A Phase 2, Single-Arm Study of the Biomarker Effects of ALZ-801 in Subjects with Early Alzheimer*s Disease Who Are Carriers of the *4 Variant of the Apolipoprotein E Gene (APOE4/4 or APOE3/4)

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This study has been transitioned to CTIS with ID 2024-515858-25-00 check the CTIS register for the current data. Objectives - Core StudyPrimary Objectives• To evaluate the effects of oral ALZ-801 in subjects with Early AD who have the APOE4/4 or...

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

Summary

ID

NL-OMON56257

Source
ToetsingOnline

Brief title
Biomarker Effects of ALZ-801 in APOE4 Carriers

Condition

- Mental impairment disorders

Synonym
Alzheimer's disease, dementia

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Alzheimer's Disease, Apolipoprotein E Gene, Biomarker

Outcome measures

Primary outcome

Endpoints - Core Study

Primary and Key Secondary Outcome

• Primary Plasma Biomarker Outcome: change from baseline to Week 104 in plasma biomarker of core AD pathology: p-tau181

• Key Imaging Outcome: change from baseline to Week 104 in hippocampal volume on vMRI

Safety Outcomes

• Incidence and nature of TEAE, serious TEAE, and TEAE leading to withdrawal

• Changes in laboratory parameters, vital signs, and physical examination

• Changes in 12-lead electrocardiogram (ECG) parameters

• MRI assessments for Amyloid-Related Imaging Abnormalities with edema (ARIA-E) or microhemorrhages (ARIA-H)

Endpoints - Long-Term Extension Year 1

Primary and Key Secondary Outcomes

• Primary Plasma Biomarker Outcome: change from study baseline to Week 156 in plasma biomarkers: p-tau181

• Key Imaging Outcome: change from study baseline to Week 156 in hippocampal volume on vMRI

Safety Outcomes

•Safety and tolerability over 156 weeks of study and over 52 weeks of the LTE Year 1 as listed in Study Protocol V7.0 Section 2.2.2

Endpoints - Long-Term Extension Year 2

Primary and Key Secondary Outcomes

• Primary Plasma Biomarker Outcome: change from study baseline to Week 208 in plasma biomarkers: p-tau181

• Key Imaging Outcome: change from baseline to Week 208 in hippocampal volume on vMRI

Safety Outcomes

•Safety and tolerability over 104 weeks of the LTE-assessments (and over 208 weeks in the overall study) as listed in Study Protocol V7.0 Section 2.2.2

Secondary outcome

Endpoints - Core Study

Secondary Fluid Biomarker Outcome

• Change from baseline to Week 104 in plasma biomarkers of other core AD pathologies: Aβ40, Aβ42, and p-tau217

Secondary Imaging Biomarker Outcome

• Change from baseline to Week 104 in cortical thickness and ventricular volume

Exploratory Fluid Biomarker Outcomes

• Change from baseline to Week 104 in biomarker of plasma GFAP

• Change from baseline to Week 104 in plasma NfL

• Change from baseline to Week 104 in CSF p-tau181, p-tau217, Aβ40, and Aβ42

• Change from baseline to Week 104 in CSF neurogranin

• Change from baseline to Week 104 in CSF t-tau and NfL

• Change from baseline to Week 104 in CSF TREM2 and YKL-40

Clinical Outcomes

• Change from baseline to Week 104 in RAVLT, DSST, A-IADL MMSE, CDR-SB

Pharmacokinetic and Pharmacodynamic Outcomes

• Plasma and CSF levels of ALZ-801, tramiprosate, and its metabolite before and after first dose, at steady state, and at later time points in the study. PK non-compartmental analysis will be performed using Phoenix WinNonlin (version 7.0 or later).

• Correlation of PK levels to biomarker outcomes.

• Correlation of PK levels to efficacy and safety parameters.

• Extended PK profile over 8 hours on Week 65 will be evaluated in approximately 24 subjects (approximately 12 APOE4/4 homozygotes and 12 APOE3/4 heterozygotes) who have consented to participate in the PK Profile Substudy.

