

COVER PAGE

Official Title	A Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (Aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205
NCT Number	NCT04241068
Document Date	26 November 2024
Name of Sponsor/Company	Biogen MA Inc./Biogen Idec Research Limited
Name of Finished Product	ADUHELM
Name of Active Ingredient	Aducanumab (BIIB037)
Study Indication	Alzheimer's Disease



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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:	<i>(For National Authority Use only)</i>
Name of Finished Product: ADUHELM	Name of Active Ingredient: Aducanumab (BIIB037)	Study Indication: Alzheimer's Disease
Title of Study: A Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (Aducanumab) in Subjects with Alzheimer's Disease who had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302, and 221AD205		
Number of Study Sites and Countries: <u>Planned:</u> Approximately 2400 participants would be enrolled across approximately 350 sites globally. <u>Enrolled:</u> A total of 1696 participants were dosed from 308 sites across 20 countries.		
Study Period: Date of first treatment: 13 March 2020 End of Study date: 22 July 2024	Phase of Development: 3b	
Study Objective(s): Below is the list of objectives for this study. Due to early termination of the study, only core primary endpoints [REDACTED] related to safety and tolerability were evaluated. [REDACTED] [REDACTED] Core Primary Objective: <ul style="list-style-type: none"> To evaluate the safety and tolerability of aducanumab over 100 weeks of treatment after a washout period imposed by discontinuation of feeder studies in participants who had previously received aducanumab (i.e., previously treated participants) or who had previously received placebo (i.e., treatment-naïve participants). [REDACTED] [REDACTED] [REDACTED]		

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Study Population:

Main inclusion criteria:

Core treatment period:

- Participant was participating in an aducanumab clinical study at the time of the announcement of early termination (feeder studies).
- Has one care partner who, in the Investigator's opinion, has adequate contact with the participant to be able to provide accurate information about the participant's cognitive and functional abilities.

LTE treatment period:

- Participant must have completed the Core treatment period (Week 102) and adequately tolerated 10 mg/kg of aducanumab during the Core study period, in the opinion of the Investigator.
- Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the participant to be able to provide accurate information about the participant's cognitive and functional abilities.

Main exclusion criteria:

Core treatment period:

- Brain magnetic resonance imaging (MRI) (performed at Screening, centrally read) evidence of any of the following:
 - Acute or subacute hemorrhage.
 - Prior macrohemorrhage (defined as > 1 cm in diameter on T2* sequence) or prior subarachnoid hemorrhage unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest participant is at risk of recurrent hemorrhage).
 - Greater than 4 (for treatment-naïve participants) or ≥ 10 (for aducanumab previously treated[aducanumab-pretreated] participants) microhemorrhages (defined as ≤ 1 cm in diameter on T2* sequence).

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<ul style="list-style-type: none"> – Cortical infarct (defined as > 1.5 cm in diameter; irrespective of anatomic location). – Any focal area of superficial siderosis (for treatment-naïve participants) or 3 or more focal areas of superficial siderosis (for aducanumab previously treated participants). • Any uncontrolled medical or neurological/neurodegenerative condition (other than Alzheimer's Disease) that, in the opinion of the Investigator, might be a contributing cause of the participant's cognitive impairment. • Stroke or any unexplained loss of consciousness within 1 year prior to Screening. • Clinically significant unstable psychiatric illness (e.g., uncontrolled major depression, uncontrolled schizophrenia, uncontrolled bipolar affective disorder) within 6 months prior to Screening. • History of unstable angina, myocardial infarction, advanced chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (e.g., unstable atrial fibrillation) within 1 year prior to Screening. • A seizure event that occurred after the last visit of the feeder study and before Screening for this study. • Evidence of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of AST and ALT $\geq 2 \times$ the upper limit of normal). • History of or known seropositivity for HIV. • Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening. • Contraindications to having a brain magnetic resonance imaging (e.g., pacemaker; MRI-incompatible aneurysm, clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed). <p>LTE treatment period:</p> <ul style="list-style-type: none"> • Any medical or psychiatric contraindication or clinically significant abnormality that, in the opinion of the Investigator, will substantially increase the risk associated with the participant's enrollment in and completion of the study.

