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

Version No.: 2.0

Date: 10 May 2024

Author: [redacted]

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

Name of Study Treatment: Aducanumab

Protocol No.: 221AD304

Study Phase: 3b

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APPROVAL

This document has been reviewed and approved by:		
[redacted] PhD	DocuSigned by: [redacted]	10-May-2024
SMT Statistician	Signature	Date
[redacted] PhD	DocuSigned by: [redacted]	10-May-2024
Program Statistician	Signature	Date
[redacted] MD	DocuSigned by: [redacted]	10-May-2024
SMT Medical Director	Signature	Date
[redacted] MD	DocuSigned by: [redacted]	10-May-2024
SMT Safety Director	Signature	Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	21-AUG-2020	Not applicable.
2.0	10-MAY-2024	Added [redacted] according protocol version 4.0. Added the core secondary objectives and endpoints according to interim analysis SAP. Added the description of the primary efficacy analysis results from the interim analysis in section 4.2. Modified for abbreviated CSR analysis.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Aβ	β-amyloid
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
[redacted]	[redacted]
[redacted]	[redacted]
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
ASL-MRI	arterial spin labeling magnetic resonance imaging
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
EOT	End of Treatment
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FU	Follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HCP	health care professional
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	institutional review board
ITT	intent-to-treat
LDH	lactate dehydrogenase
LMCI	late mild cognitive impairment
LTE	long-term extension
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MRI	magnetic resonance imaging
[redacted]	[redacted]
PCS	potentially clinically significant
[redacted]	[redacted]
pH	potential of hydrogen
PI	Principal Investigator
PK	pharmacokinetic(s)
PT	preferred term
ROI	region of interest
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
STAN	Biogen Standard Analyses
SUSAR	suspected unexpected serious adverse reaction
SUVR	standard uptake value ratio
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. Introduction

Study 221AD304 (EMBARK) is an open-label, single-arm clinical study that is being conducted to assess the long-term safety and efficacy of aducanumab in participants with Alzheimer's disease (AD) who were actively participating in aducanumab clinical studies 221AD103, 221AD205, 221AD301, or 221AD302 (hereafter denoted as "feeder studies") as of 21 March 2019. Participants in an aducanumab clinical study at the time of the announcement of early termination of the feeder studies were eligible to enroll in Study 221AD304.

Biogen initiated early termination of the Phase 3b study 221AD304 on 19 September 2023. At that time, all 221AD304 study participants had completed the core portion of the study, and therefore, the primary objective of assessing safety and tolerability of aducanumab and the core [redacted] of the study had been met. The decision to complete the study early was not based on any safety or efficacy concerns. Participants were notified that their next scheduled study visit would be their last dosing visit. Per protocol, participants were instructed to return to the site for the end of treatment visit followed by the safety follow-up visit (18 weeks after the last dose).

As there was no available post-trial compassionate access mechanism in France, Biogen allowed French participants to remain on treatment beyond September 2023 as planned and to complete the EMBARK LTE in full. These data from the French participants will be added to the dataset for the LTE. As a result, the decision for early termination of EMBARK did not impact French participants in the study. Following Biogen's 31 January 2024 decision to discontinue commercialization and development of aducanumab, study 221AD304 early termination was also initiated in France and the last dose for France participants occurred no later than 01 May 2024. The study participants in France were required to perform a safety follow-up visit 12 weeks after their last dose. The number of assessments conducted at the End of Treatment (EOT) and safety follow-up/End of Study Visit (EOS) visit were reduced to minimize the burden on site and study participants. [redacted]

The primary statistical analysis plan (SAP) version 1 was signed off on August 31, 2020. It described the analysis plan on the data by the end of the core treatment period as defined in protocol version 4. An interim analysis plan (SAP) version 2.0 was signed on 24 February 2023. This interim analysis was mainly focused on evaluating the efficacy of aducanumab versus an external control using clinical endpoints and [redacted] endpoints.

Due to the early termination of the study, an abbreviated clinical study report is planned. The focus of this SAP will be safety and tolerability of aducanumab in the core treatment period and the long-term extension period. The core primary endpoints, as well as the [redacted] related to safety and tolerability will be evaluated. All other [redacted] will not be included in this analysis. Disposition, baseline characteristics, demographics, exposure, and protocol deviation data will be also summarized to provide supporting information for the review of safety.

2. Study Overview

2.1. Study Objectives and Endpoints

Given the context of the early study termination, two types of analyses will be performed: 1) the core primary endpoints (assessed over 100 weeks) and [redacted]

2.1.1. Core Primary Objective and Endpoints

The core primary objective is to evaluate the safety and tolerability of aducanumab over 100 weeks of treatment in participants from the aducanumab feeder studies (221AD301, 221AD302, 221AD205 and 221AD103), which were the ongoing aducanumab trials at the time of program discontinuation on 21 March 2019. The study candidates had previously received aducanumab (i.e., previously treated participants) or had previously received placebo (i.e., treatment-naïve participants) after a wash-out period imposed by the discontinuation of the feeder studies.

Primary endpoints include incidence of adverse events (AEs), SAEs, amyloid related imaging abnormality (ARIA) and immunogenicity with over 100 weeks of treatment and/or re-exposure to aducanumab. Safety and tolerability parameters include:

- Incidence of all AEs; AEs leading to treatment discontinuation or study withdrawal, and all SAEs
- Incidence of amyloid related imaging abnormality-edema (ARIA-E) and amyloid related imaging abnormality-hemorrhage or superficial siderosis (ARIA-H)
- Incidence of anti-aducanumab antibodies (anti-drug antibodies, ADA) in serum.

2.1.2. Core Secondary Objectives and Endpoints

The core secondary objectives and endpoints are not described in the protocol but were developed as part of an interim statistical analysis plan (version 2.0)

The core secondary objectives defined in the interim SAP are:

- Evaluation of the efficacy of aducanumab versus an external control using clinical endpoints
- Evaluation of the efficacy of aducanumab versus an external control using [redacted]

The corresponding primary clinical efficacy endpoint is change from baseline CDR-SB at Week 78.

