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PROTOCOL NUMBER: 221AD205 / NCT03639987

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Phase 2, Multicenter, Randomized, Parallel-Group, Double-Blind, Controlled Study of Aducanumab (BIIB037) in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease or With Mild Alzheimer's Disease Dementia to Evaluate the Safety of Continued Dosing in Subjects with Asymptomatic Amyloid-Related Imaging Abnormalities

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Protocol 221AD205 was approved by:

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Date

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1. SYNOPSIS

Protocol Title:	A Phase 2, Multicenter, Randomized, Parallel-Group, Double-Blind, Controlled Study of Aducanumab (BIIB037) in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease or With Mild Alzheimer's Disease Dementia to Evaluate the Safety of Continued Dosing in Subjects with Asymptomatic Amyloid-Related Imaging Abnormalities
Protocol Number:	221AD205
Version Number:	1
Name of Study Treatment:	Aducanumab (BIIB037)
Study Phase:	2
Study Indication:	Alzheimer's disease
Study Rationale:	Amyloid-related imaging abnormalities (ARIA) encompass a spectrum of magnetic resonance imaging (MRI) signal abnormalities including vasogenic edema (ARIA-E) and heme product deposits (ARIA-H) that are known to occur as part of the natural history of Alzheimer's disease (AD). ARIA has also been identified as a treatment-related finding with some anti-amyloid beta (Aβ) monoclonal antibodies, including bapineuzumab, gantenerumab, and aducanumab. Based on the available data from the aducanumab program, the majority of cases of ARIA have been asymptomatic, and, when symptomatic, the symptoms typically have been transient and mild or moderate in severity (see Section 4.3 for details). In the ongoing aducanumab clinical studies (221AD103, 221AD301, and 221AD302) the protocol-defined dosing disposition mandates that subjects who are asymptomatic with mild severity on MRI continue dosing. Subjects with symptomatic ARIA, as well as those with asymptomatic ARIA that is moderate or severe on MRI, temporarily suspend or permanently discontinue dosing. Data from Study 221AD103, although limited, have indicated that continuing dosing with aducanumab in subjects with asymptomatic mild ARIA was not associated with clinically significant negative outcomes. However, the benefit/risk of continued dosing in subjects with asymptomatic ARIA that is moderate or severe on MRI is currently unknown. This study is being conducted to assess the safety impact of continuing aducanumab dosing in subjects with asymptomatic moderate to severe ARIA. A 2-stage approach will be taken; initially (Stage 1), dosing will be continued in mild and

moderate asymptomatic ARIA cases only. It is planned that dosing will be continued in severe ARIA cases as well (in Stage 2), contingent on the recommendation of the Data Safety Monitoring Committee (DSMC) following a review of the Stage 1 data (see Section 19.2.2 for additional details).

Study Objectives and Endpoints:

The primary objective of the study is to assess the safety impact of continuing aducanumab dosing in asymptomatic ARIA in subjects with MCI due to AD or with mild AD dementia.

The primary endpoint that relates to this objective is the incidence of clinically impactful ARIA, defined as symptoms and/or signs associated with ARIA that are life-threatening, require hospitalization, and/or result in persistent or significant disability, as assessed by the independent Adjudication Committee.

Secondary objectives and endpoints are as follows:

- To characterize ARIA, from both the imaging and the clinical perspective:
  - Incidence, severity, time to onset, and time to resolution of ARIA as obtained on MRI
  - Incidence, severity, time to onset, and time to resolution of symptomatic ARIA
- To characterize the safety, tolerability, pharmacokinetics (PK), and immunogenicity of aducanumab:
  - Incidence of adverse events (AEs) and serious adverse events (SAEs)
  - Change from baseline to Week 54 on the Montreal Cognitive Assessment (MoCA)
  - Aducanumab concentration in serum
  - Incidence of antiaducanumab antibodies in serum

Long-Term Extension Objectives and Endpoints

The primary objective of the long-term extension (LTE) is to evaluate the long-term safety and tolerability profile of aducanumab in subjects with MCI due to AD or with mild AD dementia while continuing dosing during asymptomatic ARIA events.

	The endpoint that relates to this objective is the incidence of AEs and SAEs.
Study Design:	This is a Phase 2, multicenter, randomized, parallel-group, double-blind, controlled study with a 52-week randomized treatment period followed by an optional 104-week LTE period.
Study Location:	Approximately 95 sites globally are planned.
Number of Planned Subjects:	Approximately 500 subjects will be enrolled.
Study Population:	This study will be conducted in subjects with MCI due to AD or with mild AD dementia according to 2011 National Institute on Aging and Alzheimer's Association (NIA-AA) criteria. Subjects must have positive results for cerebral amyloid pathology as measured by a positron emission tomography (PET) scan. Subjects must be 50 to 85 years old, inclusive, and, apart from a clinical diagnosis of MCI due to AD or of mild AD dementia, they must be in good health as determined by the Investigator, based on medical history and the screening assessments. Detailed criteria are described in Section 8.
Treatment Groups:	All subjects will receive aducanumab. Eligible subjects will be randomized (1:1) to 1 of 2 groups *that differ in terms of the management of asymptomatic ARIA*, as summarized below. The randomization will be stratified by apolipoprotein E (ApoE) ε4 status (carrier or noncarrier). The randomized treatment period will last 52 weeks. During the LTE, asymptomatic ARIA in all subjects will be managed according to the plan described for Group 2 below. Group 1: Continuation of dosing in asymptomatic ARIA **contingent upon** imaging severity, consistent with dose disposition in ongoing Phase 3 studies, as follows (See Section 11.2.1 for details): • Mild severity on MRI: *Continue dosing* • Moderate severity on MRI: *Suspend dosing* • Severe on MRI: *Suspend dosing (ARIA-E) or discontinue dosing (ARIA-H [microhemorrhage, superficial siderosis])* Group 2: Continuation of dosing in asymptomatic ARIA **regardless of** imaging severity, to be implemented in a 2-stage approach, as follows (see Section 11.2.1 for details):

Stage 1 (from start of trial):

- Mild or moderate severity on MRI: *Continue dosing*
- Severe on MRI: *Suspend dosing (ARIA-E) or permanently discontinue dosing (ARIA-H [microhemorrhage, superficial siderosis])*

Stage 2 (contingent on DSMC recommendation after Stage 1 data review; see Section 19.2.2):

- Any severity on MRI: *Continue dosing*

Note: To maintain the blind, placebo will be given to Group 1 subjects in prespecified cases of dose suspension/discontinuation due to asymptomatic ARIA in both Stages 1 and 2 (for details, see Table 5 and Table 6).

Management of symptomatic ARIA (any severity on MRI) and management of ARIA-H (macrohemorrhage) *will be the same in Group 1 and Group 2* and will be generally consistent with that in the ongoing Phase 3 program.

Throughout trial, Group 1 and Group 2:

- Symptomatic ARIA, any severity on MRI:
  - *Suspend dosing or permanently discontinue treatment*
- ARIA-H (macrohemorrhage) with or without symptoms:
  - *Permanently discontinue treatment*

Duration of Treatment and Follow-up:

The total duration of study participation for any given subject participating in the randomized treatment period **only** will be approximately 78 weeks, including a series of screening visits within 60 days before administration of the first dose, a 52-week treatment period, and a safety follow-up approximately 18 weeks after the final dose.

The total duration of study participation for any given subject participating in the randomized treatment period and the LTE period will be approximately 186 weeks, including a series of screening visits within 60 days before administration of the first dose, a 52-week randomized treatment period, a 4-week follow-up period, a 104-week LTE treatment period, and a safety follow-up approximately 18 weeks after the final dose.

Subjects who permanently discontinue study treatment (due to ARIA or other reasons) are to remain in the study and follow a modified schedule for tests and assessments until the end of the study period or withdrawal of consent (Table 4). The only exception is a subject who may develop severe asymptomatic ARIA-H (microhemorrhage, superficial siderosis) in Stage 2 (Section 11.2.1.2; Table 6); such a subject is to follow the regular visit schedule to maintain the blind to the subject's group assignment (Table 1).

Subjects who withdraw from the study are to return for a safety follow-up visit approximately 18 weeks after their last dose of study treatment.

2. LIST OF ABBREVIATIONS

Aβ	amyloid beta
AD	Alzheimer's disease
ADA	antidrug antibody
AE	adverse event
ApoE	apolipoprotein E
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormality (vasogenic edema)
ARIA-H	amyloid-related imaging abnormality (macrohemorrhage, or microhemorrhage, superficial siderosis)
CAA	cerebral amyloid angiopathy
CDR	Clinical Dementia Rating
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
DSST	Digital Symbol Substitution Test
ECG	electrocardiogram
ECog	Everyday Cognition
EDC	electronic data capture
EOT	end of treatment
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCP	health care professional
ICF	informed consent form
ICH	International Council for Harmonisation

Ig	immunoglobulin
IRT	interactive response technology
IV	intravenous(ly)
LTE	long-term extension
mAb	monoclonal antibody
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging and Alzheimer's Association
NFT	neurofibrillary tangle
NP	neuritic plaque
PET	positron emission tomography
PI	principal investigator
PK	pharmacokinetic(s)
RNA	ribonucleic acid
SAE	serious adverse event
SBP	systolic blood pressure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event

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

4. INTRODUCTION

4.1. Overview of Alzheimer's Disease

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]. In the United States, it is estimated that 5.2 million people suffer from dementia caused by AD [Alzheimer's Disease International 2014]. 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].

Pathologically, the disease is defined by the presence in the brain of extracellular neuritic plaques (NPs) containing Aβ peptide and intraneuronal neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. 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 NPs and mesial temporal NFTs and followed years later by neocortical NFTs, which best correlate with cognitive status and neuronal death [Nelson 2009].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition, as well as behavioral disturbances, that result in the person's inability to perform usual activities of daily living. The current view of AD is that it manifests along a continuum rather than categorical stages. Evidence suggests that the pathophysiological changes begin years before clinical onset, and as the disease progresses cognitive impairments, behavioral changes, and functional disability manifest [Jack 2013]. Thus, the scientific community has shifted its focus to people in the earlier course of the disease continuum, with the belief that those people are more likely to benefit from therapy.

4.2. Current Therapies for Alzheimer's Disease

The currently approved therapies for AD include the acetylcholinesterase inhibitors (such as Aricept™, Exelon™, Reminyl™, and Rivastach® Patch) and the N-methyl-D-aspartate antagonist memantine (Namenda™), which provide only modest symptomatic benefit but do not attenuate the course of the disease.

There are currently no therapies that modify the course of AD, but several potential disease-modifying drug candidates are under investigation. These candidates include small molecules and immunotherapy (active and passive) that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain.

Bapineuzumab (Pfizer/Elan/Johnson & Johnson), gantenerumab (Roche), BAN2401 (Eisai, Biogen), crenezumab (Genentech), and solanezumab (Eli Lilly) are anti-amyloid-targeting antibodies with different binding selectivity toward different forms of Aβ. Bapineuzumab was discontinued due to lack of efficacy as compared with placebo, while the other 4 antibodies are currently in Phase 2 and 3 trials evaluating treatment effects in different AD populations.

Rationale for Aducanumab Therapy for AD

Aducanumab (BIIB037) is a human anti-Aβ immunoglobulin (Ig) G1 monoclonal antibody (mAb) that selectively targets aggregated forms of Aβ, including soluble oligomers and insoluble fibrils. Earlier publications have demonstrated that both soluble oligomers and amyloid plaques are neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008], and clearance of amyloid plaques could lead to normalization of calcium homeostasis and neuronal activity, as well as reduction of oxidative stress in the brain of an animal model of AD [Rozkalne 2009; Spires-Jones 2009]. Moreover, an association between the presence of antibodies that recognize amyloid plaques and a slowing of cognitive decline in people with mild to moderate AD has been described [Hock 2003]. Therefore, targeting aggregated forms of Aβ, including soluble oligomers and insoluble fibrils, with aducanumab is hypothesized to attenuate the course of AD.

Amyloid-Related Imaging Abnormalities

ARIA detected on MRI have been observed in subjects with AD receiving anti-Aβ mAbs. ARIA was first observed as a treatment-related adverse effect with bapineuzumab and has more recently been associated with other anti-Aβ mAbs, including gantenerumab and aducanumab [Penninkilampi 2017; Sevigny 2016; Sperling 2011].

ARIA represents a spectrum of imaging findings that include ARIA-E and ARIA-H in the brain parenchyma (microhemorrhages and, rarely, macrohemorrhages) or in the leptomeningeal space (superficial siderosis). ARIA-E has been hypothesized to result from increased cerebrovascular permeability caused by accelerated Aβ clearance from the brain parenchyma and/or by antibody interaction with vascular Aβ [Sperling 2012; Zago 2013].