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<p>Study Treatment, Dose, and Mode of Administration:</p> <p>During the core period, participants received intravenous (IV) infusions of aducanumab approximately every 4 weeks (Q4W) for a duration of 100 weeks (a total of 26 doses). The aducanumab dosing regimen was 10°mg/kg following this titration: 1°mg/kg for the first 2°doses, 3°mg/kg for the next 2 doses, 6°mg/kg for the next 2°doses, and 10°mg/kg thereafter. Eligible participants entered the LTE treatment period and continued dosing with aducanumab 10 mg/kg Q4W for an additional 52 weeks (a total of 152 weeks of continuous treatment).</p>		
<p>Duration of Treatment and Follow-Up:</p> <p><u>Treatment Period:</u> 100-week core period and 52-week LTE period</p> <p><u>Follow-Up Period:</u> Safety FU Visit 18 weeks after the participant’s last dose of study treatment</p> <p>Note: As noted previously, the study was terminated early. As there was no available post-trial compassionate access mechanism in France, French participants were allowed to remain on treatment as planned and complete the LTE in full. As a result, the decision for early termination of the study did not impact French participants. Non-France participants were required to have the Last Dose Visit prior to 31°October 2023 and the Safety FU Visit 18 weeks (±5 days) after their last dose and no later than 08°March 2024.</p> <p>Following Biogen’s announcement of termination of the aducanumab program, study termination activities were initiated in France on 31 January 2024. Participants from France were required to have the Last Dose Visit prior to 01 May 2024, and the Safety FU Visit 12°weeks (±5 days) after their last dose and no later than 24 July 2024.</p>		
<p>Criteria for Evaluation:</p> <p>The following is a description of all safety assessments that were to be performed for this study.</p> <p><u>Safety:</u></p> <ul style="list-style-type: none"> ● Adverse event (AE) and serious AE (SAE) monitoring, including deaths and AEs of special interest ● Clinical laboratory data ● Physical examination ● Vital signs ● Electrocardiogram (ECG) ● Columbia Suicide Severity Rating Scale (C-SSRS) 		
<p>Statistical Methods:</p> <p>This study was terminated early by the Sponsor. The statistical analyses were simplified for an Abbreviated CSR due to the early termination of the study. The statistical analysis plan (SAP) supersedes the statistical considerations identified in the protocol. Briefly, the efficacy, ██████████ analyses were planned in the protocol but not included in the SAP.</p>		

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<p><u>Safety:</u> Full safety data and data on disposition, baseline, demographics, exposure, and protocol deviations were summarized. All analyses were done based on data collected during the entire study, including the core and the LTE periods. Where specified, a subset of analyses comprised the primary analysis and summarized safety and tolerability data from the core period only.</p> <p><u>Sample Size Calculations:</u> Because the study population depended on the feeder studies, no sample size was determined for this study.</p>		
<p>Results:</p> <p>The first participant was dosed with study treatment on 13 March 2020. The EOS date was 22 July 2024. Biogen announced the early termination of the study on 19 September 2023.</p> <p><u>Participant Accountability:</u></p> <p>During the core period, a total of 1857 participants (the ITTSF population) were enrolled: 253 participants in the 0 dose BIIB037 group (hereafter referred to as the aducanumab-naïve group) and 1604 participants in the pretreated BIIB037 group (hereafter referred to as the aducanumab-pretreated group). Of these, 1696 participants were dosed in the core period. A total of 1121 of 1696 participants (66.1%) completed the study treatment, and 1118/1696 participants (65.9%) completed the study. The most common reasons for discontinuing the study treatment were AEs (8.5%), withdrawal of consent (6.7%), withdrawal by a guardian or caretaker (5.2%), and disease progression (3.9%); the most common reasons for withdrawal from the study were consent withdrawn (8.4%), withdrawal by a guardian or caretaker (5.8%), and adverse events (5.4%).</p> <p>Among the 1118 participants who completed all visits of the core period, 1041 participants were enrolled and dosed in the LTE period. Of these, 530 participants (50.9%) completed the study treatment and 508 (48.8%) completed the study during the LTE period. During the LTE period, the primary reason for study discontinuation (35.8%) and withdrawal from the study (26.5%) was study termination by Sponsor.</p> <p>During the combined core and LTE periods, a total of 1857 participants (the ITTSF population) were enrolled and screened for eligibility for the study. Of these, 1696 participants were dosed. A total of 610/1696 participants (36.0%) completed the study treatment, and 585/1696 participants (34.5%) completed the study. The most common reasons for discontinuing the study treatment were consent withdrawn (8.3%), adverse events (9.9%), and study terminated by Sponsor (22.0%). The most common reasons for withdrawal from the study were study terminated by Sponsor (16.3%), consent withdrawn (12.6%), withdrawal by guardian/caretaker (7.0%), and adverse events (6.5%).</p> <p>Demographics and Baseline Disease Characteristics:</p> <p>Most of the participants were Not Hispanic or Latino (1562 [92.1%]), of whom the majority were White (1399 [82.5%]). The mean (SD) age of participants was 73.1 (7.34) years. The majority of participants were in the age group of 71 to 80 years (878 [51.8%]), followed by the age group of 61 to 70 years (453 [26.7%]). The percentage of males to females was similar across exposure groups, with more females enrolled overall (males: 815</p>		

