Alzheon Highlights ORION-E4 Phase 3 Trial Launch for Oral Valiltramiprosate/ALZ-801 and Expansion of Its Oral Anti-Amyloid Aggregation Inhibitor Portfolio at CTAD 2026 Conference in Boston, November 16–19

ORION-E4, the Second Phase 3 Trial of Oral Valiltramiprosate, Aims to Confirm Clinical Benefits Observed in the APOLLOE4 MCI Subgroup in APOE4/4 Patients with Mild Cognitive Impairment

New APOLLOE4 Phase 3 Analyses Show Valiltramiprosate Reduced the Incidence of Spontaneous Brain Microbleeds (ARIA-H) Associated with Cerebral Amyloid Angiopathy by 39%

In Phase 3 APOLLOE4, Sustained Plasma p-tau217 Reductions with Valiltramiprosate Treatment Correlated with Preserved Brain Volume and Clinical Outcomes

Portfolio Build-Out Continues with ALZ-507, a Once-Daily Next-Generation Anti-Amyloid Aggregation Inhibitor and APOE4 Corrector Completing Phase 1 Studies, and the ALZ-700 Series of Oral Prodrugs

FRAMINGHAM, Mass., November 10, 2026 — Alzheon, Inc., a clinical-stage biopharmaceutical company developing a portfolio of investigational therapies and diagnostic assays for Alzheimer's disease (AD) and other neurodegenerative disorders, today highlighted the start of ORION-E4, its second Phase 3 trial of oral valiltramiprosate/ALZ-801, and the continued build-out of its portfolio of oral anti-amyloid aggregation inhibitors, ahead of the 19th Clinical Trials on Alzheimer's Disease (CTAD) conference in Boston, Massachusetts, November 16–19, 2026. At CTAD, Alzheon will present three posters with new analyses from the 78-week Phase 3 APOLLOE4 trial that informed the design of ORION-E4 Phase 3 study.

"In 2026, Alzheon is moving from analysis of our first Phase 3 program evaluating oral valiltramiprosate to the next pivotal trials," said Martin Tolar, MD, PhD, Founder, President and CEO of Alzheon. "Launched earlier this year, ORION-E4 is a dedicated Phase 3 trial designed to confirm the clinically meaningful cognitive and functional benefits observed in APOE4/4 patients

with Mild Cognitive Impairment, when neuronal reserve is greatest. We are also expanding our industry-leading portfolio of oral anti-amyloid aggregation inhibitors targeting the same upstream mechanism of neurodegeneration in Alzheimer's disease. This effort is led by ALZ-507, a next-generation, once-daily candidate now completing Phase 1 that also acts as a novel APOE4 corrector. Together, these programs seek to provide simple, safe oral treatment options for patients at the highest genetic risk, spanning early treatment through prevention."

ORION-E4 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy, safety and biomarker effects of valiltramiprosate 265 mg twice daily over 78 weeks in approximately 550 APOE4/4 homozygotes with Mild Cognitive Impairment (MCI) due to AD, at approximately 150 sites in approximately 12 countries. The primary endpoint is the change from baseline to Week 78 on the Clinical Dementia Rating–Sum of Boxes (CDR-SB), with ADAS-Cog13 and the Disability Assessment for Dementia (DAD) as key secondary outcomes, and serial MRI monitoring of ARIA-E and ARIA-H. APOE4/4 homozygotes constitute approximately 15% of Alzheimer's patients, carry the greatest genetic risk of the disease and, because of their high prevalence of co-morbid cerebral amyloid angiopathy (CAA), are the most vulnerable to brain edema and hemorrhagic complications of anti-amyloid antibodies (ARIA-E, ARIA-H).

New APOLLOE4 Phase 3 Analyses Supporting ORION-E4 Phase 3 Study

Valiltramiprosate/ALZ-801 is an investigational oral agent that acts upstream of anti-amyloid antibodies by inhibiting the formation of neurotoxic soluble amyloid oligomers. In the APOLLOE4 trial in APOE4/4 homozygotes with MCI or Mild AD, the overall study did not achieve significant clinical effects, while the pre-specified MCI group showed meaningful and nominally significant cognitive and functional benefits, which ORION-E4 study is designed to confirm.

In the overall APOLLOE4 population, 298 subjects (149 per arm) had serial MRI scans, and the cohort entered the trial with a substantial CAA burden: 32% had at least one microhemorrhage and 10% had at least one area of superficial siderosis at baseline. Over 78 weeks, new ARIA-H lesions (microhemorrhage and/or siderosis) occurred in 26% of placebo subjects and 15% of ALZ-801 subjects, a 39% lower incidence (p=0.023), and their onset was delayed. Concurrent microhemorrhages and siderosis occurred in 6% and 1% of the placebo and active arms (89% reduction, p=0.010). Vasogenic edema occurred at the same rate in both arms (3.5%), and all ARIA events were asymptomatic. Transient, mild-to-moderate nausea was the most reported adverse event.

"Our APOLLOE4 Phase 3 analyses show that valiltramiprosate treatment reduced the occurrence of new microhemorrhages and siderosis, called ARIA-H lesions, associated with cerebral amyloid angiopathy, and delayed their onset in patients with a high baseline burden of vascular amyloid," said Susan Abushakra, MD, Chief Medical Officer of Alzheon. "New spontaneous microhemorrhages have been shown to accelerate clinical decline in AD patients, particularly at the earliest stage of disease, and cerebral amyloid angiopathy has no approved treatment (Baldaranov, 2026), making this a potentially clinically meaningful finding. Using serial MRI monitoring in the ORION-E4 trial, we seek to reproduce these unexpected, important benefits."

