



Alzheon Reports Industry-Leading Biomarker, Brain Preservation and Clinical Effects Following 12 Months of Treatment in Phase 2 Trial of Oral ALZ-801 (Valiltramiprosate) in Patients with Early Alzheimer’s Disease

41% Reduction in Plasma P-tau₁₈₁ from Baseline to 12 Months, Suggests Robust Disease Modification in Carriers of One or Two Copies of APOE4 Gene who Represent Two Thirds of Alzheimer’s Patients

Unprecedented Preservation of Hippocampal Volume Compared to Matched Group from AD Neuroimaging Initiative Indicates Neuroprotective Effects on Brain Structures: First & Only Treatment Showing Reduction of Brain Atrophy

Improvement from Baseline on Memory Tests at 3 and 6 Months, and Maintained Above Baseline at 1-Year Timepoint, Consistent with Biomarker & Brain Imaging Effects on Core Alzheimer’s Pathologies

Safety profile in ALZ-801 Studies Remains Favorable & Consistent with Prior Data in Over 2,000 AD Patients, with no Evidence of Vasogenic Brain Edema

FRAMINGHAM, Mass., September 20, 2022 — [Alzheon, Inc.](#), a clinical-stage biopharmaceutical company developing a broad portfolio of product candidates and diagnostic assays for patients suffering from Alzheimer’s disease (AD) and other neurodegenerative disorders, today reported statistically significant and clinically relevant plasma biomarker reduction, robust preservation of brain volume, and positive memory effects in Alzheimer’s patients following 12 months of treatment with investigational agent ALZ-801 in its [Phase 2 biomarker trial](#).

[ALZ-801 \(valiltramiprosate\)](#) is an oral agent in [Phase 3 development](#) as a potentially disease modifying treatment for AD that blocks formation of neurotoxic soluble beta amyloid (A β) oligomers causing cognitive decline in Alzheimer’s patients. In mechanism of action studies, ALZ-801 fully inhibited the formation of amyloid oligomers at the Phase 3 clinical dose. ALZ-801 has shown potential for robust efficacy in the highest-risk Alzheimer’s population – patients with two copies of the apolipoprotein ϵ 4 allele (APOE4/4 homozygotes), and favorable safety with no events of brain vasogenic edema, seen in trials with plaque-clearing antibodies. This population

is the focus of Alzheon's pivotal [Phase 3 APOLLOE4 trial](#) and has the highest likelihood of demonstrating successful efficacy outcomes.

The ongoing, fully enrolled [Phase 2 biomarker study](#) is evaluating ALZ-801 in Early AD patients, who carry either one or two copies of the $\epsilon 4$ allele of apolipoprotein E gene (APOE3/4 heterozygotes and APOE4/4 homozygotes, respectively), representing two thirds of Alzheimer's patients. APOE4 genotype, the leading risk factor for AD after aging, is associated with a several-fold higher brain burden of neurotoxic amyloid oligomers.

Phosphorylated tau (p-tau) levels in plasma are a sensitive and specific marker of neuronal stress and brain injury in AD, and considered a highly reliable biomarker of disease pathology. P-tau is produced by neurons as a reaction to formation of toxic beta amyloid oligomers, the key driver of AD pathology and neurodegeneration. P-tau₁₈₁ levels rise with AD progression and clinical deterioration of patients, and have been shown to fall in response to clinically effective disease modifying treatments in Alzheimer's.

"The several-fold greater reduction on the p-tau₁₈₁ biomarker in plasma compared to plaque-clearing anti-amyloid antibodies provides further support for the robust clinical benefits observed in Alzheon's prior Alzheimer's studies. Combined with preservation of brain hippocampal volume and a favorable safety profile with no events of vasogenic edema, these new biomarker data and their positive correlations with cognitive benefits further validate the disease modifying effects of ALZ-801 in Alzheimer's patients," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon. "Importantly, rather than slowing the cognitive decline of patients as seen in trials with other agents, subjects treated with ALZ-801 demonstrated cognitive gain from baseline status on memory tests and maintained their cognitive skills over 1 year. These well-differentiated results position ALZ-801 to potentially become the first oral agent that can slow or even stop and prevent Alzheimer's pathology in patients and healthy individuals at risk for the disease."

Alzheon's Phase 2 AD biomarker study ([NCT04693520](#)) enrolled 84 patients with Early AD, who carry either the APOE4/4 or APOE3/4 genotype and received oral ALZ-801 265 mg twice daily. All analyses of plasma biomarkers were performed at the laboratory of Professor Kaj Blennow at University of Gothenburg in Molndal, Sweden, audited according to Good Laboratory Practice. A total of 75 patients (mean age 69 years, 52% female) completed the Week 52 visit and were included in this pre-specified analysis. In this population, ALZ-801 demonstrated a significant 41% reduction from baseline in plasma p-tau₁₈₁ ($p=0.016$) at 52 weeks. ALZ-801 also significantly reduced the plasma p-tau₁₈₁/A β 42 ratio by 37% at 52 weeks ($p=0.032$). Given the importance of p-tau₁₈₁ and A β 42 as biomarkers of core AD pathology, these results support a disease modifying effect of ALZ-801 in Alzheimer's patients.