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participants [48.1%]; females: 881 participants [51.9%]). The mean (SD) height and weight of the participants were 166.57 cm (10.331) and 71.20 kg (15.246), respectively. The mean (SD) BMI (kg/m²) for the participants was 25.550 (4.3989).

Participants in the mITT population had a diagnosis of mild cognitive impairment (MCI) due to Alzheimer's disease, and the majority were determined to be apolipoprotein E (ApoE) ε4 carriers (1150 participants [67.8%]), 542 participants (32%) were noncarriers, and 4 participants (0.2%) were undetermined. The majority of participants had a baseline CDR global score of 0.5 (47.6%) or 1 (36.6%). Participants with a CDR global score of 2 (242 participants, 14.3%) or 3 (8 participants, 0.5%) were included in this study. The mean (SD) baseline CDR-SB score was 5.20 (3.142), the mean baseline CDR cognitive subscore was 3.17 (1.617), and the mean (SD) baseline CDR functional subscore was 2.02 (1.708). The mean (SD) baseline MMSE score was 21.3 (5.60), the mean (SD) baseline ADAS-Cog 13 score was 32.557 (12.6614), and the mean (SD) baseline ADCS-ADL-MCI score was 35.8 (10.14).

The mean (SD) number of years of formal education for the participants was 14.7 years (3.63). The mean (SD) number of years since the first Alzheimer's disease symptom was 7.05 years (2.648). The mean (SD) number of years since diagnosis of Alzheimer's disease at study baseline was 4.60 years (1.668). Participants in the aducanumab-pretreated group had a greater mean number of years since first Alzheimer's disease symptom (7.21 years) than the aducanumab-naïve group (6.03 years).

A total of 15 participants (0.9%) had a history of Alzheimer's disease treatment that was stopped prior to entering the study, whereas 1201 participants (70.8%) had a history of Alzheimer's disease symptomatic medication at baseline.

Safety:

The safety profile of aducanumab is acceptable at doses up to 10 mg/kg in individuals with Alzheimer's disease. The study did not control for baseline differences in exposure groups (e.g. exposure to aducanumab in feeder studies: aducanumab-naïve, 0 dose of 10 mg/kg, >0 dose of 10 mg/kg). Therefore, analyses and interpretation of any observed differences between participants by exposure groups is limited. Any differences noted between exposure groups are provided as observations only.

- During the core period, 1549 participants (91.3%) experienced at least 1 AE and 318 participants (18.8%) experienced SAEs. During the combined core and LTE period, similar incidences of AEs and SAEs were observed. Similar incidences of AEs were observed independent of previous exposure to aducanumab.
- Aducanumab infusions were well tolerated. During the core period, a total of 168 participants (9.9%) experienced events that led to study treatment discontinuation and 129 participants (7.6%)

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experienced events that led to study withdrawal. During the combined core and LTE period, a total of 192 participants experienced events that led to discontinuation of the study treatment and 157 participants experienced events that led to study withdrawal.