Additional core secondary clinical efficacy endpoints to be compared to an external control are:

- Change from baseline Alzheimer's Disease Composite Score (ADCOMS) at Week 78
- Change from baseline Alzheimer's Disease Assessment Scale, Cognitive subscale (ADAS-Cog 13) at Week 78
- Change from baseline Mini-Mental State Examination (MMSE) at Week 78

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

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[redacted]

- [redacted]

2.2. Study Design

Study 221AD304 is an open-label, multicenter, longitudinal, single-arm, global Phase 3b study in participants with Alzheimer's disease who had previously participated in aducanumab studies at the time of their early termination. It is calculated that up to approximately 2400 participants will be enrolled across approximately 350 sites globally. The primary study objective is to

evaluate the long-term safety and tolerability of a monthly dose (10mg/kg) of aducanumab after a gap period imposed by discontinuation of feeder studies.

The study consists of Screening, Core Treatment, LTE Treatment, and FU periods. A schematic of the study is presented in Figure 1 of protocol Section 4. According to the original protocol, study duration for each participant is approximately 178 weeks: an approximately 8-week Screening Period, a 100-week Core Treatment Period, a 52-week LTE treatment period, and a safety FU Visit 18 weeks after the last dose of study treatment.

After the Screening Period, participants who meet the eligibility criteria will receive open-label treatment. During the Core Treatment Period, participants will receive IV infusions of aducanumab approximately every 4 weeks for a total treatment duration of 100 weeks (a total of 26 doses). The aducanumab dosing regimen will be 10 mg/kg following this titration: 1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter. Eligible participants will then enter the LTE treatment period and continue dosing on 10 mg/kg aducanumab Q4W for an additional 52 weeks (a total of 152 weeks of continuous treatment). The EOT Visit will occur at Week 102 for participants who do not enter the LTE treatment period and at Week 154 for participants who enter LTE treatment period. Participants will have a safety FU Visit 18 weeks after their last dose of study treatment.

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

For Schedule of Events, see tables in protocol Section 4.2.

[redacted]

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

[redacted]

2.3. Study Conduct Following Announcement of Study Termination

On 19 September 2023, Biogen announced the decision to initiate early termination of the EMBARK study. At that time, all subjects had completed the core treatment period, and over 600 subjects were in LTE treatment period.

The requirement for scheduling the last dose visit and last safety follow-up visit was later updated as described in Table 1. Non-France participants were required to have the last-dose

visit prior to 31 October 2023, and the safety follow-up visit 18 weeks after their last dose (+/-5 days) and no later than March 8th, 2024.

As there was no available post-trial compassionate access mechanism in France, French participants were allowed to remain on treatment as planned and complete the EMBARK LTE in full. As a result, the decision for early termination of the EMBARK study did not impact French participants in the study.

Following Biogen's announcement of termination of the aducanumab program, EMBARK study termination activities were initiated in France on 31 January 2024. Participants from France were required to have the last-dose visit prior to 01 May 2024, and the safety follow-up visit 12 weeks after their last dose (+/-5 days) and no later than 24 July 2024.

Table 1 Summary of Updates on Last Dose Visit and Safety Follow-up Visit since the Announcement of Study Termination

	Global excluding France		France	
Date of study updates	**Last dose visit**	**Follow-up visit**	**Last dose visit**	**Follow-up visit**
19Sep2023	Prior to 19Oct2023	18 weeks after the last dose	Prior to 19Oct2023	18 weeks after the last dose
28Sep2023	Prior to 31Oct2023	18 weeks after the last dose	Study continues as originally planned	
31Jan2023		No later than 31Mar2024	No later than 01May2024	30 days after last dose and no later than 01Jun2024
22Feb2024		18 weeks after their last dose (+/-5 days) and no later than 08Mar2024		12 weeks (90 days) after their last dose (+/-5 days) and no later than 24Jul2024

Changes to Study Execution Following Announcement of Study Termination

The changes to study execution in France sites involve the following, as described in 221AD304 Protocol Clarification Letter 13Feb2024.

1. End of Treatment (EoT) visit (Section 4.2, Table 3)

In Version 4 of the protocol, Section 4.2 Schedule of Events Table 3 currently includes timepoints for the [redacted] as well as clinical efficacy and safety assessments.

Clarification Statement

Due to the discontinuation of the Aducanumab program and the early termination of the study, [redacted]. Also, to reduce participant burden, the clinical efficacy assessments will be removed, leaving only safety assessments.

2. Follow-up/End of Study (FU/EOS) Visit: assessments and timing (Section 4.2, Table 3)

Version 4 of the current protocol mandates that participants return for a Follow-up/End of Study visit (also referred to as the safety follow-up visit) 18 weeks after the participant's last dose at 152 weeks (see Section 4.2, Table 3, Schedule of Activities).

Clarification Statement

Due to the discontinuation of the Aducanumab program and the early termination of the study, all participants will be asked to complete their Follow-up/End of Study Visit 12 weeks (+/– 5 days) after the participant's last dose of study treatment. In addition, similar to the End of Treatment Visit, the number of assessments that need to be completed is now reduced to lessen participant burden. These assessments are reported below in Table 2. If a participant has had their last dose of study treatment and it has been more than 12 weeks since their last dose and the participant has not had their safety follow-up, then they should complete a safety follow-up within the next 30 days, as defined in Table 2.

[redacted]

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

[redacted]

Table 2 **Revised Schedule of Assessments for the End of Treatment and Follow-up Visits**

Study Assessments	Week 154/End of Treatment Visit (within 2 weeks of last dose)	Follow up/End of Study Visit (12 weeks after last dose +/- 5 days)
Body Weight	X	
Hematology, Blood Chemistry, and Urinalysis	X	
Alzheimer's Disease Status	No longer being completed	
Physical Examination	X	X
Neurological Examination	X	X
Vital Signs	X	X
12-Lead Paper ECG	X	
ADA	X	
Aducanumab Serum Concentration	X	
[redacted]		

Study Assessments	Week 154/End of Treatment Visit (within 2 weeks of last dose)	Follow up/End of Study Visit (12 weeks after last dose +/- 5 days)
C-SSRS	X	X This will now be completed
Brain MRI		X
AE Reporting	Monitor and record continuously throughout the study	
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study	
SAE Reporting	Monitor and record continuously throughout the study	

2.4. Sample Size Considerations

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

At the time that the feeder studies were stopped in March 2019, approximately 2600 participants had received treatment in 1 of the feeder studies. At the time of study planning, Biogen estimated that of these 2600 participants, approximately 2400 participants could be eligible based on inclusion and exclusion criteria to participate in Study 221AD304.