ARIA-E may be accompanied by ARIA-H, but isolated ARIA-H is also known to occur in untreated subjects in the setting of small vessel angiopathy typically caused by chronic hypertension or cerebral amyloid angiopathy, which often accompanies AD [Linn 2010]. Similarly an ARIA-E like phenomenon has been observed in rare cases in untreated subjects during screening for AD trials suggesting that spontaneous ARIA-E may occur in the natural history of AD, perhaps more commonly in subjects with genetic risk factors for high amyloid risk burden and/or cerebral amyloid angiopathy burden [Sperling 2011].

Evidence from trials of anti-Aβ mAbs has shown that the incidence of ARIA-E is increased with higher doses of the drugs and is more frequent in heterozygote and homozygote ApoE ε4 carriers than in noncarriers. Another common characteristic of treatment-related ARIA-E is its timing, occurring mostly early during the course of treatment [Ketter 2017; Salloway 2014; Sperling 2012; Sperling 2011].

4.3. Profile of Previous Experience With Aducanumab

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

4.3.1. Nonclinical Experience

Aducanumab is identified and derived from B lymphocytes using the reverse translational medicine approach. Using this technique, immune repertoires obtained from cohorts of healthy elderly human donors with excellent cognitive performance or with impaired but stable courses were screened for memory B cells against aggregated Aβ [Sevigny 2016].

In vitro studies have demonstrated that aducanumab and its analogs are highly selective for soluble oligomeric and insoluble fibrillar forms of Aβ relative to soluble low-molecular-weight forms of Aβ. In vivo pharmacology studies indicated that a murine IgG2a chimeric version of the antibody (ch12F6A) with similar properties to aducanumab significantly reduced amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD-like amyloid deposition, through a microglia-mediated phagocytic mechanism.

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

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

4.3.2. Clinical Experience

In completed Phase 1 studies in AD, 39 subjects with mild to moderate AD were exposed to a single dose of aducanumab (Study 221AD101), and 17 Japanese subjects with mild to moderate AD were exposed to aducanumab for up to 36 weeks (Study 221AD104). Additionally, 14 healthy subjects were exposed to a single intravenous (IV) dose of aducanumab and

14 healthy subjects were exposed to a single subcutaneous (SC) dose (Study 221HV102). As of 25 May 2017, 185 subjects with prodromal AD or mild AD dementia had received at least 1 dose of aducanumab in the ongoing multiple-ascending-dose Phase 1b study (Study 221AD103). As of 15 January 2018, more than 2500 additional subjects with early AD have received at least 1 dose of aducanumab or placebo in the ongoing blinded Phase 3 studies (221AD301 and 221AD302).

Overall, in the clinical studies, aducanumab has been generally well tolerated in subjects with AD, with ARIA being the primary safety and tolerability finding.

4.3.2.1. ARIA in the Aducanumab Clinical Development Program

4.3.2.1.1. Study 221AD101

In Study 221AD101, 3 subjects received a single dose of aducanumab 60 mg/kg and all 3 experienced ARIA-E, including 2 subjects with ARIA-E and 1 subject with both ARIA-E and ARIA-H (microhemorrhage). None of the subjects were hospitalized; however, these cases were reported as medically important SAEs, per protocol. Each case was considered symptomatic. Symptoms included severe generalized body aches, moderate headache, and moderate cognitive cloudiness; severe headache and severe malaise; and mild transient unsteady gait. ARIA-E severity as seen on MRI ranged from mild to severe. ARIA, as assessed by MRI, and attendant symptoms fully resolved in all 3 subjects between Weeks 8 and 15.

4.3.2.1.2. Study 221AD104

ARIA events occurred in 1 subject in this study. These included asymptomatic ARIA-E (mild vasogenic edema), asymptomatic ARIA-H (macrohemorrhage), and asymptomatic ARIA-H (superficial siderosis), which were observed on MRI approximately 3 weeks after the subject had received a single dose of aducanumab 3 mg/kg. Study treatment was discontinued, and the subject was withdrawn from study due to these imaging findings. Approximately 3 weeks later (6 weeks after receiving the single dose of aducanumab), the subject experienced an acute life-threatening cerebral hemorrhage with a coma. The subject was treated with glycerol, and 4 days after the cerebral hemorrhage had regained consciousness and was having limited conversation with some additional improvement.

4.3.2.1.3. Study 221AD103

Currently available data on ARIA are mostly based on the ongoing Study 221AD103 of aducanumab in subjects with prodromal AD or mild AD dementia. This study comprises a completed double-blind, 1-year placebo-controlled period, followed by an ongoing LTE in which all subjects receive aducanumab via monthly infusions, in a dose-blinded fashion. A total of 185 subjects have been dosed with aducanumab, in the placebo-controlled period and/or the LTE.

Based on data available as of 25 May 2017 in a prespecified interim analysis, ARIA-E (with or without ARIA-H) has been detected in 25% of all aducanumab-treated subjects (46/185). In the 12-month placebo-controlled period, in subjects receiving aducanumab in a fixed-dose regimen,

the incidence of ARIA-E increased with dose and was higher in ApoE ε4 carriers than noncarriers (3% [1/31], 6% [2/32], 37% [11/30], and 41% [13/32] in the 1, 3, 6, and 10 mg/kg dose groups, respectively). However, the incidence of ARIA-E appeared to be lower in ApoE ε4 carrier subjects receiving titration to 10 mg/kg (35% [8/23]) than in carrier subjects receiving fixed doses (43% [9/21] and 55% [11/20]) of 6 and 10 mg/kg, respectively. Furthermore, among the 8 ApoE ε4 carrier subjects receiving titration to 10 mg/kg who had ARIA-E, the abnormalities were observed at the 3 and 6 mg/kg dose levels (5 and 3 subjects, respectively).

The incidence of isolated ARIA-H was similar in the placebo and aducanumab groups (7% [3/46] and 5% [7/148], respectively), which likely indicates a background finding in this population.

ARIA was typically observed early in the course of the treatment, with the majority of cases observed between the second and fifth doses. A total of 91% of subjects (42/46) developed the first episode of ARIA-E within the first 12 months of active dosing, with 76% of subjects (35/46) developing the first episode within the first 6 months of active dosing. In most cases, ARIA-E resolved 4 to 12 weeks after onset as assessed by MRI, and ARIA-H was typically stable within 2 to 4 weeks after onset.

Of the subjects who developed ARIA-E (with or without ARIA-H), the majority (65% [30/46]) were asymptomatic with an MRI severity of mild (9 subjects), moderate (20 subjects), and severe (1 subject). In subjects with symptoms (35% [16/46]), the majority of symptoms were mild (63% [10/16]) or moderate (13% [2/16]) and resolved without sequelae. Symptoms were severe in 25% of these subjects (4/16). Symptoms of ARIA may include headache, worsening cognitive function, alteration of consciousness, seizures, unsteadiness, visual disturbances, and vomiting.

Two ARIA cases (1 symptomatic and 1 asymptomatic) resulted in hospitalization; both cases occurred in the first 12 months of active aducanumab treatment. The subject who was asymptomatic was hospitalized without any treatment to rule out a subarachnoid hemorrhage. The second subject, with severe ARIA-E, was hospitalized for a seizure and pulseless electrical activity cardiac arrest that was considered life-threatening. The subject had ongoing decreased cognition and function, complicated by secondary infection and disease progression, and withdrew from the study.

As of 27 November 2017, there were 56 episodes of ARIA-E (initial and recurrent) in the 46 subjects. In the majority of the ARIA-E episodes (45/56), aducanumab dosing was suspended or permanently discontinued, predominantly due to protocol-stipulated dose suspension or permanent discontinuation. Thirteen of the 45 episodes in which aducanumab dosing was suspended or permanently discontinued transiently progressed in severity on subsequent MRIs. Severity trended downward in 30 of the 45 episodes. All episodes of ARIA-E eventually resolved except for 2 episodes (outcomes were unknown because the subjects were lost to follow-up). Similarly, in 11 episodes of ARIA-E (10 mild and 1 moderate) that were dosed through based on an amendment to the protocol that allowed continuation of dosing at the current dose in presence of asymptomatic ARIA-E (mild MRI severity only), 6 episodes progressed in severity on subsequent MRIs before resolving completely. Of these, 1 subject

changed from asymptomatic to symptomatic ARIA-E, and the episode subsequently resolved. The remaining 5 episodes completely resolved and remained asymptomatic.

To evaluate the impact of ARIA on cognitive status, a post hoc analysis of ARIA cases that occurred during the placebo-controlled period was performed to evaluate the cognitive score changes stratified by the presence/absence of ARIA. These data suggested no apparent difference in treatment effect in subjects with and without ARIA [Sevigny 2016].

4.4. Study Rationale

During aducanumab's clinical development, the paradigm of its dosing during and after ARIA events has evolved over the years. In the ongoing aducanumab clinical studies (221AD103, 221AD301, and 221AD302), the protocol-defined dosing disposition mandates that subjects who are asymptomatic with mild severity on MRI continue dosing. Subjects with symptomatic ARIA, as well as those with asymptomatic ARIA that is moderate or severe on MRI, temporarily suspend or permanently discontinue dosing. Based on the current dosing regimen, data from Study 221AD103, although limited, have indicated that continuing dosing with aducanumab in subjects with asymptomatic mild ARIA was not associated with clinically significant negative outcomes (see Section 4.3.2.1.3).

Data on the impact of continuing dosing during ARIA events are available from other anti-Aβ mAb trials. In 3 Phase 2 studies of bapineuzumab, among 17% of subjects (36/210) who developed ARIA-E during treatment, the majority of cases (78% [28/36]) were asymptomatic [Sperling 2012]. A post hoc review revealed that 42% of asymptomatic subjects (15/36) were identified as having ARIA-E only during a retrospective MRI re-read central review. Of these, 13 subjects continued to receive bapineuzumab infusions while ARIA-E was present and remained asymptomatic.

In 2 Phase 3 studies of bapineuzumab in subjects with mild-to-moderate AD, the majority of ARIA-E cases were asymptomatic (85% of ApoE ε4 carriers and 45% to 84% of ApoE ε4 noncarriers, depending on the bapineuzumab dose) [Salloway 2014]. A retrospective MRI final read analysis identified treatment-emergent ARIA-E in 242 subjects, including 76 additional cases that were not detected previously [Ketter 2017]. The majority of missed ARIA-E cases (88%) had a radiological severity score ≤2, and only 10% had a severity score ≥3. Of the total ARIA-E cases, approximately 64% of ApoE ε4 carriers and 52% of noncarriers were dosed through during an ARIA-E event. For all ARIA-E cases, radiological severity score for subjects who were dosed through events was comparable to those who discontinued treatment, except for a higher score for ApoE ε4 noncarriers who were dosed through in the 0.5 mg/kg group. The only difference in the clinical presentation of subjects who were dosed through compared with those who discontinued treatment was the duration of the ARIA-E episodes, with a shorter duration in subjects who discontinued.

The biological mechanism of ARIA-E is poorly understood, but published hypotheses suggest that the increased cerebrovascular permeability could be caused either by increased amyloid clearance from the parenchyma, leading to saturation of the perivascular drainage system; and/or

by direct antibody interaction with deposited vascular amyloid, leading to its clearance and weakening of the vessels walls [Sperling 2012; Zago 2013].

Nonclinical studies aiming at understanding mechanism of ARIA-E or ARIA-H have been conducted in PDAPP mice and provide supporting evidence for continuation of dosing. Treatment with the 3D6 antibody, the murine parent of bapineuzumab, induced clearance of vascular Aβ that was spatially associated with a transient increase in microhemorrhage and in capillary Aβ deposition. These data suggest that vascular leakage events, such as microhemorrhage, may be due to the removal of vascular Aβ. More significantly, these studies demonstrated that, upon continuation of antibody treatment, vascular morphology was restored and further vascular leakage events were reduced [Zago 2013]. Additional studies employing T1-weighted MRI scans in PDAPP mice treated with 3D6 demonstrated blood-brain barrier leakage occurring early during treatment (after 1 to 4 doses), being transient, and resolving spontaneously upon continuation of dosing [Blockx 2016].

Collectively, these data indicate that ARIA, when observed in subjects receiving anti-Aβ agents, is a mostly asymptomatic and transient phenomenon. The current paradigm of suspending dosing during an ARIA event is based on caution rather than clinical evidence. If it could be established in a prospectively designed study that continuation of dosing with aducanumab in the absence of symptoms does not have clinically impactful safety outcomes, it would allow for more consistent exposure to treatment, thereby potentially enhancing benefit to the subjects with AD treated with aducanumab. This study will evaluate the safety impact of continuing dosing in asymptomatic subjects with ARIA in a 2-stage approach. Initially (in Stage 1), in one arm of the study (Group 2), subjects with only mild to moderate asymptomatic ARIA will be dosed through; it is planned that the impact of continuing dosing during asymptomatic ARIA events regardless of MRI severity (except ARIA-H [macrohemorrhage]) will be assessed in Stage 2, contingent upon DSMC recommendation after a review of the data (Section 19.2.2).

