Official Title:	Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (Aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302, and 221AD205
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PROTOCOL NUMBER: 221AD304

PHASE OF DEVELOPMENT: 3b

PROTOCOL TITLE: Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302, and 221AD205

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Version 4.0
FINAL

Supersedes previous Version 3.0 dated 08 March 2021

SPONSOR SIGNATURE

Protocol 221AD304 was approved by:

_____ _____

[redacted], PhD Date (*DD MMM YYYY*)
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1. SPONSOR INFORMATION

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For urgent medical issues in which the study Medical Director should be contacted, please refer to the Study Reference Manual's Official Study Contact List for complete contact information.

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

2. LIST OF ABBREVIATIONS

12F6A	recombinant, human anti-amyloid beta immunoglobulin gamma 1 monoclonal antibody with an amino acid sequence identical to aducanumab, produced in a different Chinese hamster ovary cell line
Aβ	amyloid beta (peptide derived from membrane bound amyloid precursor protein)
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
[redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
[redacted]	[redacted]
[redacted]	[redacted]
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-hemorrhage or superficial siderosis
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
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DCT	discontinue treatment
DHA	Directions for Handling and Administration
[redacted]	[redacted]
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EOT	End of Treatment

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
HbA_{1c}	glycosylated hemoglobin
HbsAg	hepatitis B surface antigen
HCP	health care provider
HCV	hepatitis C virus
[redacted]	[redacted]
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IgG	immunoglobulin G
IRB	institutional review board
IRT	interactive response technology
IV	intravenous(ly)
IWG	International Working Group
LP	lumbar puncture
LTE	long term extension
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
[redacted]	[redacted]
[redacted]	[redacted]
MRI	magnetic resonance imaging
NFT	neurofibrillary tangle
NIA-AA	National Institute on Aging (NIA) at National Institutes of Health (NIH) and the Alzheimer's Association (AA)
[redacted]	[redacted]
PD	pharmacodynamic(s)
[redacted]	[redacted]
PK	pharmacokinetic(s)
Q4W	every 4 weeks
RNA	ribonucleic acid
[redacted]	[redacted]
SAE	serious adverse event
SBP	systolic blood pressure

SUSAR	suspected unexpected serious adverse reaction
SUVR	Standard Uptake Value Ratio
TEAE	treatment-emergent adverse event
UV	Unscheduled Visit

3. SYNOPSIS

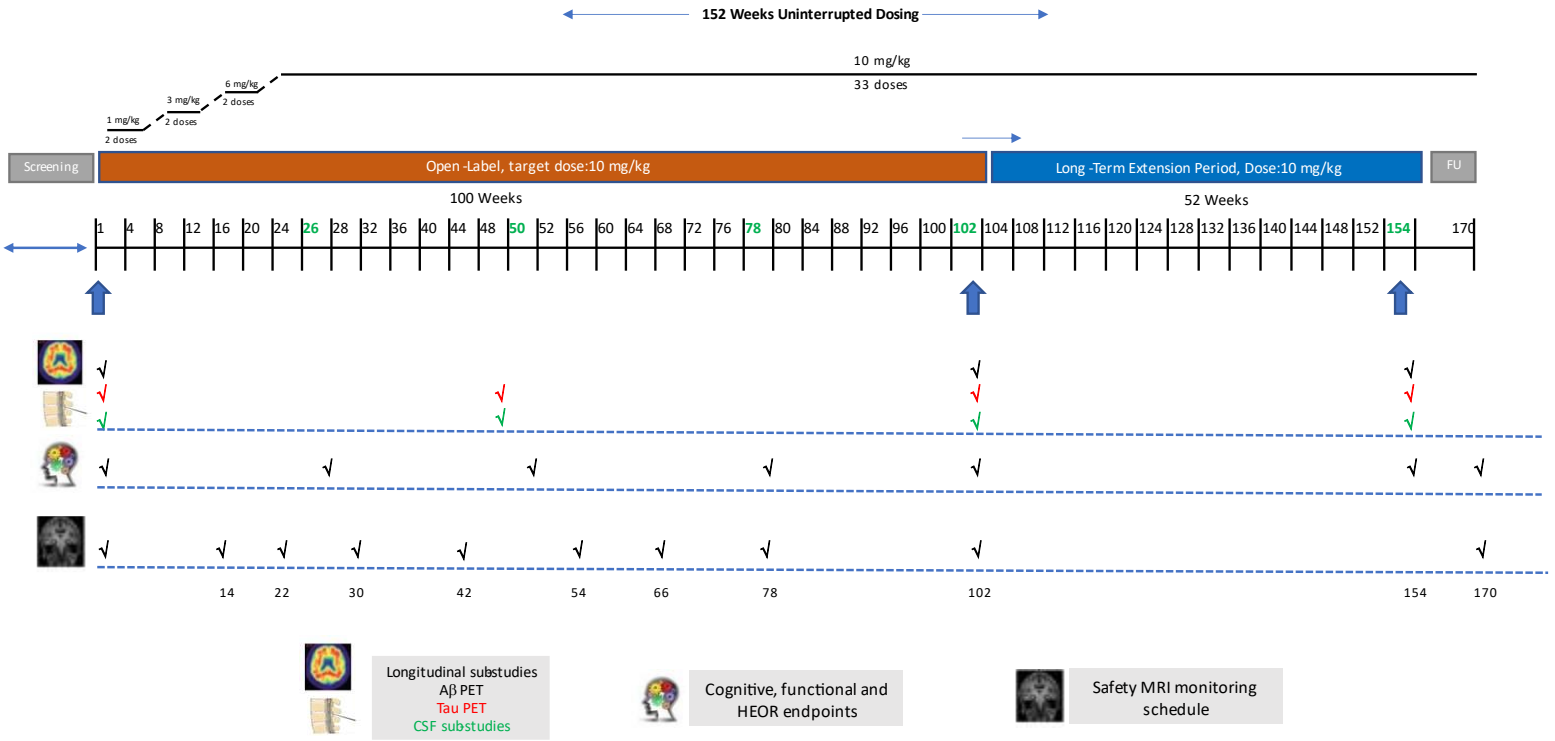
Protocol Number:	**221AD304**
Protocol Title:	Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (Aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302, and 221AD205
Version Number:	4.0
Name of Study Treatment:	Aducanumab (BIIB037)
Study Indication:	Alzheimer's disease
Study Rationale:	This open-label, single-arm clinical study is being conducted to assess the long-term safety and efficacy of aducanumab in participants with Alzheimer's disease who were actively participating in aducanumab clinical studies 221AD103, 221AD205, 221AD301, or 221AD302 (from now on named "feeder studies") as of 21 March 2019. On that date, Biogen announced the discontinuation of the Phase 3 aducanumab clinical studies, based on results from a preplanned futility analysis; discontinuation of the other ongoing studies (Studies 221AD103 and 221AD205) was also announced and implemented at the same time. The present study (221AD304) is being undertaken based on efficacy findings from additional analyses of the 2 Phase 3 studies. In these new analyses, Study 221AD302 showed that participants treated in the high-dose arm of aducanumab had significantly slower cognitive and functional decline when compared to placebo at 18 months. Results from the low-dose arm of Study 221AD302 showed trends of slowing decline compared to placebo but did not reach significance.
Phase of Development:	3b
Study Objectives and Endpoints:	The primary objective of the study is to evaluate the long-term safety and tolerability of aducanumab after a wash-out period imposed by the discontinuation of the feeder studies in participants who had previously received aducanumab (i.e., previously treated participants) or who had previously received placebo (i.e., treatment-naïve participants).

Protocol Number:	**221AD304**
	The endpoints that relate to this objective are: • Incidence of AEs, SAEs, ARIA, and immunogenicity with long-term treatment and/or re-exposure to aducanumab. Safety and tolerability parameters including: – Incidence of all AEs, AEs leading to treatment discontinuation or study withdrawal, and all SAEs – Incidence of ARIA-E and ARIA-H – Incidence of anti-aducanumab antibodies (antidrug antibodies, ADA), in serum. [redacted]
Study Design:	Single-arm, longitudinal, multicenter, open-label study with a 100-week Core Treatment Period followed by an LTE Treatment Period of an additional 52 weeks of treatment and a safety FU Visit 18 weeks after the last dose of study treatment.
Study Location:	Approximately 350 sites globally
Number of Planned Participants:	Approximately 2400 participants are planned to be enrolled.
Study Population:	This study will be conducted in participants who meet the following criteria: • Actively enrolled in an ongoing aducanumab clinical study at the time of the Sponsor's decision to stop trials on 21 March 2019. • Diagnosed with Alzheimer's disease, able to comply with study protocol-related tests and procedures, and with an [redacted] Detailed inclusion and exclusion criteria are described in Section 8.
Treatment Groups:	All participants will receive aducanumab by IV infusion Q4W. The aducanumab target dose will be 10 mg/kg, after a titration period as follows: 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.
Duration of Study Participation:	Study duration for each participant will be approximately 178 weeks: approximately 8-week Screening Period, a 100-week Core Treatment Period, a 52-week LTE Treatment Period, and a safety FU Visit 18 weeks after the last dose of study treatment.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 221AD304

4.1. Study Schematic

Figure 1: Study Design



4.2. Schedule of Events

Table 1: Core Treatment Period Schedule From Screening Through Week 48 of Treatment

Study Week	Screening (≤ 60 days before Day 1)[1]	Treatment Period														UV for a Change in Alzheimer's Disease Medication
		Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	
Study Day		**1**	**29± 5**	**57± 5**	**85± 5**	**113± 5**	**141± 5**	**169± 5**	**183± 5**	**197± 5**	**225± 5**	**253± 5**	**281± 5**	**309± 5**	**337± 5**	
Informed Consent	X															
Eligibility Criteria	X	X[2]														
Demography	X															
Medical History	X															
Alcohol/Drug Screen	X															
HbA_{1c}	X															
HIV[3]/Hepatitis	X															
[redacted]																
Coagulation	X															
Height		X														
Body Weight		X	X	X	X	X	X	X		X	X	X	X	X	X	
Serum Pregnancy Test[5]	X															
Urine Pregnancy Test[5]		X	X	X	X	X	X	X		X	X	X	X	X	X	
Aducanumab Infusion		X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology, Blood Chemistry, and Urinalysis	X[6]															
Alzheimer's Disease Status[7]	X															

Study Week	Screening (≤ 60 days before Day 1)[1]	Treatment Period													UV for a Change in Alzheimer's Disease Medication
		Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	
Study Day		**1**	**29± 5**	**57± 5**	**85± 5**	**113± 5**	**141± 5**	**169± 5**	**183± 5**	**197± 5**	**225± 5**	**253± 5**	**281± 5**	**309± 5**	**337± 5**	
Physical Examination	X							X							X	
Neurological Examination	X							X							X	
Vital Signs[8]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	
12-Lead Paper ECG	X	X														
ADA[9]		X						X							X	
Aducanumab Serum Concentration[9]		X						X							X	
[redacted]																

Study Week	Screening (≤ 60 days before Day 1)[1]	Treatment Period														UV for a Change in Alzheimer's Disease Medication
		Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	
Study Day		**1**	**29± 5**	**57± 5**	**85± 5**	**113± 5**	**141± 5**	**169± 5**	**183± 5**	**197± 5**	**225± 5**	**253± 5**	**281± 5**	**309± 5**	**337± 5**	
[redacted]																
C-SSRS	X															
AE Reporting		Monitor and record continuously throughout the study														
Concomitant Therapy[13] and Procedures		Monitor and record continuously throughout the study														
SAE Reporting		Monitor and record continuously throughout the study														

[1] 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 [redacted] and/or other logistics restrictions due to major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters) and is subject to Sponsor approval. In order to ease participant burden, the Screening Visit may be carried out over 2 separate visits, at the Investigator's discretion.

[2] All assessments must be completed prior to infusion.

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

[redacted]

[5] Required for women of childbearing potential only (see Section 15.5). Must be performed prior to scans.

[6] Chemistry assessment at Screening Visit to include lipid panel.

[7] As judged by the Investigator.

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

[redacted]

[redacted]

[13] Participants who have a change in Alzheimer's disease medication (other than study treatment) during the Treatment Period should have an unscheduled visit. A subset of the clinical efficacy assessments [redacted] should be performed prior to the change in medication if the participant alerts the Investigator before the change in medication occurs. In the event that the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments are performed within 30 days after the change in medication, the assessments do not have to be repeated.

Table 2: Core Treatment Period Schedule From Week 50 to Week 102

	Treatment Period																FU
Study Week	**50**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78**	**80**	**84**	**88**	**92**	**96**	**100**	**102**[1]	**UV for a Change in Alzheimer's Disease Medication**	**118 (or 18 wks after last dose for participants who DCT early)**[2]
Study Day	**351 ± 5**	**365 ± 5**	**393 ± 5**	**421 ± 5**	**449 ± 5**	**477 ± 5**	**505 ± 5**	**533 ± 5**	**547 ± 5**	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**714 ± 5**		**827± 5**
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			
Aducanumab Infusion		X	X	X	X	X	X	X		X	X	X	X	X	X			
Hematology, Blood Chemistry, and Urinalysis		X														X		
Alzheimer's Disease Status[4]		X														X		
Physical Examination							X									X		X
Neurological Examination							X									X		X
Vital Signs[5]		X	X	X	X	X	X	X		X	X	X	X	X	X	X		X
12-Lead Paper ECG		X														X		
ADA[6]							X									X		
Aducanumab Serum Concentration[6]							X									X		
[redacted]																		

Study Week	Treatment Period																	FU
	50	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**78**	**80**	**84**	**88**	**92**	**96**	**100**	**102**[1]	**UV for a Change in Alzheimer's Disease Medication**	**118 (or 18 wks after last dose for participants who DCT early)**[2]
Study Day	**351 ± 5**	**365 ± 5**	**393 ± 5**	**421 ± 5**	**449 ± 5**	**477 ± 5**	**505 ± 5**	**533 ± 5**	**547 ± 5**	**561 ± 5**	**589 ± 5**	**617 ± 5**	**645 ± 5**	**673 ± 5**	**701 ± 5**	**714 ± 5**		**827± 5**
[redacted]																		
C-SSRS	X															X		
LTE IC/EC Eligibility																X		
LTE Informed consent[11]																X		
AE Reporting	Monitor and record continuously throughout the study																	
Concomitant Therapy[12] and Procedures	Monitor and record continuously throughout the study																	
SAE Reporting	Monitor and record continuously throughout the study																	

[1] Eligible participants who complete the Core Treatment Period and the Week 102 visit may enter the LTE period.
[2] For all participants who do not enter the LTE, a safety FU Visit is required 18 weeks after their last dose.

[3] Required for women of childbearing potential only (Section 15.5).
[4] As judged by the Investigator.
[5] Vital signs will include body temperature, heart rate, SBP, DBP, and respiratory rate. Vital signs will be measured with the participant supine and after the participant has been resting for at least 10 minutes.
[6] Will be performed prior to infusion (where applicable).

[redacted]

[11] All participants who are eligible and continuing in the LTE must provide written informed consent.
[12] Participants who have a change in Alzheimer's disease medication (other than study treatment) during the Treatment Period should have an unscheduled visit. A subset of the clinical efficacy assessments [redacted] should be performed prior to the change in medication if the participant alerts the Investigator before the change in medication occurs. In the event that the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments are performed within 30 days after the change in medication, the assessments do not have to be repeated.

Table 3: LTE Treatment Schedule from Week 104 Through End of Treatment and Follow-Up

Study Week	LTE Treatment Period														UV for a Change in Alzheimer's Disease Medication	FU 170 (or 18 wks after last dose for participants who DCT early)
	104	108	112	116	120	124	128	132	136	140	144	148	152	154/EOT		
Study Day	**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**	**1078 ± 5**		**1190 ± 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			
Aducanumab Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hematology, Blood Chemistry, and Urinalysis														X		
Alzheimer's Disease Status[2]														X		
Physical Examination							X							X		X
Neurological Examination							X							X		X
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
12-Lead Paper ECG														X		
ADA[4]							X							X		
Aducanumab Serum Concentration[4]							X							X		

Study Week	LTE Treatment Period														UV for a Change in Alzheimer's Disease Medication	FU 170 (or 18 wks after last dose for participants who DCT early)
	104	108	112	116	120	124	128	132	136	140	144	148	152	154/EOT		
Study Day	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	1078 ± 5		1190 ± 5
[redacted]																
C-SSRS														X		
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy[9] and Procedures	Monitor and record continuously throughout the study															

Study Week	LTE Treatment Period														UV for a Change in Alzheimer's Disease Medication	FU 170 (or 18 wks after last dose for participants who DCT early)
	104	108	112	116	120	124	128	132	136	140	144	148	152	154/EOT		
Study Day	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	1078 ± 5		1190 ± 5
SAE Reporting	Monitor and record continuously throughout the study															

[1] Required for women of childbearing potential only (see Section 15.5). Must be performed prior to scans.

[2] As judged by the Investigator

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

[4] Will be performed prior to infusion (where applicable).

[redacted]

[9] Participants who have a change in Alzheimer's disease medication (other than study treatment) during the Treatment Period should have an unscheduled visit. a subset of the clinical efficacy assessments [redacted] should be performed prior to the change in medication if the participant alerts the Investigator before the change in medication occurs. In the event that the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments are performed within 30 days after the change in medication, the assessments do not have to be repeated.

Table 4: Brain MRI, ARIA Management, and Follow-Up Telephone Call Schedule During the Core and LTE Treatment Periods

Study Week	Screening (≤ 60 days before Day 1)[1]	Core Treatment Period														Core Treatment Period FU[2]	LTE Treatment Period FU[3]
		1	2	6	10	14	18	22	26	30	42	54	66	78	102/ EOT[4]	UV/MRI for ARIA[5]	118 (or 18 wks after last dose for participants who DCT early from core treatment period)	170 (or 18 wks after last dose for participants who DCT early from LTE treatment period)
Study Day		**1**	**15± 5**	**43 ± 5**	**71 ± 5**	**99 ± 5**	**127 ± 5**	**155 ± 5**	**183 ± 5**	**211 ± 5**	**295 ± 5**	**379 ± 5**	**463 ± 5**	**547 ± 5**	**714 ± 5**		**827± 5**	**1190 ± 5**
Follow-Up Telephone Call[6]			X	X	X	X	X	X	X	X								
Brain MRI	X					X		X		X	X	X	X	X	X	X		X
Aducanumab Serum Concentration[7]								X		X		X				X	X	
[redacted]																		
Physical Examination																X		X
Neurological Examination																X		X
Vital Signs[8]																X		X
[redacted]																		

[1] 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 [redacted] and/or other logistics restrictions due to major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters) and is subject to Sponsor approval. In order to ease participant burden, the Screening Visit may be carried out over 2 separate visits, at the Investigator's discretion.

[2] Participants who complete the Core Treatment Period of the study and do not enter the LTE Treatment Period are to return to the site for a safety FU Visit at Week 118. Participants who discontinue or withdraw from the study early are to have a safety FU Visit 18 weeks after the last dose of study treatment.

[3] Participants who complete the LTE Treatment Period of the study are to return to the site for a safety FU Visit at Week 170. Participants who DCT or withdraw from the LTE early are to have a safety FU Visit 18 weeks after the last dose of study treatment.

[4] Participants who discontinue prematurely are to remain in the study, attend a safety FU Visit 18 weeks after the last dose of study treatment, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 2 Table 3 and Table 4) until the end of the study per the Schedule of Events (it is possible that a clinic visit will occur before the safety FU Visit). If the safety FU Visit will occur within 2 weeks of a scheduled clinic visit, then the safety FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. Participants who withdraw from study prematurely are to return to the site for an EOT Visit; for such participants, efficacy assessments specified at the EOT Visit are not required if the participant discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the sponsor in such cases.

[redacted]

[6] Telephone visit may be performed in person if the participant will be at the study site for clinical assessments.

