COVER PAGE

Official Title:	A Phase 3b/4 Randomized, Double-Blind, Placebo-Controlled, Parallel- Group Study to Verify the Clinical Benefit of Aducanumab (BIIB037) in Participants with Alzheimer's Disease
NCT Number:	NCT05310071
Document Date:	06 May 2024

STATISTICAL ANALYSIS PLAN

Version No.: 1.0

Date: 6 May 2024

Author: [redacted]

Study Title: A Phase 3b/4 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Verify the Clinical Benefit of Aducanumab (BIIB037) in Participants with Alzheimer's Disease

Name of Study Treatment: Aducanumab

Protocol No.: 221AD305

Study Phase: 3b/4

APPROVAL

This document has been reviewed and approved by:		
[redacted], PhD SMT Statistician	DocuSigned by: [redacted] Signature	14-May-2024 Date
[redacted], MS Statistician	DocuSigned by: [redacted] Signature	14-May-2024 Date
[redacted], PhD Program Statistician	DocuSigned by: [redacted] Signature	14-May-2024 Date
[redacted], PhD SMT Medical Director	DocuSigned by: [redacted] Signature	14-May-2024 Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
V1.0	6 May 2024	Not applicable

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
Abs	antibodies
AD	Alzheimer's disease
ADA	Anti-drug antibodies
ADAS-Cog13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ApoE	apolipoprotein E
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-hemorrhage
AST	aspartate aminotransferase
BMI	body mass index
BL	baseline
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
COVID-19	coronavirus disease 2019
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DHA	Directions for handling and administration
[redacted]	[redacted]
DSF	Diagnostic staging form
[redacted]	[redacted]st
ECG	electrocardiogram

Abbreviation	Definition
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
EMACC	Early Alzheimer's Disease/Mild Cognitive Impairment Alzheimer's Cognitive Composite
EQ-5D-5L	health-related EuroQoL 5-dimension instrument
ET	early termination
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration
FU	follow-up
GST	Global statistical test
HEOR	Health economic and outcomes research
HLT	high level term
IA	interim analysis
iADRS	Integrated Alzheimer's Disease Rating Scale
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IXRS	Interactive Voice/Web Response System
LAR	Legal Authorized Representative
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
[redacted]	[redacted]
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI-10	Neuropsychiatric Inventory-10

Abbreviation	Definition
PA	primary analysis
PC	placebo-control
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)
PT	preferred term
PV4	protocol version 4
Q4W	every 4 weeks
QoL	quality of life
QoL-AD	Quality of Life in Alzheimer's Disease
RBANS	Repeatable Battery for the Assessment of Neuropsychological Disease Severity
RDV	Research Diagnostic Verification
RUD-Lite	Resource Utilization in Dementia – Lite Version
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SM	Site Monitor
SMQ	standardized MedDRA query
SOC	system organ class
SUVR	standardized uptake value ratio
TMA	Therapeutic Medical Advisor
UB	Unblinded
ULN	Upper limit of normal
[redacted]	[redacted]
WHO	World Health Organization
[redacted]	[redacted]

1. Introduction

Study 221AD305, also called the ENVISION study, was designed as a Phase 3b/4 randomized, double-blind, placebo-controlled, parallel-group study to verify the clinical benefit of aducanumab (BIIB037) in participants with Alzheimer's disease (AD). The primary study objective was to verify the clinical benefit of monthly doses of aducanumab on Clinical Dementia Rating Sum of Boxes (CDR-SB) relative to placebo at Week 78. The total duration of the study for each participant was planned to be approximately 130 weeks, including a series of screening visits within 8 weeks before administration of the first dose of study treatment, and a 104-week placebo-controlled treatment period followed by a safety follow-up (FU) visit 18 weeks after the final dose of study treatment.

Participants were scheduled to receive IV infusions of aducanumab or placebo approximately Q4W for 104 weeks. Participants were randomized to receive aducanumab: placebo in a 2:1 ratio. Aducanumab was initiated with a 6-dose titration period prior to reaching the target dose of 10 mg/kg.

Early termination of the study was announced on 31 January 2024. The decision was not related to any safety or efficacy concerns. Enrollment in 221AD305 was halted immediately upon the announcement. As a result, the planned primary analysis and optional interim analysis that were outlined in the 221AD305 protocol version 2.0, dated 15 April 2022, will not be conducted. Biogen offered the study participants the option to continue to receive treatment in a blinded fashion until 1 May 2024 to allow study participants and their health care providers sufficient time to plan future treatment decisions. Study participants were required to perform an early termination (ET) visit within 30 days of their last dose and a safety FU visit 12 weeks after their last dose. Due to the early termination of the study, an abbreviated clinical study report is planned.

The purpose of this SAP is to delineate the analyses that are planned for the final report. The primary endpoint, key secondary endpoints, and secondary endpoints of the study will not be evaluable due to the small sample size at the primary timepoint of Week 78 and key timepoints of Week 104 and Week 106. Instead, the focus of the final analysis will be summarizing the available safety data that were collected during the study to the full extent, and summarizing the available disposition, baseline characteristics, demographics, exposure, and protocol deviation data. In addition, the primary endpoint CDR-SB will be summarized by visit.

2. Study Overview

2.1. Study Objectives and Endpoints

As mentioned in Section 1, the primary endpoint, key secondary endpoints, and secondary endpoints of the study will not be evaluable due to the small sample size at the primary timepoint of Week 78. Instead, the focus of the final analysis will be to summarize the full safety data and the data on disposition, baseline characteristics, demographics, exposure, and protocol deviations that were collected during the study. The primary endpoint CDR-SB will also be summarized by visit.

As a result, the tertiary study objectives and endpoints related to safety and immunogenicity will be the only study objectives and endpoints to be described in this section.

2.1.1. Tertiary Objectives and Endpoints Related to Safety and Immunogenicity

- To assess the safety of monthly doses of aducanumab
  - Incidence of AEs and SAEs
  - Incidence of ARIA-E and ARIA-H
  - Clinical laboratory shifts in reported values
- To assess the immunogenicity of aducanumab
  - Incidence of anti-aducanumab antibodies (Abs) in serum over time

2.2. Study Design

2.2.1. Study Overview

Study 221AD305 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in participants with early Alzheimer's disease, including those with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. Enrollment will be monitored, via the IRT system, so that the population of participants with mild Alzheimer's disease represents approximately 50% of the total number of participants enrolled in the study. The study will include up to 24 months of treatment as well as screening and post-treatment FU periods. Approximately 1512 participants will be enrolled across an estimated 220 centers globally.

The primary study objective is to verify the clinical benefit of monthly doses of aducanumab on CDR-SB relative to placebo at Week 78. Key secondary objectives include assessment of the effect of monthly doses of aducanumab on clinical decline as compared to placebo at Week 78 as measured by a variety of cognitive and functional scales such as those implemented in the Phase 3 studies (i.e., ADCS-ADL-MCI, ADAS-Cog13, MMSE, and NPI-10), as well as the composite scale, iADRS, which is a linear combination of the ADAS-Cog13 and the ADCS-ADL-MCI. Secondary objectives include assessment of the effect of monthly doses of aducanumab on change in amyloid PET and tau PET signal at Week 78 and 104 as compared with placebo, as well as all clinical endpoints (i.e., CDR-SB, iADRS, ADCS-ADL-MCI, ADAS-Cog13, MMSE, and NPI-10) assessed at the Week 106 timepoint. Secondary objectives also include an assessment of the effect of monthly doses of aducanumab on the GST composite z-score, defined as the average of standardized z scores of the CDR-SB, ADCS-ADL-MCI, and ADAS-Cog13, at Weeks 78 and 106. Tertiary objectives include confirmation of the safety, tolerability, and associated immunogenicity of aducanumab and its PK characteristics, and HEOR and QoL metrics. [redacted]

[redacted]

Participants will receive IV infusions of aducanumab or placebo approximately Q4W for 104 weeks. Participants will be randomized to receive aducanumab or placebo in a 2:1 ratio. The randomization will be stratified by geographical region, baseline disease stage (MCI due to Alzheimer's disease or mild Alzheimer's disease dementia), and ApoE ε4 status (carrier or noncarrier). Randomization will be performed using IRT. Aducanumab will be initiated with a 6-dose titration period prior to reaching the target dose of 10 mg/kg, as detailed in Protocol Section 3.1.2 and Figure 1.