5. SCHEDULE OF ACTIVITIES

Table 1: Schedule of Activities: Randomized Treatment Period

	Screening Visit ≤60 Days of Day 1[1]			Randomized Treatment Period (Weeks ±3 days)																							UV for ARIA[2]	UV for Change in AD Medication[3]	FU[4]
Weeks	**V 1**	**V2**	**V 3**	**1 D1**	**2**	**4**	**6**	**8**	**10**	**12**	**1 4**	**16**	**18**	**20**	**2 2**	**24**	**26**	**28**	**30**	**32**	**3 6**	**40**	**44**	**4 8**	**52**	**54 EOT[5]**			**70 ±7d**
Assessments																													
Initial Screening Consent[6] (optional)	X																												
Full Informed Consent[7]	X																									X[8]			
Eligibility Criteria	X	X	X	X[9]																						X[8]			
Demography	X																												
Medical History	X	X	X																										
Alcohol/Drug Screen	X																												
HIV[10]/Hepatitis/ Coagulation	X																												
HbA1c	X																												
Lipid panel	X																												
Height	X																												
Body Weight	X			X		X		X		X		X		X		X		X		X	X	X	X	X	X				X
Serum Pregnancy Test[11]	X																												

	Screening Visit ≤60 Days of Day 1[1]			Randomized Treatment Period (Weeks ±3 days)																							UV for ARIA[2]	UV for Change in AD Medication[3]	FU[4]
Weeks	**V 1**	**V2**	**V 3**	**1 D1**	**2**	**4**	**6**	**8**	**10**	**12**	**1 4**	**16**	**18**	**20**	**2 2**	**24**	**26**	**28**	**30**	**32**	**3 6**	**40**	**44**	**4 8**	**52**	**54 EOT[5]**			**70 ±7d**
Assessments																													
Urine Pregnancy Test[11]				X		X		X		X		X		X		X		X		X	X	X	X	X	X				X
Randomization				X																									
Study Treatment Infusion				X		X		X		X		X		X		X		X		X	X	X	X	X	X				
Follow-up telephone call					X		X		X		X		X		X		X		X										
Aβ Positivity (PET)[1]			X																										
Brain MRI (post Day 1 central read result must be available before infusion)		X[1,12]										X[12]				X[12]				X[12]			X[12]			X[12]	X		
Neurological Assessment	X			X								X				X				X			X			X	X		X
Physical Examination	X			X								X				X							X			X	X		X
Vital Signs[13]	X			X		X		X		X		X		X		X		X		X	X	X	X	X	X				X
12-lead Paper ECG	X			X												X										X			X
Hematology, Blood Chemistry, and Urinalysis	X			X												X										X			X
CDR	X																												
MMSE	X																									X		X	

	Screening Visit ≤60 Days of Day 1[1]			**Randomized Treatment Period (Weeks ±3 days)**																							**UV for ARIA[2]**	**UV for Change in AD Medication[3]**	**FU[4]**
Weeks	**V 1**	**V2**	**V 3**	**1 D1**	**2**	**4**	**6**	**8**	**10**	**12**	**1 4**	**16**	**18**	**20**	**2 2**	**24**	**26**	**28**	**30**	**32**	**3 6**	**40**	**44**	**4 8**	**52**	**54 EOT[5]**			**70 ±7d**
Assessments																													
MoCA				X								X				X				X			X			X	X		
C-SSRS				X												X										X			
ApoE Genotyping[9]	X																												
ECog (Observer only)[14]	any screening visit																												
DSST/trail making (optional)[14]	any 2 screening visits																												
Whole blood for DNA (optional)[15]	X																												
Anti-Aducanumab Ab[16]				X								X				X				X			X			X			X
Aducanumab Concentration[17]				X								X				X				X			X			X	X		X
[redacted]																													
AE Reporting[19,20]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																												
SAE Reporting	Monitor and record continuously throughout the study																												

	Screening Visit ≤60 Days of Day 1[1]			Randomized Treatment Period (Weeks ±3 days)																							UV for ARIA[2]	UV for Change in AD Medication[3]	FU[4]
Weeks	**V 1**	**V2**	**V 3**	**1 D1**	**2**	**4**	**6**	**8**	**10**	**12**	**1 4**	**16**	**18**	**20**	**2 2**	**24**	**26**	**28**	**30**	**32**	**3 6**	**40**	**44**	**4 8**	**52**	**54 EOT[5]**			**70 ±7d**
Assessments																													

Aβ = amyloid-beta; Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ApoE = apolipoprotein E; ARIA = amyloid-related imaging abnormalities; CDR = Clinical Dementia Rating; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; DNA = deoxyribonucleic acid; DSST = Digital Symbol Substitution Test; ECG = electrocardiogram; ECog = Everyday Cognition; EOT = End of Treatment; FU = Follow-Up; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; LTE = long-term extension; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PET = positron emission tomography; SAE = serious adverse event; UV = unscheduled visit; V = visit.

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

[2]Subjects with confirmed ARIA on MRI should have the unscheduled visit for ARIA every 4 weeks (±5 days) until the ARIA have resolved or stabilized per the centrally read MRI.

[3]The UV should occur before the change in AD medication. If this is not possible, MMSE and AE assessments should be done at the subject's next scheduled visit.

[4]Subjects who complete the randomized treatment period and do not enter the LTE are to return to the site for a safety follow-up at Week 70. Subjects who permanently discontinue treatment or discontinue active dosing without receiving placebo or who withdraw from the study prematurely are to have a safety follow-up approximately 18 weeks after their final dose.

[5]Week 54 is the last visit for the randomized treatment period for subjects entering the LTE. Subjects who permanently discontinue treatment (due to ARIA or other reasons) are to remain in the study and follow a modified schedule for tests and assessments until the end of the study period or withdrawal of consent (Table 4). The only exception is a subject who may develop severe asymptomatic ARIA-H (microhemorrhage, superficial siderosis) in Stage 2; such a subject is to follow the regular visit schedule (Table 1) to maintain the blind to the subject's group assignment (Section 11.2.1.2; Table 6). Subjects who withdraw from the study prematurely are to return to the site for an EOT Visit 2 weeks after their final dose.

[6]Subjects may sign this optional form for an initial screening that allows administration of the CDR and MMSE only, as well as ApoE genotyping.

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

[8]Only for subjects entering the LTE.

[9]All assessments, including the C-SSRS, must be completed before study treatment administration, except the postdose sample to measure aducanumab concentration. The ApoE genotyping result must be available prior to randomization.

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

[11]Required for women of childbearing potential only. A negative urine pregnancy test result is required prior to each infusion.

[12]MRI scan can be performed up to 14 days prior to the clinic visit. Central MRI read results should be available at the time of the visit.

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

[14]ECog (Observer) will be performed by the informant/care partner. The test can be performed at any screening visit but must be done prior to the PET scan. The DSST may be performed at any 2 screening visits and must be done prior to the PET scan.

[15]Can be collected at any point during and after screening.

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

[redacted]

[19]AEs will be collected by the independent clinical assessor prior to each infusion. Both the subject and the informant/care partner are required to participate in the clinical interview prior to each infusion. If the informant/care partner cannot visit the clinic in person, a phone conversation with the independent clinical assessor is acceptable.

[20]Any AE suggestive or potentially considered to be related to ARIA, as per the clinical judgment of the independent clinical assessor, should be evaluated further by detailed neurological assessment and local standard of care.

Table 2: Schedule of Activities: Long-Term Extension Period From Week 56 Through Week 104

	Long-Term Extension Period (Weeks ±5 days)													UV for ARIA[1]	UV for Change in AD Medication[2]
Assessments	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**		
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine Pregnancy Test[3]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X		
Brain MRI (post Day 1 central read result must be available before infusion)							X[4]						X[4]	X	
Physical Examination							X						X	X	
Neurological Assessment							X						X	X	
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead Paper ECG	X						X						X		
Hematology, Blood Chemistry, and Urinalysis	X						X						X		
Aducanumab Concentration[6]	X						X						X		
Anti-Aducanumab Ab[6]	X						X						X		
MMSE													X		X
MoCA							X						X	X	
C-SSRS							X						X		
AE Reporting[7,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Long-Term Extension Period (Weeks ±5 days)													UV for ARIA[1]	UV for Change in AD Medication[2]
Assessments	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**		
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study														
SAE Reporting	Monitor and record continuously throughout the study														

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ARIA = amyloid-related imaging abnormalities; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; SAE = serious adverse event; UV = unscheduled visit.

[1]Subjects with confirmed ARIA on MRI should have the UV for ARIA every 4 weeks (±5 days) until the ARIA have resolved or stabilized per the centrally read MRI.
[2]The UV should occur before the change in AD medication. If this is not possible, MMSE and AE assessments should be done at the subject's next scheduled visit.
[3]Required for women of childbearing potential only. A negative result is required prior to each infusion.
[4]MRI scan can be performed up to 14 days prior to the clinic visit. Central MRI read results should be available at the time of the visit.
[5]Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes.
[6]Blood sampling for aducanumab concentration will be performed prior to infusion. For subjects who permanently discontinue treatment and remain in the study, or who discontinue active dosing and receive placebo, the final aducanumab concentration sample will be collected at the subject's next visit.
[7]AEs will be collected prior to each infusion. Both the subject and the informant/care partner are required to participate in the clinical interview prior to each infusion. If the informant/care partner cannot visit the clinic in person, a phone conversation with the independent clinical assessor is acceptable.
[8]Any AE suggestive or potentially considered to be related to ARIA, as per the clinical judgment of the independent clinical assessor should be evaluated further by detailed neurological assessment and local standard of care.

Table 3: Schedule of Activities: Long-Term Extension Period From Week 108 Through Follow-Up

	Long-Term Extension Period (Weeks ±5 days)														UV for ARIA[1]	UV for Change in AD Medication [2]	FU[3]
Assessments	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**158 EOT[4]**			**174 ±7d**
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Urine Pregnancy Test[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Study Treatment Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X				
Brain MRI (post Day 1 central read result must be available before infusion)						X[6]								X[6]	X		
Physical Examination						X								X	X		X
Neurological Assessment						X								X	X		X
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
12-lead Paper ECG	X						X							X			X
Hematology, Blood Chemistry, and Urinalysis	X						X							X			X
Aducanumab Concentration[8]	X					X								X			
Anti-Aducanumab Ab[8]	X					X								X			
MMSE														X		X	
MoCA						X								X	X		
C-SSRS							X							X			

	Long-Term Extension Period (Weeks ±5 days)														**UV for ARIA[1]**	**UV for Change in AD Medication [2]**	**FU[3]**
Assessments	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**158 EOT[4]**			**174 ±7d**
AE Reporting[9,10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study																
SAE Reporting	Monitor and record continuously throughout the study																

Ab = antibody; AD = Alzheimer's disease; AE = adverse event; ARIA = amyloid-related imaging abnormalities; C-SSRS = Columbia Suicide Severity Rating Scale; D = days; ECG = electrocardiogram; EOT = End of Treatment; FU = Follow-Up; MMSE = Mini-Mental State Examination; HCP = health care professional; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; SAE = serious adverse event; UV = unscheduled visit.

[1] Subjects with confirmed ARIA on MRI, should have the UV for ARIA every 4 weeks (±5 days) until the ARIA have resolved or stabilized per the centrally read MRI.

[2] UV should occur before the change in AD medication. If this is not possible, MMSE and AE assessments should be done at the subject's next scheduled visit.

[3] Subjects who complete the LTE period are to return to the site for a final safety follow-up at Week 174. Subjects who permanently discontinue treatment or withdraw from the study early are to have a safety follow-up visit at 18 weeks after their final dose.

[4] Week 158 is the last visit in the LTE. Subjects who permanently discontinue treatment are to remain in the study and follow a modified schedule for tests and assessments until the end of the study period or withdrawal of consent (Table 4). Subjects who withdraw from the study prematurely are to return to the site for an EOT Visit 2 weeks after their final dose.

[5] Required for women of childbearing potential only. A negative result is required prior to each infusion.

[6] MRI scan can be performed up to 14 days prior to the clinic visit. Central MRI read results should be available at the time of the visit.

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

[8] Blood sampling for aducanumab concentration will be performed prior to infusion. Note: For subjects who permanently discontinue treatment and continue in the study, the final aducanumab concentration sample will be collected at the subject's next visit.

[9] AEs will be collected prior to each infusion. Both the subject and the informant/care partner are required during the clinical interview prior to each infusion. If the informant/care partner cannot visit the clinic in person, a phone conversation with the independent clinical assessor is acceptable.

[10] Any AE suggestive or potentially considered to be related to ARIA, as per the clinical judgment of the independent clinical assessor should be evaluated further by detailed neurological assessment and local standard of care.

