These Clinical Study Results are provided for informational purposes only.

The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the overall results obtained across the product development. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult prescribing information for the product approved in their country.

2. STUDY SYNOPSIS

Name of Sponsor/Company: Biogen MA Inc./Biogen Idec Research Limited	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: Aducanumab (BIIB037)	**Name of Active Ingredient:** Aducanumab (BIIB037)	**Study Indication:** Alzheimer's Disease

Title of Study:

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

Coordinating Principal Investigator:

[redacted], MD, [redacted], US

Study Period: Date of first treatment: 13 August 2015 Date of early dosing termination: 21 March 2019 End of Study Date (date of final safety follow-up visit): 08 August 2019	**Phase of Development:** 3

Study Objectives:

Primary Objective:

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

Secondary Objectives:

- Assess the effect of doses of aducanumab administered every 4 weeks as compared with placebo on clinical progression as measured by the Mini-Mental State Examination (MMSE).
- Assess the effect of doses of aducanumab every 4 weeks as compared with placebo on clinical progression as measured by Alzheimer's Disease Assessment Scale–Cognitive Subscale-13 items (ADAS-Cog13).
- Assess the effect of doses of aducanumab administered every 4 weeks as compared with placebo on clinical progression as measured by Alzheimer's Disease Cooperative Study-Activities of Daily Living (Mild Cognitive Impairment [ADCS-ADL-MCI]).

Tertiary Objectives:

Safety and Tolerability

- To assess the safety and tolerability of doses of aducanumab administered every 4 weeks.
- To assess the immunogenicity of aducanumab.

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Biomarker/Efficacy/Health Outcomes

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

Pharmacokinetics (PK)

- To collect and characterize the PK parameters of aducanumab in serum.

Study Design:

Study 221AD301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study to assess the efficacy and safety of aducanumab in participants with early Alzheimer's disease, including mild cognitive impairment (MCI) due to Alzheimer's disease and mild Alzheimer's disease dementia. Enrollment was monitored such that participants with MCI due to Alzheimer's disease represented approximately 80% of the total enrolled in the study. The study was conducted at 169 investigational sites globally. The study comprised an 18-month placebo-controlled period followed by a long-term extension (LTE) period that was planned to continue for up to 5 years. For the placebo-controlled period, participants were randomized to receive aducanumab low-dose, aducanumab high-dose, or placebo.

On 21 March 2019, Biogen publicly announced the termination of the Phase 3 clinical studies (221AD301 and 221AD302), based on the results of an interim futility analysis. No further doses were administered after the announcement. After the futility announcement, evaluation of a larger data set was conducted. This analysis included all data available as of 01 April 2019 (April transfer data) from all randomized and dosed participants but with their efficacy data after 20 March 2019 censored. After including the additional participants and all efficacy data through 20 March 2019, which were collected under the protocol specified double-blind conditions prior to the futility declaration, the results for the high-dose group in Study 221AD301 no longer showed a marked worsening versus placebo.

This report addresses the primary, secondary, and tertiary efficacy objectives of Study 221AD301 as well as the safety and tolerability of aducanumab in the placebo-controlled period. Per protocol, results of the additional exploratory objectives, [redacted], are reported separately. A separate report describes the design and results of the LTE period. In this report, "study" refers to the placebo-controlled period unless otherwise specified.

Number of Participants (Planned and Analyzed):

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Planned: Approximately 1605 participants were planned after sample size re-estimation (535 per treatment group).

Analyzed: A total of 1653 participants were randomized; 1647 participants were dosed and thus comprised the safety and intent-to-treat (ITT) populations.

Study Population:

Main Inclusion Criteria:

This study recruited early-stage participants who were Aβ positive as assessed by PET imaging (by visual read) and who fulfilled clinical criteria for either MCI due to Alzheimer's disease or mild Alzheimer's disease dementia (as defined by the National Institute on Aging at National Institutes of Health and the Alzheimer's Association criteria, and per the Investigator's clinical assessment).

Key inclusion criteria included:

- A CDR global score of 0.5.
- A Repeatable Battery for Assessment of Neuropsychological Status score of 85 or lower, indicative of objective cognitive impairment (based on the Delayed Memory Index score).
- An MMSE score between 24 and 30 (inclusive).
- At least 6 years of education or work experience.
- Aged 50 to 85 years at screening.

Study Treatment, Dose, Mode of Administration:

For the placebo-controlled period, participants were randomized to receive aducanumab low-dose:aducanumab high-dose:placebo in a 1:1:1 ratio. Participants received intravenous (IV) infusions of aducanumab or placebo(saline) once every 4 weeks, for a total of 20 doses administered during the placebo-controlled treatment period. Aducanumab was titrated for up to 6 doses prior to reaching the target dose. Randomization was stratified by site as well as by apolipoprotein E ε4 (ApoE ε4) carrier status (carrier or noncarrier) so that each treatment group would include similar proportions of carriers and noncarriers.

Per the original study protocol (Version 1), the actual aducanumab "low" and "high" doses differed depending on a participant's ApoE ε4 carrier status. On finalization of protocol version 4 (PV4), differential dosing based on carrier status was limited to only the aducanumab "low" dose. This change was based on data from Phase 1b Study 221AD103.