[redacted]

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

[redacted]

Table 5: Participants Who Discontinue Study Treatment During the Core Treatment and LTE Periods but Remain in the Study

	Post-Treatment Visit Schedule[1] (Core Treatment and LTE Periods)														
Study Week	**12**	**24**	**26**	**48**	**50**	**72**	**78**	**92**	**102** [2]	**112**	**128**	**140**	**152**	**154/ EOT[2]**	**UV for ARIA[3]**
Study Day	**85 ± 5**	**169 ± 5**	**183 ± 5**	**337 ± 5**	**351 ± 5**	**505 ± 5**	**547 ± 5**	**645 ± 5**	**714 ± 5**	**785 ± 5**	**897 ± 5**	**981 ± 5**	**1065 ± 5**	**1078 ± 5**	
Body Weight	X	X		X		X		X	X	X	X	X	X	X	
Hematology, Blood Chemistry, and Urinalysis				X					X					X	
Urine Pregnancy Test[4]		X		X		X	X	X		X	X	X	X		
Physical Examination		X		X		X	X	X	X		X			X	
Neurological Examination		X		X		X			X		X			X	
Vital Signs[5]	X	X		X		X		X	X	X	X	X	X	X	
12-Lead Paper ECG				X					X					X	
Aducanumab Serum Concentration											X			X	X[6]
[redacted]															
Brain MRI									X						X
[redacted]															

	Post-Treatment Visit Schedule[1] (Core Treatment and LTE Periods)														
Study Week	**12**	**24**	**26**	**48**	**50**	**72**	**78**	**92**	**102** [2]	**112**	**128**	**140**	**152**	**154/ EOT[2]**	**UV for ARIA[3]**
Study Day	**85 ± 5**	**169 ± 5**	**183 ± 5**	**337 ± 5**	**351 ± 5**	**505 ± 5**	**547 ± 5**	**645 ± 5**	**714 ± 5**	**785 ± 5**	**897 ± 5**	**981 ± 5**	**1065 ± 5**	**1078 ± 5**	
[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														

[1] Participants who discontinue study treatment prematurely are to remain in the study, attend a safety FU Visit 18 weeks after the last dose of study treatment as listed in Table 2 Table 3 and Table 4 and immediately continue protocol-required tests and assessments at a subset of the clinic visits (Table 5) until the end of the study per the Schedule of Events (it is possible that a clinic visit will occur before the safety FU Visit). If the safety FU Visit will occur within 2 weeks of a scheduled clinic visit, then the safety FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit.

[2] Participants who withdraw from study prematurely are to return to the site for an EOT Visit; for such participants, efficacy assessments specified at the EOT Visit are not required if the participant discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

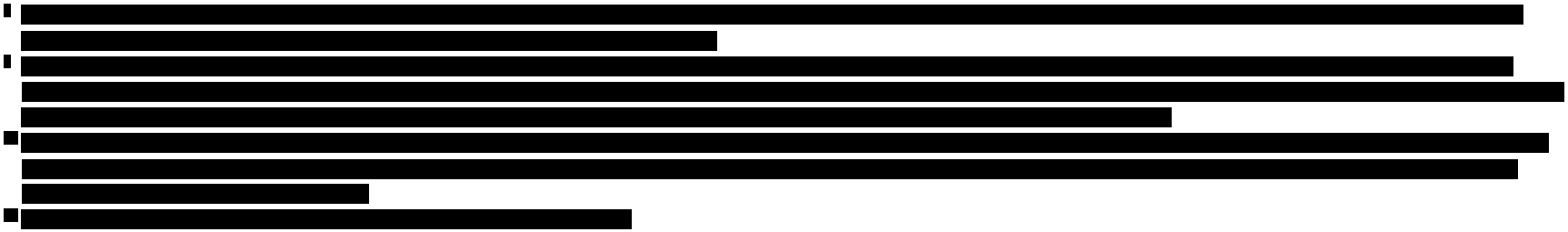
[redacted]

[4] Required only if last dose of study treatment was less than 24 weeks before the clinic visit.

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

[6] One sample will be collected within ± 2 days of the MRI visit. Exact collection date and time will be captured for all [redacted] on a specified CRF.

[7] Sample may be collected within ± 2 days of the MRI visit.



4.3. Additional Information

4.3.1. Site Staff

A minimum of 2 separate HCPs are required for this study:

1. A treating HCP (the Investigator may serve as a treating HCP) who is responsible for the following:
   - [redacted]
   - Management of routine neurological care of the participant.
   - Assessment (including assignment of causality) and treatment of AEs.
   - Review of selected hematology and blood chemistry results from the central laboratory to assess if the participant'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 Investigator of the site) who is responsible for administering the [redacted], and C-SSRS.

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 participant should have the same rating HCP perform the participant'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. Please note that the treating HCPs and rating HCPs are NOT interchangeable at the participant level.

A pharmacist (or authorized designee) will be responsible for the storage, distribution, preparation, and accountability of study treatment. The pharmacist will also be responsible for maintaining the pharmacy record.

For further details about test administration and roles and responsibilities of HCPs and study personnel, please consult the Study Reference Manual.

5. INTRODUCTION

Alzheimer's disease is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer's Disease International estimates that as of 2016, there were 47 million people living with dementia worldwide, and that this figure will increase to 131 million by 2050 [Alzheimer's Disease International 2016]. Globally, the greatest increase in dementia numbers through 2050 is expected to occur in countries in which the population is aging at an unprecedented rate [Alzheimer's Disease International 2015].

Clinically, Alzheimer's disease 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, Alzheimer's disease is defined by the presence in the brain of extracellular neuritic plaques containing 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].

Biomarker [Jack 2010], clinicopathologic [Delacourte 2002], and cohort [Amieva 2008] studies suggest that the disease process commences 10 to 20 years prior to the onset of symptoms, starting with the deposition of neocortical Aβ plaques and mesial temporal tau-containing NFTs followed years later by neocortical tau-containing NFTs, which best correlate with cognitive status and neuronal death [Nelson 2009]. As the disease progresses, cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Thus, it is hypothesized that removal of Aβ plaques and subsequent alteration of tau pathology may slow cognitive decline.

Based on this understanding of the underlying disease process, with onset decades before symptom onset, the scientific community has focused on developing treatments for patients in the earlier stages of the Alzheimer's disease continuum. This shift in focus was made possible in part by the development of diagnostic criteria for the diagnosis of earlier stages of Alzheimer's disease in clinical research studies published by the NIA-AA [Albert 2011; McKhann 2011; Sperling 2011] and by an IWG [Dubois 2010]. These criteria address the need to define the clinical diagnosis of the predementia phases of Alzheimer's disease (e.g., MCI due to Alzheimer's disease) and to improve specificity of diagnosis by incorporating biomarkers of Alzheimer's disease pathology into the diagnostic process. In 2014, IWG criteria were updated (IWG-2) [Dubois 2014]. The improved diagnostic framework, combined with the ability to confirm underlying disease pathology by use of CSF biomarkers or Aβ PET, enabled more accurate diagnosis of Alzheimer's disease in predementia participants. Most recently, in 2018, the NIA-AA Research Framework for Alzheimer's disease has further evolved the thinking on diagnosis of Alzheimer's disease, recommending that Alzheimer's disease is defined by its underlying pathologic processes that can be documented by postmortem examination or in vivo by biomarkers [Jack 2018] supporting the use of some imaging and CSF biomarkers (e.g., Aβ PET) as valid proxies for neuropathologic changes of Alzheimer's disease.

5.1. Previous Experience With Aducanumab

5.1.1. Nonclinical Experience

Aducanumab (BIIB037) is a human anti-Aβ IgG1 monoclonal antibody derived from a de-identified library of B cells collected from healthy elderly subjects with no signs of cognitive impairment and cognitively impaired elderly subjects with unusually slow cognitive decline.

In vitro characterization studies have shown that aducanumab binds with high affinity and selectivity to aggregated forms of Aβ, including soluble Aβ oligomers and protofibrils and deposited fibrillar Aβ. Additionally, the antibody binds amyloid plaques in human Alzheimer's disease brain sections ex vivo. Data exist showing that both soluble oligomers and Aβ plaques are neurotoxic-[Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008].

In vivo characterization of aducanumab was conducted in Tg2576 transgenic mice, which overexpress human amyloid precursor protein and accumulate Aβ in the brain in an age-dependent manner. Binding of aducanumab to amyloid plaques in vivo (target engagement) was demonstrated after single systemic administration of the antibody in Tg2576 mice and was evidenced by immunohistochemistry of brain sections from the dosed animals after euthanasia. Target engagement was shown to be dose-dependent, i.e., a direct correlation was established between the brain drug levels and the amount of antibody decorating the amyloid plaques.

Efficacy of aducanumab was evaluated following chronic treatment of Tg2576 mice with ^{ch}aducanumab (a murine chimeric version of aducanumab that retains the antigen-binding fragment variable regions and was used for chronic dosing studies in mice) and resulted in a statistically significant and dose-dependent reduction in brain Aβ load. A minimum efficacious dose of 3 mg/kg was determined. Immunohistochemical data suggest that binding of ^{ch}aducanumab to parenchymal Aβ plaques might trigger the recruitment of microglial cells, which might result in enhanced microglia-mediated phagocytosis of the plaques.

The nonclinical safety assessment of aducanumab was conducted in accordance with ICH guidelines for a biotechnology-derived pharmaceutical intended for chronic administration. Aducanumab (and ch12F6A, murine chimeric analog of aducanumab, in aged Tg2576 mice only) was well tolerated in the repeat-dose toxicology studies. No target organs for toxicity were identified for aducanumab or ch12F6A. In fertility studies, embryo-fetal development, and pre- and postnatal development, there were no adverse toxicity findings up to the highest weekly dose tested. A tissue cross-reactivity study and whole blood hemolysis and plasma flocculation assays demonstrated expected tissue binding and no evidence of significant hemolysis.

See the updated IB (Version 13.0) for detailed information on nonclinical studies.

5.1.2. Clinical Experience

The aducanumab clinical development program comprises 7 clinical studies, including 1 completed study in healthy volunteers and 6 completed or terminated studies in subjects with Alzheimer's disease. A summary of the clinical experience accumulated so far is provided below.

Study 221AD101

This was a Phase 1, randomized, double-blind, placebo-controlled study of aducanumab in participants with mild or moderate Alzheimer's disease. 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 IV infusions. The secondary objectives were to assess the PK and immunogenicity of aducanumab after single-dose administration.

Study 221AD103

This was a Phase 1b study comprising a randomized, double-blind, placebo-controlled design in participants with prodromal or mild Alzheimer's disease of 1 year in duration followed by an LTE in which all participants received aducanumab in an open-label fashion (yet dose-blinded). The study was designed to assess the safety, PK, and PD of aducanumab in participants with prodromal Alzheimer's disease or mild Alzheimer's disease dementia with brain Aβ pathology confirmed by ^{18}F-florbetapir (Amyvid®) PET imaging. The main PD assessment (secondary endpoint) was the effect of aducanumab on brain Aβ levels as measured by PET and quantified by a composite SUVR. [redacted] At Screening, all participants were at the prodromal stage of Alzheimer's disease ([redacted] and a global CDR score of 0.5 or 1.0) or in stages of mild dementia ([redacted] and global CDR score between 0.5 and 1.0). Doses investigated in the placebo-controlled period included 1, 3, 6, and 10 mg/kg administered Q4W as a fixed dose, and 10 mg/kg administered after a titration period of 44 weeks.

Placebo-Controlled Period Results

Results from the 1-year placebo-controlled period showed that treatment with aducanumab resulted in a statistically significant, dose-dependent reduction in brain Aβ PET composite SUVR as compared with placebo at Week 26, and a further statistically significant, dose-dependent reduction at Week 54. In addition, a dose-dependent reduction of clinical decline was observed in the fixed-dose aducanumab groups, as well as the titration group, with a statistically significant treatment effect observed for both aducanumab 10 mg/kg fixed-dose and titration on the [redacted] and for 10 mg/kg fixed dosing on the [redacted], as compared with placebo. The impact of aducanumab on Aβ PET reduction was already evident at 26 weeks, while a difference was only observed on clinical measures at 1 year.

Reduction in brain Aβ appears to be tightly associated with dose; the titration arm results are in line with the fixed-dose results based on the expected average dose in the titration arm (2.9 and 5.3 mg/kg at 6 and 12 months, respectively), with the point estimate at Week 26 (-0.047) between that in the 1 and 3 mg/kg fixed-dose groups, and the point estimate at Week 54 (-0.171) between that in the 3 and 6 mg/kg fixed-dose groups. The results demonstrate engagement of aducanumab with amyloid plaques and a PD effect of dose- and time-dependent amyloid reduction.

Safety analyses showed that aducanumab had an acceptable safety profile when given Q4W at doses up to 10 mg/kg for more than 5 years in Study 221AD103. The incidence and nature of fatal SAEs were consistent with underlying Alzheimer's disease and associated comorbidities. No notable differences were observed between aducanumab and placebo in the overall incidence

of AEs or SAEs, except for ARIA events. The incidence of ARIA events (both ARIA-E and ARIA-H) appeared to be related to aducanumab dose and [redacted]; the ARIA events were typically asymptomatic, monitorable, and clinically manageable.

Participants with ARIA events who met certain criteria (for all clinical studies with aducanumab, including Study 221AD103) were required to temporarily suspend dosing with aducanumab. Therefore, certain participants with ARIA events experienced a transient interruption in dosing during prior clinical studies of aducanumab. In addition, only a small proportion of participants experienced more than 1 ARIA-E event during treatment.

Long-Term Extension Period Results

Data from the LTE of Study 221AD103 also provide insights relevant for the study population targeted in the present study (Study 221AD304). In the LTE period, those participants who started on active treatment at the beginning of the placebo-controlled period continued treatment (at the same dose as in the placebo-controlled period, except for the 1 mg/kg cohort who were switched to 3 mg/kg), while participants from the placebo arms initiated dosing with aducanumab. The main findings in Study 221AD103 during the LTE period regarding efficacy and safety for the high-dose groups (fixed-dose regimen of 10 mg/kg and titration to 10 mg/kg, which are the 2 relevant groups regarding the target dose in Study 221AD304) were the following:

1. [redacted]
    - At Week 222, the adjusted mean changes from baseline in the 10 mg/kg fixed-dose and 10 mg/kg titration groups (3.83 and 3.68, respectively) were numerically smaller than the adjusted mean changes in the 1, 3, and 6 mg/kg groups that continued dosing (range 5.48 to 8.43) and the group that switched from placebo to aducanumab after 1 year (6.15).
2. The safety profile of aducanumab in the LTE was similar to that seen in the placebo-controlled period:
    - Participants who began treatment with aducanumab during the placebo-controlled period had a low incidence of ARIA-E in the LTE (5% for 10 mg/kg fixed dose and 17% for titration to 10 mg/kg).

The incidence of ARIA-E in participants who began treatment with aducanumab in the LTE (22%) was similar to the incidence in participants who began treatment in the placebo-controlled period (24%).

<u>Studies 221AD301 and 221AD302</u>

These were large Phase 3 randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy, PK, and safety of aducanumab in participants with early stages of Alzheimer's disease. Refer to updated IB for details for re-analysis of efficacy, PK, and safety. Highlights of efficacy re-analysis are provided in Section 5.2.

Refer to the updated IB (Version 13.0) for further data from Studies 221AD103, 221AD301, and 221AD302, as well as from other early phase aducanumab clinical studies.

5.2. Study Rationale

This open-label, single-arm clinical study is being conducted to assess the long-term safety and efficacy of aducanumab in participants with Alzheimer's disease who were active in aducanumab clinical studies (Study 221AD103 [PRIME], Study 221AD205 [EVOLVE], Study 221AD301 [ENGAGE], and Study 221AD302 [EMERGE]), from now on named "feeder studies," at the time of their early termination as of 21 March 2019. On that date, Biogen announced the discontinuation of the Phase 3 aducanumab clinical studies, based on results from a preplanned futility analysis; discontinuation of the other ongoing studies (221AD103 and 221AD205) was announced and implemented at the same time. The present study (221AD304) is being undertaken based on efficacy findings from additional analyses of the 2 Phase 3 studies (results summarized below). In these new analyses, Study 221AD302 was statistically significant on the prespecified primary endpoint (p=0.01).

Background: Interim Futility Analysis

The 221AD301 and 221AD302 studies were 2 large Phase 3 randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of aducanumab in participants with early Alzheimer's disease (MCI due to Alzheimer's disease and mild Alzheimer's dementia). The duration was planned for 18 months of placebo-controlled period and up to 5 years of LTE. The preplanned futility analysis was performed on data collected as of 26 December 2018, when approximately 50% of participants had the opportunity to complete the Week 78 Visit (57% [954 participants] from Study 221AD301 and 49% [803 participants] from Study 221AD302).

Results based on data from these participants were provided to the IDMC who reviewed the data and confirmed that the prespecified futility criteria were met. Biogen reviewed the results and concurred with the IDMC and publicly announced the decision to discontinue the Phase 3 program and the other ongoing clinical studies on 21 March 2019.

On 21 March 2019, Biogen announced the early termination of the 2 Phase 3 studies (Studies 221AD301 and 221AD302) based on results of a prespecified interim futility analysis. No participant was dosed after 20 March 2019.

Analyses Conducted Postfutility Announcement

Subsequent to these events, further analyses on the Phase 3 studies were conducted, using data from all randomized and dosed participants collected through 01 April 2019 and with data after 20 March 2019 censored for efficacy analysis. These data comprised 63% of participants from both the 221AD301 and 221AD302 studies (66% from 221AD301 and 60% from 221AD302) who had the opportunity to complete the placebo-controlled period of the study. In both the 221AD301 and 221AD302 studies, 87% of participants had the opportunity to reach Week 50 and 100% with opportunity to complete Week 26. The results from this larger dataset differed markedly from the futility results:

- In Study 221AD302, treatment with the aducanumab high dose regimen significantly reduced clinical decline compared with placebo on the primary endpoint, change from baseline to Week 78 on the CDR-SB (difference versus placebo -0.40 [-23%]; p=0.010). In addition, 2 of the 3 secondary endpoints, change from baseline to Week 78 on ADAS-Cog 13 (difference with placebo -1.395 [-27%]; p=0.0098) and ADCS-ADL-MCI (difference versus placebo 1.7 [-40%]; p=0.0009) were also positive, while the MMSE showed a positive trend but did not reach significance (difference with placebo 0.5 [-15%]; p=0.062). In the low-dose group, a nonsignificant numeric effect was observed for aducanumab-treated participants versus placebo.
- Study 221AD301 did not meet the primary endpoint in the high-dose arm.
- [redacted] consistent with findings in the Phase 1b study (Study 221AD103, PRIME).

Given the above findings, the Sponsor undertook further analyses to understand the differences in the results of the 2 Phase 3 studies after consultation with external consultants and the FDA. Considering the different timing between studies in the enrollment and the implementation of 2 critical study protocol amendments, a central hypothesis for further analyses is that differences in dose/exposure contributed to the disparity in the efficacy results. The Sponsor's exploration of the dose-exposure relationship identified a heterogeneity in exposure to high dose aducanumab between the studies. Participants in Study 221AD301 who received high doses/exposure were found to have outcomes similar to the overall Study 221AD302 results. This finding was supported by multiple analyses directed at studying the multidimensional aspects of dose-exposure relationship. Additional factors such as baseline characteristics and ARIA were also considered, and they were not found to meaningfully contribute to the differences between studies.

Together, these results led the Sponsor to determine that: (1) the conclusions based on the results of the futility analysis in March 2019 (based on a smaller, earlier dataset with less exposure to high dose aducanumab) were incorrect; (2) in Study 221AD302, based on the larger dataset, a statistically significant reduction in clinical decline was observed across multiple endpoints for aducanumab 10 mg/kg as compared with placebo; and (3) the differences between Study 221AD302 and Study 221AD301 could mostly be accounted for by the greater exposure to

10 mg/kg in Study 221AD302. These conclusions were shared with the FDA on 21 October 2019 at a Type C meeting.

Given the significance of these results, the Sponsor has reinitiated the evaluation of aducanumab in this open-label, single-arm clinical trial, to evaluate the long-term safety and efficacy of the drug in participants previously enrolled in the studies that were ongoing at the time of the futility announcement (the 2 Phase 3 studies, the LTE study for the Phase 1b study [Study 221AD103], and the safety study [Study 221AD205]). This study will also assess the degree to which [redacted] and clinical measures of the treatment effect of aducanumab are maintained following a sustained interruption in dosing.

Final database lock for both pivotal trials was only achieved in close temporal proximity to the finalization of this study protocol. Analyses of the final dataset for the primary and secondary efficacy endpoints were conducted after the final database lock and the results of these final analyses do not differ overall from the larger dataset results discussed above. The efficacy results for the 2 studies are presented in Table 6 and Table 7.

Refer to the updated IB (Version 13.0) for further efficacy results of the Phase 3 studies (221AD301 and 221AD302).