Table 4: Schedule of Activities: Subjects Who Permanently Discontinue Treatment and Remain in the Study

Assessments	Visits for Subjects Who Discontinue Treatment[1]	FU Phone Call[2]	UV for ARIA[3]	FU[4]
Body Weight				X
Urine Pregnancy Test[5]				X
Brain MRI			X	
Physical Examination	X		X	X
Neurological Assessment	X		X	X
Vital Signs[6]	X			X
12-lead Paper ECG				X
Hematology, Blood Chemistry, and Urinalysis	X			X
MoCA			X	
AE Reporting	X	X	X	X
Concomitant Therapy and Procedures	X	X	X	X
SAE Reporting	X	X	X	X

AE = adverse event; ARIA = amyloid-related imaging abnormalities; ECG = electrocardiogram; FU = Follow-Up; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; SAE = serious adverse event; UV = unscheduled visit.

[1]Subjects who permanently discontinue treatment are to remain in the study and have a visit 12 weeks after their final dose and every 6 months after the safety follow-up (18 weeks after their final dose), until the end of study or withdrawal of consent. It is possible that a clinic visit will occur before the FU Visit. If the FU Visit will occur within 2 weeks of a scheduled clinic visit, then the FU Visit can be combined with the scheduled visit and all assessments required for both visits performed at this single visit. Note: Subjects who develop severe asymptomatic ARIA-H in Stage 2 (in the randomized treatment period) are to follow the regular visit schedule per Table 1 in order to maintain the blind, even though they may have permanently discontinued active dosing and are receiving placebo (Section 11.2.1.2; Table 6).

[2]After the first visit performed 12 weeks after the final dose, subjects will continue to be followed up with a phone call every 12 weeks until the end of the study or withdrawal of consent.

[3]Subjects with confirmed ARIA on MRI should have the unscheduled visit for ARIA every 4 weeks (±5 days) until the ARIA have resolved or stabilized per the centrally read MRI.

[4]Subjects are to have a safety follow-up visit at 18 weeks after their final dose.

[5]Required for women of childbearing potential only.

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

6. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoint**
The primary objective of the study is to assess the safety impact of continuing aducanumab dosing in asymptomatic ARIA in subjects with MCI due to AD or with mild AD dementia.	The primary endpoint that relates to this objective is the incidence of clinically impactful ARIA, defined as symptoms and/or signs associated with ARIA that are life-threatening, require hospitalization, and/or result in persistent or significant disability as assessed by the independent Adjudication Committee.
Secondary Objectives	**Secondary Endpoints**
To characterize ARIA, from both the imaging and the clinical perspective	Endpoints that relate to this objective include: • Incidence, severity, time to onset, and time to resolution of ARIA as obtained on MRI • Incidence, severity, time to onset, and time to resolution of symptomatic ARIA
To characterize the safety, tolerability, PK, and immunogenicity of aducanumab	Endpoints that relate to this objective include: • Incidence of AEs and SAEs • Change from baseline to Week 54 on the MoCA • Aducanumab concentration in serum • Incidence of antiaducanumab antibodies in serum
Long-Term Extension Objectives	**Long-Term Extension Endpoints**
The primary objective of the LTE is to evaluate the long-term safety and tolerability profile of aducanumab in subjects with MCI due to AD or mild AD dementia while continuing dosing during asymptomatic ARIA events.	The endpoint that relates to this objective is the incidence of AEs and SAEs.

Any additional samples that are collected 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

This is a Phase 2, multicenter, randomized, parallel-group, double-blind, controlled study to assess the safety of continuing aducanumab dosing in subjects with MCI due to AD or mild AD dementia who experience asymptomatic ARIA. This study will initially (in Stage 1) assess the safety of continued dosing as compared with dose suspension in asymptomatic mild to moderate ARIA through a modified management plan but a similar monitoring plan as the ongoing Phase 3 studies (Studies 221AD301 and 221AD302). It is planned that the safety of continued dosing in severe cases will be assessed in Stage 2, contingent upon DSMC recommendation after a review of the Stage 1 data (Section 19.2.2).

Approximately 500 subjects aged 50 to 85 years, inclusive, will be enrolled at approximately 95 sites globally. All subjects will receive infusions of aducanumab every 4 weeks for 52 weeks during the randomized treatment period. The dose will be titrated from 1 mg/kg to 10 mg/kg (1 mg/kg for the first 2 infusions, 3 mg/kg for the next 2 infusions, 6 mg/kg for the next 2 infusions, and 10 mg/kg thereafter).

Eligible subjects will be randomized (1:1) at Day 1 to 1 of 2 groups that *differ in terms of the management of asymptomatic ARIA*, as summarized below. The randomization will be stratified by ApoE ε4 status (carrier or noncarrier). The ratio of ApoE ε4 carriers to noncarriers in the study population will generally reflect the distribution in the broader AD population.

Group 1:

Continuation of dosing in asymptomatic ARIA **contingent upon** imaging severity, consistent with dose disposition in ongoing Phase 3 trials, as described below (see Section 11.2.1 for details):

- Mild severity on MRI: *Continue dosing*
- Moderate severity on MRI: *Suspend dosing*
- Severe on MRI: *Suspend dosing (ARIA-E) or permanently discontinue dosing (ARIA-H [microhemorrhage, superficial siderosis])*

Group 2:

Continuation of dosing in asymptomatic ARIA **regardless** of imaging severity, to be implemented in a 2-stage approach, as described below (see Section 11.2.1 for details):

Stage 1 (from start of trial):

- Mild or moderate severity on MRI: *Continue dosing*
- Severe on MRI: *Suspend dosing (ARIA-E) or permanently discontinue dosing (ARIA-H [microhemorrhage, superficial siderosis])*

Stage 2 (contingent on DSMC recommendation based on review of the Stage 1 data, Section 19.2.2)

- Any severity of MRI: *Continue dosing*

Note: To maintain the blind, placebo will be given to Group 1 subjects in prespecified cases of dose suspension/discontinuation due to asymptomatic ARIA in both Stages 1 and 2 (for details see Sections 11.2.1.1 and 11.2.1.2).

Management of symptomatic ARIA (any severity of MRI) and management of ARIA-H (macrohemorrhage) *will be the same in Groups 1 and 2* and will be generally consistent with that in the ongoing Phase 3 program, as follows:

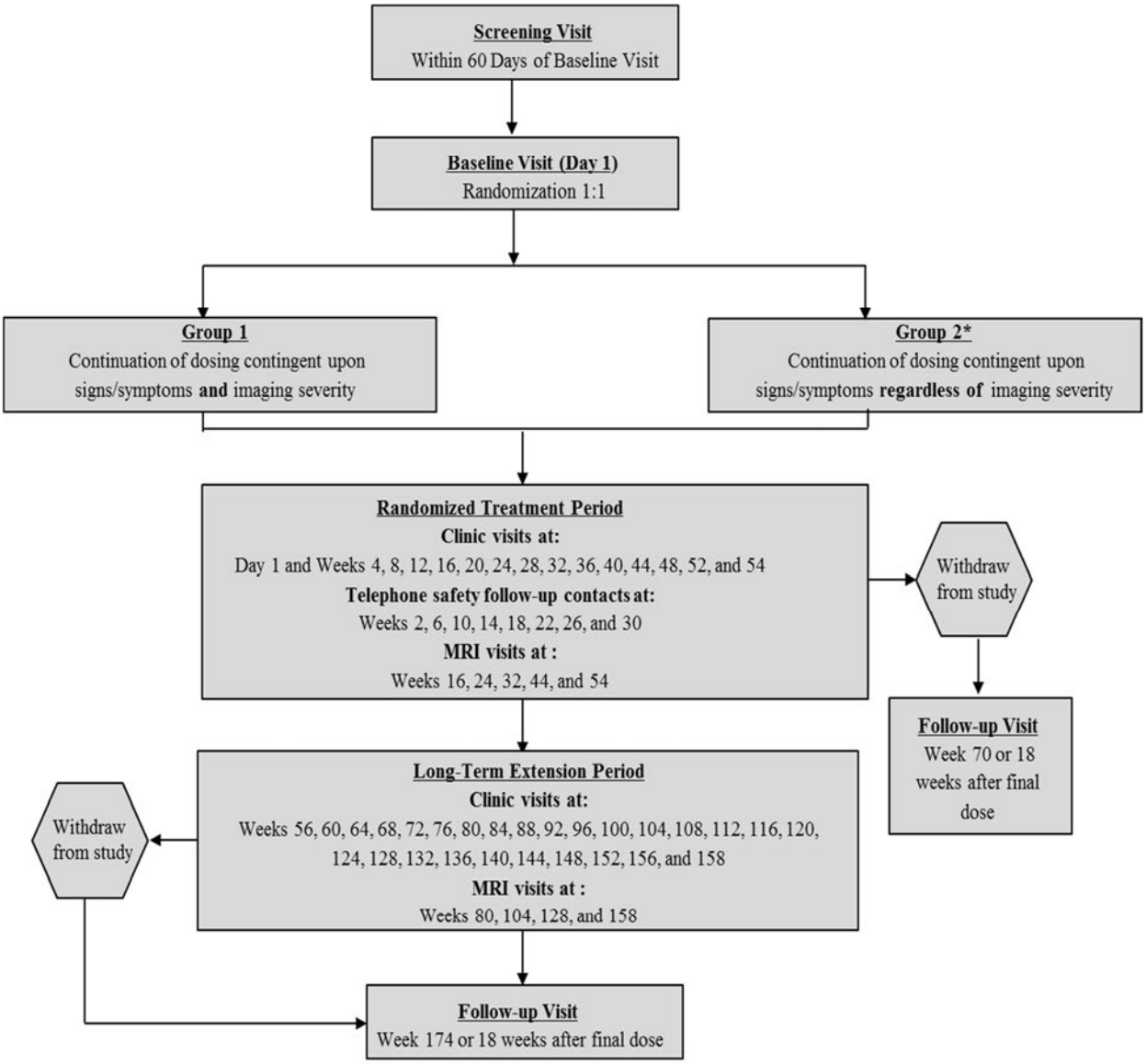
Throughout the study, Group 1 and Group 2:

- Symptomatic ARIA, any severity on MRI:
  - *Suspend or permanently discontinue treatment*
- ARIA-H (macrohemorrhage) with or without symptoms
  - *Permanently discontinue treatment*

At the end of the 52-week randomized, controlled treatment period, subjects who meet entry criteria may enter an optional LTE period in which subjects will continue to receive infusions of aducanumab at 10 mg/kg every 4 weeks for an additional 104 weeks (a total of 40 doses). During this time, asymptomatic ARIA in all subjects will be managed according to the plan described for Group 2.

See Figure 1 for a schematic of the study design.

Figure 1: Schematic of Study Design



* This study will evaluate the safety impact of continuing dosing in asymptomatic subjects with ARIA in a 2-stage approach. In Stage 1, Group 2 subjects with mild to moderate asymptomatic ARIA will be dosed through; it is planned that the impact of continuing dosing during asymptomatic ARIA that is mild, moderate, or severe on MRI (excluding ARIA-H [macrohemorrhage]) will be assessed in Stage 2, contingent upon DSMC recommendation after a review of Stage 1 data.
Note: All subjects are to receive titration to 10 mg/kg (2 doses of 1 mg/kg, then 2 doses of 3 mg/kg, then 2 doses of 6 mg/kg, then 10 mg/kg thereafter).

7.1. Study Duration for Subjects

The total duration of study participation for any given subject participating in only the randomized treatment period will be approximately 78 weeks, including a series of screening visits within 60 days before administration of the first dose, a 52-week treatment period, and a safety follow-up (FU) approximately 18 weeks after the final dose.

The total duration of study participation for any given subject participating in both the randomized treatment period and the LTE period will be approximately 186 weeks, including a series of screening visits within 60 days before administration of the first dose, a 52-week randomized treatment period, a 4-week FU period, a 104-week LTE treatment period, and a safety follow-up approximately 18 weeks after the final dose.

Subjects who permanently discontinue treatment are to remain in the study and follow a modified schedule for tests and assessments until the end of study or withdrawal of consent (Table 4). Subjects who withdraw from the study are to return for a safety follow-up approximately 18 weeks after their last dose of study treatment. The only exception is a subject who develops severe asymptomatic ARIA-H (microhemorrhage, superficial siderosis) in Stage 2; such a subject is to follow the regular visit schedule to maintain the blind to the subject's group assignment (Table 1).

Subjects will have approximately 3 planned clinic visits during screening, 24 planned clinic visits during the randomized treatment period, and up to 8 telephone safety follow-up contacts, as follows:

- Screening visits within 60 days before the first dose of study treatment on Day 1 (visits will be conducted on multiple days). All screening procedures should be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues.
- 14 outpatient dosing visits on Day 1 and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.
- 8 telephone safety follow-up contacts approximately 2 weeks after each of the first 8 dosing visits at Weeks 2, 6, 10, 14, 18, 22, 26, and 30.
- 6 planned visits for brain MRI at Screening and Weeks 16, 24, 32, 44, and 54.
- 1 End of Treatment Visit at Week 54.
- 1 safety follow-up visit at Week 70 only for subjects not participating in the LTE period.

