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

Published: 16-04-2020
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Primary objective:To evaluate the safety and tolerability of aducanumab over 100 weeks of treatment after a wash-out period imposed by discontinuation of feeder studies in participants who had previously received aducanumab (i.e., previously treated...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON52801

Source
ToetsingOnline

Brief title
EMBARK - 221AD304

Condition

- Mental impairment disorders

Synonym
Alzheimer's Disease

Research involving

Human

Sponsors and support

Primary sponsor: IQVIA RDS Netherlands B.V.
Source(s) of monetary or material Support: Biogen

Intervention

Keyword: Aducanumab, Alzheimer's Disease, Phase 3b

Outcome measures

Primary outcome

Primary endpoint

Incidence of AEs, SAEs, ARIA, and immunogenicity over 100 weeks of treatment

and/or re-exposure to aducanumab. Safety and tolerability parameters include

the following:

• Incidence of all AEs, AEs leading to treatment discontinuation or study

withdrawal, and all SAEs

• Incidence of ARIA-E and ARIA-H

• Incidence of ADAs in serum

Secondary outcome

Core Exploratory endpoints:

1. Changes in cognition, neuropsychiatric status, function, and quality of life

as measured by:

- CDR-SB score

- ADAS-Cog 13 score

- ADCS-ADL-MCI score

- MMSE score

- MOCA score

- NPI-10 total score

- Health Economics and Outcome Research measures of EQ-5D (SR); EQ-5D (IR-S); EQ-5D (IR-I); mPDQ-20; CAM; and ADCS-MCI-CGIC

2.

- PET Imaging (optional substudy): Change in: Tau PET signal (in a subset of sites and participants)

- MRI Imaging: Change in MRI morphometric measures of regional brain volume

- Fluid biomarkers (blood and optional CSF): Change in levels of fluid biomarkers related to disease which may include, but are not limited to tau proteins (in a subset of participants).

3. Minimum concentration prior to administration of the dose every 6 months

LTE exploratory endpoints:

1. Incidence of AEs, SAEs, ARIA, and immunogenicity with long-term treatment of aducanumab. Safety and tolerability parameters include the following:

• Incidence of all AEs, AEs leading to treatment discontinuation or study withdrawal, and all SAEs

• Incidence of ARIA-E and ARIA-H

• Incidence of ADAs in serum

2. Changes in cognition, neuropsychiatric status, function, and quality of life as measured by the following:

• CDR-SB score

• ADAS-Cog 13 score

• ADCS-ADL-MCI score

• MMSE score

• MOCA score

• NPI-10 total score

• RUD

• Zarit Burden

3.

• PET Imaging (substudy): Change in Amyloid PET signal (in a subset of sites

and participants)

• PET Imaging (substudy): Change in Tau PET signal (in a subset of sites and

participants)

•Fluid biomarkers (blood and optional CSF): Change in levels of fluid

biomarkers related to disease which may include, but are not limited to,

amyloid and tau proteins (in a subset of participants)

4. Minimum concentration prior to administration of the dose every 6 months

Study description

Background summary

Alzheimer*s disease (AD) is the most common cause of dementia, accounting for 50% to 75% of all cases. Alzheimer*s Disease International estimates that as of 2016, there were 47 million people living with dementia worldwide, and that this figure will increase to 131 million by 2050.

One of the most important features of AD is that a substance called amyloid beta (a protein) is found at an elevated level in the brain. These deposits of amyloid beta are known as plaques. It is assumed that these plaques disturb the normal activity of the brain cells and worsen the symptoms of the disease.

The study drug, aducanumab, is an antibody therapy. Antibodies are part of the immune system. They are produced naturally by the immune system, and they detect and remove substances in the body that do not belong there. Antibodies can also be produced in the laboratory. In this way, very specific antibodies can be produced, which bind to a harmful substance in the body to remove it. It is assumed that the study drug can fight and remove plaques in the brain of people with early stage AD. It is presumed that, in response to this, the deterioration of the AD can be slowed down.

In March 2019, an early review of the results from half of the participants of the ENGAGE and EMERGE studies showed that treatment with the study drug may not work as well as expected for participants with AD. As a result, Biogen decided to stop all the ongoing aducanumab studies on March 21, 2019. To better understand why this was observed, Biogen carried out additional reviews and analyses of the results from a higher number of participants obtained before the stopping of the trials. The new results showed that, in the EMERGE study, the group of participants who received the high dose of aducanumab (10 mg/kg) experienced benefits on the measures of cognition and function, such as memory, orientation, and language, compared to the group treated with placebo. In addition, they experienced benefits with daily activities, such as conducting personal finances, performing household chores of cleaning, shopping, and doing laundry, and independently traveling out of the home. In the ENGAGE study, although the new analyses did not show the same results for the whole group of participants who received the high dose aducanumab (10 mg/kg), the new analyses showed that participants who received 10 mg/kg in a sustained manner had similar benefits as in EMERGE.

Study objective

Primary objective:
To evaluate the safety and tolerability of aducanumab over 100 weeks of treatment after a wash-out 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).

Exploratory objectives:
1. To evaluate the long-term efficacy of aducanumab using clinical endpoints.
2. To evaluate the long-term effect of aducanumab on biomarker endpoints.
3. To evaluate the long-term effect of aducanumab on PK endpoints.