Additional Fluid and Imaging Biomarker Outcomes

• Change from baseline to Weeks 6, 13, 26, 52, and 78 for plasma biomarkers

• Change from baseline to Week 52 in hippocampal volume, cortical thickness, and ventricular volume

• Change from baseline to Week 52 and 104 in other exploratory MRI imaging outcomes (to be described in the SAP)

• Change from baseline to Week 52 for CSF biomarkers

• Potential additional exploratory analyses of plasma and CSF biomarkers, including CSF Aβ oligomer assays may be performed using state of the art methods, if available

Additional Clinical Outcomes

• Change from baseline to Weeks 13, 26, 52, and 78 for RAVLT and DSST

• Change from baseline to Weeks 13, 26, 39, 52, 65, 78, and 91 for MMSE

• Change from baseline to Week 52 for A-IADL and CDR-SB

Endpoints - Long-Term Extension Year 1

Secondary Fluid Biomarker Outcome

•Change from study baseline to Week 156 in plasma biomarkers: p-tau217, Aβ40, and Aβ42

Secondary Imaging Biomarker Outcome

•Change from study baseline to Weeks 130 and 156 in hippocampal volume

•Change from baseline to Week 130 on cortical thickness, whole brain volume and ventricular volume on vMRI

Exploratory Fluid Biomarkers Outcomes

•Change from baseline to Week 156 in plasma GFAP

•Change from baseline to Week 156 in plasma NfL

•Change from baseline to Week 156 in CSF p-tau181, p-tau217, Aβ40, and Aβ42

•Change from baseline to Week 156 in CSF neurogranin

•Change from baseline to Week 156 in CSF t-tau and NfL

•Change from baseline to Week 156 in CSF sTREM2 and YKL-40

Clinical Outcomes

•Change from baseline to Weeks 130 and156 in the clinical outcomes: RAVLT, DSST, MMSE, A-IADL, and CDR-SB

Pharmacokinetic Outcomes

•PK assessments for ALZ-801 and its metabolites as in Study Protocol V7.0 Section 2.2.7

Additional Fluid and Imaging Biomarker Outcomes

•Change from baseline to Week 130 in plasma biomarkers: GFAP, NfL, p-tau181,p-tau217, Aβ40, and Aβ42.

•Change from baseline to Weeks 130 and 156 in other exploratory MRI imaging outcomes (as described in the SAP) .

•Change from LTE baseline (Week 104) to Weeks 130 and 156 in MRI diffusion tensor imaging (DTI).

Endpoints - Long-Term Extension Year 2

Secondary Fluid Biomarker Outcome

•Change from study baseline to Week 208 in plasma biomarkers: p-tau217, Aβ40, and Aβ42

Secondary Imaging Biomarker Outcome

•Change from study baseline to Week 182 in hippocampal volume

•Change from baseline to Weeks 182 and 208 on cortical thickness, whole brain volume and ventricular volume on vMRI

Exploratory Fluid Biomarkers Outcomes

•Change from baseline to Week 208 in plasma GFAP

•Change from baseline to Week 208 in plasma NfL

Clinical Outcomes

•Change from baseline to Weeks 168, 182, 196 and 208 in the clinical outcomes: RAVLT, DSST, MMSE, A-IADL, and CDR-SB

•Change from baseline on the NPI: change from the first clinic assessment of the NPI to assessments at all later visits

Pharmacokinetic Outcomes

•PK assessments for ALZ-801 and its metabolites as in Study Protocol V7.0

Section 2.2.7

Additional Fluid and Imaging Biomarker Outcomes

•Change from baseline to Weeks 168, 182, 196 in plasma biomarkers: GFAP, NfL,

p-tau181,p-tau217, Aβ40, and Aβ42.

•Change from baseline to Weeks 182 and 208 in other exploratory MRI imaging

outcomes (as described in the SAP) .

•Change from LTE Year 1 baseline (Week 104) to Weeks 130, 156, 182 and 208 in

MRI diffusion tensor imaging (DTI) measures.

Study description

Background summary

Alzheimer disease (AD) is an irreversible, progressive neurodegenerative disorder, characterized by gradual cognitive and functional decline and personality changes. Soluble Aβ oligomers play an important role in AD pathogenesis and they appear early in the disease and induce synaptic neurotoxicity and impaired memory. Of note, AD patients who are APOE4/4 homozygotes, have brain levels of Aβ oligomers that are approximately 3 times higher than APOE4 non-carriers and they exhibit an earlier and faster rate of cognitive decline with onset of symptoms approximately a decade earlier. Tramiprosate is a small molecule that interacts directly with soluble Aβ monomers to prevent the amyloid aggregation cascade by blocking monomeric assembly, thus preventing the formation of toxic Aβ oligomers. Tramiprosate, has been studied in 3,295 adults across 16 clinical studies, including 2,800 AD subjects. In the phase 3 AD program, tramiprosate at the dose of 150 mg BID showed clinically meaningful benefit with a favorable long term safety profile in a subset analysis in APOE4 carriers.
The study drug in the present study, ALZ-801 is a pro-drug of tramiprosate, formed by the conjugation of the amino acid valine to tramiprosate that shows enhanced oral absorption, a more consistent pharmacokinetic (PK) profile of tramiprosate, and improved gastrointestinal (GI) tolerability when compared to the administration of tramiprosate.

