ENGAGE

221AD302/NCT02484547

Statistical Analysis Plan

Placebo-Controlled Period

STATISTICAL ANALYSIS PLAN
Placebo-Controlled Period

Product Studied: Aducanumab
Protocol Number: 221AD302

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

Protocol Version: Version 6.0
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List of Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ApoE ε4+	apolipoprotein E4 carrier
ApoE ε4-	apolipoprotein E4 non-carrier
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
[redacted]	[redacted]
AST	aspartate aminotransferase
BL	baseline
BLQ	below the limit of quantification
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
[redacted]	[redacted]
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CIR	copy increment from reference
C_{max}	observed maximum serum aducanumab concentration
C_{min}	observed minimum serum aducanumab concentration
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAT	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	EuroQol health status measure
[redacted]	[redacted]
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject

EQ-5D (SR)	EuroQol health status measure, subject self-reported
FU	Follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HCP	health care professional
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDH	lactate dehydrogenase
LMCI	late mild cognitive impairment
LTE	long-term extension
LOCF	last observation carried forward
MCI	mild cognitive impairment
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI-10	Neuropsychiatric Inventory-10
PCS	potentially clinically significant
PET	positron emission tomography
pH	potential of hydrogen
PI	Principal Investigator
PK	pharmacokinetic(s)
PMM	pattern mixture model
PP	per-protocol
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
SUVR	standard uptake value ratio
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1 DESCRIPTION OF OBJECTIVES AND ENDPOINTS

1.1 Primary Objective and Endpoint

The primary objective of this study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score as compared with placebo in subjects with early Alzheimer's Disease (AD).

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

1.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

- To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by the Mini-Mental State Examination (MMSE).
- To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by Alzheimer's Disease Assessment Scale-Cognitive Subscales (13 items) [ADAS-Cog 13].
- To assess the effect of monthly doses of aducanumab as compared with placebo on clinical progression as measured by Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI].

The secondary endpoints are:

- Change from baseline in MMSE score at Week 78.
- Change from baseline in ADAS-Cog 13 score at Week 78.
- Change from baseline in ADCS-ADL-MCI score at Week 78.

1.3 Tertiary Objectives and Endpoints

1.3.1 Tertiary Objectives

Safety and Tolerability

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

Biomarker/Efficacy/Quality of Life

- To assess the effect of aducanumab on cerebral amyloid plaque content as measured by amyloid positron emission tomography (PET) imaging (in a subset of approximately 400 subjects).
- To assess the effect of aducanumab on behavior as measured by the Neuropsychiatric Inventory-10 (NPI-10).
- To assess the effect of aducanumab on subject health status, measured by EuroQol health status measures (EQ-5D [informant-rated and subject self-reported]).
- To assess the effect of aducanumab on subject self-reported cognitive function, measured by the modified Perceived Deficits Questionnaire-20 (mPDQ-20).
- To assess the correlation between primary endpoint and cerebral amyloid plaque content as measured by PET imaging.

Pharmacokinetics

- To collect and characterize the pharmacokinetic (PK) parameters of aducanumab in serum

1.3.2 Tertiary Endpoints

Safety and Tolerability

- Incidence of all adverse events (AEs) and serious adverse events (SAEs).
- Brain magnetic resonance imaging (MRI) findings including incidence of amyloid related imaging abnormality-edema (ARIA-E) and amyloid related imaging abnormality-hemorrhage or superficial siderosis (ARIA-H).
- Clinical laboratory shifts in reported values.
- Clinically significant changes in vital sign measurements and electrocardiograms (ECGs).
- Incidence of anti-aducanumab antibodies in serum.

Biomarkers/Efficacy/Quality of Life

- Change from baseline in amyloid PET signal at Week 26 (in a subset of sites and subjects).
- Change from baseline in amyloid PET signal at Week 78 (in a subset of sites and subjects).
- Change from baseline in NPI-10 score at Week 78.
- Change from baseline in subject-self-reported EQ-5D index score at Week 78.
- Change from baseline in informant-rated subject EQ-5D index score at Week 78.
- Change from baseline in mPDQ-20 at Week 78.
- Correlation between the primary endpoint and cerebral amyloid plaque content as measured by PET imaging over time.

Pharmacokinetics:

- Serum concentrations and PK parameters of aducanumab.

1.4 Additional Exploratory Objectives and Endpoints

1.4.1 Additional Exploratory Objectives

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

[redacted]

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1.4.2 Additional Exploratory Endpoints

[redacted]

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

[redacted]

- [redacted]
- [redacted]

2 STUDY DESIGN

2.1 Study Overview

Study 221AD302 (EMERGE) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including mild cognitive impairment (MCI) due to AD and a subset of mild AD, followed by an optional dose-blinded long-term extension (LTE) period of up to 5 years. Approximately 1605 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated.

Table 1: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status: Placebo-Controlled Period

Dose (every 4 weeks)		1	2	3	4	5	6	7 to 20
Treatment Group	Treatment Group Stratified by ApoE Status[2]	Dose (mg/kg)						
High Dose	High Dose - ApoE ε4 (+)	1	1	3	3	6	6	10[1]
	High Dose - ApoE ε4 (-)	1	1	3	3	6	6	10
Low Dose	Low Dose - ApoE ε4 (+)	1	1	3	3	3	3	3
	Low Dose - ApoE ε4 (-)	1	1	3	3	3	3	6
Placebo	Placebo - ApoE ε4 (+)	saline						
	Placebo - ApoE ε4 (-)	saline						

[1] 10 mg/kg is the target dose for all ApoE ε4 carriers assigned to the aducanumab high-dose group. Subjects enrolled under protocol versions 1-3 and assigned to the previous high-dose of 6 mg/kg will be titrated to 10 mg/kg upon receipt of at least 2 doses at 6 mg/kg.

[2] ApoE ε4 status recorded in the Interactive Voice/Web Response System (IXRS).

Subjects will be randomized in a 1:1:1 ratio to 1 of the 3 treatment groups: aducanumab high dose, aducanumab low dose and placebo, with stratification based upon their apolipoprotein E4 (ApoE ε4) carrier status (carrier/non-carrier) and site. During the placebo-controlled period, subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Dose levels may be different in the same treatment group based upon subjects' ApoE ε4 carrier status, and specifically, ApoE ε4

carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 10 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in Table 1 and Figure 1. Note: As of Protocol Version 4, 10 mg/kg is the target dose for all ApoE ε4 carriers in the high-dose group. ApoE ε4 carriers who were randomized to the high dose group when the target dose was 6 mg/kg (under protocol versions prior to Version 4) must have received 2 or more doses at 6 mg/kg prior to being titrated up to 10 mg/kg.

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (up to a total of 65 doses over 5 years). The treatment group for the LTE period will be assigned at the same time as the randomization for the placebo-controlled period, regardless of whether a subject entering the LTE period or not. Subjects who are assigned to the placebo group during the placebo-controlled period will be assigned to 1 of 2 active treatment groups in a 1:1 ratio (aducanumab low dose: aducanumab high dose) and randomization will be stratified by their ApoE ε4 carrier status; for those who enter the LTE period, aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period. Subjects who are assigned to either aducanumab low dose or aducanumab high dose group in the placebo-controlled period will continue in the same treatment group for the LTE period; those who enter the LTE period will maintain the dosing scheme outlined in the protocol at the time of transition from the placebo-controlled period to the LTE period (e.g. subjects who are on stable dosing in the placebo-controlled period will continue on the same dose, subjects who are on a titration regimen during the transition will continue to titrate into the LTE period, and ApoE ε4 carrier subjects who are enrolled in the LTE and randomized to the high-dose group prior to implementation of version 4 of the protocol will be allowed to titrate to 10 mg/kg).

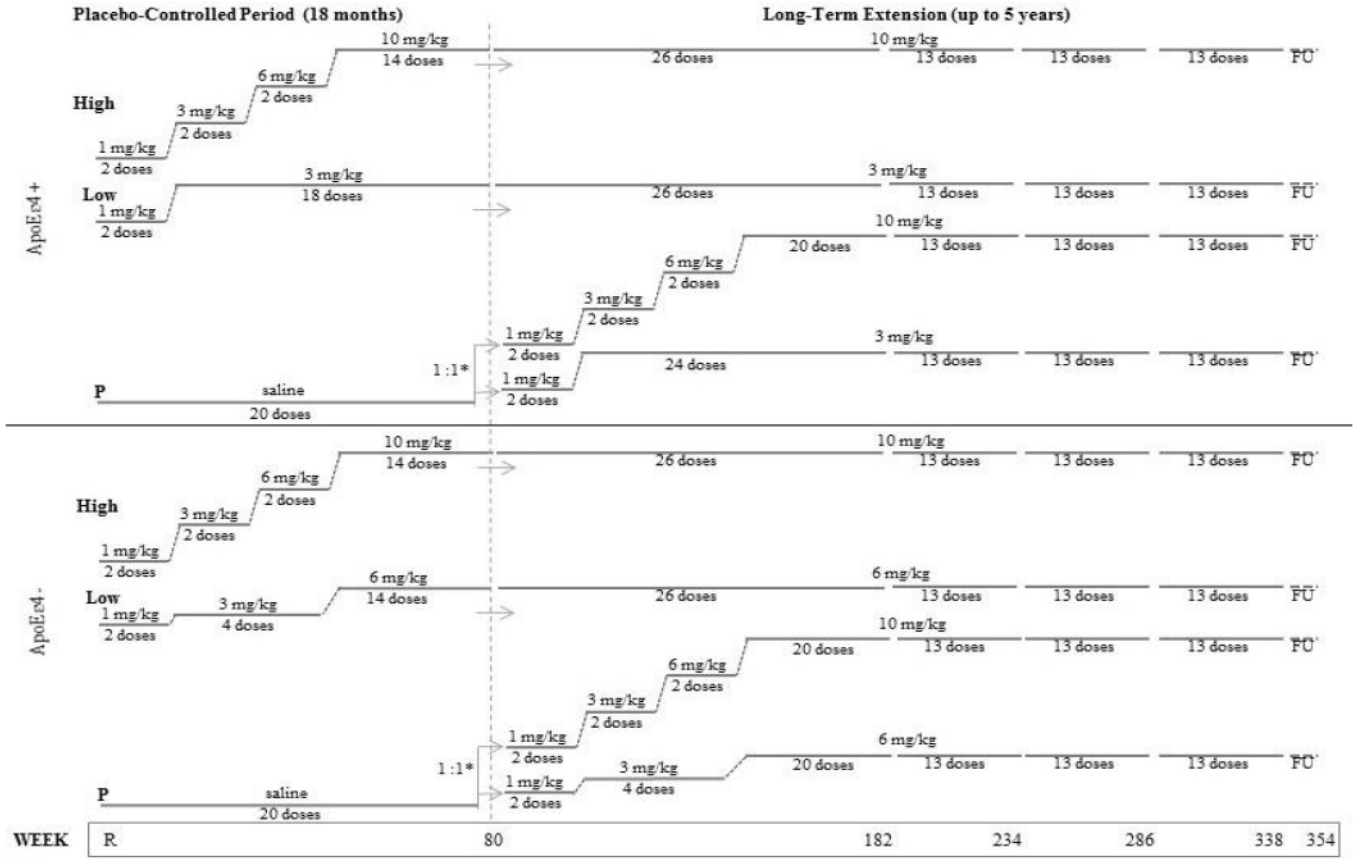
Individual dose adjustments may be implemented in subjects who develop amyloid related imaging abnormalities (ARIA). See Protocol Section 7.2.1.

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of approximately 18 weeks after the final dose. The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will vary and be up to approximately 362 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 256-week aducanumab dose-blind treatment period, and a safety FU period of approximately 18 weeks after the final dose.

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

2.2 Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; FU = follow-up; P = placebo; R = randomization date.
*Subjects who are assigned to placebo during the placebo-controlled period are randomized in a 1:1 ratio to high and low dose aducanumab treatment (stratified by their ApoE ε4 carrier status) for the long-term extension period on Study Day 1.

2.3 Schedule of Events

See Protocol Section 4.2.

3 SAMPLE SIZE JUSTIFICATION

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

A sample size of 450 subjects per treatment group (1350 in total) was planned to have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation was based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, a standard deviation (SD) of 1.92 and a drop-out rate of 30%. The SD estimate of 1.92 for Week 78 reflected a 39% increase over the SD from the protocol-specified interim analysis of 1-year data.

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

As defined in the protocol, the sample size for this study (and for the identically designed Study 221AD301) was reassessed in a blinded manner in November 2017 (approximately 3 months before enrollment completion and with about 10.6% of the data available on the primary endpoint from Studies 221AD301 and 221AD302 combined). At this timepoint, the SD of the primary endpoint was estimated based on the pooled blinded data from two studies using a modified version of Gould-Shih simple-adjustment one sample variance (Zucker et al. 1999):

$$s_{adj}^2 = s_{os}^2 - \frac{2N}{9(N-1)}\delta^2,$$

where N denotes the number of subjects included in the analysis for blinded sample size re-estimation (subjects with both baseline and Week 78 CDR-SB available at the time of sample size re-estimation), δ is the assumed true treatment effect (same treatment effect assumed for both the high dose group and low dose group in this analysis), and s_{os}^2 is the unadjusted one sample variance of the primary endpoint estimate from the pooled blinded data.

As a result of this analysis, the sample size has been increased from 1350 to 1605 (450 to 535 per treatment group) to assure adequate power for detecting a mean treatment effect of 0.5.

4 STATISTICAL ANALYSIS METHODS

4.1 General Considerations

This statistical analysis plan (SAP) only covers the analyses for the primary, secondary and tertiary objectives for the placebo-controlled portion of the study. Hereafter, the placebo-controlled portion of the study will be referred to as "the study" in the rest of this SAP (e.g.,

completion of the study means completion of the placebo-controlled portion). A separate SAP will be prepared for the analyses of the LTE period and integrated analyses across both portions of the study. The analyses of additional exploratory endpoints will be documented separately.

Summary tables will be presented using descriptive summary statistics. For continuous variables, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum and maximum. For categorical variables, this will generally include: number of subjects randomized or dosed, number with data, and the percent of those with data in each category.

There are two types of analysis displays for tables: by treatment group (analysis display A in Appendix 6.1) and by treatment group stratified by ApoE status (analysis display B in Appendix 6.1; here ApoE status refers to the status recorded in IXRS [see Table 1 for correspondence between treatment groups and treatment groups stratified by ApoE status]). The analysis display for each analysis will be defined in each section. All the listings will be presented by treatment group stratified by ApoE status, unless otherwise specified.

Unless otherwise specified, baseline value is defined as the most recent non-missing measurement collected prior to the first dose. Change from baseline will be defined as post-baseline value minus baseline value.

Unless stated otherwise, all statistical tests will be 2-sided with statistical significance level of 0.05.

The statistical software, SAS® will be used for all summaries and analyses.

4.1.1 Analysis Population

- Intent-to-treat (ITT) population:
  The Intent-to-treat population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo).

- Per-protocol (PP) population:
  The per-protocol population is defined as all subjects in the ITT population and also
  - had no violations of the following inclusion criteria:
    - Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD;
    - Must have a positive amyloid PET scan;
    - Must have:
      - A CDR-Global Score of 0.5;
      - A Repeatable Battery for Assessment of Neuropsychological Status (RBANS) score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index score);
      - An MMSE score between 24 and 30 (inclusive).
  - had at least 14 infusions.
  - did not make any change to concomitant AD symptomatic medications during the study.

- ^{18}F-florbetapir amyloid PET analysis population:
  The ^{18}F-florbetapir amyloid PET analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo), used ^{18}F-florbetapir ligand for amyloid PET scan, and had an evaluable baseline amyloid PET SUVR value for the composite region-of-interest using cerebellum as the reference region.

- ^{18}F-flutemetamol amyloid PET analysis population (applicable only to Japan):
  The ^{18}F-flutemetamol amyloid PET analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo), used ^{18}F-flutemetamol ligand for amyloid PET scan, and had an evaluable baseline amyloid PET SUVR value for the composite region-of-interest using cerebellum as the reference region.

- Safety population:
  The safety population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo). It is the same population as the ITT population.

- Safety MRI population:
  The safety MRI population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one post-baseline MRI assessment.

- PK analysis population:
  The PK analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one measurable aducanumab concentration in serum.

- Immunogenicity population:
  The analysis population for immunogenicity is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one post-dose sample evaluable for immunogenicity.

4.2 Background Characteristics

The summaries in this section will be based on the ITT population. Unless otherwise specified, summary tables will be presented by treatment group (analysis display A in Appendix 6.1) and by treatment group stratified by ApoE status (analysis display B in Appendix 6.1; here ApoE status refers to the status recorded in IXRS [see Table 1 for correspondence between treatment groups and treatment groups stratified by ApoE status]). All the listings will be presented by treatment group stratified by ApoE status, unless otherwise specified.

4.2.1 Accounting of Subject

Disposition of subjects will be summarized and the summary data will include number (%) of subjects randomized and dosed, number (%) of subjects who completed the treatment/study, and number (%) of subjects who discontinued treatment and/or withdrew from study. For subjects who discontinued treatment and/or withdrew from study, the reasons for discontinuation and/or withdrawal, and days on treatment and days on study will be summarized and listed. The number of subjects discontinuing treatment prior to each scheduled clinical efficacy assessment will be summarized (presented by treatment group), i.e., the number of subjects discontinuing treatment between Day 1 and Week 26, the number of subjects discontinuing treatment between Week 26 and Week 50 visit, etc. A similar summary will be done for subjects who withdrew from study (presented by treatment group). Time to treatment discontinuation and time to study withdrawal will be displayed by Kaplan-Meier plot (presented by treatment group).

Number of subjects in each analysis population will be summarized. Number of subjects dosed will be summarized by region, country and site. In addition, number of subjects who completed the treatment/study will be summarized by region and country (presented by treatment group).

The categorization of region is based not only on consideration of geography but also on type of health care system and access to health care in each country. This region category will be used in all analysis, including the demographics, the covariate in statistical models and subgroup analysis. The categories for regions will be:

- Region 1: United States (US);
- Region 2: European countries (including Belgium, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden and Switzerland), plus Canada;
- Region 3: Asia countries (including Japan).

4.2.2 Demographics and Baseline Characteristics

The demographic data including age, gender, ethnicity, race, height, weight, and body mass index (BMI) will be summarized. Age will also be categorized and presented using the following two groupings: <50, 50-60, 61-70, 71-80, 81-85, >85 years, and ≤ 64, 65-74, ≥ 75.

Summary of the baseline characteristics of AD includes laboratory ApoE ε4 status (carrier or non-carrier), baseline clinical stage (MCI due to AD or mild AD), baseline clinical assessment including RBANS delayed memory index, CDR global score, CDR-SB, CDR cognitive subscore, CDR functional subscore, MMSE, ADAS-Cog 13, ADCS-ADL-MCI, number of years of formal education, number of years since first AD symptom, number of years since diagnosis of AD, AD treatment use that was stopped prior to entering the study (yes or no) and AD symptomatic medication use at baseline (yes or no; see Section 4.2.3 for definition of AD symptomatic medication use at baseline). ApoE ε4 carrier will be further classified as homozygote and heterozygote. MMSE will also be categorized by the following subgroups: <24, 24-26, 27-30. Subject listings will be generated for demographics and baseline characteristics.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number (%) of subjects with history (including both ongoing and not ongoing medical conditions) will be summarized by system organ class and preferred term. A listing of medical history will be generated.

Previous therapies for the treatment of AD stopped prior to entering the study, total duration of previous therapies and reason for stopping treatment will be summarized (presented by treatment group). A listing of previous therapies will also be generated.

4.2.3 Concomitant Medications and Non-Drug Therapies

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary. All concomitant non-drug therapies will be coded using the MedDRA dictionary. A concomitant medication/therapy will be defined as any therapy that was taken on or after the day of the first dose of study drug. This includes therapies that start prior to the initiation of the first dose if their use continues on or after the date of first dose. To define concomitant use for therapies with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a therapy are missing, that therapy will be considered concomitant.
- if the start date of a therapy is missing and the stop date of that therapy fall on or after the date of the first dose, that therapy will be considered concomitant.
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is missing and the therapy is listed as continuing, that therapy will be considered concomitant, or
- if the start date of a therapy is prior to the date of the first dose and the stop date of that therapy is missing and the therapy is not listed as continuing, that therapy will be considered non-concomitant.