- During the core period, 27 participants (1.6%) experienced fatal events. During the combined core and LTE period, 37 (2.2%) experienced fatal events. Two participants died after withdrawal from the study: 1 with a fatal event of ARIA-E assessed by the Investigator as related to study treatment, and 1 due to cardiac arrest unspecified assessed by the Investigator as not related to study treatment. A higher incidence of fatal events was observed in the aducanumab-pretreated groups than in the aducanumab-naïve group, with the highest incidence in the group with prior exposure to >0 doses of 10 mg/kg aducanumab. Since the study did not control for baseline differences in exposure groups, analyses and interpretation of any observed differences between participants by exposure groups is limited.
- In both the core and the combined (core and LTE) periods, participants were stratified based on their [REDACTED]. The incidence of AEs and SAEs was higher in [REDACTED].
- During the core period, in the safety MRI population, 622 participants (37.6%) experienced ARIA events. The cumulative incidence of ARIA-E was 25.5% (422 participants experiencing 609 events), and the cumulative incidence of ARIA-H was 30.5% (505 participants), with 24.8% (411 participants) experiencing 603 events of ARIA-H microhemorrhage, 13% (216 participants) experiencing 285 events of ARIA-H superficial siderosis, and 0.4% (7 participants) experiencing ARIA-H macrohemorrhage (PT cerebral haemorrhage).
- Most participants with events of ARIA, ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis had events that were mild or moderate in MRI severity, asymptomatic (ARIA [84.1%], ARIA-E [80.8%], ARIA-H microhemorrhage [90.5%], ARIA-H superficial siderosis [92.1%]), and not serious. The incidence of serious events was <3% (ARIA [1.4%] ARIA-E [2.1%], ARIA-H microhemorrhage [0.7%], ARIA-H superficial siderosis [0%]). When symptomatic, most participants with ARIA, ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis had events that were mild or moderate in clinical severity.
- During the core period, in the immunogenicity population, 26 of 1595 participants (1.6%) had an anti-aducanumab antibody–positive response at any time, including the baseline visit. The incidence of treatment-emergent anti-aducanumab antibodies was low at all timepoints and generally transient. Four participants had a persistent positive response, whereas 15 participants had a transient positive

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<p>response. During the combined core and LTE periods, similar results were observed. There was no apparent effect of immunogenicity on aducanumab safety.</p> <ul style="list-style-type: none"> • During the combined core and LTE period, in the safety population, no clinically significant effects of aducanumab treatment on vital signs, laboratory findings, C-SSRS, or ECG trends were observed. Overall, laboratory values during the study treatment were consistent across time periods in the safety population. 		
<p>Conclusion(s):</p> <p>The primary endpoint of this study was to assess the long-term safety and efficacy of aducanumab in participants with Alzheimer’s disease who were enrolled in previous aducanumab studies. Since all study participants had completed the core portion of the study, i.e., treatment for 100 weeks, the primary objective of assessing the safety and tolerability of aducanumab and the [REDACTED] objectives of the study had been met. However, due to the early termination of the study, only a portion of the population also completed the LTE, which was added to the ongoing study to continue treatment for an additional 52 weeks.</p> <p>During both the core and combined core and LTE periods, the safety profile of aducanumab was acceptable at doses up to 10 mg/kg in individuals with Alzheimer’s disease. Since the study did not control for baseline differences in exposure groups, analyses and interpretation of any observed differences between participants who had been exposed to aducanumab in the feeder studies versus aducanumab-naïve participants who had been treated with placebo in the previous studies is limited. Overall, ARIA was the most common AE. Most of the ARIA events occurred during the first 12 doses of aducanumab, and the incidence of ARIA events was higher in ApoE ε4 carriers. Most events were asymptomatic and stabilized/resolved on follow-up MRI testing.</p> <p>In conclusion, over the core period of 100 weeks, and for up to 152 weeks in those participants with Alzheimer’s disease who had enrolled in the LTE, the safety profile of aducanumab 10 mg/kg IV was acceptable.</p>		
<p>Date of Report: 26 November 2024</p>		
<p>Version: 1</p>		

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