A total of 1865 participants were screened in study 221AD304 and were from studies 221AD301, 221AD302, 221AD103, and 221AD205. Of these, 1696 participants were enrolled across 305 sites globally.

3. Definitions

3.1. Dates and Points of Reference

1. Study Day 1: the date of the first dose of aducanumab in the study
2. Study Day
    a. For a date on or after Study Day 1

        Study Day = (Date of Interest) – (Study Day 1) + 1

    b. For a date before Study Day 1

        Study Day = (Date of Interest) – (Study Day 1)
3. First dose date and last dose date

    The first dose date in the study is date of the first dose of aducanumab in 221AD304 study, the last dose date in the study is the date of the last dose of aducanumab in 221AD304 study.

The first and last dose date in the core treatment period are the dates of the first and last dose of aducanumab received before scheduled Week 102 visit respectively.

The first and last dose date in LTE treatment period are the dates of the first and the last dose of aducanumab received after scheduled Week 102 visit.

4. End of Treatment (EOT)

   EOT date for the study is the last dose date in the core treatment period for subjects who did not receive any aducanumab in scheduled LTE visits, or the last dose date in the LTE treatment period if subject had received at least one dose of aducanumab in scheduled LTE visits.

   EOT date for the core treatment period is the last dose date in core treatment period.

   EOT date for the LTE treatment period is the last dose date in LTE treatment period.

5. End of Study (EOS)

   EOS date for the study is the End of Study date recorded on the End of Study eCRF page. If the EOS date is missing, then the EOS date will be imputed using the very last date of any assessment done as completed in RAVE or in any vendor database if the EOS date is missing.

   For subjects who received the aducanumab in LTE visits, the EOS date for the core treatment period is defined as one day before the first dose date in LTE treatment period and those subjects will be considered as completer for the core treatment period. Otherwise, the EOS date for the core treatment period is the same as the EOS date for the study.

   According to the eCRF Completion Guidelines, the End of Study eCRF must be completed for every subject enrolled in the study. For subjects who did not enter Long-Term Extension (LTE): A Completer is a subject who completed all visits as mandated by protocol inclusive of the Week 102 EOT visit and the Week 118 FU visit. A subject who discontinued treatment early and remains in study in the protocol specific follow schedule, inclusive of Week 102, is also considered as Complete.

   For subjects who entered LTE: A Completer is a subject who completed all visits as mandated by protocol inclusive of the Week 154 EOT visit and the Week 170 FU. A subject who discontinued treatment early and remains in study in the protocol specific follow schedule, inclusive of Week 154, is also considered as Complete.

6. Visit window for by-visit analysis

   For data that are summarized by visit, assessment from all scheduled visits and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme as described in each section.

   Unless otherwise specified, if there is more than 1 value in the same analysis visit window for a certain parameter for a participant, 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 participant, 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 participant, then the record with the later time will be used for the by visit analysis.

7. Baseline values is defined as the most recent non-missing measurement collected prior to the first dose in the study or as the last non-missing measurement collected during screening for subjects not dosed.
8. Change from 221AD304 baseline will be defined as post-baseline value minus 221AD304 baseline value.
9. Percent change from baseline will be defined as post-baseline value minus baseline value then divided by baseline value.
10. Treatment Emergent

    An adverse event is regarded as treatment emergent if the event has onset date/time on or after the first dose date/time of study treatment, or was reported prior to the first dose and subsequently worsens in severity after first dose date. Additional criteria to determine treatment emergent are described in Section 5.7.2.1.

3.2. Study Treatment

During the Core Treatment Period, participants will receive IV infusions of aducanumab approximately Q4W for a duration of 100 weeks (a total of 26 doses). The aducanumab dosing regimen will be 10 mg/kg following this titration: 1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter. Eligible participants will then enter the LTE treatment period and continue dosing on 10 mg/kg aducanumab Q4W for an additional 52 weeks (a total of 152 weeks of continuous treatment).

The safety analysis groups are defined based on historical exposure of BIIB037 in feeder studies including 0 dose of BIIB037, pre-treated with BIIB037 with 0 dose of 10 mg/kg, and with >0 dose of 10 mg/kg.

3.3. Study Treatment Periods

- Core period

For subjects who received at least one dose of study treatment in LTE visits, core period is from the first dose of treatment in the study to before the first dose date in LTE period. For subjects who did not receive any dose in any LTE visits, core treatment period is from the first dose in study to the very last date of any assessment done as completed in RAVE or in any vendor database.

- Long-term extension period

Long-term extension period, also called LTE period, is from the first dose date in LTE treatment period to the very last date of any assessment done as completed in RAVE or in any vendor database.

3.4. Key Derived Variables

This section is not applicable.

3.5. Stratification Factors and Subgroup Variables

3.5.1. Stratification Factors

This section is not applicable.

[redacted]

3.6. Analysis Population

- Intent-to-treat and screen failure (ITTSF) population:

  The Intent-to-treat and screen failure population is defined as all subjects screened including both enrolled and screen failure subjects.

- Enrolled population:

  The enrolled population is defined as all subjects who signed informed consent, were assigned a subject identification number, and met the eligibility criteria for study 221AD304.

- Modified Intent-to-treat (mITT) population:

  The modified Intent-to-treat population is defined as all subjects who received at least one dose of aducanumab in study 221AD304.

- Modified Intent-to-treat (mITT) population for core period:

  The modified Intent-to-treat population for core treatment period is defined as all subjects who received at least one dose of aducanumab in the core period.

- Modified Intent-to-treat (mITT) population for LTE period:

  The modified Intent-to-treat population is defined as all subjects who received at least one dose of aducanumab in the LTE period.

- Safety population:

  The safety population is defined as all subjects who received at least one dose of aducanumab in study 221AD304.

- Safety population for the core period:

  The safety population is defined as all subjects who received at least one dose of aducanumab in the core period.

- Safety MRI population:

  The safety MRI population is defined as all subjects who received at least one dose of aducanumab in study 221AD304 and had at least one post-baseline MRI assessment in study 221AD304.

- Safety MRI population for the core period:

  The safety MRI population is defined as all subjects who received at least one dose of aducanumab in the core period and had at least one post-baseline MRI assessment in the core period.