For a therapy with a partial start date, the year/month of the therapy date will be compared to that of the first dosing date to determine whether the therapy is concomitant.

The number (%) of subjects taking concomitant medication and non-drug therapies will be summarized. Non-drug therapies will be presented by treatment group. Concomitant medications and non-drug therapies will be listed.

AD symptomatic medications taken concomitantly at baseline are defined as AD symptomatic medications that were being taken at the time of the first dose, i.e., started prior to the first dose and continued until after the first dose. The number (%) of subjects taking AD symptomatic medications concomitantly at baseline will be summarized. In addition, number of subjects using Cholinesterase inhibitors only, Memantine only, or both at baseline will be summarized. Subjects who have any change in AD symptomatic medications after the initiation of study treatment will be summarized by the timing of change, i.e., the number of subjects changing between Day 1 and Week 26, the number of subjects changing between Week 26 and Week 50, etc. The summary for AD symptomatic medication use during study

will be presented by treatment group. The start and stop date of AD symptomatic medication will be listed for these subjects.

4.2.4 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as major or minor deviations based on Protocol Deviation Classification (see Appendix 6.2). The major protocol deviations will be summarized (presented by treatment group). Listings will be generated for the major and minor protocol deviations, respectively. A listing will be generated for subjects with incorrect stratification ApoE status, i.e., treatment stratification ApoE ε4 status in IXRS different from the laboratory ApoE ε4 status.

4.2.5 Study Drug Exposure and Study Drug Compliance

A summary table of study drug exposure and compliance will be provided. Number of infusions (aducanumab or placebo) received will be summarized as a categorical variable (categories as integers from 1 to 20, and 1-5, 6-10, 11-15, and 15-20) as well as a continuous variable. Number of weeks on study treatment (aducanumab or placebo), calculated as (date of last dose – date of first dose + 29)/7, will be summarized as a categorical variable (every 8 weeks from 0 to >= 72 weeks) as well as a continuous variable. Percentage of study treatment taken up to the last dose, calculated as (the actual number of infusions / by the number of infusions a subject is expected to take until the date of last infusion)*100, will be summarized as a continuous variable. This table will be presented by treatment group.

Due to the use of titration regimen in the study and possible dose reduction due to ARIA, another summary table will be provided including the following information: number of total infusions (categories of 1-5, 6-10, 11-15, and 15-20) as well as a continuous variable, number of infusions at each dose level (1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg, respectively) summarized as a categorical variable as well as a continuous variable, number of subjects with dose increase (placebo to 1 mg/kg, 1 to 3 mg/kg, 3 to 6 mg/kg and 6 to 10 mg/kg, respectively), number of subjects with dose reduction (1 mg/kg to placebo, 3 to 1 mg/kg, 6 to 3 mg/kg and 10 to 6 mg/kg, respectively), maximum dose level received, and cumulative dose (as a continuous variable). This table will be presented by treatment group stratified by ApoE status.

A listing of study drug administration records, including dose level at each infusion, cumulative number of infusions and cumulative dose will be provided. A listing of aducanumab lot numbers will be provided.

A listing of study drug administration records for placebo subjects who received any doses of active treatment will be provided.

4.3 Efficacy Analysis

4.3.1 General Considerations

For efficacy endpoints, the following treatment groups of aducanumab (per randomization) will be evaluated and compared with placebo:

- Aducanumab high-dose (10 mg/kg in ApoE ε4 carriers [including 6 mg/kg for subjects enrolled under protocol versions 1-3 who do not have the opportunity to uptitrate to 10 mg/kg prior to completing Week 78 of the study] and 10 mg/kg in ApoE ε4 non-carriers).
- Aducanumab low-dose (3 mg/kg in ApoE ε4 carriers and 6 mg/kg in ApoE ε4 non-carriers).

All efficacy analyses will be performed on the ITT population. In addition, the primary and secondary endpoints will also be performed on the per-protocol population. The efficacy analysis will be presented by treatment group (per randomization), i.e., aducanumab high-dose, aducanumab low-dose and placebo (analysis display A in Appendix 6.1).

The primary, sensitivity and supplementary analyses for the primary and secondary endpoints are listed in Table 2.

Table 2. Analysis for Primary and Secondary Endpoints

Endpoint	Analysis	Analysis Population	SAP Section
CDR-SB	Primary: Analysis of change from baseline at Week 78 (MMRM)	ITT	4.3.2.1
	Sensitivity: Pattern mixture model (ANCOVA)	ITT	4.3.2.2.1
	Sensitivity: Copy increment from reference method (ANCOVA)	ITT	4.3.2.2.2
	Sensitivity: Imputation by natural disease progression (ANCOVA)	ITT	4.3.2.2.3
	Sensitivity: Tipping point analysis (ANCOVA)	ITT	4.3.2.2.4
	Supplementary: Censoring after intercurrent events (MMRM)*	ITT	4.3.2.3.1
	Supplementary: Per-protocol analysis (MMRM)	Per-protocol	4.3.2.3.2
	Supplementary: Responder analysis (Logistic regression)	ITT	4.3.2.3.3
	Supplementary: Slope analysis (MMRM)	ITT	4.3.2.3.4
	Supplementary: Divergence effect analysis (MMRM)	ITT	4.3.2.3.5
MMSE,	Primary: Analysis of change from baseline at Week 78 (MMRM)	ITT	4.3.3.1, 4.3.3.2, 4.3.3.3

ADAS-Cog 13, ADCS-ADL-MCI	Sensitivity: Pattern mixture model (ANCOVA)	ITT	4.3.3.4
	Supplementary: Censoring after intercurrent events (MMRM)*	ITT	4.3.3.4
	Supplementary: Per-protocol analysis (MMRM)	Per-protocol	4.3.3.4
	Supplementary: Slope analysis (MMRM)	ITT	4.3.3.4
	Supplementary: Divergence effect analysis (MMRM)	ITT	4.3.3.4

* Analysis excludes data collected after the following intercurrent events: (1) premature discontinuation of the study treatment and (2) any change to concomitant AD symptomatic medications during the study. All other analyses will include data collected after intercurrent events [ICH E9 (R1) Addendum 2017].

Visit windows for mapping efficacy endpoint

For efficacy data that are summarized or analyzed by visit, data collected on all scheduled visits and all unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Table 3. If there are 2 or more assessments available in the same analysis window for a subject, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments in the same analysis window with the same distance from the target visit day, the later assessment will be used.

Table 3. Visit Windows for Efficacy Endpoints

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 26	183	[92, 266]
Week 50	351	[267, 448]
Week 78	547	[449, the end day of the placebo-controlled period *]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

Handling of missing items for scales

If any of the individual items for the primary and secondary endpoints is missing, the total score of the corresponding endpoint will be imputed by prorating the observed scores [van Ginkel 2010].

For ADAS-Cog13, if 3 or fewer of 13 items (<25%) are missing, the total score will be imputed by the following algorithm: Total score = total score from the completed items * [maximum total score (=85) / maximum total score for the completed items]. The imputed number will be rounded up to the nearest integer. If more than 3 items are missing, the total score of ADAS-Cog 13 at that visit will be considered missing.

For ADCS-ADL-MCI, if 4 or fewer of 18 items (<25%) are missing, the total score will be imputed by a similar algorithm as that for ADAS-Cog 13. The imputed number will be

rounded up to the nearest integer. If more than 4 items are missing, the total score for ADCS-ADL-MCI at that visit will be considered missing.

The same imputation algorithm will be applied to CDR-SB and MMSE, if only 1 box (of 6) of CDR is missing or if only 2 or fewer items (out of 11) are missing for MMSE. If the score from more than 1 box of CDR or more than 2 items of MMSE is not available, the CDR-SB or MMSE at that visit will be considered missing.

The total score of the tertiary endpoint NPI-10 will be imputed using the same prorating principle if only 1 item (out of 10) is missing. For EQ-5D and mPDQ-20, if any item is missing, any total or sum involving that item will be considered missing.

Considerations for multiple comparison adjustments

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. The order of treatment comparisons is as follows: aducanumab high-dose versus placebo and aducanumab low-dose versus placebo. All comparisons after the initial comparison with $p > 0.05$ will not be considered statistically significant.

Secondary endpoints have been rank prioritized, in the order shown in Section 1.2. In order to control for a Type I error for the secondary endpoints, a sequential closed testing procedure will be used and will include both the order of the secondary endpoints and treatment comparisons. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure, as for the primary endpoint, will be used to control the overall Type I error rate due to multiple treatment comparisons. If statistical significance is not achieved for 1 or 2 treatment comparisons, all endpoint(s) of a lower rank will not be considered statistically significant for that 1or 2 treatment comparisons, respectively.

There will be no multiple comparison adjustments for the sensitivity and supplementary analyses for the primary and secondary efficacy endpoints, the tertiary efficacy endpoints, the subgroup analyses or the additional analyses.

4.3.2 Primary Efficacy Endpoint

4.3.2.1 Primary analysis

The estimand of the primary analysis is the mean difference of the change from baseline CDR-SB scores at Week 78 between treatment groups in the ITT population [ICH E9 (R1) Addendum 2014, 2017]. All observed data will be included in the primary analysis, including data collected after intercurrent events [ICH E9 (R1) Addendum 2017], i.e., treatment discontinuation or a change in concomitant use of AD symptomatic medication.

The change from baseline CDR-SB scores will be summarized by treatment group at each post-baseline visit. A mixed model repeated measures (MMRM) model will be used as the primary analysis to analyze change from baseline CDR-SB using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline CDR-SB, baseline CDR-SB by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no; see Section 4.2.3 for definition of AD symptomatic medication use at baseline),

region, and laboratory ApoE ε4 status (carrier/non-carrier). An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. In the primary analysis, missing data are assumed to be missing at random [Rubin 1976].

4.3.2.2 Sensitivity analysis

The following sensitivity analyses will be performed to assess the robustness of the primary analysis to deviation from the missing-at-random assumption. All the sensitivity analyses will be conducted for the ITT population.

4.3.2.2.1 Pattern mixture model

The pattern mixture model (PMM) represents a general and flexible framework to model the predictive distribution of missing data conditional on the observed data [Little 1993, 1994]. It allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner.

In the PMM framework, subjects are grouped into missing patterns so that subjects in the same pattern share similar missingness characteristics. In this analysis, missing patterns will be defined according to the reasons for early withdrawal from study as reported on the electronic case report form (eCRF). The following two patterns will be considered:

- Subjects who withdraw due to reasons that may be related to efficacy, including consent withdrawn, withdrawal by parent/guardian, investigator decision, loss of capacity, change of treatment, and disease progression;
- Subjects who withdraw due to reasons that are unlikely related to efficacy, including adverse event, lost to follow-up, death, pregnancy, relocation, protocol amendment, site terminated by sponsor/investigator, study visit burden, and other.

Subjects who withdraw due to reasons that may be related to efficacy will be penalized and their missing data will be imputed using the copy increment from reference (CIR) method [Carpenter et al. 2013] (see Section 4.3.2.2.2 for description of the CIR method). Subjects who withdraw due to reasons that are unlikely related to efficacy will be handled using the missing-at-random assumption and their missing data will be imputed using the standard multiple imputation method [Rubin 1987]. Subjects with missing data due to reasons other than early withdrawal (such as item missing, out of window, etc.) will be handled using the missing-at-random assumption. For both imputation methods, the following covariates will be included in the imputation model: treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). Implementation details can be found in Appendix 6.3.2.

The imputed datasets will be analyzed by an analysis of covariance (ANCOVA) model adjusting treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The analyzed results from the imputed datasets will be combined based on Rubin's rules [Rubin

1987] assuming that the statistics estimated from each imputed dataset are normally distributed.

If intermediate missing values are encountered (such as data missing at Week 26 but are available at subsequent visits), a Markov chain Monte Carlo (MCMC) method that assumes multivariate normality will be used to impute the intermediate missing values and produce a monotone missing pattern (data with only terminal missing and no intermediate missing) [Li 1988; Schafer 1997].

4.3.2.2.2 Copy increment from reference method

The copy increment from reference (CIR) method will be applied to impute the post-withdrawal data for any aducanumab-treated subject who withdraws from study early based on data from the placebo group rather than the subject's own randomized treatment group [Carpenter et al. 2013]. Specifically, for a subject on aducanumab high dose (or aducanumab low dose) who withdraws early, his or her mean trajectory after early withdrawal is assumed to be parallel to the mean trajectory of the placebo group, and the difference between the two means is the same as the difference at the time of withdrawal. This method assumes that any benefit gained from previous treatment will be retained, but subjects progress as if they were on placebo after withdrawal from study. For any subject on placebo who withdraws early, his or her post-withdrawal profile will be imputed following the missing-at-random principle. Implementation details can be found in Appendix 6.3.1.

After all missing data have been imputed, an ANCOVA model adjusting treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier) will be applied to analyze the change from baseline CDR-SB.

4.3.2.2.3 Imputation by natural disease progression

Subjects are assumed to exhibit an evolution of the disease similar as the natural disease progression after early withdrawal from study (for all treatment groups). The natural disease progression is determined based on a snapshot of the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [Mueller et al. 2005] obtained in May 2017. A subpopulation was defined that satisfies the major inclusion criteria of Study 221AD302 (and the identically designed Study 221AD301). In this subpopulation, the mean change from baseline CDR-SB at Week 78 is estimated to be about 1.52 for subjects with late mild cognitive impairment (LMCI) and about 2.06 for subjects with mild AD. The missing data at Week 78 for this study will be imputed using the linear extrapolation approach based on subjects' baseline clinical stage (MCI due to AD or mild AD). For example, assuming a mild AD patient whose last non-missing change from baseline CDR-SB measurement is 0.5 at Week 26, the change from baseline CDR-SB at Week 78 for this patient will be imputed as 0.5+2.06*(78-26)/78, which is 1.87. A similar algorithm will be applied to the MCI patients. After imputation, the change from baseline CDR-SB at Week 78 will be analyzed by an ANCOVA model adjusting treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier).

4.3.2.2.4 Tipping point analysis

The tipping-point analysis is a progressive stress-testing to assess how severe departures from missing-at-random must be in order to overturn the conclusion of the primary analysis [Yan et al. 2009]. For our study, subjects are assumed to have worse scores after early withdrawal from study compared to subjects who remain on study.

The missing data are first imputed by the standard multiple imputation (assuming missing at random). To reflect the worse performance after early withdrawal, pre-specified shift parameters δ_c and δ_t are added to the imputed values for subjects on placebo and aducanumab (include both low dose and high dose), respectively. The adjusted multiple imputed datasets will then be analyzed by an ANCOVA model and the results will be combined using the Rubin's rule for inference.

A range of shift parameters δ_c and δ_t will be applied and p-value will be calculated for each combination of δ_c and δ_t. The tipping region is defined as the combinations of δ_c and δ_t such that the treatment effect is no longer significant (p-value greater than the significance level).

The scientific plausibility of the tipping region will be evaluated. If implausible departures from the missing-at-random assumption (large δ) are needed in order to change the results from statistically significant to insignificant, the results of the primary analysis are considered to be robust to departure from the missing-at-random assumption.

4.3.2.3 Supplementary analysis

4.3.2.3.1 Censoring after intercurrent events

The primary analysis (Section 4.3.2.1) will be repeated with the data censored after any of the following intercurrent events (if multiple events occur to the same subject, data after the earliest event will be censored):

- premature discontinuation of the study treatment;
- any change to concomitant AD symptomatic medications during the study.

The estimate of this analysis reflects the treatment effect of aducanumab if the drug is taken as directed.

4.3.2.3.2 Per-protocol analysis

The per-protocol analysis will be done using the same model as the primary analysis (Section 4.3.2.1) and applying in the per-protocol population (Section 4.1.1).

4.3.2.3.3 Responder analysis

To further assess whether subjects on aducanumab progress differently from those on placebo, responder analysis will be conducted. The responders will be determined by a threshold of the primary endpoint, i.e., subjects whose change from baseline CDR-SB at Week 78 is smaller than or equal to the threshold will be classified as responders and otherwise will be classified as non-responders. All subjects with missing data at Week 78 will be classified as non-responders.

The responder analysis will be conducted for two threshold values: 0.5 or 1.5, i.e., subjects whose change from baseline CDR-SB at Week 78 ≤ 0.5 or ≤ 1.5. The number of responders

and the response rate will be summarized by treatment group. The dichotomized response, responder vs. non-responder, will be modeled using a logistic regression with the following covariates: treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratoy ApoE ε4 status (carrier/non-carrier). In addition to the two selected threshold values, the continuous responder curve that displays the percentage of responders under a wide range of threshold values will be presented by treatment group.

Since all missing data will be considered as non-response, which is a special form of missing-not-at-random, this analysis can provide additional insights for the robustness of the primary analysis results.

4.3.2.3.4 Slope analysis

Slope analysis will be conducted to assess the difference between each aducanumab treatment group and placebo in the slope of change from baseline in CDR-SB up to Week 78. A reduction in the slope of the aducanumab treatment group compared with placebo would indicate a slower rate of disease progression, thus reflecting a disease modifying effect of aducanumab. An MMRM model will be used, with dependent variable as the change from baseline CDR-SB score at each visit and with fixed effects of treatment group, time (as a continuous variable), treatment group-by-time interaction, baseline CDR-SB, baseline CDR-SB by time, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The continuous time variable is calculated as number of years since the 1st infusion, so the slope estimate reflects the annual rate of change. The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

4.3.2.3.5 Divergence effect analysis

A divergence effect analysis will be performed to assess whether the treatment difference between the aducanumab treated patients and the placebo patients increases over time [Li 2017]. A linear trend test will be conducted on treatment difference at Week 26, 50 and 78 estimated from the MMRM model of Section 4.3.2.1, to assess if the slope of the treatment difference is positive or not. Let the estimate of treatment difference be δ_i at time point t_i, where $t_i = 26$, 50 and 78 (week). The least-square estimate of the slope is

$$\beta_{DIF} = \frac{\sum(t_i - \bar{t})\delta_i}{\sum(t_i - \bar{t})^2},$$

where $\bar{t}$ is the mean of t_i's. The hypothesis to be tested is

$$H_0: \beta_{DIF} \leq 0 \quad \text{versus} \quad H_a: \beta_{DIF} > 0.$$

Given β_{DIF} is a linear combination of the treatment difference δ_i, this analysis can be implemented by the "estimate" statement in the SAS proc mixed procedure.

4.3.2.4 CDR subscores and CDR global score

The CDR is comprised of 6 domains: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. CDR-SB is the sum of the scores

for these 6 domains. In addition, two CDR subscores have been proposed [Tractenberg 2005]: a "cognitive" subscore equaling the sum of the Memory, Orientation, and Judgment and Problem Solving box scores, and a "functional" subscore equaling the sum of Community Affairs, Home and Hobbies and Personal Care box scores. For each of the 6 box scores, and the CDR cognitive subscore and CDR functional subscore, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. The same MMRM model as the primary analysis will also be applied to the CDR cognitive subscore and CDR functional subscore.

The CDR global score is a composite score obtained by combining the 6 box scores using a scoring algorithm that weights memory as the primary domain and all other domains as secondary [Morris 1993]. The distribution of CDR global score will be summarized (as a categorical variable) by treatment group at each post-baseline visit.

4.3.3 Secondary Efficacy Endpoints

4.3.3.1 Primary analysis of MMSE

The change from baseline MMSE scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze change from baseline MMSE using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline MMSE value, baseline MMSE by time interaction, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

4.3.3.2 Primary analysis of ADAS-Cog 13

The change from baseline ADAS-Cog 13 scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze change from baseline ADAS-Cog 13 using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

4.3.3.3 Primary analysis of ADCS-ADL-MCI

The change from baseline ADCS-ADL-MCI scores will be summarized by treatment group at each post-baseline visit. An MMRM model will be used as the primary analysis to analyze change from baseline ADCS-ADL-MCI using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). The same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

The primary analysis of ADCS-ADL-MCI will use the pooled data from both Studies 221AD301 and 221AD302 (analysis for each individual study will also be performed). Pooled data will be used for the primary analysis because functional outcomes are expected to be less sensitive to change within the study duration than cognition measures due to ceiling effects [Rockwood 2007], as subjects entering the study will have no or little measurable impairment at baseline. It has also been observed in previous studies of more impaired patients (mild to moderate/severe) that functional outcome treatment effect sizes are small [Hansen 2007].