The aim of the present study is to investigate the effects of ALZ-801 on CSF and plasma biomarkers of disease progression, neurodegeneration, and microglial activation in APOE4 carriers. The study will enroll Early AD subjects with APOE4/4 or APOE3/4 genotypes who are already receiving symptomatic medication. The study will also evaluate the effects of ALZ-801 on hippocampal volume as measured by MRI; explore the efficacy on measures of cognition and function; The study will also allow for PK-pharmacodynamic correlations between exposures of tramiprosate and its metabolite with the plasma, CSF and MRI biomarker effects; and evaluation of long term safety of ALZ-801 in AD.
To date, no other program has specifically targeted symptomatic APOE4/4 subjects with cognitive and early functional deficits. A convenient oral drug that can selectively target the formation of amyloid oligomers, with a favorable safety and tolerability profile, would provide an optimal drug for AD patients with the APOE4 genotype, who constitute 65% to 70% of all AD patients in clinical trials.

The option of TID dosing has been added for LTE Year 2 throughout the protocol for eligible subjects. The LTE Year 2 timeframe covers the fourth year of this Phase 2 study. Subjects with mild AD who are at the lower end of the range (MMSE score 22-24) are likely to show lower scores over the subsequent 2-3 years, reaching a mild to moderate AD stage (MMSE 18-22) or moderate AD stage with MMSE <18. The inclusion criteria at the start of this study (for the *core study*) required MMSE scores of 22 to 30. Therefore, there may be subjects who would benefit from this dose escalation if their MMSE score falls below 22.

Study objective

This study has been transitioned to CTIS with ID 2024-515858-25-00 check the CTIS register for the current data.

Objectives - Core Study
Primary Objectives
• To evaluate the effects of oral ALZ-801 in subjects with Early AD who have the APOE4/4 or APOE3/4 genotype, on the plasma biomarkers of core AD pathology and brain volumes
* Primary Plasma Biomarker Outcome: p-tau181
* Key Imaging Outcome: hippocampal volume on vMRI

Safety Objectives
• To evaluate the safety and tolerability of chronic treatment with ALZ-801 in subjects with Early AD who are APOE4 carriers

Secondary Objectives
• To evaluate the effects of oral ALZ-801 on other plasma biomarkers of core AD pathology and brain volumes
* Secondary Plasma Biomarker Outcomes: Aβ40, Aβ42, and p-tau217
* Secondary Imaging Biomarker Outcomes: cortical thickness and ventricular

volume

Exploratory Fluid Biomarker Objectives
• To evaluate the effects of oral ALZ-801 on other plasma and CSF biomarkers:
* Plasma biomarker of astrocytic activation: glial fibrillary acidic protein (GFAP)
* Plasma biomarker of neurodegeneration: NfL
* CSF biomarkers of core AD pathology: p-tau181, p-tau217, Aβ40, and Aβ42
* CSF biomarker of synaptic toxicity: neurogranin
* CSF biomarkers of neurodegeneration: total tau (t-tau) and NfL
* CSF neuroinflammation markers: TREM2 (microglia) and YKL-40 (astrocytes)

Clinical Objectives
• To evaluate the efficacy of ALZ-801 on tests of cognition and function: RAVLT, DSST, A-IADL, MMSE, and CDR-SB

Pharmacokinetic Objectives
• To evaluate the PK of ALZ-801 and its metabolites in AD subjects
• To evaluate the extended PK profile over 8 hours in 24 subjects (12 APOE4/4 homozygotes and 12 APOE3/4 heterozygotes) after 65 weeks of treatment (PK Profile Substudy)

Additional Exploratory Objectives
• To evaluate the effect of ALZ-801 on other AD biomarkers as assays become available (Aβ oligomers, other p-tau isoforms, or other emerging AD biomarkers)
• To evaluate the effect of ALZ-801 on other MRI imaging measures

Objectives - Long-Term Extension Year 1 and Year 2:
The objectives of the LTE periods of the study are to evaluate the long-term safety and efficacy of ALZ-801 over a total of 156 and 208 weeks, or 3 and 4 years, of treatment. This includes evaluation of safety parameters, fluid biomarkers, vMRI and clinical outcomes over an additional 52 weeks of treatment in LTE Year 1, and over an additional 104 weeks of treatment in LTE periods (52 weeks in LTE Year 1 and 52 weeks in LTE Year 2). In addition, the safety and tolerability of TID dosing in subjects who are eligible for dose excalation will be evaluated.
Additional Clinical Outcome in the LTE Weeks 156-208: The 12-item Neuropsychiatric Inventory (NPI).
PK plasma sampling in approximately 12-18 subjects over 6 hours in the LTE Year 2 (PK Profile Sub-study).

