Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

ALZ-801

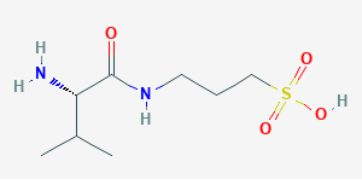
Evidence Summary

An ongoing phase 3 trial is testing the efficacy and safety of ALZ-801 in people with APOE4/4 and early Alzheimer's disease. ALZ-801 inhibits the formation of soluble Aβ oligomers in preclinical studies.

Neuroprotective Benefit: An open-label phase 2 trial in APOE4 carriers with early AD showed less hippocampal volume decline and improved verbal learning compared to a historical cohort, but placebo effects cannot be ruled out. A phase 3 trial is ongoing.

Aging and related health concerns: No studies have evaluated ALZ-801 for the treatment of age-related diseases other than Alzheimer's disease.

Safety: Phase 1 and 2 studies have reported that ALZ-801 at the dose proposed for Alzheimer's disease is well-tolerated. Most adverse events were gastrointestinal in nature (nausea and vomiting) and incidences were reduced when taken with food.

Availability: in clinical development	**Dose**: A phase 2 trial tested ALZ-801 at a dose of 265 mg twice daily (once daily for 2 weeks and twice daily thereafter) in APOE4 carriers with early Alzheimer's disease.	**Chemical formula:** $C_8H_{18}N_2O_4S$ **MW**: 238.3  Source: PubChem
Half-life: 0.7 to 0.81 hours (tramiprosate, the active drug has a half-life of 13-19 hours)	**BBB**: penetrant	
Clinical trials: An open-label single-arm phase 2 trial enrolled 84 APOE4 carriers with early Alzheimer's disease.	**Observational studies**: none available	

What is it?

ALZ-801 is a valine-conjugated prodrug of homotaurine (also known as tramiprosate) and is an oral small molecule that inhibits the formation of neurotoxic soluble amyloid oligomers. Homotaurine had high interindividual pharmacokinetic variability and some gastrointestinal irritation leading to nausea and vomiting (Hey et al., 2018). After homotaurine (tramiprosate) failed in phase 3 trials, Alzheon Inc. purchased the rights to homotaurine and developed ALZ-801, a prodrug that has improved pharmacokinetics, gastrointestinal tolerability, and metabolic stability compared to homotaurine (Alzheon Inc.). In 2017, ALZ-801 received Fast Track designation from the US FDA. An ongoing phase 3 randomized double-blind placebo-controlled study is testing the efficacy, safety, and biomarker effects of ALZ-801 in people with APOE4/4 and early Alzheimer's disease (NCT04770220)

Neuroprotective Benefit: An open-label phase 2 trial in APOE4 carriers with early AD showed less hippocampal volume decline, and improved verbal learning compared to a historical cohort, but placebo effects cannot be ruled out. A phase 3 trial is ongoing.

Types of evidence:

- One phase I study
- One phase 2 study (press release)
- Several review articles

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested whether ALZ-801 can prevent dementia or age-related cognitive decline. Based on the mechanism of action, it is not likely that ALZ-801 would produce cognitive benefits in people who do not have amyloid pathology.

A phase I bridging study of 127 healthy men, women, and elderly volunteers reported that ALZ-801, when administered in capsule and tablet forms, showed good oral safety and tolerability, with improved pharmacokinetic properties over oral homotaurine (e.g., prolonged elimination half-life and reduced interindividual variability)(Hey et al., 2018). An ALZ-801 oral dose of 265 mg twice daily achieved the area under the curve exposure equivalent to an oral homotaurine dose of 150 mg twice daily (the dose of homotaurine that achieved cognitive improvement in E4/E4 homozygous Alzheimer's patients; Abusharkra et a, 2016; Abusharkra et al, 2017). The elimination half-life of the prodrug ALZ-801 in plasma was short (≤ 30 min) at all doses studied, but the elimination half-life for homotaurine was much longer (~ 18 h), likely reflecting the consistent release of homotaurine from the prodrug (Hey et al., 2018). Oral ALZ-801 was rapidly absorbed from the gastrointestinal tract and underwent rapid and completed cleavage of the valine moiety with hepatic or plasma amidase, leading to the release of homotaurine in plasma. Based on a urine drug recovery study, the estimated oral bioavailability of the ALZ-801 tablet was 52%.