4.3.3.4 Sensitivity/Supplementary analysis

The following sensitivity and supplementary analyses that are planned for the primary efficacy endpoint will also be conducted for the secondary efficacy endpoints:

- Pattern mixture model
- Censoring after intercurrent events
- Per-protocol analysis
- Slope analysis
- Divergence effect analysis

4.3.4 Tertiary Endpoints for Efficacy and Quality of Life

The baseline value and the change from baseline at each post-baseline visit for NPI-10 will be summarized by treatment group. An MMRM model will be used to analyze the change from baseline in NPI-10 using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline NPI-10, baseline NPI-10 by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). Same methods as in the primary analysis will be considered for the covariance structure and the degrees of freedom.

For the following tertiary endpoints for patient-reported outcomes and quality of life, subject self-reported EQ-5D index score (SR), informant-rated subject EQ-5D index score (IR-S), and mPDQ-20, the baseline value and the change from baseline at each post-baseline visit will be summarized by treatment group. Additional analyses for these endpoints will be provided in a separate document.

4.3.5 Subgroup Analysis

Subgroup analyses will be performed for the primary endpoint (CDR-SB) and secondary endpoints (MMSE, ADAS-Cog13, ADAS-ADL-MCI). The following pre-defined subgroups will be considered:

- Laboratory ApoE ε4 status (carrier or non-carrier)
- Baseline clinical stage (MCI due to AD or mild AD) per the Investigator's assessment based on the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria
- Use of AD symptomatic medication at baseline (yes or no)

- Baseline MMSE (MMSE ≤ 26 or MMSE ≥ 27)
- Region (US, Europe/Canada/Australia, Asia; see Section 4.2.1 for definition of region)
- Age category (≤ 64, 65-74, ≥ 75)
- Gender (female or male)

A selective set of subgroup analyses will be performed for Amyloid PET data. Details will be defined in Sections 4.4.

4.4 Amyloid PET Analysis

4.4.1 Amyloid PET substudy

Every subject enrolled into the study must have a positive amyloid PET scan by visual read either at screening or obtained within 12 months of screening. Subjects enrolled into the amyloid PET substudy will have the quantitative standard uptake value ratio (SUVR) scores at screening and at each planned post-baseline visit. The amyloid PET substudy will include a subset of approximately 400 subjects in countries other than Japan where PET scans will be performed using ^{18}F-florbetapir ligand, and a small subset of subjects in Japan where either ^{18}F-florbetapir ligand or ^{18}F-flutemetamol ligand will be used. In the placebo-controlled period, amyloid PET assessments are scheduled at screening, Week 26, and Week 78.

4.4.2 Amyloid PET SUVR regions-of-interest and reference regions

Amyloid PET standardized uptake value ratio (SUVR) is a quantitative measure of cerebral amyloid plaque burden. The SUVR will be calculated for the following target brain regions-of-interest (ROIs): composite ROI, frontal cortex, parietal cortex, lateral temporal cortex, sensorimotor cortex, anterior cingulate cortex, posterior cingulate cortex, medial temporal cortex, occipital cortex, striatum, and statistical ROI normalized to reference region activity. Additionally, SUVR ROIs including pons and deep subcortical white matter which are believed to be least affected by amyloid pathology will also be evaluated. The composite ROI will comprise of major cortical regions part of the frontal, parietal, lateral temporal, sensorimotor, anterior, posterior cingulate and occipital cortices to serve as a summary measure of global cerebral amyloid burden. The statistical ROI is a region of interest consisting of the posterior cingulate cortex, precuneus and medial frontal cortex that has been demonstrated to yield optimal group separation between subjects with low and high amyloid burden across different reference regions. A negative change from baseline in composite ROI SUVR indicates a reduction in amyloid burden and a negative treatment difference (aducanumab minus placebo) favors aducanumab. The composite ROI will serve as the ROI of primary focus.

The following reference regions will be employed: cerebellum, cerebellum cropped, cerebellar white matter, cerebellar grey matter, deep subcortical white matter, pons, cerebellum + pons, cerebellar white matter + pons, deep subcortical white matter + cerebellum, deep subcortical white matter + pons and deep subcortical white matter + cerebellum + pons. Cerebellum will serve as the reference region of primary focus.

The composite ROI SUVR using cerebellum as the reference region will be used as the primary endpoint for amyloid PET analysis.

4.4.3 Amyloid PET analysis population

There are two amyloid PET analysis population: ^{18}F-florbetapir amyloid PET analysis population and ^{18}F-flutemetamol amyloid PET analysis population.

The following background characteristics tables will be generated for the ^{18}F-florbetapir amyloid PET analysis population and will be presented by treatment group: number of subjects enrolled by region and country, demography, baseline disease characteristics, medical history. The content of these tables will be the same as those described in section 4.2 for the ITT population, with the addition of baseline amyloid PET SUVR values summarized for the baseline characteristics of AD.

4.4.4 By visit summary and MMRM model

The baseline and change from baseline amyloid PET SUVR values will be summarized by treatment groups (placebo, low dose and high dose) and by visit for each of the target ROIs using cerebellum as the reference region for each of the amyloid PET analysis populations. In addition, the baseline and change from baseline amyloid composite ROI values will be summarized by treatment groups by visit for each of the reference regions for each of the amyloid PET analysis populations.

For the ^{18}F-florbetapir amyloid PET analysis population, an MMRM model will be used to analyze change from baseline SUVR for each target ROI with cerebellum as the reference region. Fixed effects of the model will include treatment groups (placebo, low dose and high dose), visit (Week 26 and Week 78), treatment group-by-visit interaction, baseline SUVR (continuous), baseline SUVR by visit interaction, baseline MMSE (continuous), laboratory ApoE ε4 status (carrier and non-carrier), and baseline age (continuous). Visit and treatment group will be treated as categorical variables in the model along with their interactions. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence in any of the parameters, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used for all the parameters. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Adjusted means for each treatment group, pairwise adjusted differences with placebo, 95% confidence intervals for the differences and associated p-values will be presented at week 26 and week 78. The same MMRM model will also be used to analyze the change from baseline SUVR for the composite ROI with each of the reference regions. No multiple comparison adjustment will be used for amyloid PET analysis.

Subgroup analysis will be conducted on the ^{18}F-florbetapir amyloid PET analysis population using the same MMRM model for composite ROI using cerebellum as reference region for the following stratification factors: laboratory ApoE status (carrier or non-carrier, and this model will not use ApoE status as a covariate), baseline clinical stage (MCI due to AD or mild AD) and baseline composite ROI SUVR value in quartiles.

Visit windows for by visit analysis

For amyloid PET by visit summaries and MMRM models, the analysis visit should be defined using visit windows (see Table 4 below). The rationale is to use the same analysis visit windows as for the efficacy endpoints for Week 26 and Week 78. If there is more than 1 value in the same analysis visit window (>1 value for the same analysis visit) for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If they are with the same distance from the target visit day, then the record with the later time will be used for the by visit analysis.

Table 4: Visit Windows for amyloid PET data

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 26	183	[92, 266]
Week 78	547	[449, the end day of the placebo-controlled period**]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter in LTE, and is the last day in study for subjects who do not enter LTE.		

4.4.5 Correlation between amyloid PET and CDR sum of boxes

Pearson and Spearman correlation

Pearson and Spearman correlations between change from baseline amyloid PET composite ROI using cerebellum as reference region at Week 78 and change from baseline CDR-SB at Week 78 will be conducted by treatment groups (placebo, low dose and high dose, and active total) in the ^{18}F-florbetapir amyloid PET analysis population. Pearson and Spearman partial correlations adjusting for baseline amyloid PET composite ROI and baseline CDR-SB will also be conducted by treatment groups at Week 78. The estimated correlation coefficients, p-values and the 95% confidence intervals will be provided. Given that reductions in cerebral β-amyloid (Aβ) content may precede clinical effects (e.g., slowing of clinical decline), Pearson and Spearman correlations and partial correlations between change from baseline amyloid PET composite ROI at Week 26 and change from baseline CDR-SB at Week 78 will also be conducted.

Correlation analysis will be done on each individual study as well as in the pooled data of the 221AD301 and 221AD302 studies. The correlation analysis based on the pooled data will be considered as the primary analysis.

4.5 Safety Analysis

4.5.1 General Considerations

Analysis population

Safety population will be used for safety analyses of AEs, clinical laboratory data, Columbia Suicide Severity Rating Scale (C-SSRS) data, ECG data and vital sign data (all the safety data except for ARIA data). Safety MRI population will be used for analyses of ARIA data.

Safety treatment groups

Different from the randomization treatment groups, if a subject who was randomized to placebo group accidentally received one or more doses of the active treatment during the study, he/she will be classified as either low or high dose group for all the safety analyses, depending on the ApoE status and the maximal dose level of the active treatment received (Table 5). A listing of such subjects will be provided, as described in section 4.2.5. Safety treatment groups will be the same as the randomization treatment groups for other subjects (subjects randomized to active treatment groups, and subjects randomized to placebo without any accidental active dose). Safety treatment groups will be used for all the safety analyses unless otherwise specified.

Table 5: Safety treatment groups for placebo subjects with accidental active treatment

Randomization treatment group	Randomization ApoE status	Safety treatment group classification based on the maximum dose level of the accidental active treatment		
		>0 to 3 mg/kg	>3 to 6 mg/kg	>6 mg/kg
Placebo	ApoE ε4 (+)	Low dose	High dose	High dose
	ApoE ε4 (-)	Low dose	Low dose	High dose

Safety analysis displays

AEs, clinical laboratory data, C-SSRS data, ECG data and vital sign data (all the safety data except for ARIA data) will be summarized by treatment group (placebo, low dose, high dose and BIIB037 total; analysis display A in Appendix 6.1), unless otherwise specified. All the ARIA related tables will be presented by treatment group stratified by ApoE status (3 columns under each treatment group: ApoE ε4+, ApoE ε4- and total; analysis display B in Appendix 6.1), unless otherwise specified. A subset of AE tables will also be presented by treatment group stratified by ApoE status in addition to by treatment group. All the listings will be presented by treatment group stratified by ApoE status.

Incidence, incidence proportion and incidence rate

- Incidence and incidence proportion will be provided in incidence tables. Incidence is defined as the number of subjects who experienced an event. Incidence proportion is defined as the number of subjects who experienced an event divided by total number of subjects in the analysis population, i.e., percentage. Each subject will be counted only once within each category.

- Incidence and incidence rate will be provided in incidence rate tables. Two different kinds of incidence rate tables will be provided as appropriate for different analyses. Definitions are provided below.

  (1) Follow-up adjusted incidence rate – defined as the number of subjects who experienced an event divided by the total of entire follow-up time among the subjects in the analysis population. The entire follow-up time for a subject is defined as the time from the first dose until the last day on study. Each subject will be counted only once within each category.
  (2) Exposure-adjusted incidence rate (EAIR) – defined as the number of subjects who experience an event divided by the total exposure adjusted follow-up time among the subjects in the analysis population. The exposure adjusted follow-up time is defined as the time from the first dose until the initial occurrence of the event for those who experienced an event, or from the first dose until the end of follow-up (the last day on study) for those who did not. Each subject will be counted only once within each category.

4.5.2 Clinical Adverse Events

Treatment-emergent AEs (TEAEs)

All AEs will be analyzed based on the principle of treatment emergence. A treatment-emergent AE was defined as an AE that started or worsened after the start of first infusion of study treatment.

To define treatment emergence for AEs with missing start or stop date or time the following additional criteria will be used:

- if both the start and stop dates for a particular AE are missing, then that AE is considered treatment emergent;
- if the start date for a particular AE is missing and the stop date/time falls after the first dose date/time, then that AE is considered treatment emergent;
- if the start date for a particular AE was the same as the first dose date, and the start time was missing, then that event is considered treatment emergent.

For AEs with a partial start date, the year/month of the event date will be compared to that of the first dosing date to determine whether the event is treatment emergent.

In addition, SAEs that occurred since a subject was screened in the study and prior to the first infusion of study treatment, which by definition are not treatment-emergent, will be analyzed separately.

Only TEAEs will be included in the AE tables, unless otherwise specified. Listings of AEs will include all events, whether treatment-emergent or not.

As specified in the protocol, subjects were expected to return to the study site for an End of Study visit 18 weeks after the last administration of study treatment. However, some subjects may elect to continue study participation on a modified schedule after discontinuing treatment, possibly in substantial excess of 18 weeks. For most general AE summaries, AEs

with an onset more than 18 weeks after the last dose will be excluded (will specify in the footnote of the specific table). For incidence rate analyses excluding AEs more than 18 weeks after the last dose, the "last day on study" in follow-up time calculation will be replaced with "18 weeks after last dose or last day on study, whichever earlier". Summaries of deaths and AEs leading to study withdrawal, and other selected analyses will include all AEs regardless of the time since the last dose. Listings will include all AEs, unless otherwise specified.

4.5.2.1 Summary and incidence analysis

Overall summary of AE table will summarize the number of subjects with any AE, with any AE by maximum severity, the number of subjects with any related AE (related to study drug as assessed by investigator), the number of subjects with SAE, the number of subjects with related SAE, the number of subjects with AE leading to study drug discontinuation, the number of subjects with AE leading to study withdrawal, and the number of deaths. This table will be done by treatment group as well as by treatment group stratified by ApoE status.

The sorting order for AE incidence tables, unless otherwise specified, will be by decreasing frequency order of "BIIB037 total" column within each category in the tables presented by treatment group, and by decreasing frequency order of "BIIB037 high dose total" column within each category in the tables presented by treatment group stratified by ApoE status. A subject is counted only once within each category in each table. For example, for the table of AEs by system organ class and preferred terms sorted by decreasing frequency presented by treatment group, system organ class will be presented in decreasing frequency order of BIIB037 total column, and within each system organ class, preferred terms will be presented in decreasing frequency order of BIIB037 total column. A subject is counted only once within each system organ class and preferred term.

The following AE incidence tables will be provided (presented both by treatment group and by treatment group stratified by ApoE status, unless otherwise specified):

1. AEs by system organ class and preferred term sorted by decreasing frequency
2. AEs by system organ class and preferred term sorted by alphabetical order (by treatment group)
3. AEs by system organ class, high level group term and preferred term (by treatment group only)
4. AEs by system organ class (by treatment group)
5. AEs with at least 2% higher in incidence for either low or high dose compared to placebo by system organ class and preferred term
6. AEs by preferred term
7. AEs with an incidence of 5% or more in any treatment group by preferred term
8. Severe AEs by system organ class and preferred term (by treatment group)
9. Severe AEs by preferred term
10. AEs by maximum severity by system organ class and preferred term (by treatment group) (System organ class will be presented alphabetically. Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, unknown and total. A

subject will be counted only once at the maximum severity within each system organ class and preferred term.)

11. AEs by maximum severity by preferred term (by treatment group) (Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, unknown and total. A subject will be counted only once at the maximum severity within each preferred term.)
12. Related AEs by system organ class and preferred term
13. SAEs by system organ class and preferred term
14. SAEs by preferred term
15. Related SAEs by system organ class and preferred term
16. AEs that led to discontinuation of study treatment by system organ class and preferred term
17. AEs that led to withdrawal from study by system organ class and preferred term
18. SAEs with fatal outcome by system organ class and preferred term
19. AEs that occurred within 2 hours from infusion start by system organ class and preferred term (by treatment group)
20. AEs by12 weeks intervals from first infusion to the end of study by system organ class and preferred term (by treatment group)
21. Pre-treatment SAEs that occurred since screening and prior to first infusion by system organ class and preferred term

The following listings will be provided.

1. Listing of AEs
2. Listing of SAEs
3. Listing of AEs that led to discontinuation of study treatment
4. Listing of AEs that led to withdrawal from study
5. Listing of AEs that occurred within 2 hours from infusion start
6. Listing of AEs related to PET ligands
7. Listing of SAEs with fatal outcome
8. Listing of AEs for subjects with treatment-emergent positive anti-BIIB037 antibody

4.5.2.2 Incidence rate analysis

Follow-up adjusted incidence rate for the placebo-controlled period will be summarized by system organ class and preferred terms both by treatment group and by treatment group stratified by ApoE status.

4.5.2.3 Subgroup analysis for protocol version 4

Due to the change in maximal dose from 6 mg/kg to 10 mg/kg for ApoE ε4 carrier high dose group in protocol version 4, not all subjects have had opportunity to receive the protocol specified high dose (6 doses in titration before receive 10mg/kg) in the placebo-controlled period. Incidence tables of AEs and SAEs will be provided for ApoE ε4 carriers who were randomized to the high dose group, stratified by the expected number of doses at 10 mg/kg (categories of 0, 1-6, 7-13, 14, and a total column of having at least one dose) a subject would have received based on the first infusion date and the date consenting to protocol version 4. Randomization treatment groups will be used for this analysis.

4.5.3 ARIA – AE of special interest

4.5.3.1 Background

ARIA is an AE of special interest in this study. Please see protocol section 7.2.1 for ARIA management and dose disposition guidelines. Since ARIA is a brain MRI finding, ARIA data are collected under two data sources: (1) safety MRI data as recorded on brain MRI worksheet by central MRI reader; (2) AE eCRF. For each ARIA event, the information of start/end date, severity, locations in brain regions and status on MRI scan is collected on the brain MRI worksheet by central MRI reader. ARIA severity is determined by central MRI reader based on number and size of the ARIA regions on imaging. An AE record is then entered into the eCRF by the investigator with the start/end date and severity information from brain MRI worksheet, and with information on the symptomatic status and action taken towards study drug. If ARIA is symptomatic, the symptoms will be entered into AE eCRF and the severity of the symptoms will be determined by the investigator. AE eCRF data will be used as the primary source for ARIA analysis as it contains the complete information of ARIA as well as associated symptoms. Safety MRI data will also be used to show the consistency between two data sources, provide details on MRI assessments, and for any specific analysis that requires information from MRI.

ARIA includes ARIA-E (vasogenic edema) and ARIA-H (hemorrhage). ARIA-H includes ARIA-H microhemorrhage, ARIA-H macrohemorrhage and ARIA-H superficial siderosis. Table 6 shows the reported term on MRI worksheet, the corresponding reported term on AE eCRF, and the MedDRA preferred term and lower level term for each type of ARIA.

Table 6: Reported and MedDRA terms for ARIA

Reported term on MRI worksheet	Reported term on AE eCRF	MedDRA version 21.0 preferred term	MedDRA version 21.0 lower level term
ARIA-E	Asymptomatic ARIA-E Symptomatic ARIA-E	Amyloid related imaging abnormality-oedema/effusion	ARIA-E

ARIA-H microhemorrhage	Asymptomatic ARIA-H (Microhemorrhage) Symptomatic ARIA-H (Microhemorrhage)	Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	ARIA-H
ARIA-H macrohemorrhage	Asymptomatic ARIA-H (Macrohemorrhage) Symptomatic ARIA-H (Macrohemorrhage)	Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	ARIA-H
ARIA-H superficial siderosis	Asymptomatic ARIA-H (Superficial Siderosis) Symptomatic ARIA-H (Superficial Siderosis)	superficial siderosis of the central nervous system	superficial siderosis of the central nervous system

For any specific ARIA event, the start date of the duration based on MRI is the date of the MRI assessment that initially identifies the ARIA event, and the end date of the duration based on MRI is the date of the MRI assessment that shows the complete resolution of this ARIA event (in the case of ARIA-E), or the date of the MRI assessment that shows ARIA being stable (in the case of ARIA-H). Stable was defined as 'No change' or 'decrease' in number, size, severity or number of locations between 2 consecutive MRIs including the initial detection MRI and the follow-up MRIs.

For symptomatic ARIA events, if there is any related symptom that proceeds the first MRI identification, then the symptom onset date will be used as the start date of the symptomatic ARIA duration. The end date of the symptomatic ARIA duration will be the date of the resolution or stable MRI as defined above for the duration based on MRI.

If the severity increases, or the event changes from asymptomatic to symptomatic, or from non-serious to serious, more than one AE records will be added to eCRF to capture the change with new start/end AE dates (the end date of the previous record will be the start date of the next record). For analysis, records with changes in severity or symptomatic status or seriousness are considered as a single ARIA event. The severity/symptomatic status/seriousness for that event is defined as the worst level among all the AE records that belong to that event.

