Alzheon Announces Peer-Reviewed Publication Showing Oral Valiltramiprosate/ALZ-801 Achieves Sustained Plasma Biomarker Reductions Linked to Better Cognitive, Functional, and Brain Atrophy Outcomes in APOE4 Carriers with Early Alzheimer's Disease

Phase 3 and Phase 2 Studies Show Early, Sustained Declines in Plasma p-tau217 and p-tau217/Aβ42 in APOE4 Homozygotes and Heterozygotes Treated with Oral Valiltramiprosate, Supporting Amyloid Target Engagement

Plasma p-tau217 and Neurofilament Light Correlate with Cognitive, Functional, and Brain Volume Benefits in Patients with Mild Cognitive Impairment

Phase 2 Findings Show Sustained Plasma Biomarker Reductions over Four Years, Supporting Valiltramiprosate's Long-Term Disease-Modifying Potential in APOE4 Carriers

Favorable Safety Profile Maintained, with No Increase in ARIA-E Versus Placebo and No Symptomatic ARIA on Valiltramiprosate

Valiltramiprosate Has Potential to Become the First Oral Agent to Slow Alzheimer's Pathology in Patients

FRAMINGHAM, Mass., September 8, 2026 – Alzheon, Inc., a clinical-stage biopharmaceutical company developing investigational therapies and diagnostic assays for Alzheimer's disease (AD) and other neurodegenerative disorders, today announced the peer-reviewed publication of *"Plasma Biomarker Effects of Oral Valiltramiprosate/ALZ-801 in Early Alzheimer's Disease from Phase 3 and Phase 2 Trials: Analysis of Core Biomarkers and Correlations with Clinical and Neuroimaging Outcomes"* in *Drugs*. Full text is available here. The publication presents plasma p-tau217, p-tau217/Aβ42, and neurofilament light chain (NfL) findings from the Phase 3 APOLLOE4 trial, along with four-year fluid biomarker data from the single-arm, open-label Phase 2 study, supporting amyloid target engagement and potential for disease modification in APOE4 carriers with early AD treated with oral valiltramiprosate.

“Valiltramiprosate has emerged as one of the few late-stage treatments with the potential to meaningfully change Alzheimer’s therapy in the near term,” said Martin Tolar, Founder, President, and CEO of Alzheon. “Across our Phase 3 and Phase 2 trials, valiltramiprosate produced early, and sustained reductions in key blood-based biomarkers including plasma p-tau217 and p-tau217/Aβ42 ratio that closely tracked with cognitive, functional, and brain-volume outcomes. Based on analyses from the APOLLOE4 Phase 3 trial and its long-term extension, we are now moving forward with plans for the next Phase 3 study while we expand the valiltramiprosate platform, develop new candidates, and explore additional patient populations.”

Valiltramiprosate is an investigational oral small molecule designed to act early in the amyloid cascade by inhibiting the formation of neurotoxic soluble amyloid oligomers, the precursors to amyloid plaques, before plaque deposition and tau hyperphosphorylation. This publication integrates plasma biomarker data from the Phase 3 APOLLOE4 trial in APOE4/4 homozygotes with data from the Phase 2 biomarker study in APOE4 homozygotes and heterozygotes to evaluate whether these upstream effects are detectable in blood and align with clinical and imaging outcomes.

“The ability to track a therapy’s effect on Alzheimer’s pathology using accessible blood-based biomarkers is an important advancement for the field,” said Anton P. Porsteinsson, MD, Director, Alzheimer's Disease Care, Research and Education Program (AD-CARE), University of Rochester School of Medicine and Dentistry. “What is notable in this work is the consistency of the signal in MCI patients: reductions in plasma p-tau217 aligned with cognitive, functional, and brain-volume outcomes and were sustained over time. Together, these findings strengthen the biological rationale for intervening upstream in the amyloid pathway and support practical tools for confirming target engagement and monitoring treatment response in APOE4 carriers, who face the highest genetic risk for AD dementia.”

Alzheimer’s disease is a progressive neurodegenerative disorder with limited treatment options, with the greatest unmet need among APOE4/4 homozygotes, who have the highest genetic risk and face the greatest risk of neurovascular injury, or ARIA, with approved amyloid antibody therapies. Approximately 15% of Alzheimer’s patients are APOE4/4 homozygotes. Blood-based biomarkers including plasma p-tau217, the p-tau217/Aβ42 ratio, and neurofilament light chain (NfL) are emerging as accessible, minimally invasive measures of amyloid pathology and neurodegeneration that can help assess whether a therapy engages its molecular target and alters disease progression.