- Immunogenicity population:

  The analysis population for immunogenicity is defined as all subjects who received at least one dose of aducanumab in study 221AD304 and had at least one post-dose sample evaluated for immunogenicity.

- Immunogenicity population for the core period:

  The analysis population for immunogenicity is defined as all subjects who received at least one dose of aducanumab in the core period and had at least one post-dose sample evaluated for immunogenicity in the core period.

4. List of Planned Study Analyses

4.1. Interim Analysis

According to the protocol, interim analyses may be conducted when the last patient is enrolled and when 50% of the enrolled patients have completed the study. Other interim analyses may be conducted at the discretion of the sponsor.

The following interim analyses in Table 3 occurred prior to the completion of the core treatment period:

Table 3 Summary of Interim Analysis

Data	Focus of analyses	Amount of 221AD304 post-baseline data
Data cutoff of July 15th, 2021 (Baseline Analysis)	Gap period between feeder studies and 221AD304 baseline	NA
Data cutoff of March 15th, 2022	221AD304 post-baseline data (No analyses comparing to external control were done)	420 of 1675 (25%) participants from feeder studies 221AD301 and 221AD302 had an opportunity to complete the 221AD304 Week-78 visit
Data cutoff of August 15th, 2022	First analysis of 221AD304 versus external control: • 221AD304 post-baseline data for participants from feeder studies 221AD301 and 221AD302. • A selected number of analyses will be performed including participants from feeder studies 221AD103 and 221AD205. • The focus of analyses will include the primary and secondary objectives as well as selected [redacted]	• Approximately 1180 of 1675 (70%) participants from feeder studies 221AD301 and 221AD302 will have had an opportunity to complete the 221AD304 Week-78 visit. • All but one participant will have had an opportunity to complete the 221AD304 Week-52 visit.

4.2. Primary Analysis

The primary analysis of Study 221AD304 focuses on the core primary endpoints described in Section 2.1.1 and will be performed after all subjects have completed the core treatment period, either by completing the Week 118 follow-up visit or by entering the LTE treatment period. At the time of announcement of early study termination on 19 September 2023, all subjects had completed the Week 102 visit and only a few subjects had not completed the Week 118 follow-up visit.

As described in Section 2.1, the core primary and LTE [redacted]

[redacted]. However, the core primary endpoints assess these variables during the core period only (see Section 3.3 for further details), while the [redacted]

The core secondary objectives and endpoints (see Section 2.1.2) are not described in the protocol but were developed as part of an interim statistical analysis plan (version 2.0). This interim analysis used a data cutoff date of August 15th, 2022 (see Table 3) and comprised the primary efficacy analysis of study 221AD304 versus an external control using clinical endpoints and [redacted]. The analysis of the secondary objectives and endpoints will be summarized in the 221AD304 (EMBARK) CSR addendum.

4.3. Final Analysis

The final analysis of study 221AD304 will be performed at the end of the study after the last participant completes the last visit of the study and the final database is locked. The final analysis will include all data collected during the entire Study including both the core period and the LTE period.

Following the decision to terminate the study early, an abbreviated CSR is planned. As such, the final analysis will focus on evaluating the long-term safety and tolerability of aducanumab as described in the [redacted] in Section 2.1.4. Disposition, baseline characteristics, demographics, exposure, and protocol deviation data will also be summarized to provide supporting information for the review of safety.

5. Statistical Methods for Planned Analyses

5.1. General Principles

This statistical analysis plan (SAP) defines the analysis scope for the Primary Analysis and the Final Analysis.

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.

All analyses will be summarized by safety analysis groups (0 dose of BIIB037, pre-treated with BIIB037 with 0 dose of 10 mg/kg, >0 dose of 10 mg/kg, subtotal of pre-treated with BIIB037, and overall total; analysis display SA in Appendix 9), unless otherwise specified. Where indicated, the analyses will be repeated by safety analysis group stratified by [redacted]

As noted in Section 1, due to the early termination of the study, an abbreviated CSR is planned. [redacted] The data that will be summarized are full safety data, and data on disposition, baseline, demographics, exposure, and protocol deviations.

All analyses will be done based on data collected during the entire study including the core and the LTE periods. Where specified, a subset of analyses will comprise the Primary Analysis and summarize safety and tolerability data from the core period only.

There will be no statistical testing for any endpoints.

The statistical software, SAS® version 9.4 or above will be used for all summaries and analyses.

5.2. Participant Accountability

Disposition will be summarized for all subjects enrolled by safety analysis groups (see Appendix 9). The summary data will include number of subjects enrolled, number of subjects withdrawn prior to dosing, number (%) of subjects dosed, number (%) of subjects who completed the treatment/study, and number (%) of subjects who discontinued treatment and/or withdrew from the study. The denominator for all the percentage calculation is the number of subjects dosed. For subjects who discontinued treatment and/or withdrew from the study, the reasons for discontinuation and/or withdrawal, days on treatment and days on study will be listed. The disposition will also be summarized by core period and LTE period separately.

Number of subjects dosed will be summarized by feeder studies.

5.3. Demographic and Baseline Characteristics

Demographics, baseline characteristics, medical history and AD treatment history will be summarized for the mITT population.

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 subgroups: <=60, 61-70, 71-80, 81-85, >85. In addition, Asian ethnicity will be summarized for the following subclassification: Chinese, Indian, Japanese, Korean, and other.

Summary of the baseline characteristics of AD includes [redacted], 221AD304 baseline clinical assessment including CDR global score, CDR-SB, CDR cognitive subscore, CDR functional subscore, MMSE, ADAS-Cog 13, [redacted], number of years of formal education, number of years since first AD symptom, number of years since diagnosis of AD, and AD symptomatic medication use at 221AD304 baseline (yes or no; see Section 5.5.2 for definition of AD symptomatic medication use at 221AD304 baseline). [redacted] MMSE will also be categorized by the following subgroups: ≤10, 11-20, 21-26, 27-30. Subject listings will be generated for demographics and baseline characteristics.

Medical history collected at EMBARK baseline will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 26.1 or later). The number (%) of subjects with history

(including both ongoing and not ongoing medical conditions) will be summarized by system organ class and preferred term.