If the same type of ARIA event happens again after the previous event has ended, then it is considered a recurrent event of ARIA of that type. Recurrent events will be referred as the second event, the third event, and etc.

If the duration based on MRI of an ARIA-E event overlaps with the duration based on MRI of an ARIA-H event, then these 2 ARIA events are considered as concurrent events.

4.5.3.2 Incidence and summary of ARIA

Incidence of ARIA-E, ARIA-H, ARIA-E and ARIA-H (not necessarily concurrent), concurrent ARIA-E and ARIA-H, ARIA-E or ARIA-H, isolated ARIA-H (only ARIA-H, no ARIA-E), ARIA-H microhemorrhage, ARIA-H macrohemorrhage and ARIA-H superficial siderosis will be summarized based on both AE eCRF and MRI data. If there is any discrepancy in incidence between the two data sources, a listing of the subjects and ARIA events with discrepancy will be provided. In addition, the incidence table based on AE eCRF source will also be done by treatment group (placebo, low dose, high dose and BIIB037 total; analysis display A in Appendix 6.1).

Number of subjects with each type of ARIA, maximum severity and worst symptomatic status of the type of ARIA being analyzed will be summarized based on AE eCRF. For subjects with symptomatic ARIA, the maximum severity of symptoms will also be summarized.

Number of subjects with ARIA-H microhemorrhage events post-baseline (broken down by categories of 1-4, 5-9 and >=10) stratified by whether they have had microhemorrhage at baseline will be summarized based on safety MRI data. The summary will be conducted based on the MRI that shows the maximum number of microhemorrhages as well as the last MRI in the study period.

Summary of concurrent ARIA-E and ARIA-H will be provided including the following information: number of subjects with concurrent ARIA-E and ARIA-H (and further broken down to each type of ARIA-H), the severity of ARIA-E based on MRI, the symptomatic status of ARIA-E, the severity of symptoms based on AE eCRF. For subjects with recurrent ARIA-E events, if there is an event concurrent with ARIA-H, it will be used for the summary, and the first concurrent event will be used if there are more than one event concurrent with ARIA-H.

An incidence table of AEs considered by the investigator to be related to ARIA by system organ class and preferred term for subjects with symptomatic ARIA will be provided, as well as a listing of these AEs. Similarly, an incidence table of AEs related to ARIA for subjects with symptomatic ARIA and severe symptoms will be provided, as well as a listing of these AEs.

Listings of AE records for each type of ARIA events and listings of MRI assessments for subjects with each type of ARIA events will be provided.

Montreal Cognitive Assessment (MOCA) is performed at baseline and at each unscheduled ARIA monitoring visit for ARIA subjects (approximately every 4 weeks) except for mild asymptomatic microhemorrhage subjects. An incidence table of subjects with ARIA events whose MOCA total scores decrease 2 points or more from baseline will be provided. A listing of MRI assessments and MOCA total scores for subjects with ARIA events will be provided.

Line plots of MMSE mean change from baseline values and standard errors at each planned visit (baseline, Week 26, Week 50 and Week 78) will be provided by treatment group stratified by ApoE status and with stratification on the following factors:

(1) ARIA-E severity based on MRI. The groups are: subjects without ARIA-E, subjects with mild ARIA-E, subjects with moderate ARIA-E and subjects with severe ARIA-E.

(2) Within ARIA-E subjects, stratify by the severity of the concurrent symptoms based on AE eCRF. The groups are: subjects without symptoms, subjects with mild symptoms, subjects with moderate symptoms, and subjects with severe symptoms.

For subjects with recurrent ARIA-E events, the first ARIA-E event will be used for the classification for each of the factors.

4.5.3.3 Summary of recurrent ARIA-E

Follow-up adjusted incidence rate of subjects with ARIA-E, with 2 or more events of ARIA-E, with 3 or more events of ARIA-E and with more than 3 events of ARIA-E based on their entire follow-up time will be summarized based on AE eCRF. The entire follow-up time is from the first dose until the last day in the placebo-controlled period.

Number of total ARIA-E events and the MRI severity of each event will be summarized based on AE eCRF. Number of total symptomatic ARIA-E events, the MRI severity of each symptomatic event and the severity of the symptoms of each symptomatic event will be summarized based on AE eCRF.

Summary of first ARIA-E events table based on AE eCRF will summarize the number of subjects with a first event of ARIA-E, the MRI severity of the events, the symptomatic status of the events, the severity of the symptoms for symptomatic events, whether SAE or not, number of resolved and unresolved events, duration of the resolved events, time from first infusion in study (active or placebo) to onset, number of doses received since the start of the study to onset, dose level of the last infusion received prior to onset, dosing status (continue as planned, dose interrupted, dose reduced, or dose discontinued) after the events, and the number of subjects with recurrent ARIA-E events. The same summary of first ARIA-E events table will also be done on subjects who had recurrent ARIA-E events.

Summary of recurrent ARIA-E events table based on AE eCRF will summarize the following information for both the second and third event of ARIA-E events: the number of subjects with the previous event of ARIA-E, the number of subjects with at least one dose and one MRI after the previous ARIA-E resolution, the number of subjects with this event of ARIA-E, the MRI severity of the events, the symptomatic status of the events, the severity of the symptoms for symptomatic events, whether SAE or not, number of resolved and unresolved events, duration of the resolved events, time from first infusion in study (active or placebo) to onset, time from previous resolution to onset, number of doses received since the start of the study to onset, dose level of the last infusion received prior to onset, dosing status (continue as planned, dose interrupted, dose reduced, or dose discontinued) after the events. The number of subjects with more than 3 events of ARIA-E, and the number of subjects who discontinued study treatment after recurrent ARIA-E onset will also be summarized.

A listing of subjects who withdrew from the study with unresolved ARIA-E or subjects with ongoing ARIA-E at the time of data cutoff (also considered as unresolved) will be provided with the details of the event including the duration from onset to last follow-up.

For subjects with recurrent ARIA-E, a listing of study drug administration, MRI assessments, severity and symptomatic status of each event, and end-of-treatment reason (if present) will be provided.

4.5.3.4 Exposure adjusted analysis

Exposure adjusted incidence rate of ARIA-E events will be summarized based on safety MRI data. The exposure adjusted follow-up time is from the first dose until the initial occurrence of ARIA-E for those who experienced ARIA-E, and until the end of follow-up for those who did not. Since ARIA is an MRI finding, the day of the last MRI assessment in the placebo-controlled period will be used as the end of follow-up for those who didn't experience the event.

Study drug administration information prior to first ARIA-E onset will be summarized for ARIA-E subjects, including number of total infusions, number of infusions at each dose level (placebo, 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg), dose level of the last infusion, maximum dose level received, and cumulative dose as a continuous variable.

4.5.3.5 Time to event analysis

Kaplan-Meier plot of time to first ARIA-E event will be produced based on safety MRI data. Time to event is calculated as date of the MRI assessment that initially detects ARIA-E event - date of first infusion (aducanumab or placebo) +1. Censor time for subjects without ARIA-E is calculated as date of last MRI assessment in the placebo-controlled period - date of first infusion (aducanumab or placebo) +1. Estimated proportion with ARIA-E and number of subjects at risk at selected timepoints will also be presented. The plot will be presented by treatment group stratified by ApoE status.

4.5.3.6 Subgroup analysis for protocol version 4

Due to the change in maximal dose from 6 mg/kg to 10 mg/kg for ApoE ε4 carrier high dose group in protocol version 4, not all subjects have had opportunity to receive the protocol specified high dose (6 doses in titration before receive 10mg/kg) in the placebo-controlled period. Incidence of ARIA events and summary of first ARIA-E events tables will be provided for ApoE ε4 carriers who were randomized to the high dose group, stratified by the expected number of doses at 10 mg/kg (categories of 0, 1-6, 7-13, 14, and a total column of having at least one dose) a subject would have received based on the first infusion date and the date consenting to protocol version 4. Randomization treatment groups will be used for this analysis.

4.5.4 Clinical Laboratory Data

The following clinical laboratory parameters are assessed in the protocol and will be analyzed:

- Hematology:
  - White blood cells (leukocytes), lymphocytes, neutrophils, monocytes, eosinophils, basophils
  - Red blood cells (erythrocytes), erythrocytes distribution width, erythrocytes mean corpuscular volume, erythrocytes mean corpuscular hemoglobin, erythrocytes mean corpuscular hemoglobin concentration

- Hemoglobin
- Hematocrit
- Platelet count

- Blood chemistry:
  - Liver: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl-transferase (GGT)
  - Renal: blood urea nitrogen (BUN), creatinine
  - Electrolytes: sodium, potassium, chloride, bicarbonate
  - Other: glucose, calcium, phosphorus, albumin, uric acid, lactate dehydrogenase (LDH), total protein
- Urinalysis: specific gravity, potential of hydrogen (pH), color, blood, glucose, ketones, protein, white blood cells, red blood cells

4.5.4.1 Quantitative analyses

For numeric laboratory parameters, actual values, change from baseline and percent change from baseline will be summarized by visit. Number of evaluable subjects, mean, standard deviation, median, 25% and 75% quartiles, minimum and maximum values will be presented at each visit.

Plots of mean values (with standard error) for numeric laboratory parameters at each visit will be provided.

Listings of individual laboratory measurements by patients for all the parameters will be provided.

Visit windows for by visit summaries

For laboratory by visit summaries, the analysis visit should be defined using visit windows (see Table 7 below). If there is more than 1 value in the same analysis visit window for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis.

Table 7: Visit Windows for Laboratory by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 24	169	[2, 252]
Week 48	337	[253, 420]
Week 72	505	[421, 525]

Analysis visit	Target visit day	Analysis visit window
Week 78	547	[526, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

4.5.4.2 Qualitative analyses

For all qualitative analyses, all values will be included (not just the "analyzed record" within each visit window in the quantitative analyses).

Shift analyses

Laboratory data will be summarized using shift tables where appropriate. Each subject's hematology, blood chemistry and urinalysis numeric values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory or as "unknown" if no result is available. Each subject's urinalysis categorical values will be flagged as "positive" or "negative", or "unknown" if no value is available.

Shifts from baseline to high/low status will be presented for hematology, blood chemistry and urinalysis numeric parameters, and shifts from baseline to abnormal (positive) will be presented for urinalysis categorical parameters. Shift to low includes normal to low, high to low, and unknown to low; Shift to high includes normal to high, low to high, and unknown to high. Subjects need to have at least one post-baseline evaluation and a baseline value not low or high or positive (including missing) in order to be included in the analysis. A listing of laboratory normal ranges will be provided.

Grade analyses

Worst post-baseline grade will be summarized for each laboratory parameter in both exclusive way and cumulative way. Subjects need to have at least one post-baseline evaluation in order to be included in the analysis. Common Toxicity Criteria for Adverse Events v4.0.3 (CTCAE) published on 2010-06-14 will be used for grade determination. Grade determination is based solely on laboratory values not taking AEs into account.

Potentially Clinically Significant laboratory abnormalities analyses

For hematology, blood chemistry and urinalysis, the number of subjects with potentially clinically significant laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 8. Subjects need to have at least one post-baseline evaluation and a baseline value not potentially clinically significant (including missing) in order to be included in the analysis.

Table 8: Criteria to Determine Potentially Clinically Significant (PCS) Laboratory Abnormalities

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
HEMATOLOGY		

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
White blood cells	<3.0 x 10^9/L	>16 x 10^9/L
Lymphocytes	<0.8 x 10^9/L	>12 x 10^9/L
Neutrophils	<1.5 x 10^9/L	>13.5 x 10^9/L
Monocytes	N/A	>2.5 x 10^9/L
Eosinophils	N/A	>1.6 x 10^9/L
Basophils	N/A	>1.6 x 10^9/L
Red blood cells	≤3.5 x 10^{12}/L	≥6.4 x 10^{12}/L
Hemoglobin - Females	≤95 g/L	≥175 g/L
Hemoglobin - Males	≤115 g/L	≥190 g/L
Hematocrit - Females	≤32%	≥54%
Hematocrit - Males	≤37%	≥60%
Platelet count	≤75 x 10^9/L	≥700 x 10^9/L
BLOOD CHEMISTRY		
Alanine aminotransferase (ALT)	N/A	>3 x ULN
Aspartate aminotransferase (AST)	N/A	>3 x ULN
Alkaline phosphatase (ALP)	N/A	>3 x ULN
Total bilirubin	N/A	>1.5 x ULN
Blood urea nitrogen (BUN)	N/A	≥10.7 mmol/L
Creatinine	N/A	≥176.8 umol/L
Sodium	≤126 mmol/L	≥156 mmol/L
Potassium	≤3 mmol/L	≥6 mmol/L
Chloride	≤90 mmol/L	≥118 mmol/L
Bicarbonate	≤16 mmol/L	≥35 mmol/L
Glucose	≤2.2 mmol/L	≥9.7 mmol/L
Calcium	≤2 mmol/L	≥3 mmol/L
Phosphorus	≤0.6 mmol/L	≥1.7 mmol/L
Albumin	≤25 g/L	≥625 g/L
Total protein	≤45 g/L	≥100 g/L
URINALYSIS		
Glucose	N/A	≥ ++++
Ketones	N/A	≥ ++++
Protein	N/A	≥ ++
ULN = upper limit of normal		

Potential serious hepatotoxicity

Potential serious hepatotoxicity is defined as ALT or AST > 3x ULN and total bilirubin > 2x ULN at any time post-baseline, not necessarily concurrent. A scatterplot of the maximum post-baseline ALT or AST value relative to ULN and maximum post-baseline total bilirubin value relative to ULN (not necessarily concurrent) for each subject will be provided. A line plot of ALT, AST, ALK and total bilirubin values over time for subjects with potential serious hepatotoxicity will be provided. In addition, subjects with ALT > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with AST > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with total bilirubin >1x ULN or >2x ULN, subjects with ALP >1x ULN or >1.5x ULN, and subjects with AST or ALT > 3x ULN post-baseline accompanied by concurrently elevated total bilirubin >1.5x ULN or > 2x ULN will be presented. Concurrent is defined as on the same day. A listing of subjects with potential serious hepatotoxicity will be provided.

4.5.5 C-SSRS Data

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior. There are 5 "Yes/No" questions on suicidal ideation following the increasing severity order: (1) Wish to be dead, (2) Non-specific active suicidal thoughts, (3) Active suicidal ideation with any methods (not plan) without intent to act, (4) Active suicidal ideation with some intent to act, without specific plan, (5) Active suicidal ideation with specific plan and intent, and 6 "Yes/No" questions on suicidal behavior following the increasing severity order: (6) Preparatory acts or behavior, (7) Aborted attempt, (8) Interrupted attempt, (9) Actual attempt, (10) Suicidal behavior, (11) Suicide (only at post-baseline visits). Another "Yes/No" question of whether the subject has engaged in non-suicidal self-injurious behavior is also collected.

In the summary table for C-SSRS, number of subjects who answered "Yes" to each of the 11 questions post-baseline, subjects who answered "Yes" to at least one question for suicidal ideation, subjects who answered "Yes" to at least one question for suicidal behavior, and subjects who have engaged in non-suicidal self-injurious behavior will be presented. A listing of subjects with any suicidal ideation or behavior at baseline or post-baseline will be provided.

4.5.6 ECG Data

Shift from normal or unknown ECG at baseline to abnormal, not adverse event or abnormal, adverse event post-baseline ECG will be summarized for the placebo-controlled period. Subjects with abnormal post-baseline ECG status will be listed.

4.5.7 Vital Sign Data

Vital sign parameters include body temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and weight. Vital signs will be measured with the subject supine and after the subject has been resting for at least 10 minutes. The descriptive statistics for actual values and change from baseline will be summarized at each visit. Plot of mean vital sign values at each visit will be provided.

The analysis of vital signs will also focus on the incidence of clinically relevant outliers based on the following criteria. The incidence and percentage of clinically relevant outliers determined by each criterion will be summarized. A listing of subjects with clinically relevant vital signs will be provided.

Table 9: Criteria Used to Assess Potential Clinically Relevant Outliers in Vital Signs

Variable	Low	High
Systolic Blood Pressure	<90 mm Hg or ≥20 mm Hg decrease from Baseline (BL)	>180 mm Hg or ≥20 mm Hg increase from BL

Diastolic Blood Pressure	< 50 mm Hg or ≥15 mm Hg decrease from BL	>105 mg Hg or ≥15 mm Hg increase from BL
Heart Rate	<50 bpm or ≥ 15 bpm decrease from BL	>120 bpm or ≥ 15 bpm increase from BL
Temperature	>2 degree C decrease from BL	>38.5 C or >2 degrees C increase from BL
Respiration Rate	< 10 breaths per minute or ≥ 50% decrease from BL	>25 breaths per minute or ≥50% increase from BL
Weight	≥7% decrease from BL	≥7 % increase from BL
BL= baseline; bpm = beats per minute		

Visit windows for by visit summaries

For vital sign by visit summaries, the analysis visit should be defined using windows (see Table 10 below). If there is more than 1 value in the same analysis visit window for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis.

Table 10: Visit Windows for Vital Sign by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 4	29	[2, 42]
Week 8	57	[43, 70]
Week 12	85	[71, 98]
Week 16	113	[99, 126]
Week 20	141	[127, 154]
Week 24	169	[155, 182]
Week 28	197	[183, 210]
Week 32	225	[211, 238]
Week 36	253	[239, 266]
Week 40	281	[267, 294]
Week 44	309	[295, 322]
Week 48	337	[323, 350]
Week 52	365	[351, 378]
Week 56	393	[379, 406]
Week 60	421	[407, 434]
Week 64	449	[435, 462]
Week 68	477	[463, 490]
Week 72	505	[491, 518]
Week 76	533	[519, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

4.6 Pharmacokinetics Analysis

The PK analysis population will be used for the description of the concentration-time profiles and for the estimation of PK parameters. Randomization treatment groups will be used for

PK analysis. Tables and figures, if not otherwise specified, will be presented by treatment group stratified by ApoE status (3 columns under each treatment group: ApoE ε4+, ApoE ε4- and total; analysis display B in Appendix 6.1). Listings will be presented by treatment group stratified by ApoE status.

PK evaluation will be based on the concentration of aducanumab in serum samples collected prior to infusion and between 10 and 60 minutes after completion of the infusion and line flush for the visits specified per protocol.

Concentrations of aducanumab that are below the limit of quantification (BLQ) will be imputed as 0. When summarizing concentrations or PK parameters in serum, a minimum of 2 values are required to show the arithmetic mean and geometric mean, and at least 3 values are required to show the standard deviation and coefficient of variation.

4.6.1 Serum Concentration Profile

Serum concentration data will be summarized by nominal visit. Number of evaluable subjects, arithmetic mean, standard deviation, median, 25% and 75% quartiles, minimum, maximum, geometric mean, and coefficient of variation will be presented at each visit. A listing of individual concentration data will be provided.

A semi-logarithmic plot of the mean serum concentration-time curves of aducanumab from first visit to last visit through nominal times will be provided.

4.6.2 Serum PK Parameters

Two PK parameters C_{max} and C_{min} will be computed by noncompartmental methods, as data permit, from serum concentration-time data:

Parameter	Definition	Units
C_{max}	Observed maximum serum aducanumab concentration	ug/mL
C_{min}	Observed minimum serum aducanumab concentration	ug/mL

Number of evaluable subjects, arithmetic mean, standard deviation, median, 25% and 75% quartiles, minimum, maximum, geometric mean, and coefficient of variation will be presented for the PK parameters.

4.6.3 Subgroup analysis for protocol version 4

Due to the change in maximal dose from 6 mg/kg to 10 mg/kg for ApoE ε4 carrier high dose group in protocol version 4, not all subjects have had opportunity to receive the protocol specified high dose (6 doses in titration before receive 10mg/kg) in the placebo-controlled period. Summary tables for serum concentration and PK parameters will be provided for ApoE ε4 carriers who were randomized to the high dose group, stratified by the expected number of doses at 10 mg/kg (categories of 0, 1-6, 7-13, 14, and a total column of having at least one dose) a subject would have received based on the first infusion date and the date consenting to protocol version 4.

4.7 Immunogenicity Analysis

4.7.1 Background

Definition of baseline value

Baseline value is defined as the latest immunogenicity data collected prior to the first dose. If no immunogenicity data are collected prior to the first dose, baseline value is missing and will be imputed as anti-drug antibody negative for immunogenicity analyses.

