Statistical Analysis Plan

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Name of Study Treatment: Aducanumab

Protocol No.: 221AD205 / NCT03639987

Study Phase: II

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APPROVAL

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List of Abbreviations

AD	Alzheimer's disease
AE	adverse event
ApoE ε4	apolipoprotein E4
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-edema
ARIA-H	amyloid related imaging abnormality-hemorrhage or superficial siderosis
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
WHO	World Health Organization

1 INTRODUCTION

Study 221AD205 was a Phase 2, multicenter, randomized, parallel-group, double-blind, controlled study in participants with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) or with mild AD dementia, with a randomized treatment period followed by an optional long-term extension period. The primary study objective was to assess the safety impact of continuing aducanumab (BIIB037) dosing in asymptomatic amyloid-related imaging abnormalities (ARIA) in participants with MCI due to AD or mild AD dementia.

Eligible participants were randomized (1:1) at Visit 1 to 1 of 2 groups that differed in terms of the management of asymptomatic ARIA found on magnetic resonance imaging (MRI) during the randomized treatment period. All randomized participants received aducanumab titrated up to 10 mg/kg (identical titration protocol as in the phase 3 program). In certain cases of asymptomatic ARIA as described in the study protocol, Group 1 participants were required to suspend or discontinue aducanumab dosing whereas the Group 2 participants were to continue aducanumab treatment. In these cases, to maintain the study blind, Group 1 participants were to receive placebo.

Termination of the study was announced on 21 March 2019, based on the results of an interim futility analysis in the aducanumab Phase 3 studies 221AD301 and 221AD302. Enrollment and dosing in 221AD205 were halted immediately upon the announcement. All participants were to return to the site within 4 weeks of the announcement to do the EOT (week 54) visit, and again 18 weeks after their last dose for the final follow up visit (Week 70). Due to the small amount of data collected in this study, only a synopsis clinical study report is planned.

The purpose of this statistical analysis plan (SAP) is to describe the analyses that are planned for the final report. The primary endpoint and most secondary endpoints of the study will not be evaluable due to the small actual sample size and short exposure time. Instead, the focus of the final analysis is summarizing the available baseline, exposure, and adverse event data that were collected during the study.

2 STATISTICAL ANALYSIS METHODS

2.1 General Considerations

Summary tables will be presented using descriptive summary statistics. For continuous variables, summary statistics will generally include: number of participants with data, mean, standard deviation, median, minimum and maximum. For categorical variables, this will generally include: number of participants in the analysis population, number with data, and the percent of those with data in each category. Due to the minimal amount of data collected in the study, most endpoints will not be summarized; instead, listings will be provided. Any straightforward listings that are routinely produced for Biogen clinical studies will not necessarily be mentioned in this plan.

Unless otherwise specified, summaries will be presented by study group and overall. Each table will typically have three columns, ordered as follows: Group 1, Group 2, and BIIB037 Total. Summaries presented by decreasing or increasing frequency will be sorted based on the aducanumab total column.

2.2 Analysis Study Group

Data will be analyzed by study group based on randomization. A listing of any participants who were dosed contrary to their randomization study group will be presented. This includes any Group 1 participant who received accidental aducanumab during an ARIA episode when placebo should have been administered, and any Group 2 participant who accidentally received placebo.

2.3 Analysis Populations

The follow analysis populations will be utilized in the interim analysis:

- Safety population:
  The safety population is defined as all randomized participants who received at least one dose of aducanumab.
- Safety MRI population:
  The safety MRI population is defined as all randomized participants who received at least one dose of aducanumab and had at least one post-baseline MRI assessment.
- Differential study treatment population:
  The differential study treatment population is defined as all participants in the safety MRI population who experienced asymptomatic ARIA resulting in assignment of at least one infusion of study treatment that would have been different had the participant been in the other study group. Any Group 1 participant who receives placebo is in the differential study treatment population, as is any Group 2 participant who would have received placebo had they been assigned to Group 1. If there are few or no subjects in the differential study treatment population, analyses in this population may be omitted.

2.4 Background Characteristics

Background characteristics will be summarized based on the safety population.

2.4.1 Accounting of Participants

Disposition of participants will be summarized. This will include number of participants randomized and dosed, as well as the number and percentage of participants who completed each visit.

The reasons for treatment discontinuation and study withdrawal will be summarized. Because study termination was not a check box option on the End of Treatment and End of Study electronic case report forms (eCRFs), the reason will be categorized as "Study Termination" in the summary based on study team review of the verbatim reason provided on the eCRF, the date of last dose, and date of withdrawal. The reasons provided on the eCRFs will be listed.