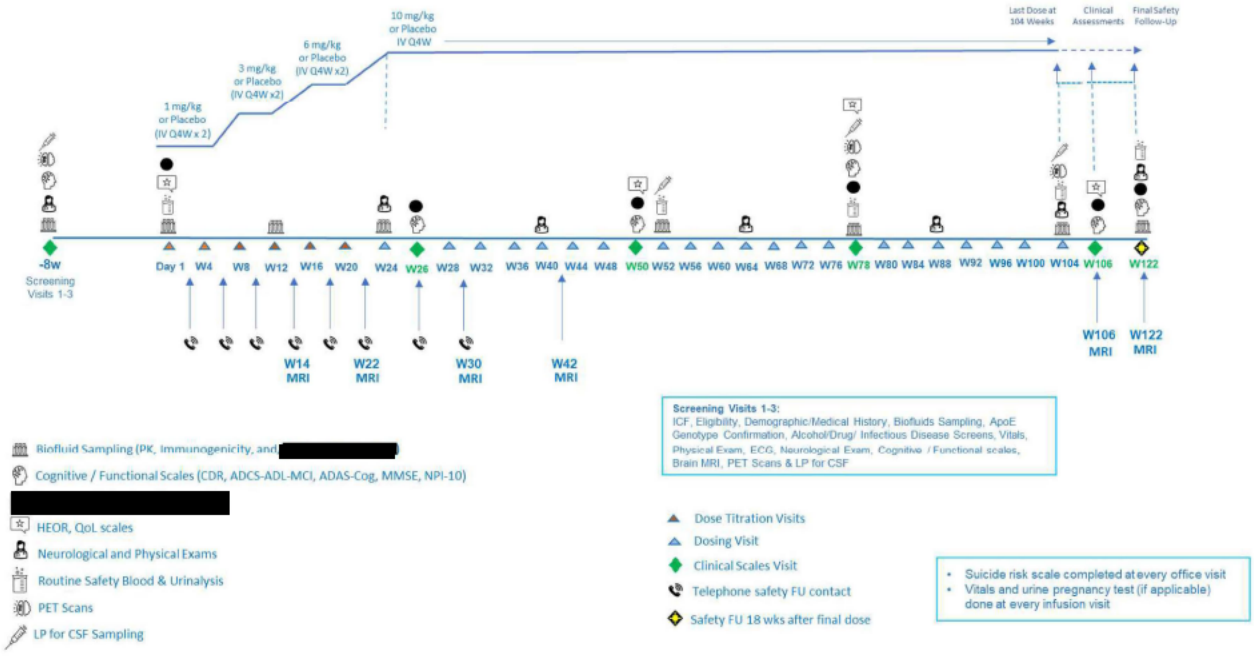
Investigators, outcome assessors, study site staff (except for the designated unblinded pharmacist/technician), study participants, and informants will be blinded to the randomized treatment assignment.

In the original study design per protocol, the total duration of the study for each participant was approximately 130 weeks, including a series of screening visits within 8 weeks before administration of the first dose, and a 104-week placebo-controlled treatment period. Participants were additionally planned to undergo a safety FU visit 18 weeks after the final dose of aducanumab.

See Figure 1 for originally planned schematic of the study design per protocol.

For schedule of activities, see Protocol Section 1.3.

Figure 1 Study Design Schematic



2.2.2. Substudies

In the original study design per protocol, three optional longitudinal substudies were planned to be completed within this study in subsets of consenting participants, as follows:

- An amyloid PET substudy involving assessments of amyloid by PET scan at Screening and at Weeks 78 and 104
- A tau PET substudy involving assessments of tau by PET scan at Screening and at Weeks 78 and 104
- [redacted]

For participants of these studies, study-specific procedures were required for provision of baseline PET scans [redacted]

2.2.3. Study Conduct Following Announcement of Study Termination

On 31 January 2024, Biogen announced the early termination of Study 221AD305. The decision was not related to any safety or efficacy concerns. Enrollment in 221AD305 was halted immediately upon the announcement. At that time, over 1000 participants had been enrolled in the study.

Following early termination of the study, Biogen offered the study participants the option to continue to receive treatment in a blinded fashion until 1 May 2024 to allow study participants and their health care providers sufficient time to plan future treatment decisions.

2.2.4. Procedures for Releasing Treatment Assignments Following Announcement of Study Termination

As described in 221AD305 unblinding plan version 3.4, Biogen also decided to provide the treatment assignment information to the investigators, site staff and study participants in a patient-centric fashion, such that all study participants' treatment assignments are planned to be released to the investigators and designated site staff after the date of last patient last dose and prior to the date of the final database lock. In the event that a study participant is not interested in continuing treatment within the study until 1 May 2024 and decides to request the treatment assignment release prior to the date of last patient last dose, Biogen agreed to release treatment assignment to the corresponding investigator and the designated site staff following such requests. Blinded Biogen/IQVIA study team members will remain blinded and will not have access to the subject treatment assignments until final database lock.

2.2.5. Changes to Study Execution Following Announcement of Study Termination

1) On 31 January 2024, it was announced that as the study is early terminated, participants enrolled in the study may continue receiving treatment until 01 May 2024. Screening and enrollment would be closed for the study. The participant and care partner, as applicable, should return to the site for a safety follow-up visit 30 days after their last dose. On 16 February 2024, Biogen released a document 221AD305 ENVISION Clarification Letter_16FEB2024_Final Signed, which updated the changes to study execution: Early Termination Visit: assessments and timing (Protocol Section 1.3, Table 2)

Due to the early termination of the study, all participants will be asked to complete this early termination (ET) visit, which, to reduce participant burden, will be limited to assessments related

to participant safety. These assessments are reported in Table 1. Participants should complete this ET visit within 30 days of their last dose of study treatment.

2) Follow-up/End of Study (FU/EOS) Visit: assessments and timing (Protocol Section 1.3, Table 2)

Due to the early termination of the study, all participants are asked to complete their Follow-up/End of Study visit (also referred to as the safety follow-up visit) at 12 weeks (+/- 3 days) after the participant's last dose of study treatment. Participants who wish to withdraw and not receive additional dosing through 01 May 2024 are still encouraged to have a safety follow-up visit 12 weeks from their last dose of study treatment. In addition, similar to the ET visit, the number of assessments that need to be completed is now reduced to lessen participant burden. These assessments are reported below in Table 1. 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 visit within 30 days, as defined in Table 1.

3) Substudies (Protocol Section 5.1)

Due to the early termination of the study, all the longitudinal substudies are terminated and samples will no longer be collected for amyloid PET, tau PET, [redacted] at Weeks 52, 78, and 104/ET.

4) Management of participants who had already discontinued treatment and who were following the visit schedule defined in Table 3 (Protocol Section 1.3, Table 3)

Due to the early termination of the study, participants who discontinued treatment but agreed to remain in the study and follow the abbreviated visit schedule will be asked to complete their ET visit within 30 days and their FU/EOS visit (safety follow-up) visit 12 weeks after their last dose. If they have already had an ET visit following their last dose of treatment, then the ET visit does not need to be repeated. If 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 visit within 30 days, as defined in Table 1.

5) Visits at Week 26, Week 50, and unscheduled for Change in AD Meds (Protocol Section 1.3, Table 1 and Table 2)

Due to the discontinuation of the Aduhelm program and the early termination of the study, the visits at Week 26, Week 50, and unscheduled for change in AD medication will no longer need to be conducted as only clinical efficacy assessments are collected at these visits.

Table 1 Revised Schedule of Activities for Early Termination Visit and Follow-up/End of Study Visit for the Terminated ENVISION Study

Study Assessments[1]	**Early Termination Visit (within 30 days of last dose)**	**Follow up/End of Study Visit[2,3] (12 weeks after last dose +/- 3 days)**
Body Weight	X	X
Urine Pregnancy Test[4]	X	X

Study Assessments[1]	**Early Termination Visit (within 30 days of last dose)**	**Follow up/End of Study Visit[2,3] (12 weeks after last dose +/- 3 days)**
Physical Exam	X	X
Neurological Exam	X	X
12-Lead ECG	X	X
Vital Signs[5]	X	X
Hematology, Blood Chemistry, and Urinalysis	X	X
Anti-Aducanumab Ab	X	X
Coagulation Panel	X	X
Brain MRI[6]	X	X
C-SSRS-SLV	X	X
Concomitant Therapy and Procedures	Monitor and record continuously throughout the study	
SAE Reporting	Monitor and record continuously throughout the study	
AE Reporting	Monitor and record continuously throughout the study	

[1]Clinical efficacy assessments (MMSE, CDR, ADAS-Cog13, ADCS-ADL-MCI, NPI-10, [redacted], [redacted] RUD-Lite, [redacted], QoL-AD) have been removed from the Early Termination Visit and safety follow-up visit to reduce participant burden.