In the overall Phase 3 population, baseline plasma p-tau217 levels were comparable between treatment arms and were significantly lower with valiltramiprosate than placebo at Weeks 26, 52, and 78 (all $p<0.025$). A similar effect was observed in the pre-specified MCI subgroup ($p<0.05$ at Weeks 52 and 78), while the Mild AD subgroup showed a numerical trend. In Phase 3 MCI subjects, baseline p-tau217 correlated significantly with baseline disease severity measures, including CDR-SB ($r = 0.403$, $p = 0.002$), hippocampal volume ($r = -0.393$, $p = 0.002$), and cortical

thickness (r = −0.601, p<0.0001). In the valiltramiprosate arm, p-tau217 reductions at Week 78 correlated with less decline on ADAS-Cog13 (r = 0.276, p = 0.039) and CDR-SB (r = 0.377, p = 0.005), as well as less hippocampal atrophy (r = −0.353, p = 0.013). Plasma NfL was also significantly lower than placebo at Week 78 in MCI patients (p = 0.032), and its values correlated with cognitive improvement (r = 0.29, p = 0.03) and p-tau217 reduction (r = 0.42, p = 0.001).

"These results provide direct biological evidence that valiltramiprosate engages its molecular target by inhibiting formation of neurotoxic soluble amyloid oligomers, reducing amyloid aggregation and producing measurable downstream effects on tau hyperphosphorylation and neurodegeneration," said John A. Hey, PhD, Chief Scientific Officer of Alzheon and the lead author of publication. "Plasma p-tau217 declined early and remained lower over time, tracking with cognitive, functional, and volumetric MRI outcomes, while plasma NfL remained stable over 78 weeks on valiltramiprosate compared with progressive increases on placebo supporting a disease-modifying effect of valiltramiprosate in Alzheimer's disease. Consistency of these effects in APOE4 homozygotes and heterozygotes, together with their durability over four years in the Phase 2 program, highlight the potential of valiltramiprosate in treating APOE4/4 MCI patients, and reinforce continued development of valiltramiprosate for APOE4 carriers with early Alzheimer's disease."

About ALZ-801

Valiltramiprosate/ALZ-801 is an investigational oral agent currently in Phase 3 development as a potential first-in-class, disease-modifying treatment for Alzheimer's disease.[4-8,10,13] Valiltramiprosate is designed to inhibit the formation of neurotoxic soluble beta amyloid oligomers that contribute to cognitive decline in individuals with AD.[5-9,11,16] Preclinical mechanism-of-action studies have demonstrated that ALZ-801 can completely block the formation of these neurotoxic oligomers at the dosage used in Phase 3 clinical trials.[4,10,13,15] Valiltramiprosate employs an enveloping molecular mechanism of action intended to prevent the aggregation of soluble amyloid oligomers in the human brain,[15] which are associated with the onset and progression of cognitive impairment in AD patients.[4,5,8,10,11] In recognition of its therapeutic promise, valiltramiprosate received Fast Track designation from the U.S. Food and Drug Administration in 2017 for the treatment of Alzheimer's disease. Clinical trial data indicate that valiltramiprosate exhibits strong clinical efficacy at the MCI stage, and a favorable safety profile, with no observed increase in the risk of brain vasogenic edema.[2-11,14,16] The initial Phase 3 program for valiltramiprosate targets Early AD patients who are homozygous for the apolipoprotein ε4 allele (APOE4/4), with plans to expand future research to include AD treatment and prevention in individuals carrying one copy of the APOE4 gene.[4–11]

Valiltramiprosate APOLLOE4 Phase 3 Trial

An Efficacy and Safety Study of Valiltramiprosate in APOE4/4 Early Alzheimer's Disease Subjects (NCT04770220): This trial was designed to evaluate the efficacy, safety, biomarker and imaging effects of 265 mg twice daily oral dose of valiltramiprosate in Early AD subjects with two copies of the apolipoprotein ε4 allele (APOE4/4 homozygotes), who constitute approximately 15% of Alzheimer's patients. This double-blind, randomized trial compared oral valiltramiprosate to

placebo treatment over 78 weeks. The APOLLOE4 trial was supported by a grant from the National Institute on Aging to Alzheon, with Susan Abushakra as the principal investigator.

Valiltramiprosate APOLLOE4 Long Term Extension Trial (Phase 3 LTE)

A long-term extension of the trial, APOLLOE4-LTE, evaluated valiltramiprosate in subjects who complete the core APOLLOE4 study for an additional 104 weeks of treatment for a total of 182 weeks or 3.5 years over the core and LTE study. This LTE study ended in January 2026 (NCT06304883).

Valiltramiprosate Phase 2 Biomarker Trial

Biomarker Effects of Valiltramiprosate in APOE4 Carriers with Early Alzheimer's Disease (NCT04693520): This trial was designed to evaluate the effects of 265 mg twice daily oral dose of valiltramiprosate on biomarkers of AD pathology in subjects with Early AD, who have either the APOE4/4 or APOE3/4 genotype and constitute 65-70% of Alzheimer's patients. The primary outcome was the change from baseline in plasma p-tau181. The trial also included evaluation of clinical efficacy, safety, tolerability, and pharmacokinetic profile of valiltramiprosate over 104 weeks of treatment. A completed long-term extension of the trial evaluated the same dose of valiltramiprosate for an additional 104 weeks of treatment for a total of 208 weeks. [4,8,9]