Table 6: Final Analysis of Primary and Secondary Endpoints From EMERGE (Study 221AD302)

		Difference vs. placebo (%) p-value	
	Placebo decline (n=548)	**Low dose (n=543)**	**High dose (n=547)**
CDR-SB	1.74	-0.26 (-15%) 0.0901	-0.39 (-22%) 0.0120
MMSE	-3.3	-0.1 (3%) 0.7578	0.6 (-18%) 0.0493
ADAS-Cog 13	5.162	-0.701 (-14%) 0.1962	-1.400 (-27%) 0.0097
ADCS-ADL-MCI	-4.3	0.7 (-16%) 0.1515	1.7 (-40%) 0.0006

Table 7: Final Analysis of Primary and Secondary Endpoints From ENGAGE (Study 221AD301)

		Difference vs. placebo (%) p-value	
	Placebo decline (n=545)	**Low dose (n=547)**	**High dose (n=555)**
CDR-SB	1.56	-0.18 (-12%) 0.2250	0.03 (2%) 0.8330
MMSE	-3.5	0.2 (-6%) 0.4795	-0.1 (3%) 0.8106
ADAS-Cog 13	5.140	-0.583 (-11%) 0.2536	-0.588 (-11%) 0.2578
ADCS-ADL-MCI	-3.8	0.7 (-18%) 0.1225	0.7 (-18%) 0.1506

5.3. Rationale for Dose and Schedule Selection

The dose selected for this study (10 mg/kg IV Q4W after a 24-week titration period) is based on the findings that the high-dose arm in Study 221AD302 met its primary efficacy endpoint, which was a statistically significant difference on clinical decline as measured by the [redacted] at 18 months compared to matching placebo. This finding was supported by dose-dependent reductions in [redacted] and in [redacted], both of which were statistically significant. These efficacy findings were supported by evidence from the subset of 10 mg/kg-treated participants in the Phase 1b, Study 221AD103, and several post hoc analyses in Study 221AD301 evaluating dose-response. Safety and tolerability for this 10 mg/kg dosing regimen is consistent across aducanumab clinical studies and is being deemed acceptable after review of Study 221AD301 and 221AD302 safety data.

5.3.1. Dosing Scheme

Doses will be administered approximately 4 weeks apart, over approximately 100 weeks (a total of 26 doses) during the Core Treatment Period and 52 weeks during the LTE Treatment Period (an additional 13 doses). Participants will receive aducanumab 10 mg/kg under a titration regimen of 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.

5.4. Benefit-Risk Assessment

There are currently no available therapies that modify the clinical course of Alzheimer's disease. Analyses of data collected through the end of the study (Study 221AD301 database lock on 15 November 2019 and Study 221AD302 database lock on 13 November 2019, with efficacy data after 20 March 2019 censored) in the 2 Phase 3 aducanumab clinical studies showed that, in Study 221AD302, treatment with aducanumab significantly reduced clinical decline in patients with early Alzheimer's disease as measured by the prespecified primary endpoint (CDR-SB) and by the 3 secondary endpoints (MMSE, ADCS-ADL-MCI, and ADAS-Cog 13) in the high-dose group. In addition, Study 221AD301 contained supportive data, based on post-hoc analyses of subsets of participants who received sufficient exposure to the highest dose (10 mg/kg) of aducanumab. Additionally, data from the Study 221AD103 of aducanumab, with up to 4 years of FU data on treatment, suggested a continued benefit on the rate of clinical decline with continued aducanumab treatment (changes from baseline in the groups that received either 10 mg/kg fixed dose or 10 mg/kg titration since the beginning of the study were numerically smaller than those in the groups that switched from placebo to aducanumab).

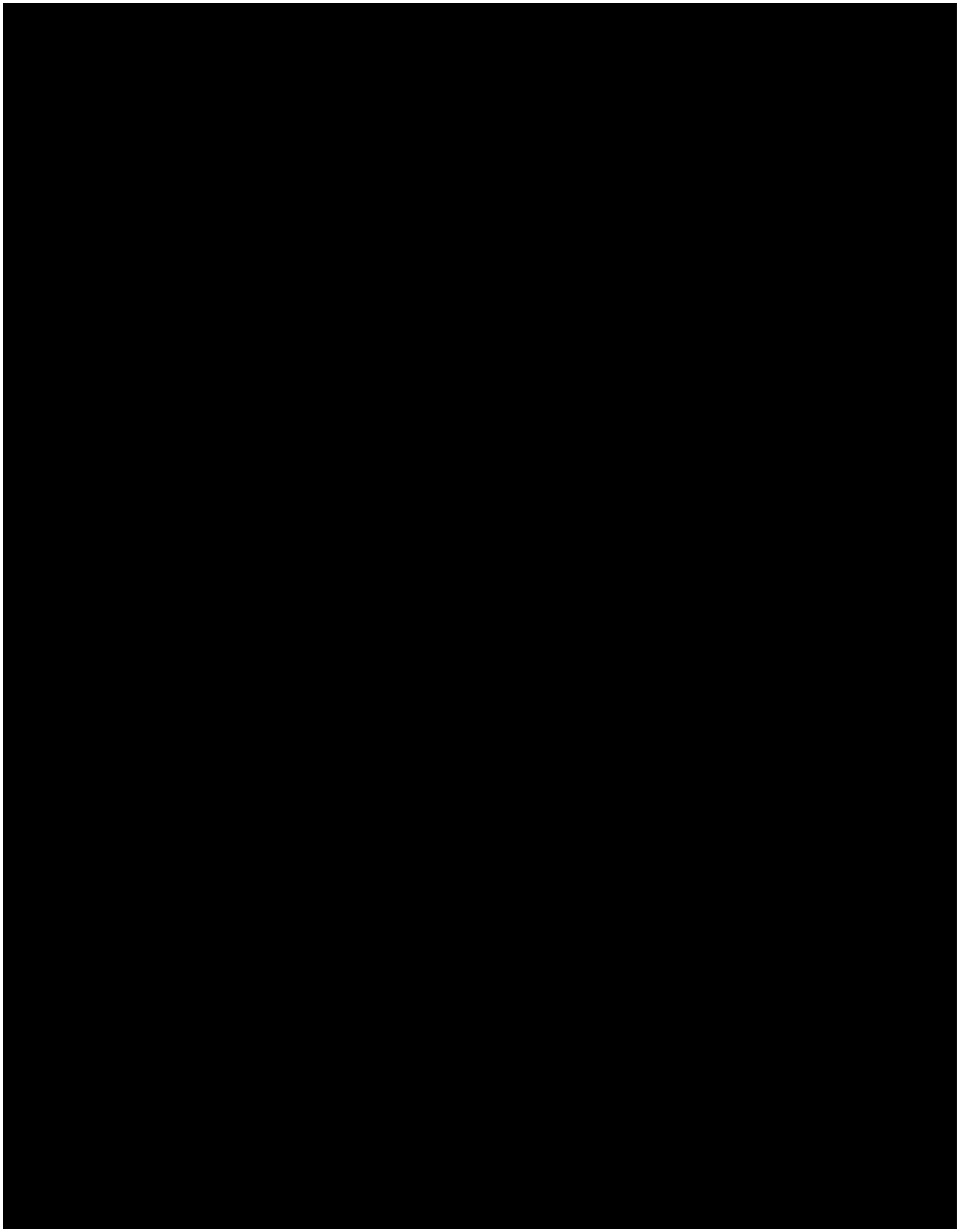
As of 04 May 2020, a total of 3078 participants have been exposed to aducanumab across completed or terminated clinical studies (including 3050 participants with Alzheimer's disease and 28 healthy volunteers). Of those, 2757 participants were enrolled in the Phase 3, placebo-controlled studies (Studies 221AD301 and 221AD302) for approximately 3983.5 person-years of exposure and totaling 4736.1 person-years of FU. The most frequent AE, among participants from Studies 221AD301 and 221AD302 with a target dose of 10 mg/kg, was ARIA-E (35.4%). The majority of participants with ARIA-E were asymptomatic, and participants with symptomatic ARIA-E had symptoms that were predominantly mild or moderate in clinical severity. Symptoms reported during ARIA-E episodes included headache, confusional state, dizziness, fatigue, nausea, or rarely seizures, including prolonged seizures.. In the majority

of participants with ARIA-E, the first ARIA-E events were documented to have fully resolved (800 of 815 participants [98.2%]). In the clinical studies, some participants with an initial episode of ARIA-E that resolved subsequently experienced a second, later episode of ARIA-E. This was referred to as "recurrent ARIA-E" in the clinical studies. Recurrent ARIA-E events were less likely to be symptomatic than first ARIA-E events (recurrent: 13.1% versus first: 23.6%). As with first ARIA-E events, in nearly all participants with second ARIA-E events, the events resolved during the study (231 of the 236 participants [97.9%] with second ARIA-E), and in the majority of participants with resolved second events, ARIA-E resolved within 12 weeks. Other frequent AEs, among participants from Studies 221AD301 and 221AD302 with a target dose of 10 mg/kg, included headache (20.5%), ARIA-H micro-hemorrhage (19.1%), fall (15.0%), nasopharyngitis (14.5%), and ARIA-H superficial siderosis (14.6%). Similar to ARIA-E, the majority of participants with ARIA-H micro-hemorrhage and ARIA-H superficial siderosis were asymptomatic. Notably, transient treatment interruption has been routinely implemented in all aducanumab studies for participants with ARIA events meeting certain criteria. Resumption of dosing after this treatment-free period was not associated with an increased incidence of AEs or immunogenicity.

The benefit-risk profile of aducanumab is considered positive for investigational use in both treatment-naïve participants as well as in previously treated participants who have had a treatment-free period.

6. STUDY OBJECTIVES AND ENDPOINTS

Core Primary Objective	Core Primary Endpoints
To evaluate the safety and tolerability of aducanumab over 100 weeks of treatment after a wash-out period imposed by discontinuation of feeder studies in participants who had previously received aducanumab (i.e., previously treated participants) or who had previously received placebo (i.e., treatment-naïve participants)	Incidence of AEs, SAEs, ARIA, and immunogenicity with over 100 weeks of treatment and/or re-exposure to aducanumab. Safety and tolerability parameters include the following: • Incidence of all AEs, AEs leading to treatment discontinuation or study withdrawal, and all SAEs • Incidence of ARIA-E and ARIA-H • Incidence of ADAs in serum
[redacted]	



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

7. STUDY DESIGN

7.1. Study Overview

Study 221AD304 is an open-label, multicenter, longitudinal, single-arm, global Phase 3b study in participants with Alzheimer's disease who had participated in feeder studies. It is calculated that up to approximately 2400 participants (see Section 16.7) will be enrolled across approximately 350 sites globally. The primary study objective is to evaluate the long-term safety and tolerability of a monthly dose (10 mg/kg) of aducanumab after a gap period imposed by discontinuation of feeder studies.

After a Screening Period of approximately 8 weeks, participants who meet the eligibility criteria will receive open-label treatment. During the Core Treatment Period, participants will receive IV infusions of aducanumab approximately Q4W for a duration of 100 weeks (a total of 26 doses). The aducanumab dosing regimen will be 10 mg/kg following this titration: 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. Eligible participants will then enter the LTE treatment period and continue dosing on 10 mg/kg aducanumab Q4W for an additional 52 weeks (a total of 152 weeks of continuous treatment). The EOT Visit will occur at Week 154. Participants will have a safety FU Visit 18 weeks after their last dose of study treatment.

See Section 5.3.1 for details of dosing scheme.

Individual dose adjustments may also be implemented in participants who develop ARIA. See Section 7.2.1.

7.2. Study Specifics

7.2.1. Dose Suspension or Discontinuation for ARIA Events

Discontinuation of Dosing for a Given Participant

The central MRI reading center will report incident events of ARIA-E and ARIA-H to both the Sponsor and the Investigator within a specified time after observing the finding on MRI per the imaging manual procedures. All events of ARIA will be reviewed by the Sponsor and the Investigator; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the radiographic severity scoring on the MRI report provided by the central reader. The Investigator must review the MRI report prior to next dosing. Guidelines on the management and disposition of ARIA-E and ARIA-H events (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. After each ARIA event, [redacted] will be collected at the time of the first unscheduled visit following the event. 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 Events

Table 8: Disposition of ARIA-E Events

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 participant may resume dosing at the same dose.	
Mild	Suspend dosing. Once ARIA-E and clinical symptoms resolve, the participant may resume dosing at the same dose.		
Moderate			
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 participant 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.

- Participants who develop **mild ARIA-E, per central MRI reading, with no clinical symptoms** during the episode of ARIA-E, may continue in the study at their current dose. Participants should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and [redacted] until the ARIA-E has resolved per the centrally read MRI.
- Participants who develop **moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms** during the episode of ARIA-E will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and [redacted] until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E resolves and the participant remains asymptomatic (in the Investigator's opinion), the participant may resume treatment at the same dose.
- Participants who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by clinical symptoms** during the episode of ARIA-E will temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and [redacted] until the ARIA-E has resolved per the centrally read MRI. If the ARIA-E

resolves and the clinical symptoms resolve (in the Investigator's opinion), the participant may resume treatment at the same dose.

- Participants who develop **mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except "other medically important event") clinical symptoms** related to the current episode of ARIA-E will permanently DCT but remain in the study. Participants should complete a safety FU Visit 18 weeks after the last dose of study treatment, protocol-required tests and assessments at a subset of the clinic visits (see Table 5), and, in addition, have an unscheduled visit for an MRI and [redacted] 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 (Micro-hemorrhage)

In this study, new incident micro-hemorrhages are defined as micro-hemorrhages that start after aducanumab infusion per this study (221AD304) and do not include micro-hemorrhages seen on the baseline MRI done for this study.

Table 9: Disposition of ARIA-H (Micro-hemorrhage) Events

<table>
<tr><th rowspan="3">Clinical Symptom Severity</th><th colspan="3">New Incident Micro-hemorrhages[1] (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><th>≥ 1 and ≤ 4</th><th>≥ 5 and ≤ 9</th><th>≥ 10</th></tr>
<tr><td>Asymptomatic</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing. Once ARIA-H is stable, the participant 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 participant 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 incidence of micro-hemorrhages = new micro-hemorrhages that start after aducanumab infusion per this study (221AD304), does not include micro-hemorrhages seen on the baseline MRI done for this study.

[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 participant 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 (Micro-hemorrhage)

- Participants who develop a **≥ 1 and ≤ 4 new incident micro-hemorrhage(s) [mild]** at any time during the study may continue treatment at the current dose. Participants should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and [redacted] until the ARIA-H micro-hemorrhage is confirmed stable per the centrally read MRI.
  Micro-hemorrhages 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.

- Participants who develop **≥ 5 and ≤ 9 new incident micro-hemorrhages (moderate)** 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 [redacted] until the micro-hemorrhage is confirmed as stable per the centrally read MRI. Once the micro-hemorrhage is deemed stable, participants may resume treatment at the same dose.
- Participants who develop **≥ 10 new incident micro-hemorrhages (severe)** at any time during the study will permanently DCT but remain in the study. Participants should complete a safety FU Visit 18 weeks after the last dose of study treatment, protocol-required tests and assessments at a subset of the clinic visits (see Table 5), and, in addition, have an unscheduled visit for an MRI and [redacted] until the micro-hemorrhages are deemed stable per centrally read MRI.

Symptomatic ARIA-H (Micro-hemorrhage)

- Participants who develop **≤ 9 new incident micro-hemorrhages (mild or moderate) and associated 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 [redacted] until the ARIA-H micro-hemorrhage(s) is confirmed stable per the centrally read MRI. Once ARIA-H (micro-hemorrhage) is deemed stable and the clinical symptoms have resolved (in the Investigator's opinion), the participant may resume treatment at the same dose.
- Participants who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with micro-hemorrhage(s) (independent of the radiographic severity of the event)** will permanently DCT but remain in the study. Participants should complete a safety FU Visit 18 weeks after the last dose of study treatment, protocol-required tests and assessments at a subset of the clinic visits (see Table 5), and, in addition, have an unscheduled visit for an MRI and [redacted] until the micro-hemorrhage(s) is confirmed stable per centrally read MRI.
- Participants who develop **≥ 10 new incident micro-hemorrhages (severe)**, regardless of the presence of clinical symptoms, during the study, will permanently DCT but remain in the study. Participants should complete a safety FU Visit 18 weeks after the last dose of study treatment, protocol-required tests and assessments at a subset of the clinic visits (see Table 5), and, in addition, have an unscheduled visit for an MRI and [redacted] until the micro-hemorrhages 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)

In this study, for participants previously treated with aducanumab, new incident focal areas of superficial siderosis are defined as new incident focal areas of superficial siderosis that occur on treatment and do not include focal areas of superficial siderosis seen on baseline MRI.

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

<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 participant 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 participant 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 participant 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)

- Participants who develop a **single new incident focal area of hemosiderosis** (**also referred to as superficial siderosis) [mild]** at any time during the study may continue treatment at the current dose, but must have an unscheduled visit for an MRI and [redacted] until the superficial siderosis is confirmed as stable per the centrally read MRI. 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.

- Participants who develop **2 new 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 [redacted] until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI. Once the superficial siderosis is deemed stable, the participants may resume treatment at the same dose.
- Participants who develop **> 2 new focal areas of hemosiderosis (superficial siderosis) [severe]** at any time during the study must permanently DCT but remain in the study. Participants should complete a safety FU Visit 18 weeks after the last dose of study treatment, protocol-required tests and assessments at a subset of the clinic visits (see Table 5), and, in addition, have an unscheduled visit for an MRI and [redacted] until the ARIA-H (superficial siderosis) is confirmed as stable per the centrally read MRI.

Symptomatic ARIA-H (Superficial Siderosis)

- Participants who develop **≤ 2 new focal areas of superficial siderosis (mild or moderate) associated with 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 [redacted] until the ARIA-H superficial siderosis is confirmed stable per the centrally read MRI. 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 participants may resume treatment at the same dose.
- Participants who experience **serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with ARIA-H (superficial siderosis)** will permanently DCT but remain in the study. Participants should complete a safety FU Visit 18 weeks after the last dose of study treatment, protocol-required tests and assessments at a subset of the clinic visits (see Table 5), and, in addition, have an unscheduled visit for an MRI and [redacted] until the superficial siderosis is confirmed stable per centrally read MRI.
- Participants who develop **>2 new focal areas of superficial siderosis (severe)**, regardless of the presence of clinical symptoms, will permanently DCT but remain in the study. Participants should complete a safety FU Visit 18 weeks after the last dose of study treatment, protocol-required tests and assessments at a subset of the clinic visits (see Table 5), and, in addition, have an unscheduled visit for an MRI and [redacted] 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 (Macro-hemorrhage)

Participants who develop any new incident of macro-hemorrhage (defined as > 1 cm in diameter on T2* MRI sequence), regardless of the presence of clinical symptoms, will permanently DCT, but should remain in the study. Participants should complete a safety FU Visit 18 weeks after the last dose of study treatment, protocol-required tests and assessments at a subset of the clinic visits (see Table 5) and, in addition, have an unscheduled visit for MRI and [redacted], or as clinically indicated, until the macro-hemorrhage is confirmed stable per centrally read MRI. A macro-hemorrhage 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.

7.2.1.5. Coincident ARIA-H and ARIA-E Events

Participants 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 participant must be asymptomatic. For example, if a participant experiences radiographically mild ARIA-H (1 to 4 micro-hemorrhages) coincident with radiographically moderate ARIA-E, the participant will temporarily suspend treatment per the ARIA-E guidelines summarized in Table 8. In addition, unscheduled visits should occur as described in Section 7.2.1.1, Section 7.2.1.2, Section 7.2.1.3, and 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 [redacted] will be performed 2 weeks (± 5 days) after the second administration of the restarted dose. This visit will also include a physical and neurological examination and collection of vital signs.

In addition, if treatment was suspended during the dose titration prior to the participant reaching the 10 mg/kg dose, an MRI and [redacted] will be performed 2 weeks (± 5 days) after every second dose until completion of the titration period with a final MRI after the second dose at 10 mg/kg, not counting unscheduled MRI visits for monitoring of ongoing 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

Participants who suspend treatment due to ARIA may resume treatment at the same dose if they meet the criteria as described in Section 7.2.1.1, Section 7.2.1.2, Section 7.2.1.3, Section 7.2.1.4, and Section 7.2.1.5. Participants who suspend and then resume dosing after having already reached 10 mg/kg are to continue dosing at that dose. However, if dosing is suspended prior to a participant reaching 10 mg/kg, the participant (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 the titration schedule, as outlined in the right column of Table 11.

