Topline Results from Pivotal APOLLOE4 Phase 3 Trial of Oral Valiltramiprosate/ALZ-801 in Patients with Early Alzheimer's Disease Carrying Two Copies of APOE4 Gene

Primary Endpoint of Slowing Cognitive Decline as Assessed by Alzheimer's Disease Assessment Scale-Cognitive Subscale Was Not Met in APOLLOE4 Study

Valiltramiprosate Improved Cognition and Function in Prespecified Analysis in Patients at Mild Cognitive Impairment Stage

Valiltramiprosate Slowed Brain Atrophy Across Multiple Brain Regions in Overall Study Population, Suggesting Potential Neuroprotective Benefits

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

FRAMINGHAM, Mass., April 10, 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 topline results from the pivotal APOLLOE4 Phase 3 trial of oral valiltramiprosate/ALZ-801 in patients with Early AD comprised of Mild Cognitive Impairment (MCI) and Mild AD dementia, who carry two copies of the ε4 allele of the apolipoprotein E gene (APOE4/4 homozygotes). Valiltramiprosate is an investigational oral treatment in Phase 3 clinical development that inhibits formation of soluble neurotoxic amyloid aggregates and acts upstream in the amyloid cascade. APOLLOE4 Phase 3 trial results were presented on April 1, 2025, at the International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD) in Vienna.

The APOLLOE4 study was the first Phase 3 trial focusing on APOE4/4 homozygotes and included 325 Early AD patients from study sites throughout North America and Europe. The study enrolled 51% females, 50-80 years old, with MCI or Mild AD dementia. APOLLOE4's primary outcome was the 13-item Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog13), with two measures that capture function associated with AD as key secondary outcomes: Clinical Dementia Rating–Sum of Boxes (CDR-SB) and Amsterdam-Instrumental Activities of Daily Living (A-IADL). Hippocampal volume was assessed as the main imaging outcome and fluid biomarkers

as additional outcomes. In the overall study population, the APOLLOE4 study did not meet the primary endpoint of slowing cognitive decline as assessed by ADAS-Cog13. A prespecified analysis in patients at the MCI stage of AD (earliest symptomatic stage) showed nominally statistically significant cognitive benefits as measured by ADAS-Cog13 and clinically meaningful functional effects as measured by CDR-SB and Disability Assessment for Dementia (DAD). No increased risk of vasogenic brain edema or microhemorrhages described as amyloid-related imaging abnormalities (ARIA-E, ARIA-H) was observed on magnetic resonance imaging (MRI) scans. Analysis of brain volumetric endpoints on MRI showed slowing of brain atrophy across multiple brain regions, suggesting potential neuroprotective benefits of valiltramiprosate.

"This research is important for patients with the APOE4/4 genotype who have Mild Cognitive Impairment, as they have unique needs that may not be fully addressed by current therapies," said Anton P. Porsteinsson, M.D., Director of the University of Rochester's Alzheimer's Disease Care, Research and Education Program. "Valiltramiprosate offers a different approach – it is an oral treatment with a differentiated mechanism that works upstream in the amyloid cascade inhibiting the formation of neurotoxic amyloid oligomers implicated in Alzheimer's pathogenesis, and in the APOLLOE4 study showed cognitive and functional effects in patients with Mild Cognitive Impairment, without increased incidence of vasogenic brain edema."

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 stages of disease.

"Results from the APOLLOE4 Phase 3 trial showed promising clinical and brain volume effects in Alzheimer's patients with the APOE4/4 genotype. While the APOLLOE4 study did not show a statistically significant cognitive benefit in the overall APOE4/4 patient population, we observed nominally statistically significant and clinically meaningful cognitive benefits compared to placebo in ADAS-Cog13, as well as functional benefits, in a prespecified group of patients who could benefit from early intervention," said Susan Abushakra, M.D., Chief Medical Officer of Alzheon. "APOLLOE4 is the largest clinical trial conducted to date in symptomatic APOE4/4 homozygotes who have a desperate need for additional treatment options. A precision medicine approach is key to addressing the needs of Alzheimer's patients who have the APOE4/4 genotype, and we are committed to this patient population."

APOLLOE4 Topline Results

Efficacy results at the Week 78 timepoint showed:

- In the overall study population, no significant benefit on ADAS-Cog13 with valiltramiprosate versus placebo (11% benefit, p=0.607).

Full Analysis Set Placebo (N=158) Active (N=162)	**Difference in LS Mean**	**P Value**	**% Slowing vs. Placebo in Overall**
ADAS-Cog13	D= -0.504	p=0.607	+11% Favors valiltramiprosate
CDR-SB	D= -0.312	p=0.309	+23%

			Favors valiltramiprosate
A-IADL	D= +0.011	p=0.997	0% Favors placebo
DAD	D= +2.629	p=0.279	+29% Favors valiltramiprosate
MMSE	D= +0.349	p=0.454	+17% Favors valiltramiprosate

- In the prespecified MCI population, a nominally statistically significant 52% clinical benefit on ADAS-Cog13 (p=0.041) with valiltramiprosate versus placebo, a clinically meaningful 102% benefit on CDR-SB (p=0.053), and a nominally statistically significant 96% benefit on disability scale DAD (p=0.016).