[2]All participants enrolled in the study are to return to the study site at 12 weeks after the last dose of study treatment for Follow up/End of Study visit. The follow-up visit is important and is intended to monitor the participant after a washout period that is based on the drug's half-life. However, if a study participant with their healthcare provider decides to initiate a disease-modifying Alzheimer's treatment outside of the clinical trial prior to completing all mandated protocol study visits, then the participant should withdraw from the study as per protocol (Protocol Section 8.3, Withdrawal of Participants from Study). For these patients when they are withdrawn, no further study visits should be completed.

[3]If it has been more than 12 weeks since the participant's last dose, participants who had discontinued treatment early but had agreed to remain in the study (following the Table 3 Schedule of Activities in the protocol) should complete this Follow-up visit within 30 days of the clarification letter.

[4]Pregnancy testing will only be required for women of childbearing potential.

[5]Vital signs will include SBP, DBP, heart rate, body temperature, and respiratory rate. Vital signs will be measured with the participant supine and after the participant has been resting for at least 10 minutes. [6]If an MRI is performed within 14 days of the ET visit, the MRI can be omitted at the ET visit.

2.2.6. Sample Size Considerations

The sample size was mainly based on results from the primary analysis of Study 221AD302. Results from the post-PV4 population (i.e., the 221AD302 and 221AD301 protocol amendment in which the high dose of aducanumab was increased from 6 mg/kg to 10 mg/kg) in pooled data from Studies 221AD302 and 221AD301 were also considered. A total sample size of 1512 participants was planned to have approximately 90% power to detect a mean difference of 0.48 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power

calculation was based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, an SD of 2.33, a dropout rate through Week 78 of 27%, and a randomization ratio of 2:1. The assumed mean difference of 0.48 between the 2 treatment groups represented an approximately 24% reduction in the placebo mean change from baseline at Week 78 if the placebo mean change is estimated to be 2.

In the original study design per protocol, a blinded assessment of the pooled SD for the primary efficacy endpoint may be performed approximately 3 months prior to the completion of enrollment and the sample size may be increased as a result. The sample size could also be increased using internal and external clinical study results that become available after the start of this study. In addition, the sample size may be increased if the dropout rate through Week 78 is estimated to exceed 27%. The sample size will not be reduced based on this assessment.

Following the study early termination decision on 31 January 2024, the blinded assessment of the pooled SD will not be conducted.

3. Definitions

3.1. Dates and Points of Reference

- Study Day 1: the date of the first dose of study treatment (aducanumab or placebo)
- Study Day
  - For a date on or after Study Day 1

    Study Day = (Date of Interest) – (Study Day 1) + 1
  - For a date before Study Day 1

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

  Unless otherwise specified, the first dose date is equivalent to study Day 1 defined above, the last dose date is the date of the last administration of study treatment.
- End of Treatment (EOT)

  EOT date is the last dose date, i.e., Week 104 for treatment completers and at any time during the placebo-controlled (PC) treatment period for early study treatment terminators.
- Early Termination (ET)

  Participants who are withdrawn from the study after receiving ≥ 1 dose(s) of study treatment should complete the ET visit after the reason for withdrawal is identified. For such participants, efficacy assessments specified at the ET visit are not required if the participant discontinues treatment within 3 months of the previous efficacy assessment visit, and no significant changes in cognitive status are suspected by the Investigator; the site should notify the Sponsor and Medical Monitor in such cases. Participants who are withdrawn from the study are also to return to the site for a FU visit 18 weeks after receiving their last dose of study treatment. Participants should undergo an ET visit unless withdrawal is due to death or withdrawal of consent.

  Following the study early termination decision on 31 January 2024, all study participants should complete an ET visit within 30 days after their last dose.

  The ET visit date refers to the date of visit for the ET visit.
- End of Study (EOS)

  For participants who complete the study, the EOS visit is defined as the Week 122 visit; for participants who early terminate in the study, the EOS visit is defined as the scheduled follow-up (FU) visit, 18 weeks after their final dose.

  Following the study early termination decision on 31 January 2024, study participants were required to perform a FU visit 12 weeks after their last dose, instead of 18 weeks.

  The EOS date is the End of Study date recorded on the End of Study eCRF page.
- Visit window for 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 Section 9.1.

3.2. Study Treatment

Participants will be assigned to 1 of 2 treatment groups in a 2:1 ratio of aducanumab or placebo administered IV Q4W, respectively. Treatment is initiated via titration, which has been demonstrated to result in a lower incidence of ARIA. Titration will start at 1 mg/kg and will escalate to 3, 6 and 10 mg/kg.

Study treatment in this SAP, unless otherwise specified, refers to the blinded treatment of either aducanumab or placebo that is administrated based on the dosing regimen in this study. Throughout this SAP, study treatment and study drug are equivalent and used interchangeably.

3.3. Study Periods

- Study baseline period

  The study baseline period is defined as the period from Screening Visit 1 to the day prior to the first administration of study treatment.

- On treatment period

  On treatment period is defined as the period from the first administration of study treatment to 28 days after the last administration of study treatment.

- Baseline value

  Baseline value is defined as the most recent non-missing measurement collected prior to Study Day 1 dose date/time. If the time of the measurement is missing, measurements taken on Day 1 are considered as prior to Study Day 1 dose for the following data domains: demography, disease history, disease activity and characteristics, clinical endpoint, ECG, laboratory test result, medical history, physical examinations, participant status, and vital signs. Exceptions are specified as below:
  - Tau PET baseline value is defined as the most recent non-missing measurement relative to Study Day 1 dose date/time and collected prior to the third dose date or scheduled Week 12 visit date whichever comes first for participants who received more than one dose of study treatment, or within 84 days of the first dose for participants who only received one dose of study treatment, or as the last non-missing measurement collected during screening for not dosed participants.

- Change from baseline is defined as post-baseline value minus baseline value
- Percent change from baseline is defined as post-baseline value minus baseline value then divided by baseline value
- 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 5.7.1.1.

3.4. Key Derived Variables

3.4.1. Composite Score Derivation of 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.

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].

3.5. Stratification Factors

The study randomization stratification factors and corresponding categories are listed as follows:

- Geographical region:
  - North/South America
  - Europe/Australia
  - Asia (Korea/Japan)
  - China
- Baseline disease stage:
  - MCI due to Alzheimer's disease
  - Mild Alzheimer's disease dementia
- ApoE ε4 status:
  - Carrier
  - Noncarrier

3.6. Analysis Sets

Randomized Set

The randomized set includes all the participants who were randomized.

Full Analysis Set (FAS)

The FAS includes all participants who were randomized and received at least 1 dose of study treatment (aducanumab or placebo). In analyses performed on the FAS, participants will be analyzed, based on the intention-to-treat principle, according to their randomized treatment assignment regardless of treatment received.

Safety Analysis Set

The Safety Analysis Set includes all participants who were randomized and received at least 1 dose of study treatment (aducanumab or placebo), essentially the same set of participants included in the FAS. In analyses performed on the Safety Analysis Set, participants will be analyzed according to their actual treatment received.

Safety MRI Analysis Set

The Safety MRI Analysis Set includes all participants who were randomized and received at least 1 dose of study treatment (aducanumab or placebo) and had at least one post-baseline MRI assessment.

Immunogenicity Analysis Set

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

4. List of Planned Study Analyses

Below is a list of planned study analyses per protocol.

4.1. Interim Analysis

According to the protocol, interim analyses for superiority may be performed after approximately 60% of the participants have completed the 18-month visit (or discontinued). The alpha level at the interim analysis will be determined using the O'Brien-Fleming boundary approach. The alpha level for the final analysis will be adjusted to achieve an overall type I error of 0.05.
If an interim analysis is performed, the interim analysis will be performed by an independent group external to the Sponsor that will not be involved in the conduct of the study after unblinding. A potential role for the IDMC in this interim analysis will be fully described in the IDMC charter. The aim of this interim analysis is to allow the possibility to verify the clinical treatment benefit of aducanumab early.

