatment-by-time interaction, baseline MMSE value, baseline MMSE by time interaction, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status

16.2.2.5.2. Change From Baseline to Week 78 in ADAS-Cog 13

The population will be subjects in the ITT population. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment, time, treatment-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

16.2.2.5.3. Change From Baseline to Week 78 in ADCS-ADL-MCI

The population will be subjects in the ITT population. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment, time, treatment-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

16.2.2.6. Tertiary Endpoints Analysis

16.2.2.6.1. Placebo-Controlled Period

Where appropriate, an MMRM model will be used as the primary analysis to analyze change from baseline using fixed effects of treatment, time, treatment by time interaction, baseline value, baseline value by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

Otherwise, an analysis of covariance may be used to analyze these exploratory endpoints or descriptive summary statistics may be presented.

16.2.2.6.2. Long-Term Extension Period

The endpoints for the LTE period are change from baseline over the placebo-controlled and LTE periods of the study. Analyses will be presented by treatment group in the LTE period using the placebo-controlled period baseline. Details of the analyses will be prespecified in the statistical analysis plan (SAP).

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for PK analysis is defined as all subjects who were randomized, were dosed with study treatment, and had at least 1 measurable aducanumab concentration in serum.

16.3.2. Method of Analysis

The serum concentrations and PK parameters of aducanumab will be summarized descriptively.

16.4. Additional Exploratory Analyses

[redacted]

16.5. Safety

16.5.1. Analysis Population

The safety population is defined as all subjects who were randomized and received at least 1 dose of study treatment (including placebo and aducanumab).

16.5.2. Methods of Analysis

All AEs, laboratory data, ECG, neurological and physical examinations and vital signs will be evaluated for safety.

16.5.2.1. Adverse Events

Only treatment-emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent 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 study treatment for the placebo-controlled period and up to 5 years of LTE period. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

16.5.2.2. 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. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.5.2.3. Vital Signs

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

16.5.2.4. ECG

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

16.5.2.5. Columbia Suicide Severity Rating Scale

The C-SSRS data will be summarized by treatment group.

16.6. Immunogenicity Data

16.6.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects in the safety population who have at least 1 post-dose sample evaluated for immunogenicity.

16.6.2. Methods of Analysis

Anti-aducanumab serum antibodies will be summarized using shift tables.

16.7. Interim Analyses

16.7.1. Interim Futility Analysis

An interim analysis for futility of the primary endpoint will occur after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). In order to maintain the treatment blind, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim futility analysis. This independent group will present the unblinded interim analysis to the IDMC. The IDMC may recommend terminating the study for futility if it is evident that the efficacy of aducanumab is unlikely to be achieved.

The futility criteria will be discussed in detail in the SAP.

16.7.2. Interim Superiority Analysis

An interim analysis for superiority may be performed after approximately 50% of the subjects have completed the Week 78 Visit (or discontinued). The O'Brien-Fleming boundary approach will be used for the analysis. In order to maintain the treatment blind in the event of this interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim superiority analysis. The independent group will present the unblinded interim analysis to the IDMC. The aim of this interim analysis is to allow the possibility to demonstrate treatment effect early. The analysis will be discussed in detail in the SAP.

16.8. Sample Size Considerations

The study's sample size is based, in part, on results from a protocol-specified interim analysis from Study 221AD103, which included 1-year data from 1, 3, and 10 mg/kg treatment groups.

A sample size of 450 subjects per treatment group (1350 in total) was planned to have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation was based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, an SD of 1.92, and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflected a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

The assumed true mean difference of 0.5 between the 2 treatment groups represents an approximately 25% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

As defined in the prior versions of the protocol, the sample size for this study (and for the identically designed Study 221AD302) was reassessed in a blinded manner approximately 3 months before enrollment completion. At the time of this reassessment (November 2017), about 10.6% of the data was available on the primary endpoint from Study 221AD301 and Study 221AD302 combined; based on the pooled blinded data (i.e., treatment groups combined) from the 2 studies, the SD for the primary endpoint was estimated. As a result of this analysis, the sample size has been adjusted from 1350 to 1605 (450 to 535 per treatment) to assure adequate power to detect a mean treatment effect of 0.5.

17. ETHICAL REQUIREMENTS

Biogen, [redacted], and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

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.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee/Institutional Review Board

The Investigator must obtain EC/IRB approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites worldwide in compliance with local requirements.

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

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

Biogen must receive a letter documenting EC/IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC/IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC/IRB and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations. Subjects can complete the neurocognitive scales (CDR, MMSE, and RBANS) as well as ApoE genotyping as an initial optional screening under a separate consent process. If the subject meets inclusion criteria for these 3 scales, the full consent process must be completed prior to the administration of further screening assessments.

Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

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

Subjects will be informed that their race and/or ethnicity will be collected and will be used during analysis of study results (only in countries where permitted by local law/regulation).

A copy of the signed and dated ICF must be given to the subject, caregiver and/or legally authorized representative. The 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 (wet signature) and copies of the signed and dated ICFs.

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

17.4. Subject Data Protection

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

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), EC/IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

During the study, subjects' race and/or ethnicity will be collected (only in countries where permitted by local law/regulation). These data may be used in the analysis of the safety, efficacy, and/or pharmacokinetic profile of the study treatment. It is unknown if the potency or effects of the study treatment are influenced by race or ethnicity.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partner[s]) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. 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 subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or randomized, the IRT vendor will provide each study site with appropriate training, access rights, and a user manual.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool developed by [redacted] and configured by the EDC vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Biogen 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, [redacted] and DNA for specialized ApoE ε4 genotyping, PK, biomarker, and ADA 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.

19.1.5. Central Facility for Other Assessments

A central imaging laboratory has been selected by Biogen 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 PI 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 collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen 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 per project-specific plans.

19.2. Study Committees

19.2.1. 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 subject accrual and oversee study conduct, including advising on study design and execution. The advisory committee will be blinded to subject treatment assignments during the study.

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

19.2.2. Independent Data Monitoring Committee

The IDMC will be formed to review ongoing safety and tolerability data. 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 subjects. The IDMC, based on the nature, frequency, and/or severity of an AE(s) may recommend protocol modification(s), 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.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC/IRB 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, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. 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 Sections 17.2 and 17.3).

19.4. Ethics Committee/Institutional Review Board Notification of Study Completion or Termination

Where required, the regulatory authorities and EC/IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. 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 laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen 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.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study 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 subject enrollment, or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early 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.

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Investigator's Signature Date

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Investigator's Name (Print)

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Study Site (Print)