About Alzheon

Alzheon, Inc. is a clinical-stage biopharmaceutical company dedicated to advancing a diverse portfolio of product candidates and diagnostic assays for individuals affected by Alzheimer's disease and other neurodegenerative disorders. The company is focused on innovating therapeutic solutions that directly target the underlying pathology of neurodegeneration. Its lead Alzheimer's clinical candidate, valiltramiprosate/ALZ-801, is a first-in-class oral agent currently in Phase 3 clinical development as a potentially disease-modifying treatment for Alzheimer's disease. Valiltramiprosate is an orally administered small molecule shown in preclinical studies to completely inhibit the formation of neurotoxic soluble amyloid oligomers. Its well-differentiated follow-on candidate, ALZ-507, is a once daily oral therapy designed to inhibit the formation of amyloid oligomers while also correcting the high risk APOE4 gene. Leveraging clinical expertise and a robust technology platform, Alzheon pursues drug discovery and development using a precision medicine approach that incorporates individual genetic and biomarker profiles, aiming to advance therapies with meaningful benefits for patients.

Alzheon Scientific Publications

[1]Hey JA, et al: *Plasma Biomarker Effects of Oral Valiltramiprosate/ALZ-801 in Early Alzheimer's Disease from Phase 3 and Phase 2 Trials: Analysis of Core Biomarkers and Correlations with Clinical and Neuroimaging Outcomes*, **Drugs** 2026.

[2]Abushakra S, et al: *Hippocampal Atrophy on Magnetic Resonance Imaging as a Surrogate Marker for Clinical Benefit and Neurodegeneration in Early Symptomatic Alzheimer's Disease: Synthesis of Evidence from Observational and Interventional Trials,* **CNS Drugs** 2026; 40(2), 199-214.

[3]Abushakra S, et al: *Clinical Efficacy, Safety and Imaging Effects of Oral Valiltramiprosate in APOEε4/ε4 Homozygotes with Early Alzheimer's Disease: Results of the Phase III, Randomized, Double-Blind, Placebo-Controlled, 78-Week APOLLOE4 Trial,* **Drugs** 2025; 85(11), 1455-1472.
[4]Pearson D, et al: *Polymorph Analysis of ALZ-801 (Valiltramiprosate), a Valine-Conjugated Oral Prodrug of Tramiprosate in Late-Stage Clinical Development for Alzheimer's Disease,* **Journal of Chemical Crystallography** 2025; 55, 206-215.
[5]Hey JA, et al: *Clinical Pharmacokinetics of Oral ALZ-801/Valiltramiprosate in a Two-Year Phase 2 Trial of APOE4 Carriers with Early Alzheimer's Disease,* **Clinical Pharmacokinetics** 2025; 64(3), 407-424.
[6]Aye S, Tolar M, et al: *Point of View: Challenges in Implementation of New Immunotherapies for Alzheimer's Disease,* **The Journal of Prevention of Alzheimer's Disease** 2025;12(1):100022.
[7]Abushakra S, et al: *APOLLOE4 Phase 3 Study of Oral ALZ-801/Valiltramiprosate in APOE ε4/ε4 Homozygotes with Early Alzheimer's Disease: Trial Design and Baseline Characteristics,* **Alzheimer's & Dementia** 2024; 10(3): e12498.
[8]Tolar M, et al: *The Single Toxin Origin of Alzheimer's Disease and Other Neurodegenerative Disorders Enables Targeted Approach to Treatment and Prevention,* **International Journal of Molecular Sciences** 2024; 25(5), 2727.
[9]Hey JA, et al: *Analysis of Cerebrospinal Fluid, Plasma β Amyloid Biomarkers, and Cognition from a 2-Year Phase 2 Trial Evaluating Oral ALZ-801/Valiltramiprosate in APOE4 Carriers with Early Alzheimer's Disease Using Quantitative Systems Pharmacology Model,* **Drugs** 2024; 84(7), 825-839.
[10]Hey JA, et al: *Effects of Oral ALZ-801/Valiltramiprosate on Plasma Biomarkers, Brain Hippocampal Volume, and Cognition: Results of 2-Year Single Arm, Open Label, Phase 2 Trial in APOE4 Carriers with Early Alzheimer's Disease,* **Drugs** 2024; 84(7), 811-823.
[11]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(12), 6355.
[12]Abushakra S, et al: *APOE ε4/ε4 Homozygotes with Early Alzheimer's Disease Show Accelerated Hippocampal Atrophy and Cortical Thinning that Correlates with Cognitive Decline,* **Alzheimer's & Dementia** 2020; 6(1): e12117.
[13]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(1): 95.
[14]Tolar M, et al: *The Path Forward in Alzheimer's Disease Therapeutics: Reevaluating the Amyloid Cascade Hypothesis,* **Alzheimer's & Dementia** 2020; 16(11):1553-1560.
[15]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.
[16]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.

[17]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.
[18]Kocis P, et al: *Elucidating the Aβ42 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.
[19]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.

Media Contact
Yasemin Khakian, JD, Alzheon, Inc.
508.808.2301
yasemin.khakian@alzheon.com

Investor Contact
Erwan de Naurois, Alzheon, Inc.
802.735.8789
erwan.denaurois@alzheon.com