Treatment-emergent anti-aducanumab antibody positive responses

Post-baseline positive anti-aducanumab antibody responses are defined as treatment-emergent if a subject is either (1) antibody negative at baseline; or (2) antibody positive at baseline but the post-baseline antibody response is more than 2-fold increase in titer compared to the baseline response.

Persistent and transient positive responses for the placebo-controlled period

Subjects with treatment-emergent positive anti-aducanumab antibody responses in the placebo-controlled period will be further classified as transient positive, if only a single positive evaluation occurs or more than 1 positive evaluation but occur with < 112 days (16 weeks) apart, or as persistent positive, if more than one consecutive positive evaluation occurs ≥ 112 days (16 weeks) apart or a positive evaluation occurs at the last available time point with no further negative results available (including long-term extension).

4.7.2 Immunogenicity analysis

Immunogenicity population will be used to analyze immunogenicity data. Safety treatment groups will be used for immunogenicity analysis. Tables will be presented by treatment group (placebo, low dose, high dose and BIIB037 total; analysis display A in Appendix 6.1). Listings will be presented by treatment group stratified by ApoE status.

A summary table of subjects with treatment-emergent positive anti-aducanumab antibody responses results will be provided. The number and percentage of anti-aducanumab positive responses will be summarized at each visit and at any time post-baseline. Subjects with persistent response and subjects with transient response will be presented. A listing of subjects with anti-aducanumab antibody positive results will also be provided.

Visit windows for by visit summaries

For immunogenicity by visit summaries, the analysis visit should be defined using visit windows (see Table 11Table 7 below). If there is more than 1 value in the same analysis visit window for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance

from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis.

Table 11: Visit Windows for Immunogenicity by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 24	169	[2, 196]
Week 32	225	[197, 308]
Week 56	393	[393, 470]
Week 78	547	[470, the end day of the placebo-controlled period*]
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

4.8 Additional Exploratory Endpoints

[redacted]

5 INTERIM ANALYSIS

An interim analysis will occur after approximately 50% of the subjects have had the opportunity to complete the Week 78 visit for both 221AD301 and 221AD302. To maintain the integrity of the study in the event of the interim analysis, an independent group external to Biogen that will not be involved in the conduct of the study after unblinding will perform the interim analysis. The IDMC will review the unblinded results of the interim analysis provided by the independent group and will make a recommendation to Biogen based on pre-specified criteria.

An interim analysis for futility of the primary endpoint will be performed to allow early termination of the studies if it is evident that the efficacy of aducanumab is unlikely to be achieved. The futility criteria will be based on conditional power, which is the chance that the primary efficacy endpoint analysis will be statistically significant in favor of aducanumab at the planned final analysis, given the data at the interim analysis. The conditional power is calculated assuming that the future unobserved effect is equal to the maximum likelihood estimate of what is observed in the interim data:

$$CP\left(Z(1) \geq Z_\alpha | Z(t)\right) = 1 - \phi\left(\frac{Z_\alpha \sqrt{n_2} - Z(t)\sqrt{n_1}}{\sqrt{n_2 - n_1}} - \frac{Z(t)\sqrt{n_2 - n_1}}{\sqrt{n_1}}\right)$$

where t is the fraction of information and $Z(t)$ is the observed Z-statistic at the interim analysis, $Z(1)$ is the Z-statistic and α is the type I error at the final analysis, n_1 and n_2 are the number of subjects at the interim and at the final analysis, respectively.

The futility decision will primarily be based on the conditional power for the primary efficacy endpoint. The study will not be considered as futile unless both studies 221AD301 and 221AD302 have conditional power for the primary efficacy endpoint less than 20% in both the high-dose and low-dose treatment groups. Given the insufficient knowledge of aducanumab's potential effects on various functional/cognition endpoints or in certain subgroups at the present time, other data in addition to the pre-specified futility criteria will be considered as well, and the IDMC may recommend the studies to be continued as planned based on the weight of the evidence.

An interim analysis for superiority may be performed, to allow the possibility to demonstrate the treatment effect early. If an interim analysis for superiority is performed, the O'Brien-Fleming stopping boundary will be used. If an interim analysis for superiority is not performed, then no alpha adjustment will be used for the final analysis after all subjects have had the chance to complete the Week 78 visit.

6 APPENDIX

6.1 Analysis Display

Analysis display A

Placebo	BIIB037 low dose	BIIB037 high dose

Analysis display B

Placebo			BIIB037 low dose			BIIB037 high dose		
ApoE e4+ placebo	ApoE e4- placebo	Total	ApoE e4+ 3 mg/kg	ApoE e4- 6 mg/kg	Total	ApoE e4+ 10 mg/kg	ApoE e4- 10 mg/kg	Total

6.2 Protocol Deviation Classification

Deviation Category	Deviation Description	Severity Classification
Administrative criteria	Study team member performing study assessments without being authorized as per delegation log.	Minor
Administrative criteria	Unblinded information made available to the blinded CRA.	Major
Administrative criteria	Unblinded information made available to the blinded site personnel.	Major
Administrative criteria	Incorrect version of any assessments used	case by case
Administrative criteria	Filing issues misfiling of documents	N/A
Administrative criteria	Correction of source data not compliant with GCP	N/A
Administrative criteria	Sharing of account credentials between raters on the MedAvante Virgil tablet/Portal, or sharing of accounts on any study system	Major
Concomitant Medications	Administration of any vaccination/booster should be given < 10 days prior to any dosing visit or 10 days after a dosing visit.	Minor
Concomitant Medications	Administration of any disallowed concomitant therapy to the subject.	Major
Concomitant Medications	Change of medications that subjects were receiving at enrollment or start of new medications or herbal preparations during the study period, without consultation with the investigator and review with the Medical Monitor	Case by case basis
Concomitant Medications	Change in AD medications during course of the study.	Minor
Eligibility and Entry criteria	Any "no" response to inclusion criteria and/or any "yes" response to exclusion criteria and subject was subsequently randomized for criteria.	Major
Eligibility and Entry criteria	Any eligibility assessment not performed.	Major
Eligibility and Entry criteria	Any eligibility assessment performed after the randomization of the patient (including lab samples), and subject is ineligible based upon assessment.	Major
Eligibility and Entry Criteria	Exclusionary lab value results but subject was dosed.	Major
Eligibility and Entry criteria	Subject not eligible based on scores of CDR, MMSE, RBANS DMI, as defined by inclusion criterion #6.	Major
Eligibility and Entry criteria	Subject on allowed chronic medications that have not been stable for at least 4 weeks prior to Screening V1 or use of AD medications at doses that have not been stable for at least 8 weeks prior to Screening V1.	Major

Informed Consent	Subject/informant/legally authorized representative did not sign Main ICF, PET ICF, and/or Substudy ICFs (and substudy procedures were conducted). Not clear on the ICF who has been signing the document (patient or legal representative).	Major
Informed Consent	Principal Investigator / individual obtaining consent did not sign Main ICF, PET ICF, and/or Substudy ICFs (and substudy procedures were conducted).	Major
Informed Consent	Not clear on the the ICF who has been signing the document (patient or legally authorized representative).	Major
Informed Consent	ICF signed by either only patient or only care giver/legally authorized representative, when ICF should have been signed by both.	Major
Informed Consent	Incorrect or outdated version of Main ICF, PET ICF, and/or Substudy ICFs signed by subject/informant/legally authorized representative.	Major
Informed Consent	IEC/IRB contact details or site's contact details not included on ICF.	Minor
Informed Consent	Incorrect completion of ICF (i.e., subject/study partner/LAR/person obtaining consent did not provide date of signature; subject/study partner/LAR/person obtaining consent noted incorrect date of signature; subject/study partner/LAR/person obtaining consent printed name when should have signed, subject/study partner/LAR/person obtaining consent signed on line for printed name, printed name on line for signature, etc.)	Minor
Informed Consent	Site personnel who signed ICF is not on Site Personnel Signature Delegation Log and/or not authorized by PI to sign ICF	Major
Informed Consent	No evidence (source documentation) that Informed Consent was obtained from the study subject / study partner.	Major
Informed Consent	ICF obtained by subject is not in subject's native language.	Major
Informed Consent	Protocol specific procedures such as physical exam, medical history, neurological history, ECGs, rater scales, lab tests, blood draws, including first study drug dose performed prior to the date of the consent.	Major
Informed Consent	Subject and/or Study Partner/Caregiver not signing ICFs at time of reconsent.	Major
Informed Consent	Untimely reconsenting of subject/caregiver on newly approved ICFs.	Major
Investigational Product Compliance	IP storage temperature out of range and site used IP without confirmation from Biogen regarding usability	Case by case basis
Investigational Product Compliance	Incorrect cohort IP dispensed to subject	Major
Investigational Product Compliance	IP is not stored in blinded manner.	Major
Investigational Product Compliance	Unblinded pharmacist discarded/destroyed used IP vial prior to IP accountability being conducted by unblinded CRA and without previous approval.	case by case basis
Investigational Product Compliance	IP temperature log is not being maintained nor checked by the unblinded pharmacist.	Major
Investigational Product Compliance	Non-compliant with IP usage according to DHA (note: this does not include deviation regarding removing overfill on saline bag)	Major
Investigational Product Compliance	Dosing based on weight calculation is inaccurate (i.e., discrepancies between Weight Communication Form and IXRS entry, ratio not respected when preparing dose, etc.)	Major
Investigational Product Compliance	Overdose of IP occurs.	Major
Investigational Product Compliance	Overdose Form not faxed to Quintiles Lifecycle Safety within 24 hours of site being made aware of an overdose.	Major
Investigational Product Compliance	Titration schedule not respected when dosing subject.	Major
Investigational Product Compliance	Down-dosing / discontinuation of dosing not respected by the unblinded pharmacist following ARIA-H and ARIA-E cases, as prescribed by the protocol, investigator, Medical Monitor, and/or sponsor.	Major

Investigational Product Compliance	Missed infusion visit (not due to temporary discontinuation of dosing as prescribed by the protocol, investigator, Medical Monitor, and/or sponsor due to ARIA-H or ARIA-E case).	case by casis
Investigational Product Compliance	IP storage temperature out of range (2-8 °C).	Minor
Investigational Product Compliance	Administration of expired IP.	Major
Investigational Product Compliance	IP rounding discrepancies not in accordance with the Directions for Handling & Administration document (DHA).	Minor
Investigational Product Compliance	Administration of IP that was rejected after a temperature excursion.	Major
Investigational Product Compliance	IP administered in less than 21 days.	Minor
Laboratory assessments criteria	Ambient samples received at central laboratory that should have been shipped frozen.	Minor
Laboratory assessments criteria	Frozen samples received at central laboratory that should have been shipped ambient.	Minor
Laboratory assessments criteria	Lab samples not drawn, or results unavailable.	Minor
Laboratory assessments criteria	Laboratory results not acknowledged by PI, or medically qualified and delegated study personnel.	case by case
Laboratory assessments criteria	Pre-dose and/or post-dose PK samples not collected, or not collected within protocol specified time.	Minor
Laboratory assessments criteria	CSF cell counts and differentials not sent to local laboratory for analysis (for subjects participating within CSF substudy).	Minor
Laboratory assessments criteria	Lab specimens temperature log is not being maintained nor checked by applicable study personnel.	Major
Laboratory assessments criteria	Use of incorrect lab kit.	Minor
Laboratory assessments criteria	PBMC not collected, or not collected within protocol specified time.	Minor
Other	Site repeatedly commits same minor deviations.	Major
Randomization criteria	Subject recorded as randomized in IXRS by mistake but not dosed.	Major
Randomization criteria	Subject randomized to wrong arm due to mis-entry of ApoE ε4 carrier status.	Major
Regulatory or Ethics Approval Criteria	No evidence that IRB / CEC / LEC approved the final protocol.	Major
Regulatory or Ethics Approval Criteria	No evidence that IRB / CEC / LEC was notified of protocol amendments in a timely manner.	Minor
Regulatory or Ethics Approval Criteria	Failure to notify or obtain approval from the IRB / CEC / LEC of a change of investigator.	Minor
Regulatory or Ethics Approval Criteria	Failure to obtain or keep updated regulatory authorization to conduct a study.	Major
Regulatory or Ethics Approval Criteria	Failure to obtain IRB / CEC / LEC approval of a subject directed document (e.g., subject questionnaires, advertisements, etc.)	Major
Regulatory or Ethics Approval Criteria	Failure in Safety Reporting as per local requirements (SUSARS, line listings, progress reports, etc.)	Minor
Serious Adverse Event Criteria	SAEs not appropriately reported (i.e., reported as an AE when SAE criteria have been met, or SAE not reported within 24 hours).	Major
Serious Adverse Event Criteria	Pregnancies not appropriately reported within 24 hours of study site staff becoming aware of the pregnancy.	Major
Serious Adverse Event Criteria	Adverse Events of Special Interest not reported within 72 hours following the receipt of abnormal MRI findings from the central MRI reader.	Major
Serious Adverse Event Criteria	SAEs not appropriately reported to the IRB/EC.	Minor
Study Procedures criteria	Inconsistent rater used for primary, secondary endpoints	Major

Study Procedures criteria	CDR raters were performing other assessments on subjects they performed CDRs for.	Major
Study Procedures criteria	Secondary endpoint assessments raters were performing other assessments on subjects they performed these assessments for.	Major
Study Procedures criteria	MOCA was administered by a rater rather than the treating HCP.	Major
Study Procedures criteria	Assessment performed by non-qualified rater	Major
Study Procedures criteria	Any eligibility criteria not confirmed prior to dosing, but deemed eligible post-randomization (including verification of eligibility based on cancer criteria with Medical Monitor [inclusion criterion #10]).	Minor
Study Procedures criteria	MRI and/or PET scan being conducted as part of Screening Visit 2 or Screening Visit 3 procedures without PI verification of eligibility at Screening Visit 1 (including laboratory and cognitive assessment eligibility) without permission of the sponsor/Medical Monitor. Please note that ApoE ε4 results are not necessary to move onto Screening Visits 2 or 3.	Minor
Study Procedures criteria	PET scan being conducted as part of Screening Visit 3 prior to MRI central read confirming eligibility at Screening Visit 2, without permission of the sponsor/Medical Monitor.	Minor
Study Procedures criteria	Dose reduction administered by PI/sub-I when protocol requires return to last dose following temporary discontinuation of IP following ARIA event under Protocol v. 3.	case by case
Study Procedures criteria	[redacted] was not administered.	Minor
Study Procedures criteria	Primary endpoint assessment not conducted or administered at a study visit, as per protocol. Please note that deviation will not apply for any cognitive assessments that were not administered or completed, due to subject's decline in cognition.	Major
Study Procedures criteria	Secondary endpoint assessments not conducted or administered at a study visit, as per protocol. Please note that deviation will not apply for any cognitive assessments that were not administered or completed, due to subject's decline in cognition.	Major
Study Procedures criteria	Tertiary endpoint efficacy assessments (with the exception of the [redacted] and [redacted]) not conducted or administered at a study visit, as per protocol. Please note that deviation will not apply for any cognitive assessments that were not administered or completed, due to subject's decline in cognition.	Minor
Study Procedures criteria	C-SSRS not conducted or administered at a study visit, as per protocol.	Minor
Study Procedures criteria	Systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and/or respiratory rate not assessed as part of vital signs, or vital signs not measured with the subject supine and/or after the subject has been resting for at least 10 minutes.	Minor
Study Procedures criteria	Serum pregnancy test not conducted at Screening Visit 1, or urine pregnancy test not conducted at applicable study visits for subjects of child-bearing potential.	Major
Study Procedures criteria	MRI and/or PET scan being conducted on subsequent subjects should site not receive passing QC report on first in-vivo scan.	Minor
Study Procedures criteria	ARIA management not being followed as per protocol specifications.	Major
Study Procedures criteria	Non-IEC/IRB approved document(s) dispensed to subject	Major
Study Procedures criteria	Unscheduled visit not conducted due to AD medication change, or conducted after AD medication change occurred.	Major
Study Procedures criteria	Study MRIs not conducted within study visit schedule.	Minor
Study Procedures criteria	Study MRIs missed	Major
Study Procedures criteria	Administration of rating scales over the telephone.	Minor
Study Procedures criteria	Missed MOCA at an Unscheduled MRI visit.	Major
Study Procedures criteria	Missed MOCA at Day 1 Visit.	Minor
Study Procedures criteria	Missed physical exam, neurological exam, or ECG at study visit.	Minor

Study Procedures criteria	Missed PET scan at timepoints for PET substudy subjects.	Major
Study Procedures criteria	Ligand dose administration error	Major
Study Procedures criteria	Infusion conducted prior to receipt and review of MRI central read results	Case by case
Visit Schedule Criteria	Study visit or procedures conducted out of window. Please note special attention to the ADCS-ADL-MCI, ADAS-Cog, and NPI at Screening Visit 2 being conducted within 14 days of Screening Visit 1.	Minor
Visit Schedule Criteria	Occurrence of randomization outside of 60-day screening window without sponsor approval.	Minor
Visit Schedule Criteria	Occurrence of randomization outside of 90 days.	Major

6.3 Implementation of the Copy Increment from Reference and Pattern Mixture Model

6.3.1 Copy Increment from Reference

The dataset will first be imputed to monotone missing using PROC MI with the MCMC and impute=monotone option. Imputation will be carried out 1000 times and any internal missing observations, including missing baseline covariates and intermediate missing in the response variable will be replaced with the average across all imputations.

For the resulted data with monotone missing, the following steps will be used to create imputed datasets:

(1) Data from all patients will be used to fit a multivariate normal distribution with unstructured mean and unstructured variance using a Bayesian approach with a noninformative prior for the mean and a conjugate prior for the variance covariance matrix.

(2) Draw a pseudo-independent sample for the linear predictor parameters and the covariance parameters from the joint posterior distribution obtained in step (1). Both steps (1) and (2) will be done using PROC MCMC in SAS.

(3) Use the linear predictor parameters and the covariance parameters obtained in step (2) to construct new mean vectors separately for each treatment group (placebo, aducanumab low dose, aducanumab high dose). Specifically, the newly constructed mean vector for someone on treatment group T whose last observed visit was visit k is calculated as

$$\mu_T^{(k)} = \begin{cases} \mu_{i,T}, & if\ i \le k \\ \mu_{k,T} - \mu_{k,P} + \mu_{i,P}, & if\ i > k \end{cases}$$

Here P represents the placebo group. For patients with no post-baseline records, or patients on the placebo group, the newly constructed mean vector is the same as the placebo mean.

(4) Using $\mu_T^{(k)}$ from step (3) and covariance parameters from step (2), find the conditional normal distribution of the visit with missing data, and use this conditional distribution to impute the missing data.

6.3.2 Pattern Mixture Model

Subjects will be assigned one of the following three patterns:

1. Completer: subjects with no missing data at Week 26, 50 and 78
2. Subjects who withdrew due to reasons that may be related to efficacy, including consent withdrawn, withdrawal by parent/guardian, investigator decision, loss of capacity, change of treatment, and disease progression;
3. All the other subjects with missing data.

The dataset will first be imputed to monotone missing using PROC MI with the MCMC and impute=monotone option. Imputation will be carried out 1000 times and any internal missing observations, including missing baseline covariates and intermediate missing in the response variable will be replaced with the average across all imputations.

For the resulted data with monotone missing, the following steps will be used to create imputed datasets:

(1) Subset subjects in pattern 1 and pattern 2, and impute the missing data using the copy increment from reference method described in Section 6.3.1.
(2) Subset subjects in pattern 1 and pattern 3, and impute the missing data using PROC MI with the MONOTONE REG option.
(3) Combined datasets obtained in steps (1) and (2).