"Alzheon has pioneered precision medicine in Alzheimer's disease targeting neurotoxic amyloid oligomers, and now very promising biomarker, imaging and clinical data with ALZ-801 provide further support for this approach," said Kaj Blennow, MD, PhD, Professor of Clinical Neurochemistry at the University of Gothenburg, Sweden, a member of Alzheon's Scientific

Advisory Board and developer of the p-tau₁₈₁ assay. “Across many trials of anti-amyloid treatments, p-tau₁₈₁ has emerged as a consistent plasma biomarker that correlates with clinical benefit. Upon analysis of the plasma p-tau₁₈₁ data in our laboratory, we have observed an unprecedented reduction in this leading biomarker of Alzheimer’s pathology in patients taking ALZ-801 tablet for 12 months. This suggests a downstream effect on neuronal function and the potential for clinical efficacy of this novel treatment.”

ALZ-801 shows rapid and robust plasma p-tau₁₈₁ reductions at 13, 26 and 52 weeks that correspond with preservation of hippocampal volume and improvements in memory tests. These early p-tau₁₈₁ effects are enabled by the robust 40% brain penetration of ALZ-801 compared to approximately 1% brain penetration of plaque-clearing antibodies. As p-tau₁₈₁ is primarily of brain origin and is actively cleared from brain into plasma, the significant lowering of p-tau₁₈₁ in response to ALZ-801 treatment validates the drug’s target engagement and action in AD brain.

“These positive results represent the latest evidence confirming the promise of ALZ-801, extending other key discoveries made by Alzheon scientists over the last 9 years. The significant effect on plasma p-tau₁₈₁, combined with hippocampus volume preservation and clinical stabilization after 12 months of treatment, support the anti-amyloid oligomer action of ALZ-801 in brains of patients with Alzheimer’s disease. Consistency across these three outcomes, including structural effects, is very encouraging and supports the disease modifying profile of ALZ-801 in Alzheimer’s patients,” said Susan Abushakra, MD, Chief Medical Officer of Alzheon. “Alzheon has developed a well-differentiated approach to both treatment and prevention of Alzheimer’s disease with the small molecule ALZ-801, which acts upstream on the same pathway as anti-amyloid antibodies, preventing the formation of neurotoxic soluble amyloid oligomers without disrupting the insoluble plaque deposits in brain tissue and small vessels. ALZ-801 is, therefore, in a class of its own as an easy to administer oral tablet that has shown the potential for robust efficacy with a favorable safety profile, avoiding the vascular complications of brain edema and microbleeds seen with infusions of plaque-clearing antibodies.”

With support from the National Institute on Aging in the form of a [\\$47M grant to fund the APOLLOE4 Phase 3 study with ALZ-801](#), Alzheon’s drug candidate is well positioned to become one of the first disease-modifying treatments approved for slowing and even preventing cognitive decline in Alzheimer’s patients. Pioneering a precision medicine approach in Alzheimer’s, the APOLLOE4 Phase 3 trial is enrolling the highest-risk homozygous APOE4/4 AD patients and incorporates the latest volumetric MRI measures and biomarkers to track patient benefit – levels of p-tau₁₈₁ and beta amyloid in plasma and cerebrospinal fluid, hippocampal volume, and other volumetric brain measures, along with the gold-standard primary clinical endpoint, ADAS-Cog 13 (Alzheimer's Disease Assessment Scale-Cognitive Subscale).

About ALZ-801

[ALZ-801 \(valiltramiprosate\)](#) is an investigational oral agent in [Phase 3 development](#) as a potentially disease modifying treatment for AD.^{1,3} In mechanism of action studies, ALZ-801 has been shown to fully inhibit the formation of neurotoxic soluble beta amyloid oligomers at the Phase 3 clinical dose.^{5,6} ALZ-801 acts through a novel [enveloping molecular mechanism of action](#) to fully block formation of neurotoxic soluble amyloid oligomers in the human brain⁷ associated with the onset of cognitive symptoms and progression of AD.¹⁻⁴ ALZ-801 received Fast Track designation from the U.S. Food and Drug Administration in 2017. The clinical data for ALZ-801 and Alzheon's safety database indicate a favorable safety profile.^{5-7,9} The initial [Phase 3 program for ALZ-801](#) is focusing on Early AD patients with the APOE4/4 genotype, with future expansion to AD treatment and prevention in patients carrying one copy of the APOE4 gene and noncarriers.¹⁻⁴

ALZ-801 APOLLOE4 Phase 3 Study

An Efficacy and Safety Study of ALZ-801 in APOE4/4 Early Alzheimer's Disease Subjects ([NCT04770220](#)): This ongoing study is designed to evaluate the efficacy, safety, biomarker and imaging effects of 265 mg twice daily oral dose of ALZ-801 in Early AD subjects with the APOE4/4 genotype, who constitute approximately 15% of Alzheimer's patients. This is a double-blind, randomized trial comparing oral ALZ-801 to placebo treatment over 78 weeks. The APOLLOE4 trial is supported by a \$47 million [grant from the National Institute on Aging](#).

