Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer*s Disease

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This study has been transitioned to CTIS with ID 2023-507303-55-00 check the CTIS register for the current data. To assess the effect of donanemab versus placebo on clinical progression in participants with early symptomatic AD with demonstrated...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON52785

Source
ToetsingOnline

Brief title
I5T-MC-AACI / TRAILBLAZER-ALZ 2

Condition

- Other condition

Synonym
Alzheimer, senile psychosis

Health condition

Early Symptomatic Alzheimer's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Alzheimer's Disease, Phase 3

Outcome measures

Primary outcome

iADRS change from baseline through Week 76

Secondary outcome

Change from baseline through Week 76 as measured by:

• iADRS

• CDR-SB

• ADAS-Cog13 score

• ADCS-iADL score

• MMSE score

Change in brain amyloid plaque deposition from baseline through Week 76 as measured by florbetapir F18 PET scan

Change in brain tau deposition from baseline through Week 76 as measured by flortaucipir F18 PET scan

Change in volumetric MRI measures from baseline through Week 76

Standard safety assessments: Spontaneously reported AEs, Clinical laboratory tests, Vital sign and body weight measurements, 12-lead ECGs, Physical and neurological examinations

- MRI (ARIA and emergent radiological findings)

- Infusion related reactions

- C-SSRS

Plasma PK of donanemab

ADAs against donanemab including

• treatment emergent ADAs

• neutralizing antibodies

Study description

Background summary

Donanemab is an antibody directed at the pyroglutamate modification of the third amino acid of amyloid beta (N3pG Aβ) epitope that is present only in brain amyloid plaques. It is being studied for the treatment of Alzheimer*s disease (AD). The mechanism of action of donanemab antibody is to target and remove deposited amyloid plaque, a key pathological hallmark of AD, via microglial-mediated clearance. The clinical strategy for donanemab identifies early symptomatic AD patients with existing brain amyloid load, as measured using the amyloid plaque biomarker florbetapir F18 positron emission tomography (PET) imaging in conjunction with the presence of tau burdenpathology in the brain. This strategy is based on the amyloid hypothesis of AD, which postulates that the production and deposition of Aβ is an early and necessary event in the pathogenesis of AD (Selkoe 2000). Clinical data supporting this hypothesis comes from the observation that parenchymal Aβ levels are elevated prior to the manifestation of AD symptoms, and further supported by genetic variants of AD that overproduce brain Aβ and genetic variants that protect against Aβ production (Jonsson et al. 2012; Fleisher et al. 2015). Furthermore, early in the disease, the presence of brain amyloid appears to increase the risk of conversion from mild cognitive impairment (MCI) to AD dementia (Doraiswamy et al. 2012). These data suggest that removal of deposited amyloid and clearance of Aβ can result in the slowing of AD progression.

Study objective

This study has been transitioned to CTIS with ID 2023-507303-55-00 check the CTIS register for the current data.

To assess the effect of donanemab versus placebo on clinical progression in participants with early symptomatic AD with demonstrated presence of low-medium tau pathology.

Study design

Study AACI is a multicenter, randomized, double-blind placebo-controlled, Phase 3 study of donanemab in participants with early symptomatic AD. Participants who meet entry criteria will be randomized in a 1:1 ratio to one of the following treatment groups:

- Donanemab: 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W
- Placebo

Intervention

Patients will be randomized in a 1:1 ratio to receive respectively:
- Donanemab: 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W
- Placebo

Treatment will occur every four weeks, where patient will come in to receive their respective treatment intravenously.

The study participant will go through the following study phases:
- Screening period (7 weeks)
- Double-blind treatment period (76 weeks)
- Follow-up period (44 weeks)

Study burden and risks

Risks:
Unwanted events of donanemab. The unwanted events that were determined in relation to patients using donanemab are listed in section E9.
The subjects undergo a number of study procedures such as: physical/neurological examination, several tests in relation to the participants alzheimer's disease, administration of the study drug, blood draws and others. For a comprehensive overview, please refer to section 1.3 in the protocol.
These tests and procedures may come with associated risks. For a full overview of the risks associated with these procedures, please refer to the informed consent form.