Human research to suggest benefits to patients with dementia:

Alzheon announced in a press release in September 2023 that their open-label single-arm phase 2 trial testing ALZ-801 (265 mg once daily for 2 weeks and twice daily thereafter) for 104 weeks in 84 APOE4 carriers with early Alzheimer's disease resulted in a significant reduction in plasma p-tau181, slowing of hippocampal volume decline by 28%, and stabilization of cognitive function compared to historical controls (from the ADNI cohort)(Alzheon press release, September 2023). A total of 70 subjects completed the Week 104 visit and 68 subjects provided plasma for biomarker assays. ALZ-801 treatment resulted in a 31% reduction in plasma p-tau181 levels (p=0.045) compared to baseline. Plasma Aβ42 levels were reduced by 4% at Week 104 compared to baseline (p=0.042). For cognitive functions, the Rey Auditory Verbal Learning Test (RAVLT) and the Digit Symbol Substitution Test (DSST) were used. Patients treated with ALZ-801 showed improved performance compared to baseline through the 104-week treatment period. Patients treated with ALZ-801 showed a significant 24% improvement at Week

104 on the RAVLT compared to historical controls from the ADNI cohort. However, because of the open-label design and the lack of placebo control, practice effects and placebo effects cannot be ruled out.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Based on the brain to plasma ratio obtained from a study in mice using 14C-homotaurine, long-term administration of 265 mg ALZ-801 twice daily is estimated to reach brain exposure of homotaurine (~550 nM) that are 5000- to 15,000-fold in excess of cerebral spinal fluid (CSF) Aβ42 levels (Hey et al., 2018). Brain penetration of ALZ-801 is estimated to be 30% higher compared to homotaurine based on pharmacokinetic/pharmacodynamic projections using 14C-homotaurine. In preclinical studies, a 1000-fold molar excess of homotaurine fully inhibited the formation of Aβ oligomers from monomers (Kocis et al., 2017).

The primary metabolite of ALZ-801 (and homotaurine) is 3-sulfopropanoic acid (3-SPA), an endogenous molecule in the human brain that is present in the CSF of patients with Alzheimer's disease and other neurodegenerative conditions (Hey et al., 2018). 3-SPA was also present in the CSF of drug-naïve elderly people with memory deficits due to Alzheimer's disease. The levels of 3-SPA were up to 12.6-fold higher in patients with Alzheimer's disease receiving homotaurine treatment (mean, 144.7 nM; range, 112.3 to 231.8 nM; n=6) compared to drug-naïve Alzheimer's patients (11.7 ± 4.3 nM). CSF concentrations of 3-SPA was 40- to 700-fold higher than soluble Aβ42 monomers. *In vitro* studies showed an interaction of 3-SPA with monomeric Aβ42 such that it inhibited the aggregation of Aβ42 into oligomers. However, the kinetics of the inhibition of Aβ oligomer formation was slower for 3-SPA than for homotaurine. In rats, 3-SPA was 100% orally bioavailable and showed 25% brain penetration.

APOE4 interactions:
Subgroup analyses of the two phase 3 trials testing homotaurine in Alzheimer's patients reported statistically significant cognitive benefits (measured by ADAS-Cog) in ApoE4 homozygotes, while no benefit was seen in non-carriers (Abusharkra et a, 2016; Abusharkra et al, 2017). Because of these findings, the initial phase 3 trial of ALZ-801 is enrolling participants who are APOE4/4 homozygotes (NCT04770220).

Aging and related health concerns: No studies have evaluated ALZ-801 for the treatment of age-related diseases other than Alzheimer's disease.

Types of evidence:

- No studies

There have not been any preclinical or clinical studies testing ALZ-801 for age-related diseases other than Alzheimer's disease.

Safety: Phase 1 and 2 studies have reported that ALZ-801 at the dose proposed for Alzheimer's disease is well-tolerated. Most adverse events were gastrointestinal in nature (nausea and vomiting) and incidences were reduced when taken with food.