ApoE ε4 carrier

- Low-dose (3 mg/kg), 1 mg/kg for the first 2 doses, 3 mg/kg thereafter
- High-dose (10 mg/kg), 1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter *(PV4 and higher)*
  - High-dose (6 mg/kg), 1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter *(protocol version 1 through version 3)*
- Placebo

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ApoE ε4 noncarrier

- Low-dose (6 mg/kg), 1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, and 6 mg/kg thereafter
- High-dose (10 mg/kg), 1 mg/kg for the first 2 doses, 3 mg/kg for the next 2 doses, 6 mg/kg for the next 2 doses, and 10 mg/kg thereafter *(all protocol versions)*
- Placebo

A total of 30 lots of aducanumab were used during the combined placebo-controlled and LTE periods of the study.

Comparator Therapy/Therapies, Dose, Mode of Administration:

Placebo (0.9% sodium chloride) was provided by the study sites. Placebo was administered by IV infusion.

Planned Duration of Treatment and Follow-Up:

For participants in the placebo-controlled period only, the total duration of the study was up to approximately 102 weeks; this included a series of screening visits within approximately 8 weeks prior to the first dose, a 76-week placebo-controlled treatment period, and a safety follow-up period of 18 weeks after the final dose.

Participants who completed the placebo-controlled period and entered the LTE were not required to have a safety follow-up visit.

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Criteria for Evaluation:

Following is a description of all efficacy, PK, pharmacodynamic, health outcome, and safety assessments that were planned for this study.

Efficacy:

- CDR-SB
- MMSE
- ADAS-Cog13
- ADCS-ADL-MCI
- NPI-10

Pharmacokinetics:

Serum concentrations of aducanumab were measured using a validated assay.

Pharmacodynamics:

Serial measurement of Aβ plaque levels in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 participants participating in the amyloid PET cohort).

Health Outcomes:

- EQ-5D (informant rated and participant self-reported)
- mPDQ-20

Safety:

- Adverse event (AE) and serious AE (SAE) monitoring
- Physical examination, including height and weight
- Neurological examination
- Vital signs (body temperature, heart rate, blood pressure, and respiratory rate)
- 12-lead electrocardiogram (ECG)
- Brain MRI
- Concomitant medication, therapy, and procedure monitoring
- Montreal Cognitive Assessment
- Columbia Suicide Severity Rating Scale (C-SSRS)

Additional exploratory assessments are reported separately.

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Statistical Methods:

Planned Analyses:

Planned analyses were described in the Statistical Analysis Plan (dated 11 September 2018) and in the Statistical Analysis Plan Addendum (dated 04 November 2019) and summarized below.

The ITT population was defined as all randomized participants who received at least 1 dose of study treatment (placebo or aducanumab). The ^{18}F-florbetapir Aβ PET Analysis Population was defined as participants in ITT population that participated in the longitudinal amyloid PET substudy, used ^{18}F-florbetapir ligand for Aβ PET scan, and had an evaluable baseline amyloid PET standard uptake value ratio (SUVR) value for the composite region-of-interest (ROI) using cerebellum as the reference region.

Demographics, Baseline Disease Characteristics, Exposure:

Demographics, baseline disease characteristics, medical history, prior and concomitant medications, and exposure to study treatment were summarized using descriptive statistics.

Efficacy:

Primary Endpoint

A mixed-model repeated measures (MMRM) model was used as the primary analysis to analyze change from baseline CDR-SB. The estimand of this analysis was the mean difference of the change from baseline CDR-SB scores at Week 78 between treatment groups. Primary analyses for efficacy were conducted for the ITT population, with data collected after 20 March 2019 excluded, and missing data were assumed to be missing at random. Sensitivity analyses and supplementary analyses were conducted. Analyses were performed for the following prespecified subgroups: laboratory determined ApoE ε4 status, baseline clinical stage, use of Alzheimer's disease symptomatic medication at baseline, baseline MMSE, region, age category, and sex.

Secondary Endpoints

An MMRM was used as the primary analysis for change from baseline scores for MMSE, ADAS-Cog13, and ADCS-ADL-MCI. Selected sensitivity and supplementary analyses were conducted for secondary endpoints. The same subgroup analyses as the primary endpoint were conducted for the secondary endpoints.

Tertiary Endpoint

An MMRM was used to analyze the change from baseline in NPI-10.

Pharmacokinetics:

Serum concentration data were summarized by nominal visit. Minimum and maximum observed concentrations (C_{min} and C_{max}, respectively) were determined by noncompartmental methods from serum-concentration time data, as permitted.

Pharmacodynamics:

Pharmacodynamic assessments were performed for the ^{18}F-florbetapir Aβ PET Analysis Population. For analyses of aducanumab's effect on cerebral Aβ plaque levels as measured by PET, a composite SUVR was calculated for a composite ROI comprising the main cortical regions of the brain (frontal, parietal, lateral temporal, sensorimotor, anterior, and posterior cingulate) with whole cerebellum serving as a reference region. This Aβ PET composite SUVR was used as the primary endpoint for Aβ PET analysis. SUVRs were calculated for additional brain regions of interest and reference region combinations as well.

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An MMRM model was used to analyze change from baseline SUVR. Analyses were performed for the following prespecified subgroups: laboratory-determined ApoE ε4 status, baseline clinical stage, and baseline composite SUVR in quartiles.

Pearson and Spearman correlations between change from baseline Aβ PET composite SUVR using whole cerebellum as a reference region at Weeks 26 and 78 and change from baseline CDR-SB at Week 78 were conducted by treatment group.