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

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
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 participant has more than one occurrence of ARIA (i.e., a second episode of ARIA-E or new incident ARIA-H micro-hemorrhages or superficial siderosis), after the ARIA resolves or stabilizes, the participant 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 11 apply if the participant is still in the titration period. If a participant resumes treatment after ARIA, an MRI and [redacted] 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 (if applicable). MRIs will otherwise be performed as indicated in the Schedule of Events (Section 4.2).

7.2.2. Infusion Interruption

If any mild or moderate symptoms occur during a treatment infusion, the infusion should be slowed or interrupted, and supportive treatment should be instituted at the discretion of the Investigator. After resolution of symptoms, if the infusion had been slowed, the original infusion rate may be resumed; if the infusion had been interrupted, the infusion may be restarted at a rate that does not exceed the original infusion rate. An infusion must be discontinued if not completed within 3 hours.

Refer to the DHA for infusion rate information.

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

Severity of events is described in Section 15.2.3.

7.3. Overall Study Duration and Follow-Up

The study will consist of Screening, Core Treatment, LTE Treatment, and FU periods. A schematic of the study is presented in Figure 1.

Study duration for each participant will be approximately 178 weeks: an approximately 8-week Screening Period, a 100-week Core Treatment Period, a 52-week LTE treatment period, and a safety FU Visit 18 weeks after the last dose of study treatment.

Participants will have approximately 59 scheduled clinic visits during the study. All visits should be performed ± 5 days from the nominal visit day.

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (Screening Visits may be carried out over 2 separate visits, at the Investigator's discretion). 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 [redacted] and/or other logistics restrictions due to major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters) and is subject to Sponsor approval.
- 39 outpatient dosing visits.
- 8 telephone safety FU contacts approximately 2 weeks after each of the first 8 doses.
- 7 visits for clinical assessments, including Screening and FU at Week 170 (or 18 weeks after the last dose of study treatment for participants who DCT early).
- 10 visits for brain MRI.
- [redacted]

Participants who have a change in Alzheimer's disease medication (other than study treatment) during either the Core or LTE Treatment Period should have an unscheduled visit; a subset of the clinical efficacy assessments [redacted] should be performed prior to the change in medication if the participant alerts the Investigator before the

change in medication occurs. In the event that the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments are performed within 30 days after the change in medication, the assessments do not have to be repeated.

Participants who experience ARIA during the Treatment Period should have unscheduled visits per the guidelines in Section 7.2.1.

7.3.1. Screening

Participant eligibility for the study will be determined no more than 60 days prior to the first dose of study treatment on Day 1. It is recommended that all screening procedures be completed within 60 days (Screening Visits may be carried out over 2 separate visits, at the Investigator's discretion); however, the overall Screening Period may be extended up to 90 days in the event of [redacted] and/or other logistics restrictions due to major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters) and is subject to Sponsor approval. Only in the event of inadequate tracer supplies or [redacted] availability, the Screening [redacted] may be performed after Day 1, upon Sponsor approval. The scan should be performed as close to the first infusion date as possible and must occur prior to the second infusion. In case the Screening Period is extended beyond 60 days, clinical efficacy assessments [redacted] will be re-assessed.

Participants who fail screening will be permitted to be rescreened up to 2 times at the Sponsor's/designee's discretion. Rescreened participants will be assigned a new number. At rescreening, all assessments should be repeated except for [redacted]

7.3.2. Treatment

After a Screening Period of approximately 8 weeks, participants who meet the eligibility criteria will receive an open-label treatment. During the Core Treatment Period, participants will receive IV infusions of aducanumab approximately Q4W for a duration of 100 weeks (a total of 26 doses). The aducanumab dosing regimen will be 10 mg/kg following this titration: 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. Eligible participants will then enter the LTE treatment period, and continue dosing with 10 mg/kg aducanumab Q4W for an additional 52 weeks (a total of 152 weeks of continuous treatment).

7.3.3. Follow-Up

All participants enrolled in the study are to return to the study site at Week 170 or 18 weeks after the last dose of study treatment for clinical assessments. For participants who do not enter the LTE, this FU visit will occur at Week 118.

Participants who DCT are to remain in the study, attend a safety FU Visit 18 weeks after the last dose of study treatment, and immediately continue protocol required tests and assessments at a subset of the clinic visits (see Table 5) until the end of the study or until withdrawal of consent.

Participants who withdraw from the study are encouraged to return for FU assessments 18 weeks after the last dose of study treatment.

7.4. Study Stopping Rules

Biogen may terminate this study at any time, after informing the 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 on safety and tolerability data, or at the discretion of the Sponsor; therefore, there are no study-specific stopping rules defined in this protocol.

7.5. Unscheduled Visits

Data collected during unscheduled visits should be recorded on CRFs only if the data support protocol objectives and/or are required for safety monitoring.

7.6. End of Study

The end of study is last protocol-specified contact with the last participant.

8. SELECTION OF PARTICIPANTS

8.1. Core 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 of the participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the study, to provide signed and dated informed consent, and to authorize the use of confidential health information in accordance with national and local privacy and ethics regulations.
    - Participant was participating in an aducanumab clinical study at the time of the announcement of early termination (feeder studies). Note #1: Participants who formerly participated in feeder studies and had to permanently discontinue the investigational product and/or exited a feeder study due to protocol mandatory requirements for discontinuation that are no longer applicable at the time of screening will be evaluated by the Sponsor on a case-by-case basis. Note #2: Participants who completed screening in Study 221AD205 and were confirmed eligible prior to 21 March 2019 but were not randomized due to the discontinuation of the trial may have the opportunity to screen on this study upon review/approval from the Sponsor.

[redacted]

3. Has one care partner who, in the Investigator's opinion, has adequate contact with the participant as to be able to provide accurate information about the participant's cognitive and functional abilities. The care partner must be available to provide information to the Investigator and site staff about the participant and attend in-person clinic visits that require care partner input for clinic assessments. The care partner should be available for the duration of the study.
4. Female participants of childbearing potential must practice effective contraception during the study and for 5 times the half-life or 24 weeks (whichever is longer) after their last dose of study treatment. Refer to Section 15.5.
5. Apart from a clinical diagnosis of Alzheimer's disease, the participant must be in good health as determined by the Investigator, based on medical history and screening assessments.

8.2. Core 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 Alzheimer's disease) that, in the opinion of the Investigator, might be a contributing cause of the participant'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. Stroke or any unexplained loss of consciousness within 1 year prior to Screening.
4. Brain MRI (performed at Screening, centrally read) evidence of any of the following:
   - Acute or subacute hemorrhage.
   - Prior macro-hemorrhage (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 participant is at risk of recurrent hemorrhage).
   - Greater than 4 (for treatment-naïve participants) or ≥ 10 (for aducanumab previously treated participants) micro-hemorrhages (defined as ≤ 1 cm in diameter on T2* sequence).
   - Cortical infarct (defined as > 1.5 cm in diameter; irrespective of anatomic location).
   - Any focal area of superficial siderosis (for treatment-naïve participants) or 3 or more focal areas of superficial siderosis (for aducanumab previously treated participants).
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 SBP/DBP readings > 165 mmHg and/or > 100 mmHg at Screening (blood pressure measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the participant to be eligible for the study), or persistent SBP and/or DBP

readings > 180 mmHg and/or >100 mmHg, respectively, 3 months prior to treatment (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:
    - Participants whose cancer is in remission according to the cancer specialist prior to Screening.
    - Participants with a history of excised or treated basal cell or squamous carcinoma of the skin.
11. A seizure event that occurred after the last visit of the feeder study and before Screening for this study.
12. Evidence of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of AST and 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 nonprescription 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 HIV.
17. Current hepatitis C infection (defined as positive HCV antibody and detectable HCV RNA. Participants with positive HCV antibody and undetectable HCV RNA are eligible to participate in the study (Reference: United States Centers for Disease Control and Prevention).
18. Current hepatitis B infection (defined as positive for HBsAg and/or total anti-HBc). Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive anti-HBs) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.
19. 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).
20. 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 participant's safety or interfere with the study assessments.

Medications

21. Use of any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the participant at higher risk for AEs, or impair the participant's ability to perform cognitive testing or complete study procedures.
22. Use of allowed medications for chronic conditions at doses that have not been stable for at least 4 weeks prior to Screening up to Day 1, or use of Alzheimer's disease medications (including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine) at doses that have not been stable for at least 8 weeks prior to Screening up to Day 1.
23. Chronic use of systemic immunosuppressive drugs (including systemic corticosteroids) as indicated in Section 11.5.1.2. Local and/or topical immunosuppressants will be allowed.
24. Use of chemotherapeutic agents and checkpoint inhibitors.
25. Use of parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, or plasmapheresis.
26. Use of vaccinations within 10 days prior to Day 1.
27. Use of medications with platelet anti-aggregant or anticoagulant properties (the use of aspirin at a dose ≤ 325 mg daily is allowed).
28. Use of illicit narcotic medication.
29. Participation in any study in which the participant is taking an investigational product for Alzheimer's disease (with purported disease-modifying treatment or not) unless the participant has fulfilled a wash-out period of at least 5 half-lives for that particular investigational product or is able to provide documentation of having received placebo in that investigational product study.

Study Procedures

30. 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).

[redacted]

[redacted]

Others

33. Female participants who are pregnant or currently breastfeeding.
34. Participant currently living in an organized care facility with extensive intervention and/or support of daily living activities.
35. Blood donation (≥ 1 unit) within 1 month prior to Screening.

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

8.3. LTE Inclusion Criteria

To be eligible to participate in the LTE period, participants must meet the following eligibility criteria at Week 102:

1. Participant must have completed the Core study period (week 102) and adequately tolerated 10 mg/kg of aducanumab during the Core study period in the opinion of the Investigator.
2. The participant will continue to derive clinical benefit from treatment with aducanumab, in the opinion of the Investigator.
3. The participant (or the participant'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 participants of childbearing potential and male participants 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 participant 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 opinion, has frequent and sufficient contact with the participant as to be able to provide accurate information about the participant'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 participant 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. LTE Exclusion Criteria

Participants will be excluded from entering the LTE period if at Week 102 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 participant's enrollment in and completion of the study.
2. Any other unspecified reasons that, in the opinion of the Investigator or Biogen, make the participant unsuitable for enrollment.

9. ENROLLMENT AND REGISTRATION

9.1. Screening and Enrollment

Participants (or their legally authorized representative, where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When a participant signs the ICF, that participant is considered to be enrolled in the study. [redacted]

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 [redacted] and/or other logistics restrictions due to major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters) and is subject to Sponsor approval. Only in the event of inadequate tracer supplies or [redacted] availability, the Screening [redacted] may be performed after Day 1, upon Sponsor approval. The scan should be performed as close to the first infusion date as possible and must occur prior to the second infusion. If a participant is excluded from the study, the reasons for exclusion will be documented in the participant's source documents and on the screening log. The total study duration for each enrolled participant will be approximately 178 weeks (approximately 8-week Screening Period, a Core Treatment Period of 100 weeks of aducanumab dosing (with clinical assessments at Week 102), an additional LTE Treatment Period of 52 weeks of aducanumab dosing, and a safety FU Visit 18 weeks after the last dose of study treatment).

9.2. Registration of Participants

Participants will be registered at the Screening Visit and enrolled only after all baseline assessments have been completed and the Investigator has verified that the participants are eligible per criteria in Section 8.1 and Section 8.2. No participant may begin treatment prior to assignment of a unique identification number (registration). Any participant identification numbers that are assigned will not be reused even if the participant does not receive treatment. Rescreened participants will be assigned a new number.

Participants will receive aducanumab as per the treatment regimen. Participants who withdraw from the study may not be replaced.

Refer to the Study Reference Manual for details on registration.

9.3. Blinding Procedures

This is an open-label study.

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

10.1. Discontinuation of Study Treatment

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

- The participant 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 (micro-hemorrhages) with serious clinical symptoms except for "other medically important event" as defined in Table 9.
  - Symptomatic ARIA-H (superficial siderosis) with serious clinical symptoms except for "other medically important event" as defined in Table 10.
  - ARIA-H with ≥ 10 new incident micro-hemorrhages and/or > 2 new incident focal areas of superficial siderosis. (Note: Only new, treatment-emergent events occurring in the study are counted).
  - Any new incident macro-hemorrhage (defined as > 1 cm in diameter on T2* sequence).

  See Section 7.2.1 for full details regarding discontinuation due to ARIA-E or ARIA-H.
- The participant becomes pregnant. Study treatment must be discontinued immediately and pregnancy must be reported according to the instructions in Section 15.4.1.
- The participant withdraws consent to continue study treatment.
- The participant experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The participant experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria (see Section 11.5.1.2).
- The participant experiences a severe infusion reaction.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance or other reasons.

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

A participant who discontinues treatment is to remain in the study, attend a safety FU Visit 18 weeks after the last dose of study treatment, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see Table 5) until the end of the study per the Schedule of Events or until the participant withdraws consent.

10.2. Lost to Follow-Up

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

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

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

10.3. Withdrawal of Participants From Study

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

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

Note: A participant who discontinues study treatment will not be automatically withdrawn from the study, regardless of the number of doses missed.

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

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

11. STUDY TREATMENT

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 Treatment Period of the study.

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

The Sponsor will provide aducanumab to study sites.

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 site staff.

11.5. Prior and Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

Prior Alzheimer's disease medication use within the gap period between 21 March 2019 and Screening will be captured. This includes any investigational drug for Alzheimer's disease that the participant may have participated after 21 March 2019.

A concomitant therapy is any drug or substance administered between the signing of the informed consent and until the participant's final clinic visit (including the safety 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 participant has been stable on the medication(s) for at least 4 weeks prior to Screening up to Day 1.
- Symptomatic therapies for Alzheimer's disease, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, are allowed provided

that participants are receiving a stable dose for at least 8 weeks prior to Screening up to Day 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.

Participants 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. Participants should inform the Investigator of any changes in medication. The Investigator needs to ensure pertinent communication with the study Medical Monitor if there are changes in medication of any nature that will have an effect on cognitive assessment. Medications used to treat AEs would not result in automatic permanent study treatment discontinuation. However, as noted in Section 10.1, if a participant requires continued use of a disallowed therapy, the participant must permanently discontinue study treatment. The Sponsor may be consulted if required.

11.5.1.2. Disallowed Concomitant Therapy

- Medications with platelet anti-aggregant or anticoagulant properties, except the use of aspirin at a dose of ≤ 325 mg per day.
- Nonprescription narcotic medication.
- Cannabinoids (prescription or recreational).
- Systemic immunosuppressive drugs (including systemic corticosteroids). Local and/or topical immunosuppressants will be allowed. Local corticosteroids (including inhaled and topical corticosteroids) are allowed; certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- Chemotherapeutic agents and checkpoint inhibitors.
- Parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis.
- Any investigational drug.

Participants who have a change in Alzheimer's disease medication (other than study treatment) during the Treatment Period should have an unscheduled visit; a subset of the clinical efficacy assessments [redacted] should be performed prior to the change in medication if the participant alerts Investigator before the change in medication occurs. In the event that the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments are performed within 30 days after the change in medication, the assessments do not have to be repeated.

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 participant is enrolled in the study and until the participant's final clinic visit (including safety FU Visit), unless the participants is being followed for study-related toxicity.

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

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 will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice. Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to that participant. Study treatment vials are for one-time use only; any study treatment remaining in the vial must not be used for another participant.

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

Synonyms: Human, IgG1, anti-Aβ monoclonal antibody

Aducanumab is a human antibody expressed in a Chinese hamster ovary cell line, purified to a high degree of purity and formulated as a liquid. Aducanumab is an IgG1 consisting of 2 heavy and 2 kappa light chains connected by inter-chain disulfide bonds. Aducanumab has 1 carbohydrate moiety linked to Asn-304. Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing:

- aducanumab 100 mg/mL (excipients: L-histidine hydrochloride monohydrate, L-histidine, L-arginine hydrochloride, L-methionine, and polysorbate-80)

The concentration for each vial (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 8ºC until use. If administration of the prepared aducanumab is delayed for more than 24 hours, it must be discarded. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

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 staff 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 (participant-by-participant accounting), and accounts of any study treatment accidentally or deliberately destroyed and/or lost.

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. Additional Protocol-Designated Products

Refer to the DHA for infusion-related supply specifications.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

14. SAFETY ASSESSMENTS

See Section 4.2 for the timing of assessments.

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

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
- [redacted]
- C-SSRS

14.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice-validated assays. The following laboratory assessments will be performed to evaluate the safety profile of aducanumab:

- Hematology: complete blood count with 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.
- Lipid panel: total cholesterol, high-density lipoproteins, low density lipoproteins, and triglycerides.
- 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 ADAs will be determined using a validated assay. A standard 3-tiered 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 participant. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each participant 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 participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal 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 participant to receive specific corrective therapy.
- A laboratory abnormality that the Investigator considers to be clinically significant.

Pretreatment, nonserious AEs that occur within 48 hours after receipt of a [redacted] will be recorded in the CRF.

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

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

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 participant 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 participant'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 participant's consent to be in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
  - If a participant is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 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 and, if applicable, the [redacted].

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.
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

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 participant or does not make participant 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 participant.
Moderate	Symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in the study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or participant hospitalized.

15.2.4. Expectedness of Events

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

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the participant between the time of first dose of study treatment and the participant's final clinic visit (including the safety FU Visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit the Investigator will assess the participant for AEs and will record any new AEs or updates to previously reported AEs on the CRF Pretreatment, nonserious AEs that occur within 48 hours after receipt of a ligand will be captured by the sites on the AE form. AEs that are ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will be recorded on the CRF, as applicable.

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 IQVIA Lifecycle Safety.

15.3.3. Serious Adverse Events

Any SAE experienced by the participant between signing of the ICF and the participant's final clinic visit (including the safety 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 participant's final clinic visit (including the safety 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 participant 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 IQVIA Lifecycle Safety 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 participant has signed the ICF and the participant's final clinic visit (including the safety FU Visit) must be reported to IQVIA Lifecycle Safety 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 IQVIA Lifecycle Safety regardless of the following:

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

To report initial or FU information on an SAE, fax or email a completed SAE form. Refer to the Study Reference Manual for complete contact information.

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

Biogen or designee will submit SUSARs to regulatory agencies and Investigators according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Female participants should not become pregnant during the study and for 5 times the half-life or 24 weeks (whichever is longer) after their last dose of study treatment. If a female participant becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female participant from first dose of study treatment to up to 24 weeks after last dose by faxing or emailing the appropriate form to IQVIA Lifecycle Safety within 24 hours of the study site staff becoming aware of the pregnancy. Refer to the Study Reference Manual's official study contact list for complete contact information. The Investigator or study site staff must report the outcome of the pregnancy to IQVIA Lifecycle Safety.

Congenital abnormalities and birth defects in the offspring of female participants should be reported as an SAE if conception occurred during the study Treatment Period or up to 24 weeks after last dose.

15.4.2. Overdose

An overdose is any dose of study treatment given to a participant or taken by a participant 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 or emailed to IQVIA Lifecycle Safety within 24 hours of the site becoming aware of the overdose. An overdose must be reported to IQVIA Lifecycle Safety even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to IQVIA Lifecycle Safety. 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 IQVIA 24-hour emergency medical support number. Refer to the Study Reference Manual's Official Contact List for complete contact information.

15.5. Contraception Requirements

All women of childbearing potential must ensure that acceptable effective contraceptive methods are used during the study and for 5 times the half-life or 24 weeks (whichever is longer) after their last dose of study treatment. In addition, participants should not donate eggs for the duration of the study and for at least 24 weeks after their last dose of study treatment.

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

- Postmenopausal
  - For women ≤ 55 years of age, 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level ≥ 40 mIU/mL.
  - For women > 55 years of age, 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level ≥ 40 mIU/mL, or at least 5 continuous years of natural (spontaneous) amenorrhea without an alternative medical cause.
  - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

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

- For females of childbearing potential:
  - Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
  - 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 (where applicable).
  - Male sexual partners underwent surgical sterilization with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate.
  - True abstinence, when this is consistent with the preferred and usual lifestyle of the participant, can be considered an acceptable method of contraception based on

the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, 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, on the CRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and FU on the outcome of the pregnancy in female participants.
- Complete an SAE form for each SAE and fax it to Biogen (or designee) within 24 hours of the 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 site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the participants' medical records.
- Pursue AE FU information, if possible, until the event has resolved or become stable. Record AE FU information, including resolution, on the CRF, as applicable.
- Report SAEs to local EC/IRBs, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before a site can enroll any participants, the Clinical Monitor (IQVIA) 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 with summary statistics (mean, SD, median, and range) or with frequency distributions.