Study design

Your participation will last about 3.5 years and will consist of 4 main periods:
- The screening period lasts approximately 12 weeks
- The core treatment period, in which you receive the study drug, lasts 100

weeks
- The optional long-term extension treatment period. If you decide to participate you will receive the study drug for another 52 weeks
- A follow-up period, in which you no longer receive the study drug, lasts for 18 weeks.

After a Screening Period, participants who meet the eligibility criteria will receive open-label treatment. During the Treatment Period, participants will receive IV infusions of aducanumab approximately every 4 weeks for a total treatment duration of 100 weeks (a total of 26 doses). Eligible participants will then enter the LTE Treatment Period and continue dosing on 10 mg/kg aducanumab Q4W for an additional 52 weeks (a total of 152 weeks of continuous treatment). The EOT Visit will occur at Week 154. Participants will have a safety follow up visit 18 weeks after their last dose of study treatment. For participants who do not enter the LTE, this FU visit will occur at Week 118.

Intervention

In the core treatment period, the subject will receive the study drug as an infusion through a vein once a month (every 4 weeks) for about 2 years. Subjects will receive 26 infusions and each infusion will last about 1 hour. During the LTE Treatment Period subjects will receive the study drugs for another 52 weeks (an additional 13 doses).

As this is an open-label study the subject and the investigator will know which dose you are receiving. Subjects will receive the study drug Aducanumab at increasing doses as follows:
o Infusions 1 and 2 (Weeks 1 and 4): 1 mg/kg
o Infusions 3 and 4 (Weeks 8 and 12): 3 mg/kg
o Infusions 5 and 6 (Weeks 16 and 20): 6 mg/kg
o Infusions 7 to 39 (once every 4 weeks during Weeks 24-100): 10 mg/kg

Study burden and risks

There are currently no available therapies that modify the clinical course of Alzheimer*s disease. Analyses of data collected through the end of the study (Study 301 database lock on 15 Novebmer 2019 and Study 302 database lock on 13 November 2019, with efficacy data after 20 March 2019 censored) in the 2 Phase 3 aducanumab clinical studies showed that, in Study 302, treatment with aducanumab significantly reduced clinical decline in patients with early Alzheimer*s disease as measured by the prespecified primary (CDR-SB) and by the 3 secondary endpoints (ADAS-Cog 13, MMSE and ADCS-ADL-MCI) in the high-dose group. In addition, Study 301 contained supportive data, based on post-hoc analyses of subsets of participants who received sufficient exposure to the highest dose (10 mg/kg) of aducanumab.

As of 01 April 2019, an estimated 3075 participants have been exposed to aducanumab. These include 2755 Aducanumab-treated subjects from Studies 301 and 302, of whom 1345 were assigned to a target dose of 10 mg/kg. The most frequent adverse event, among subjects from Studies 301 and 302 with a target dose of 10 mg/kg, was ARIA-E (32.9%). The majority of participants who experienced ARIA-E did not experience symptoms during an ARIA-E episode. Symptoms reported during ARIA-E episodes included headache, confusion, dizziness, fatigue, nausea, or rarely seizures, including prolonged seizures. Such symptoms typically resolved and were generally not associated with long-term clinical sequelae. Other frequent adverse events, among subjects from Studies 301 and 302 with a target dose of 10 mg/kg, included headache (18.7%), ARIA-H microhemorrhage (17.0%) and ARIA-H superficial siderosis of the central nervous system (13.8%). Similar to ARIA-E, the majority of participants with ARIA-H microhemorrhage and ARIA-H superficial siderosis were asymptomatic. The benefit-risk profile of aducanumab is considered positive.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Inclusion criteria

Core treatment period
- Participant was participating in an aducanumab clinical study at the time of the announcement of early termination (Studies 221AD301, 221AD302, 221AD103 and 221AD205, referred to as "feeder studies").
- Has one care partner who, in the Investigator's opinion, has adequate contact with the participant as to be able to provide accurate information about the participant's cognitive and functional abilities.

LTE Treatment Period:
- Participant must have completed the Core study 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 as to be able to provide accurate information about the participant's cognitive and functional abilities.

Other protocol defined Inclusion criteria may apply.

Exclusion criteria

Core treatment period
- Any medical or neurological condition (other than Alzheimer's Disease) that might be a contributing cause of the subject's cognitive impairment.
-Stroke or any unexplained loss of consciousness within 1 year prior to Screening.
-Clinically significant unstable psychiatric illness in past 6 months.
-History of unstable angina, myocardial infarction, advanced chronic heart failure, or clinically significant conduction abnormalities 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.
- History of or known seropositivity for HIV.
- Clinically significant systemic illness or serious infection within 30 days prior to or during Screening.
- Contraindications to having a brain magnetic resonance imaging (MRI).

LTE Treatment Period:

- 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.

Other protocol defined Exclusion criteria may apply.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-01-2021
Enrollment:	29
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	aducanumab
Generic name:	aducanumab

Ethics review

Approved WMO

Date:	16-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	26-10-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004368-22-NL
ClinicalTrials.gov	NCT04241068
CCMO	NL72580.056.20

Study results

Date completed:	29-02-2024
Results posted:	07-02-2025
Actual enrolment:	29

Summary results
please see CSR

Baseline characteristics
please see CSR

Participant flow
please see CSR

Adverse events
please see CSR

Outcome measures
please see CSR