Health Outcomes:

The baseline value and the change from baseline at each postbaseline visit were summarized by treatment group.

Safety:

Incidence and incidence proportion were calculated by treatment group for AEs, SAEs, related AEs, AEs leading to treatment discontinuation and/or study withdrawal and deaths, as well as for AEs by severity and by onset time.

Incidence and incidence proportion of brain MRI findings were calculated by treatment group and ApoE ε4 carrier status for amyloid-related imaging abnormalities edema/effusion (ARIA-E) and amyloid-related imaging abnormalities-hemorrhage or superficial siderosis (ARIA-H), and for AEs related to ARIA. Severity and symptomatic status were summarized for each type of ARIA by treatment group and ApoE ε4 carrier status. Analyses of recurrent ARIA-E, exposure-adjusted incidence rates, and time-to-event analyses also were performed.

Change and percent change from baseline for clinical laboratory data and shifts in reported values were summarized by treatment group at each visit. Postbaseline shifts to abnormal, worst grade, potentially clinically significant abnormalities, and potentially serious hepatotoxicity were summarized by treatment group.

Potentially clinically significant changes from baseline in vital sign measurements and postbaseline shifts to abnormal in ECGs were summarized by treatment group.

For the C-SSRS, the number of participants who engaged in nonsuicidal self-injurious behavior and the number of participants who answered "Yes" to each of the 11 questions postbaseline, to at least 1 question for suicidal ideation, and to at least 1 question for suicidal behavior were summarized by treatment group.

Incidence and incidence proportion of treatment-emergent anti-aducanumab antibodies in serum were calculated by treatment group. In addition, participants were classified as having persistent or transient anti-aducanumab antibody responses.

Sample Size Calculations:

The study's sample size was based in part on results from a protocol-specified interim analysis from Study 221AD103, which included 1-year data from aducanumab 1, 3, and 10 mg/kg treatment groups. The sample size was to have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. As defined in the prior versions of the protocol, the sample size for this study (and for the identically designed Study 221AD301) was reassessed in a blinded manner approximately 3 months before enrollment completion. As a result of this analysis, the sample size was adjusted from 1350 to 1605 (450 to 535 per treatment) to ensure adequate power to detect a mean treatment effect of 0.5.

Results:

Participant Accountability:

Of the 1647 participants dosed, 56.3% completed treatment and 43.7% discontinued treatment. The percentages of participants who completed and withdrew from the study were 57.0% and 43.0%, respectively. The primary reason

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for both treatment discontinuation and study withdrawal was "other" (30.2% and 31.0%, respectively) and the predominant "other reason" was early study termination by the Sponsor.

Besides the "other reason", differences across treatment groups were observed in the percentages of participants who discontinued treatment due to AEs (placebo, 5.1%; low-dose, 8.2%; high-dose, 11.4%) and consent withdrawn (placebo, 2.6%; low-dose, 1.6%; high-dose, 2.9%). Besides the "other reason", differences across treatment groups were observed in the percentages of participants who withdrew from study due to AEs (placebo, 2.9%; low-dose, 4.6%; high-dose, 5.0%) and due to consent withdrawn (placebo, 4.8%; low-dose, 2.9%; high-dose, 4.9%).

"Administrative termination" for participants' end of study status was applied to any participant still on study as of 20 March 2019, the day before the termination of the study was publicly announced. There were 516 participants (31.3%) administratively terminated.

Exposure:

The protocol-defined treatment period in the placebo-controlled portion of the study was 76 weeks, during which participants were to receive 20 infusions. The mean time on study treatment was 66.65 weeks, and mean percentage of study treatment received was 96.4% overall. The mean time on study treatment (placebo, 68.48 weeks; low-dose, 67.47 weeks; high-dose, 64.05 weeks) and the mean percentage of study treatment taken up to the last dose (placebo, 98.3%; low-dose, 96.2%; high-dose, 94.9%) were similar across treatment groups.

Demographics and Baseline Disease Characteristics:

In the ITT population, treatment groups were well balanced with respect to demography and baseline disease characteristics. Participants ranged in age from 50 to 85 years (median: 71.0 years) at baseline, were predominantly White (75.2%), and slightly more than half (52.4%) were female. A majority had a baseline clinical stage of MCI due to Alzheimer's disease (80.4%) while 19.6% had mild Alzheimer's disease dementia. A majority were ApoE ε4 carriers (69.5%). Almost all (99.8%) had a baseline CDR global score of 0.5 and the median MMSE score was 26.0.

When participants were further stratified based on their ApoE ε4 carrier status at randomization, demographics and baseline characteristics for Alzheimer's disease were generally similar across treatment groups. In the ^{18}F-florbetapir Aβ PET Analysis Population, demographics and baseline disease characteristics also were similar across treatment groups and were consistent with the ITT population.

Efficacy:

- The primary efficacy endpoint analysis, change from baseline in CDR-SB at Week 78, did not show a reduction in the aducanumab high-dose group compared with the placebo group (0.03, 2%, p = 0.8330). A numeric difference in favor of the aducanumab low-dose group over the placebo group was observed on the CDR-SB at Week 78 (-0.18, -12% compared to placebo, p = 0.2250).
- The changes from baseline in the secondary endpoints at Week 78 showed a numeric difference in favor of the aducanumab high- and low-dose groups over the placebo group for ADAS-Cog13 (-11% compared to placebo for both dose groups) and ADCS-ADL-MCI (-18% compared to placebo for both dose groups). A numeric difference in favor of only the aducanumab low-dose group over the placebo group was observed for MMSE (-6% compared to placebo).