Burden:

Total participation on the study is 72 weeks, inclusive of 21 visits and potential follow-up visits. The treatment part of the study lasts for the full 72 weeks, where subjects receive the medication intravenously.
Patients may experience returning, or worsening of symptoms.
A comprehensive list of the burden associated with participation in this study is described in the informed consent form

Contacts

Public
Eli Lilly

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IE
Scientific
Eli Lilly

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IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Elderly (65 years and older)

Inclusion criteria

1. 60 to 85 years of age inclusive, at the time of signing the informed consent.
2. Gradual and progressive change in memory function reported by the participant or informant for >=6 months.
3. An MMSE score of 20 to 28 (inclusive) at LEAD-IN SCREENING or COMPLETE SCREENING,

4. Meet flortaucipir F18 scan (central read) criteria
5. Meet florbetapir F18 scan (central read) criteria
6. Have a study partner who will provide written informed consent to participate, is in frequent contact with the participant (defined as at least 10 hours per week), and will accompany the participant to study visits or be available by telephone at designated times.
7. Have adequate literacy, vision, and hearing for neuropsychological testing in the opinion of the investigator at the time of screening.
8. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.
9. Males and females will be eligible for this study.
10.Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion criteria

12. Significant neurological disease affecting the central nervous system (CNS), other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson*s disease, multiple concussions, or epilepsy or recurrent seizures (except febrile childhood seizures).
13. Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator*s opinion, could interfere with the analyses in this study; or has a life expectancy of <24 months.
14. History of cancer within the last 5 years, with the exception of non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, nonprogressive prostate cancer, or other cancers with low risk of recurrence or spread.
15. Participants with any current primary psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the participant*s ability to complete the study. Participants with history of schizophrenia or other chronic psychosis are excluded.
16. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
17. History of alcohol or drug use disorder (except tobacco use disorder) within 2 years before the screening visit.
18. Have a history of clinically significant multiple or severe drug allergies, significant atopy, or severe posttreatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and/or exfoliative dermatitis).
19. Have any clinically important abnormality at screening, as determined by

investigator, in physical or neurological examination, vital signs, ECG, or clinical laboratory test results that could be detrimental to the patient, could compromise the study, or show evidence of other etiologies for dementia.
20. Screening MRI which shows evidence of significant abnormality that would suggest another potential etiology for progressive dementia or a clinically significant finding that may impact the patient*s ability to safely participate in the study.
21. Have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants/cardiac pacemaker.
22. Have a centrally read MRI demonstrating presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease at screening.
23. Sensitivity to florbetapir F18 or flortaucipir F18.
24. Poor venous access.
25. Contraindication to PET.
26. Present or planned exposure to ionizing radiation that, in combination with the planned administration of study PET ligands, would result in a cumulative exposure that exceeds local recommended exposure limits.
27. A corrected QT (QTcF) interval measurement >450 msec (men) or >470 msec (women) at screening (as determined at the investigational site). The site may request a central read prior to making determination of this criterion.
28. Calculated creatinine clearance <30 mL/min (Cockcroft-Gault formula; Cockcroft and Gault 1976) at screening.
29. Alanine transaminase (ALT) >=2X the upper limit of normal (ULN) of the performing laboratory, aspartate aminotransferase (AST) >=2X ULN, total bilirubin level (TBL) >=1.5X ULN, or alkaline phosphatase (ALP) >=1.5X ULN at screening.
30. Have received treatment with a stable dose of an acetylcholinesterase inhibitor (AChEI) and/or memantine for less than 2 months before randomization. [If a patient has recently stopped an AChEI and/or memantine, he or she must have discontinued treatment at least 2 months before randomization.]
31. Changes in concomitant medications that could potentially affect cognition and their dosing should be stable for at least 1 month before screening, and between screening and randomization (does not apply to medications discontinued due to exclusions or with limited duration of use, such as antibiotics).
32. Have had prior treatment with a passive anti-amyloid immunotherapy <5 half-lives prior to randomization.
33. Have received active immunization against Aβ in any other study.
34. Have known allergies to donanemab, related compounds, or any components of the formulation.
35. Are currently enrolled in any other interventional clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
36. Have participated, within the last 30 days (4 months for studies conducted in Japan; 3 months for studies conducted in the UK), in a clinical trial involving an investigational product. If the previous investigational product is scientifically or medically incompatible with this study and has a long

half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening (Participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor).
37. Have previously completed or withdrawn from this study or received donanemab in any prior investigational study. (This exclusion criterion does not apply to patients who are allowed to rescreen before randomization in this study).
38. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
39. Are Lilly employees or are employees of third-party organizations (TPOs) involved in study who require exclusion of their employees, or have study partners who are Lilly employees or are employees of TPOs involved in a study which require exclusion of their employees.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	05-02-2021
Enrollment:	27
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Donanemab

Generic name:	-

Ethics review

Approved WMO Date:	28-05-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-09-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-03-2021
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	22-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-07-2024
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
EU-CTR	CTIS2023-507303-55-00

Register	ID
EudraCT	EUCTR2020-000077-25-NL
ClinicalTrials.gov	NCT04437511
CCMO	NL73209.056.20