If an IA is to be performed, prior to the unblinding for interim analysis, the SAP for the interim analysis will be finalized and signed off. The criteria for determining superiority for the interim analysis will be defined in the interim analysis SAP. This is to ensure that all interim analysis statistical analyses will be pre-specified before the interim analysis.
Following the study early termination decision on 31 January 2024, the optional interim analysis will not be conducted.

4.2. Primary Analysis

The primary analysis (PA) of the study will be conducted when all the participants have had an opportunity to complete the Week 78 visit. After the last patient completes Week 78, the data will be soft locked, and all efficacy endpoints and available safety data will be analyzed while the study is ongoing and continues to capture efficacy, safety, and immunogenicity data beyond Week 78. The PA aims to address all study objectives that use data up to Week 78. This primary analysis will support registration with regulatory agencies. Analyses of Week 78 endpoints will only include data up to Week 78 visit.

This unblinded analysis will be performed by a small internal independent team (separate from the study team).

Following the study early termination decision on 31 January 2024, the planned primary analysis will not be conducted.

4.3. Final Analysis

The final analysis (FA) of the study will be conducted at the end of the study after the last participant completes the last visit of the study and the final database is locked. The FA will evaluate all efficacy endpoints and available safety data, and a review of the complete efficacy and safety collected during the entire study is included.

Following the study early termination decision on 31 January 2024, the final analysis will be conducted at the end of the study after the last participant completes the last visit of the study and the final database is locked following the study conduct that was described in Section 2.2.3. All analyses specified in this SAP will be conducted in the FA with all data collected during the entire study and available in the database.

5. Statistical Methods for Planned Analyses

5.1. General Principles

5.1.1. High Level Description of Analyses

This SAP defines the analysis scope for FA. This SAP document supersedes the statistical section in the protocol and provides details for those analyses pre-specified before any planned study unblinding of the Biogen/IQVIA blinded team and before the final database lock. Additional ad hoc analyses may be conducted if needed after data unblinding at the final database lock. If there are any significant modifications in the SAP after data unblinding at the final database lock, those must be documented in the clinical study report accordingly.

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

As mentioned in Section 1., due to the early termination of the study, an abbreviated CSR is planned. Accordingly, many endpoints will not be summarized. The data that will be summarized are full safety data, and data on disposition, baseline, demographics, exposure, protocol deviations and CDR-SB. Also, any listings that are routinely produced for Biogen clinical studies will not necessarily be mentioned in this SAP.

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.

5.1.2. Handling of Missing Data on Clinical Measures

If any of the individual items for the CDR-SB, ADAS-Cog13, ADCS-ADL-MCI, and MMSE are missing, the total score of the corresponding endpoint will be imputed by prorating the observed scores [van Ginkel 2010].

For ADAS-Cog 13, 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 NPI-10 will be imputed using the same prorating principle if only 1 item (out of 10) is missing.

5.2. Participant Accountability

Disposition of participants will be summarized, and the summary data will include number (%) of participants randomized and dosed, number (%) of participants who completed the treatment/study, number (%) of participants who discontinued treatment and/or withdrew from study. For participants 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.

5.3. Demographic and Baseline Characteristics

The demographic data including age, gender, ethnicity, race, region, height, weight, and body mass index (BMI) will be summarized. Age will also be categorized and presented using the following subgroups: <60, 60-70, 71-80, 81-85, >85.

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 CDR-SB, CDR cognitive subscore, CDR functional subscore, CDR global score, MMSE, ADAS-Cog 13, ADCS-ADL-MCI, NPI-10, amyloid PET SUVR, tau PET SUVR (available in a subset of sites and participants), 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). 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.

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

Previous treatment of AD stopped prior to the date of first infusion, duration of previous therapies and reason for stopping treatment will be summarized by treatment group.

The data will be summarized by treatment groups for participants in FAS. Participants listings will be generated for demographics and baseline characteristics.

Note that ApoE ε4 status is defined as follows:

- ApoE ε4 carrier: ε2/ ε4, ε3/ ε4, ε4/ ε4
  - Heterozygote: ε2/ ε4, ε3/ ε4
  - Homozygote: ε4/ ε4
- ApoE ε4 noncarrier: ε2/ ε2, ε2/ ε3, ε3/ ε3

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 (see Section 9.2). The major protocol deviations will be summarized for FAS participants by treatment groups. Major protocol deviations for all FAS participants will be listed. Major protocol deviations related to coronavirus disease (COVID-19) may also be summarized and listed.

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 COVID-19 Impact log CRF page.

A listing will be generated for subjects whose treatment assignments were released to the investigators and designated site staff prior to the final database lock, with the date of treatment assignment release presented. See Section 2.2.2. for details about this unblinding procedure.

5.5. Study Treatment Exposure and Concomitant Medications

5.5.1. Study Drug Exposure and Study Drug Compliance

A summary table of study drug exposure and compliance will be provided for participants in FAS. 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, and >26) 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) 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 participant is expected to take until the date of last infusion) ×100, will be summarized as a continuous variable.

Due to the use of a 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 participants 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), maximum dose level received, and cumulative dose (as a continuous variable).

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

A listing of subjects whose actual treatment group is different from their randomized treatment group will be provided.

5.5.2. Concomitant Medications

The number (%) of participants taking concomitant medication and non-drug therapies will be summarized for participants in FAS. 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. 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 ongoing, 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 ongoing, 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 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. AD symptomatic medications are defined as anticholinesterase (cholinesterase inhibitors) and memantine drugs in the WHO medication dictionary (version: WHODrug Global B3 Sep2023 or a later version if applicable). The number (%) of participants taking concomitant AD symptomatic medications at baseline, number of participants using Cholinesterase inhibitors only, Memantine only, or both at the baseline will be summarized by treatment group for FAS.

5.6. Efficacy Endpoints

A summary table of change from baseline by visit in CDR-SB will be presented using descriptive summary statistics, on the FAS.

No statistical modeling will be performed.

5.7. Safety Endpoints

5.7.1. Adverse Events

Analysis Methods

AEs will be analyzed based on safety analysis set. 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 the first dose 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 as 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 general, AEs will be analyzed based on incidence proportion. The incidence proportion (%) is defined as the number of subjects with an event divided by the total number of subjects in the analysis population. In determining incidence proportion, both single occurrence and multiple

occurrences of events will be counted as one incidence in the numerator. In the remainder of this document and in table titles, incidence proportion may be referred to simply as "incidence".

Adverse events are coded using the MedDRA dictionary. This coding system provides more than five levels to classify AEs. In general, AEs will be presented by SOC and PT but other classifications may be used if warranted.

An overall summary of AEs will be provided by treatment group and by treatment group stratified by ApoE status. This will generally include the following numbers and percentages of subjects: with any AE, with any AE by maximum severity, with any related AE (related to study drug as assessed by the investigator), with SAE, with related SAE (related to study drug as assessed by the investigator), with AE leading to drug discontinuation, with AE leading to study withdrawal, and fatal events.

5.7.1.1. Common Adverse Events

Table 2 lists the planned analyses of all AEs, most frequently reported AEs, related AEs (related to study drug as assessed by the investigator), and AEs by severity. All analyses will present incidence proportion by treatment group. Where indicated, the analyses will be repeated by treatment group stratified by ApoE status.

Table 2 Planned Analyses of all AEs, most frequent reported AEs, related AEs, and AEs by severity.

Analyses of AE incidence proportion	Repeat stratified by ApoE status?
AEs by SOC/PT by descending frequency	Yes
AEs at least 2% higher in incidence for aducanumab compared to placebo by SOC/PT	No
AEs with an incidence of 5% or more by PT	Yes
Severe AEs by SOC/PT	Yes
AEs by maximum severity by SOC/PT	Yes
Related AEs by SOC/PT	Yes

A listing presenting all adverse events will be provided containing 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.

A listing of all adverse events related to amyloid PET ligand, related to tau PET ligand or related to lumbar puncture based on data on adverse event CRF page will be provided.

A listing of non-treatment emergent adverse events will be given too.

5.7.1.2. Deaths

Adverse events with fatal outcome will be summarized by SOC/PT, by treatment group and stratified by ApoE status. A listing of deaths will be provided.

5.7.1.3. Serious Adverse Events

Table 3 lists analyses for incidence proportion for SAEs by treatment group. A listing of SAE will also be provided.