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- Primary and secondary efficacy endpoint results across prespecified baseline characteristic and demographic subgroups at Week 78 were consistent with those of the primary analysis, with point estimates favoring aducanumab low-dose for most of the subgroups.
- In post-hoc analyses of the primary and secondary endpoints based on consenting to PV4, participants in the high-dose group who had consented to PV4 or later versions on or before Week 16 (i.e., had the opportunity to receive 14 doses of aducanumab 10 mg/kg if ApoE ε4 carriers) showed a trend toward slowed disease progression at Week 78 compared with participants receiving placebo (CDR-SB: -27% compared to placebo; MMSE: -13% compared to placebo; ADAS-Cog13: -20% compared to placebo; ADCS-ADL-MCI: -60% compared to placebo).

Pharmacodynamics:

- A dose-dependent reduction in brain levels of Aβ was observed for both aducanumab groups in the Aβ PET substudy. The adjusted mean change from baseline in Aβ PET composite SUVR relative to placebo was statistically significant in favor of aducanumab at both dose levels at Week 78 (high-dose, -0.232 [$p < 0.0001$]; low-dose, -0.167 [$p < 0.0001$]). No correlation was observed between the reduction in Aβ plaque levels as measured by 18F-florbetapir and change over time in CDR-SB scores. Subgroup analyses on the 18F-florbetapir Aβ PET Analysis Population were consistent with the primary model results.

Pharmacokinetics:

- The PK of aducanumab was dose-dependent, and after Week 24, serum concentrations increased as expected for each dose level. The highest aducanumab concentrations were observed in participants who were expected to receive 14 doses of aducanumab 10 mg/kg based on randomization. C_{max} and C_{min} followed a dose-dependent response as expected for the respective dose groups.

Safety:

- Aducanumab was generally well tolerated in the placebo-controlled period of this study.
- Overall, the incidence of AEs was comparable between the placebo and both aducanumab dose groups (placebo, 86.5%; low-dose, 90.0%; high-dose, 90.1%). The incidence of SAEs was also comparable between the placebo and both aducanumab dose groups (placebo, 13.0%; low-dose, 13.8%; high-dose, 14.2%). Five participants experienced a fatal SAE (placebo, 0; low-dose, 3; high-dose, 2).
- Except for ARIA, the incidence and nature of AEs, SAEs, and fatal SAEs were generally consistent with the underlying diagnosis of Alzheimer's disease and the expected comorbidities for the age of the study population (median age: 71 years). There were no fatal outcomes due to ARIA.

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- The most common AEs occurring more frequently in aducanumab-treated participants compared with placebo participants (incidence ≥ 2% higher in either the aducanumab low- or high-dose group than in the placebo group) in the Safety Population were ARIA-E (placebo, 3.0%; low-dose, 25.7%; high-dose, 35.7%), headache (placebo, 15.0%; low-dose, 18.0%; high-dose, 20.6%), brain microhemorrhages (termed ARIA-H microhemorrhage in the study: placebo, 6.3%; low-dose, 16.2%; high-dose, 18.6%), localized superficial siderosis (termed ARIA-H superficial siderosis in the study: placebo, 1.9%; low-dose, 9.3%; high-dose, 15.9%), fall (placebo, 10.6%; low-dose, 14.6%; high-dose, 15.4%), and contusion (placebo, 4.3%; low-dose, 6.0%; high-dose, 6.5%).
- Overall, ARIA-E was detected in 30.9% of aducanumab-treated participants in the Safety MRI Population.
  - Most participants with ARIA-E remained on treatment without interruption or resumed treatment after a temporary suspension. Overall, 5.1% of participants in the low-dose group and 7.2% of participants in the high-dose group permanently discontinued treatment due to ARIA. The study protocol required permanent treatment discontinuation under certain circumstances in study participants with ARIA.
  - In addition to being higher in the high-dose group compared to that in the low-dose group, the incidence of ARIA-E was higher in ApoE ε4 carriers (low-dose, 29.2%; high-dose, 42.1%) than in noncarriers (low-dose, 17.4%; high-dose, 22.7%).
  - In most participants with ARIA-E (> 80%), events were of mild or moderate radiographic severity. ARIA-E events were most common early during treatment (first 8 doses). The majority of ARIA-E events resolved within 12 weeks after detection (low-dose, 68.7%; high-dose, 72.1%).
  - The majority of participants with ARIA-E experienced a single ARIA-E event. Among those who continued treatment after resolution of a first ARIA-E event, 38.4% of low-dose and 40.8% of high-dose participants experienced a recurrent ARIA-E event.
  - Most participants with ARIA-E did not experience symptoms associated with ARIA-E (termed asymptomatic ARIA-E: low-dose, 81.6%; high-dose, 70.4%). When present, common symptoms of ARIA included headache, confusional state, dizziness, and nausea, and the majority of symptoms were typically mild to moderate and transient.
  - Overall, the characteristics of ARIA-E (duration, radiographic severity, and presence of symptoms) were consistent across dose groups and independent of ApoE ε4 carrier status.
  - Compared to participants without ARIA-E, an increased incidence of brain microhemorrhages (low-dose, 46.1%; high-dose, 41.7%) and localized superficial siderosis (low-dose, 31.2%; high-

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dose, 42.2%) was observed in participants who experienced ARIA-E. In these participants, brain microhemorrhages and localized superficial siderosis were frequently concurrent with ARIA-E. In the absence of ARIA-E, the incidence of brain microhemorrhages (placebo, 6.2%; low-dose, 5.9%; high-dose, 5.9%) and localized superficial siderosis (placebo, 1.2%; low-dose, 1.7%; high-dose, 1.4%) was comparable between the aducanumab-treated and placebo groups.