[redacted]

[redacted]

16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all participants who received at least 1 dose of aducanumab.

16.4.2. Methods of Analysis- Primary Endpoint

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

16.4.2.1. Adverse Events

Only TEAEs will be presented in the summary tables for treatment-naïve participants and treatment-experienced participants. 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 severity, and by relationship to aducanumab. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using MedDRA.

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

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 postbaseline value and the shift from baseline to the minimum postbaseline status will be presented for each laboratory test. 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 participants with shifts to categorical values (abnormal not AE, or abnormal AE) will be summarized.

16.4.2.5. Columbia Suicide Severity Rating Scale

The baseline and postbaseline C-SSRS data will be summarized. C-SSRS data will be summarized using descriptive statistics (number of participants, mean, standard deviation, median, minimum, and maximum) for continuous variables, and using frequency and percentage for discrete variables.

16.5. Immunogenicity Data

16.5.1. Analysis Population

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

16.5.2. Methods of Analysis- Primary Endpoint

ADAs in serum will be summarized using shift tables.

16.6. Interim Analyses

The Sponsor plans to conduct interim analyses when appropriate milestones of the study are achieved.

16.7. Sample Size Considerations

Given that the study population depends on the feeder studies, no sample size was determined for this study.

At the time that the feeder studies were stopped in March 2019, approximately 2600 participants had received treatment in 1 of those feeder studies. Approximately 400 participants were on placebo ("aducanumab treatment-naïve participants") and approximately 2200 participants had received aducanumab ("aducanumab previously treated participants"). Biogen estimates that of these 2600 participants, 2400 participants could be eligible based on inclusion and exclusion criteria to participate in the current study.

17. ETHICAL REQUIREMENTS

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

The 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 participant 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. Participant 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 participant or participant's legally authorized representative (e.g., legal guardian), as applicable, in accordance with local practice and regulations. Should the participant be under the care of a care partner, the care partner will sign a separate ICF.

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

Participants 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). These data will be used in the analysis of the safety and/or pharmacokinetic profile of the study treatment.

A copy of the signed and dated ICF must be given to the participant, care partner, and/or legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the participant's medical record. When additional information that may affect participants' willingness to continue in the study becomes available, the Investigators will be notified in a timely manner, according to all local and applicable law. An updated ICF may be required.

17.4. Participant Data Protection

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

The participant 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 participant's personal medical data confidential.

During the study, participants' race and/or ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). 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.

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

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

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

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

During these visits, CRFs 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 participants 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 participants are screened, the IRT vendor will provide each study site with appropriate training, access rights, and a user manual.

19.1.3. Electronic Data Capture

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

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 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 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.

A central imaging laboratory will also be utilized to facilitate collection and analysis of [redacted].

19.1.6. Central Review of Raters

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

19.1.7. 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 participant accrual and oversee study conduct, including advising on study design and execution.

Members of the advisory committee will include external experts in Alzheimer's disease. 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 participants. 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. As of 5 Oct 2021, the meeting frequency of the IDMC was updated to ad hoc only.

19.3. Changes to Final Protocol

All protocol amendments must be submitted to the EC/IRB and regulatory authorities if required by local law. Protocol modifications that affect participant safety, the scope of the investigation, or the scientific quality of the study must be approved by the 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 participant. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 17.2 and Section 17.3).

19.4. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify 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.

19.5. Study Report Signatory

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

20. REFERENCES

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Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353-6. Epub 2002 Jul 20.

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[redacted]

[redacted]

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205", and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

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AMENDMENT SUMMARY

Biogen Protocol 221AD304

Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302, and 221AD205

Version 4

Date: 19 January 2022

EUDRA CT Number: 2019-004368-22

Version 4.0 of the protocol has been prepared for this amendment, which supersedes Version 3.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 221AD304 is to add a 52-week long-term extension (LTE) period (13 additional doses) to the ongoing study.

In combination with the phase 3 studies, the EMBARK study represents one of the largest and most comprehensive longitudinal clinical and [redacted] in early symptomatic AD. As such, Biogen remains committed, alongside the scientific community, to continue learning from this dataset. Rationale for continuation of the EMBARK study stems from the following:

- Further characterization of the long-term safety of aducanumab
- Further elucidation of the long-term efficacy of 10 mg/kg aducanumab in subjects as a continuation of the phase 3 studies
- [redacted]
- Provision of additional data generation for aducanumab, as requested from all major global regulatory agencies
- Continuation of treatment for patients who are deriving meaningful clinical benefit from aducanumab at no financial cost for an additional 12 months

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

Section 7.1, Study Overview

Now reads:

……

After a Screening Period of approximately 8 weeks, participants who meet the eligibility criteria will receive open-label treatment. During the **Core** Treatment Period, participants will receive IV infusions of aducanumab approximately Q4W for a ~~total treatment~~ duration of 100 weeks (a total of 26 doses). The aducanumab dosing regimen will be 10 mg/kg following this titration: 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. **Eligible participants will then enter the LTE treatment period, and continue dosing on 10 mg/kg aducanumab Q4W for an additional 52 weeks (a total of 152 weeks of continuous treatment). The EOT Visit will occur at Week 154.** Participants will have a safety FU Visit 18 weeks after their last dose of study treatment. ~~The EOT Visit will occur at Week 102.~~

…….

Rationale: These changes were made to include the 1-year LTE period for the Study 221AD304.

This change also affects Section 4.2., Schedule of Events; Section 4.3.1., Site Staff; Section 5.3.1., Dosing Scheme; Section 7.3., Overall Study Duration and Follow-Up; Section 9.1., Screening and Enrollment; [redacted].

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3., Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 4.2., Schedule of Events, Table 3

Change: A new schedule of events table was added.

Now reads:**Table 1: LTE Treatment Schedule from Week 104 Through End of Treatment and Follow-Up**

Study Week	LTE Treatment Period														UV for a Change in Alzheimer's Disease Medication	FU 170 (or 18 wks after last dose for participants who DCT early)
	104	108	112	116	120	124	128	132	136	140	144	148	152	154/ EOT		
Study Day	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	1078 ± 5		1190 ± 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			
Aducanumab Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hematology, Blood Chemistry, and Urinalysis														X		
Alzheimer's Disease Status[2]														X		
Physical Examination							X							X		X

Study Week	LTE Treatment Period														UV for a Change in Alzheimer's Disease Medication	FU 170 (or 18 wks after last dose for participants who DCT early)
	104	108	112	116	120	124	128	132	136	140	144	148	152	154/ EOT		
Study Day	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	1078 ± 5		1190 ± 5
Neurological Examination							X							X		X
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
12-Lead Paper ECG														X		
ADA[4]							X							X		
Aducanumab Serum Concentration[4]							X							X		
[redacted]																

Study Week	LTE Treatment Period														UV for a Change in Alzheimer's Disease Medication	FU 170 (or 18 wks after last dose for participants who DCT early)
	104	108	112	116	120	124	128	132	136	140	144	148	152	154/ EOT		
Study Day	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	1078 ± 5		1190 ± 5
[redacted]																
C-SSRS														X		
AE Reporting	Monitor and record continuously throughout the study															
Concomitant Therapy [9] and Procedures	Monitor and record continuously throughout the study															
SAE Reporting	Monitor and record continuously throughout the study															

[1] Required for women of childbearing potential only (see Section 15.5). Must be performed prior to scans.

[2] As judged by the Investigator

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

[4] Will be performed prior to infusion (where applicable).

[redacted]

[9] Participants who have a change in Alzheimer's disease medication (other than study treatment) during the Treatment Period should have an unscheduled visit. a subset of the clinical efficacy assessments [redacted] should be performed prior to the change in medication if the participant alerts the Investigator before the change in medication occurs. In the event that the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments are performed within 30 days after the change in medication, the assessments do not have to be repeated.

Rationale: The new schedule of events table was included to reflect the addition of the LTE period and assessments during the LTE period.

Section 4.2., Schedule of Events, Table 4

Change: Table 4 was updated.

Now reads:Table 2: Brain MRI, ARIA Management, and Follow-Up Telephone Call Schedule During the **Core and LTE** Treatment Periods

Study Week	Screening (≤ 60 days before Day 1)[1]	**Core** Treatment Period														**Core Treatment Period FU**[2]	**LTE Treatment Period FU**[3]
		1	2	6	10	14	18	22	26	30	42	54	66	78	102 / EOT[4]	UV/MRI for ARIA 5	118 (or 18 wks after last dose for participants who DCT early **from core treatment period**)	**170 (or 18 wks after last dose for participants who DCT early from LTE treatment period)**
Study Day		1	15± 5	43 ± 5	71 ± 5	99 ± 5	127 ± 5	155 ± 5	183 ± 5	211 ± 5	295 ± 5	379 ± 5	463 ± 5	547 ± 5	714 ± 5		827± 5	**1190 ± 5**
Follow-Up Telephone Call[6]			X	X	X	X	X	X	X	X								
Brain MRI	X					X		X		X	X	X	X	X	X	X		**X**
Aducanumab Serum Concentration[7]								X		X		X				X	X	
[redacted]																		
Physical Examination																X		**X**
Neurological Examination																X		**X**

Study Week	Screening (≤ 60 days before Day 1)[1]	**Core** Treatment Period														**Core Treatment Period FU[2]**	**LTE Treatment Period FU[3]**
		1	2	6	10	14	18	22	26	30	42	54	66	78	102 / EOT[4]	UV/MRI for ARIA[5]	118 (or 18 wks after last dose for participants who DCT early **from core treatment period**)	**170 (or 18 wks after last dose for participants who DCT early from LTE treatment period)**
Study Day		1	15± 5	43 ± 5	71 ± 5	99 ± 5	127 ± 5	155 ± 5	183 ± 5	211 ± 5	295 ± 5	379 ± 5	463 ± 5	547 ± 5	714 ± 5		827± 5	**1190 ± 5**
Vital Signs[8]																X		**X**

[redacted]

[1] 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 [redacted] and/or other logistics restrictions due to major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters) and is subject to Sponsor approval. In order to ease participant burden, the Screening Visit may be carried out over 2 separate visits, at the Investigator's discretion.

[2] Participants who complete the **Core** Treatment Period of the study **and do not enter the LTE Treatment Period** are to return to the site for a safety FU Visit at Week 118. Participants who discontinue or withdraw from the study early are to have a safety FU Visit 18 weeks after the last dose of study treatment.

[3] **Participants who complete the LTE Treatment Period of the study are to return to the site for a safety FU Visit at Week 170.** Participants who DCT **or withdraw from the LTE early are to have a safety FU Visit 18 weeks after the last dose of study treatment**

[4] **Participants who ~~DCT~~ discontinue prematurely** are to remain in the study, attend a safety FU Visit 18 weeks after the last dose of study treatment, and immediately continue protocol-required tests and assessments at a subset of the clinic visits (see **Table 2, Table 3 and Table 4**) until the end of the study per the Schedule of Events (it is possible that a clinic visit will occur before the safety FU Visit). If the safety FU Visit will occur within 2 weeks of a scheduled clinic visit, then the safety FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. Participants who withdraw from study prematurely are to return to the site for an EOT Visit; for such participants, efficacy assessments specified at the EOT Visit are not required if the participant discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the sponsor in such cases.

[redacted]

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

[redacted]

Rationale: The table was updated to include the MRI and other assessments at the follow-up visit after LTE treatment period (Week 170).

Section 4.2., Schedule of Events, Table 5

Change: Table 5 was updated.

Now reads:Table 5: Participants Who Discontinue Study Treatment **During the Core Treatment and LTE Periods** but Remain in the Study

	Post-Treatment Visit Schedule[1] (Core Treatment and LTE Periods)														
Study Week	**12**	**24**	**26**	**48**	**50**	**72**	**78**	**92**	**102** [2] ~~EOT~~	**112**	**128**	**140**	**152**	**154/ EOT[2]**	**UV for ARIA[3]**
Study Day	**85 ± 5**	**169 ± 5**	**183 ± 5**	**337 ± 5**	**351 ± 5**	**505 ± 5**	**547 ± 5**	**645 ± 5**	**714 ± 5**	**785 ± 5**	**897 ± 5**	**981 ± 5**	**1065 ± 5**	**1078 ± 5**	
Body Weight	X	X		X		X		X	X	**X**	**X**	**X**	**X**	**X**	
Hematology, Blood Chemistry, and Urinalysis				X					X					**X**	
Urine Pregnancy Test[4]		X		X		X	X	X		**X**	**X**	**X**	**X**		
Physical Examination		X		X		X	X	X	X		**X**			**X**	
Neurological Examination		X		X		X			X		**X**			**X**	
Vital Signs[5]	X	X		X		X		X	X	**X**	**X**	**X**	**X**	**X**	
12-Lead Paper ECG				X					X					**X**	
Aducanumab Serum Concentration											**X**			**X**	X[6]
[redacted]															
Brain MRI									X						X
[redacted]															

	Post-Treatment Visit Schedule[1] (Core Treatment and LTE Periods)														
Study Week	**12**	**24**	**26**	**48**	**50**	**72**	**78**	**92**	**102** [2] ~~EOT~~	**112**	**128**	**140**	**152**	**154/ EOT[2]**	**UV for ARIA[3]**
Study Day	**85 ± 5**	**169 ± 5**	**183 ± 5**	**337 ± 5**	**351 ± 5**	**505 ± 5**	**547 ± 5**	**645 ± 5**	**714 ± 5**	**785 ± 5**	**897 ± 5**	**981 ± 5**	**1065 ± 5**	**1078 ± 5**	
[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														

[1] Participants who discontinue study treatment prematurely are to remain in the study, attend a safety FU Visit 18 weeks after the last dose of study treatment as listed in Table 2, Table 3 and ~~Table 3~~ Table 4 and immediately continue protocol-required tests and assessments at a subset of the clinic visits ~~Table 4~~ (Table 5) until the end of the study per the Schedule of Events (it is possible that a clinic visit will occur before the safety FU Visit). If the safety FU Visit will occur within 2 weeks of a scheduled clinic visit, then the safety FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit.

[2] Participants who withdraw from study prematurely are to return to the site for an EOT Visit; for such participants, efficacy assessments specified at the EOT Visit are not required if the participant discontinues treatment within 3 months of the previous efficacy assessment visit and no significant changes in cognitive status are suspected by the Investigator. The site should notify the Sponsor in such cases.

[3] For the frequency of required brain MRI and [redacted] assessments, [redacted] for participants who develop ARIA-E and/or ARIA-H, see Section 7.2.1.1, Section 7.2.1.2, Section 7.2.1.3, Section 7.2.1.4, and Section 7.2.1.5. This includes [redacted] at the first unscheduled visit for ARIA monitoring per episode only. For the frequency of brain MRI and [redacted] 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 only if last dose of study treatment was less than 24 weeks before the clinic visit.

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

[6] One sample will be collected within ± 2 days of the MRI visit. Exact collection date and time will be captured for all [redacted] on a specified CRF.

[7] Sample may be collected within ± 2 days of the MRI visit.

[redacted]

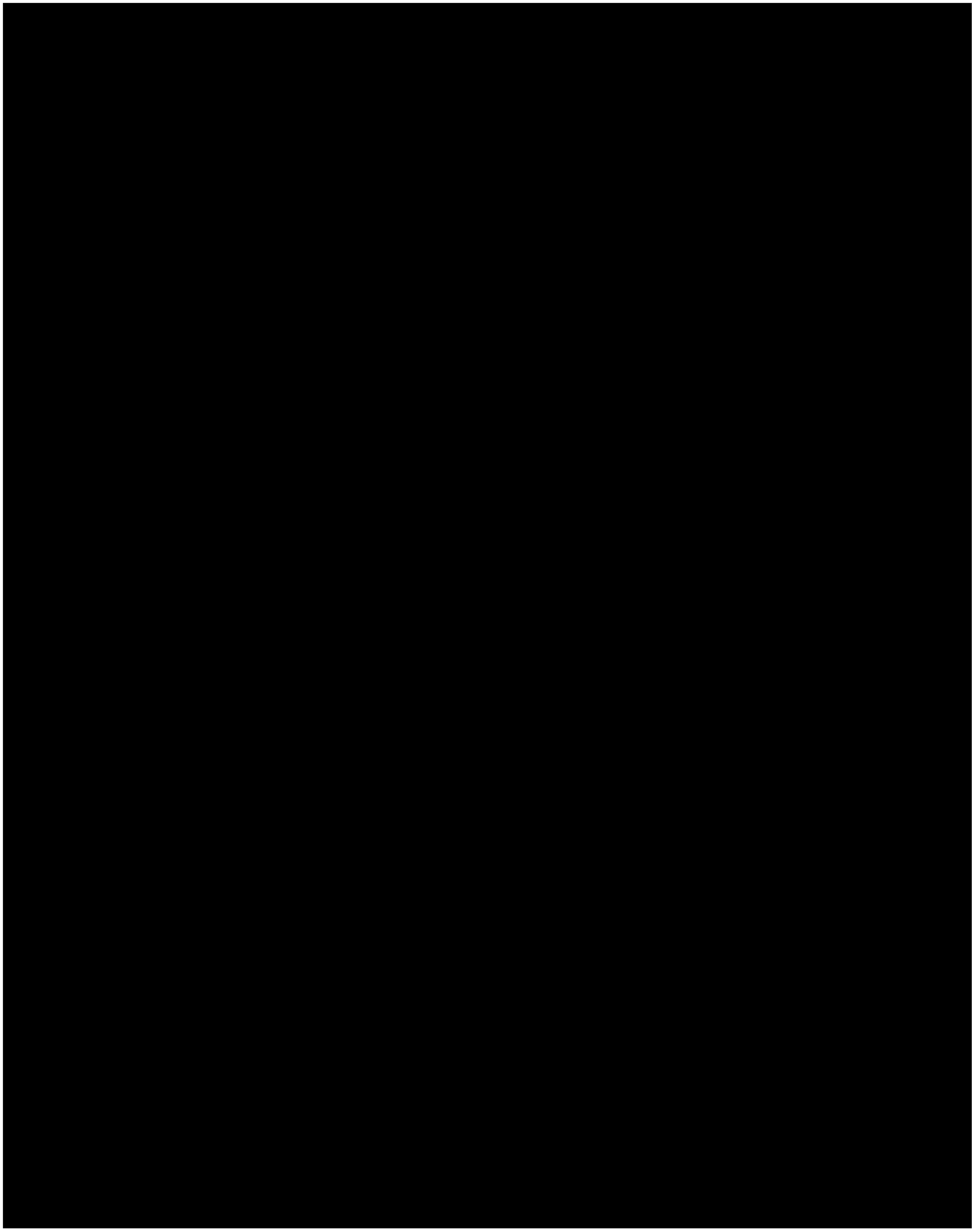
Rationale: The table was updated to include the assessments during LTE period for participants who discontinue study treatment.

Section 6., Study Objectives and Endpoints

Change: The study objectives and endpoints were updated, and [redacted] objectives and endpoints for the LTE period were added.

Now reads:

Core Primary Objective	**Core** Primary Endpoints
To evaluate the ~~long-term~~ safety and tolerability of aducanumab **over 100 weeks of treatment** after a wash-out period imposed by discontinuation of feeder studies in participants who had previously received aducanumab (i.e., previously treated participants) or who had previously received placebo (i.e., treatment-naïve participants)	Incidence of AEs, SAEs, ARIA, and immunogenicity with ~~long-term~~ **over 100 weeks of** treatment and/or re-exposure to aducanumab. Safety and tolerability parameters include the following: • Incidence of all AEs, AEs leading to treatment discontinuation or study withdrawal, and all SAEs • Incidence of ARIA-E and ARIA-H • Incidence of ADAs in serum
[redacted]	



Rationale: The study objectives and endpoints for the Core Treatment Period were updated to reflect changes in the duration of that study period and the 52-week LTE period was added. Separate LTE objectives and endpoints were added to the study.

Section 8.3., LTE Inclusion Criteria

Change: Inclusion criteria for the LTE Period were added.