Table 3 Analyses of Incidence Proportion for SAE

Analysis	Repeat stratified by ApoE status?
SAEs by SOC/PT	Yes
Related SAEs by SOC/PT	Yes

5.7.1.4. Other Significant Adverse Events

Analysis of other significant AEs will focus on AEs that lead to a substantial intervention, including premature discontinuation of study treatment and withdrawal from study. Adverse events leading to treatment discontinuation will be summarized by SOC/PT, by treatment group and stratified by ApoE status. The same analyses will be repeated for AEs leading to study withdrawal.

Additional summary will be provided for AEs that lead to drug interruption and drug withdrawal.

A separate summary will be provided for ARIA leading to treatment discontinuation as these were protocol-mandated in some circumstances.

Listings of adverse events that led to discontinuation of study drug and adverse events that led to withdrawal from the study will be provided.

5.7.1.5. Adverse Events of Special Interest

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

Radiographic ARIA (ARIA-E and ARIA-H), as well as any symptoms of ARIA, are considered AEs of special interest and will be entered on the Adverse Event of Special Interest CRF within 72 hours following the receipt of abnormal MRI findings from the central MRI reader.

In order to guarantee uniformity in ARIA reporting, the AE eCRF has a set verbatim term for cases of ARIA. The verbatim terms together with the corresponding MedDRA preferred terms are shown in Table 4.

Table 4 Verbatim Terms and MedDRA Preferred Terms

AESI	Verbatim term	MedDRA preferred term
ARIA-E	Asymptomatic ARIA-E or Symptomatic ARIA-E	Amyloid related imaging abnormality-oedema/effusion

AESI	Verbatim term	MedDRA preferred term
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
Cerebral hemorrhage > 1cm	Cerebral Hemorrhage > 1cm	Cerebral hemorrhages > 1cm refers to Intraparenchymal hemorrhages in the eCRF, and could be coded to various preferred terms, depending on type of hemorrhage and location of hemorrhage.

Seizures, falls, and hypersensitivity reactions are also considered AEs of special interest.

5.7.1.6. ARIA Data Handling Principles

If the radiographic severity of an ARIA event increases or the event changes from asymptomatic to symptomatic, additional 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 are considered as a single ARIA event. The severity/symptomatic status for that event is defined as the worst level among all the AE records that belong to that event.

In general, the start date of the event is the earliest start date among the AE records for the ARIA event, and the end date is the latest end date.

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

If the duration based on MRI for an ARIA-E event overlaps with the duration based on MRI for an ARIA-H event, then these two ARIA events will be defined as concurrent.

If a subject experienced ARIA-E but no ARIA-H then this ARIA-E event will be defined as isolated, and similarly for ARIA-H.

The MRI duration of an ARIA event is determined based on MRI assessments. The start date is the date of the MRI assessment that initially identifies the ARIA event, and the end date is the date of the MRI assessment that shows the complete resolution of this ARIA event (in the case of ARIA-E), or 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 of ARIA-H microhemorrhage or ARIA-H superficial siderosis between 2 consecutive MRIs.

The AE eCRF data will be used as the primary source for the ARIA analysis as it contains the complete information of ARIA as well as associated symptoms. The safety MRI data collected

under the 'Neurological Examination' eCRF page will only be used for specific analyses that require information that was not available in the AE eCRF.

5.7.1.7. Analysis of Adverse Events of Special Interest

ARIA (ARIA-E, ARIA-H) and cerebral hemorrhage > 1cm events will be summarized based on the Safety MRI Analysis Set. The incidence of ARIA events tables will summarize the number of subjects with any ARIA, ARIA-E, any ARIA-H, ARIA-H microhemorrhage, ARIA-H superficial siderosis, subjects experiencing both ARIA-E and ARIA-H, concurrent ARIA-E and ARIA-H, isolated ARIA-E and isolated ARIA-H.

Cerebral hemorrhage >1 cm will be summarized. Cerebral hemorrhages >1 cm will be identified by the eCRF and by using a customized MedDRA query, consisting of selected preferred terms within the Standardized MedDRA Query (SMQ) of "Haemorrhagic central nervous system vascular conditions (SMQ)" (narrow search). The customized query SMQ list may be modified based on newer version of MedDRA when available and safety team's discretion.

Seizures, hypersensitivity, and fall events will be summarized on the Safety Analysis Set. Seizures will be identified using a customized MedDRA query, consisting of selected preferred terms within the Standardized MedDRA Query (SMQ) of "Convulsions (SMQ)" (narrow search). ARIA status of subjects with seizures 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 a customized MedDRA query, consisting of selected preferred terms within the Standardized MedDRA Query (SMQ) of "Hypersensitivity (SMQ)" (narrow scope). The hypersensitivity SMQ list may change due to newer version of MedDRA and at safety team's discretion.

Falls will be identified based on the preferred term "Fall" and number of falls will be presented by treatment group.

Other analyses of AEs within this SMQ may be performed, including exploration of potential association with ARIA-E. Analyses to describe and characterize the incidence of AESIs are listed in Table 5 below. Unless otherwise specified, results will be presented by treatment group.

Table 5 Analyses to Describe Incidence of AESIs and to Characterize AESI Events

Analysis
Incidence of ARIA events
Incidence of ARIA events by ApoE e4 genotype
Maximum MRI severity and worst symptomatic status of ARIA events
Maximum MRI severity and worst symptomatic status of ARIA events by ApoE genotype
Maximum MRI severity and worst symptomatic status of ARIA events among participants with ARIA
Onset of ARIA events
Resolution of ARIA-E and stabilization of ARIA-H
Recurrent ARIA-E
ARIA-related adverse events by SOC/PT

Analysis
Summary of symptomatic ARIA
Summary of serious and severe ARIA and symptoms
Serious or severe ARIA-related adverse events by PT
Cerebral hemorrhage > 1cm
Haemorrhagic CNS vascular conditions events by PT[12]
Haemorrhagic CNS vascular conditions events excluding subdural hematomas by PT[12]
Hypersensitivity events by PT[13]
Serious hypersensitivity events by PT[13]
Related hypersensitivity events by PT[13]
Seizures by PT[13]
Falls[13]

[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".

The following listings will also be provided with the relevant information:

- Listing of MRI assessments for subjects with ARIA-E
- Listing of MRI assessments for subjects with ARIA-H microhemorrhage
- Listing of MRI assessments for subjects with ARIA-H superficial siderosis
- Listing of MRI assessments for subjects with Cerebral hemorrhage > 1cm
- Listing of MRI assessments for subjects with other postbaseline MRI abnormalities
- Listing of MRI assessments for subjects with postbaseline MRI ischemic abnormalities
- Listing of ARIA-related adverse events for subjects with symptomatic ARIA based on Adverse Event CRF
- Listing of haemorrhagic CNS vascular conditions
- Listing of hypersensitivity adverse events
- Listing of seizures
- Listing of falls

5.7.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations include hematology, blood chemistry and urinalysis. Baseline for laboratory parameters is defined as the last available value prior to the first dose.

For each laboratory category, the following analyses will be presented:

- Summaries of actual values by visit and respective figures displaying the mean values by visit
- Summaries of change from baseline by visit
- Summaries of percent change from baseline by visit

- Shift from baseline
- Potentially serious hepatotoxicity evaluation will be presented in a figure with respective listing. For subjects with potential serious hepatotoxicity, values over time will also be presented in a figure.

Note: Potentially serious hepatotoxicity is defined as ALT or AST > 3x ULN and total bilirubin > 2x ULN at any time post-baseline, not necessarily concurrent.

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

Table 6 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
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		

5.7.3. Vital Signs

Vital sign parameters include body temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and body weight. Baseline is defined in a similar way as with clinical laboratory parameters.

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

5.7.4. 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.

5.7.5. Electrocardiograms

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. The ECG outlier in the uncorrected QT and Fridericia's corrected QTc intervals are the values exceeding a threshold of particular concern in clinical trials and are defined using criteria listed in FDA guidance - E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. The number and percentage of subjects

with ECG outlier in the uncorrected QT and Fridericia's corrected QTc interval will be summarized by treatment group.

- Absolute QTc interval prolongation:
  - QTc interval > 450
  - QTc interval > 480
  - QTc interval > 500
- Change from baseline in QTc interval:
  - QTc interval increases from baseline > 30
  - QTc interval increases from baseline > 60

Baseline is defined in a similar way as with clinical laboratory data. The worst post-baseline value of each subject will be used.

5.7.6. Immunogenicity

5.7.6.1. 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 will be treated as anti-drug antibody (ADA) negative for immunogenicity analyses.