  – One aducanumab-treated participant with ARIA-E experienced brain hemorrhage > 1 cm with no fatal outcome.

- Infusions were generally well tolerated, and the incidence of AEs 2 hours within an infusion was comparable between the placebo and aducanumab groups.
- The incidence of treatment-emergent anti-aducanumab antibodies in the placebo-controlled period was low at any timepoint and comparable between aducanumab treatment groups (placebo, 0%; low-dose, 0.4%; high-dose, 0.2%).
- No clinically significant vital sign, laboratory, or ECG trends were observed.
- There was no increase in suicidal ideation or behavior related to treatment with aducanumab, as assessed by the C-SSRS.

Conclusions:

In conclusion, the primary efficacy endpoint analysis did not show a reduction in decline in CDR-SB in the aducanumab high-dose group compared with placebo in patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. Numeric differences in favor of aducanumab high-dose over placebo were observed in ADAS-Cog13 and ADCS-ADL-MCI scores at Week 78. The aducanumab low-dose group had a numeric difference in favor of aducanumab over placebo in CDR-SB, MMSE, ADAS-Cog13, and ADCS-ADL-MCI scores at Week 78. In a post-hoc analysis of the primary and secondary endpoints, participants in the high-dose group who had consented to PV4 or later versions on or before Week 16 (i.e., had the opportunity to receive 14 doses of aducanumab 10 mg/kg if ApoE ε4 carriers) showed a trend toward slowed disease progression at Week 78 compared with participants receiving placebo. Additionally, a dose- and time-dependent reduction in brain Aβ as measured by Aβ PET was observed, which provided evidence that aducanumab is targeting the underlying pathophysiology by removing Aβ. The safety profile of aducanumab in this study was acceptable. With the exception of ARIA, the AEs reported were generally consistent with the underlying diagnosis of Alzheimer's disease and the expected comorbidities for the age of the study population.

Date of Report: 01 June 2020

Version: 1

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2. STUDY SYNOPSIS

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Title of Study:

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

Coordinating Principal Investigator:

[redacted], MD, [redacted], US

Study Period: Date of first treatment (LTE period): 22 February 2017 Date of early dosing termination: 21 March 2019 End of study date (date of final safety follow-up visit): 08 August 2019	**Phase of Development:** 3

Study Objectives:

Tertiary Objectives:

- Evaluation of the long-term safety and tolerability profile of aducanumab in participants with early Alzheimer's disease.
- Evaluation of the long-term efficacy of aducanumab treatment as measured by clinical, radiological, and health outcome assessments.

Study Design:

Study 221AD301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study to assess the efficacy and safety of aducanumab in participants with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia. The study was conducted at 169 investigational sites globally. The study comprised an 18-month placebo-controlled (PC) period followed by a long-term extension (LTE) period that was planned to continue for up to 5 years. Of the 169 sites that participated in the study, 142 sites enrolled participants into the LTE period.

During the LTE period, participants who were randomized to aducanumab (low-dose or high-dose) in the PC period continued to receive aducanumab on the same dose, and participants who were randomized to placebo during the PC period were switched to receive aducanumab (high-dose or low-dose as randomized at study entry); aducanumab dosing for late start participants during the LTE period was pre-defined at the beginning of the study.

On 22 February 2017, the first participant was dosed in the LTE period. The Sponsor announced the termination of the Phase 3 studies on 21 March 2019; the last participant visit was on 08 August 2019. Due to the early termination, the number of participants enrolled in the LTE period was lower than planned and no participants completed the LTE period.

This report addresses the tertiary safety, tolerability, clinical, radiological, and health outcome objectives of the LTE period of the study as well as the combined PC and LTE active treatment periods. Per protocol, results of the additional exploratory objectives are reported separately. A separate report describes the design and results of the

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PC period.

Number of Participants (Planned and Analyzed):

Planned: Approximately 1605 participants were planned for the combined PC and LTE study periods after sample size re-estimation (535 per treatment group); participants who completed the PC period were eligible to enroll in the LTE period.

Analyzed: A total of 1653 participants were randomized, and 1647 were dosed in the PC period. 1084 participants had the opportunity to complete Week 78 by 20 March 2019 of which 938 participants completed the PC period. 852 participants entered the LTE period and received aducanumab.

Study Population:

Main Inclusion Criteria:

Key eligibility criteria for the LTE period were completion of the PC period, including the Week 78 visit. In addition, participants must have taken ≥ 70% of doses during the PC period and not missed more than 4 consecutive doses (except for participants whose dose was suspended due to ARIA).