Now reads:**8.3 LTE Inclusion Criteria**

To be eligible to participate in the LTE period, participants must meet the following eligibility criteria at Week 102:

1. **Participant must have completed the Core study period (week 102) and adequately tolerated 10 mg/kg of aducanumab during the core study period in the opinion of the Investigator.**

2. **The participant will continue to derive clinical benefit from treatment with aducanumab, in the opinion of the Investigator.**

3. **The participant (or the participant'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 participants of childbearing potential and male participants 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 participant 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 opinion, has frequent and sufficient contact with the participant as to be able to provide accurate information about the participant'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 participant 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.**

Rationale: The inclusion criteria for the 52-week LTE treatment period were added to the revised protocol.

Section 8.4., LTE Exclusion Criteria

Change: Exclusion criteria for the LTE period were added.

Now reads:**8.4 LTE Exclusion Criteria**

Participants will be excluded from entering the LTE period if at Week 102 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 participant's enrollment in and completion of the study.**

2. **Any other unspecified reasons that, in the opinion of the Investigator or Biogen, make the participant unsuitable for enrollment.**

Rationale: The exclusion criteria for the 52-week LTE treatment period was added to the revised protocol.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected.
- Table and Figure numbers were updated.
- The study schematic (Section 4.1.) was updated to include the 1-year LTE and other assessments.
- The footnotes in Table 1., Core Treatment Period Schedule From Screening Through Week 48 of Treatment, were updated to exclude C-SSRS from the assessments needed to be completed prior to infusion, since that assessment was not relevant.
- Table 2., Core Treatment Period Schedule From Week 50 to Week 102, was updated to include LTE eligibility and LTE informed consent. The table footnotes were updated accordingly.
- The initial treatment period (Week 1 to Week 100) was renamed “Core Treatment Period” and the extension period was renamed “Long Term Extension (LTE)” throughout the protocol.
- In Section 5.4. Benefit-Risk Assessment, symptoms related to ARIA-E episodes were updated (rarely seizures, including prolonged seizures).
- In Section 7.2. Dose Suspension or Discontinuation for ARIA Events, the text was updated to include the review of MRI report by the Investigator prior to next dosing.
- In Section 7.2.1.6.1. MRI Monitoring, the text was updated to include physical and neurological examination and collection of vital signs.
- In Section 19.2.2. Independent Data Monitoring Committee, the occurrence of the IDMC meeting was updated to “ad-hoc only” as of 05 October 2021.

LIST OF ABBREVIATIONS

ADA	antidrug antibody
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
AE	adverse event
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-hemorrhage or superficial siderosis
[redacted]	[redacted]
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
COVID-19	coronavirus disease 2019
CRF	case report form
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DCT	discontinue treatment
ECG	electrocardiogram
EOT	End of Treatment
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FU	follow-up
[redacted]	[redacted]
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IV	intravenous(ly)
LTE	long term extension
MCI	mild cognitive impairment
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MRI	magnetic resonance imaging
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
Q4W	every 4 weeks
[redacted]	[redacted]
SAE	serious adverse event
SBP	systolic blood pressure
UV	Unscheduled Visit

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AMENDMENT SUMMARY

Biogen Protocol 221AD304

Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302, and 221AD205

Version 3.0

Date: 08 March 2021

EUDRA CT Number: 2019-004368-22

Version 3.0 of the protocol has been prepared for this amendment, which supersedes Version 2.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 221AD304 is to revise text describing the rescreening criteria.

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

7.3.1, Screening

Now reads:

[…]

Participants who fail screening will be permitted to be rescreened up to 2 times at the Sponsor's/**designee's** discretion ~~in cases when a participant fails screening due to logistics restrictions due to major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters)~~. Rescreened participants will be assigned a new number. At rescreening, all assessments should be repeated except for [redacted]

Rationale:

The revision was made to remove text that had been included in error.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected.

LIST OF ABBREVIATIONS

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

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AMENDMENT SUMMARY

Biogen Protocol 221AD304

Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302, and 221AD205

Version 2.0

Date: 26 August 2020

EUDRA CT Number: 2019-004368-22

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

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 221AD304 is to update the protocol with safety data from the Phase 3 Studies 221AD301 and 221AD302 and with additional supporting information on the efficacy of aducanumab at 10 mg/kg dosing from the Phase 1b study, Study 221AD103. The new pieces of information reinforce the benefit-risk assessment of the aducanumab 10 mg/kg dose, the one chosen in this study.

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

Section 5.4, Benefit-Risk Assessment

Now reads:

There are currently no available therapies that modify the clinical course of Alzheimer's disease. Analyses of data collected through the end of the study (Study **221AD**301 database lock on 15 ~~Novebmer~~ **November** 2019 and Study **221AD**302 database lock on 13 November 2019, with efficacy data after 20 March 2019 censored) in the 2 Phase 3 aducanumab clinical studies showed that, in Study **221AD**302, treatment with aducanumab significantly reduced clinical decline in patients with early Alzheimer's disease as measured by the prespecified primary **endpoint** (CDR-SB) and by the 3 secondary endpoints (**MMSE, ADCS-ADL-MCI, and** ADAS-Cog 13~~MMSE, and ADCS-ADL-MCI~~) in the high-dose group. In addition, Study **221AD**301 contained supportive data, based on post-hoc analyses of subsets of participants who received sufficient exposure to the highest dose (10 mg/kg) of aducanumab. **Additionally, data from the Study 221AD103 of aducanumab, with up to 4 years of FU data on treatment, suggested a continued benefit on the rate of clinical decline with continued aducanumab treatment (changes from baseline in the groups that received either 10 mg/kg fixed dose or 10 mg/kg titration since the beginning of the study were numerically smaller than those in the groups that switched from placebo to aducanumab).**

As of ~~01 April 2019~~ **04 May 2020**, ~~an estimated~~ **a total of** ~~3075~~ **3078** participants have been exposed to aducanumab~~. These include 2755 Aducanumab-treated subjects from Studies 301 and 302, of whom 1345 were assigned to a target dose of 10 mg/kg.~~ **across completed or terminated clinical studies (including 3050 participants with Alzheimer's disease and 28 healthy volunteers). Of those, 2757 participants were enrolled in the Phase 3, placebo-controlled studies (Studies 221AD301 and 221AD302) for approximately 3983.5 person-years of exposure and totaling 4736.1 person-years of FU.** The most frequent ~~adverse event~~ **AE**, among ~~subjects~~ **participants** from Studies **221AD**301 and **221AD**302 with a target dose of 10 mg/kg, was ARIA-E (~~32.9~~**35.4**%). The majority of participants ~~who experienced~~ **with** ARIA-E ~~did not experience~~ **were asymptomatic, and participants with symptomatic ARIA-E had** symptoms ~~during an ARIA-E episode~~ **that were predominantly mild or moderate in clinical severity.** Symptoms reported during ARIA-E episodes included headache, ~~confusion~~ **confusional state**, dizziness, ~~visual disturbances,~~ **fatigue, and** nausea~~, and vomiting. Such symptoms typically~~**. In the majority of participants with ARIA-E, the first**

ARIA-E events were documented to have fully resolved ~~and were generally not associated with long-term clinical sequelae.~~**(800 of 815 participants [98.2%])**. **In the clinical studies, some participants with an initial episode of ARIA-E that resolved subsequently experienced a second, later episode of ARIA-E. This was referred to as "recurrent ARIA-E" in the clinical studies. Recurrent ARIA-E events were less likely to be symptomatic than first ARIA-E events (recurrent: 13.1% versus first: 23.6%). As with first ARIA-E events, in nearly all participants with second ARIA-E events, the events resolved during the study (231 of the 236 participants [97.9%] with second ARIA-E), and in the majority of participants with resolved second events, ARIA-E resolved within 12 weeks.** Other frequent ~~adverse events~~ **AEs**, among ~~subjects~~ **participants** from Studies **221AD**301 and **221AD**302 with a target dose of 10 mg/kg, included headache (~~18.7~~**20.5**%), ARIA-H ~~microhemorrhage~~ **micro-hemorrhage** (~~17.0~~**19.1**%), **fall (15.0%), nasopharyngitis (14.5%),** and ARIA-H superficial siderosis ~~of the central nervous system (13.8~~**14.6%**). Similar to ARIA-E, the majority of participants with ARIA-H ~~microhemorrhage~~ **micro-hemorrhage** and ARIA-H superficial siderosis were asymptomatic. **Notably, transient treatment interruption has been routinely implemented in all aducanumab studies for participants with ARIA events meeting certain criteria. Resumption of dosing after this treatment-free period was not associated with an increased incidence of AEs or immunogenicity.**

The benefit-risk profile of aducanumab is considered positive **for investigational use in both treatment-naïve participants as well as in previously treated participants who have had a treatment-free period**.

Rationale: Safety information from Phase 3 studies was updated to reflect the final high-level safety findings. These updated data are consistent with previous data from April 2019 and continue to support a positive benefit-risk profile of aducanumab. In addition, adding the observation from the LTE of the Phase 1b study helps in informing the efficacy of aducanumab in participants with long-term exposure to study treatment in an independent study. Providing this supporting information from previous studies is the main reason for this amendment.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 4.2, Schedule of Events, Table 1

Change: Visit windows were updated to 5 days for all visits in Table 1.

Now reads:

Study Week	Screening (≤ 60 days before Day 1)[1]	Treatment Period													UV for a ~~e~~**C**hange in ~~AD~~ **Alzheimer's Disease** ~~m~~**M**edication
		Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	
Study Day		1	29±~~3~~ **5**	57±~~3~~ **5**	85±~~3~~ **5**	113±~~3~~ **5**	141±~~3~~ **5**	169±~~3~~ **5**	183±~~3~~ **5**	197±~~3~~ **5**	225±~~3~~ **5**	253±~~3~~ **5**	281±~~3~~ **5**	309±~~3~~ **5**	337±~~3~~ **5**	

Rationale: Additional time for visits was allowed to accommodate institutional restrictions.

This change also affects Section 4.2, Schedule of Events, Tables 2, 3, and 4.

Section 4.2, Schedule of Events, Table 1

Change: Timepoints for some assessments were removed.

Now reads:

Study Week	Screening (≤ 60 days before Day 1)[1]	Treatment Period														UV for a ~~e~~**C**hange in ~~AD~~ **Alzheimer's Disease** ~~m~~**M**edication
		Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	
Study Day		1	29± ~~3~~ **5**	57± ~~3~~ **5**	85±~~3~~ **5**	113±~~3~~ **5**	141±~~3~~ **5**	169±~~3~~ **5**	183± ~~3~~ **5**	197± ~~3~~ **5**	225±~~3~~ **5**	253±~~3~~ **5**	281±~~3~~ **5**	309±~~3~~ **5**	337±~~3~~ **5**	
Hematology, **Blood** ~~e~~**C**hemistry, **and** ~~u~~**U**rinalysis	X[6]	~~X~~														
~~AD~~ **Alzheimer's Disease** ~~s~~**S**tatus[7]	X	~~X~~														
Physical ~~e~~**E**xamination	X							X							X	~~X~~

Study Week	Screening (≤ 60 days before Day 1)[1]	Treatment Period														UV for a ~~e~~**C**hange in ~~AD~~ **Alzheimer's Disease** ~~m~~**M**edication
		Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	
Study Day		1	29±~~3~~ **5**	57±~~3~~ **5**	85±~~3~~ **5**	113±~~3~~ **5**	141±~~3~~ **5**	169±~~3~~ **5**	183±~~3~~ **5**	197±~~3~~ **5**	225±~~3~~ **5**	253±~~3~~ **5**	281±~~3~~ **5**	309±~~3~~ **5**	337±~~3~~ **5**	
Neurological ~~e~~**E**xamination	X							X							X	~~X~~
Vital ~~s~~**S**igns[8]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	~~X~~
…																
C-SSRS	X								~~X~~							

Rationale: Hematology, blood chemistry, and urinalysis assessments were not needed at Day 1; Alzheimer's disease status did not need to be re-established on Day 1; physical examination, neurological examination, and vital signs were not needed for the UV visit for change in Alzheimer's disease medication; and C-SSRS was updated to be performed yearly.

The change to the C-SSRS assessment timing also affects Section 4.2, Schedule of Events, Tables 2 and 4.

Section 4.2, Schedule of Events, Table 1

Change: [redacted].

Now reads:

Study Week	Screening (≤ 60 days before Day 1)[1]	Treatment Period														UV for a ~~e~~**C**hange in ~~AD~~ **Alzheimer's Disease** ~~m~~**M**edication
		Wk 1, Day 1	4	8	12	16	20	24	26	28	32	36	40	44	48	
Study Day		1	29±~~3~~ **5**	57±~~3~~ **5**	85±~~3~~ **5**	113±~~3~~ **5**	141±~~3~~ **5**	169±~~3~~ **5**	183±~~3~~ **5**	197±~~3~~ **5**	225±~~3~~ **5**	253±~~3~~ **5**	281±~~3~~ **5**	309±~~3~~ **5**	337±~~3~~ **5**	
[redacted]																

Rationale: [redacted]

[redacted]

Section 4.2, Schedule of Events, Table 1

Change: Footnote 2 was updated.

Now reads:

[2] All assessments, including the C-SSRS, must be completed ~~before study treatment administration, except the postdose sample to measure aducanumab concentration~~ **prior to infusion**.

Rationale: Removed postdose sample for aducanumab concentration, as there is no plan to measure [redacted] in postdose samples. Language was adjusted to maintain consistency.

Section 4.2, Schedule of Events, Table 1

Change: Footnote 5 was updated.

Now reads:

[5] Required for women of childbearing potential only (see Section 15.5**). Must be performed prior to scans.**

Rationale: Clarified that serum pregnancy test must be performed before scans to ensure no pregnant participant undergoes the scans used for screening in the study.

Section 4.2, Schedule of Events, Table 1

Change: Footnotes 9, 10, and 11 were combined.

Now reads:

[9] ~~Sample collection for anti-aducanumab antibody will~~**Will** be performed prior to ~~study treatment~~ infusion (where applicable).

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

[redacted]

Rationale: These footnotes were merged because the samplings for ADAs, serum aducanumab, and [redacted] each were to be performed prior to infusion.

This change also affects Section 4.2, Schedule of Events (footnote numbers in Table 1, footnotes in Table 2, and footnote numbers in Table 2).

Section 4.2, Schedule of Events, Table 1

Change: Footnote 10 (previously Footnote 12 in Version 1.0) was updated.

Now reads:

[redacted]

Rationale: A[redacted]

[redacted]

Section 4.2, Schedule of Events, Table 1

Change: Footnote 11 (previously Footnote 13 in Version 1.0) was updated.

Now reads:

[redacted]

Rationale: [redacted]

[redacted]

Section 4.2, Schedule of Events, Table 1

Change: Footnote 12 (previously Footnote 14 in Version 1.0) was updated.

[redacted]

Rationale: [redacted]

Section 4.2, Schedule of Events, Table 2

Change: New footnote 8 was added.

Now reads:

[redacted]

Rationale: [redacted]

Section 4.2, Schedule of Events, Table 2

Change: Footnote 10 was deleted.

Now reads:

[redacted]

Rationale: To avoid redundancy with footnotes 6 and 7.

Section 4.2, Schedule of Events, Table 2

Change: A timepoint for collecting body weight was added, and missing text that AE, concomitant therapy and procedures, and SAE reporting will be monitored continuously throughout the study was added.

Now reads:

	Treatment Period																FU
Study Week	50	52	56	60	64	68	72	76	78	80	84	88	92	96	100	102/ EOT	UV for a ~~e~~**C**hange in ~~AD~~ **Alzheimer's Disease** ~~m~~**M**edication	118 (or 18 wks after ~~final~~ **last** dose for participants who DCT early)
Study Day	351 ± ~~35~~	365 ± ~~35~~	393 ± ~~35~~	421 ± ~~35~~	449 ± ~~35~~	477 ± ~~35~~	505 ± ~~35~~	533 ± ~~35~~	547 ± ~~35~~	561 ± 5	589 ± 5	617 ± 5	645 ± 5	673 ± 5	701 ± 5	714 ± 5		827± 5
Body Weight		X	X	X	X	X	X	X		X	X	X	X	X	X	**X**		
.....																		
AE Reporting	**Monitor and record continuously throughout the study**																	
Concomitant Therapy[9] and Procedures	**Monitor and record continuously throughout the study**																	
SAE Reporting	**Monitor and record continuously throughout the study**																	

[9] **Participants who have a change in Alzheimer's disease medication (other than study treatment) during the Treatment Period should have an unscheduled visit. A subset of the clinical efficacy assessments [redacted] should be performed prior to the change in medication if the participant alerts the Investigator before the change in medication occurs. In the event that the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments are performed within 30 days after the change in medication, the assessments do not have to be repeated.**

Rationale: Because body weight is part of the safety assessments, this assessment was added at EOT (Week 102). The text for AE, concomitant therapy and procedures, and SAE reporting was inadvertently not included in the previous version and is now added. Also added a footnote to provide guidance on changes in concomitant medication, specifically related to Alzheimer's disease. This change also affects Section 7.3, Overall Study Duration and Follow-Up.

Section 4.2, Schedule of Events, Table 3

Change: Footnote 6 was modified to provide clarity on collection window for UV.

Now reads:

[6] One sample will be collected within ±~~2~~ **5** days of the MRI visit. Exact collection date and time will be captured for all [redacted] on a specified ~~case report form~~ **CRF**. Collection of aducanumab serum for [redacted] **will** also **be** performed at Weeks 1, 24, and 48 (see Table 1) and ~~Week~~ **Weeks 72 and** 102 (see Table 2). **For UV due to ARIA, sample will be collected within ± 2 days of the MRI visit.**

Rationale: A missing timepoint for [redacted] was added. Text was added to clarify that the [redacted] time window in case of ARIA event will be within ± 2 days of the MRI visit to capture the change due to ARIA closer to the event.

Clarified blood as serum for [redacted].

This change also affects Section 4.2, Schedule of Events (footnotes of Table 4).

Section 4.2, Schedule of Events, Table 3

Change: [redacted]

Now reads:

Study Week	Screening (≤ 60 days before Day 1)[1]	Treatment Period														UV/MRI for ARIA[4]	FU[2]
		1	2	6	10	14	18	22	26	30	42	54	66	78	102/ EOT[3]		118 (or 18 wks after ~~final~~ **last** dose for participants who DCT early)
Study Day		1	15 ~~±3~~ **5**	43 ~~±3~~ **5**	71 ~~±3~~ **5**	99 ~~±3~~ **5**	127 ~~±3~~ **5**	155 ~~±3~~ **5**	183 ~~±3~~ **5**	211 ~~±3~~ **5**	295 ~~±3~~ **5**	379 ~~±3~~ **5**	463 ~~±3~~ **5**	547 ~~±3~~ **5**	714 ± 5		827± 5
[redacted]																	
Physical Examination																**X**	
Neurological Examination																**X**	
Vital Signs[7]																**X**	

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

Rationale: [redacted] Physical examination, neurological examination, and vital sign collection were added for UVs due to ARIA to monitor participants. A footnote was added to provide details about vital sign collection, for consistency with other occurrences.

Section 4.2, Schedule of Events, Table 3

Change: Footnote 8 was modified (previously Footnote 7 in Version 1.0).

Now reads:

[8] Sample may be collected **within** ± 2 days of the MRI visit ~~at the same time as sample collection for aducanumab concentration.~~

Rationale: Clarified that [redacted] collection time window in case of ARIA event will be ± 2 days of the MRI visit to capture the change due to ARIA closer to the event.

This change also affects Section 4.2, Schedule of Events (footnotes of Table 4).

Section 4.2, Schedule of Events, Table 4

Change: Urine pregnancy testing and [redacted] and corresponding footnotes were added.

Now reads:

	Post-Treatment Visit Schedule[1]									
Study Week	12	24	26	48	50	72	78	92	102 (EOT)[2]	UV for ARIA[3]
Study Day	85 ± ~~35~~	169 ± ~~35~~	183 ± ~~35~~	337 ± ~~35~~	351 ± ~~35~~	505 ± ~~35~~	547 ± ~~35~~	645 ± 5	714 ± 5	
Urine Pregnancy Test[4]		**X**		**X**		**X**	**X**	**X**		
……..										
[redacted]										

[4] **Required only if last dose of study treatment was less than 24 weeks before the clinic visit.**

Rationale: Urine pregnancy screening and a corresponding footnote were added to ensure that female participants are followed up until 24 weeks after the last dose of study treatment to abide by the protocol. [redacted] was added because it was inadvertently missed in the previous version.

Section 4.2, Schedule of Events, Table 4

Change: Collection timepoints for some assessments were removed.