Subjects who meet the LTE inclusion and exclusion criteria (see Section 8.3 and Section 8.4) will be eligible to enter the LTE period. Subjects who enter the LTE period will have approximately 29 additional planned visits as follows:

- 26 outpatient dosing visits on Weeks 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, and 156.
- 4 planned visits for brain MRI at Weeks 80, 104, 128, and 158.
- 1 End of Treatment Visit at Week 158.
- 1 follow-up safety visit at Week 174.

During the randomized treatment period and the LTE, subjects may have an Unscheduled Visit for safety and/or before the subject starts any new AD medication.

The end of study date for a subject is the last study visit or, if the subject has ongoing AEs that are being followed, the date of AE resolution.

7.2. Responsibilities of Site Personnel

7.2.1. Health Care Professionals

To maintain data integrity, each site will have a minimum of 3 separate health care professionals (HCPs), with roles and responsibilities defined as follows:

1. An independent clinical assessor (neurologist, designated by the Treating HCP/Principal Investigator [PI] of the site) who is **blinded** to the subject's treatment group assignment and not made aware of the MRI information from either the central or local MRI reads. The minimum qualification requirement of the independent clinical assessor is a medically qualified individual (Doctor of Medicine [M.D.] degree or equivalent) with at least 1 year of neurology specialty training. It is recommended that the same clinical assessor be assigned for the duration of the study. The independent clinical assessor will be expected to complete the ARIA education program, specifically designed to aid in symptomology decisions, as part of the study qualification requirement. The independent clinical assessor will be responsible for the following:

    - Physical and neurological examinations at protocol-specified visits.
    - Collection of medical history, review of selected hematology and blood chemistry results from the central laboratory, administration of MoCA and MMSE at the protocol-specified visits. Note: It is acceptable for the independent rater to perform the MoCA and MMSE (see Section 7.2.2).
    - Assessment of AEs prior to each infusion. Any AE suggestive of or potentially considered to be related to ARIA, as per the clinical judgment of the independent clinical assessor, should be evaluated further by detailed neurological assessment and local standard of care.

- Assessment of whether the subject has symptoms or signs (AEs) potentially related to ARIA, based on the assessor's clinical judgment, prior to each infusion. Note: the subject and the subject's caregiver must be instructed that they are not to share ARIA-related information with the clinical assessor.

2. A treating HCP (PI) who is **blinded** to the subject's treatment assignment. The minimum qualification requirement of the treating HCP is a medically qualified individual (M.D. or equivalent) with at least 1 year of direct clinical experience in managing people with dementia. The treating HCP will receive the medical record of the subject from the independent clinical assessor (based on the assessments described above), and from the independent rater (if applicable; see Section 7.2.2), as well as the assessment from the independent clinical assessor on whether the subject has symptoms or signs potentially related to ARIA. The treating HCP will have access to the MRI scans and will receive the central MRI report as well as the local radiology assessment. The treating HCP will be responsible for the following:

   - Management of subject's routine clinical care according to standard of practice.

   - Review of selected hematology and blood chemistry results from the central laboratory.

   - Management of AEs and/or SAEs.

   - Physical and neurological examinations at unscheduled visits, as needed. Management of the follow-up procedures according to the protocol when the subject develops ARIA. Note: It is acceptable for the independent rater to perform the MoCA (see Section 7.2.2).

   - Review of the clinical information collected from the independent clinical assessor, prior to each infusion.

     Note: The final determination about whether signs or symptoms are associated with ARIA resides solely with the independent clinical assessor.

     Note: if it is not possible for the subject to be seen by the clinical assessor and the treating HCP on the same day, the subject must be seen by the treating HCP on the next calendar day. The treating HCP may request a reassessment by the clinical assessor only if there is new relevant clinical information after the assessment by the independent clinical assessor; to avoid bias, the HCP must not share any ARIA-related MRI information with the clinical assessor. The treating HCP is encouraged to contact Biogen to discuss such situations.

   - The treating HCP must not change or influence the protocol-specified action with aducanumab dosing based upon his or her knowledge of ARIA-related MRI findings (see Section 7.2.2).

3. A local radiologist who will be **blinded** to the subject's treatment group assignment. The radiologist will be expected to complete the ARIA education program, specifically designed to aid in ARIA reading, as part of the study qualification requirement. The local radiologist will be responsible for the following:

   - Generation of an independent MRI report related to ARIA.

   - Reporting any MRI findings, including ARIA-related and incidental findings, to the treating HCP. (Note: the treating HCP may communicate any relevant incidental [i.e., non-ARIA] findings to the independent clinical assessor, as deemed necessary.) However, the local radiologist is not to discuss any MRI findings with the independent clinical assessor, the subject, or the informant/care partner.

7.2.2. Other Site Personnel

1. The **unblinded** pharmacist must consult the interactive response technology system prior to preparing the study treatment for each subject prior to infusion. The unblinded pharmacist will be responsible for the storage, distribution, preparation, and accountability of study treatment. The unblinded pharmacist will also be responsible for maintaining the unblinded pharmacy record separate from the main study file in order to support the study blind. (Note: if dosing is to continue, the subject should be infused on the same day or +1 calendar day after evaluation by the treating HCP.)

2. The **blinded** independent rater (designated by the treating HCP/PI of the site) is responsible for administering the Clinical Dementia Rating (CDR) at screening. The independent rater may perform the MoCA or MMSE, if it is not feasible for the clinical assessor or treating HCP to perform this assessment. The independent rater is blinded to the subject's group assignment, and must not be involved with any other aspect of subject care and management, and must remain blinded to imaging data or any other data that have the potential of revealing the treatment group assignment, ARIA-related imaging finding from either the central or local MRI reads, or the visit schedule being the unscheduled visit due to ARIA. To ensure consistency across sites, the independent rater must complete the standardized study-specific qualification process on clinical assessment scoring prior to administration of the specific assessment at the site. All sites must attempt to maintain the same rater throughout the study for specific assessments (i.e., MoCA and MMSE) in an attempt to remain consistent. Each subject should have the same rater perform the subject's specific rating assessment throughout the study. A qualified, approved back-up rater should conduct assessments in place of the primary rater only due to extenuating circumstances resulting in unavailability (e.g., due to illness, vacation, or travel). If a rater has to be replaced, the new rater must undergo the study-specific qualification process prior to administration of the assessment. The same rater qualification process applies to the clinical assessor and the treating physician if they are the MoCA and/or MMSE raters.

7.3. Study Stopping Rules

Biogen may terminate this study at any time, after informing Investigators. Biogen (or designee) will notify Investigators when the study is to be placed on hold, completed, or terminated. Biogen and the DSMC will review safety data on an ongoing basis. The study may be modified or terminated by Biogen based on the recommendation of the DSMC, internal review of the safety data, and per study-specific stopping recommendations as described in the DSMC charter.

7.4. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria for Randomized Treatment Period

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 subject or his/her legally authorized representative to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations. Note: the subject's legally authorized representative may or may not be the subject's informant/care partner (see inclusion criterion #9).

2. Age 50 to 85 years old, inclusive, at the time of informed consent.

3. All women of childbearing potential and all men must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, see Section 15.5.

4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI due to AD or mild AD dementia.

5. Must have evidence of cerebral Aβ accumulation, based on a positive PET scan of the brain. Previously obtained PET scan (within 12 months of Screening) is permissible. Previous PET scan images must be submitted to the central imaging vendor to confirm that study inclusion criteria are met.

6. Must meet all of the following clinical criteria for MCI due to AD or mild AD dementia according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have the following:

    - MCI due to AD:
        - A CDR global score of 0.5.
        - An MMSE score between 24 and 30 (inclusive).
    - Mild AD dementia:
        - A CDR global score of 0.5 or 1.
        - An MMSE score between 20 and 26 (inclusive).

Note: Subjects with a CDR global score of 0 but who meet the other entry criteria may repeat the screening CDR evaluation after 6 months past the initial evaluation.

7. Apart from a clinical diagnosis of MCI due to AD or mild AD dementia, the subject must be in good health as determined by the Investigator, based on medical history and screening assessments.

8. Must consent to ApoE genotyping.

9. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's overall health condition, including any adverse event the subject may have. The informant/care partner must minimally be available in person for one screening visit and by phone thereafter, monthly prior to each infusion, to provide information to the Investigator and study staff about the subject. An informant/care partner should be available for the duration of the study, and a consistent informant/care partner is encouraged.

8.2. Exclusion Criteria for the Randomized Treatment Period

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

Medical History

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

2. Clinically significant unstable psychiatric illness (e.g., uncontrolled major depression, uncontrolled schizophrenia, uncontrolled bipolar affective disorder) within 6 months prior to Screening.

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

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

   - Acute or subacute hemorrhage.

   - Prior macrohemorrhage (defined as >1 cm in diameter on T2* sequence) or prior subarachnoid hemorrhage unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).

   - More than 4 microhemorrhages (defined as ≤1 cm in diameter on T2* sequence).

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

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

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

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

8. Clinically significant 12-lead electrocardiogram (ECG) abnormalities, as determined by the Investigator.

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

10. History of malignancy or carcinoma. The following exceptions may be made after discussion with Biogen:
    - Subjects with cancers in remission ≥5 years prior to Screening.
    - Subjects with a history of excised or treated basal cell or squamous carcinoma of the skin.
    - Subjects with localized prostate cancer with treatment cycles that completed at least 6 months prior to Screening.

11. History of seizure within 10 years prior to Screening.

12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening. This includes but is not limited to repeated values of aspartate aminotransferase and alanine aminotransferase ≥2 × 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 human immunodeficiency virus.

17. History of, or positive test result at Screening for, hepatitis C virus antibody.

18. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [anti-HBc]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive hepatitis B surface antibody [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; history of hypersensitivity to any of the inactive ingredients in the drug product.

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

Medications

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

22. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 and during Screening up to Day 1, or use of AD medications (including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine) at doses that have not been stable for at least 8 weeks prior to Screening Visit 1 and during Screening up to Study Day 1. Subjects who fail Screening because allowed chronic medications have not been at stable doses for at least 4 weeks prior to Screening Visit 1 or during Screening up to Study Day 1, or whose use of AD medications has not been at stable doses for at least 8 weeks prior to Screening Visit 1 or

during Screening up to Study Day 1, may return for rescreening after use of these medications has been stabilized for the required period.

23. Use of medications with platelet antiaggregant or anticoagulant properties (the use of aspirin at a prophylactic dose [≤325 mg daily] is allowed).

24. Use of illicit narcotic medication.

25. Vaccinations within 10 days prior to randomization (Day 1).

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

27. Participation in any passive immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.

28. Participation in any study with purported disease-modifying effect in AD within 12 months prior to Screening unless documentation of receipt of placebo is available. Subjects who developed ARIA during a previous disease-modifying trial should be excluded.

29. Prior participation in a study with aducanumab.

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).

31. Contraindication to having a PET scan (e.g., inability to lie flat or still for the duration of the scan) or intolerance to previous PET scans (i.e., previous hypersensitivity reactions to any PET ligand or imaging agent, failure to participate in and comply with previous PET scans).

32. A negative PET scan result with any amyloid-targeting ligand within 6 months prior to Screening.

33. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

Others

34. Female subjects who are pregnant or currently breastfeeding.

35. Previous participation in this study. Subjects who fail Screening due to not meeting entry criteria for PET, MMSE, hepatitis B or C results, having a CDR global score >1, or having abnormal MRI findings will not be allowed to rescreen. Note: Subjects with a

CDR global score of 0 but who meet the other entry criteria may repeat the screening CDR evaluation after 6 months past the initial evaluation.

36. Subject currently living in an organized care facility with extensive intervention and/or support for daily living activities.

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

38. Inability to comply with study requirements.

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

8.3. Inclusion Criteria for the Long-Term Extension Period

To be eligible to participate in the LTE period, subjects must meet the following eligibility criteria at Week 54:

1. Subjects must have completed the randomized treatment period of the study, including the Week 52 Visit. Subject must have received at least 8 doses and not have missed more than 4 consecutive doses, except for subjects whose dosing was suspended due to ARIA. Subjects who do not meet these criteria may enter the LTE period only with Biogen's approval.

2. The subject (or the subject's legally authorized representative) has the ability to understand the purpose and risks of the study and to provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations. Note: the subject's legally authorized representative may or may not be the subject's informant/care partner (see inclusion criterion #6).

3. Female subjects of childbearing potential and male subjects must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment.

4. Apart from a clinical diagnosis of AD, the subject must be in good health as determined by the Investigator, based on medical history.

5. Must have the ability to comply with procedures for protocol-related tests.

6. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's overall health condition. At a minimum, the informant/care partner must be available by phone to provide information to the Investigator and study staff about the subject. An informant/care partner should be available for the duration of the study.