The number of participants in each analysis population will be summarized.

2.4.2 Demographics and Baseline Characteristics

Demographic data including age, gender, ethnicity, and race will be summarized.

Summary of the baseline characteristics of AD includes laboratory ApoE ε4 genotype, baseline clinical stage (MCI due to AD or mild AD), number of years of formal education, number of years since first AD symptoms, and number of years since diagnosis of AD.

Medical history and previous therapies for AD will be listed.

2.4.3 Concomitant Medications and Non-Drug Therapies

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary. All concomitant non-drug therapies will be coded using the MedDRA dictionary. All reported concomitant medications/therapies will be listed, regardless of start and stop dates.

2.4.4 Study Drug Exposure

The number of aducanumab infusions received will be summarized. A listing of all study drug administration records will be provided, including any placebo infusions.

2.5 Adverse Events

In general, the safety population will be used for analyses of adverse events. Where applicable for ARIA analyses, the safety MRI population may be used.

Adverse events will be included in the summaries based on the principle of treatment emergence. Treatment emergent is defined as having an onset date that is on or after the start of study treatment, or as worsening after the start of study treatment. For AEs with missing or partial start or stop dates, all available information will be used to determine if the event was treatment-emergent. If it cannot be ascertained based on partial information, the AE will be assumed to be treatment-emergent.

A listing of all AEs, whether treatment-emergent or not, will be provided.

2.5.1 Incidence of adverse events

The overall summary of AEs will present the number of participants with any AE, with any AE by maximum severity, with any related AE (related to study drug as assessed by investigator), with any SAE, with any related SAE, with an AE leading to study drug discontinuation, with an AE leading to study withdrawal, and the number of deaths.

Adverse events will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA). The incidence of AEs by MedDRA system organ class and preferred term will be presented by decreasing frequency. Depending on the number of SAEs, this table may be repeated for serious events.

2.5.2 ARIA

2.5.2.1 ARIA Events

Since the diagnosis of ARIA requires brain MRI findings, ARIA data were collected under two data sources: (1) safety MRI data as recorded on brain MRI worksheet by central MRI reader; (2) AE electronic case report form. For each ARIA event, the information of start/end date, severity, location(s) in brain regions and evolution status on MRI scan is collected from the brain MRI worksheet by central MRI reader. ARIA severity on MRI is determined by central MRI reader based on number of brain regions involved and size of ARIA lesions on imaging. An AE record was then entered into the eCRF with the start/end date and severity information from brain MRI worksheet, and with information on the symptomatic status and action taken with study drug. If ARIA was symptomatic, the symptomswere entered into the AE eCRF. The AE eCRF data will be used as the primary source for ARIA analysis as it contains the complete information on ARIA as well as associated symptoms; unless otherwise specified, analyses of incidence or incidence rates are based on AE eCRF data.

ARIA types include ARIA-E (vasogenic edema) and ARIA-H (hemorrhage). ARIA-H includes ARIA-H microhemorrhage, ARIA-H macrohemorrhage and ARIA-H superficial siderosis.

2.5.2.2 Clinically impactful ARIA

The primary endpoint of the study was the incidence of clinically impactful ARIA, as assessed by an independent Adjudication Committee. At the time the study was terminated, the Adjudication Committee had not been formed. This endpoint will not be evaluated due to lack of data.

2.5.2.3 Incidence of ARIA

The incidence of ARIA will be summarized, including ARIA-E, ARIA-H microhemorrhage, ARIA-H superficial siderosis and ARIA-H macrohemorrhage. Listings of all ARIA events and listings of MRI assessments for participants with ARIA events will be provided. The listing will be repeated for the differential study treatment population, if applicable.

2.5.3 MoCA

Scores from the Montreal Cognitive Assessment (MoCA) will be listed. For participants with ARIA events, the MoCA total scores will be included with the listing of MRI assessments.

2.6 Other Safety Assessments

Safety analyses in this study focus on adverse events. Due to the limited enrollment and lack of long term aducanumab exposure in this study, the interpretability of aggregate results of other assessments is limited. Therefore, no summaries of clinical laboratory parameters and other measures will be provided, and analysis will be limited to individual review of participant-level data listings.

Listings will be provided for the following:

- hematology
- blood chemistry
- urinalysis
- vital signs
- electrocardiograms (ECGs)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- aducanumab concentration (PK) data
- anti-aducanumab antibody assessments

List of Planned Tables

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