5.4. 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. The major protocol deviations will be summarized for the mITT population. Major and minor protocol deviations for all mITT subjects will be listed. Major protocol deviations related to COVID-19 will be summarized and all protocol deviations related to COVID-19 will be listed.

Subjects with protocol alternations due to COVID-19 will be listed based on the data on the protocol alternations due to COVID-19 collected from the COVID-19 Impact log CRF page.

5.5. Study Treatment Exposure and Concomitant Medications

5.5.1. Study Treatment Exposure and Study Drug Compliance

Summary of study drug exposure and compliance will be provided. Number of infusions (aducanumab) received will be summarized as a categorical variable (categories of 1-5, 6-10, 11-15, 16-20, 21-25, 26-30, 31-35, 36-39, and >39) as well as a continuous variable. Number of weeks on study treatment (aducanumab), calculated as (date of last dose – date of first dose +29)/7, will be summarized as a categorical variable (every 8 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.

Due to the use of titration regimen in the study and possible dose suspension due to ARIA, another summary table will be provided including the following information in the study: 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 (1 to 3 mg/kg, 3 to 6 mg/kg and 6 to 10 mg/kg, respectively), maximum dose level received, and cumulative dose (as a continuous variable).

Both drug exposure/compliance and titration summary tables will be repeated for the core period.

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

5.5.2. Concomitant Medications and Non-Drug Therapies

The number (%) of subjects taking concomitant medication and non-drug therapies will be summarized for the mITT population. Concomitant medications and non-drug therapies will be listed.

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 (version 26.1 or later). 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.

AD symptomatic medications taken concomitantly at 221AD304 baseline are defined as AD symptomatic medications that were being taken at the time of the first dose in 221AD304 study, i.e., started prior to the first dose and continued until after the first dose. AD symptomatic medications are defined as anticholinesterase (cholinesterase inhibitors) and memantine drugs in the WHO medication dictionary (version: WHODrug Global B3 Sep2023 or later version if applicable).

The number (%) of subjects taking concomitant AD symptomatic medications, number of subjects using Cholinesterase inhibitors only, Memantine only, or both at the 221AD304 baseline will be summarized.

5.6. Efficacy Endpoints

As discussed in Section 2.1, no efficacy analysis will be performed.

5.7. Safety Endpoints

5.7.1. General Considerations

The primary estimand employs the treatment-policy strategy to evaluate the safety of BIIB037 determined by the following 4 attributes:

- Population: Intended population for BIIB037 defined through the study inclusion/exclusion criteria. All subjects in the safety population will be used in analyzing this estimand
- Variable: adverse events

- Handling intercurrent events: regardless of intercurrent events including treatment discontinuation and use of concomitant therapies
- Population-level summary: incidence of adverse events

The 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.

In general, AEs will be summarized based on incidence and incidence proportion. 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.

All AEs will be coded using the MedDRA dictionary (version 26.1).

When analyzing data for the core period or LTE period, an event will be assigned to one period by the start date. The event duration will be based on the start date and the end date of that event.

5.7.2. Clinical Adverse Events

5.7.2.1. Treatment-emergent AEs (TEAEs)

All AEs will be analyzed based on the principle of treatment emergence. A treatment-emergent AE is defined as an AE that started or worsened after the start of first infusion of study treatment in 221AD304 study.

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.

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

5.7.2.2. Summary and incidence analysis

An overall summary of AE table will be presented by safety analysis group as well as safety analysis group stratified by [redacted] 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 SAEs, the number of subjects with related SAEs, 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 subjects with a fatal event.

Table 4 lists the planned analyses of all AEs, most frequently reported AEs, related AEs (related to study drug as assessed by the investigator), AEs by severity, serious AEs, AE led to drug interrupted or drug withdraw, AE led to discontinuation of treatment, AE led to withdraw from study, and fatal events. All analyses will present incidence proportion by safety analysis groups for the overall study. Where indicated, the analyses will be repeated by safety analysis groups stratified by [redacted] or for the core period.

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 safety analysis group, and by decreasing frequency order of last column within each category in the tables presented by safety analysis group stratified by laboratory [redacted]. 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 safety analysis 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.

Table 4 List of Planned Analyses for AE

Analysis	**Repeat stratified by [redacted]?**	**Repeat by Core Treatment Period?**
Overall summary of AE	Yes	Yes
AEs by SOC/PT by descending frequency	Yes	Yes
AEs with an incidence of 5% or more by PT	Yes	Yes
Severe AEs by SOC/PT	Yes	Yes
AEs by maximum severity by SOC/PT	Yes	Yes
Related AEs by SOC/PT	Yes	Yes
SAEs by SOC/PT	Yes	Yes

Analysis	**Repeat stratified by [redacted]?**	**Repeat by Core Treatment Period?**
Related SAE by SOC/PT	Yes	Yes
AEs led to discontinuation of study treatment by SOC/PT	Yes	Yes
AEs led to withdraw from study by SOC/PT	Yes	Yes
AEs led to drug interrupted, drug withdrawn by SOC/PT	Yes	Yes
SAEs with fatal outcome by SOC/PT	Yes	Yes
ARIA events led to treatment discontinuation	No	No

The following listings will be provided:

(a) Listing of AEs

(b) Listing of SAEs

(c) Listing of AEs that led to discontinuation of study treatment

(d) Listing of AEs that led to withdrawal from study

[redacted]

(g) Listing of Deaths

(h) Listing of non-treatment emergent AEs

(i) Listing of AEs for participants with treatment-emergent anti-aducanumab antibody positive response

The listing of AEs contains the following information: participant number, investigator term, PT with reference ID, onset date, onset study day, end date, end study day, duration of AE (in days), outcome, severity, relation (related to study drug as assessed by the investigator), symptom of ARIA (yes/no), serious (yes/no), study withdrawal (yes/no), concomitant treatment (yes/no), and action on study treatment.

5.7.3. AE of Special Interest

5.7.3.1. Background

ARIA-E and ARIA-H are considered AEs of special interest in this study. Protocol section 7.2.1 describes 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 the 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 5 shows the reported term on MRI worksheet, the corresponding reported term on AE eCRF, and the MedDRA preferred term for each type of ARIA.