8.4. Exclusion Criteria for the Long-Term Extension Period

Subjects will be excluded from entering the LTE period if any of the following exist at Week 54:

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

9. SCREENING AND RANDOMIZATION

9.1. Screening

Subjects or their legally authorized representative (which may or may not be the subject's informant/care partner) must provide informed consent before any screening tests are performed (see Section 17.3).

During Screening, subjects may complete the neurocognitive scales (CDR and MMSE) and ApoE genotyping to determine study eligibility under a separate, optional initial consent process. If the subject meets inclusion criteria for these 2 scales, the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process, which will allow the administration of all screening assessments. When a subject signs the full informed consent form (ICF), that subject is considered to be enrolled in the study.

The neurocognitive assessments that have exclusion cut points (CDR and MMSE) and the ApoE genotyping must be performed at Screening Visit 1. ApoE genotyping may be performed at Screening Visit 1 prior to other screening assessments (and the result must be available prior to randomization). The MRI at Screening Visit 2 should be done only after subject eligibility based on clinical and laboratory criteria is confirmed during Screening Visit 1. The PET scan at Screening Visit 3 should be completed only after the MRI inclusion criterion is met. The ECog (Observer) assessment may be performed by the informant/care partner at any visit when (s)he is available in person, but must be completed prior to the PET scan. The DSST/trail making (optional) may be performed at any 2 separate screening visits but must be completed prior to the PET scan.

Participating study sites are required to document all screened candidates who are initially considered for inclusion in this study. It is recommended that all screening procedures be completed within 60 days; however, the overall screening period may be extended up to 90 days in the event of logistical issues and is subject to Biogen approval.

9.1.1. Screen Failures

Screen failures are defined as subjects who sign the ICF but do not meet all entry criteria. If a subject is considered a screen failure, the reasons for exclusion must be documented in the subject's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects in order to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and SAEs.

9.1.2. Rescreening

Subjects who fail Screening may be permitted to be rescreened once at Biogen's discretion. Subjects who fail Screening due to not meeting entry criteria for PET, MMSE, hepatitis B or C results, having a CDR global score >1.0, or having abnormal MRI findings will not be allowed to rescreen. Note: Subjects with a CDR global score of 0 but who meet the other entry criteria may repeat the screening CDR evaluation after 6 months past the initial evaluation.

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

9.2. Randomization

Subjects will be randomized after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. Subjects will be assigned a unique identification number that will be used on study-related documents pertaining to the subject. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment or continue in the study. Rescreened subjects will be assigned a new number.

Randomization will be performed using interactive response technology (IRT). Subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups. The randomization will be stratified by ApoE ε4 status (carrier or noncarrier). The ApoE genotyping results must be available prior to randomization.

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

9.3. Blinding Procedures

During the randomized treatment period of the study, the 3 HCPs (Section 7.2.1), other site personnel (Section 7.2.2) and study staff (except for designated pharmacy staff), and the subjects will be blinded to the treatment group assignment. During the LTE period, all subjects will receive dosing as defined for Group 2 of the randomized treatment period.

To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or at Biogen, except the unblinded pharmacy staff and designated Biogen personnel.

To maintain the blind to subjects' group assignments during the randomized treatment period, placebo will be given to subjects in prespecified cases of dose suspension or discontinuation due to asymptomatic ARIA (see Table 5 and Table 6). Should subjects who might permanently discontinue active dosing and receive placebo not be allowed to participate in the LTE, per Sponsor's decision or DMSC recommendation, the treatment assignment will be disclosed at the end of the randomized treatment period.

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

9.4. ARIA/MRI Information

Throughout the study, the independent clinical assessor will not be made aware of ARIA information from either the central or local MRI reads.

The treating HCP may have access to the MRI scans and will be provided with both the central MRI report and the local radiologist's assessment. The treating HCP may communicate information on incidental findings to the clinical assessor, as deemed necessary.

Subjects and the subject's informant/care partner may be informed by the treating HCP about ARIA findings, as appropriate. The treating HCP may divulge the MRI severity information, as necessary. The subject and informant/care partner must be reminded that they are not to share ARIA information with the clinical assessor or the independent rater.

9.5. ApoE ε4 Carrier Status

Throughout the study, the 3 HCPs, study staff, and subjects will not be made aware of the subject's ApoE ε4 carrier status.

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

10.1. Discontinuation of Study Treatment

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

- The subject develops any of the following:
  - Symptomatic ARIA-E accompanied by serious clinical symptoms that are life-threatening (in the opinion of the investigator) and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect (see Table 5 for details).
  - Symptomatic ARIA-H (microhemorrhage or superficial siderosis) accompanied by serious clinical symptoms that are life-threatening (in the opinion of the investigator) and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect (see Table 6 for details).
  - Symptomatic ARIA-H (microhemorrhage or superficial siderosis) that is severe on MRI (≥10 microhemorrhages and/or >2 focal areas of superficial siderosis), regardless of clinical symptom severity (see Table 6 for details).
  - Asymptomatic ARIA-H (microhemorrhage or superficial siderosis) that is severe on MRI (≥10 microhemorrhages and/or >2 focal areas of superficial siderosis) (*Stage 1 only*) [see Table 6 for details].

    Note: In Stage 2, following DSMC review of the Stage 1 data and contingent upon DSMC recommendation (see Section 19.2.2), aducanumab dosing will be continued in subjects in Group 2 with asymptomatic ARIA-H that is severe on MRI (≥10 microhemorrhages and/or >2 focal areas of superficial siderosis). To maintain the blind, subjects in Group 1 will permanently discontinue active dosing and receive placebo (see Table 6 for details).
  - Any new incident macrohemorrhage (defined as >1 cm in diameter on T2* sequence), regardless of whether symptoms are present and, if present, regardless of symptom severity.
- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.

- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment or unblinding of the subject's treatment assignment.
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusionary criteria (see Section 11.5.1.2).
- The subject experiences a severe infusion reaction.
- At the discretion of the Investigator or Biogen for medical reasons.
- At the discretion of the Investigator or Biogen for noncompliance.

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

Subjects who permanently discontinue study treatment are to remain in the study and follow a modified schedule for tests and assessments until the end of study or withdrawal of consent (Table 4). The only exception is a subject who may develop severe asymptomatic ARIA-H (microhemorrhage, superficial siderosis) in Stage 2; such a subject is to follow the regular visit schedule, to maintain the blind to the subject's group assignment (see Table 1).

10.2. Lost to Follow-Up

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

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

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

10.3. Withdrawal of Subjects From Study

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

- The subject withdraws consent.

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

Note: A subject who permanently discontinues study treatment will not be automatically withdrawn from the study, regardless of the number of doses missed, if they continue to attend clinic visits and complete assessments as scheduled (Table 4).

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

Subjects who are withdrawn from the study after receiving ≥1 doses of study treatment must undergo an End of Treatment Visit unless withdrawal is due to death or withdrawal of consent. Subjects who are withdrawn from the study are also to return to the site for a safety follow-up visit 18 weeks after receiving their last dose of study treatment.

Subjects who withdraw from the study may be replaced.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the Directions for Handling and Administration (DHA) for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

The study treatment infusion schedule during the randomized treatment period and the LTE period of the study is provided in Section 5.

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

11.1.1. Aducanumab

Biogen will provide aducanumab to the study sites.

11.1.2. Placebo

All subjects receive aducanumab in this study.

To maintain the blind to subjects' group assignment, subjects in Group 1 who have asymptomatic ARIA (except macrohemorrhage) that requires dose suspension or discontinuation of active dosing as per protocol will receive placebo. Placebo (0.9% sodium chloride) will be supplied by the study site.

11.2. Modification of Dose and/or Treatment Schedule

11.2.1. Continuation, Suspension, or Discontinuation for ARIA Events During the Randomized Treatment Period

A central MRI reading center will report incident cases of ARIA-E and ARIA-H to both Biogen and the treating HCP within a specified time. The unblinded pharmacy staff will prepare the treatment after consulting the interactive response technology system, which will provide integrated information based on the clinical assessor's symptomatology assessment, the ARIA information from the central MRI read, and the subject's treatment group assignment.

Biogen and a DSMC will review safety data on an ongoing basis, including comprehensive ARIA information. The study may be modified or terminated by Biogen based on the recommendation of the DSMC, internal review of the safety data, and per study-specific stopping recommendations as described in the DSMC charter. In addition, the DSMC will make a recommendation of dosing through asymptomatic severe ARIA cases in Group 2. A DSMC charter will provide full guidance on the function and practices to be followed by the DSMC (Section 19.2.2).

Guidelines on the management and disposition of ARIA-E and ARIA-H cases are provided in the following subsections. See Section 10.1 for the full list of criteria for discontinuing study treatment.

11.2.1.1. ARIA-E Cases

The management and disposition of subjects who develop ARIA-E during the randomized treatment period are detailed in Table 5.

All subjects who develop ARIA-E should have unscheduled visits every 4 weeks (±5 days) for follow-up MRI and ARIA safety assessments (as detailed in Section 5, Table 1), until the ARIA-E has resolved per centrally read MRI. [redacted] PK samples will be collected at the first unscheduled visit following an episode of ARIA.

Subjects who continue dosing during the first or subsequent recurring ARIA-E events will do so in accordance with the aducanumab dosing regimen (for details, see Section 11.2.3).

Subjects for whom treatment is temporarily suspended due to the first or recurrent ARIA-E events may resume treatment at the same dose, once ARIA-E and (if present) clinical signs and symptoms have resolved, in the treating HCP's opinion (for details see Section 11.2.3).

Management of ARIA-E after it resolves is described in Section 11.2.4.

Subjects who continue dosing during an ARIA-E event or who suspend dosing (including due to an ARIA-E event) should complete all scheduled clinic visits for assessments (as detailed in Section 5, Table 1). Subjects who permanently discontinue treatment due to ARIA-E (as with subjects who discontinue for other reasons) are to remain in the study and follow a modified schedule for tests and assessments until the end of study or withdrawal of consent (Table 4). This is in addition to completing the unscheduled visits as described above.

Subjects who withdraw from the study are to return for a safety follow-up visit 18 weeks after their last dose of study treatment.

Table 5: Disposition of ARIA-E Cases During Randomized Treatment Period

<table>
<tr><th rowspan="2">Clinical Symptom Severity (if present)</th><th colspan="3">ARIA-E Severity on MRI (Central Read)</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><td>Asymptomatic</td><td colspan="3">Stage 1</td></tr>
<tr><td>Group 1</td><td>Continue dosing at current dose and schedule</td><td>Suspend dosing and receive placebo. Once ARIA-E resolves the subject may resume dosing at the same dose.</td><td rowspan="2">Suspend dosing (without receiving placebo). Once ARIA-E resolves, subject may resume dosing at same dose</td></tr>
<tr><td>Group 2</td><td colspan="2">Continue dosing at current dose and schedule[1]</td></tr>
<tr><td>Asymptomatic</td><td colspan="3">Stage 2</td></tr>
<tr><td>Group 1</td><td>Continue dosing at current dose and schedule</td><td colspan="2">Suspend dosing and receive placebo. Once ARIA-E resolves, subject may resume dosing at same dose.</td></tr>
<tr><td>Group 2</td><td colspan="3">Continue dosing at current dose and schedule[1]</td></tr>
<tr><td>Symptomatic</td><td colspan="3">Throughout Study, Groups 1 and 2</td></tr>
<tr><td>Mild</td><td colspan="3" rowspan="4">Suspend dosing. Once ARIA-E and clinical symptoms resolve, the subject may resume dosing at the same dose.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td></tr>
<tr><td>Serious “other medically important event” only[2]</td></tr>
<tr><td>Serious “hospitalization” only</td><td colspan="3">Suspend or permanently discontinue treatment at treating HCP’s discretion</td></tr>
<tr><td>Serious, except for “other medically important event” and “hospitalization”[3]</td><td colspan="3">Permanently discontinue treatment</td></tr>
</table>

[1]In Group 2, dosing initially (Stage 1) will be continued in mild and moderate cases only. Following a review of the data and contingent on recommendation from the DSMC (i.e., in Stage 2), dosing will be continued regardless of MRI severity (as described in Sections 7 and 19.2.2). The only exception is a subject who has severe asymptomatic ARIA-E in Stage 1 and who develops recurrent asymptomatic severe ARIA-E in Stage 2; in this case, the subject will follow the Group 1 treatment paradigm, i.e., suspend active dosing and, after ARIA-E resolves, resume dosing at the same dose.

[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 that may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above and as described in Section 15.1.

[3]SAEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator) and/or that result in persistent or significant disability/incapacity or a congenital anomaly/birth defect, as described in Section 15.1.

11.2.1.2. ARIA-H (Microhemorrhage or Superficial Siderosis) Cases

The management and disposition of subjects who develop ARIA-H (microhemorrhage or superficial siderosis) is detailed in Table 6.