Now reads:

	Post-Treatment Visit Schedule[1]									
Study Week	12	24	26	48	50	72	78	92	102 (EOT)[2]	UV for ARIA[3]
Study Day	85 ± ~~35~~	169 ± ~~35~~	183 ± ~~35~~	337 ± ~~35~~	351 ± ~~35~~	505 ± ~~35~~	547 ± ~~35~~	645 ± 5	714 ± 5	
Hematology, Blood Chemistry, and Urinalysis		~~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	
…										
[redacted]										

Rationale: Timepoints for assessments were removed to maintain consistency with the Schedule of Events for participants receiving treatment.

Section 4.2, Schedule of Events, Table 4

Change: Footnote 4 regarding infusion was deleted.

Now reads:

[4] ~~Samples will be collected prior to infusion (where applicable).~~

Rationale: Because this applies to participants who discontinue study treatment, this footnote was removed.

Section 4.3.1, Site Staff

Change: Language around treating HCPs was simplified.

Now reads:

A minimum of 2 separate HCPs are required for this study:

1. A treating HCP (the ~~PI or Sub-investigator~~ **Investigator** may serve as a treating HCP) who is responsible for the following:

Rationale: The terms "PI" and "Sub-investigator" were changed to "Investigator."

This was a global change made in the protocol to keep consistency in usage of the term "Investigator."

Section 4.3.1, Site Staff

Change: [redacted]

Now reads:

[redacted]

Rationale: [redacted]

Section 4.3.1, Site Staff

Change: Assessments to be administered and the role of the rating HCP were updated.

Now reads:

An independent rating HCP (designated by the Investigator of the site) who is responsible for administering the [redacted] and ~~CAM~~**C-SSRS**.

~~The 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 introducing bias.~~

Rationale: All [redacted] and C-SSRS were included to be administered by independent HCP raters to maintain consistency in assessments. Text that was not consistent with independent HCP rater responsibility was deleted.

Section 4.3.1, Site Staff

Change: Language regarding personnel involved in test administration was added.

Now reads:

A pharmacist (or authorized designee) will be responsible for the storage, distribution, preparation, and accountability of study treatment. The pharmacist will also be responsible for maintaining the pharmacy record.

For further details about test administration and roles and responsibilities of HCPs and study personnel, please consult the Study Reference Manual.

Rationale: This change was made to provide reference to roles and responsibilities of personnel administering tests.

Section 5.1.2, Clinical Experience

Change: Results from Studies 221AD103, 221AD301, and 221AD302 were added.

Now reads:

~~Aducanumab has been evaluated in one~~ **The aducanumab clinical development program comprises 7 clinical studies, including 1** completed ~~single ascending dose~~ study ~~(221AD101) and one~~ **in healthy volunteers and 6** completed ~~multiple ascending dose study (221AD103).~~**or terminated studies in subjects with Alzheimer's disease**. **A summary of the clinical experience accumulated so far is provided below.**

Study 221AD101

~~Study 221AD101~~ **This** was a Phase 1, randomized, double-blind, placebo-controlled~~,~~ study of aducanumab in participants with mild or moderate ~~AD~~ **Alzheimer's disease**. 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 IV infusions. The secondary objectives were to assess the PK and immunogenicity of aducanumab after single-dose administration.

~~The tolerability, safety, PK, and PD of aducanumab given once every 4 weeks was first assessed in a Phase 1b study (Study 221AD103);~~ [redacted] ~~. Interim data from this study informed the design of the Phase 3 program.~~

Study 221AD103

~~Study 221AD103~~ **This** was a Phase 1b study comprising a randomized, double-blind, placebo-controlled **design** in participants with prodromal or mild ~~AD~~ **Alzheimer's disease** ~~with a~~ **of** 1 year in duration followed by ~~a long-term extension~~ **an LTE** in which all participants received aducanumab in an open-label fashion (yet dose-blinded). The study was designed to assess the safety, PK, and PD of aducanumab in participants with prodromal Alzheimer's disease or mild Alzheimer's disease dementia with brain Aβ pathology confirmed by ~~[~~^{18}F~~]~~florbetapir **(Amyvid®)** PET imaging. The main PD assessment (secondary endpoint) was the effect of aducanumab on brain Aβ levels as measured by PET and quantified by a composite SUVR. [redacted] **At Screening, all participants were at the prodromal stage of Alzheimer's disease (**[redacted] **and a global CDR score of 0.5 or 1.0) or in stages of mild dementia (**[redacted] **and global CDR score between 0.5 and 1.0).** Doses investigated in the ~~P~~**p**lacebo-controlled ~~P~~**p**eriod included~~:~~ 1, 3, 6, and 10 mg/kg administered ~~every 4 weeks~~ **Q4W** as a fixed dose, and 10 mg/kg administered after a titration period of 44 weeks.

Placebo-Controlled Period Results

Results from the 1-year ~~Placebo~~ **placebo**-controlled ~~Period~~ **period** showed that treatment with aducanumab resulted in a statistically significant, dose-dependent reduction in brain Aβ PET composite SUVR as compared with placebo at Week 26, and a further statistically significant, dose-dependent reduction at Week 54. In addition, a dose-dependent reduction of clinical decline was observed in the fixed-dose aducanumab groups, as well as the titration group, with a statistically significant treatment effect observed for both aducanumab 10 mg/kg fixed-dose and titration on the [redacted] and for 10 mg/kg fixed dosing on the [redacted], as compared with placebo. The impact of aducanumab on Aβ PET reduction was already evident at 26 weeks, while a difference was only observed on clinical measures at 1 year.

Reduction in brain Aβ appears to be tightly associated with dose; the titration arm results are in line with the fixed-dose results based on the expected average dose in the titration arm (2.9 and 5.3 mg/kg at 6 and 12 months, respectively), with the point estimate at Week 26 (-0.047) between that in the 1 and 3 mg/kg fixed-dose groups, and the point estimate at Week 54 (-0.171)

between that in the 3 and 6 mg/kg fixed-dose groups. The results demonstrate engagement of aducanumab with amyloid plaques and a PD effect of dose- and time-dependent amyloid reduction.

Safety analyses showed that aducanumab had an acceptable safety ~~and tolerability~~ profile when given Q4W at doses up to 10 mg/kg for more than 5 years~~. Incidences and causes~~ **in Study 221AD103. The incidence and nature** of ~~death~~ **fatal SAEs** were consistent with underlying Alzheimer's disease and associated comorbidities. No **notable** differences were observed between aducanumab and placebo in the overall incidence of AEs or SAEs, except for ARIA events. The incidence of ARIA events (both ARIA-E and ARIA-H) appeared to be related to aducanumab dose and [redacted]; the **ARIA** events were typically asymptomatic, monitorable, and clinically manageable. ~~A small proportion of participants experienced more than 1 ARIA-E event during treatment, and ARIA was generally not associated with negative long-term clinical outcomes.~~

Participants with ARIA events who met certain criteria (for all clinical studies with aducanumab, including Study 221AD103) were required to temporarily suspend dosing with aducanumab. Therefore, certain participants with ARIA events experienced a transient interruption in dosing during prior clinical studies of aducanumab. In addition, only a small proportion of participants experienced more than 1 ARIA-E event during treatment.

Long-Term Extension Period Results

Data from the LTE of Study 221AD103 also provide insights relevant for the study population targeted in the present study (Study 221AD304). In the LTE period, those participants who started on active treatment at the beginning of the placebo-controlled period continued treatment (at the same dose as in the placebo-controlled period, except for the 1 mg/kg cohort who were switched to 3 mg/kg), while participants from the placebo arms initiated dosing with aducanumab. The main findings in Study 221AD103 during the LTE period regarding efficacy and safety for the high-dose groups (fixed-dose regimen of 10 mg/kg and titration to 10 mg/kg, which are the 2 relevant groups regarding the target dose in Study 221AD304) were the following:

1. [redacted]

    - **At Week 222, the adjusted mean changes from baseline in the 10 mg/kg fixed-dose and 10 mg/kg titration groups (3.83 and 3.68, respectively) were numerically smaller than the adjusted mean changes in the 1, 3, and 6 mg/kg groups that continued dosing (range 5.48 to 8.43) and the group that switched from placebo to aducanumab after 1 year (6.15).**

2. **The safety profile of aducanumab in the LTE was similar to that seen in the placebo-controlled period:**

    - **Participants who began treatment with aducanumab during the placebo-controlled period had a low incidence of ARIA-E in the LTE (5% for 10 mg/kg fixed dose and 17% for titration to 10 mg/kg).**

The incidence of ARIA-E in participants who began treatment with aducanumab in the LTE (22%) was similar to the incidence in participants who began treatment in the placebo-controlled period (24%).

Studies 221AD301 and 221AD302

~~Studies 221AD301 and 221AD302~~ **These** were large Phase 3 randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy**, PK,** and safety of aducanumab in participants with early stages of Alzheimer's disease. ~~Preliminary results from these studies provide the rationale for the present study and are described~~ **Refer to the updated IB for details for re-analysis of efficacy, PK, and safety. Highlights of efficacy re-analysis are provided** in Section 5.2.

Refer to the updated IB **(Version 13.0)** for further data from Studies **221AD**103, **221AD**301, and **221AD**302, as well as from other early phase aducanumab clinical studies.

Rationale: New information from Study 221AD103 was added to provide supporting information on the long-term efficacy of aducanumab. A reference to the most recent version of the IB was provided for final results from Studies 221AD301 and 221AD302 (these results were not added in the body of the protocol due to the extent of changes, but a clear reference to the IB was provided for Investigators).

Section 5.2, Study Rationale

Change: Study rationale was updated with new available information.

Now reads:

This open-label, single-arm clinical study is being conducted to assess the long-term safety and efficacy of aducanumab in participants with Alzheimer's disease who were active in ~~Aducanumab~~ **aducanumab** clinical studies **(Study 221AD**103 **[PRIME]**, **Study 221AD**205 **[EVOLVE]**, **Study 221AD**301 **[ENGAGE]**, ~~or~~ **and Study 221AD**302 **[EMERGE]), from now on named "feeder studies," at the time of their early termination** as of 21 March 2019. On that date, Biogen announced the discontinuation of the Phase 3 aducanumab clinical studies, based on results from a preplanned futility analysis; discontinuation of the other ongoing studies (~~Studies~~ **221AD**103 and **221AD**205) was announced **and implemented** at the same time. The present study (221AD304) is being undertaken based on ~~analyses~~ **efficacy findings** from additional ~~data~~ **analyses** of the ~~two~~ **2** Phase 3 studies (results summarized below). In these new analyses, ~~Specifically, the analysis of this larger dataset showed~~ Study **221AD**302 ~~to be~~ **was**

statistically significant on the ~~pre-specified~~ **prespecified** primary endpoint (~~P~~**p**=0.01). ~~Study 301 did not meet its primary endpoint; however, participants in Study 301 who received high aducanumab doses/exposure had outcomes similar to the Study 302 results and these Study 301 data support the findings from Study 302.~~

Background: Interim Futility Analysis

The **221AD**301 and **221AD**302 studies were 2 large Phase 3 randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of aducanumab in participants with early Alzheimer's disease (MCI due to Alzheimer's disease and mild Alzheimer's dementia). The duration was planned for 18 months of placebo-controlled period and up to 5 years of ~~long-term extension~~ **LTE**. The preplanned futility analysis was performed on data collected as of 26 December 2018, when approximately 50% of participants had the opportunity to complete the Week 78 ~~visit~~ **Visit** (57% [954 participants] from Study **221AD**301 and 49% [803 participants] from Study **221AD**302).

Results based on data from these participants were provided to the ~~independent data monitoring committee (~~IDMC~~)~~ who reviewed the data and confirmed that the prespecified futility criteria were met. Biogen reviewed the results and concurred with the IDMC and publicly announced the decision to discontinue the Phase 3 program and the other ongoing clinical studies on 21 March 2019.

On 21 March 2019, Biogen announced the early termination of the 2 Phase 3 studies (Studies 221AD301 and 221AD302) based on results of a prespecified interim futility analysis. No participant was dosed after 20 March 2019.

Analyses Conducted Postfutility Announcement

Subsequent to these events, further analyses on the Phase 3 studies were conducted, using data from all randomized and dosed participants collected through 01 April 2019 **and** with data after 20 March 2019 censored for efficacy analysis. These data comprised 63% of participants from both the **221AD**301 and **221AD**302 studies (66% from **221AD**301 and 60% from **221AD**302) who had the opportunity to complete the placebo-controlled period of the study. In both the **221AD**301 and **221AD**302 studies, 87% of participants had the opportunity to reach Week 50 and 100% with opportunity to complete Week 26. The results from this larger dataset differed markedly from the futility results:

- In Study **221AD**302, treatment with the aducanumab high-dose regimen significantly reduced clinical decline compared with placebo on the primary endpoint**, –**change from baseline to Week 78 on the CDR-SB (difference versus placebo -0.40 [-23%]; p=0.010). In addition, 2 of the 3 secondary endpoints**, –**change from baseline to Week ~~79~~**78** on ADAS-Cog 13 (difference with placebo -1.395 [-27%]; p=0.0098) and ADCS-ADL-MCI (difference versus placebo 1.7 [-40%]; p=0.0009) were also positive, while the MMSE showed a positive trend but ~~didn't~~ **did not** reach significance (difference with placebo 0.5 [-15%]; p=0.06**2**). In the low-dose group, a

~~non-significant~~ **nonsignificant** numeric effect was observed for aducanumab-treated participants versus placebo.

- Study **221AD**301 did not meet the primary endpoint in the high-dose arm~~, while non-significant numeric advantages over placebo were seen for 2 of 3 secondary endpoints. Results for the low-dose group were similar to those in Study 302 low-dose group~~.

- [redacted] consistent with findings in the Phase 1b study (Study 221AD103, PRIME).

…….

Given the significance of these results, the Sponsor ~~is reinitiating~~ **has reinitiated** the evaluation of aducanumab in this open-label, single-arm clinical trial, to evaluate the long-term safety and efficacy of the drug in participants previously enrolled in the studies that were ongoing at the time of the futility announcement (the 2 Phase 3 studies, the ~~long-term extension~~ **LTE** study for the Phase 1b study [Study **221AD**103], and the safety study [Study 221AD205]). **This study will also assess the degree to which [redacted] and clinical measures of the treatment effect of aducanumab are maintained following a sustained interruption in dosing.**

Final database lock for both pivotal trials was only achieved in close temporal proximity to the finalization of this study protocol. Analyses of the final dataset for the primary and secondary efficacy endpoints were conducted after the final database lock and the results of these final analyses do not differ overall from the larger dataset results discussed above. The efficacy results for the ~~two~~**2** studies are presented in Table 5 and Table 6.

Refer to the updated IB (Version 13.0) for further efficacy results of the Phase 3 studies (221AD301 and 221AD302).

Rationale: Clarification that no dosing happened in feeder studies after 20 March 2019 was added. A reference to the most recent version of the IB was provided for final efficacy results from Studies 221AD301 and 221AD302 (these results were not added in the body of the protocol due to the extent of changes, but a clear reference to the IB was provided for Investigators).

This change also affects Section 7.1, Study Overview, where the definition of feeder studies was removed.

Section 7.2.1, Dose Suspension or Discontinuation for ARIA Events

Change: A general statement about [redacted] was added.

Now reads:

Discontinuation of Dosing for a Given Participant

The central MRI reading center will report incident events of ARIA-E and ARIA-H to both the Sponsor and the Investigator within a specified time after observing the finding on MRI per the imaging manual procedures. All events of ARIA will be reviewed by the Sponsor and the Investigator; decisions on dosing continuation, interruption, or discontinuation will be based on clinical symptoms, and the radiographic severity scoring on the MRI ~~recport~~ **report** provided by the central reader. Guidelines on the management and disposition of ARIA-E and ARIA-H events (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. **After each ARIA event,** [redacted] **will be collected at the time of the first unscheduled visit following the event.** 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.

…….

- Participants who develop mild ARIA-E, per central MRI reading, with no clinical symptoms during the episode of ARIA-E, may continue in the study at their current dose. Participants should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and [redacted] ~~every 4 weeks~~ **Q4W** (± 5 days) until the ARIA-E has resolved per the centrally read MRI. ~~In addition,~~ [redacted] ~~will be collected at the first unscheduled visit following an episode of ARIA.~~

- Participants who develop moderate or severe ARIA-E, per central MRI reading, with no clinical symptoms during the episode of ARIA-E will ~~have their treatment~~ temporarily ~~suspended~~ **suspend treatment**, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and [redacted] ~~every 4 weeks~~ **Q4W** (± 5 days) until the ARIA-E has resolved per the ~~centrally read~~ **centrally read** MRI. ~~In addition,~~ [redacted] ~~will be collected at the first unscheduled visit following an episode of ARIA.~~ If the ARIA-E resolves and the participant remains asymptomatic (in the Investigator's opinion), the participant may resume treatment at the same dose.

- Participants who develop mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by clinical symptoms during the **episode of** ARIA-E ~~episode should~~ **will** temporarily suspend treatment, but should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and

[redacted] ~~every 4 weeks~~ **Q4W** (± 5 days) until the ARIA-E has resolved per the ~~centrally-read~~ **centrally read** MRI. ~~In addition,~~ [redacted] ~~will be collected at the first unscheduled visit following an episode of ARIA.~~ If the ARIA-E resolves and the clinical symptoms resolve (in the Investigator's opinion), the participant may resume treatment at the same dose.

- Participants who develop mild, moderate, or severe ARIA-E, per central MRI reading, accompanied by serious (except "other medically important event") clinical symptoms related to the current episode of ARIA-E will permanently ~~discontinue treatment~~ **DCT** but remain in **the** study. Participants should complete ~~an~~**a safety** FU Visit 18 weeks after the ~~final~~ **last** dose **of study treatment**, protocol-required tests and assessments at a subset of the clinic visits (see Table 4), and, in addition, have an unscheduled visit for an MRI and [redacted] ~~every 4 weeks~~ **Q4W** (± 5 days) until the ARIA-E has resolved per ~~centrally-read~~ **centrally read** MRI~~. In addition,~~ [redacted] ~~will be collected at the first unscheduled visit following an episode of ARIA~~.

Rationale: Language was rearranged to remove redundancy.

This change also affects Section 7.2.1.2, ARIA-H (Micro-hemorrhage); Section 7.2.1.3, ARIA-H (Superficial Siderosis); and Section 7.2.1.4, ARIA-H (Macro-hemorrhage).

Section 7.2.1.2, ARIA-H (Micro-hemorrhage)

Change: Text was updated to clarify what will be considered micro-hemorrhages for the study.

Now reads:

In this study, new incident ~~microhemorrhages~~ **micro-hemorrhages** are defined as ~~new incident microhemorrhages~~ **micro-hemorrhages** that ~~occur on treatment~~ **start after aducanumab infusion per this study (221AD304)** and do not include ~~microhemorrhages at~~ **micro-hemorrhages seen on the** baseline **MRI done for this study**.

Rationale: This change was made to clearly define the criteria for counting new ARIA-H (micro-hemorrhages) events that occur in this study.

This change also affects Section 7.2.1.2, ARIA-H (Micro-hemorrhage) (footnote of Table 8); Section 10.1, Discontinuation of Study Treatment.

Section 7.2.1.2, ARIA-H (Micro-hemorrhage)

Change: Collection of PBMCs and resuming treatment after ARIA-H is deemed stable were removed.

Now reads:

Asymptomatic ARIA-H (~~Microhemorrhage~~ **Micro-hemorrhage**)

- Participants who develop a ≥ 1 and ≤ 4 new incident ~~microhemorrhage~~ **micro-hemorrhage**(s) [mild] at any time during the study may continue treatment at the current dose. Participants should complete all scheduled clinic visits for assessments and, in addition, have an unscheduled visit for an MRI and [redacted] ~~every 4weeks~~ **Q4W** (± 5 days) until the ARIA-H ~~microhemorrhage~~ **micro-hemorrhage** is confirmed stable per the ~~centrally-read~~ **centrally read** MRI. ~~In addition, [redacted], and PBMC samples will be collected at the first unscheduled visit following an episode of ARIA. Microhemorrhages~~ **Micro-hemorrhages** 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, the subject may resume treatment at the same dose~~.

- …..... ~~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.~~

  ……

- Participants who experience serious (except "other medically important event" [Section 15.1.2]) clinical symptoms associated with ~~microhemorrhage(s)~~ **micro-hemorrhage(s) (independent of the radiographic severity of the event)** will permanently ~~discontinue treatment~~ **DCT** but remain in **the** study.