Table 5 Verbatim Terms and MedDRA terms for ARIA

AESI	Verbatim term	MedDRA preferred term
ARIA-E	Asymptomatic ARIA-E or Symptomatic ARIA-E	Amyloid related imaging abnormality-oedema/effusion
ARIA-H microhemorrhage	Asymptomatic ARIA-H (Microhemorrhage) or Symptomatic ARIA-H (Microhemorrhage)	Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits
ARIA-H superficial siderosis	Asymptomatic ARIA-H (Superficial Siderosis) or Symptomatic ARIA-H (Superficial Siderosis)	Superficial siderosis of the central nervous system
ARIA-H macrohemorrhage	Asymptomatic ARIA-H (Macrohemorrhage) or Symptomatic ARIA-H (Macrohemorrhage)	ARIA-H macrohemorrhages could be coded to various preferred terms, depending on type of hemorrhage and location of hemorrhage. Example: cerebral haemorrhage

Events of ARIA-H macrohemorrhage have been added to the analysis of ARIA events based on historical considerations for the aducanumab program. These AEs were reported by Investigators based on designation of "macrohemorrhage > 1 cm diameter" by central MRI readers on the brain MRI worksheet. Because of the limitations of the MedDRA coding for such events (there is no MedDRA PT that is consistently used for ARIA-H macrohemorrhage), the event reporting included additional free text to describe other pertinent details of the event, such as the hemorrhage location.

For any specific ARIA event, the start date of the duration is the date of the MRI assessment that initially identifies the ARIA event, and the end date of the duration 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 is defined as 'No change' or a decrease in number, size, severity, or number of locations between 2 consecutive MRIs including the initial detection MRI and the follow-up MRIs performed 4 weeks (±5 days) later.

If the severity increases, or the event changes from asymptomatic to symptomatic, or from non-serious to serious, more 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 and both events occurred within the 221AD304 study, then it is considered a recurrent event of ARIA of that type. Recurrent events will be referred as the second event, the third event, 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.

All planned analyses described below are listed in Table 6. All analyses will be presented by safety analysis groups for the overall study. Where indicated, the analyses will be repeated by safety analysis groups stratified by [redacted] or for the core period.

5.7.3.2. 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, which will be stratified by ARIA-E status (No ARIA-E vs Had ARIA-E) in the feeder study when applicable. 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.

Number of subjects with each type of ARIA, maximum severity and worst symptomatic status of the type of ARIA will be summarized based on AE eCRF by safety analysis groups and safety analysis groups stratified by [redacted]. The summary of maximum severity and worst

symptomatic status of each type of ARIA will also be summarized by safety analysis groups among subjects with ARIA in the study.

Onset of ARIA events will be summarized to present number of first and total ARIA and ARIA-E events, number of first and total symptomatic ARIA and ARIA-E events, and number of first and total serious ARIA and ARIA-E events.

ARIA-E resolution and ARIA-H stabilization will be summarized, and the following information will be presented: number of subjects with ARIA-E and ARIA-H, total number of ARIA-E and ARIA-H events, number of ARIA-E and ARIA-H events resolved and not resolved while on study, and MRI duration of the resolved ARIA-E and ARIA-H events. The MRI duration will be summarized as categorical variable (categories of 0-4, 0-8, 0-12, 0-16, 0-20, and >20 weeks).

An incidence table of AEs considered by the investigator to be related to ARIA by system organ class and preferred term will be provided, as well as a listing of these AEs.

Symptomatic ARIA will also be summarized. Number of subjects with symptomatic ARIA, number of symptomatic ARIA events, and MRI severity and symptomatic severity will be presented.

Number of subjects with serious or severe ARIA, or serious or severe ARIA symptoms will be summarized. Serious or severe ARIA-related AEs will be summarized by preferred term.

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 the event is an SAE, number of resolved and unresolved events, duration of the resolved events, time from first infusion in study 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.

Summary of recurrent ARIA-E events based on AE eCRF will present the following information: number of ARIA-E event per subject, number of cumulatively ARIA-E events per subject, number of subjects with a first ARIA-E event and at least 1 dose and MRI after resolution of the first ARIA-E event, number of subjects experienced recurrent ARIA-E.

A listing of subjects who withdrew from the study with unresolved ARIA-E will be provided with the details of the event including the duration from onset to last follow-up.

A summary of ARIA-H will be provided for participants with or without ARIA-E in the study.

MRI assessments for subjects with ARIA-E, ARIA-H microhemorrhage, ARIA-H superficial siderosis, ARIA-H macrohemorrhage, other MRI abnormalities at postbaseline, and other ischemic abnormalities at postbaseline will be listed. The last dose level received before the MRI scan will be provided in those listings.

5.7.4. Other Significant AEs

CNS Hemorrhage, Seizures, falls, and hypersensitivity reactions are considered significant AEs and are being monitored in this study. As listed in Table 6, CNS hemorrhage, seizures, hypersensitivity, and fall events will be summarized by safety analysis groups and will be listed.

CNS hemorrhage events will be identified by the eCRF and by using a standardized MedDRA query (SMQ), consisting of selected preferred terms within SMQ of "Haemorrhagic central nervous system vascular conditions" (narrow and broad scope). The SMQ list of PTs may be modified based on newer version of MedDRA when available and safety team's discretion. All CNS hemorrhage events will be summarized by preferred term. A separate summary table will be presented with all hemorrhagic CNS vascular conditions except subdural hematomas.

Seizure events will be identified using the SMQ of "Convulsions" (narrow and broad scope). ARIA status of subjects with seizure will be presented, splitting by the number of subjects with non-evaluable ARIA status (no post-baseline MRI), subjects with no ARIA event during the study and subjects who experienced ARIA during the study.

Hypersensitivity events will be identified using the SMQ of hypersensitivity (narrow and broad scope), SMQ of angioedema (narrow and broad scope) and SMQ of anaphylactic reaction (narrow and broad scope). The SMQ list of PTs may change due to the newer version of MedDRA and at the safety team's discretion.

Fall events will be identified based on the preferred term "Fall" and number of falls will be presented.

