A Phase 3, Multicenter, Randomized, Double-blind, Placebo-Controlled Study of the Efficacy, Safety and Biomarker Effects of ALZ-801 in Subjects with Early Alzheimer's Disease and APOE4/4 Genotype

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON54459

Source
ToetsingOnline

Brief title
ALZ-801-AD301 (ICON 3799/0004)

Condition

- Dementia and amnestic conditions

Synonym
Early Alzheimer□s Disease and APOE4/4 genotype. Understanding if ALZ-801 will affect cognition.

Research involving
Human

Sponsors and support

Primary sponsor: Alzheon Inc.
Source(s) of monetary or material Support: Alzheon Inc.

Intervention

Keyword: APOE4/4 genotype, Early Alzheimer's Disease, Phase 3

Outcome measures

Primary outcome

Primary Efficacy Endpoint * Cognitive Endpoint: Change from baseline (CBL) to Week 78 in ADAS-Cog 13 scores Primary Fluid Biomarker Endpoints * CBL to Week 78 in CSF p-tau181 (in CSF sub-study) * CBL to Week 78 in plasma p-tau181 in all subjects Primary Imaging Biomarker Endpoint * CBL to Week 78 in total hippocampal volume as assessed by vMRI Safety and Tolerability * Incidence and nature of treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to withdrawal. * CBL in vital signs and physical exam, including body weight * CBL in laboratory parameters (clinical chemistry, hematology, coagulation tests) * CBL in 12-lead electrocardiogram (ECG) parameters. * CBL in MRI central readings for amyloid-related imaging abnormalities with vasogenic edema (ARIA-E) or due to haemosiderin deposition (ARIA-H) * CBL in the Columbia-Suicide Severity Rating Scale (C-SSRS) Analysis Population The primary efficacy population will be the Modified Intent-To-Treat (mITT) Population, which is defined as all randomized subjects who have received at least one dose of study drug, have one baseline assessment, and have also completed at least one scheduled post-baseline visit with at least one valid

post baseline assessment. Analysis of Primary Efficacy Endpoints Analyses of the primary efficacy endpoint (CBL in ADAS-Cog 13 scores) will be performed on the mITT Population using on-treatment observed case (OC) data. Effects between treatment groups will be assessed using a mixed effects model with repeated measures (MMRM) that includes treatment and stratification factors: use of concomitant AD medications [acetyl cholinesterase inhibitors or none], age group (50 through 65 years or > 65 years), gender, disease severity based on MMSE, baseline ADAS-Cog 13 values, visit (VISIT), and treatment by visit interaction. Justification of the Sample Size For the primary efficacy outcome of ADAS-Cog 13, this study is powered to detect a 3.0 point difference between ALZ-801 and placebo in the CBL to Week 78. This assumes a within-treatment SD of approximately 8.1 in the drug arm and 5.6 in the placebo arm. A sample size of 125 subjects per arm will provide approximately 90% power to show a 3-point difference between the two treatment groups at a significance level of $\alpha = 0.05$ (2-sided). The drop-out rate is estimated to be approximately 17% at 78 weeks, thus a total of 300 subjects enrolled would provide approximately 250 completers or approximately 125 per arm.

Secondary outcome

NA

Study description

Background summary

ALZ-801 is an oral agent that is being developed as a potential disease modifying treatment for AD. This 78-week Phase 3 study will focus on Early AD

subjects who carry the APOE4/4 genotype, and is designed according to current regulatory guidance for trials in symptomatic patients with Early AD.

The active agent in ALZ-801 is tramiprosate, a small molecule that inhibits the formation of soluble beta amyloid (Aβ42) oligomers. Tramiprosate had been evaluated in 5 clinical trials in AD patients, across all apolipoprotein E (APOE) genotypes. In a Phase 3 trial in Mild to Moderate AD, efficacy was not achieved in the overall study population, but a meaningful signal was observed in subjects who are either heterozygous or homozygous for the *4 allele of apolipoprotein E gene (APOE4 carriers), which was further analyzed to identify the optimal study population. Tramiprosate showed promising clinical efficacy in APOE4 homozygotes and heterozygtoes subgroups. These positive clinical effects were especially significant in APOE4/4 homozygotes and were observed at a tramiprosate dose (150mg BID) that showed favorable long term safety.