A summary of treatment-emergent anti-aducanumab positive responses will also be presented using the following definitions:

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 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 evaluation occurs thereafter;

Subjects with treatment-emergent positive anti-aducanumab antibody responses in the placebo-controlled period 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

5.7.6.2. Immunogenicity analysis

Immunogenicity analysis set will be used for immunogenicity analysis. Tables will be presented by treatment group. Listings will be presented by treatment group stratified by ApoE status.

A summary table will be presented showing the number of subjects with treatment-emergent anti-aducanumab antibody positive response at any time post-baseline, the number of subjects with treatment-emergent anti-aducanumab antibody positive response at each visit, the number of subjects with persistent and transient response, the number of subjects positive at baseline with a treatment-emergent response and without a treatment-emergent response, and the number of subjects positive post-baseline or at baseline (with or without a treatment-emergent response).A listing of immunogenicity assessments as well as a listing of adverse events for subjects with any anti-aducanumab antibody positive results will also be provided.

5.7.7. C-SSRS

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 showing:

- The number of subjects with at least one post-baseline C-SSRS assessment
- The number of subjects with suicidal ideation
- Number of subjects with suicidal behavior
- Number of subjects with suicidal ideation or behavior
- Non-suicidal self-injurious behavior

The listing of subjects with post-baseline suicidal ideation, suicidal behavior, or non-suicidal self-injurious behavior, the listing of subjects with post-baseline suicidal ideation, and the listing of subjects with post-baseline suicidal behavior will also be presented.

6. Changes from Protocol-Specified Analyses

On 31 January 2024, the early termination of Study 221AD305 was announced. Consequently, protocol-specified final analysis that was designed to verify the clinical benefit of aducanumab will not be performed; only the analyses described in Section 5 will be performed. All protocol pre-specified analysis that were designed to assess the safety of monthly doses of aducanumab will be performed. Specifically, the changes in the planned analysis are as follows:

6.1. Primary Endpoint, Key Secondary Endpoints and Secondary Endpoints

Primary endpoint CDR-SB will be summarized. There will be no statistical testing.

The protocol-specified key secondary endpoints and secondary endpoints will not be analyzed.

6.2. Tertiary Endpoints

Protocol specified tertiary endpoints individual items of the RUD-Lite and QoL-AD scores will not be analyzed.

Protocol specified tertiary endpoints serum concentrations and PK parameters of aducanumab over time will not be analyzed.

[redacted]

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

This section is not applicable as there is no previous version of the SAP.

8. References

221AD305 ENVISION Clarification Letter 16FEB2024 Final Signed

221AD305 Unblinding Plan v3.4 29APR2024

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43(11):2412–2414.

Tractenberg RE, Weiner MF, Cummings JL, Patterson MB, Thal LJ. Independence of changes in behavior from cognition and function in community-dwelling persons with Alzheimer's disease: a factor analytic approach. Journal of Neuropsychiatry and Clinical Neuroscience. 2005;17(1):51–60.

van Ginkel JR, SijtsmaK, van der Ark LA, & Vermunt, JK . Incidence of missing item scores in personality measurement, and simple item-score imputation. Methodology: European Journal of Research Methods for the Behavioral and Social Sciences, 2010; 6(1), 17-30.

9. Appendix

9.1. Visit Window

For analyses summarized by visit, data collected during all scheduled and unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown below. If there are 2 or more assessments available in the same analysis window for a participant, 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.

As illustrated in Section 2.2.2., there are changes in the timing and the assessments to be collected for the safety follow-up visit following the study early termination. Because of these changes, the visit window mapping will vary depending on whether the corresponding assessment is collected at the follow-up visit and if the participant has achieved Week 122 as of January 31, 2024. Specifically:

(1) If an assessment is not collected in the revised safety follow-up visit, the visit window mapping is not impacted and will be the same for all participants
(2) If an assessment is collected in the revised safety follow-up visit
    a. For those participants who have reached Week 122 as of January 31, 2024, the visit window mapping will use the windowing scheme that assumes safety follow-up visit is at Week 122 (18 weeks after Week 104)
    Because Study 221AD305's first participant was randomized and dosed on July 27, 2022, the expected Week 122 visit would have occurred in November 2024. Therefore, as of January 31, 2024, there should be no participants who had Week 122 visit.
    b. For those participants who have not reached Week 122 as of January 31, 2024, the visit window mapping will use the windowing scheme that the safety follow-up visit is Week 116 (12 weeks after Week 104).

9.1.1. Visit Windows for Mapping Efficacy Endpoint CDR-SB

For CDR-SB summaries by visit, data collected during all scheduled and unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Table 7. If there are 2 or more assessments available in the same analysis window for a participant, 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 6 Visit Windows for Efficacy Endpoint CDR-SB

Endpoints	Analysis Visit	Target Visit Day	Analysis Visit Window
Clinical Efficacy Endpoint			
CDR-SB score	Baseline	1	Most recent non-missing pre-dose value
	Week 26	183	[92, 266]
	Week 50	351	[267, 448]
	Week 78	547	[449, 644]
	Week 106	743	[645, 798]
	Week 122[1]	855	≥ 799

1: CDR has been removed from the revised schedule of activities of follow-up visit. Therefore, visit window mapping is not impacted by the revised schedule of follow-up visit.

9.1.2. Visit Windows for Mapping Laboratory Parameters

Table 7 Visit Windows for Laboratory Parameters

Endpoints	Analysis Visit	Target Visit Day	Analysis Visit Window
For participants who have reached Week 122 as of January 31, 2024			
Hematology, Blood Chemistry, and Urinalysis	Baseline	1	Most recent non-missing pre-dose value
	Week 52	365	[2, 546]
	Week 104	729	[547, 791]
	Week 122	855	≥ 792
For participants who have not reached Week 122 as of January 31, 2024			
Hematology, Blood Chemistry, and Urinalysis	Baseline	1	Most recent non-missing pre-dose value
	Week 52	365	[2, 546]
	Week 104	729	[547, 770]
	Week 116	813	≥ 771

9.1.3. Visit Windows for Mapping Vital Sign Parameters

Table 8 Visit Windows for Vital Sign Parameters

Endpoints	Analysis Visit	Target Visit Day	Analysis Visit Window
For participants who have reached Week 122 as of January 31, 2024			
Vital Signs	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, 539]
	Week 78	547	[540, 553]
	Week 80	561	[554, 574]
	Week 84	589	[575, 602]
	Week 88	617	[603, 630]
	Week 92	645	[631, 658]
	Week 96	673	[659, 686]
	Week 100	701	[687, 714]
	Week 104	729	[715, 791]
	Week 122	855	≥ 792
For participants who have not reached Week 122 as of January 31, 2024			
Vital Signs	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, 539]
	Week 78	547	[540, 553]
	Week 80	561	[554, 574]
	Week 84	589	[575, 602]
	Week 88	617	[603, 630]
	Week 92	645	[631, 658]
	Week 96	673	[659, 686]
	Week 100	701	[687, 714]
	Week 104	729	[715, 770]
	Week 116	813	≥ 771

9.1.4. Visit Windows for Mapping Immunogenicity

Table 9 Visit Windows for Immunogenicity

Endpoints	**Analysis Visit**	**Target Visit Day**	**Analysis Visit Window**
For participants who have reached Week 122 as of January 31, 2024			
Anti-Aducanumab Ab	Baseline	1	Most recent non-missing pre-dose value
	Week 12	85	[2, 126]
	Week 24	169	[127, 266]
	Week 52	365	[267, 455]
	Week 78	547	[456, 637]
	Week 104	729	[638, 791]
	Week 122	855	≥ 792
For participants who have not reached Week 122 as of January 31, 2024			
Anti-Aducanumab Ab	Baseline	1	Most recent non-missing pre-dose value
	Week 12	85	[2, 126]
	Week 24	169	[127, 266]
	Week 52	365	[267, 455]
	Week 78	547	[456, 637]
	Week 104	729	[638, 770]
	Week 116	813	≥ 771

