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.

Valiltramiprosate (ALZ-801)

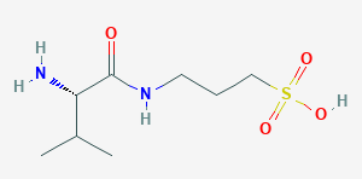
Evidence Summary

Although the phase 3 trial in early AD E4/E4 individuals did not meet its primary clinical endpoint, there may be some benefit in MCI. Valiltramiprosate treatment is not associated with ARIA-E/H in E4 carriers.

Neuroprotective Benefit: Although the phase 3 trial in early AD E4/E4 individuals did not meet its primary clinical endpoint, the MCI group showed nominally significant clinical benefits with valiltramiprosate, accompanied by slowing of brain atrophy.

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

Safety: The phase 3 trial in E4/E4 homozygotes with early AD reported adverse events including nausea, vomiting, and decreased appetite, which occurred more frequently than placebo, but there was no increased risk of brain edema or microhemorrhages.

Availability: in clinical development	**Dose**: not established; A phase 3 trial tested ALZ-801 at a dose of 265 mg twice daily in APOE4/E4 homozygotes with early Alzheimer's disease.	**Chemical formula:** $C_8H_{18}N_2O_4S$ **MW**: 238.3  Source: PubChem
Half-life: 1.2 hours (tramiprosate, the active drug has a half-life of 13-19 hours)	**BBB**: penetrant	
Clinical trials: A phase 3 trial enrolled 325 APOE4/E4 homozygotes with early Alzheimer's disease.	**Observational studies**: none available	

What is it?

Valiltramiprosate (also known as 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. A phase 3 randomized double-blind placebo-controlled study of valiltramiprosate (APOLLOE4 trial) in people with APOE4/4 and early Alzheimer's disease was completed in 2025 (Abushakra et al., 2025; NCT04770220).

Neuroprotective Benefit: Although the phase 3 trial in early AD E4/E4 individuals did not meet its primary clinical endpoint, the MCI group showed nominally significant clinical benefits with valiltramiprosate, accompanied by slowing of brain atrophy.

Types of evidence:

- One double-blind randomized placebo-controlled phase 3 study in E4/E4 homozygotes with mild cognitive impairment or mild Alzheimer's disease
- One open-label phase 2 study in E4 carriers with early Alzheimer's disease
- One phase 1 study in healthy volunteers
- 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:

In a phase 3, double-blind randomized placebo-controlled trial of 325 APOE4/E4 homozygotes with mild cognitive impairment (MCI) or mild Alzheimer's disease (AD), valiltramiprosate treatment (265 mg twice daily, orally) for 78 weeks did not significantly affect cognitive function (measured by ADAS-Cog13) in the overall population, which was the primary outcome, but showed significant slowing of hippocampal atrophy (18%, p=0.017)(Abushakra et al., 2025). Since the primary clinical outcome did not achieve statistical significance, all subsequent p-values were considered nominal, and were not adjusted for multiplicity testing.

Also in the overall population, the cognitive/functional composite (CDR-SB) at 78 weeks worsened by +1.36 points in placebo and by +1.05 with valiltramiprosate (nominal p=0.309). The Disability Assessment for Dementia worsened from baseline by −9.2 points in placebo and −6.5 points with valiltramiprosate (nominal p=0.279). There were no differences between placebo and valiltramiprosate groups with the activities of daily living score (A-IADLw).

Prespecified analyses by disease severity showed no significant clinical effects in the mild AD group, but in the MCI group, nominally significant positive effects were seen on cognition (measured by ADAS-Cog13; by 52%, nominal p=0.041)(Abushakra et al., 2025). ADAS-Cog13 worsened (increased) by +4.10 in the placebo group and +1.97 in the valiltramiprosate group. Nominally significant positive effects were seen in the MCI group for Disability Assessment for Dementia (by 96%, nominal p=0.016), where scores worsened (decreased) by −6.30 in the placebo group and by −0.2 points in the valiltramiprosate group. Also in the MCI group, a positive trend was seen for the cognition/function composite (measured by CDR-SB; by 102%, nominal p=0.053), where scores worsened (increased) by +0.63 in the placebo group and improved slightly (decreased) by −0.02 in the valiltramiprosate group.