In the Phase 3 studies which included 2025 AD patients, oral tramiprosate showed favorable long-term safety over 2.5 years, with nausea and vomiting being the main TEAEs. There were no events of vasogenic edema in these studies. PK analyses from these studies also showed high variability in plasma levels of tramiprosate. ALZ-801 was therefore developed as a pro-drug of tramiprosate to improve its oral bioavailability and gastrointestinal (GI) tolerability.
ALZ-801 is composed of tramiprosate conjugated to the essential amino acid valine [Figure 2]. Upon absorption into systemic circulation, ALZ-801 is rapidly converted into free tramiprosate and valine.

The development of ALZ-801 was based on a bridging strategy to tramiprosate data. The bridging approach was discussed with the US FDA, which requested nonclinical safety and clinical PK and safety studies to compare ALZ-801 and tramiprosate. Nonclinical safety studies showed enhanced safety margins with ALZ-801 [Data on file]. ALZ-801 was evaluated in four bridging studies in 134 subjects, including elderly and AD subjects. These studies allowed the selection of an ALZ-801 dose (265mg BID) that provides plasma levels bioequivalent to tramiprosate 150mg BID that showed efficacy in APOE4/4 homozygotes. In these Phase 1b studies, ALZ-801 showed improved GI tolerability with reports of mild and transient nausea.

For more information see protocol section 2. Background

Study objective

ALZ-801 is an oral agent that is being developed as a potential disease modifying treatment for AD. This 78-week Phase 3 study will focus on Early AD subjects who carry the APOE4/4 genotype, and is designed according to current regulatory guidance for trials in symptomatic patients with Early AD.

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Study design

This is a Phase 3, mulitcenter, randomized, double-blind, placebo-controlled, parallel-group, two-arm study, with a treatment duration of 78 weeks (18 months).

Intervention

NA

Study burden and risks

See protocol section 2.4 Benefit/Risk assessment.

Contacts

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Scientific
Alzheon Inc.

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

1. Male or female between the ages of 50 and 80 years (inclusive) at the Screening - Part 1 Visit.
2. Clinical diagnosis of MCI or Mild Dementia due to AD consistent with the NIA-AA Working Group Criteria
3. Homozygous for the *4 allele of the APOE gene (APOE4/4).
4. MMSE score of 22 to 30 (inclusive) at the Screening - Part 1 Visit.
5. CDR Global score at Screening of 0.5 or 1, and a CDR Memory Box score >= 0.5.
6. RBANS delayed memory index score <= 85.
7. Evidence of progressive memory loss over the last 12 months per investigator assessment as captured on the diagnostic verification form.
8. Can complete the cognitive testing and all other required study procedures.
9. Has completed at least 6 years of formal education after age of 5 years, and is able to read at minimum of 6th grade level or equivalent per investigator assessment.
10. Lives at home independently, in a senior living facility, or in an assisted

living facility.
11. Has a body mass index (BMI) between 17-40 (inclusive).
12. Except for a diagnosis of AD and the presence of stable medical conditions, is, in the opinion of the Investigator, in good general medical health based upon the results of medical history, physical examination, laboratory tests, vital signs, and ECG.
13. Has a reliable caregiver or study partner who is willing and able to sign an ICF, to accompany the subject to study visits, and adhere to study requirements (The caregiver or study partner, in the Investigator's opinion, has adequate contact with the subject to be able to provide accurate information about the participant's cognitive and functional ability).
See protocol for further inclusion criteria