All subjects who develop ARIA-H (microhemorrhage or superficial siderosis) should have an unscheduled visit(s) every 4 weeks (±5 days) for follow-up MRI and ARIA safety assessments, as detailed in Section 5 (Table 1), until the microhemorrhages/superficial siderosis are deemed stable (defined as no change or a decrease in the number, size, severity, or number of locations between 2 consecutive MRIs, which can include the initial MRI) per centrally read MRI. [redacted] PK samples will be collected at the first unscheduled visit following an episode of ARIA.

Subjects who continue dosing during the first or subsequent recurring ARIA-H events, will do so in accordance with the aducanumab dosing regimen (for details see Section 11.2.3).

Subjects for whom treatment is temporarily suspended due to a first or recurrent ARIA-H may resume treatment at the same dose once the ARIA-H is deemed stable and (if present) the clinical signs and symptoms have resolved in the treating HCP's opinion (for details see Section 11.2.3).

Management of ARIA-H after stabilization is described in Section 11.2.4.

Subjects who continue dosing through an ARIA-H event or who suspend dosing (including due to an ARIA-H event) should complete all scheduled clinic visits as detailed in Section 5 (Table 1). Subjects who permanently discontinue treatment due to an ARIA-H event (as with subjects who permanently discontinue treatment for other reasons) are to remain in the study and follow a modified schedule for tests and assessments until the end of study or withdrawal of consent (Table 4). The only exception is a subject who may develop severe asymptomatic ARIA-H in Stage 2 as outlined in Table 6; such a subject is to follow the regular visit schedule (Table 1) in order to maintain the blind to the subject's group assignment.

Subjects who withdraw from the study are to return for a safety follow-up visit 18 weeks after their last dose of study treatment.

Table 6: Disposition of ARIA-H (Microhemorrhage or Superficial Siderosis) Cases During the Randomized Treatment Period

Clinical Symptom Severity (if present)	New Incident ARIA-H Severity on MRI (Central Read)[1]		
	Mild	**Moderate**	**Severe**
Microhemorrhage	≥1 and ≤4	≥5 and ≤9	≥10
Superficial siderosis	1	2	>2
Asymptomatic	**Stage 1**		
Group 1	Continue dosing at current dose and schedule	Suspend dosing *and receive placebo*. Once ARIA-H is stable, the subject may resume dosing at the same dose.	Permanently discontinue treatment[3]
Group 2	Continue dosing at current dose and schedule[2]		
Asymptomatic	**Stage 2**		
Group 1	Continue dosing at current dose and schedule	Suspend dosing *and receive placebo*. Once ARIA-H is stable, the subject may resume dosing at the same dose.	Permanently discontinue active dosing *and receive placebo*[3]
Group 2	Continue dosing at current dose and schedule[2]		
Symptomatic	**Throughout Study, Groups 1 and 2**		
Mild	Suspend dosing. Once ARIA-H is stable and clinical signs and symptoms resolve, the subject may resume dosing at the same dose.		Permanently discontinue treatment[3]
Moderate			
Severe			
Serious, "other medically important event" only[4]			
Serious, "hospitalization" only	Suspend or permanently discontinue treatment at treating HCP's discretion. In case of dosing suspension, once ARIA-H is stable and clinical signs and symptoms resolve, the subject may resume dosing at the same dose.		Permanently discontinue treatment[3]
Serious, except for "other medically important event" and "hospitalization"[5]	Permanently discontinue treatment[3]		

[1]"New incident microhemorrhages" refers to new incident microhemorrhages while subject is receiving study treatment; does not include microhemorrhages observed at baseline.

[2]In Group 2, dosing initially (Stage 1) will be continued in mild and moderate cases only. After a review of the Stage 1 data and based on recommendation from the DSMC, dosing will be continued in Stage 2 regardless of severity (Section 19.2.2).

[3]Subjects who permanently discontinue treatment are to remain in the study and follow a modified schedule for tests and assessments until the end of study or withdrawal of consent (Table 4). The only exception is a subject who

may develop severe asymptomatic ARIA-H in Stage 2 as outlined in Table 6; such a subject is to follow the regular visit schedule (Table 1) to maintain the blind to the subject's group assignment.

[4]"Other medically important events" requiring dosing suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient hospitalization or prolongation of existing hospitalization, and do not result in significant/permanent disability or congenital anomalies/fetal defects, but may (in the opinion of the Investigator) jeopardize the subject or may require intervention to prevent one of the outcomes listed above and as described in Section 15.1.

[5]AEs requiring permanent discontinuation of study treatment include those that are life-threatening (in the opinion of the Investigator) and/or result in persistent or significant disability/incapacity or a congenital anomaly/birth defect, as described in Section 15.1.

11.2.1.3. Macrohemorrhage

Subjects in either Group 1 or 2 who develop any new incident macrohemorrhage (defined as >1 cm in diameter on T2* sequence), regardless of whether symptoms are present and, if present, regardless of symptom severity, will permanently discontinue treatment but will remain in the study. Subjects will follow a modified schedule for tests and assessments until the end of the study period or withdrawal of consent (Table 4). In addition, subjects should have an unscheduled visit(s) every 4 weeks (±5 days) for a follow-up MRI and ARIA safety assessments as detailed in Section 5, until the macrohemorrhage is confirmed stable per centrally read MRI. A macrohemorrhage is considered stable if it there is either 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. [redacted] PK samples will be collected at the first unscheduled visit following an episode of ARIA.

11.2.1.4. Coincident ARIA-E and ARIA-H Cases

Subjects who develop ARIA-E coincident with ARIA-H in either Group 1 or Group 2 will follow the most restrictive applicable guidelines as described in Sections 11.2.1.1, 11.2.1.2 and 11.2.1.3.

11.2.2. Continuation, Suspension, or Discontinuation for ARIA Events During the Long-Term Extension Period

Dose continuation, suspension, or discontinuation for ARIA-E or ARIA-H cases during the LTE period will be based on the previously mentioned criteria for Group 2 for asymptomatic and symptomatic cases.

11.2.3. Dosing in Subjects Continuing on Aducanumab During an ARIA Event and in Subjects Resuming Aducanumab After Dose Suspension due to ARIA

Subjects who *continue dosing* per protocol during a first occurrence or recurrence of asymptomatic ARIA will do so in accordance with the protocol-specified aducanumab dosing regimen (2 doses of 1 mg/kg, then 2 doses of 3 mg/kg, then 2 doses of 6 mg/kg, and 10 mg/kg thereafter). For example, if asymptomatic ARIA occurs after the first dose of 3 mg/kg, the subject will continue dosing and receive 3 mg/kg; and if asymptomatic ARIA recurs after the second dose of 6 mg/kg, the subject will continue dosing and receive 10 mg/kg.

Subjects who *suspend dosing* due to a first occurrence or recurrence of ARIA and who resume dosing per protocol are to resume dosing at the same dose level. However, if dosing is suspended before a subject reaches 10 mg/kg, the subject must receive at least 2 doses at the dose level at which ARIA occurred before titrating up to the next dose level and continuing the titration to 10 mg/kg.

11.2.4. MRI Monitoring After Resolution of ARIA in Subjects Continuing or Resuming Dosing

If ARIA occurs during the titration phase (e.g., during the first 28 weeks in the case of incident ARIA):

- After ARIA has resolved or stabilized, an MRI and MoCA will be performed 2 weeks (±5 days) after every second dose until completion of the titration period, with subjects assumed to be titrating to 10 mg/kg, and a final MRI and MoCA after the second dose at 10 mg/kg. MRIs will otherwise be performed as indicated in the Schedule of Activities (Section 5).

- This applies regardless of whether the subject is continuing dosing, is resuming dosing after suspension of active dosing, or has discontinued active dosing and is receiving placebo.

If ARIA occurs after the end of the titration phase (e.g., after Week 28):

- After ARIA has resolved or stabilized, an MRI and MoCA will be performed 2 weeks (±5 days) after the second administration of the restart dose. MRIs will otherwise be performed as indicated in the Schedule of Activities (Section 5).

- This applies regardless of whether the subject is continuing dosing, is resuming dosing after dose suspension, or has discontinued active dosing and is receiving placebo.

11.2.5. Infusion Interruption

If any mild or moderate infusion-related reactions (e.g., headache, chills/rigors, and nausea/vomiting) occur during an infusion, the infusion should be slowed or interrupted and supportive treatment should be instituted at the discretion of the Investigator. After resolution of

symptoms, if the infusion had been slowed, the original infusion rate may be resumed; if the infusion had been interrupted, the infusion may be restarted at a rate that does not exceed the original infusion rate. An infusion must be discontinued if not completed within 3 hours.

Refer to the DHA for infusion rate information.

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

Severity of events is described in Section 15.2.3.

11.3. Precautions

Not applicable.

11.4. Compliance

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

11.5. Concomitant Therapy and Procedures

11.5.1. Prior and Concomitant Therapy

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

A concomitant therapy is any drug or substance administered between the informed consent and until the subject's final clinic visit (including the safety follow-up 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 at a stable dose during the study as long as the subject has been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1 and during the screening period.

- Symptomatic therapies for AD, including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine, provided that subjects are receiving a stable dose for at least 8 weeks prior to Screening Visit 1 and during the screening period, and that they stay on a stable dose while in the study.

- Vaccinations with live or attenuated vaccines. Administration of any vaccination/booster should not be given < 10 days prior to any dosing visit and for 10 days after a dosing visit.

11.5.1.2. Disallowed Concomitant Therapy

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

Subjects should be instructed to continue the medications that they were receiving at enrollment without any changes (see allowed concomitant therapy, above) and avoid starting any new medications or herbal preparations during the study period, since these may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in medication. The change should be reviewed by the Investigator and the study medical monitor to determine whether the subject's study treatment should be suspended. Medications used to treat AEs will not result in automatic permanent study treatment discontinuation. However, as noted in Section 10.1, if a subject requires continued use of a disallowed therapy, the subject must permanently discontinue study treatment. Biogen may be consulted if required.

Subjects should have an unscheduled visit for a change in AD medication; required assessments per schedule of activities (MMSE and AEs) should be performed prior to any change in medication.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, routine colonoscopy, bacterial cultures) performed between the time the subject is enrolled in the study and until the subject's final clinic visit (including the safety follow-up visit), unless the subject is being followed for study treatment-related toxicity.

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

11.6. Continuation of Treatment

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

12. STUDY TREATMENT MANAGEMENT

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

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

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

12.1. Aducanumab

Research Name: BIIB037

Generic Name: Aducanumab

Trade Name(s): Not applicable

Synonyms: Fully 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 interchain disulfide bonds. [redacted] Aducanumab is purified from the media and formulated as a liquid.

Aducanumab is supplied as a liquid drug product containing:

- aducanumab [redacted] mg/mL (excipients: [redacted])

The concentration for each vial appears on the label.

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 study treatment, do not use the study treatment. The vial in question should be saved at the study site and the problem immediately reported to Biogen.

12.1.2. Aducanumab Storage

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

12.1.3. Aducanumab Handling and Disposal

The Investigator must return all used and unused vials of aducanumab as instructed by Biogen 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 (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed 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, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo

Placebo (0.9% sodium chloride) will be supplied by the study site in the form of 100 mL saline IV bags.

12.3. Other Protocol-Designated Product

Refer to the DHA for infusion-related supply specifications.

PET scans at screening will be performed using Amyvid™ (^{18}F-florbetapir), Vizamyl™ (^{18}F-flutemetomol), or Neuraceq™ (^{18}F-florbetaben). For details on PET imaging ligands, refer to the procedural manual for PET.

13. EFFICACY, PHARMACOKINETIC, AND OTHER ASSESSMENTS

See Section 5 for the timing of all assessments.

13.1. Efficacy Assessments

No efficacy assessments are planned for this study.

13.2. Pharmacokinetic Assessments

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

[redacted]

13.4. Pharmacogenetics and Genetic Assessments

13.4.1. ApoE Genotyping

Whole blood samples for deoxyribonucleic acid (DNA) ApoE genotyping will be collected from all subjects at the Screening Visit. The ApoE ε4 carrier status will be available and provided to the IRT system for stratification during randomization.

[redacted]

[redacted]

13.6. Other Assessments

The CDR is used to assess a subject's cognitive and functional performance in 6 areas applicable to AD and related dementias: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. It is administered by a qualified health professional using a semistructured interview. Scores are combined to obtain a global dementia severity score ranging from 0 to 3 (0=normal, 0.5=very mild, 1=mild, 2=moderate, 3=severe).

The MMSE is a widely used, validated test of cognitive status. It includes items that assess orientation, word recall, attention and calculation, language abilities, and visuospatial ability. Scores range from 0 to 30, with lower scores indicating greater symptomatology.

The CDR and MMSE are used in this study to assess eligibility for participation in the study. The MMSE is also administered during the study to monitor cognitive status.

