Alzheon Announces Peer-Reviewed Scientific Publication of Results from Pivotal APOLLOE4 Phase 3 Trial of Oral Valiltramiprosate/ALZ-801 in APOE4/4 Homozygous Individuals with Early Alzheimer's Disease

Publication Describes Efficacy by Disease Severity and Highlights Prespecified Analysis of Mild Cognitive Impairment Stage Patients that Showed Cognitive and Functional Benefits, and Neuroprotective Effects on Brain Atrophy

Volumetric MRI Measures Show Protection from Brain Atrophy and Correlate with Clinical Outcomes

Favorable Safety Profile and No Increased Risk of Vasogenic Brain Edema Observed in Patients Treated with Valiltramiprosate

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

FRAMINGHAM, Mass., October 14, 2025 — Alzheon, Inc., a clinical-stage biopharmaceutical company developing a broad portfolio of investigational therapies and diagnostic assays for patients with Alzheimer's disease (AD) and other neurodegenerative disorders, today announced the peer-reviewed publication of *"Clinical Efficacy, Safety and Imaging Effects of Oral Valiltramiprosate in APOEε4/ε4 Homozygotes with Early Alzheimer's Disease: Results of Phase 3, Randomized, Double-Blind, Placebo-Controlled, 78-Week APOLLOE4 Trial"* in the scientific journal *Drugs*. The full text can be accessed at https://link.springer.com/article/10.1007/s40265-025-02250-5. This publication provides an overview of effects of valiltramiprosate in the APOLLOE4 Phase 3 trial in patients with Early AD, comprised of Mild Cognitive Impairment (MCI) and Mild AD dementia, who carry two copies of the apolipoprotein E ε4 allele (APOE4/4 homozygotes).

Valiltramiprosate/ALZ-801 is an investigational oral disease-modifying therapy in Phase 3 development designed to inhibit the formation of soluble neurotoxic amyloid oligomers and acts upstream in the amyloid cascade. The APOLLOE4 study, the first interventional Phase 3 trial dedicated exclusively to APOE4/4 patients with symptomatic AD, enrolled 325 participants across North America and Europe.

“Despite the progress in approved therapies for Alzheimer’s disease, there remains a major unmet need for disease modifying treatments with improved safety, efficacy, and access. The primary clinical outcome was not achieved in the overall population of the APOLLOE4 trial, however, prespecified analyses demonstrated nominally statistically significant and clinically meaningful cognitive and functional benefits in patients at the MCI stage. This is an important advancement for the field and underserved population, and the publication of APOLLOE4 Phase 3 results in a leading peer-reviewed journal represents an important step forward,” said Susan Abushakra, MD, Chief Medical Officer of Alzheon. “The pre-specified MCI group also showed large, consistent, and significant slowing of atrophy across multiple brain regions, together with reduced water diffusivity consistent with slowing of neurodegeneration, a key hallmark of AD. The APOLLOE4 trial provides the most comprehensive dataset to date on APOE4/4 homozygotes, underscoring our precision medicine approach and our commitment to addressing the needs of patients most at risk for Alzheimer’s disease.”

Importantly, valiltramiprosate treatment was associated with a favorable safety profile, showing no increased risk of amyloid-related imaging abnormalities (ARIA), comprising brain edema and microhemorrhage, and no observed symptomatic ARIA. APOE4/4 homozygotes represent approximately 15% of people with Alzheimer’s worldwide and there are currently no treatment options for them that can slow the progression of the disease without serious safety concerns.

“APOLLOE4 is the largest clinical trial ever conducted in symptomatic APOE4/4 patients, who face rapid disease progression and have few treatment options. The clinically meaningful benefits observed in patients at the Mild Cognitive Impairment stage support early intervention as a key strategy, and the favorable safety profile differentiates valiltramiprosate from other anti-amyloid approaches, particularly in the context of APOE4/4 homozygotes, who are most susceptible to serious side effects such as ARIA,” said Aidan Power, MB, BCh, MRCPsych, Chief Development Officer of Alzheon. “The publication of the APOLLOE4 results reinforces valiltramiprosate’s potential to become the first oral agent capable of slowing Alzheimer’s pathology in these genetically distinct patients, as Alzheon continues to advance its clinical development programs and explore regulatory pathways to bring this differentiated therapy to patients.”