Exclusion criteria

1. Screening brain MRI indicative of significant abnormality per central reader, other than AD related atrophy, including, but not limited to; prior large vascular territorial infarct, > 2 lacunar infarcts (size > 1.5 cm) outside the brain stem, severe white matter changes (deep white matter changes Fazekas grade = 3), ventriculomegaly related to normal pressure hydrocephalus (after clinical correlation), or aneurysm, subdural hematoma, abscess or brain tumor (other than meningiomas or benign pituitary adenoma). 2. Diagnosis of a neurodegenerative disorder other than AD. 3. Diagnosed with MDD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5), within one year prior to the Baseline Visit. A subject who does not meet criteria for MDD and who is on stable doses of antidepressants or mood stabilizers may be included in the study at the discretion of the Investigator. 4. Currently taking memantine or has taken memantine within 12 weeks prior to the Baseline Visit. 5. History of suicidal behavior within one year prior to the Baseline Visit; or has ongoing suicidal ideation with intent, with or without a specific plan or method (e.g., positive response to C-SSRS items 4 or 5 during the past 6 months). 6. History of seizures, excluding febrile seizures of childhood or a single distant seizure (>= 5 years prior to the Baseline Visit). 7. Medically confirmed history of recent cerebral infarct or transient ischemic attack within one year prior to the Baseline Visit. 8. Medically confirmed history of recent myocardial infarction or unstable, untreated coronary artery disease, or angina pectoris (within 1 year prior to the Baseline Visit). 9. Lifetime history of schizophrenia, schizoaffective disorder, or bipolar disorder. 10. History of, or currently has, any clinically significant ECG finding, or a QT interval corrected by Fridericia*s method (QTcF) of > 450 msec for males and > 470 msec for females. 11. History of cancer, diagnosed and treated within the last 3 years prior to the Baseline Visit, with the exception of the following: (a) treated basal cell carcinoma of the skin, (b) treated cutaneous squamous cell carcinoma in situ, (c) treated in situ or Stage 1 prostate cancer, (d) treated

in situ cervical cancer, and (e) resected and cured early stage cutaneous melanoma (all require approval by the Sponsor's Medical Officer). 12. Has donated blood > 250 mL within 6 weeks prior to the Baseline Visit. 13. History of alcohol or drug dependence or abuse according to the criteria of the DSM-5 within 2 years prior to the Baseline Visit. Note: A positive urine drug screen does not automatically exclude subject, but requires review by Sponsor Medical Officer. 14. Any significant medical condition or infection (e.g., uncontrolled cardiovascular, GI, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal, or other major disease or malignancy) that is unstable and that would either: (a) place the subject at undue risk from administration of study drug or from undergoing study procedures, or (b) interfere with the interpretation of safety or efficacy evaluations obtained in the course of the study. 15. Unable to swallow ALZ-801 tablets or has a known intolerance or hypersensitivity to tramiprosate or any of the excipients contained in the ALZ-801 tablets. 16. Except when otherwise specified, has clinical laboratory tests outside normal limits per the laboratory*s specification and considered clinically significant by the investigator at the Screening - Part 2 Visit 17. Clinically relevant abnormalities in serum thyroid-stimulating hormone (TSH) or calcium. If the subject is taking thyroid hormone replacement therapy, corresponding Screening test values must be considered not clinically significant by the investigator. 18. Serum vitamin B12 below the lower limit of normal at the Screening - Part 2 Visit. A subject can be treated with vitamin B12 replacement during screening period, and enrolled if the value has normalized approximately four weeks post-treatment. 19. Any clinical chemistry laboratory value greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE; version 5.0; National Cancer Institute 2018) Grade 2, unless considered not clinically relevant by the Investigator. 20. One or more of the following at the Screening - Part 2 Visit: Alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN), Aspartate aminotransferase (AST) > 3 × ULN, or Total bilirubin (TBL) > 1.5 × ULN. (except for subjects with diagnosed Gilbert syndrome with isolated hyperbilirubinemia). 21. Estimated glomerular filtration rate (eGFR) < 40 mL/min per 1.73 m2 according to the Modification of Diet in Renal Disease (MDRD) formula [see National Institute of Diabetes and Digestive and Kidney Diseases website for formula MDRD formula for eGFR (SI units)]. See protocol for further exclusion criteria

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:	Recruitment stopped
Start date (anticipated):	23-03-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ALZ-801
Generic name:	ALZ-801

Ethics review

Approved WMO Date:	14-06-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	15-10-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	19-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-05-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-05-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-07-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-09-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2020-005755-20-NL
ClinicalTrials.gov	NCT04770220
CCMO	NL77867.100.21