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ENGAGE

221AD302

Statistical Analysis Plan

Long-Term Extension Period

STATISTICAL ANALYSIS PLAN
Long-Term Extension Period

Product Studied: Aducanumab
Protocol Number: 221AD302

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

Protocol Version: Version 6.0
Date of Protocol: 28 Jun 2018

Date of Statistical Analysis Plan: 11 Sep 2018, Final V1.0

Written By:

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SMT Statistician, [redacted] PhD — 12 Sep 2018 Date

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Table of Contents

List of Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
ApoE ε4	apolipoprotein E4
ApoE ε4+	apolipoprotein E4 carrier
ApoE ε4-	apolipoprotein E4 non-carrier
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
[redacted]	[redacted]
AST	aspartate aminotransferase
BL	baseline
BLQ	below the limit of quantification
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
[redacted]	[redacted]
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CIR	copy increment from reference
C_{max}	observed maximum serum aducanumab concentration
C_{min}	observed minimum serum aducanumab concentration
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAT	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	EuroQol health status measure
[redacted]	[redacted]
EQ-5D (IR-S)	EuroQol health status measure, informant reported on subject
EQ-5D (SR)	EuroQol health status measure, subject self-reported

FU	Follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HCP	health care professional
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDH	lactate dehydrogenase
LMCI	late mild cognitive impairment
LTE	long-term extension
LOCF	last observation carried forward
MCI	mild cognitive impairment
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI-10	Neuropsychiatric Inventory-10
PCS	potentially clinically significant
PET	positron emission tomography
pH	potential of hydrogen
PI	Principal Investigator
PK	pharmacokinetic(s)
PMM	pattern mixture model
PP	per-protocol
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
SUVR	standard uptake value ratio
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1 DESCRIPTION OF LONG-TERM EXTENSION (LTE) OBJECTIVES AND ENDPOINTS

1.1 Tertiary LTE Objectives

- To evaluate the long-term safety and tolerability profile of aducanumab in subjects with early Alzheimer's Disease (AD).
- To evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health outcomes assessments.

1.2 Tertiary LTE Endpoints

- The incidence of adverse events (AEs) and serious adverse events (SAEs); brain magnetic resonance imaging (MRI) findings (including the incidence of amyloid related imaging abnormality-edema [ARIA-E] and amyloid related imaging abnormality-hemorrhage or superficial siderosis [ARIA-H]); and the incidence of anti-aducanumab antibodies in serum over the placebo-controlled and LTE periods of the study.
- Change in the following measures over the placebo-controlled and LTE periods of the study:
  - Clinical Dementia Rating sum of boxes (CDR-SB) score.
  - Mini-Mental State Examination (MMSE) score.
  - Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13 score].
  - Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI score].
  - Amyloid positron emission tomography (PET) signal (in a subset of sites and subjects).
  - Neuropsychiatric Inventory-10 (NPI-10) total scores.
  - Informant-rated EuroQol health status measures (EQ-5D) index score.

1.3 Additional Exploratory LTE Objective

- [redacted]

1.4 Additional Exploratory LTE Endpoints

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

2 STUDY DESIGN

2.1 Study Overview

Study 221AD302 (EMERGE) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with early AD, including mild cognitive impairment (MCI) due to AD and a subset of mild AD, followed by an optional dose-blinded long-term extension (LTE) period of up to 5 years. Approximately 1605 subjects will be enrolled across approximately 150 centers globally. The primary study objective is to evaluate the efficacy of monthly doses of aducanumab on the CDR-SB relative to placebo. Secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical progression as compared to placebo. The safety of monthly doses of aducanumab will also be evaluated. The objectives of LTE are to evaluate the long-term safety and tolerability profile of aducanumab in subjects with early AD, and to evaluate the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health-outcomes assessments.

Subjects will be randomized in a 1:1:1 ratio to 1 of the 3 treatment groups: aducanumab high dose, aducanumab low dose and placebo, with stratification based upon their apolipoprotein E4 (ApoE ε4) carrier status (carrier/non-carrier) and site. During the placebo-controlled period, subjects will receive infusions of aducanumab or placebo approximately every 4 weeks for approximately 18 months (a total of 20 doses). Dose levels may be different in the same treatment group based upon subjects' ApoE ε4 carrier status, and specifically, ApoE ε4 carriers will receive placebo, aducanumab 3 mg/kg, or aducanumab 10 mg/kg whereas ApoE ε4 non-carriers will receive placebo, aducanumab 6 mg/kg, or aducanumab 10 mg/kg. Aducanumab will be titrated for up to 6 doses prior to reaching the target dose as shown in

Table 1 and Figure 1. Note: As of Protocol Version 4, 10 mg/kg is the target dose for all ApoE ε4 carriers in the high-dose group. ApoE ε4 carriers who were randomized to the high dose group when the target dose was 6 mg/kg (under protocol versions prior to Version 4) must have received 2 or more doses at 6 mg/kg prior to being titrated up to 10 mg/kg.

Table 1: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status: Placebo-controlled Period

Dose (every 4 weeks)		1	2	3	4	5	6	7 to 20
Treatment Group	Treatment Group Stratified by ApoE Status[2]	Dose (mg/kg)						
High Dose	High Dose - ApoE ε4 (+)	1	1	3	3	6	6	10[1]
	High Dose - ApoE ε4 (-)	1	1	3	3	6	6	10
Low Dose	Low Dose - ApoE ε4 (+)	1	1	3	3	3	3	3
	Low Dose - ApoE ε4 (-)	1	1	3	3	3	3	6
Placebo	Placebo - ApoE ε4 (+)	saline						
	Placebo - ApoE ε4 (-)	saline						

[1] 10 mg/kg is the target dose for all ApoE ε4 carriers assigned to the aducanumab high-dose group. Subjects enrolled under protocol versions 1-3 and assigned to the previous high-dose of 6 mg/kg will be titrated to 10 mg/kg upon receipt of at least 2 doses at 6 mg/kg.

[2] ApoE ε4 status recorded in the Interactive Voice/Web Response System (IXRS).

At the end of the double-blind, placebo-controlled treatment period, subjects who meet the extension entry criteria may enter a long-term safety and efficacy extension period, with all subjects receiving aducanumab approximately every 4 weeks (up to a total of 65 doses over 5 years). The treatment group for the LTE period will be assigned at the same time as the randomization for the placebo-controlled period, regardless of whether a subject entering the LTE period or not. Subjects who are assigned to the placebo group during the placebo-controlled period will be assigned to 1 of 2 active treatment groups in a 1:1 ratio (aducanumab low dose: aducanumab high dose) and randomization will be stratified by their ApoE ε4 carrier status; for those who enter the LTE period, aducanumab will be titrated for up to 6 doses prior to reaching the target dose following the same schedule described for the placebo-controlled period. Subjects who are assigned to either aducanumab low dose or aducanumab high dose group in the placebo-controlled period will continue in the same treatment group for the LTE period; those who enter the LTE period will maintain the dosing scheme outlined in the protocol at the time of transition from the placebo-controlled period to the LTE period (e.g. subjects who are on stable dosing in the placebo-controlled period will continue on the same dose, subjects who are on a titration regimen during the transition will continue to titrate into the LTE period, and ApoE ε4 carrier subjects who are enrolled in the LTE and randomized to the high-dose group prior to implementation of version 4 of the protocol will be allowed to titrate to 10 mg/kg). Aducanumab will be titrated for up to 6 doses prior to reaching the target dose for the late start subjects as shown in Table 2 and Figure 1.

Table 2: Dosing Scheme for Aducanumab by Treatment Group and ApoE ε4 Carrier Status: Long-Term Extension Period

Doses (every 4 weeks)		1	2	3	4	5	6	7-EOS
LTE Treatment Group	LTE Treatment Group Stratified by ApoE Status[1]	Dose (mg/kg)						
Early Start High Dose	Early Start High Dose – ApoE ε4 (+)	10						
	Early Start High Dose – ApoE ε4 (-)	10						
Early Start Low Dose	Early Start Low Dose – ApoE ε4 (+)	3						
	Early Start Low Dose – ApoE ε4 (-)	6						
Late Start High Dose	Late Start High Dose – ApoE ε4 (+)	1	1	3	3	6	6	10
	Late Start High Dose – ApoE ε4 (-)	1	1	3	3	6	6	10
Late Start Low Dose	Late Start Low Dose – ApoE ε4 (+)	1	1	3				
	Late Start Low Dose – ApoE ε4 (-)	1	1	3	3	3	3	6

[1] ApoE ε4 status recorded in the Interactive Voice/Web Response System (IXRS).

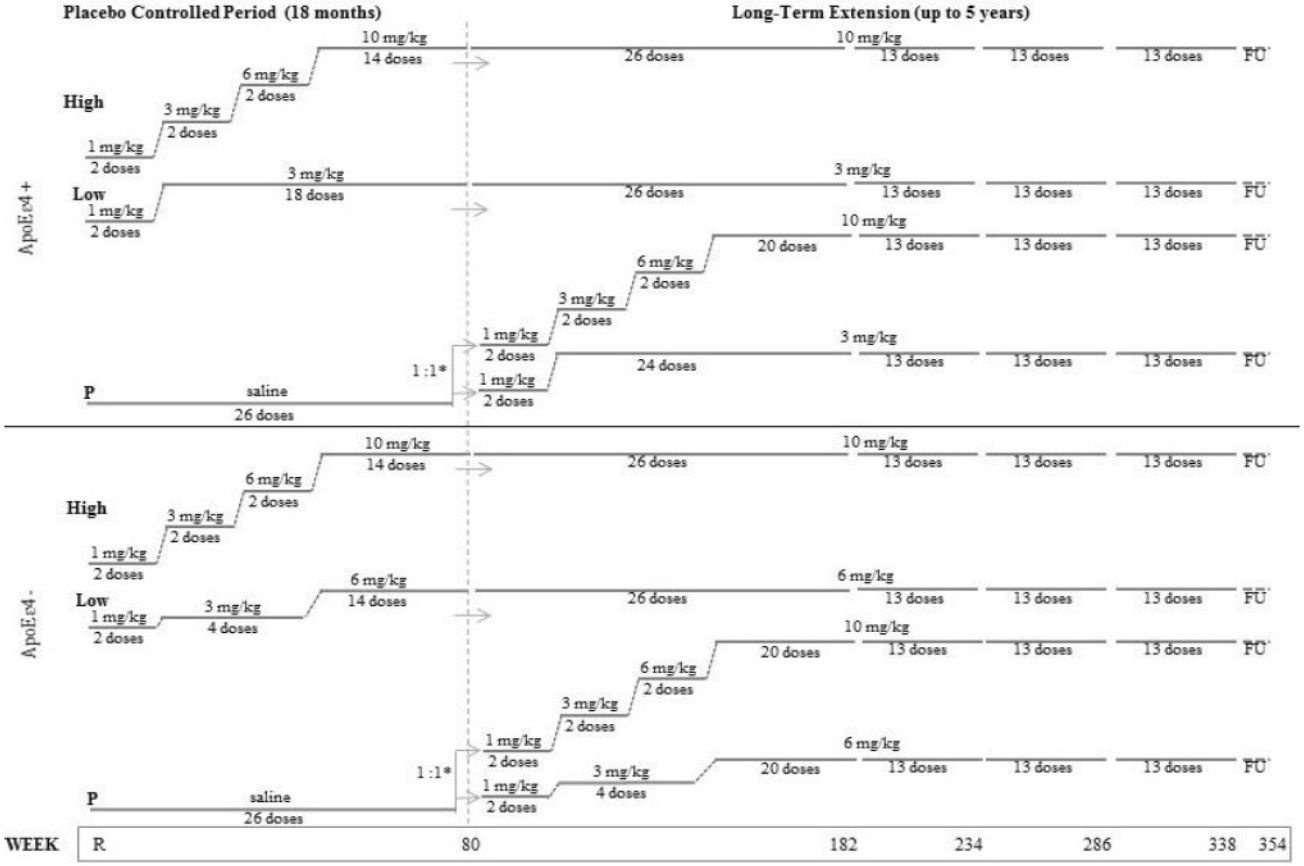
Individual dose adjustments may be implemented in subjects who develop amyloid related imaging abnormalities (ARIA). See Protocol Section 7.2.1.

The total duration of study participation for each subject only participating in the placebo-controlled period of the study will be up to approximately 102 weeks, including a series of screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up (FU) period of approximately 18 weeks after the final dose. The total duration of study participation for each subject participating in the placebo-controlled period and the LTE period will vary and be up to approximately 362 weeks, including a series of Screening visits within 8 weeks before administration of the first dose, a 76-week placebo-controlled treatment period, a 4-week FU period, a 256-week aducanumab dose-blind treatment period, and a safety FU period of approximately 18 weeks after the final dose.

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

2.2 Study Schematic

Figure 1: Study Design



ApoE ε4 +/- = apolipoprotein E4 positive/negative; FU = follow-up; P = placebo; R = randomization date.
*Subjects who are assigned to placebo during the placebo-controlled period are randomized in a 1:1 ratio to high and low dose aducanumab treatment (stratified by their ApoE ε4 carrier status) for the long-term extension period on Study Day 1.

2.3 Schedule of Events for LTE period

See protocol section 4.2.

3 STATISTICAL ANALYSIS METHODS

3.1 General Considerations

This statistical analysis plan (SAP) covers the analyses of the LTE period and the analyses across both the placebo-controlled period and the LTE period.

Summary tables will be presented using descriptive summary statistics. For continuous variables, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum and maximum. For categorical variables, this will generally include: number of subjects randomized or dosed, number with data, and the percent of those with data in each category.

There are two types of analysis displays for the analyses of the LTE period: by LTE treatment group (analysis display A in Appendix 4.1) and by LTE treatment group stratified by ApoE status (analysis display B in Appendix 4.1; here ApoE status refers to the status recorded in IXRS [see Table 2 for correspondence between LTE treatment groups and LTE treatment groups stratified by ApoE status]). The analysis display for each analysis will be defined in each section. All the listings will be presented by LTE treatment group stratified by ApoE status, unless otherwise specified.

Unless otherwise specified, baseline refers to the baseline value for the placebo-controlled period and is defined as the most recent non-missing measurement collected prior to the first dose. Change from baseline will be defined as post-baseline value minus baseline value.

Unless stated otherwise, all statistical tests will be 2-sided with statistical significance level of 0.05.

The statistical software, SAS® will be used for all summaries and analyses.

3.1.1 Analysis Population

- Intent-to-treat (ITT) population:
  The Intent-to-treat population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo).

- ^{18}F-florbetapir amyloid PET analysis population:
  The ^{18}F-florbetapir amyloid PET analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo), used ^{18}F-florbetapir ligand for amyloid PET scan, and had an evaluable baseline amyloid PET SUVR value for the composite region-of-interest using cerebellum as the reference region.

- ^{18}F-flutemetamol amyloid PET analysis population:

The ^{18}F-flutemetamol amyloid PET analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo), used ^{18}F-flutemetamol ligand for amyloid PET scan, and had an evaluable baseline amyloid PET SUVR value for the composite region-of-interest using cerebellum as the reference region.

- Safety population:
  The safety population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo). It is the same population as the ITT population.

- Safety MRI population:
  The safety MRI population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one post-baseline MRI assessment.

- PK analysis population:
  The PK analysis population is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one measurable aducanumab concentration in serum.

- Immunogenicity population:
  The analysis population for immunogenicity is defined as all randomized subjects who received at least one dose of study treatment (aducanumab or placebo) and had at least one post-dose sample evaluated for immunogenicity.

3.1.2 Analyses period

Depending on the purpose, different analyses will be conducted on the following study periods:

1. LTE period. Only data in the LTE period will be included in these analyses. For example, incidence table of adverse events in the LTE period.
2. Placebo-controlled and LTE period. All the data in the placebo-controlled and LTE periods will be included in these analyses. For example, mean plot of actual laboratory values in the placebo-controlled and LTE period.
3. Placebo-controlled and LTE active treatment period. Active treatment period is defined as the study period(s) that a subject is assigned to aducanumab. For early start subjects – subjects who are assigned to aducanumab in both placebo-controlled and LTE period, all the data (placebo-controlled and LTE periods) will be included in the analyses. For late start subjects – subjects who are assigned to aducanumab in the LTE period, only data in the LTE period will be included. For example, incidence table of adverse events in the placebo-controlled and LTE active treatment period.

Subjects to be included in a certain output is determined by both the analysis population and the analysis period. For example, the incidence table of adverse events in the LTE period will include subjects in the safety population for the LTE period, i.e., all randomized subjects who received at least one dose of study treatment in the LTE period. The incidence table of adverse events in the placebo-controlled and LTE active treatment period will include subjects in the safety population for the active treatment period, i.e., all randomized subjects who received at least one dose of study treatment in the active treatment period. In this SAP we do not separately define the analysis population in each analysis period.

3.2 Background Characteristics

The summaries in this section will be based on the ITT population. Analysis period will be specified for each table or figure. Unless otherwise specified, summary tables will be presented by LTE treatment group and by LTE treatment group stratified by ApoE status (see Table 2 for correspondence between LTE treatment groups and LTE treatment groups stratified by ApoE status). Listings will include all data in the placebo-controlled and LTE periods (all data in the study), with an indicator of the study period (pre-dosing, placebo-controlled, or LTE) for each record to indicate when the event occurred. Listings will be presented by LTE treatment group stratified by ApoE status.

3.2.1 Accounting of Subject

Disposition in the LTE period will be summarized for subjects enrolled in LTE. The summary data will include number (%) of subjects dosed in the LTE period, number (%) of subjects who completed the treatment/study in LTE, and number (%) of subjects who discontinued treatment and/or withdrew from study in LTE. For subjects who discontinued treatment and/or withdrew from study, the reasons for discontinuation and/or withdrawal, days on treatment and days on study will be summarized and listed. Time to treatment discontinuation and time to study withdrawal in the LTE period will be displayed by Kaplan-Meier plot (presented by LTE treatment group).

3.2.2 Demographics and Baseline Characteristics

Demographics, baseline characteristics, medical history and AD treatment history will be summarized for subjects enrolled in the LTE period and subjects not enrolled in the LTE period, respectively. Demographics and baseline characteristics will also be summarized for all ITT subjects (presented by LTE treatment group). Please refer to the SAP for the placebo-controlled period for more details.

3.2.3 Concomitant Medications and Non-Drug Therapies

The number (%) of subjects taking concomitant medication and non-drug therapies in the LTE period will be summarized. Non-drug therapies will be presented by LTE treatment group. In addition, number of subjects in the ITT population that have taken any concomitant medications in the placebo-controlled and LTE active treatment period will be summarized. Concomitant medications and non-drug therapies will be listed.

For subjects enrolled in the LTE period, the number (%) of subjects taking concomitant AD symptomatic medications, number of subjects using Cholinesterase inhibitors only, Memantine only, or both at the baseline of the placebo-controlled period will be summarized. A similar summary will be provided for subjects taking AD symptomatic medication concomitantly at the baseline of the LTE period. Subjects who have any change in AD symptomatic medications during the LTE period will be summarized by the timing of change, i.e., the number of subjects changing between Week 80 and Week 106, the number of subjects changing between Week 106 and Week 134, etc. The summary for AD symptomatic medication use during the LTE period will be presented by LTE treatment group. The start and stop date of AD symptomatic medication will be listed for subjects who have any change to AD symptomatic medications during the combined placebo-controlled and LTE periods. Please refer to the placebo-controlled SAP for definitions of concomitant therapies and AD symptomatic medication use at baseline.

3.2.4 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a Protocol Deviation log and categorized as major or minor deviations based on Protocol Deviation Classification (see Appendix of the placebo-controlled SAP). The major protocol deviations occurred in the LTE period will be summarized for subjects enrolled in LTE. The major protocol deviations for all ITT subjects in the combined placebo-controlled and LTE periods will also be summarized. Major and minor protocol deviations for all ITT subjects will be listed, respectively, across the placebo-controlled period and the LTE period. All summaries for protocol deviations will be presented by LTE treatment group.

3.2.5 Study Drug Exposure and Study Drug Compliance

A summary table of study drug exposure and compliance in the LTE period will be provided. Number of infusions (aducanumab or placebo) received will be summarized as a categorical variable (categories of 1-5, 6-10, 11-15, 16-20, 21-26, 27-39, 40-52 and 53-65) as well as a continuous variable. Number of weeks on study treatment (aducanumab or placebo), calculated as (date of last dose – date of first dose +29)/7, will be summarized as a categorical variable (every 6 months for the first 2 years of LTE, and then every year) as well as a continuous variable. Percentage of study treatment taken up to the last dose, calculated as (the actual number of infusions / by the number of infusions a subject is expected to take until the date of last infusion)*100, will be summarized as a continuous variable. This table will be presented by LTE treatment group. A similar table will also be provided on the placebo-controlled and LTE active treatment period in order to summarize the exposure data while subjects are on aducanumab.