Study design

This is a Phase 2, multicenter, single-arm, study, with a treatment duration of 114 weeks (25 months). The study will enroll subjects with a diagnosis of AD who are APOE 4 carriers (APOE4/4, APOE3/4), and who are at the Early stage of disease: MMSE 22-30 inclusive, Clinical Dementia Rating (CDR) - Global score of

0.5 or 1, and a CDR Memory Box score of at least 0.5. Approximately 85 subjects will be enrolled and dosed across study sites, with a goal of enrolling approximately 50% of subjects who are APOE4/4 homozygous and 50% who are APOE3/4 heterozygous. Approximately 200 subjects with AD may need to be pre-screened (Screening - Part 1), since subjects heterozygous or homozygous for APOE4 constitute approximately 60% of AD patients. Eligible subjects will receive treatment with oral ALZ-801 at a dose of ALZ-801 (265 mg tablets twice daily [BID]). A dose titration scheme will be used to reach the full dose over the first 2 weeks of treatment. All subjects are required to participate in the CSF and MRI components of the study and to provide samples for plasma biomarkers.

PK Profile Sub-study:
Twenty-four (24) subjects participating in the study (approximately 12 APOE4/4 homozygotes and 12 APOE3/4 heterozygotes) will be consented to participate in a sub-study (the PK Profile Sub-study) to evaluate the extended PK profile of ALZ-801 and its metabolites. Subjects will come to the site to provide plasma samples at a dedicated Week 65 visit.

PK Profile Sub-study - LTE Year 2 - BID Dose:
Approximately 12 subjects (6 APOE4/4 homozygotes and 6 APOE4 heterozygotes) will be consented to participate in a PK substudy in the LTE Year 2 at Week 168 (Visit 6E) or an additional visit between Week 168 and Week 182 (called Visit 6E-PK).

PK Profile Sub-study - LTE Year 2 - TID Dose:
Approximately 6 subjects (3 APOE4/4 homozygotes and 3 APOE4 heterozygotes) from this group will be consented to participate in a PK substudy in the LTE Year 2, and plasma samples will be obtained for PK analysis. For subjects who escalate to TID dose at Week 168 (Visit 6E), this will occur at Week 182 (Visit 7E) or at an additional visit between Week 182 and Week 196 (called Visit 7E-PK). For subjects who escalate to TID dose at Week 182 (Visit 7E), this will occur at Week 196 (Visit 8E) or at an additional visit between Week 196 and Week 208 (called Visit 8E-PK) or at Week 208 (Visit 9E) for subjects who escalate at Week 196.

Long-Term Extension Year 1
Subjects who complete the core study through Week 104 will be offered participation in the LTE for an additional 52 weeks (for a total of 156 weeks of treatment). These subjects will go directly into the LTE study and will not complete the safety follow-up period of the core study. Subjects who are not enrolled in the LTE will be followed for safety for 4 weeks after the last dose of ALZ-801.
After providing written informed consent to participate in the LTE study, subjects will be dispensed study drug and will continue to take ALZ-801, 265 mg BID. Subjects will be dispensed study drug at the LTE Day 1 (Visit 1E) and Week 130/Month 6 (Visit 3E) visits. Study drug will be shipped to the subjects*

residences at Week 117/Month 3 (Visit 2E) and Week 143/Month 9 (Visit 4E). Subjects will be instructed to return their study drug bottles to the study site at the Week 130/Month 6 (Visit 3E) and Week 156/Month 12 (Visit 5E) clinic visits.
Subjects will return to the clinic at Week 130/Month 6 (Visit 3E) and Week 156/Month 12 (Visit 5E) for efficacy, biomarker, and safety assessments.
Subjects will be contacted by telephone at Week 117/Month 3 (Visit 2E) and at Week 143/Month 9 (Visit 4E) to inquire about any AEs and changes in concomitant medications since the previous visit.
All subjects who complete the entire treatment period and those who prematurely withdraw from the LTE study will be followed for safety for 4 weeks after the last dose of ALZ-801.