Table 6 List of Planned Analyses for ARIA and Other Significant AEs

Analysis	**Repeat stratified by [redacted]?**	**Repeat by Core Treatment Period?**
Incidence of ARIA events by previous ARIA-E experience	Yes	Yes
Maximum MRI severity and worst symptomatic status of ARIA events	Yes	Yes
Maximum MRI severity and worst symptomatic status of ARIA events among participants with ARIA	No	Yes
Onset of ARIA events	No	Yes

Analysis	**Repeat stratified by [redacted]?**	**Repeat by Core Treatment Period?**
Resolution of ARIA-E and stabilization of ARIA-H	No	Yes
Summary of first ARIA-E	No	Yes
Recurrent ARIA-E	No	Yes
ARIA-related adverse events by SOC/PT	No	Yes
Summary of symptomatic ARIA	No	Yes
Summary of serious and severe ARIA and symptoms	No	Yes
Serious or severe ARIA-related adverse events by PT	No	Yes
Summary of ARIA-H events by ARIA-E status	No	Yes
Haemorrhagic CNS vascular conditions events[12]	No	No
Haemorrhagic CNS vascular conditions events excluding subdural hematomas[12]	No	No
Hypersensitivity events[13]	No	Yes
Serious hypersensitivity events[13]	No	Yes
Related hypersensitivity events[13]	No	Yes
Seizures[14]	No	Yes

Analysis	Repeat stratified by [redacted]?	Repeat by Core Treatment Period?
Fall[15]	No	Yes

[1]On safety population.
[2]Haemorrhagic CNS vascular conditions event is defined by haemorrhagic central nervous system vascular conditions SMQ (broad and narrow scope).
[3]Hypersensitivity reaction event is defined by hypersensitivity SMQ (narrow and broad scope), angioedema SMQ (narrow and broad scope) and anaphylactic reaction SMQ (narrow and broad scope).
[4]Seizures event is defined by Convulsions SMQ (broad and narrow scope).
[5]Fall event is defined by the preferred Term "Fall".

5.7.5. Clinical Laboratory Data

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

1. 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
2. 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
3. Urinalysis: specific gravity, potential of hydrogen (pH), color, blood, glucose, ketones, protein, white blood cells, red blood cells

5.7.5.1. Quantitative analyses

For numeric laboratory parameters, actual values 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 actual values (with standard error) for numeric laboratory parameters at each visit will be provided.

Summary of change from 221AD304 baseline and percent change from 221AD304 baseline for numeric laboratory parameters will be presented at each visit. Number of evaluable subjects, mean, standard deviation, median, 25% and 75% quartiles, minimum and maximum values will be presented at each visit.

Visit windows for by visit summaries

For laboratory by visit summaries, the analysis visit should be defined using visit windows (see Table 7).

Table 7 Visit Windows for Laboratory by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
221AD304 baseline	1	Last value prior to the first dose of aducanumab
Week 52	365	[2, 539]
Week 102	714	[540, 896]
Week 154	1078	>=897

5.7.5.2. 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. 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 221AD304 baseline to high/low status will be presented for hematology, blood chemistry and urinalysis numeric parameters, and shifts from 221AD304 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) to be included in the analysis.

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 in the active treatment period and a baseline value not potentially clinically significant (including missing) to be included in the analysis.

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

Clinical Laboratory Abnormality Criteria		
Parameter name	**PCS Low**	**PCS High**
HEMATOLOGY		
White blood cells	<3.0 x 109/L	>16 x 109/L
Lymphocytes	<0.8 x 109/L	>12 x 109/L
Neutrophils	<1.5 x 109/L	>13.5 x 109/L
Monocytes	N/A	>2.5 x 109/L
Eosinophils	N/A	>1.6 x 109/L
Basophils	N/A	>1.6 x 109/L
Red blood cells	≤3.5 x 1012/L	≥6.4 x 1012/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 109/L	≥700 x 109/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

Clinical Laboratory Abnormality Criteria		
Parameter name	**PCS Low**	**PCS High**
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		

This table is from 221AD301 and 221AD302 study SAPs.

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. A listing of subjects with potential serious hepatotoxicity will be provided.

5.7.6. C-SSRS Data

The Columbia Suicide Severity Rating Scale (C-SSRS) is an assessment that evaluates suicidal ideation and behavior.

A summary of post-baseline C-SSRS results will be presented the following information: number of subjects with at least one post-baseline C-SSRS assessment, number of subjects with post-baseline suicidal ideation, number of subjects with post-baseline suicidal behavior, number of subjects with post-baseline suicidal ideation or behavior, and number of subjects with post-baseline non-suicidal self-injurious behavior.

The following listings will be provided:

a) Listing of C-SSRS for subjects with post-baseline suicidal ideation, suicidal behavior, or non-suicidal self-injurious behavior

b) Listing of C-SSRS for subjects with post-baseline suicidal ideation

c) Listing of C-SSRS for subjects with post-baseline suicidal behavior

5.7.7. ECG Data

The 12-lead electrocardiograms (ECG) data will be summarized using shift table based on subjects with at least one post-baseline ECG assessment and whose baseline ECG assessment was not abnormal. This includes shift from normal or unknown at baseline to abnormal post-baseline, shift from normal or unknown at baseline to not adverse event or abnormal post-baseline, and shift from normal or unknown at baseline to adverse event post-baseline.

The number and percentage of subjects with shifts to abnormal ECG, not adverse events, and subjects with shift to abnormal ECG, adverse events at any time during post-baseline will be summarized.

5.7.8. 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.

Clinically relevant post-baseline abnormalities in vital signs will be presented with criteria defined below:

- < 36 °C and > 38°C for body temperature
- < 60 bpm and > 100 bpm for pulse
- < 90 mmHg, > 140 mmHg and > 160 mmHg for systolic blood pressure
- < 50 mmHg, > 90 mmHg and > 100 mmHg for diastolic blood pressure
- ≥ 7% increase and ≥ 7% decrease from baseline in weight
- < 12 breaths/min and > 20 breaths/min for respiratory rate

5.7.9. Physical Examination and Neurological Examination

Clinically significant abnormalities found at a physical examination or neurological examination will be reported as AEs and will be included in the analyses of AEs.

[redacted]

5.10. Immunogenicity

5.10.1. Background

Definition of baseline value

221AD304 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, 221AD304 baseline value is missing and will be treated 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 (1) a subject is antibody negative at 221AD304 baseline; or (2) a subject is antibody positive at 221AD304 baseline but the post-baseline antibody response is more than 2-fold increase in titer compared to the 221AD304 baseline response.