9.1.5. Visit Windows for Mapping Brain MRI

Table 10 Visit Window for Brain MRI

Endpoints	Analysis Visit	Target Visit Day	Analysis Visit Window
For participants who have reached Week 122 as of January 31 ,2024			
Brain MRI assessment	Baseline	1	Most recent non-missing pre-dose value
	Week 14	99	[2, 126]
	Week 22	155	[127, 182]
	Week 30	211	[183, 252]
	Week 42	295	[253, 518]
	Week 106	743	[519, 798]
	Week 122	855	>=799
For participants who have not reached Week 122 as of January 31, 2024			
Brain MRI assessment	Baseline	1	Most recent non-missing pre-dose value
	Week 14	99	[2, 126]
	Week 22	155	[127, 182]
	Week 30	211	[183, 252]
	Week 42	295	[253, 518]
	Week 106	743	[519, 777]
	Week 116	813	>=778

9.2. Protocol Deviation Classification

Table 11 Summary of Protocol Deviation Classification

Deviation Category	Deviation Description	Severity Classification
IP administration	IP administered < 21 days from previous dose	Major
Concomitant Medications	Change in AD medications during course of the study without completion of the unscheduled AD medication visit before the change or within 30 days after the change (if the investigator is notified after the change already occurs)	Minor
Concomitant Medications	The subject used prohibited concomitant medication (or therapies)	Major

Deviation Category	**Deviation Description**	**Severity Classification**
Randomization	Mis-stratification due to entry error related to disease stage or ApoE carrier status in IRT	Major
IP administration	ARIA Dosing Rules not followed as per protocol: includes dose suspended when it should have been continued, dose continued when it should have been suspended, titration schedule not followed upon dose resumption As this may be noted by the blinded team on infusion notes and/or the unblinded team on the IP preparation documents both may report. This type of PD will need to be reconciled regularly to prevent duplication in the final log and to make sure none are missed.	Major
Laboratory assessment	Required lab samples not done at first ARIA management visit (for each new ARIA)	Minor
Study Procedures (Study Procedures (not safety not efficacy related)	Follow up phone call / visit not done at unscheduled ARIA visit	Minor
Informed Consent and Process	Care partner did not sign consent prior to study participant beginning study procedures.	Major
Study Procedures (Study Procedures (not safety not efficacy related)	Missed CSF sample at timepoints for CSF substudy participants.	Minor
Concomitant Medications	Administration of any disallowed concomitant therapy or non-adherence to the limits of those medications that are permitted but have limitations on use (protocol section 7.7.1.2.1)	Major
IP preparation	Mis-dose (underdose) due to rounding errors (not following DHA) or errors in weight calculations	Minor if isolated; Major if there is a trend
Exclusion criteria	Exclusionary lab value results but subject was randomized and dosed.	Major Possibly critical depending on whether there is an immediate safety concern from the lab value

Deviation Category	**Deviation Description**	**Severity Classification**
Inclusion Criteria or Exclusion Criteria (depending on criterion)	Any eligibility assessment other than Inclusion criterion #2, #5, #7 not performed such that eligibility could not be confirmed at the time of enrollment but when done after the fact the participant is confirmed as eligible. NOTE: If participant is confirmed as ineligible follow the classification for ineligible participant and PD is major.	Minor
Exclusion criteria	Any confirmed deviation from exclusion criteria such that participant was not eligible for participation. SM is to note which criterion was violated in the PD text. Note: this does NOT include cases where participants met the exception criteria for malignancy and are eligible for the study following TMA review.	Major
Inclusion Criteria	Any confirmed deviation from inclusion criteria such that participant was not eligible for participation. SM is to note which criterion was violated in the PD text.	Major
Inclusion Criteria	Subject not eligible based on scores of CDR, MMSE, RBANS-DMI, as defined by inclusion criterion # 7	Major
Inclusion Criteria	CDR, MMSE, RBANS-DMI not done prior to randomization such that eligibility could not be assessed.	Major
Inclusion Criteria	Amyloid PET or CSF not done prior to randomization such that eligibility could not be assessed but participant is confirmed as eligible after the fact.	Major
Efficacy	Inconsistent rater used for primary, secondary endpoints <u>if for reasons other than allowed by the protocol</u>	Major
Informed Consent and Process	ICF obtained by subject is not in a language understandable by the participant/LAR	Major/ Potentially Critical

Deviation Category	**Deviation Description**	**Severity Classification**
Informed Consent and Process	Incorrect completion of ICF (i.e., subject/care partner/LAR/person obtaining consent did not provide date of signature; subject/care partner/LAR/person obtaining consent noted incorrect date of signature; subject/care partner/LAR/person obtaining consent printed name when should have signed, subject/care partner/LAR/person obtaining consent signed on line for printed name, printed name on line for signature, etc.)	Minor
Informed Consent and Process	Subject/informant/legally authorized representative OR PI/site staff administering consent did not sign consent (main or sub study prior to procedures covered by that consent being performed	Major
Informed Consent and Process	Incorrect or outdated version of ICF signed (applies to main, sub studies/optional consents and care partner).	Major
IP administration	Site used IP without waiting for confirmation that it was usable following a temperature excursion	Minor or Major (see comments)
IP administration	Use of IP that was rejected following a temperature excursion	Major
IP administration	Titration schedule not respected when preparing IP	Major
IP administration	Use of expired IP	Minor
Subject IP compliance	Unblinded pharmacist not maintaining appropriate packaging or labels to allow the UB SM to verify IP accountability.	Major
Blinding	IP is not stored in blinded manner or according to the site's signed Blind Maintenance Plan NOTE: if anyone at the site or sponsor/IQVIA team has been unblinded as a result of the storage issue, follow the PD guidance for treatment unblinding	Major
IP conditions	IP storage temperature out of range (2-8 ºC).	Minor unless trend
IP conditions	Temperature excursions not reported as per Biogen's process	Major
IP conditions	IP temperature monitoring documentation is not being maintained	Minor unless trend

Deviation Category	**Deviation Description**	**Severity Classification**
Laboratory assessment	Samples not received at the central laboratory according to shipment requirements (frozen samples received ambient; ambient samples received frozen)	Minor
Laboratory assessment	Laboratory result not acknowledged by PI, or medically qualified and delegated study personnel in a timely manner. NOTE: If delayed lab review potentially impacted eligibility, please refer to the inclusion/exclusion PD guidance.	Minor (unless trending)
Laboratory assessment	Pre-dose and/or post-dose PK samples not collected, or not collected within protocol specified time.	Minor
Laboratory assessment	Lab specimens temperature log (freezer) is not being maintained nor checked by applicable study personnel.	Minor
Laboratory assessment	Coagulation tests not completed per protocol prior to lumbar puncture (within 35 days normally and within 7 days for participants with elevated risk for bleeding)	Major
Laboratory assessment	Lab samples not drawn, drawn out of window, or results unavailable	Minor
Laboratory assessment	Use of incorrect lab kit.	Minor
Study Procedures (Study Procedures (not safety not efficacy related)	Participant is eligible per malignancy exceptions noted in the protocol but the SAF was submitted for review retrospectively.	Minor
Study Procedures (Study Procedures (not safety not efficacy related)	Baseline tau PET scan not done for participant at a mandatory tau site	Minor
Exclusion criteria	Participant has been randomized and received first dose of study medication but used allowed chronic concomitant medications at doses that were not been stable for at least 4 weeks prior to Screening Visit 1 and during Screening up to Day 1, or used Alzheimer's disease medications at doses that were not stable for at least 8 weeks prior to Screening 1 up to Day 1 or used allowed chronic	Major

Deviation Category	**Deviation Description**	**Severity Classification**
	concomitant medications that affect cognition at doses that were not stable for at least 8 weeks prior to screening Visit 1 and during screening up to Day 1.	
Randomization	Subject enrolled (for treatment) in IXRS but not treated	Major
Randomization	Subject randomized to wrong arm due to mis-entry of ApoE ε4 carrier status.	Major
IP administration	Wrong study drug dispensed	Major
IP administration	Subject received IP despite meeting discontinuation or withdrawal criteria	Major
IP administration	Missed infusion not due to ARIA	Major
Efficacy	CDR, ADCS-ADL-MCI, ADAS-Cog 13, MMSE, NPI-10 not administered SM may record one PD at the visit level, including all the assessments, as long as there is no difference in the category or severity. A second PD should be included for minor assessments missed at the same visit.	Major
Study Procedures (Study Procedures (not safety not efficacy related)	Any individual procedure not conducted per protocol requirements (either skipped or out of window) except those noted in the note. SM may record one PD at the visit level, including all the assessments, *as long as there is no difference in the category or severity*. NOTE: Does not apply to MRI, Infusions, CDR, ADCS-ADL-MCI, ADAS-Cog 13, MMSE, NPI-10, C-SSRS and labs, which, if missed, are considered major PD per this classification document	Minor
Safety	Participant dosed based on local read of MRI rather than central read as required by protocol	Major
Safety	MRI visit or individual MRI not done (scheduled or unscheduled ARIA visit)	Major / potentially critical