Due to the use of titration regimen in the study and possible dose reduction due to ARIA, another summary table will be provided including the following information in the LTE period: number of total infusions (categories of 1-5, 6-10, 11-15, 16-20, 21-26, 27-39, 40-52 and 53-65) as well as a continuous variable, number of infusions at each dose level (1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg, respectively) summarized as a categorical variable as well as a continuous variable, number of subjects with dose increase (placebo to 1 mg/kg, 1 to 3 mg/kg, 3 to 6 mg/kg and 6 to 10 mg/kg, respectively), number of subjects with dose reduction (1 mg/kg to placebo, 3 to 1 mg/kg, 6 to 3 mg/kg and 10 to 6 mg/kg, respectively), maximum

dose level received, and cumulative dose (as a continuous variable). This table will be summarized by LTE treatment group stratified by ApoE status. A similar table will also be provided on the placebo-controlled and LTE active treatment period in order to summarize the titration and dose reduction data while subjects are on aducanumab.

A listing of study drug administration records, including dose level at each infusion, cumulative number of infusions and cumulative dose will be provided for the placebo-controlled and LTE period. A listing of aducanumab lot numbers will be provided for the placebo-controlled and LTE period.

3.3 Efficacy Analysis

3.3.1 General Considerations

The analysis population for efficacy analysis is the same as the ITT population and data from both the placebo-controlled and LTE periods will be included. All efficacy analyses will be presented by LTE treatment group, i.e, late start low dose, late start high dose, early start low dose, early start high dose (analysis display A in Appendix 4.1).

The following two comparisons will be evaluated for the long-term efficacy of aducanumab:

- The early start low dose compared with the late start low dose;
- The early start high dose compared with the late start high dose.

There will be no multiple comparison adjustments.

Visit windows for mapping efficacy endpoint

For efficacy data that are summarized or analyzed by visit, data collected on all scheduled visits and all unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Table 3. If there are 2 or more assessments available in the same analysis window for a subject, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments in the same analysis window with the same distance from the target visit day, the later assessment will be used.

Table 3: Visit Windows for Efficacy Endpoints

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 26	183	[92, 266]
Week 50	351	[267, 448]
Week 78	547	[449, the end day of the placebo-controlled period*]
Week 106	743	[645, 840]
Week 134	939	[841, 1036]
Week 162	1135	[1037, 1204]

Analysis visit	Target visit day	Analysis visit window
Week 182	1275	[1205, 1365]
Week 232	1625	[1535, 1715]
Week 284	1989	[1899, 2079]
Week 338	2367	≥ 2277
* The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, and is the last day in study for subjects who do not enter LTE.		

Handling of missing items for scales

Please refer to the placebo-controlled SAP for the imputation method. Same method will be applied to efficacy endpoints collected in the LTE period.

3.3.2 By Visit Summary and MMRM Model

The baseline and change from baseline CDR-SB scores at each post-baseline visit will be summarized by LTE treatment group. A mixed model repeated measures (MMRM) model will be used to analyze change from baseline CDR-SB using fixed effects of LTE treatment group, time (categorical), LTE treatment group-by-time interaction, baseline CDR-SB, baseline CDR-SB by time interaction, baseline MMSE, AD symptomatic medication use at baseline (yes/no), region, and laboratory ApoE ε4 status (carrier/non-carrier). An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Visits with too few data may be excluded from the MMRM analysis and be analyzed by ANCOVA instead.

The by visit summary and MMRM analysis will be similarly performed for CDR cognitive subscore, CDR functional subscore, MMSE, ADAS-Cog 13, ADCS-ADL-MCI and NPI-10. Only the by visit summary will be performed for CDR box scores and informant-rated EQ-5D. The distribution of CDR global score will be summarized as a categorical variable at each post-baseline visit.

3.4 Amyloid PET analysis

3.4.1 Amyloid PET substudy

Please refer to the placebo-controlled SAP.

3.4.2 Amyloid PET regions-of-interest and reference regions

Please refer to the placebo-controlled SAP.

3.4.3 Amyloid PET Analysis Population

Please refer to the placebo-controlled SAP.

3.4.4 By Visit Summary and MMRM Model

All the analyses will be presented by LTE treatment group (early start low dose, early start high dose, late start low dose, late start high dose). The following two comparisons will be evaluated for amyloid PET SUVR in the LTE period:

- The early start low dose compared with the late start low dose;
- The early start high dose compared with the late start high dose.

The baseline and change from baseline amyloid PET SUVR values will be summarized by LTE treatment groups by visit for all the visits in the placebo-controlled and LTE period for each of the target ROIs using cerebellum as the reference region for each of the amyloid PET analysis populations. In addition, the baseline and change from baseline amyloid composite ROI values will be summarized by LTE treatment groups by visit for each reference regions for each of the amyloid PET analysis populations.

For the ^{18}F-florbetapir amyloid PET analysis population, an MMRM model will be used to analyze change from baseline SUVR for each target ROI with cerebellum as the reference region for all the visits in the placebo-controlled and LTE period. Fixed effects of the model will include LTE treatment groups, visit, treatment group-by-visit interaction, baseline SUVR (continuous), baseline SUVR by visit interaction, baseline MMSE (continuous), laboratory ApoE ε4 status (carrier and non-carrier), and baseline age (continuous). Visit and treatment group will be treated as categorical variables in the model along with their interactions. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence in any of the parameters, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be used for all the parameters. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Adjusted means for each treatment group, pairwise adjusted differences for the comparisons, 95% confidence intervals for the differences and associated p-values will be presented at each visit. Visits with too few data may be excluded from the MMRM analysis and be analyzed by ANCOVA instead. The same MMRM model will also be used to analyze the change from baseline SUVR for the composite ROI with each of the reference regions. No multiple comparison adjustment will be used for amyloid PET analysis.

Visit Windows for by visit analyses

For amyloid PET by visit summaries and MMRM models, the analysis visit should be defined using visit windows (see Table 4 below). The rationale is to use the same analysis visit windows as for the efficacy endpoints for the visits that the efficacy endpoints are also collected. Since the visit for the efficacy measurements is on Week 134, while the visit for amyloid PET measurements is on Week 132, the start of the analysis visit window for Week 132 amyloid PET is 2 weeks earlier than that for efficacy, while the same end of the analysis visit window as Week 134 is used to be conservative. If there is more than 1 value in the same analysis visit window (>1 value for the same analysis visit) for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If they are with the same distance from the target visit day, then the record with the later time will be used for the by visit analysis.

Table 4. Visit Windows for amyloid PET data

Analysis visit *	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value
Week 26	183	[92, 266]
Week 78	547	[449, the end day of the placebo-controlled period[1]]
Week 132	925	[827, 1036]
Week 182	1275	[1205, 1365]
Week 260	1821	[1731, 1911]
Week 338	2367	≥ 2277

* Analysis visit is the visit at which the specific week started.
1. The end day of the placebo-controlled period is the last day before the first infusion in LTE, and is the last day in study for subjects who do not enter LTE.
2. The start day of the LTE period is the day of first infusion in LTE period.

3.5 Safety Analyses

3.5.1 General Considerations

Analysis population

Safety population will be used for safety analyses of AEs, clinical laboratory data, Columbia Suicide Severity Rating Scale (C-SSRS) data, ECG data and vital sign data (all the safety data except for ARIA data). Safety MRI population will be used for analyses of ARIA data.

LTE safety treatment groups

Since all the subjects are supposed to receive active treatment in LTE, the LTE safety treatment groups which are exactly the same as the LTE randomization treatment groups will be used for all the safety analyses. Subjects who were randomized to placebo group but accidentally received one or more doses of the active treatment during the placebo-controlled period will still be classified as late start for all the safety analyses that involves LTE, but their applicable safety data in the placebo-controlled period will be included in the analysis for placebo-controlled and LTE active treatment period.

Safety analysis period

Analysis period will be specified for each output. Safety data in the specified analysis period will be included in the analysis. Listings will include all data in the placebo-controlled and LTE period, unless otherwise specified.

Safety analysis displays

For either analysis period in this SAP (LTE period, placebo-controlled and LTE period, or placebo-controlled and LTE active treatment period), AEs, clinical laboratory data, C-SSRS data, ECG data and vital sign data (all the safety data except for ARIA data) will be summarized by LTE treatment group (late start low dose, late start high dose, early start low dose, early start high dose, and in addition late start total, early start total and BIIB037 total; analysis display A in Appendix 4.1), unless otherwise specified. ARIA tables will be presented by LTE treatment group stratified by ApoE status (3 columns under each of the 4 LTE treatment groups: ApoE ε4+, ApoE ε4- and total, and in addition late start total and early start total; analysis display B in Appendix 4.1), unless otherwise specified. A subset of AE tables will also be presented by LTE treatment group stratified by ApoE status in addition to by LTE treatment group. Listings will be presented by LTE treatment group stratified by ApoE status, with an indicator of the study period (pre-dosing, placebo-controlled, or LTE) for each record when the event/assessment occurred.

LTE baseline for late start subjects

Placebo-controlled baseline is defined as the last non-missing measurement collected prior to the first dose (the baseline used for placebo-controlled period analyses). LTE baseline is defined as the last non-missing measurement collected prior to the first dose of the LTE period. For analyses on the LTE period or on the placebo-controlled and LTE active treatment period, LTE baseline will be used for late start subjects who are assigned to receiving aducanumab in the LTE period. Study day and analysis visit window for analyses using LTE baseline will be derived based on the first day of study drug in LTE.

Incidence, incidence proportion and incidence rate

- Incidence and incidence proportion will be provided in incidence tables. Incidence is defined as the number of subjects who experienced an event. Incidence proportion is defined as the number of subjects who experienced an event divided by the total number of subjects in the analysis population, i.e., percentage. Each subject will be counted only once within each category.

- Incidence and incidence rate will be provided in incidence rate tables. Two different kinds of incidence rate tables will be provided as appropriate for different analyses. Definitions are provided below.

(1) Follow-up adjusted incidence rate – defined as the number of subjects who experienced an event divided by the total of entire follow-up time among the subjects in the analysis population. The entire follow-up time for a subject is defined as the time from the first dose until the last day on study. Each subject will be counted only once within each category.
(2) Exposure-adjusted incidence rate (EAIR) – defined as the number of subjects who experience an event divided by the total exposure adjusted follow-up time among the subjects in the analysis population. The exposure adjusted follow-up time is defined as the time from the first dose until the initial occurrence of the event for those who experienced an event, or from the first dose until the end of follow-up (the last day on study) for those who did not. Each subject will be counted only once within each category.

3.5.2 Clinical Adverse Events

Treatment-emergent AEs (TEAEs)

All AEs will be analyzed based on the principle of treatment emergence. A treatment-emergent AE was defined as an AE that started or worsened after the start of first infusion of study treatment.

To define treatment emergence for AEs with missing start or stop date or time the following additional criteria will be used:

- if both the start and stop dates for a particular AE are missing, then that AE is considered treatment emergent;
- if the start date for a particular AE is missing and the stop date/time falls after the first dose date/time, then that AE is considered treatment emergent;
- if the start date for a particular AE was the same as the first dose date, and the start time was missing, then that event is considered treatment emergent.

For AEs with a partial start date, the year/month of the event date will be compared to that of the first dosing date to determine whether the event is treatment emergent.

In addition, SAEs that occurred since a subject was screened in the study and prior to the first infusion of study treatment, which by definition are not treatment-emergent, will be analyzed separately.

Only TEAEs will be included in the AE tables, unless otherwise specified. Listings of AEs will include all events, whether treatment-emergent or not.

As specified in the protocol, subjects were expected to return to the study site for an End of Study visit 18 weeks after the last administration of study treatment. However, some subjects may elect to continue study participation on a modified schedule after discontinuing treatment, possibly in substantial excess of 18 weeks. For most general AE summaries, AEs with an onset more than 18 weeks after the last dose will be excluded (will specify in the footnote of the specific table). For incidence rate analyses excluding AEs more than 18 weeks after the last dose, the "last day on study" in follow-up time calculation will be replaced with

"18 weeks after last dose or last day on study, whichever earlier". Summaries of deaths and AEs leading to study withdrawal, and other selected analyses will include all AEs regardless of the time since the last dose. Listings will include all AEs, unless otherwise specified.

3.5.2.1 Summary and incidence analysis

Overall summary of AE table will be done for the LTE period, as well as for the placebo-controlled and LTE active treatment period presented by LTE treatment group as well as LTE treatment group stratified by ApoE status. The following information will be summarized: the number of subjects with any AE, with any AE by maximum severity, the number of subjects with any related AE (related to study drug as assessed by investigator), the number of subjects with SAE, the number of subjects with related SAE, the number of subjects with AE leading to study drug discontinuation, the number of subjects with AE leading to study withdrawal, and the number of deaths.

The sorting order of AE incidence tables, unless otherwise specified, will be by decreasing frequency order of "BIIB037 total" column within each category in the tables presented by LTE treatment group, and by decreasing frequency order of "BIIB037 early start total" column within each category in the tables presented by LTE treatment group stratified by ApoE status. A subject is counted only once within each category in each table. For example, for the table of AEs by system organ class and preferred terms sorted by decreasing frequency presented by LTE treatment group, system organ class will be presented in decreasing frequency order of BIIB037 total column, and within each system organ class, preferred terms will be presented in decreasing frequency order of BIIB037 total column. A subject is counted only once within each system organ class and preferred term.

The following AE incidence tables will be provided for the LTE period (presented both by LTE treatment group and by LTE treatment group stratified by ApoE status, unless otherwise specified):

1. AEs by system organ class and preferred term sorted by decreasing frequency
2. AEs by system organ class and preferred term sorted by alphabetical order analysis (by LTE treatment group)
3. AEs by system organ class, high level group term and preferred term (by LTE treatment group)
4. AEs by system organ class (by LTE treatment group)
5. AEs by preferred term
6. AEs with an incidence of 5% or more in any treatment group by preferred term
7. Severe AEs by system organ class and preferred term
8. Severe AEs by preferred term (by LTE treatment group)
9. AEs by maximum severity by system organ class and preferred term (by LTE treatment group) (System organ class will be presented alphabetically. Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, unknown and total.

A subject will be counted only once at the maximum severity within each system organ class and preferred term.)

10. AEs by maximum severity by preferred term (by LTE treatment group) (Preferred terms will be presented in decreasing frequency order. Maximum severity will be presented within each preferred term in the order of mild, moderate, severe, unknown and total. A subject will be counted only once at the maximum severity within each preferred term.)
11. Related AEs by system organ class and preferred term
12. SAEs by system organ class and preferred term
13. SAEs by preferred term
14. Related SAEs by system organ class and preferred term
15. AEs that led to discontinuation of study treatment by system organ class and preferred term
16. AEs that led to withdrawal from study by system organ class and preferred term
17. SAEs with fatal outcome by system organ class and preferred term
18. AEs that occurred within 2 hours from infusion start by system organ class and preferred term (by LTE treatment group)

The following listings will be provided for the placebo-controlled and LTE period:

1. Listing of AEs
2. Listing of SAEs
3. Listing of AEs that led to discontinuation of study treatment
4. Listing of AEs that led to withdrawal from study
5. Listing of AEs that occurred within 2 hours from infusion start
6. Listing of AEs related to PET ligands
7. Listing of SAEs with fatal outcome
8. Listing of AEs for subjects with treatment-emergent positive anti-BIIB037 antibody

3.5.2.2 Incidence and incidence rate analysis for placebo-controlled and LTE active treatment period

Due to the different length of placebo-controlled and LTE active treatment period in early start versus late start subjects, both incidence tables and follow-up adjusted incidence rate tables will be used for AE analyses in this period. The entire follow-up time is from the first dose in active treatment period (first dose in placebo-controlled period for early start subjects and first dose in LTE period for late start subjects) until the last day in the study.

The following incidence and follow-up adjusted incidence rate tables will be provided for the placebo-controlled and LTE active treatment period (presented both by LTE treatment group and by LTE treatment group stratified by ApoE status, unless otherwise specified):

1. AEs by system organ class and preferred term sorted by decreasing frequency
2. AEs by system organ class, high level group term and preferred term (by LTE treatment group)
3. AEs by preferred term
4. Severe AEs by system organ class and preferred term (by LTE treatment group)
5. Severe AEs by preferred term
6. Related AEs by system organ class and preferred term
7. SAEs by system organ class and preferred term
8. SAEs by preferred term
9. Related SAEs by system organ class and preferred term

3.5.3 ARIA - AE of Special Interest

3.5.3.1 Background

Please refer to the placebo-controlled SAP for details.

3.5.3.2 Incidence and summary of ARIA

Incidence of ARIA-E, ARIA-H, ARIA-E and ARIA-H (not necessarily concurrent), concurrent ARIA-E and ARIA-H, ARIA-E or ARIA-H, isolated ARIA-H (only ARIA-H, no ARIA-E), ARIA-H microhemorrhage, ARIA-H macrohemorrhage and ARIA-H superficial siderosis in the LTE period and in the placebo-controlled and LTE active treatment period will be summarized based on both AE eCRF and MRI data. If there is any discrepancy in incidence between the two data sources, a listing of the subjects and ARIA events with discrepancy will be provided. In addition, the incidence table based on AE eCRF source will also be done by LTE treatment group (analysis display A in Appendix 4.1).

Number of subjects with each type of ARIA, maximum severity and worst symptomatic status of the type of ARIA being analyzed in the LTE period and in the placebo-controlled and LTE active treatment period will be summarized based on AE eCRF. For subjects with symptomatic ARIA, the maximum severity of symptoms will also be summarized.

Summary of concurrent ARIA-E and ARIA-H will be provided including the following information for the LTE period and for the placebo-controlled and LTE active treatment period: number of subjects with concurrent ARIA-E and ARIA-H (and further broken down to each type of ARIA-H), the severity of ARIA-E based on MRI, the symptomatic status of ARIA-E, the severity of symptoms based on AE eCRF. For subjects with recurrent ARIA-E

events, if there is an event concurrent with ARIA-H, it will be used for the summary, and the first concurrent event will be used if there are more than one event concurrent with ARIA-H.

An incidence table of AEs considered by the investigator to be related to ARIA by system organ class and preferred term for subjects with symptomatic ARIA in the placebo-controlled and LTE active treatment period will be provided, as well as a listing of these AEs. Similarly, an incidence table of AEs related to ARIA for subjects with symptomatic ARIA and severe symptoms will be provided, as well as a listing of these AEs.

Listings of AE records for each type of ARIA events and listings of MRI assessments for subjects with each type of ARIA events will be provided.

Montreal Cognitive Assessment (MOCA) is performed at baseline, Week 80 (the first visit in LTE) and each unscheduled ARIA monitoring visit for ARIA subjects (approximately every 4 weeks) except for mild asymptomatic microhemorrhage subjects. An incidence table of late start subjects with ARIA events only in the LTE period (no ARIA in the placebo-controlled period) whose MOCA total scores decrease 2 points or more from Week 80 will be provided. Since Week 80 MOCA was not a planned study event until protocol version 4, some subjects may not have a Week 80 MOCA score. For these subjects, their Week 80 MOCA will be imputed as their baseline MOCA plus the mean change from baseline at Week 80 from subjects who have a Week 80 MOCA and did not experience any ARIA in the placebo-controlled period within each treatment group and ApoE status. A listing of MRI assessments and MOCA total score for subjects with ARIA events in either placebo-controlled or LTE period will be provided.

3.5.3.3 Summary of recurrent ARIA-E

Follow-up adjusted incidence rate of subjects with ARIA-E, with 2 or more events of ARIA-E, with 3 or more events of ARIA-E and with more than 3 events of ARIA-E over their entire follow-up time for the placebo-controlled and LTE active treatment period will be summarized based on AE eCRF.

Number of total ARIA-E events in the placebo-controlled and LTE active period and the MRI severity of each event will be summarized based on AE eCRF. Number of symptomatic ARIA-E events in the placebo-controlled and LTE active period, and the severity of the symptoms of each symptomatic event will be summarized based on AE eCRF.

Summary of first ARIA-E events table based on AE eCRF will summarize the number of subjects with a first event of ARIA-E, the MRI severity of the events, the symptomatic status of the events, the severity of the symptoms for symptomatic events, whether SAE or not, number of resolved and unresolved events, duration of the resolved events, time from first active infusion in study to onset, number of doses received since the start of the period to onset, dose level of the last infusion received prior to onset, dosing status (continue as planned, dose interrupted, dose reduced, or dose discontinued) after the events, and the number of subjects with recurrent ARIA-E events. This table will be done on the placebo-controlled and LTE active treatment period. The same summary of first ARIA-E events table will also be done on the subset of subjects who had recurrent ARIA-E events.