APOE4/4 homozygotes represent a high-risk patient population, as they are 8–12 times more likely to develop AD and more likely to progress quickly into advanced disease stages. Currently available disease-modifying therapies carry increased safety risks in this distinct population, further underscoring the need for new treatment approaches.

“The findings from APOLLOE4 trial are highly encouraging,” said Marwan Sabbagh, MD, FAAN, an APOLLOE4 investigator. “The slowing of brain atrophy across multiple regions, combined with meaningful cognitive and functional effects in MCI patients, provide compelling evidence of potential neuroprotection. Just as importantly, the absence of vasogenic edema strengthens the case for valiltramiprosate as a safe oral alternative for this high-risk patient group.”

APOLLOE4 was a Phase 3 randomized, double-blind, placebo-controlled, parallel-arm, multicenter study of 78-week duration, enrolling APOE4/4 individuals at the early symptomatic

stages of AD, which include MCI and Mild AD dementia per Alzheimer's Association clinical criteria. After two stages of screening, patients aged 50-80 years, with Mini-Mental State Examination score ≥22, CDR-G=0.5 or 1 and RBANS-delayed memory ≤85, with stable medical conditions and no exclusionary findings on brain MRI were enrolled. A total of 325 subjects were eligible and randomized into either placebo or active arm at 265 mg ALZ-801 administered orally twice daily. There was a dedicated effort in the United States to enroll subjects from underrepresented populations to maximize the diversity, equity, and inclusiveness of the study. Importantly, the study allowed inclusion of subjects with any number of microbleeds and up to 2 siderosis lesions on MRI, markers of underlying cerebral amyloid angiopathy (CAA) that is common in APOE4/4 individuals. Individuals with more than four microbleeds are typically excluded from trials of anti-amyloid antibodies. This resulted in 31% of all enrolled participants having at least one microhemorrhage and included participants with up to 160 microhemorrhages and up to five superficial siderosis lesions in the active arm at baseline.

About Valiltramiprosate /ALZ-801

Valiltramiprosate/ALZ-801 is a potential first-in-class, investigational oral agent in Phase 3 development as a potentially disease-modifying treatment for AD.[2-6,8,11] Valiltramiprosate is designed to block the formation of neurotoxic soluble beta amyloid oligomers implicated in cognitive decline in Alzheimer's patients.[2-6,8,13] In preclinical mechanism of action studies, ALZ-801 has fully inhibited the formation of neurotoxic soluble beta amyloid oligomers at the Phase 3 clinical trial dose.[2,8,11,13] Valiltramiprosate is designed to act through a novel enveloping molecular mechanism of action to block formation of neurotoxic soluble amyloid oligomers in the human brain[13] associated with the onset and progression of cognitive decline in AD patients.[2,3,6,8,9] Valiltramiprosate received Fast Track designation from the U.S. Food and Drug Administration in 2017 for Alzheimer's disease. In clinical trials, valiltramiprosate has shown potential for robust clinical efficacy and favorable safety results with no increased risk of brain vasogenic edema.[4-9,12,14] The initial Phase 3 program for valiltramiprosate is focusing on Early AD patients with two copies of the apolipoprotein ε4 allele (APOE4/4 homozygotes), with potential future program expansion to AD treatment and prevention in patients carrying one copy of the APOE4 gene and noncarriers.[2–9]

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)

An ongoing long-term extension of the trial, APOLLOE4-LTE evaluates 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 is currently ongoing in the US, UK and Canada (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-tau$_{181}$. The trial also included evaluation of clinical efficacy, safety, tolerability, and pharmacokinetic profile of valiltramiprosate over 104 weeks of treatment. An ongoing long-term extension of the trial evaluates the same dose of valiltramiprosate for an additional 104 weeks of treatment for a total of 208 weeks[2,6,7].

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, valiltramiprosate/ALZ-801, is a first-in-class oral agent in Phase 3 development as a potentially disease-modifying treatment for AD. Valiltramiprosate is an oral small molecule that has been observed to fully block the formation of neurotoxic soluble amyloid oligomers in preclinical tests. 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]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.

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[3]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.

[4]Aye S, 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.

[5]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.

[6]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.

[7]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.
[8]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.
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[11]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.
[12]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.
[13]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.
[14]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.
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[17]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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