Types of evidence:

- One phase I study
- One phase 2 study (press release)

Alzheon announced in a press release in September 2023 that their open-label single-arm phase 2 trial testing ALZ-801 (265 mg twice daily for 104 weeks) in APOE4 carriers with early Alzheimer's disease demonstrated a favorable safety profile, with no events of vasogenic brain edema (i.e., ARIA) that are common with anti-amyloid antibody therapeutics (Alzheon press release, September 2023). This may be due to the mechanism of action of ALZ-801, which targets soluble Aβ42 monomers and not the insoluble fibrillar amyloid or amyloid plaques (Tolar et al., 2021). Common adverse events (experienced in more than 10% of subjects) from the phase 2 study included COVID infection, nausea, and decreased appetite (Alzheon press release, September 2023).

A phase I bridging study of 127 healthy men, women, and elderly volunteers reported that ALZ-801, when administered in capsule and tablet forms, showed good oral safety and tolerability, and there were no serious adverse events or adverse events leading to discontinuation of ALZ-801 (Hey et al., 2018). There were no specific trends or clinically significant findings in safety laboratory measures, vitals, physical examinations, or electrocardiograms. No subjects reached the subject withdrawal criteria for QTc prolongation. In the fasting state, 17 (63.0%) subjects experienced a total of 65 treatment-emergent adverse events with ALZ-801, compared with 6 (66.7%) subjects following dosing with placebo reporting a total of 12 treatment-emergent adverse events. Most treatment-emergent adverse events

were mild in severity, with gastrointestinal disorders (nausea and vomiting) being the most common. Compared to the incidence of gastrointestinal side effects with homotaurine treatment, adverse events were less frequent with ALZ-801 and did not exhibit dose or exposure dependency, suggesting a mild local upper gastrointestinal tract irritation. In the 14-day multiple ascending dose study, following an initial titration with a reduced dose in the first week, the incidence of nausea and vomiting was markedly reduced during the second week, suggesting development of tolerance with continued use. The highest dose of ALZ-801 evaluated (342 mg; equivalent to 200 mg homotaurine), administered once or twice daily, was well tolerated following initial titration using a reduced dose for the first week. Gastrointestinal symptoms in some subjects were reduced when ALZ-801 was taken with food, without affecting plasma homotaurine exposure. ALZ-801 treatment at the 265 mg twice daily dose in the fed state resulted in the incidence of treatment-emergent adverse events that was equivalent to that of placebo. For most subjects, the onset of nausea was approximately 0.5-1.0 and 1.5-2.5 hours following fasted and fed conditions, respectively. No dose-limiting toxicity was observed over 2 weeks at doses up to 342 mg twice daily (higher than the 265 mg twice daily regimen used in the ongoing phase 3 study). There was no apparent age-related or sex-related effect on pharmacokinetic parameters.

In chronic toxicology studies in 1-month- and 6-month-old rats, ALZ-801 administration was well-tolerated and exhibited a no-observed-adverse-effect-level of 2000 and 1500 mg/kg, respectively (Alzheon data discussed in Hey et al., 2018).

Drug interactions: Drug interactions for ALZ-801 have not been documented.

Sources and dosing:

ALZ-801 is under clinical development by Alzheon Inc. The ongoing phase 3 trial in people with APOE4/4 and early Alzheimer's disease is testing a dose of 265 mg twice daily (NCT04770220).

Research underway:

A phase 3 multicenter randomized double-blind placebo-controlled study is testing the efficacy, safety, and biomarker effects of ALZ-801 in people with APOE4/4 and early Alzheimer's disease (NCT04770220). This study is enrolling 300 participants and is evaluating a 265 mg twice daily dose of ALZ-801 (oral tablet) over 78 weeks of treatment. The primary outcome is change in cognition (ADAS-cog) and secondary outcomes include disability assessment for dementia (DAD), clinical dementia rating (CDR-

SB), and activities of daily living (the Amsterdam-iADL). Other primary biomarker endpoints include hippocampal volume (MRI), and CSF and plasma measures of p-tau181. The study is supported by a grant from the National Institute on Aging and is estimated to be completed in June 2024.

Search terms:
Pubmed, Google: ALZ-801

Websites visited for ALZ-801:

- Clinicaltrials.gov
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
- DrugBank.ca (0)
- Cafepharma
- Pharmapro.com (0)