In a sensitivity analysis, the effects of valiltramiprosate on ADAS-Cog13, CDR-SB, and DAD showed a greater magnitude of effects, the earlier the stage of disease (Abushakra et al., 2025). A positive trend of $p<0.1$ was seen at MMSE scores of 26-30 with a placebo-adjusted valiltramiprosate effect of 1.84 (p=0.067), which is a larger numeric difference than the 1.5-1.7 points observed with approved anti-amyloid antibodies. On the CDR-SB, valiltramiprosate showed a positive trend starting at MMSE 24-30 with a placebo-adjusted valiltramiprosate effect of 0.52 (p=0.090), which is a larger numeric difference than the ~0.5 points achieved with lecanemab. On the DAD, a positive trend favoring valiltramiprosate was seen (by 4.50 points, nominal p=0.039).

In the overall population that underwent imaging (n=290), volumetric MRI outcomes consistently favored valiltramiprosate treatment over placebo; there was slowing of hippocampal atrophy and whole brain cortical thickness atrophy by 18% (p=0.017) and 22% (p=0.002), respectively (Abushakra et al., 2025). In MCI participants, the volumetric MRI effects compared with placebo were larger across all brain regions with 26% slowing of hippocampal volume atrophy (p=0.004), 35% slowing of whole brain cortical thinning (p<0.0001), and 22% slowing of whole brain atrophy compared with placebo (p=0.027). In mild AD participants, there was directional slowing of atrophy in the hippocampus and cortical thickness compared to placebo (12% and 11%, respectively) but these differences were not statistically significant. The mild AD group, however, showed significantly less ventricular expansion (19%, nominal p=0.007).

The full analysis of plasma biomarkers, including Aβ42, Aβ40, and p-tau over 78 weeks, is ongoing as of November 2025 and will be presented in a future publication.

In an open-label single-arm phase 2 trial in 84 APOE4 carriers with early Alzheimer's disease (with positive biomarkers of amyloid and tau pathology in the CSF), ALZ-801 treatment (265 mg once daily for 2 weeks and twice daily thereafter) for 104 weeks arrested the progressive decline in CSF Aβ42 level and plasma Aβ42/Aβ40 ratio (analyzed using a quantitative systems pharmacology approach) and stabilized cognitive function measured by the Rey Auditory Verbal Learning Test (RAVLT) compared to historical controls from the ADNI cohort (Hey et al., 2024). RAVLT total score showed an annualized increase of 1.4% with ALZ-801 treatment versus a decrease of 2.7% without ALZ-801 treatment. People with MCI exhibited a larger biomarker response compared to mild AD subjects.

In the same open-label phase 2 trial described above, ALZ-801 treatment (265 mg once daily for 2 weeks and twice daily thereafter) for 104 weeks significantly reduced plasma p-tau181 (by 31%) compared to baseline (p=0.042) and slowed hippocampal volume decline by 28% (p=0.0014)(Hey et al., 2024). However, because of the open-label design and the lack of placebo control, placebo effects cannot be ruled out. While the ADNI cohort served as an external control with adjustment for baseline differences, statistical adjustments may not fully correct for inherent differences between the two cohorts.

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/E4 homozygotes, while no benefit was seen in non-carriers (Abusharkra et a, 2016; Abusharkra et al, 2017). Because of these findings, the phase 3 trial of ALZ-801 enrolled participants who are APOE4/4 homozygotes (Abushakra et al., 2025). The phase 3 trial in early AD E4/E4 individuals did not meet its primary clinical endpoint, but people with MCI showed nominally significant clinical benefits with valiltramiprosate, accompanied by slowing of brain atrophy. No clinical benefits were observed in E4/E4 homozygotes with mild AD.

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: The phase 3 trial in E4/E4 homozygotes with early AD reported adverse events including nausea, vomiting, and decreased appetite, which occurred more frequently than placebo, but there was no increased risk of brain edema or microhemorrhages.