Long-Term Extension Year 2
Subjects who complete the core study through Week 104 and LTE Year 1 through Week 156 will be offered participation in LTE Year 2 for an additional 52 weeks (for a total of 208 weeks of treatment). These subjects will go directly into the LTE Year 2 study and will not complete the safety follow-up period of the core study. Due to the timing of the start of LTE Year 2, some subjects may have already completed visit 5E. Their study drug intake is temporarily interrupted. In that case, there are two possibilities:
1. The gap between the visits is equal or less than 13 weeks: Subjects will be invited to additional visit 5Ex ('short gap' - additional safety follow-up).
2. The gap between visits is longer than 13 weeks: Subjects will be invited to additional visit 5Ey ('long gap' - additional safety & efficacy follow-up).
Subjects who are not enrolled in the LTE Year 2 will be followed for safety for 4 weeks after the last dose of ALZ-801.
After providing written informed consent to participate in the LTE Year 2 study, subjects will be dispensed study drug and will continue to take ALZ-801, 265 mg BID. Subjects will be dispensed study drug at the LTE Year 2 Day 1 (Visit 5E - ór 5Ex/5Ey), Week 168/Month 15 (visit 6E), Week 182/Month 18 (Visit 7E), Week 196/Month 21 (Visit 8E) and Week 208/month 24 (visit 9E). Subjects will return to the clinic at Week 168/Month 15 (V6E), Week 182/Month 18 (Visit 7E), Week 196/Month 21 (V8E) and Week 208/Month 24 (Visit 9E) for efficacy, biomarker, and safety assessments. Subjects will be instructed to return their study drug bottles to the study site during these visits.

After institution of Amendment 6, subjects who are enrolled in the LTE Year 2 and who have an MMSE score of <22 at the Week 156 Visit or a later clinic visit, will be eligible to receive ALZ-801 at a dose of 265 mg TID at that visit and all subsequent visits where study drug is dispensed (Weeks 168, 182, and 196). Subjects who previously completed Visit 6E as a telephone visit (prior to institution of Amendment 6) have the option of completing an additional visit between Week 168 and Week 182 (called Visit 6Ex) to determine if they are eligible for TID dosing.

All subjects who complete the entire treatment period and those who prematurely

withdraw from the LTE study will be followed for safety for 4 weeks after the last dose of ALZ-801.

Intervention

Investigational Medical Product: ALZ-801 (pro-drug of tramiprosate). Provided as white, oval-shaped, immediate release tablets for oral administration. Each tablet contains 265 mg of ALZ-801 and should be taken in whole. ALZ-801 will be administered beginning at the Baseline Visit (Day 1). The first dose of study drug will be administered in the clinic and must be administered to the study subject only after all pre-dose assessments (including pre-dose drawing of blood) are performed. A single dose will be taken at baseline (Day 1) and continue for the first 2 weeks of study treatment. Starting on Day 15, study drug will be taken twice daily (at 265 mg BID) approximately 12 hours apart through the end of the study. The study drug should be taken with a meal or within 30 minutes after a meal. The last dose of study drug will be administered at the clinic on the morning of the Week 104 visit, or at the Week 156 visit if the subject participates in the LTE Year 1, or at the Week 208 if the subject participates in the LTE Year 2.
Subjects whose MMSE score declines below 22 (MMSE <22) are eligible to receive ALZ801 265 mg TID.

Study burden and risks

Side effects of ALZ-801: nausea, vomiting, weight loss, diarrhoea and dizziness. As ALZ-801 is still under the development, currently unknown or unexpected side effects may be experienced.
In case the patient experiences any new health problem, or worsening of the your existing condition, the Investigator will be contacted.

Collections of blood samples may cause discomfort, painful swelling, bruising and rarely infection at the site of the needle puncture.

Collection of CSF: The sample is taken by spinal punction. The patient will receive medication to reduce the pain, if necessary.
The main risk is rare headache, which is uncommon and it that should ease within a few days. To prevent such headache it is recommended to drink at least 3 litres of fluids in the 24 hours from sample collection and avoid long standing or sitting in the next 1 or 2 days. Other risks are very rare and they may include bleeding inside the spine and intracranial bleeding.

MRI: No specific risks, only discomfort like noise and to lie down in the machine for 30 minutes.