ALZ-801 Phase 2 Biomarker Study

Biomarker Effects of ALZ-801 in APOE4 Carriers With Early Alzheimer's Disease ([NCT04693520](#)): This ongoing study is designed to evaluate the effects of 265 mg twice daily oral dose of ALZ-801 on biomarkers of Alzheimer's pathology in subjects with Early AD, who have either the APOE4/4 or APOE3/4 genotypes, who together constitute 65-70% of Alzheimer's patients. The study also includes evaluation of clinical efficacy, safety, tolerability, and pharmacokinetic profile of ALZ-801 over 104 weeks of treatment.

About Alzheon

[Alzheon, Inc.](#) is a clinical-stage biopharmaceutical company developing a broad portfolio of product candidates and diagnostic assays for patients suffering from Alzheimer's disease and other neurodegenerative disorders. We are committed to developing innovative medicines by directly addressing the underlying pathology of neurodegeneration. Our lead Alzheimer's clinical candidate, [ALZ-801 \(valiltramiprosate\)](#), is an oral agent in [Phase 3 development](#) as a potentially disease modifying treatment for AD. ALZ-801 is an oral small molecule that fully blocks formation of neurotoxic soluble amyloid oligomers in the brain. Our clinical expertise and technology platform are focused on developing drug candidates and diagnostic assays using a [precision medicine approach](#) based on individual genetic and biomarker information to advance therapies with the greatest impact for patients.

Alzheon Scientific Publications

- ¹ Tolar M, et al: [Neurotoxic Soluble Amyloid Oligomers Drive Alzheimer's Pathogenesis and Represent a Clinically Validated Target for Slowing Disease Progression, *International Journal of Molecular Sciences*, 2021; 22, 6355.](#)
- ² Abushakra S, et al: [APOE \$\epsilon\$ 4/ \$\epsilon\$ 4 Homozygotes with Early Alzheimer's Disease Show Accelerated Hippocampal Atrophy and Cortical Thinning that Correlates with Cognitive Decline, *Alzheimer's & Dementia*, 2020; 6: e12117.](#)
- ³ Tolar M, et al: [Aducanumab, Gantenerumab, BAN2401, and ALZ-801—the First Wave of Amyloid-Targeting Drugs for Alzheimer's Disease with Potential for Near Term Approval, *Alzheimer's Research & Therapy*, 2020; 12: 95.](#)
- ⁴ Tolar M, et al: [The Path Forward in Alzheimer's Disease Therapeutics: Reevaluating the Amyloid Cascade Hypothesis, *Alzheimer's & Dementia*, 2019; 1-8.](#)
- ⁵ Hey JA, et al: [Discovery and Identification of an Endogenous Metabolite of Tramiprosate and Its Prodrug ALZ-801 that Inhibits Beta Amyloid Oligomer Formation in the Human Brain, *CNS Drugs*, 2018; 32\(9\): 849-861.](#)
- ⁶ Hey JA, et al: [Clinical Pharmacokinetics and Safety of ALZ-801, a Novel Prodrug of Tramiprosate in Development for the Treatment of Alzheimer's Disease, *Clinical Pharmacokinetics*, 2018; 57\(3\): 315–333.](#)
- ⁷ Abushakra S, et al: [Clinical Effects of Tramiprosate in APOE4/4 Homozygous Patients with Mild Alzheimer's Disease Suggest Disease Modification Potential, *Journal of Prevention of Alzheimer's Disease*, 2017; 4\(3\): 149-156.](#)
- ⁸ Kocis P, et al: [Elucidating the A \$\beta\$ 42 Anti-Aggregation Mechanism of Action of Tramiprosate in Alzheimer's Disease: Integrating Molecular Analytical Methods, Pharmacokinetic and Clinical Data, *CNS Drugs*, 2017; 31\(6\): 495-509.](#)
- ⁹ Abushakra S, et al: [Clinical Benefits of Tramiprosate in Alzheimer's Disease Are Associated with Higher Number of APOE4 Alleles: The "APOE4 Gene-Dose Effect," *Journal of Prevention of Alzheimer's Disease*, 2016; 3\(4\): 219-228.](#)

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