Summary of recurrent ARIA-E events table based on AE eCRF will summarize the following information for both the second and third event of ARIA-E events: the number of subjects

with the previous event of ARIA-E, the number of subjects with at least one dose and one MRI after the previous ARIA-E resolution, the number of subjects with this event of ARIA-E, the MRI severity of the events, the symptomatic status of the events, the severity of the symptoms for symptomatic events, whether SAE or not, number of resolved and unresolved events, duration of the resolved events, time from first infusion in study (active or placebo) to onset, time from previous resolution to onset, number of doses received since the start of the period to onset, dose level of the last infusion received prior to onset, dosing status (continue as planned, dose interrupted, dose reduced, or dose discontinued) after the events. The number of subjects with more than 3 events of ARIA-E, and the number of subjects who discontinued study treatment after recurrent ARIA-E onset will also be summarized. This table will be done on the placebo-controlled and LTE active treatment period.

A listing of subjects who withdrew from the study with unresolved ARIA-E or subjects with ongoing ARIA-E at the time of data cutoff (also considered as unresolved) will be provided with the details of the event including the duration from onset to last follow-up.

For subjects with recurrent ARIA-E, a listing of study drug administration, MRI assessments, severity and symptomatic status of each event, and end-of-treatment reason (if present) will be provided.

3.5.3.4 Exposure adjusted analysis

Exposure adjusted incidence rate of ARIA-E events will be summarized based on safety MRI data for the placebo-controlled and LTE active treatment period. The exposure adjusted follow-up time is from the first active dose until the initial occurrence of ARIA-E for those who experienced ARIA-E, and until the end of follow-up for those who did not. Since ARIA is an MRI finding, the day of the last MRI assessment in the placebo-controlled and LTE active treatment period will be used as the end of follow-up for those who didn't experience the event.

Study drug administration information prior to first ARIA-E onset will be summarized for ARIA-E subjects for the placebo-controlled and LTE active treatment period, including number of total infusions, number of infusions at each dose level (placebo, 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg), dose level of the last infusion, maximum dose level received, and cumulative dose as a continuous variable.

3.5.3.5 Time to event analysis

Kaplan-Meier plot of time to first ARIA-E event will be produced based on safety MRI data for the placebo-controlled and LTE active treatment period. Only ARIA-E events that occurred during this period will be included. Time to event is calculated as date of the MRI assessment that initially detects the ARIA-E event - date of the first active infusion +1. Censor time for subjects without ARIA-E is calculated as date of the last MRI assessment in the study - date of the first active infusion +1. Estimated proportion with ARIA-E and number of subjects at risk at selected timepoints will also be presented. The plot will be presented by LTE treatment group stratified by ApoE status.

3.5.4 Clinical Laboratory Data

The following clinical laboratory parameters are assessed in the protocol and will be analyzed:

- Hematology:
  - White blood cells (leukocytes), lymphocytes, neutrophils, monocytes, eosinophils, basophils
  - Red blood cells (erythrocytes), erythrocytes distribution width, erythrocytes mean corpuscular volume, erythrocytes mean corpuscular hemoglobin, erythrocytes mean corpuscular hemoglobin concentration
  - Hemoglobin
  - Hematocrit
  - Platelet count
- Blood chemistry:
  - Liver: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl-transferase (GGT)
  - Renal: blood urea nitrogen (BUN), creatinine
  - Electrolytes: sodium, potassium, chloride, bicarbonate
  - Other: glucose, calcium, phosphorus, albumin, uric acid, lactate dehydrogenase (LDH), total protein
- Urinalysis: specific gravity, potential of hydrogen (pH), color, blood, glucose, ketones, protein, white blood cells, red blood cells

3.5.4.1 Quantitative analyses

For numeric laboratory parameters, actual values will be summarized by visit for all the visits in the placebo-controlled and LTE period. Number of evaluable subjects, mean, standard deviation, median, 25% and 75% quartiles, minimum and maximum values will be presented at each visit.

Plots of mean actual values (with standard error) for numeric laboratory parameters at each visit for all the visits in the placebo-controlled and LTE period will be provided.

Summary of change from baseline and percent change from baseline for numeric laboratory parameters will be done on the placebo-controlled and LTE active treatment period. Placebo-controlled baseline will be used for early start subjects and LTE baseline will be used for late start subjects. Change and percent change from baseline will be calculated based on the LTE baseline for late start subjects. Number of evaluable subjects, mean, standard deviation, median, 25% and 75% quartiles, minimum and maximum values will be presented at each visit.

Listings of individual laboratory measurements by patients for all the parameters will be provided.

Visit windows for by visit summaries

For laboratory by visit summaries, the analysis visit should be defined using visit windows (see Table 5 below). If there is more than 1 value in the same analysis visit window for a certain parameter for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis.

Table 5: Visit Windows for Laboratory by Visit Summaries

Analysis visit	Analysis visit window[1]	
	For subjects who received the first dose of aducanumab in the placebo-controlled period	**For subjects who received the first dose of aducanumab in the LTE period**
Baseline	Last value prior to the first dose of aducanumab	Last value prior to the first dose of aducanumab
Week 24	[2, 252]	[2, 252]
Week 48	[253, 420]	[253, 420]
Week 72	[421, 525]	[421, 588]
Week 78	[526, end day of the placebo-controlled period[2]]	NA
Week 104	[start day of the LTE period[3], 812]	[589, 868]
Week 128	[813, 980]	NA
Week 152	[981, 1148]	[869, 1246]
Week 176	[1149, 1428]	NA
Week 232	[1429, 1806]	[1247, 1708]
Week 284	[1807, 2170]	≥ 1709
Week 336	≥2171	NA

1. Visit windows are defined based on days relative to the first dose of aducanumab.
2. The end day of the placebo-controlled period is the last day before the first infusion in LTE, or the last day in study for subjects who do not enter LTE.
3. The start day of the LTE period is the day of first infusion in LTE period.

3.5.4.2 Qualitative analyses

For qualitative analyses, all values will be included (not just the "analyzed record" within each visit window in the quantitative analyses).

Shift analyses

Laboratory data will be summarized using shift tables where appropriate for the placebo-controlled and LTE active treatment period. Each subject's hematology, blood chemistry and urinalysis numeric values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory or as "unknown" if no result is available. Each subject's urinalysis categorical values will be flagged as "positive" or "negative", or "unknown" if no value is available.

Shifts from baseline to high/low status will be presented for hematology, blood chemistry and urinalysis numeric parameters, and shifts from baseline to abnormal (positive) will be presented for urinalysis categorical parameters. Shift to low includes normal to low, high to low, and unknown to low; Shift to high includes normal to high, low to high, and unknown to high. Subjects need to have at least one post-baseline evaluation and a baseline value not low or high or positive (including missing) in order to be included in the analysis.

For early start subjects, the placebo-controlled baseline will be used and shifts that occurred in either placebo-controlled or LTE period will be included. For late start subjects, the LTE baseline will be used and shifts that occurred in the LTE period based on LTE baseline will be included.

Grade analyses

Worst post-baseline grade will be summarized for each laboratory parameter in both exclusive way and cumulative way for the placebo-controlled and LTE active treatment period. Subjects need to have at least one post-baseline evaluation in the active treatment period in order to be included in the analysis. Common Toxicity Criteria for Adverse Events v4.0.3 (CTCAE) published on 2010-06-14 will be used for grade determination. Grade determination is based solely on laboratory values not taking AEs into account.

Potentially Clinically Significant laboratory abnormalities analyses

Please refer to the placebo-controlled SAP for the parameters and criteria for potentially clinically significant laboratory abnormalities analyses.

The number of subjects with potentially clinically significant laboratory abnormalities post-baseline will be summarized for the placebo-controlled and LTE active treatment period.

Subjects need to have at least one post-baseline evaluation in the active treatment period and a baseline value not potentially clinically significant (including missing) in order to be included in the analysis.

Same as the shift analysis, for early start subjects, the placebo-controlled baseline will be used and abnormalities that occurred in either placebo-controlled or LTE period will be included. For late start subjects, the LTE baseline will be used and PCS abnormalities that occurred in the LTE period based on LTE baseline will be included.

Potential serious hepatotoxicity

In this SAP, we define potential serious hepatotoxicity as ALT or AST > 3x ULN and total bilirubin > 2x ULN at any time post-baseline in the placebo-controlled and LTE active

treatment period (not necessarily concurrent). A scatterplot of the maximum post-baseline ALT or AST value relative to ULN and maximum post-baseline total bilirubin value relative to ULN (not necessarily concurrent) for each subject will be provided. A line plot of ALT, AST, ALK and total bilirubin values over time in the active treatment period for subjects with potential serious hepatotoxicity will be provided. In addition, subjects with ALT > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with AST > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with total bilirubin >1x ULN or >2x ULN, subjects with ALP >1x ULN or >1.5x ULN, and subjects with AST or ALT > 3x ULN post-baseline accompanied by concurrently elevated total bilirubin >1.5x ULN or > 2x ULN in the active treatment period will be presented. Concurrent is defined as on the same day. A listing of subjects with potential serious hepatotoxicity will be provided.

3.5.5 C-SSRS Data

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior. There are 5 "Yes/No" questions on suicidal ideation following the increasing severity order: (1) Wish to be dead, (2) Non-specific active suicidal thoughts, (3) Active suicidal ideation with any methods (not plan) without intent to act, (4) Active suicidal ideation with some intent to act, without specific plan, (5) Active suicidal ideation with specific plan and intent, and 6 "Yes/No" questions on suicidal behavior following the increasing severity order: (6) Preparatory acts or behavior, (7) Aborted attempt, (8) Interrupted attempt, (9) Actual attempt, (10) Suicidal behavior, (11) Suicide (only at post-baseline visits). Another "Yes/No" question of whether the subject has engaged in non-suicidal self-injurious behavior is also collected.

The summary table for C-SSRS will be conducted for the placebo-controlled and LTE active treatment period. Number of subjects who answered "Yes" to each of the 11 questions post-baseline, subjects who answered "Yes" to at least one question for suicidal ideation, subjects who answered "Yes" to at least one question for suicidal behavior, and subjects who have engaged in non-suicidal self-injurious behavior will be presented. A listing of subjects with any suicidal ideation or behavior at baseline or post-baseline will be provided for placebo-controlled and LTE period.

3.5.6 ECG Data

Shift from normal or unknown ECG at baseline to abnormal, not adverse event or abnormal, adverse event post-baseline ECG will be summarized for the placebo-controlled and LTE active treatment group. For early start subjects, the placebo-controlled baseline will be used. For late start subjects, the LTE baseline will be used. Subjects with abnormal ECG status will be listed.

3.5.7 Vital Sign Data

Vital sign parameters include body temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and weight. Vital signs will be measured with the subject

supine and after the subject has been resting for at least 10 minutes. The descriptive statistics for actual values will be summarized at each visit in the placebo-controlled and LTE period. Plot of mean vital sign values in the placebo-controlled and LTE period will be provided.

Summary of change from baseline including number of evaluable subjects, mean, standard deviation, median, 25% and 75% quartiles, minimum, and maximum values will be summarized at each visit in the placebo-controlled and LTE active treatment period. Placebo-controlled baseline will be used for early start subjects and LTE baseline will be used for late start analysis.

The analysis of vital signs will also focus on the incidence of clinically relevant outliers. Please refer to the placebo-controlled SAP for the criteria to assess potential clinically relevant outliers in vital sign. The incidence and percentage of clinically relevant outliers determined by each criterion will be summarized in the placebo-controlled and LTE active treatment period. A listing of subjects with clinically relevant vital signs in the placebo-controlled and LTE active treatment period will also be provided.

Visit windows for by visit summaries

For vital sign by visit summaries, the analysis visit should be defined using windows (see Table 6 below). For the same parameter for a subject, if there is more than 1 record in the same analysis visit window, then select the record closest to the target visit day. If there are 2 records in the same analysis visit window with the same distance from the target visit day, then select the record with the later date.

Table 6: Visit Windows for Vital Sign by Visit Summaries

	Analysis visit window[1]	
Analysis visit	**For subjects who received the first dose of aducanumab in the placebo-controlled period**	**For subjects who received the first dose of aducanumab in the LTE period**
Baseline	Last value prior to the first dose of aducanumab	Last value prior to the first dose of aducanumab
Week 4	[2, 42]	[2, 42]
Week 8	[43, 70]	[43, 70]
Week x	[7x -13, 7x+14] for 8 ≤ x ≤72	[7x -13, 7x+14] for 8 ≤ x ≤252
…	…	…
Week 76	[519, the end day of the placebo-controlled period[1]]	[7x -13, 7x+14] for 8 ≤ x ≤252
Week 80	[the start day of the LTE period[2], 574]	[7x -13, 7x+14] for 8 ≤ x ≤252
Week x	[7x -13, 7x+14] for 84 ≤ x ≤176	[7x -13, 7x+14] for 8 ≤ x ≤252
…	…	…
Week 180	[1247, 1267]	[7x -13, 7x+14] for 8 ≤ x ≤252
Week 182	[1268, 1281]	NA
Week 184	[1282, 1302]	[7x -13, 7x+14] for 8 ≤ x ≤252
Week 188	[1303, 1330]	[7x -13, 7x+14] for 8 ≤ x ≤252
Week x	[7x -13, 7x+14] for 188 ≤ x ≤332	[7x -13, 7x+14] for 8 ≤ x ≤252
…	…	…
Week 256	[7x -13, 7x+14] for 188 ≤ x ≤332	[1779, 1799]
Week 260	[7x -13, 7x+14] for 188 ≤ x ≤332	≥ 1800
…	…	…
Week 336	[2339, 2359]	NA

	Analysis visit window[1]	
Analysis visit	**For subjects who received the first dose of aducanumab in the placebo-controlled period**	**For subjects who received the first dose of aducanumab in the LTE period**
Week 338	≥ 2360	NA

1. Visit windows are derived based on the first dose of aducanumab.
2. The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, or the last day in study for subjects who do not enter LTE.
3. The start day of the LTE period is the day of first dose in the LTE period.

3.6 Pharmacokinetics Analysis

The PK analysis population will be used for the description of the concentration-time profiles and for the estimation of PK parameters. Randomization treatment groups will be used for PK analysis. Tables will be presented by LTE treatment group stratify by ApoE status (analysis display B in Appendix 4.1). Listings will be presented by LTE treatment group stratified by ApoE status. Listings will include all data in the study, with an indicator of the study period (pre-dosing, placebo-controlled, or LTE) for each record when the assessment occurred.

PK evaluation will be based on the concentration of aducanumab, in serum samples collected prior to infusion and between 10 and 60 minutes after completion of the infusion and line flush for the visits specified per protocol.

Concentrations of aducanumab that are below the limit of quantification (BLQ) will be imputed as 0. When summarizing concentrations or PK parameters in serum, a minimum of 2 values are required to show the arithmetic mean and geometric mean, and at least 3 values are required to show the standard deviation and coefficient of variation.

3.6.1 Serum Concentration Profile

Serum concentration data will be summarized by nominal visit for the placebo-controlled and LTE period. Number of evaluable subjects, arithmetic mean, standard deviation, median, 25% and 75% quartiles, minimum, maximum, geometric mean, and coefficient of variation will be presented at each visit. A listing of individual concentration data will be provided.

3.6.2 Serum PK Parameters

Two PK parameters C_{max} and C_{min} will be computed by noncompartmental methods, as data permits, from serum concentration-time data:

Parameter	Definition	Units
C_{max}	Observed maximum serum aducanumab concentration	ug/mL
C_{min}	Observed minimum serum aducanumab concentration	ug/mL

Number of evaluable subjects, arithmetic mean, standard deviation, median, 25% and 75% quartiles, minimum, maximum, geometric mean, and coefficient of variation will be presented for the PK parameters.

3.7 Immunogenicity Analysis

3.7.1 Background

Definition of LTE baseline value

Placebo-controlled baseline value is defined as the latest immunogenicity data collected prior to the first dose. If no immunogenicity data are collected prior to the first dose, baseline value is missing and will be imputed as anti-drug antibody negative for immunogenicity analyses. LTE baseline is defined as the last non-missing measurement collected prior to the first dose of the LTE period. For analyses on the placebo-controlled and LTE active treatment period, LTE baseline will be used for late start subjects who are assigned to receiving aducanumab in the LTE period. Study day and analysis visit window for analyses using LTE baseline will be derived based on the first day of study drug in LTE.

Treatment-emergent anti-aducanumab antibody positive responses for the placebo-controlled and LTE active treatment period

Post-baseline positive anti-aducanumab antibody responses for the active treatment period are defined as treatment-emergent if a subject is either (1) antibody negative at baseline; or (2) antibody positive at baseline but the post-baseline antibody response is more than 2-fold increase in titer compared to the baseline response. Placebo-controlled baseline will be used for early start subjects and LTE baseline will be used for late start subjects.

Persistent and transient positive responses for the placebo-controlled and LTE active treatment period

Subjects with treatment-emergent post-baseline positive anti-aducanumab antibody responses in the placebo-controlled and LTE active treatment period will be further classified as transient positive, if only a single positive evaluation occurs or more than 1 positive evaluation but occur with < 112 days (16 weeks) apart, or as persistent positive, if more than one consecutive positive evaluation occurs ≥112 days (16 weeks) apart in the active treatment period or a positive evaluation occurs at the last available time point with no further negative results available.

3.7.2 Immunogenicity analysis

Immunogenicity population will be used to analyze immunogenicity data. LTE safety treatment groups will be used for immunogenicity analysis. Tables will be presented by LTE treatment group (late start low dose, late start high dose, early start low dose, early start high dose, and in addition late start total, early start total and BIIB037 total; analysis display A in Appendix 4.1). Listings will be presented by treatment group stratified by ApoE status.

A summary table of subjects with treatment-emergent positive anti-aducanumab antibody responses in the placebo-controlled and LTE active treatment period will be provided. The number and percentage of anti-aducanumab positive results will be summarized at each visit as well as at any time post-baseline in this period. Subjects with persistent response and

subjects with transient response in this period will be presented. A listing of immunogenicity data in placebo-controlled and LTE period for subjects with anti-aducanumab antibody positive results will also be provided.

Visit windows for by visit summaries

For immunogenicity by visit summaries, the analysis visit should be defined using visit windows (see Table 7 below). If there is more than 1 value in the same analysis visit window for a subject, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a subject, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a subject, then the record with the later time will be used for the by visit analysis.

Table 7: Visit Windows for Immunogenicity by Visit Summaries

Analysis visit	Analysis visit window[1]	
	For subjects who received the first dose of aducanumab in the placebo-controlled period	**For subjects who received the first dose of aducanumab in the LTE period**
Baseline	Last value prior to the first dose of aducanumab	Last value prior to the first dose of aducanumab
Week 24	[2, 196]	[2, 252]
Week 32	[197, 308]	NA
Week 56	[309, 470]	[253, 420]
Week 78	[471, end day of the placebo-controlled period[2]]	[421, 609]
Week 80	[start day of the LTE period[3], 644]	NA
Week 104	[645, 812]	[610, 1260]
Week 128	[813, 980]	NA
Week 152	[981, 1169]	NA
Week 182	[1170, 1820]	≥ 1261
Week 338	≥ 1821	NA

1. Visit windows are derived based on the first dose of aducanumab.
2. The end day of the placebo-controlled period is the last day before the first infusion in LTE for subjects who enter LTE, or the last day in study for subjects who do not enter LTE.
3. The start day of the LTE period is the day of first dose in the LTE period.

4 Appendix

4.1 Analysis Display

Analysis display A

BIIB037 late start			BIIB037 early start			BIIB037 total
Low dose	High dose	Total	Low dose	High dose	Total	

Analysis display B

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BIIB037 late start low dose			BIIB037 late start high dose			BIIB037 late start total
ApoE e4+ 3 mg/kg	ApoE e4- 6 mg/kg	Total	ApoE e4+ 10 mg/kg	ApoE e4- 10 mg/kg	Total	

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BIIB037 early start low dose			BIIB037 early start high dose			BIIB037 early start total
ApoE e4+ 3 mg/kg	ApoE e4- 6 mg/kg	Total	ApoE e4+ 10 mg/kg	ApoE e4- 10 mg/kg	Total	