Extra visits to the research centre.
Protocol V7.0 replaces 2 telephone visits (visits 6E and 8E) with 2 visits to

the research center. The clinic visit schedule and assessments are the same for the BID and TID dose groups including the two additional clinic visits at Weeks 168 and 196, with an interval of ~13 weeks between visits.
This has two advantages:
1. Some subjects with MMSE 22-24 may decline rapidly to score <22 over 3 months. This interval of clinic visits would allow earlier detection of progressors at Weeks 168 or 196 and would allow for earlier dose escalation.
2. Since MCI and Mild AD subjects can develop neuropsychiatric symptoms, subjects with MMSE >22 who remain on BID dose in the LTE Year 2 should also be evaluated for emergence of these symptoms. The BID dose group will therefore have the same clinic visits as the TID dose group, with the added NPI scale at each visit.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Be between the ages of 50 and 80 years, inclusive.
2. Has a body weight >= 50 kg.
3. Has a diagnosis of Probable AD Dementia or MCI due to AD in accordance with the National Institute on Aging-Alzheimer*s Association (NIA-AA) Working Group Criteria [Albert et al, 2011; McKhann et al, 2011].
4. Has a biomarker profile reflecting AD, according to the NIA-AA Research Framework [Jack et al, 2018] defined as follows:
a) Positive amyloid PET scan on file prior to Screening
OR
b) CSF AD biomarker result using the Lumipulse (Fujirebio) assay at Screening with:
i. Aβ42/Aβ40 ratio < 0.61
AND
ii. p-tau > 61 ng/L
OR
iii. If p-tau181 concentration = 50 to 61 ng/L, ratio of p-tau/Aβ42 > 0.11
OR
c) CSF AD biomarker result on file within 12 months prior to Screening that is positive for Aβ42 (below the cut-off) AND p-tau (above the cut-off) OR a p-tau181/Aβ42 ratio above the cut-off for that assay (amyloid AND p-tau positive)
Note 1: Subjects without a prior CSF result must provide a new CSF sample at the Screening - Part 2 Visit.
Note 2: Subjects with a prior positive CSF result (allowing study enrollment) must provide 2 to 3 aliquots of CSF from their prior diagnostic assessment; and the prior CSF result must be recorded.
5. Be willing to undergo LP for CSF testing according to the Schedule of Assessments.
6. Has one of the following apolipoprotein E (APOE) genotypes - either APOE4/4 (homozygous) or APOE3/4 (heterozygous).
Note: For subjects with a prior (historical) APOE genotype blood test, the test result must be provided and recorded in the CRF.
7. Has an MMSE score at Screening of 22 to 30 inclusive (> 26 for MCI; 22 to 26 for Mild AD).
8. Has a CDR Global Score at Screening of 0.5 (MCI, Mild AD) or 1 (Mild AD) and a CDR Memory Box Score of >= 0.5.
9. Has a reliable caregiver or study partner who is willing and able to sign an informed consent form (ICF), to accompany the subject to study visits, and adhere to study requirements.
10. Be willing to sign an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved ICF indicating that he/she understands the purpose of the study and the procedures that are required for the study, and that he/she is willing to participate in the study. Subjects are free to withdraw consent at any time. If a subject is unable or deemed not competent to sign the consent

form, the subject*s legally authorized representative may sign the consent form with the subject*s assent, except where local regulations and IRB/IEC approval do not allow subjects who are unable or deemed not competent to sign the consent form, to participate in the study.
Note: Subjects who participate in the PK Profile Substudy for extended PK sampling will sign an additional consent form specific for the substudy.
11. Can complete the cognitive testing procedures. Corrected visual and auditory acuity must be adequate to comply with the protocol.
12. Lives at home independently, in a senior living facility, or in an assisted living facility.
13. Both subject and caregiver/study partner are fluent in, and able, to read the local language in which study assessments are administered at the study site.
14. Subject and caregiver/study partner agree to be compliant with study procedures and appear to have a high probability of completing the study.
15. Caregiver/study partner agrees not to administer any prohibited concomitant medications during the study.
16. If female, must have a negative serum pregnancy test and
EITHER be of non-childbearing potential, described as either:
• Post-menopausal (defined as at least 12 months without any menses) prior to the Screening - Part 2 Visit, or
• Documented surgically sterile (has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy with or without hysterectomy and greater than 6 weeks have passed since the surgery)
OR
• If subject is of child-bearing potential, must have a negative urine pregnancy test prior to dosing at baseline, use a highly effective method of contraception (with a failure rate of less than 1% per year when used consistently and correctly) for the duration of the study and for 8 weeks after the last dose of study medication.
Note: Highly effective methods include surgical sterilization, intrauterine device (IUD). intrauterine hormone-releasing system (IUS), hormonal contraception associated with inhibition of ovulation (e.g., pills, patches, vaginal ring, or injections). Total abstinence is also acceptable if it is the preferred and usual lifestyle of a subject.
17. Has a Screening brain MRI that is not inconsistent with the diagnosis of AD and determined to be of adequate quality.
Note: This MRI will provide baseline data for MRI biomarker and safety assessments.
18. If treated with an AChEI, subject must be on stable treatment for at least 12 weeks prior to the Screening - Part 2 Visit and must be able to continue on the same dose/regimen for the duration of the study.
Note: Memantine is not allowed and must not be taken within 12 weeks of the Screening - Part 2 visit.
19. With the exception of 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.
20. If treated with antidepressants, mood stabilizers, or other psychotropic medications, is on a stable dose.
21. If taking permitted, non-psychotropic medications for the treatment of non-excluded medical conditions, is on a stable dose.