Prespecified MCI Placebo (N=58) Active (N=67)	**Difference in LS Mean**	**P Value**	**% Slowing vs. Placebo in MCI**
ADAS-Cog13	D= -2.144	p=0.041	+52% Favors valiltramiprosate
CDR-SB	D= -0.646	p=0.053	+102% Favors valiltramiprosate
A-IADL	D= -3.408	p=0.268	+70% Favors valiltramiprosate
DAD	D= +6.093	p=0.016	+96% Favors valiltramiprosate
MMSE	D= +0.830	p=0.094	+59% Favors valiltramiprosate

- In the overall imaging population, nominally statistically significant decrease in brain atrophy with valiltramiprosate versus placebo: 18% benefit on hippocampal volume (p=0.0174), 20% benefit on whole brain cortical thickness (p=0.0020), and 16% benefit on whole brain volume (p=0.0400).
- In the prespecified MCI population, the imaging effects were larger and nominally statistically significant: 26% benefit on hippocampal volume (p=0.0042), 35% benefit on whole brain cortical thickness (p<0.0001), and 22% benefit on whole brain volume (p=0.0267).

Overall Imaging Population Placebo (N=144) Active (N=146)	**P Value**	**% Effect vs. Placebo**
Hippocampal volume (HV, µL)	p=0.0174 (D= +74 µL)	18% Favors valiltramiprosate
Cortical thickness/Mayo Index (mm)	p=0.0040	18% Favors valiltramiprosate

Cortical thickness/whole brain average (mm)	p=0.0020	20% Favors valiltramiprosate
Ventricular volume (VV, µL)	p=0.0018	22% Favors valiltramiprosate
Whole brain volume (WBV, µL)	p=0.0400	16% Favors valiltramiprosate

- Nominally statistically significant correlations were observed in the overall population between volumetric and clinical outcomes, including hippocampal volume and cognition as assessed by ADAS-Cog13 (p<.0001).

Safety results in the overall safety population (N=325) showed:

- No serious adverse reactions and no deaths.
- No increased risk of ARIA with edema (ARIA-E; 5/149 or 3.4% in each arm, all asymptomatic), ARIA with siderosis (5% in valiltramiprosate arm, 6% in placebo) and ARIA with microhemorrhages (9% in valiltramiprosate arm, 14% in placebo).
- Serious adverse event (SAE) rates were similar in the valiltramiprosate and placebo arms. In the MCI group, SAE rates were lower with valiltramiprosate (5%) than placebo (8%).
- The most common treatment emergent adverse events were nausea, weight decrease, decreased appetite, and vomiting. The majority of nausea events were mild and showed tolerance with continued treatment.
- The dropout rate was higher in the valiltramiprosate arm (19%) than in the placebo arm (9%).

“Learning that you carry two copies of the APOE4 gene variant can be life changing and result in tremendous anxiety,” said Jamie TenNapel Tyrone, CEO and Founder of Beating Alzheimer's by Embracing Science and author of *Fighting for My Life: How to Thrive in the Shadow of Alzheimer’s*. “Positive lifestyle changes and a focus on brain health are important, but it may not be enough. The development of effective and safe treatments to address the unique challenges of APOE4/4 homozygotes with Alzheimer’s disease is incredibly important. I am grateful for efforts regarding this urgent unmet need.”

Alzheon plans to publish the APOLLOE4 study results in a peer-reviewed publication.

About 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.[1-5,7,10] Valiltramiprosate is designed to block the formation of neurotoxic soluble beta amyloid oligomers implicated in cognitive decline in Alzheimer’s patients.[1-5,7,12] In mechanism of action studies, ALZ-801 fully inhibited the formation of neurotoxic soluble beta amyloid oligomers at the Phase 3 clinical dose.[1,7,10,12] Valiltramiprosate acts through a novel enveloping molecular mechanism of action to block formation of neurotoxic soluble amyloid oligomers in the human brain[12] associated with the onset and progression of cognitive decline in AD patients.[1,2,5,7,8] Valiltramiprosate received

Fast Track designation from the U.S. Food and Drug Administration in 2017 for Alzheimer's disease. In the APOLLOE4 Phase 3 trial, valiltramiprosate showed improved cognition and function in patients with mild cognitive impairment and slowed brain atrophy across multiple brain regions in the overall study population, with favorable safety results showing no increased risk of brain vasogenic edema. 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.[1–8]

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 was a double-blind, randomized trial comparing oral valiltramiprosate to placebo treatment over 78 weeks. The APOLLOE4 trial was supported by a $51 million grant from the National Institutes of Health's National Institute on Aging (R01AG065253) to Alzheon, with Susan Abushakra as the principal investigator.

NIA statement: "This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health's National Institute on Aging."

Valiltramiprosate APOLLOE4 Long Term Extension Trial (LTE)

An ongoing long-term extension of the trial, APOLLOE4-LTE evaluates valiltramiprosate in subjects who complete the core APOLLOE4 study for an additional 52 weeks of treatment for a total of 130 weeks or 2.5 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 trial also included evaluation of clinical efficacy, safety, tolerability, and pharmacokinetic profile of valiltramiprosate over 104 weeks of treatment (primary endpoint). 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.[1,5,6]

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]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.

[2]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.

[3]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.

[4]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.

[5]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.

[6]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]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.

[12]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.

[13]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.

[14]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.
[15]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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