Rationale: PBMC collection for mild asymptomatic ARIA-H (micro-hemorrhage) was removed to keep management of this subtype of ARIA consistent with that of the other subtypes. Because there is no suspension of treatment in asymptomatic mild ARIA-H, the sentence about resuming treatment was removed. Text was deleted concerning what is considered a stable microhemorrhage to avoid redundancy. It was also added that for serious symptomatic ARIA-H, discontinuation is independent of radiographic correlation.

Section 7.2.1.3, ARIA-H (Superficial Siderosis)

Change: Text was updated to clarify conditions for severe symptomatic superficial siderosis.

Now reads:

Participants who develop >2 new focal areas of superficial siderosis (severe)**,** regardless of **the presence of** clinical ~~symptom severity~~**symptoms,** will permanently ~~discontinue treatment~~**DCT** but remain in **the** study.

Rationale: Provided clarification that treatment should be discontinued for any radiographically severe superficial siderosis, regardless of the presence of clinical symptoms.

Section 7.2.1.5, Coincident ARIA-H and ARIA-E Events

Change: Clarification in an example situation was added.

Now reads:

Participants 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 participant must be asymptomatic. For example, if a participant experiences radiographically mild~~, asymptomatic~~ ARIA-H (~~1-4 microhemorrhages~~ **1 to 4 micro-hemorrhages**) coincident with ~~ARIA-E assessed as~~ **radiographically** moderate ~~on MRI and accompanied by mild clinical symptoms, the dose~~ **ARIA-E, the participant will** ~~should be~~ **temporarily** ~~suspended~~ **suspend treatment** per the ARIA-E guidelines summarized in Table 7. In addition, unscheduled visits should occur as described in Section 7.2.1.1**, Section 7.2.1.2, Section 7.2.1.3, and** ~~through~~ Section 7.2.1.4.

Rationale: Text was updated for clarity regarding specifications for the instance in which participants develop ARIA-H coincident with ARIA-E.

Section 7.3, Overall Study Duration and Follow-Up

Change: Text was updated to clarify the number of weeks in the Treatment Period.

Now reads:

The study ~~period~~ will consist of Screening, Treatment, and FU **periods**. **A schematic of the study is presented in Figure 1.**

Study duration for each participant will be approximately 126 weeks: an **approximately** 8-week ~~screening period~~ **Screening Period**, a ~~100~~**102**-week ~~treatment period~~ **Treatment Period**, and a ~~18-week~~ safety ~~follow-up visit~~ **FU Visit 18 weeks after the last dose of study treatment**.

Rationale: Treatment Period was clarified to last 102 weeks instead of 100 weeks so the EOT visit would be included as part of the Treatment Period. Added reference to study schematic.

This change also affects Section 4.1, Study Schematic (Figure 1).

Section 7.3, Overall Study Duration and Follow-Up

Change: Adjusted number of scheduled clinical visits.

Now reads:

Participants will have up to ~~33~~**38** scheduled clinic visits during the study. All visits should be performed ± 5 days from the nominal visit day.

Rationale: MRI visits were also counted to update the number of clinical site visits.

Section 7.3, Overall Study Duration and Follow-Up

Change: A contingency plan for COVID-19 and/or other challenging circumstances for Screening Visit was added.

Now reads:

- Screening Visits no more than 60 days before the first dose of study treatment on Day 1 (~~visits~~ **Screening Visits** may be ~~conducted on multiple days)~~ **carried out over 2 separate visits, at the Investigator's discretion)**. It is recommended that all screening procedures be completed within 60 days; however, the overall ~~screening period~~ **Screening Period** may be extended up to 90 days in the event of ~~logistical issues related to~~ [redacted] **and/or other logistics restrictions due major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters)** and is subject to Sponsor approval.

Rationale: Flexibility around Screening Visits was added to accommodate study participation restrictions owing to major disasters.

This change also affects Section 4.2, Schedule of Events (Footnotes of Table 1 and Table 3); Section 7.3.1, Screening; and Section 9.1, Screening and Enrollment.

Section 7.3, Overall Study Duration and Follow-Up

Change: Updated clinical assessment visits.

Now reads:

- 4**6** visits for clinical assessments, **including Screening and FU at Week 118 (or 18 weeks after the last dose of study treatment for participants who DCT early).**

- …..
- ~~1 FU safety visit at Week 118 (or 18 weeks after last dose of study treatment for those participants who discontinue early).~~

Rationale: Updated clinical assessments visits to include Screening and FU Visits, and consequently deleted separate FU visit.

Section 7.3, Overall Study Duration and Follow-Up

Change: Rearranged and grouped visits for substudies.

Now reads:

Rationale: [redacted]

Section 7.3, Overall Study Duration and Follow-Up

Change: Information regarding medication dose changes was added.

Now reads:

Participants who have a change in ~~AD~~ **Alzheimer's disease** medication (other than study treatment) during the Treatment Period should have an unscheduled visit; a subset of the clinical efficacy assessments [redacted] should be performed prior to the change in medication **if the participant alerts the Investigator before the change in medication occurs. In the event that the change in medication occurs before clinical efficacy assessments are performed, the clinical efficacy assessments must be performed within 30 days of the Investigator being notified about the change. If clinical efficacy assessments are performed within 30 days after the change in medication, the assessments do not have to be repeated**.

Rationale: Communication scenarios in case a participant has a change in Alzheimer's disease medication (other than study treatment) were added.

This change also affects Section 4.2, Schedule of Events (Table 1 and Table 2, added new footnotes) and Section 11.5.1.2, Disallowed Concomitant Therapy.

Section 7.3.1, Screening

Change: Details of re-assessing were added.

Now reads:

Participant eligibility for the study will be determined no more than 60 days prior to **the first dose of** study ~~entry.~~ **treatment on Day 1**. It is recommended that all screening procedures be completed within 60 days **(Screening Visits may be carried out over 2 separate visits, at the Investigator's discretion);** however, the overall ~~screening period~~**Screening Period** may be extended up to 90 days in the event of ~~logistical issues related to~~ [redacted] **and/or other logistics restrictions due to major causes (i.e., institutional restrictions or participant disposition due to COVID-19 or other major disasters)** and is ~~dependent on~~**subject to** Sponsor approval. **Only in the event of inadequate tracer supplies or** [redacted]

[redacted]

Section 7.3.1, Screening

Change: Details for rescreening were provided.

Now reads:

Participants who fail screening will be permitted to be rescreened ~~once~~ **up to 2 times** at the Sponsor's discretion~~. Participants who fail~~ **in cases when a participant fails** screening ~~because allowed chronic medications have not been at stable doses for at least 4 weeks prior~~ to ~~Screening whose use of AD medications has not been at stable doses for at least 8 weeks prior to Screening Visit may return for~~ **due to logistics restrictions owing to major causes (i.e., institutional restrictions or disposition due to COVID-19 or other major disasters)** ~~rescreening after use of these medications has been stabilized for the required period~~. **Rescreened participants will be assigned a new number. At rescreening, all assessments should be repeated except for** [redacted]**.**

Rationale: Clarity was provided on 1) the number of allowed rescreens (up to 2) to account for COVID-19 situations (previously in aducanumab Phase 3 trials, 1 rescreening was allowed mainly due to medication washout per inclusion/exclusion criteria) and 2) assessments that need to be repeated when participants are rescreened.

Section 7.5, Unscheduled Visits

Change: An incorrect statement was removed.

Now reads:

Data collected during unscheduled visits should be recorded on CRFs only if the data support protocol objectives and/or are required for safety monitoring.

~~If participants return for unscheduled visits, no study-related data should be collected.~~

Rationale: A sentence that had inconsistent information regarding an UV was deleted.

Section 8.1, Inclusion Criteria

Change: Inclusion language in inclusion criterion 1 for participants from feeder studies was clarified.

Now reads:

Participant was participating in an aducanumab clinical study at the time of the announcement of early termination (~~Studies 221AD301, 221AD302, 221AD103, and 221AD205, referred to as~~ "feeder studies"). Note **#1**: Participants who ~~had~~ formerly participated in feeder studies and had

to permanently discontinue the investigational product and/or exited a feeder study due to ~~circumstances~~ **protocol mandatory requirements for discontinuation** that are no longer applicable at the time of screening will be evaluated by the Sponsor on a ~~case by case~~ **case-by-case** basis. Note #2: Participants who completed screening ~~on~~ **in Study** 221AD205 and were confirmed eligible prior to 21 March 2019 but were not randomized due to the discontinuation of the trial~~,~~ may have the opportunity to screen on this study upon review/approval from the Sponsor.

Rationale: Text was revised to specify that participants who discontinued feeder studies can be considered for participation in Study 221AD304 if their discontinuation in the feeder study was due to protocol requirements and not general circumstances.

Section 8.1, Inclusion Criteria

Change: [redacted]

Now reads:

[redacted]

Rationale: The inclusion criterion was updated to provide disease-specific inclusion criteria to assess disease stage.

Section 8.1, Inclusion Criteria

Change: Practice of effective contraception with respect to half-life of the study treatment was added to inclusion criterion 4.

Now reads:

4. Female participants of childbearing potential ~~and male participants~~ must practice effective contraception during the study and for **5 times the half-life or** 24 weeks (whichever is longer) after their last dose of study treatment. Refer to Section 15.5.

Rationale: To keep consistent with the required timeframe to maintain effective contraception mentioned in Section 15.5.

This change also affects Section 15.4.1, Pregnancy.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 4 was updated regarding MRI findings for the study.

Now reads:

4. Brain MRI (performed at ~~screening~~**Screening**, ~~centrally-read~~ **centrally read**) evidence of any of the following:

    - Acute or subacute hemorrhage.
    - Prior ~~macrohemorrhage~~ **macro-hemorrhage** (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 participant is at risk of recurrent hemorrhage).
    - Greater than 4 (for treatment-naïve participants) or ≥ 10 (for aducanumab ~~previously-treated~~ **previously treated** participants) ~~microhemorrhages~~ **micro-hemorrhages** (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).~~
    - Any focal area of superficial siderosis (for treatment-naïve participants) or 3 or more focal areas of superficial siderosis (for aducanumab previously treated participants).

Rationale: The definition of macro-hemorrhage was corrected for consistency. The occurrence of more than 1 lacunar infarct as exclusionary was removed.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 10 was updated to provide exception for cancer patients.

Now reads:

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

    - Participants ~~with~~ **whose** cancer **is** in remission ~~more than 2 years~~ **according to the cancer specialist** prior to Screening.
    - Participants with a history of excised or treated basal cell or squamous carcinoma of the skin.
    - ~~Participants with localized prostate cancer with treatment cycles that completed at least 6 months prior to Screening.~~

Rationale: Modified malignancy exclusion criteria and its exceptions to align with the conduct around intercurrent cancers during the Phase 3 trials. In these studies, participants with intercurrent cancers were able to reinitiate dosing once their cancer was treated without any stipulations/requirements for a cancer-free period. Therefore, the first sub-bullet was modified to request a report that confirms a "cancer in remission" status by the cancer specialist. The second sub-bullet was left intact because an excised basal cell or squamous cell carcinoma is de facto in remission. The third sub-bullet was deleted because it was a description of "localized prostate cancer" in remission and therefore was redundant with the first sub-bullet.

Section 8.2, Exclusion Criteria

Change: New exclusion criteria 23, 24, 25, and 26 were added to include additional medications that will not be allowed during the study.

Now reads:

22. Use of allowed ~~chronic~~ medications **for chronic conditions** at doses that have not been stable for at least 4 weeks prior to Screening up to ~~Study~~ Day 1, or use of ~~AD~~ **Alzheimer's disease** medications (including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine) at doses that have not been stable for at least 8 weeks prior to Screening up to ~~Study~~ Day 1.

23. **Chronic use of systemic immunosuppressive drugs (including systemic corticosteroids) as indicated in Section 11.5.1.2. Local and/or topical immunosuppressants will be allowed.**

24. **Use of chemotherapeutic agents and checkpoint inhibitors.**

25. **Use of parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, or plasmapheresis.**

26. **Use of vaccinations within 10 days prior to Day 1.**

27. Use of medications with platelet anti-aggregant or ~~anti-coagulant~~ **anticoagulant** properties (the use of aspirin at a dose ≤ 325 mg daily is allowed).

Rationale: Systemic immunosuppressants, chemotherapeutic agents and checkpoint inhibitors, and immunoglobulins were added to the exclusion criteria for consistency with disallowed concomitant medication and vaccination.

This change also affects Section 11.5.1.2, Disallowed Concomitant Medication.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 29 (exclusion criterion 25 in Version 1.0) was updated regarding investigational product use.

Now reads:

29. Participation in any study **in which the participant is taking an investigational product for Alzheimer's** disease **(**with purported disease-modifying ~~effect in AD~~ **treatment or not)** unless **the** participant has fulfilled a ~~wash out~~ **wash-out** period of at least 5 half-lives for that particular investigational product or is able to provide documentation of having received placebo in that investigational product study.

Rationale: Participation in other investigational studies while in the current study was restricted.

Section 9, Enrollment and Registration

Change: Updated section subheading.

Now reads:

Enrollment~~,~~ **and** Registration~~, and Randomization~~

Rationale: Corrected because there is no randomization.

This change also affects Section 8.2, Exclusion Criterion (specifically #9).

Section 11.5.1.1, Allowed Concomitant Therapy

Change: Language about Investigator's communication was changed.

Now reads:

However, medically indicated medication or treatment should not be withheld. Participants should inform the Investigator of any changes in medication. The ~~change should be reviewed by the~~ Investigator ~~and~~ **needs to ensure pertinent communication with** the study ~~m~~**M**edical ~~m~~**M**onitor ~~to determine whether the participant's study treatment should be suspended~~ **if there are changes in medication of any nature that will have an effect on cognitive assessment**. Medications used to treat AEs would not result in automatic permanent study treatment discontinuation.

Rationale: This update provided flexibility in terms of the Investigator's communication with the Medical Monitor while implementing changes in medication that will have an impact on cognitive assessment.

Section 11.5.1.2, Disallowed Concomitant Therapy

Change: Clarification on disallowed medications was provided.

Now reads:

- Nonprescription narcotic medication.
- ~~Immunosuppressive~~ **Cannabinoids (prescription or recreational)**.
- **Systemic immunosuppressive** drugs (including systemic corticosteroids). **Local or topical immunosuppressants will be allowed.** Local corticosteroids (including inhaled and topical corticosteroids) are allowed; certain systemic corticosteroids may be permitted at the Sponsor's discretion.
- **Chemotherapeutic agents and checkpoint inhibitors.**

Rationale: Text was updated to clarify that the excluded narcotics include cannabinoids and that systemic immunosuppressants are excluded (while local and topical immunosuppressants are allowed).

[redacted]

Change: Added remote visit language.

Now reads:

Refer to Section 4.2 for the timing of assessments.

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

Rationale: Added information on how efficacy assessments will be collected during remote visits.

[redacted]

Change: Added a sentence about audio recording of some scales.

Now reads:

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

Rationale: Added to indicate that there will be training and evaluation for some scales.

[redacted]

Change: [redacted]

Now reads:

Where local regulations and EC approval allow, an optional [redacted] will be collected for future [redacted] from participants ~~who did not previously consent for this collection in the feeder study~~.

Rationale: Updated to clarify that all participants must provide consent for [redacted].

[redacted]

Change: Updated to change the number of years samples will be stored.

Now reads:

The [redacted] will be coded with the participant's identification number and stored for ~~15~~**25** years or a duration dictated by local, national, or regional laws or regulations.

Rationale: Increased the number of years that the [redacted] can be stored.

[redacted]

Change: This entire section was deleted.

Now reads:

[redacted]

[redacted]

[redacted]

Rationale: This section was deleted because this is not part of the current plan for this study.

Section 14, Safety Assessments

Change: Added remote visit language.

Now reads:

Refer to Section 4.2 for the timing of assessments.

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

Rationale: Added information on how safety assessments will be collected during remote visits.

Section 15.5, Contraception Requirements

Change: Information on postmenopausal status was updated.

Now reads:

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
  - **For women ≤ 55 years of age,** 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum ~~follicle-stimulating hormone (~~FSH~~)~~ level ~~>~~≥40 mIU/mL~~, or 6 weeks after surgical bilateral oophorectomy with or without hysterectomy~~.
  - **For women > 55 years of age, 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level ≥ 40 mIU/mL, or at least 5 continuous years of natural (spontaneous) amenorrhea without an alternative medical cause.**
  - **6 weeks after surgical bilateral oophorectomy with or without hysterectomy.**
- Posthysterectomy.
- Female surgical sterilization (e.g., bilateral tubal ligation).

Rationale: This update was made to clarify the postmenopausal FSH levels based on age.

Section 15.5, Contraception Requirements

Change: Male contraception requirements and sperm donation were removed.

Now reads:

- For females of childbearing potential:
  - Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action**.**
  - 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 (where applicable).
  - 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 (where applicable).~~
- ~~Female sexual partners who underwent surgical sterilization (e.g., bilateral tubal ligation), are postmenopausal, are posthysterectomy, or are using effective contraception as listed above for female participants.~~

~~For males and females of childbearing potential:~~

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

Rationale: Based on the toxicology profile update for aducanumab (from Patient Safety Information), male contraception is no longer required per Clinical Trials Facilitation and Coordination Group guidelines.

This change also affects other areas in Section 15.5, Contraception Requirements, and Section 8.1, Inclusion Criteria.

[redacted]

Change: [redacted]

Now reads:

[redacted]

[redacted]

Rationale: [redacted]

Section 16.4.2.2, Clinical Laboratory Results

Change: An inconsistent phrase was removed.

Now reads:

In addition, the shift from baseline to the maximum postbaseline value and the shift from baseline to the minimum postbaseline status will be presented for each laboratory test ~~by treatment group~~.

Rationale: Because all participants receive the same treatment, this phrase is not needed.

Section 16.7, Sample Size Considerations

Change: The projected sample size was added.

Now reads:

At the time that the feeder studies were stopped in March 2019**,** approximately 2600 participants had received treatment in 1 of those feeder studies. Approximately 400 participants were on placebo ("aducanumab treatment-naïve participants") and approximately 2200 participants had received aducanumab ("aducanumab ~~previously-treated~~ **previously treated** participants"). **Biogen estimates that of these 2600 participants, 2400 participants could be eligible based on inclusion and exclusion criteria to participate in the current study.**

Rationale: There was no sample size calculation because the sample size for this study is only a projected value from the feeder studies.

Section 18.3, Monitoring of the Study

Change: Language to allow remote data verification was added.

Now reads:

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

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

Rationale: This language was updated for consistency with the current template language.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- The title of the sponsor signatory was updated.
- Running headers were updated to be consistent with the present study design.
- Clarified that the IB referenced is Version 13.
- Change to use “care partner” throughout rather than “care giver” and “informant” (global change).
- [redacted]
- Clarified FU Visits as safety FU Visits (except in Tables 1 and 2).
- Clarified that safety FU is 18 weeks after last dose of study treatment (global change).
- Change to use “telephone” instead of “phone” for consistency.
- [redacted]
- Section 2, List of Abbreviations, was updated.
- Section 4.2, Schedule of Events (Table 4), updated the order of assessments to keep consistency across the different Schedule of Events tables for participants who were on treatment or off treatment.
- Section 12.1, Aducanumab, minor update to name of the drug to match updated style guide.
- Section 15.5, Contraception Requirements, the term “effective” was added to contraception methods, to keep consistent with inclusion criterion 4.
- Minor clarifications and editorial changes were made throughout the protocol.
- Typographical errors and formatting were corrected.

LIST OF ABBREVIATIONS

Aβ	amyloid beta (peptide derived from membrane-bound amyloid precursor protein)
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
[redacted]	[redacted]
AE	adverse event
[redacted]	[redacted]
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
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
CRF	case report form
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DCT	discontinue treatment
[redacted]	[redacted]
EOT	End of Treatment
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration

FSH	follicle-stimulating hormone
FU	follow-up
HCP	health care provider
[redacted]	[redacted]
IB	Investigator's Brochure
LTE	long-term extension
MCI	mild cognitive impairment
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
[redacted]	[redacted]
[redacted]	[redacted]
MRI	magnetic resonance imaging
[redacted]	[redacted]
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)
Q4W	once every 4 weeks
[redacted]	[redacted]
SAE	serious adverse event
SBP	systolic blood pressure
SUVR	Standard Uptake Value Ratio
UV	Unscheduled Visit