Long-Term Extension (LTE) Year 1 (Weeks 104-160)
Inclusion Criteria
To be eligible for the LTE Year 1, the subject must:
1. Complete the last visit (Week 104) of the core study.
2. Be willing to sign an IRB/IEC-approved ICF indicating that he/she understands the purpose of the study and the procedures that are required for the study and that he/she is willing to participate in the study. Subjects are free to withdraw consent at any time. If a subject is unable or deemed not competent to sign the consent form, the subject*s legally authorized representative may sign the consent form with the subject*s assent, except where local regulations and IRB/IEC approval do not allow subjects who are unable or deemed not competent to sign the consent form, to participate in the study.
3. Agree (subject and caregiver/study partner) to be compliant with study procedures and, in the opinion of the Investigator, have a high probability of completing the study.
4. Have stable medical conditions in the opinion of the Investigator.

Long-Term Extension (LTE) Year 2 (Weeks 156-212)
Inclusion Criteria
To be eligible for the LTE Year 2, the subject must:
1. Complete the last visit (Week 156) of the LTE Year 1.
2. Be willing to sign an IRB/IEC-approved ICF indicating that he/she understands the purpose of the study and the procedures that are required for the study and that he/she is willing to participate in the study. Subjects are free to withdraw consent at any time. If a subject is unable or deemed not competent to sign the consent form, the subject*s legally authorized representative may sign the consent form with the subject*s assent, except where local regulations and IRB/IEC approval do not allow subjects who are unable or deemed not competent to sign the consent form, to participate in the study.
3. Agree (subject and caregiver/study partner) to be compliant with study procedures and, in the opinion of the Investigator, have a high probability of completing the study.
4. Have stable medical conditions in the opinion of the Investigator.

In addition, to be eligible for dose escalation to TID dosing, the subject must:
5. Have MMSE score <22 at clinic visit between Weeks 156-196 (Visits 5E-8E).
6. When the MMSE score is <22, be willing to sign the TID dosing section of the IRB/IECapproved ICF indicat

Exclusion criteria

1. Has a brain MRI at screening indicative of significant abnormality, including, but not limited to, prior hemorrhage (> 1 cm) or large infarct (> 1 cm), > 2 lacunar infarcts outside the brain stem, severe white matter changes (Fazekas grade 3), superficial hemosiderosis > 1 cm, aneurysm, vascular malformation, subdural hematoma, space-occupying lesion (e.g., abscess or brain tumor such as meningioma), or ventricular enlargement consistent with normal pressure hydrocephalus.
• Note: Ventricular enlargement consistent with AD atrophy (hydrocephalus ex-vacuo) is not exclusionary
• Note: Subjects who have > 10 microbleeds, require approval by Sponsor Medical Monitor
2. Has a diagnosis of neurodegenerative disorder other than AD.
3. Has a current diagnosis of Major Depressive Disorder (MDD) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition. Subjects who do not meet current criteria for MDD and who are on stable doses of antidepressants or mood stabilizers may be included in the study at the discretion of the Investigator.
4. Has a history of suicidal behavior or has ongoing suicidal ideation.
5. Has a history of seizures (excluding febrile seizures of childhood, or a single distant seizure > 10 years). Subjects with a history of one seizure, but without evidence of vascular or mixed dementia, or brain tumor on MRI, may be allowed into the study at the discretion of the Medical Monitor.
6. Has a medically confirmed history of recent cerebral infarct or recent transient ischemic attack (within 1 year prior to the Screening - Part 2 Visit).
7. Has a medically confirmed history of recent myocardial infarction or unstable, untreated coronary artery disease, or angina pectoris (within 1 year prior to the Screening - Part 2 Visit).
8. Has a history of cancer, diagnosed and treated within the last 3 years prior to the Screening - Part 2 Visit, with the exception of the following: (a) treated basal cell carcinoma of the skin, or (b) treated in situ or Stage 1 cancers of skin (squamous cell only), colon, prostate, breast, or colon (requires approval by the Medical Monitor).
9. Has a hemoglobin level < 11 g/dL in male subjects or < 10 g/dL in female subjects, or a hemoglobin level > 16 g/dL.
10. Has a prothrombin time as measured by INR >= 1.5 and a platelet count <= 50 x 10^9/L.
11. Has donated blood within 8 weeks prior to the Screening - Part 2 Visit.
12. Has clinically relevant abnormalities in serum thyroid-stimulating hormone or calcium. If the subject is taking replacement therapy, corresponding Screening test values must be clinically acceptable.
13. Has serum vitamin B12 below the lower limit of normal.
14. Has any clinical chemistry laboratory value greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE; version 4.0; National Cancer Institute 2009) Grade 2, unless considered not clinically relevant by the