Study Treatment, Dose, Mode of Administration:

For the PC period, participants were randomized to receive aducanumab low-dose:aducanumab high-dose:placebo in a 1:1:1 ratio. Participants received intravenous (IV) infusions of aducanumab or placebo (saline) once every 4 weeks, for a total of 20 doses administered during the PC treatment period. Per the original study protocol (version 1), the actual aducanumab "low" and "high" doses differed depending on a participant's ApoE ε4 carrier status. On finalization of protocol version 4, differential dosing based on carrier status was limited to only the aducanumab "low" dose. This change is described in detail in the PC CSR 221AD301. During the LTE period, participants who were randomized to aducanumab in the PC period continued to receive aducanumab on the same dose and participants who were randomized to placebo during the PC period were switched to receive aducanumab. Per randomization, the following treatment groups were defined for the purpose of analyses:

- Early start: Participants who at the start of the PC period were randomized to aducanumab were, in the LTE, to continue their originally assigned treatment.
  - Early start low-dose
  - Early start high-dose
- Late start: participants who at the start of the PC period were randomized to placebo were also at that time randomized to receive dose-blinded aducanumab (low:high 1:1) during the LTE; the randomization was stratified by ApoE ε4 carrier status and site.
  - Late start low-dose
  - Late start high-dose

Comparator Therapy/Therapies, Dose, Mode of Administration:

Not applicable. All participants received IV aducanumab during the LTE period.

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Planned Duration of Treatment and Follow-Up:

The planned total duration of study participation for each participant in the PC period and the LTE period was to vary depending on the timing of the participant's entry to the study and could have been up to approximately 362 weeks depending on the time of the enrollment. The planned treatment duration ended either at the participant's End-of-Treatment Visit at Week 338 or when the last participant had their Week 182 Visit, whichever occurred first. As the study was terminated approximately 2 years after the first participant was dosed in the LTE period, no participants had the opportunity to complete the study.

Criteria for Evaluation:

Following is a description of all safety, efficacy, PK, pharmacodynamic, and health outcome assessments that were planned for this study.

Safety:

- Adverse event (AE) and serious AE (SAE) monitoring
- Physical examination, including height and weight
- Vital signs (heart rate and blood pressure)
- 12-lead electrocardiogram (ECG)
- Brain MRI
- Concomitant medication, therapy, and procedure monitoring
- Montreal Cognitive Assessment
- Columbia Suicide Severity Rating Scale (C-SSRS)

Efficacy:

- CDR-SB
- MMSE
- ADAS-Cog 13
- ADCS-ADL-MCI
- NPI-10

Health Outcomes:

- EQ-5D (informant rated)

Pharmacodynamics:

Serial measurement of Aβ plaque levels in certain areas of the brain as measured by amyloid PET (in a subset of approximately 400 participants participating in the amyloid PET cohort).

Pharmacokinetics:

Serum concentrations of aducanumab were measured using a validated assay.

Additional exploratory assessments are reported separately.

Statistical Methods:

Planned Analyses:

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Planned analyses were described in the Statistical Analysis Plan (SAP) dated 11 September 2018 and the SAP Addendum dated 04 November 2019 and are summarized below.

Analysis Populations:

Analysis populations were defined independent of whether a participant entered the LTE or not:

- ITT population: All participants who were randomly assigned to treatment and received at least 1 dose of study treatment (aducanumab or placebo).
- ^{18}F-florbetapir Aβ PET analysis population: All randomized participants who received at least 1 dose of study treatment (aducanumab or placebo), used ^{18}F-florbetapir ligand for Aβ PET scan, and had an evaluable baseline Aβ PET SUVR score value for the composite ROI using cerebellum as the reference region.
- Safety population: All randomized participants who received at least 1 dose of study treatment (aducanumab or placebo). It is the same population as the ITT population.
- Safety MRI population: All randomized participants who received at least 1 dose of study treatment (aducanumab or placebo) and had at least 1 post-baseline MRI assessment.
- PK analysis population: All randomized participants who received at least 1 dose of study treatment (aducanumab or placebo) and had at least 1 measurable aducanumab concentration in serum.
- Immunogenicity population: All randomized participants who had at least 1 dose of study treatment (aducanumab or placebo) and had at least 1 postdose sample evaluable for immunogenicity.

Analysis Periods:

Participants and data included in a certain output were determined by both the analyses population and the analysis period. The active treatment period was defined as the study period(s) that a participant was assigned to aducanumab.

- For early start participants – participants who were assigned to aducanumab in both PC and LTE periods, all the data (PC and LTE periods) were included in the analyses.
- For late start participants – participants who were assigned to aducanumab in the LTE period, only data in the LTE period were included.

Demographics, Baseline Disease Characteristics, Exposure:

Demographics, baseline disease characteristics, medical history, prior and concomitant medications, and exposure to study treatment were summarized using descriptive statistics.

Safety:

- Incidence and incidence proportion were calculated by treatment group for AEs, SAEs, related AEs, AEs leading to treatment discontinuation and/or study withdrawal and deaths, as well as for AEs by severity for both the LTE and active treatment periods. For the AE analyses, the SAP stipulated that AEs with onset more than 18 weeks after the last dose would be excluded from most incidence tables. In order to take a more conservative approach, this restriction was removed.
- Incidence and incidence proportion of brain MRI findings were calculated by treatment group and ApoE ε4 carrier status for both the LTE and active treatment periods for amyloid-related imaging abnormalities edema/effusion (ARIA-E) and amyloid-related imaging abnormalities-hemorrhage or superficial siderosis (ARIA-H). Radiographic severity, symptomatic status, and AEs related to ARIA were also summarized.
- Change and percent change from baseline for clinical laboratory data were summarized by treatment

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group at each visit in both the PC and LTE periods. Postbaseline shifts to abnormal, worst grade, potentially clinically significant abnormalities, and potentially serious hepatotoxicity were summarized by treatment group for the active treatment period.