Deviation Category	**Deviation Description**	**Severity Classification**
Safety	MRI conducted on subsequent participants without receiving passing QC report on first in-vivo scan	Major
Safety	Infusion conducted prior to receipt and/or review of MRI central read results or QC report	Major / potentially critical
Efficacy	Assessment performed by non-qualified rater (this applies to all scales for which MedAvante is confirming qualification and not only cognitive scales	Major
Efficacy	CDR, ADCS-ADL-MCI, ADAS-Cog 13, MMSE, NPI-10 administered out of window (OOW) SM may record one PD at the visit level, including all the assessments, as long as there is no difference in the category or severity. A second PD should be included for minor assessments missed at the same visit.	Minor
IP preparation	Overdose of study medication, includes mis-dose (overdose) due to rounding errors or errors related to weight calculation	Major
IP administration	Overdose Form not submitted to IQVIA Lifecycle Safety within 24 hours of site being made aware of an overdose.	Major
Study Procedures (Study Procedures (not safety not efficacy related)	PET scan conducted on subsequent participants without receiving passing QC report on first in-vivo scan	Minor
Study Procedures (Study Procedures (not safety not efficacy related)	Missed PET scan at timepoints for PET substudy participants.	Minor
Study Procedures (Study Procedures (not safety not efficacy related)	Ligand dose administration error for either PET	Major
Safety	Pregnancies not appropriately reported within 24 hours of study site staff becoming aware of the pregnancy.	Major
Efficacy	Administration of rating scales over the telephone.	Major
Efficacy	CDR raters were performing other assessments on subjects they performed CDRs for.	Major

Deviation Category	Deviation Description	Severity Classification
Efficacy	Independent Rater 2 performed CDR on participant for which they already performed ADAS-Cog, ADCS-ADL-MCI, MMSE, RBANS, C-SSRS	Major
Efficacy	Independent Rater 2 performed CDR on participant for which they already performed NPI, EQ-5D-5L, Rud-Lite, QoL-AD	Minor
Efficacy	RDV / DSF rater performed RBANS or C-SSRS on the same subject (PV2)	Minor
Efficacy	RDV / DSF rater performed CDR, ADAS-Cog 13, ADCS-ADL-MCI, MMSE, NPI, EQ-5D-5L, Rud-Lite, QoL-AD on the same subject	Major
Safety	C-SSRS not administered or administered out of window (applies to both protocol scheduled and ARIA unscheduled visits)	Major
Informed Consent and Process	Participant not reconsented in a timely manner, expected at the first clinical visit following availability of a newly EC/IRB approved ICF (applies to main, sub study and optional ICFs)	Major
Informed Consent and Process	Care partner is not reconsented in a timely manner, expected at the first care partner visit following receipt of a newly EC/IRB approved care partner ICF.	Minor
Study Procedures (Study Procedures (not safety not efficacy related)	Re-screening not approved in advance by Medical	Major
Study assessments criteria	Essential baseline evaluations were not performed prior to initiation of study drug. CDR-SB ADCS-ADL-MCI ADAS-Cog13 MMSE NPI-10	Major
Study assessments criteria	Dose reduction or dose increase administered by PI/sub-I when protocol requires return to same dose that participant was given prior to the ARIA event following temporary discontinuation of IP following ARIA event	Major
Study assessments criteria	Primary endpoint assessment CDR-SB 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	Major

Deviation Category	Deviation Description	Severity Classification
	administered or completed, due to subject's decline in cognition.	
Study assessments criteria	Secondary endpoint assessments PET scan 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 assessments criteria	ARIA management not being followed as per protocol specifications.	Major
Study assessments criteria	Study MRIs missed.	Major
Safety	SAEs or AESI (ARIA, Fall, Hypersensitivity, Seizure) not reported to safety within the required timeframe (within 24 hours of awareness for SAE; within 72 hours of awareness for AESI)	Major / potentially critical
Study Procedures (Study Procedures (not safety not efficacy related)	MRI or PET done before SV1 eligibility confirmed (lab and cog scales)	Major
Study Procedures (Study Procedures (not safety not efficacy related)	Tau PET scan conducted at Screening V3 with no confirmation of a positive amyloid result (either PET or CSF) from Screening Visits 1 or 2, or after meeting all other eligibility criteria, including MRI criteria, at Screening Visits 1 and 2.	Major
Study Procedures	Screening and baseline assessments not done, unless protocol allows them to be performed after day 1	Major
Study Procedures	Infusion rate exceeds 100mL/hour	Major
Safety Monitoring	Dosing suspension decision has not been followed per protocol, MRI follow-up not performed correctly.	Major
Randomization	Screening window extended past 60 days without approval.	Minor (unless trending)
Visit schedule	Screening window extended beyond 90 days	Major

Deviation Category	**Deviation Description**	**Severity Classification**
Study Procedures (Study Procedures (not safety not efficacy related)	PET done prior to SV1 and MRI eligibility confirmed	Major
Blinding	First participant randomized at a site without signed Blind Maintenance Plan	Major
Visit schedule	Full visit not done NOTE: If MRI visit is skipped (either scheduled or unscheduled due to ARIA), see separate PD guidance for MRIs categorized under safety.	PD is MAJOR if any of the following apply: • > 2 consecutive visits are skipped • visit includes an infusion that was skipped for reasons other than ARIA (missed infusion reported separately) • visit includes CDR
Blinding	IP unblinded to blinded study team member or blinded site personnel	Major
Exclusion criteria	Vaccinations (including COVID-19 vaccines and boosters) within 5 days prior to randomization (Day 1).	Major
Concomitant Medications	Vaccination < 5 days before a dosing visit and/or < 10 days after a dosing visit	Minor
Visit schedule criteria	Subject missed 2 or more scheduled consecutive visits.	Major
Visit schedule criteria	Failure to perform a required study visit that may affect subject safety or data integrity.	Major
Visit schedule criteria	Failure to perform follow-up visit and/or End of Study Visit	Major
Visit schedule	Full study visit out of window (For full visits ONLY, this does not apply to individual procedures that may be done out of window)	Minor

Deviation Category	**Deviation Description**	**Severity Classification**
IP preparation	Site does not use the current weight, assessed at the current visit, for IP preparation As this may be noted by the blinded team in the source documents (copies of weight communication to pharmacist and copy of weight at visit) or the unblinded team on the IP preparation documents both may report. This type of PD will need to be reconciled regularly to prevent duplication in the final log and to make sure none are missed.	Major if the weight at the current visit is $\geq$ 5kg different from the weight communicated dose preparation (regardless of under or overdose) Minor if the weight at the current visit is < 5 kg different from the weight communicated for the dose preparation
Other criteria	An unplanned unblinding of the subject or site to the subject's treatment information occurred during the study.	Major

DocuSign

Certificate Of Completion

Envelope Id: B3D41C54827343CAADEBFDDC529AE824
Subject: Complete with DocuSign: ENVISION SAP FINAL V1.0.pdf
Vendor Name:
Source Envelope:
Document Pages: 52
Certificate Pages: 2
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Signatures: 4
Initials: 0

Status: Completed

Envelope Originator:
[redacted]
225 Binney St
Cambridge, MA 02142
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
14 May 2024 | 09:22

Holder: [redacted]

Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] [redacted] [redacted] Biostatistician Biogen Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 14 May 2024 | 09:25 Viewed: 14 May 2024 | 09:46 Signed: 14 May 2024 | 09:47
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] [redacted], Biostatistics Biogen Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 14 May 2024 | 09:47 Viewed: 14 May 2024 | 09:52 Signed: 14 May 2024 | 09:52
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] [redacted], Biostatistics Biogen Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 14 May 2024 | 09:52 Viewed: 14 May 2024 | 09:53 Signed: 14 May 2024 | 12:46
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 14 May 2024 | 12:46 Viewed: 14 May 2024 | 23:47 Signed: 14 May 2024 | 23:47
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	14 May 2024 | 09:25
Certified Delivered	Security Checked	14 May 2024 | 23:47
Signing Complete	Security Checked	14 May 2024 | 23:47
Completed	Security Checked	14 May 2024 | 23:47

Payment Events	Status	Timestamps