Investigator and the Medical Monitor.
15. The subject at Screening has one or more of the following:
a. Alanine aminotransferase (ALT) >= 3 × upper limit of normal (ULN), OR
b. Aspartate aminotransferase (AST) >= 3 × ULN, OR
c. Total bilirubin (TBL) >= 1.5 × ULN.
16. Has an estimated glomerular filtration rate < 40 ml/min per 1.73 m2 according to the Modification of Diet in Renal Disease formula [see National Institute of Diabetes and Digestive and Kidney Diseases website for formula https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/mdrd-adults-si-units].
17. Has a glycosylated hemoglobin (HbA1c) > 8% (National Glycohemoglobin Standardization Program) or 64 mmol/mol (International Federation of Clinical Chemistry) at the Screening - Part 1 Visit.
18. Has a history of alcohol or drug dependence or abuse within 2 years of the Screening - Part 2 Visit or tests positive for drugs of abuse (i.e., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine) at the Screening - Part 2 Visit.
Note 1: If positive for opiates, the subject must be taking prescription medicines for pain and be on a stable dose of medication for more than 4 weeks prior to the Screening - Part 2 Visit.
Note 2: If positive for benzodiazepines, the subject must be taking prescription medicines containing benzodiazepines and be on a permitted dose.
19. Has a lifetime history of schizophrenia, schizoaffective disorder, or bipolar disorder.
20. Has any significant medical condition (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.
21. Has participated in a clinical study of any potential disease-modifying AD treatment, and received active drug within 6 months prior to the Screening - Part 2 Visit.
22. Has participated in a clinical study and received active treatment with an anti-amyloid or anti-tau vaccine.
23. Has received any of the treatments listed in Table 3 more recently than the indicated period before the Screening - Part 2 Visit.
24. Anticipates receiving any of the treatment listed in Table 3, during the current clinical study (unless meeting criteria for exceptions to prohibition as listed in Table 3).
25. Is 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.
26. Has a 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.
27. Has positive serology for the human immunodeficiency virus (HIV) or for hepatitis B or C virus.

Long-Term Extension (LTE) Year 1 (Weeks 104-160)
Exclusion Criteria
Subjects will be excluded from the LTE Year 1 for any of the following reasons:
1. Withdrew from core study before completing the Week 104 visit.
2. Were noncompliant (<70%) with the study medication or, in the Investigator*s or Sponsor*s
opinion, with the study procedures in the core study.
3. Had a clinically significant medical, surgical, laboratory, or other abnormality at the Week
104 visit of the core study that would compromise their participation in the LTE Year 1 or
compromise their safety in the opinion of the Investigator.

Long-Term Extension (LTE) Year 2 (Weeks 156-212)
Exclusion Criteria
Subjects will be excluded from the LTE Year 2 for any of the following reasons:
1. Withdrew from LTE Year 1 before completing the Week 156 visit.
2. Were noncompliant (<70%) with the study medication or, in the investigator*s or Sponsor*s
opinion, with the study procedures in the LTE Year 1.
3. Had a clinically significant medical, surgical, laboratory, or other abnormality at the Week
156 visit of the LTE Year 1 that would compromise their participation in the continued LTE or
compromise their safety in the opinion of the Investigator.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-11-2020
Enrollment:	42
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	no INN proposed yet
Generic name:	ALZ-801

Ethics review

Approved WMO Date:	01-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-10-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-05-2021
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	10-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-12-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	23-01-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	23-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	CTIS2024-515858-25-00
EudraCT	EUCTR2020-000986-17-NL
CCMO	NL74182.041.20