- Postbaseline incidence of clinically relevant outliers in vital sign measurements and postbaseline shifts to abnormal in ECGs were summarized by treatment group for the active treatment period.
- Incidence and incidence proportion of treatment-emergent anti-aducanumab antibodies in serum were calculated by treatment group for the active treatment period. In addition, participants were classified as having a persistent or transient anti-aducanumab antibody response.

Efficacy:

The primary analysis specified in the SAP addendum stated that all efficacy endpoints were to be analysed with data collected after 20 March 2019 censored. In addition, an uncensored analysis including all data collected was also performed. All analyses were conducted for the ITT population, data from both the PC and LTE periods were included, missing data were assumed to be missing at random (MAR) and there were no multiple comparison adjustments. A mixed-model repeated measures (MMRM) model was used to analyze change from baseline in all efficacy endpoints up to Week 134. The following two comparisons were evaluated for the long-term efficacy of aducanumab:

- early start high-dose compared with the late start high-dose
- early start low-dose compared with the late start low-dose

PK:

Serum concentration data were summarized by nominal visit.

Pharmacodynamics:

Pharmacodynamic assessments were performed for the ^{18}F-florbetapir Aβ PET population. For analyses of aducanumab's effect on cerebral Aβ plaque levels as measured by PET, a composite SUVR was calculated for a composite ROI comprising the main cortical regions of the brain (frontal, parietal, lateral temporal, sensorimotor, anterior, and posterior cingulate) with whole cerebellum serving as a reference region. This Aβ PET composite SUVR was used as the primary endpoint for Aβ PET analysis. SUVRs were calculated for additional brain regions of interest and reference region combinations as well. A MMRM model was used to analyze change from baseline SUVR up to Week 132.

Sample Size Calculations:

A description of how the study sample size was determined is provided in PC CSR 221AD301.

Results:

Participant Accountability:

A total of 1647 participants in the ITT population were dosed (including placebo) in the PC period. A total of 852 participants in the ITT population were dosed with aducanumab in the LTE period. A total of 1404 participants received at least one dose of aducanumab in either the PC or LTE periods i.e. during the active treatment period.

"Administrative termination" for participants' end of study status was applied to any participant still on study as of 20 March 2019, the day before the termination of the study was publicly announced. There were 799 participants (93.8%) administratively terminated.

Of the 22 (7.3%) late-start participants who discontinued due to non-administrative reasons, 9 (3.0%) discontinued due to AE, 4 (1.3%) due to disease progression, 4 (1.3%) due to consent withdrawn, and 3 (1.0%) due to

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withdrawal by parent/guardian; all other reasons recorded were for 1 participant only. Of the 31 (5.6%) early-start participants who discontinued due to non-administrative reasons, 9 (1.6%) discontinued due to AE, 5 (0.9%) due to consent withdrawn, 4 (0.7%) due to study visit burden, 3 (0.5%) due to site terminated by Sponsor, 2 (0.4%) due to death, 2 (0.4%) due to withdrawal by parent/guardian, 2 (0.4%) due to disease progression, and 2 (0.4%) due to other; all other reasons recorded were for 1 participant.

Exposure:

All participants were to receive aducanumab approximately every 4 weeks (up to a maximum of 65 doses per protocol) during the LTE period. However, due to the early termination of the study, no participants completed the study.

For the late start group, the median time on study treatment during the LTE period was 0.76 years, with 26.2% of participants receiving 1 to 5 infusions, 32.1% of participants receiving 6 to 10 infusions, and 23.5% of participants receiving 11 to 15 infusions.

For the early start group, the median time on study treatment during the LTE period was 0.76 years, with 28.4% of participants receiving 1 to 5 infusions, 27.6% of participants receiving 6 to 10 infusions, and 20.0% of participants receiving 11 to 15 infusions.

Demographics and Baseline Disease Characteristics:

Demographic and baseline disease characteristics were collected at Baseline of the PC period. When evaluated by LTE treatment group (late start and early start), no major differences in demographic or baseline data were observed.

For the ITT population, when participants were further stratified based on their ApoE ε4 carrier status at randomization, demographics and baseline characteristics for Alzheimer's disease were generally similar across early and late start treatment groups and consistent with the overall ITT population.

Efficacy:

- Based on the primary analysis which excludes data after 20 March 2019 (censored analysis), no differences in change from baseline in the CDR-SB, MMSE, ADAS-Cog 13, and ADCS-ADL-MCI were observed at Week 106 between participants receiving aducanumab high-dose in both the PC and LTE periods and participants receiving placebo in the PC period and aducanumab high-dose in the LTE period in participants with MCI due to Alzheimer's disease and mild Alzheimer's disease dementia.
- No differences in change from baseline in the CDR-SB, MMSE, ADAS-Cog 13, and ADCS-ADL-MCI were observed at Week 106 between participants receiving aducanumab low-dose in both the PC and LTE periods and participants receiving placebo in the PC period and aducanumab high-dose in the LTE period.
- Consistent results were observed including data after 20 March 2019 (uncensored analysis).