Plasma biomarker analyses were pre-specified outcomes of APOLLOE4 Phase 3 trial, with core results published in *Drugs*. In the overall study, plasma p-tau217 evaluated on the FDA-cleared Lumipulse platform rose progressively on placebo, while on valiltramiprosate it was already lower at Week 26 and remained lower through Week 78 (p=0.011). In the pre-specified MCI subgroup, p-tau217 decreased by approximately 36% from baseline over 78 weeks versus a 17% increase on placebo, a 53% difference (p=0.02). In valiltramiprosate-treated MCI subjects, these decreases were associated with less decline on ADAS-Cog13 ($r = 0.28$, $p = 0.039$) and CDR-SB ($r = 0.38$, $p = 0.005$), and with lower hippocampal atrophy ($r = -0.35$, $p = 0.013$), cortical thinning ($r = -0.34$, $p = 0.018$) and whole brain atrophy ($r = -0.31$, $p = 0.029$). Exploratory analyses using the ultrasensitive NULISA assay showed reductions in the neuroinflammatory markers IL-18 and IL-15 and in the endothelial vascular injury marker ICAM-1, providing a potential mechanistic basis for the observed ARIA-H reduction.

"We interpret the sustained reduction in plasma p-tau217 and its association with preserved hippocampal volume, cortical thickness and whole brain volume as compelling evidence that valiltramiprosate targets amyloid pathology by inhibiting neurotoxic soluble amyloid oligomers upstream and subsequently reducing neurodegeneration," said John A. Hey, PhD, Chief Scientific Officer of Alzheon. "These effects were strongest in the APOLLOE4 MCI subgroup, which also showed clinically meaningful cognitive and functional benefits. These findings informed the design of the recently launched Phase 3 ORION-E4 trial."

Expanding Portfolio of Oral Anti-Amyloid Aggregation Inhibitors

Alzheon is building a portfolio of oral, small-molecule anti-amyloid aggregation inhibitors that share valiltramiprosate's upstream mechanism. ALZ-507 is a well-differentiated, once-daily next-generation candidate designed to inhibit the formation of neurotoxic soluble amyloid oligomers while also acting as an APOE4 corrector. The first subject was dosed in a Phase 1 single and multiple ascending dose trial of ALZ-507 in April 2026, after an IND program that demonstrated a favorable nonclinical safety and pharmacokinetic profile supporting once-daily dosing. Findings from the Phase 1 trial are intended to guide dose selection and formulation for Phase 2 studies in Alzheimer's disease, Down syndrome–associated AD and CAA, with longer-term potential in Alzheimer's prevention. The ALZ-700 series of oral prodrugs of ALZ-507 extends the platform to dry age-related macular degeneration, and an undisclosed small-molecule anti-aggregation library targets other neurodegenerative disorders.

Details of Presentations at the 19th Clinical Trials on Alzheimer's Disease (CTAD) Conference
Poster Presentations

Monday, November 16, 2026, 2:00 p.m. ET – Tuesday, November 17, 2026, 5:30 p.m. ET

Poster #11: *The Effects of Oral Valiltramiprosate on Plasma p-tau217 and p-Tau217/Aβ42 Ratio in APOE4/4 Homozygotes and their Correlations to Clinical and Imaging Outcomes: Results of Phase 3 APOLLOE4 Clinical Trial in Early AD*
Presenter: John A. Hey, PhD, Chief Scientific Officer, Alzheon, Inc.

Poster #12: *The Oral Anti-Amyloid Agent Valiltramiprosate Reduces Spontaneous ARIA Rates in APOE4/4 Early AD Subjects: Results of the Phase 3 Placebo-Controlled APOLLOE4 Trial*
Presenter: Susan Abushakra, MD, Chief Medical Officer, Alzheon, Inc.

Poster #13: *Effects of Valiltramiprosate on Plasma P-tau217 and Select Pro-Inflammatory and Vascular Injury Biomarkers with the NULISA CNS Panel: Exploratory Analyses from the Phase 3 APOLLOE4 Trial in APOE4/4 Homozygotes with Early AD*
Presenter: Susan Abushakra, MD, Chief Medical Officer, Alzheon, Inc.

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 completely blocked 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] 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 for valiltramiprosate showed clinical efficacy at the MCI stage, and favorable safety results, 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 ORION-E4 Phase 3 Trial
ORION-E4 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of the efficacy, safety and biomarker effects of valiltramiprosate in participants with Mild Cognitive Impairment due to Alzheimer's disease who are homozygous for the ε4 variant of the apolipoprotein E gene (APOE4/4). Approximately 550 participants at approximately 150 sites in approximately 12 countries will be randomized to valiltramiprosate 265 mg or placebo twice daily for 78 weeks. The primary endpoint is the change from baseline to Week 78 on CDR-SB.

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 completed 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 ALZ-507

ALZ-507 is a novel investigational oral drug candidate designed for once-daily administration that inhibits the formation of neurotoxic soluble amyloid oligomers and also acts as an APOE4 corrector. ALZ-507 is being evaluated in a Phase 1 single and multiple ascending dose trial assessing safety, tolerability and pharmacokinetics, which is intended to guide dose selection and formulation for subsequent Phase 2 studies in Alzheimer's disease, Down syndrome–associated Alzheimer's disease and cerebral amyloid angiopathy (CAA).

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 in Phase 1 designed to inhibit the formation of amyloid oligomers while also correcting the high-risk APOE4 gene, and the ALZ-700 series of oral ALZ-507 prodrugs extends the platform beyond Alzheimer's disease. 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.

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