The Everyday Cognition (ECog) scale consists of 39 questions about a person's ability to complete common tasks, such as keeping track of a conversation or shopping for a few items without a list. ECog (Observer) will be completed by the informant/care partner at the Screening Visit. The result might be utilized to identify a predictive marker associated with amyloid positivity in clinically diagnosed subjects with MCI and/or with mild AD dementia.

Digital Symbol Substitution Task (DSST) and Trails Making Test (TMT) are neuropsychological tests used to assess the cognitive domains of processing speed, episodic memory, and executive function. DSST/TMT tests are optional, and will be administered by a rater at any 2 Screening Visits. The test performance within, and learning effect across, the 2 test sessions may be utilized to identify a predictive marker associated with amyloid positivity in clinically diagnosed subjects with MCI and/or with mild AD dementia.

14. SAFETY ASSESSMENTS

See Section 5 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

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

- AE and SAE recording
- Brain MRI
- Physical examination, including height and weight
- Neurological examinations
- Vital sign measurements: temperature, heart rate, systolic and diastolic blood pressure, and respiratory rate
- 12-lead ECG
- Concomitant therapy and procedure recording
- Columbia Suicide Severity Rating Scale (C-SSRS)
  - The C-SSRS is a suicidal ideation and behavior rating scale used to evaluate suicide risk.
- MoCA for ARIA monitoring and management
  - The MoCA is a 30-point test widely used to detect cognitive dysfunction and is used in this study as a safety measure.

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, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium

- Urinalysis: color, specific gravity, pH, protein, glucose, blood, ketones, and microscopic examination (if abnormal)

- Serum and urine pregnancy test (women of childbearing potential only)

- Coagulation, virology (including HIV at the Investigator's discretion after consideration of risk factors), glycosylated hemoglobin (HbA1c), lipid panel, and alcohol/drug screen (at Screening only)

14.3. Immunogenicity Assessments

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

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

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

15.1. Definitions

15.1.1. Adverse Event

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

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

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

15.1.2. Serious Adverse Event

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

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

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

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

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3

15.2.2. Relationship of Events to Study Treatment

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

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational product 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 investigational product and the AE, 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 product 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 investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

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

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

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the subject's final clinic visit (including FU Visit) is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

AEs that are ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will be recorded on the CRF, as applicable.

15.3.2. Adverse Events of Special Interest

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

15.3.3. Serious Adverse Events

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

Subjects will be followed for all SAEs until the final clinic visit (including FU Visit). Thereafter, the event should be reported to Biogen only if the Investigator considers the SAE to be related to study treatment.

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

15.3.4. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen within 24 hours of the 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

A report ***must be submitted*** to Biogen regardless of the following:

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

To report initial or follow-up information on an SAE, fax or email a completed SAE form; refer to the Study Reference Guide's Official Study Contact List for country-specific fax numbers or email addresses.

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 Biogen. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. Suspected Unexpected Serious Adverse Reactions

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

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

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

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

The Investigator must report a pregnancy occurring in a female subject by faxing the appropriate form to Biogen within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The Investigator or site staff must report the outcome of the pregnancy to Biogen. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

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

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed to Biogen within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to Biogen. 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, site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

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

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

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

15.5. Contraception Requirements

All women of childbearing potential and all men must ensure that highly effective contraception is used during the study and for 24 weeks after their last dose of study treatment. In addition, subjects should not donate sperm or eggs for the duration of the study and for at least 24 weeks after their last dose of study treatment.

For the purposes of this study, women who do not meet one of the following criteria are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
    - 12 continuous months of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle-stimulating hormone level >40 mIU/mL
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation), where applicable according to local guidelines

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

For females:

- Combined (estrogen and progesterone) hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable).
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- *Where applicable according to local guidelines*, 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.
- Bilateral tubal occlusion.
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For males:

- Vasectomy with negative semen analysis at Follow-up Visit.
- Where applicable according to local guidelines, condoms with spermicide.
- Sex with a woman who uses the highly effective methods described above for females if she is of childbearing potential.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical study. 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 fulfilling all roles and responsibilities listed in Section 7.2. Additionally, 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 follow up on the outcome of all pregnancies in female subjects.
- Complete an SAE form for each SAE and fax it to Biogen within 24 hours of the site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen within 24 hours of the site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before a site can enroll any subjects, the Clinical Monitor (Biogen designee) is responsible for reviewing with site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ethics committees, 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. In general, study data will be summarized using standard descriptive statistics, and no formal statistical hypothesis testing is planned. Additional details of the analysis of study data will be provided in a separate Statistical Analysis Plan.

16.1. Demography and Baseline Disease Characteristics

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

16.2. Primary and Secondary Endpoint Analysis

16.2.1. Analysis Population

The safety population, defined as all subjects who were randomized and received at least 1 dose of aducanumab will be used for the primary and secondary endpoint analyses.

16.2.2. Method of Analysis

16.2.2.1. Analysis of the Primary Endpoint

No formal hypothesis testing is planned for the primary endpoint. The incidence rate and 90% exact binomial confidence interval (CI) for each treatment group will be provided. The rate difference between 2 groups and its 90% exact CI will be provided. The list of events specified in the primary endpoint (as determined by the Adjudication Committee; see Section 19.2.1) will be provided by group.

16.2.2.2. Analysis of the Secondary Endpoints

The incidence of ARIA and their severity by imaging as well as clinical perspectives, will be summarized for each group and overall. These analyses will also be performed for the different types of ARIA (e.g., ARIA-E, ARIA-H). Kaplan-Meier plots will be produced to describe time to ARIA onset, time to symptomatic ARIA, and time to asymptomatic ARIA. Summary statistics will be presented to describe the time to resolution of ARIA.

The incidence of AEs, SAEs, and antiaducanumab antibodies, as well as clinical changes in vital signs and ECGs, will be summarized for each group and overall.

16.3. Pharmacokinetics

16.3.1. Analysis Population

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

16.3.2. Method of Analysis

The serum concentrations and PK parameters of aducanumab will be summarized descriptively.

16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who were randomized and received at least 1 dose of aducanumab.

16.4.2. Methods of Analysis

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

16.4.2.1. Adverse Events

Only treatment emergent adverse events (TEAEs) will be presented in the summary tables. Treatment emergent is defined as having an onset date that is on or after the start of study treatment, or as worsening after the start of study treatment.

Incidence of TEAEs will be summarized by treatment group, overall, by severity, and by relationship to study treatment for the randomized treatment period and the LTE period. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities.

16.4.2.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, blood chemistry, and urinalysis. 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 by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

16.4.2.3. Vital Signs and ECGs

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

16.4.2.4. Columbia Suicide Severity Rating Scale

C-SSRS data will be summarized by treatment group.

16.5. Immunogenicity Data

16.5.1. Analysis Population

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

16.5.2. Methods of Analysis

Antiaducanumab serum antibodies will be summarized will be summarized for each group and overall.

16.6. Interim Analyses

An interim analysis for the primary endpoint may be performed.

16.7. Sample Size Considerations

Based on the data from Study 221AD103, 2 out of 185 subjects (1%) experienced serious ARIA events resulting in hospitalization within the first 12 months of treatment with aducanumab. In addition, there were no deaths or persistent significant disability due to ARIA. Of the 185 subjects, 31 subjects were in the 10 mg/kg titration group, and none of them experienced clinically impactful ARIA. By applying the current definition of clinically impactful events as the primary endpoint to this study, a low incidence of clinically impactful ARIA events is expected to be observed during the study.

This is an estimation study. No formal hypothesis testing is planned. In Study 221AD103, of the 185 subjects, 20 subjects developed asymptomatic moderate ARIA-E and 1 subject developed severe asymptomatic ARIA-E. In order to enroll 25 subjects with asymptomatic moderate to severe ARIA-E in each treatment group, a sample size of approximately 500 subjects is selected to provide a preliminary estimate of incidence rates. The sample size may be re-estimated based on evolving learning from external sources and blinded review of this study. Subjects will be randomized in a 1:1 ratio to each of the 2 treatment groups. When 1 clinically impactful ARIA event is observed, the incidence rate will be 0.004 and the 90% exact CI will be (0.0002, 0.0188). If 2 events are observed, the incidence rate will be 0.008 and the 90% exact CI will be (0.0014, 0.0250), and if 3 events are observed, the incidence rate will be 0.012 and the 90% exact CI will be (0.0033, 0.0307).

The assumed incidence rates and the probability of observing events in each group are presented in the following table.

Incidence Rate in Group 1	**Incidence Rate in Group 2**	**Probability of Observing Same Number of Events in Group 1 and Group 2**	**Probability of Observing at Least 1 More Event in Group 2 vs. Group 1**	**Probability of Observing at Least 2 More Events in Group 2 vs. Group 1**	**Probability of Observing at Least 3 More Events in Group 2 vs. Group 1**
1%	1%	18%	41%	24%	13%
1%	2%	10%	77%	64%	49%
1%	3%	3%	93%	87%	79%

17. ETHICAL REQUIREMENTS

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

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

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

The Investigator must obtain ethics committee 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 ethics committee. 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 ethics committee and Biogen.

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

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

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

At the completion or termination of the study, the study site must submit a close-out letter to the ethics committee and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. (The subject's informant/care partner may or may not be the subject's legally authorized representative.) Subjects can complete the neurocognitive scales (CDR and MMSE) as well as ApoE genotyping as an initial optional screening under a separate consent process. If the subject meets inclusion criteria for these 2 scales, the full consent process must be completed prior to the administration of further screening assessments. Subjects may also proceed directly to the full consent process that would allow the administration of all screening assessments.

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

Subjects will be informed that their race and ethnicity will be collected during the study (unless the collection is not permitted by applicable law or not approved by the governing ethics committee) and the data will be used during analysis of study results.

A copy of the signed and dated ICF must be given to the subject or the subject's care partner/ 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 subject's medical record.

17.4. Subject Data Protection

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

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

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

17.5. Compensation for Injury

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

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

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

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

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

18.2. Quality Control and Quality Assurance

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

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

18.3. Monitoring of the Study

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

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

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

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

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts 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

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

19.1.1. Contract Research Organization

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

19.1.2. Interactive Response Technology

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

19.1.3. Electronic Data Capture

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

19.1.4. Central Laboratories for Laboratory Assessments

Biogen has selected a central laboratory service to perform all standard hematology, blood chemistry, and urinalysis testing for the study. This central laboratory will also receive, track, and ship all urine and blood samples, and DNA for specialized ApoE ε4 genotyping, PK, [redacted], and ADA testing, including aliquots from these samples retained as backup in case original samples are lost or not evaluable. Blood samples collected [redacted] stored by the central laboratory.

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

19.1.5. Central Facility for Other Assessments

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

The central imaging laboratory will also collect PET scans and assess the screening scan for eligibility criteria.

19.1.6. Neurocognitive Assessments

Biogen selected a rater management group to establish rater qualification, study-specific training, and oversight. The study raters are required to complete qualifications steps and required training prior to administering study assessments. The rater management group will oversee the assessments per project-specific plans. All neurocognitive data, with the exception of DSST and MoCA assessments, will be captured via electronic means.

19.2. Study Committees

19.2.1. Adjudication Committee

The Adjudication Committee will be formed to review all symptomatic ARIAs and ARIAs reported as SAEs, and adjudicate if any event meets the criteria of the primary endpoint. The adjudication process is considered independent of AE/SAE data collection and analysis.

An Adjudication Committee charter will provide full guidance on the function and practices to be followed.

19.2.2. Data Safety Monitoring Committee

The DSMC will be formed to review ongoing safety data. Members of the DSMC will not be allowed to participate as Investigators in this study.

The DSMC will review safety data on an ongoing basis to ensure safe and proper treatment of subjects, assess the safety of the study interventions, and monitor the overall conduct of the study. The DSMC, based on the nature, frequency, and/or severity of any adverse events, may recommend protocol modification(s), dose suspension, dose termination, or study termination. In addition, during the study, the DSMC will make a recommendation to continue dosing in subjects with asymptomatic severe ARIA in Group 2. This may be triggered as early as when the first 150 subjects have had the opportunity to complete at least 6 months of treatment, or when the first 20 asymptomatic subjects have completed at least 2 additional doses since the initial identification of ARIA (ARIA-E with or without ARIA-H, or isolated ARIA-H), as moderate in severity, whichever occurs first.

A DSMC charter will provide full guidance on the function and practices to be followed.

19.3. Changes to Final Study Protocol

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

law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

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

In the event of a protocol modification, the ICF may require similar modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

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

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, 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.

19.6. 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 subject enrollment; or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 2, Multicenter, Randomized, Parallel-Group, Double-Blind, Controlled Study of Aducanumab (BIIB037) in Subjects with Mild Cognitive Impairment due to Alzheimer's Disease or with Mild Alzheimer's Disease Dementia to Evaluate the Safety of Continued Dosing in Subjects with Asymptomatic Amyloid-Related Imaging Abnormalities," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

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Investigator's Signature Date

_____

Investigator's Name (Print)

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Study Site (Print)