Pharmacodynamics:

- For participants in the early start high-dose group, continued reductions in brain Aβ plaque levels relative to baseline (as measured by Aβ PET composite SUVR) was evident at Week 132 (-0.291, 95% CI: -0.3148, -0.2670). These results indicate longer duration of treatment with aducanumab was associated with a greater reduction in Aβ plaque levels as measured by Aβ PET.
- The reduction from baseline in Aβ PET composite SUVR for early start high-dose participants was greater compared to late start high-dose participants at Week 132 (-0.105 [$p < 0.0001$]) due to the

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longer treatment duration.

Pharmacokinetics:

- Serum concentrations of aducanumab were relatively stable during the LTE period for participants receiving aducanumab (low- and high-dose) in both the PC and LTE periods. The dose-dependent increases in serum aducanumab concentration during the LTE period for participants receiving placebo in the PC period and aducanumab (low- and high-dose) in the LTE period were similar to the increases observed for participants receiving aducanumab (low- and high-dose) during the PC period.

Safety:

- Aducanumab was generally well tolerated in the PC and LTE periods of this study.
- In the LTE, the overall incidence of SAEs was balanced between early start and late start participants, whereas the incidence of AEs was higher in the late start group. The higher incidence of ARIA-E in late start participants compared to early start participants in the LTE is likely to have contributed to this.
- The most frequent AEs for early start participants in the active treatment period were the same as those observed during the PC period.
- Except for ARIA, the nature of AEs, SAEs, and fatal events were generally consistent with the underlying diagnosis of Alzheimer's disease and the expected comorbidities for the age of the study population. There were no fatal outcomes due to ARIA.
- Overall, the incidence of AEs during the active treatment period (including PC and LTE) was higher in early start participants compared to late start participants. This difference was likely due to the longer duration of follow-up time in early start participants.
- During the active treatment period, ARIA-E was detected in 32.0% of early start participants treated with aducanumab in the safety MRI population.
  - During the LTE period, the incidence of ARIA-E was higher in late start participants compared to early start participants (late start, 26.3%; early start, 7.0%). These data are consistent with the observation that ARIA-E typically occurred early in treatment in the PC period (within the first 8 doses) and that the risk of ARIA-E then decreased over time.
  - Most participants with ARIA-E remained on treatment without interruption or resumed treatment after a temporary suspension. During the combined PC and LTE active treatment periods, 74/1094 early start participants discontinued treatment due to ARIA. The study protocol required permanent treatment discontinuation under certain circumstances in study participants with ARIA.
  - In addition to being higher in the high-dose groups compared to the low-dose groups (early start low-dose, 26.7%; early start high-dose, 37.2%; late start low-dose, 23.6%; late start high-dose, 28.9%), the incidence of ARIA-E during the active treatment period was higher in ApoE◦ε4 carriers than in noncarriers among both early and late start participants. In the aducanumab high-dose group (early start) in the combined PC and LTE periods, incidence of ARIA-E was 44.0% in ApoE ε4 carriers and 22.7% in noncarriers.
  - During the active treatment period, most participants with ARIA-E had events that were of mild or moderate radiographic severity and most were asymptomatic. ARIA-E was most common early during active treatment.

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  - Overall, the characteristics of ARIA-E in the active treatment period (duration, radiographic severity, and presence of symptoms) were consistent across aducanumab dose groups and independent of ApoE◦ε4◦carrier status. These characteristics were also generally similar when comparing late start participants in the LTE to early start participants in the PC period.
  - Incidence rates for AEs commonly reported as ARIA-related symptoms were relatively consistent between the active treatment period and the PC period for early start participants: headache (active treatment period, 11.0; PC period, 13.5), dizziness (active treatment period, 5.6; PC period, 6.5), and confusional state (active treatment period, 2.3; PC period, 2.6).
  - During the active treatment period, brain microhemorrhages and localized superficial siderosis were observed more frequently in both early and late-start participants who experienced ARIA-E, compared to participants who did not experience ARIA-E.
  - ARIA-E occurred early in treatment among late start participants in the LTE, similar to what was observed among early start participants in the PC period.
- Infusions were generally well tolerated, and the incidence of AEs 2 hours within an infusion was infrequent and comparable between early and late start treatment groups during the LTE period.
- The incidence of treatment-emergent anti-aducanumab antibodies in the PC and LTE periods was low and comparable between early start (0.5%) and late start (0.3%) groups. There was no apparent effect of immunogenicity on the incidence of AEs.
- No clinically significant vital sign, laboratory, or ECG trends were observed with long-term treatment with aducanumab or in those exposed to aducanumab for the first time in the LTE.
- The incidence of suicidal ideation or behavior among participants with long-term treatment with aducanumab was low, as assessed by the C-SSRS.

Conclusion:

As observed for participants receiving aducanumab during the PC period of this study, ARIA-E was the most common AE during the LTE period for participants receiving aducanumab for the first time. Results from the combined PC and LTE periods further support the acceptability of the safety profile of aducanumab.

The results of this study did not show a reduction in decline in CDR-SB, MMSE, ADAS-Cog 13, and ADCS-ADL-MCI in participants receiving aducanumab high dose in both the PC and LTE periods compared to participants receiving placebo in the PC period and aducanumab high dose in the LTE period. A reduction in decline in CDR-SB, MMSE, ADAS-Cog 13, and ADCS-ADL-MCI was also not observed in participants receiving aducanumab low dose in both the PC and LTE periods.

Further reductions in brain Aβ levels as measured by Aβ PET composite SUVR were observed in participants receiving high- or low-dose aducanumab in both the PC and LTE periods.

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