Types of evidence:

- One double-blind randomized placebo-controlled phase 3 study in E4/E4 homozygotes with mild cognitive impairment or mild Alzheimer's disease
- One open-label phase 2 study in E4 carriers with early Alzheimer's disease
- One phase 1 study in healthy volunteers

In a phase 3, double-blind randomized placebo-controlled trial of 325 APOE4/E4 homozygotes with mild cognitive impairment (MCI) or mild Alzheimer's disease (AD), valiltramiprosate treatment (265 mg twice daily, orally) for 78 weeks resulted in more than double the rate of some adverse events including nausea (valiltramiprosate, 26%; placebo, 5%), vomiting (valiltramiprosate, 9.8%; placebo, 1.2%), and decreased appetite (valiltramiprosate, 9.8%; placebo, 1.9%), but there was no increased risk of brain edema or microhemorrhages (Abushakra et al., 2025). Weight loss occurred primarily at or after 26 weeks, was reversible or stabilized at a lower weight, and was manageable with nutritional supplements. Electrocardiogram and laboratory tests did not show any safety signals. The incidence of serious treatment-emergent adverse events in valiltramiprosate and placebo arms was 8.6% and 8.0%, respectively. These included cardiac disorders (active 1.2%, placebo 2.5%), nervous system disorders (valiltramiprosate, 1.8%; placebo, 1.9%), and injury/procedural complications (valiltramiprosate, 1.8%; placebo, 1.9%). Syncope (n=2) was the only serious adverse event that occurred in more than one participant. Study discontinuation rates were 9% in the placebo group and 19% in the valiltramiprosate group. Among 298 participants with serial MRI data, there were 5 cases of ARIA-E in each treatment arm (3.5%). The incidence of ARIA due to hemosiderin deposition (ARIA-H) was lower in the valiltramiprosate group than in the placebo group. New microhemorrhages were reported in 30% of participants in the valiltramiprosate group and in 36% of participants in the placebo group. Siderosis was reported in 13% and 17% of participants in the valiltramiprosate and placebo groups, respectively. None of the ARIA events were symptomatic.

In an open-label single-arm phase 2 trial in 84 APOE4 carriers with early Alzheimer's disease (with positive biomarkers of amyloid and tau pathology in the CSF), ALZ-801 treatment (265 mg once daily for 2 weeks and twice daily thereafter) for 104 weeks did not result in any drug-related serious adverse events, with common adverse events including COVID infection and mild nausea (Hey et al., 2024).

Nausea was generally mild and showed tolerance with continued treatment. Of 14 early terminations, 6 were due to nonserious treatment-emergent adverse events, 4 subjects experienced psychiatric symptoms, 1 had dizziness, 1 had gastrointestinal symptoms, and there was 1 death due to COVID (not related to ALZ-801). There were no vasogenic brain edema (ARIA-E) events in subjects treated with ALZ-801 over 2 years. 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). The safety laboratory tests and ECG showed no abnormal patterns, and there was no evidence of organ toxicity with long-term treatment.

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: The plasma exposures (both Cmax and AUC8h) of ALZ-801 were not affected by concomitant use of acetylcholine esterase inhibitors (Hey et al., 2025). Other drug interactions with ALZ-801 have not been documented.

Sources and dosing:

ALZ-801 is under clinical development by Alzheon Inc. The phase 3 trial in people with APOE4/4 and early Alzheimer's disease tested an oral dose of 265 mg twice daily (Abushakra et al., 2025). In a phase 2 study of APOE4 carriers with early AD, the plasma exposures (both Cmax and AUC8h) of ALZ-801 (or its active moieties, tramiprosate and 3-SPA) were not affected by sex, APOE genotype, age, or body mass index (Hey et al., 2025).

Research underway:

There are 2 ongoing clinical trials testing ALZ-801. One phase 2 trial is investigating the biomarker effects of ALZ-801 in 84 APOE4 carriers with early AD (NCT04693520). This study had an estimated completion date of August 2024. A long-term extension of the phase 3 study of ALZ-801 in 163 E4/E4 homozygotes with early AD is ongoing with an estimated study completion of January 2027 (NCT06304883). Subjects will be treated for 104 weeks with ALZ-801, followed by a 4-week safety follow-up visit after the final dose. Primary endpoints include ADAS-Cog13, the incidence, nature, and severity of treatment-emergent adverse events, and change from baseline in total hippocampal volume.

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)

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