Persistent and transient positive responses:

Subjects with treatment-emergent positive anti-aducanumab antibody responses will be further classified as transient positive under the following conditions:

- if only a single positive evaluation occurs which is not at the last available time point
- or if more than 1 positive evaluation occurs < 112 days (16 weeks) apart and there is at least 1 negative evaluation that occurs thereafter

Subjects with treatment-emergent positive anti-aducanumab antibody responses will be further classified as persistent positive under the following conditions:

- if more than one consecutive positive evaluation occurs ≥ 112 days (16 weeks) apart
- or if a single positive evaluation occurs at the last available time point with no further negative results available

5.10.2. Immunogenicity Analysis

Immunogenicity population will be used to analyze immunogenicity data. An immunogenicity summary table will be presented showing the number of subjects with anti-aducanumab antibody positive response at any time (including baseline), the number of subjects with treatment-emergent anti-aducanumab antibody positive response at each scheduled test visit, the number of subjects with transient positive response, and the number of subjects with persistent positive response. A listing of immunogenicity data for subjects with anti-aducanumab antibody positive results will also be provided. The immunogenicity summary table will be repeated for the core period.

Visit windows for by visit summaries

For immunogenicity by visit summaries, the analysis visit should be defined using visit windows (see Table 9 below).

Table 9 Visit Windows for Immunogenicity by Visit Summaries

Analysis visit	Target visit day	Analysis visit window
221AD304 baseline	1	Last value prior to the first dose of aducanumab
Week 24	169	[2, 252]
Week 48	337	[253, 420]
Week 72	505	[421, 609]
Week 102	714	[609, 804]
Week 128	897	[805, 986]
Week 154	1078	>=987

6. Changes from Protocol-Specified Analyses

Table 10 lists the changes from protocol-specified analyses, including all analyses that are added, removed, and modified from those originally outlined in the protocol along with associated rationale/background for each change.

Table 10 Summary of Changes from Protocol-Specified Analyses

Protocol	SAP	Rationale/Background
[redacted]	Excluded	[redacted]
16.4.2.2. Clinical Laboratory Results Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created	Excluded	CTCAE toxicity grade analyses are replaced with potential clinically significant (PCS) abnormality analyses.

7. Summary of Changes from the Previous Version of the SAP

Due to early termination of the study, all displays will be presented by safety analysis groups (0 dose of BIIB037, 0 dose of 10 mg/kg, >0 dose of 10 mg/kg in feeder studies), or safety analysis groups stratified by laboratory [redacted] if needed.

Analysis related to exposure/follow-up adjusted incidence rate, by previous exposure duration groups, and time-to-event analyses (Kaplan-Meier analysis) are excluded.

Table 11 provides details on the changes and reasons for changes from the previous version of the SAP.

Table 11 Changes and Reasons for Changes from the Previous Version of the SAP

SAP Version 1.0	SAP Version 2.0	Rationale/Background
Section 1 Description of objective and endpoints	• [redacted]	[redacted]
Section 3.2 Background Characteristics	Excluding non-STAN mandatory analysis on: • Time to treatment discontinuation and study withdraw. • Screening failure subjects. • Number of subjects by region, country. • Number of subjects completed the treatment/study by region and country. • Change in AD symptomatic medications. • Exposure in the feeder studies period. • Baseline clinical stage Modifications: • Add categories "27-39, 40-52, 53-65, and >65" to exposure dose categories.	Early termination of the study and abbreviated CSR 221AD304 baseline clinical stage (MCI due to AD, mild dementia, moderate dementia, or severe dementia) - In the opinion of the Investigator and not based on National Institute on Aging - Alzheimer's Association criteria (NIA-AA) [McKhann 2011]. Modified due to the LTE treatment period was added to the study after SAP 1.0 signoff.

SAP Version 1.0	SAP Version 2.0	Rationale/Background
	• Add "A listing will be generated for subjects with protocol alternations due to COVID-19, based on the data on the protocol alternations due to COVID-19 collected from the protocol alternation CRF page."	
3.3 Efficacy Analysis	Excluded	Early termination of the study and abbreviated CSR
[redacted]	Excluded	[redacted]
3.5 Safety Analysis	AE summary Exclude: 1. Summary of AEs stratified by ARIA-E in feeder study 2. AEs occurred within 2 hours from infusion 3. AEs by 12 weeks intervals from first infusion 4. AE from subjects with treatment-emergent positive anti-BIIB037 antibody AE changes: [redacted] 6. Add listing of non-treatment emergent AEs. ARIA summary exclude: 7. ARIA analysis by previous exposure duration. [redacted] ARIA summary changes: 9. ARIA duration will be only based on MRI dates, no matter for symptomatic or asymptomatic ARIA. Laboratory analysis:	Early termination of the study and abbreviated CSR AE and ARIA analyses that being considered not informative are excluded and additional analyses are added.

SAP Version 1.0	SAP Version 2.0	Rationale/Background
	10. Exclude Grade analysis based on CTCAE. AESI: 11. Add other significant AE analyses on CNS hemorrhages, hypersensitivity, seizure, and fall.	
[redacted]	Excluded	[redacted]
5.7.7 Vital Signs	The clinically relevant abnormalities criteria are updated.	Updated based on Biogen standard analysis table.

8. References

EMBARK_Site Communications Letter_Final_19Sep2023

EMBARK_Site Communications Letter_Final_28Sep2023_All Countries (excluding France)

EMBARK_Site Communications Letter_Final_28Sep2023_(FRANCE)

EMBARK Important Study Update – (Global) excluding France_31Jan2024

EMBARK Important Study Update – (France Only)_31Jan2024

EMBARK_Updated Communication_Global_22Feb2024_Final_signed

EMBARK_Updated Communication_France only_22Feb2024_FinalSigned

221AD304 Protocol Clarification Letter 13Feb2024

9. APPENDICES

9.1. Safety, [redacted], and Immunogenicity Analysis Display

Analysis display SA

0 dose of BIIB037	Pre-treated with BIIB037			Total
	0 dose of 10 mg/kg	>0 dose of 10 mg/kg	Total	

Analysis display SB

0 dose of BIIB037			Pre-treated with BIIB037					
			0 dose of 10 mg/kg			>0 dose of 10 mg/kg		
[redacted]	[redacted]	Total	[redacted]	[redacted]	Total	[redacted]		Total