Alzheon to Present Insights into Oral Valiltramiprosate/ALZ-801 Mode of Action and Clinical Efficacy at Dedicated Symposium at Alzheimer's Association International Conference in Toronto on July 30th, 2025

Valiltramiprosate Evaluated in APOLLOE4 Trial, First Interventional Phase 3 Alzheimer's Trial Focused on High-Risk APOE4/4 Homozygotes

Anti-Amyloid Oligomer Action Underpins Valiltramiprosate's Potential Benefit in Alzheimer's Disease at MCI Stage of Disease

Valiltramiprosate Designed to Inhibit Amyloid Aggregation by Distinct Upstream Mode of Action to Slow Progression of Alzheimer's Disease

Precision Medicine Approach Supported by Valiltramiprosate's Favorable Safety in High-Risk APOE4 Carriers with Major Unmet Medical Need

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

FRAMINGHAM, Mass., July 15, 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 it will present new data on its lead investigational product, valiltramiprosate, highlighting the differentiated mode of action that acts upstream in the amyloid pathway, blocking formation of neurotoxic amyloid oligomers that drive disease progression. Valiltramiprosate showed positive clinical and volumetric MRI effects in patients with Mild Cognitive Impairment (MCI) who carry one or two copies of the ε4 allele of the apolipoprotein E gene (APOE3/4 heterozygotes and APOE4/4 homozygotes, respectively). The first of-its-kind data will be presented in a symposium during the Alzheimer's Association International Conference (AAIC) in Toronto, Canada.

"Valiltramiprosate represents a promising advancement in targeting the early highly toxic forms of beta amyloid that drive Alzheimer's disease onset and progression," said Sam Gandy, M.D., Ph.D., Professor of Neurology and Psychiatry at Icahn School of Medicine at Mount Sinai. "By focusing on oligomer formation upstream, this oral therapy has the potential to change the

treatment paradigm for patients at risk for Alzheimer's and those with early symptomatic disease, particularly the high-risk APOE4 carriers."

Valiltramiprosate is an investigational oral AD treatment in Phase 3 clinical development with an upstream mechanism of action from anti-amyloid antibodies that prevents formation of neurotoxic amyloid oligomers. A prodrug of tramiprosate with optimized pharmacokinetics and brain penetration, valiltramiprosate was designed to prevent amyloid aggregation at the initial stage of the amyloid cascade. Soluble amyloid oligomers play a central role in the pathogenesis and progression of Alzheimer's disease.

"Results from the APOLLOE4 Phase 3 trial evaluating valiltramiprosate showed promising clinical and volumetric MRI effects in Alzheimer's patients with the APOE4/4 genotype at the earliest symptomatic stage of disease. With a mechanism of action directly blocking the formation of neurotoxic beta amyloid oligomers, valiltramiprosate addresses the upstream pathology of Alzheimer's disease and offers a potential safe, effective, and accessible oral treatment," said John Hey, PhD, Chief Scientific Officer of Alzheon. "These findings reinforce our understanding of how valiltramiprosate works at the molecular level and provide a mechanistic foundation for the positive clinical, fluid biomarker and imaging outcomes observed in our Phase 2 and Phase 3 studies in APOE4 carriers and homozygotes, respectively, with early symptomatic AD."

Preclinical and clinical studies demonstrate that valiltramiprosate interacts with monomeric beta amyloid and prevents the formation of soluble oligomers that drive synaptic toxicity and neuronal loss. Quantitative systems pharmacology (QSP) analysis further supports the clinical relevance of this mechanism of action by linking reductions in formation of toxic amyloid oligomers to preservation of hippocampal volume, attenuation of neurodegeneration in all brain regions, and slowing of disease progression. These effects are most pronounced in the high risk APOE4/4 population, which has a high burden of neurotoxic amyloid oligomers.

These clinical and biomarker results support Alzheon's precision medicine approach of focusing on high-risk APOE4 carriers with Alzheimer's disease, and provide the scientific rationale for targeting beta amyloid oligomers upstream in the disease process and at the early symptomatic stages of AD.

Details of Symposium at AAIC 2025
The symposium will be held in the afternoon on July 30th and will be available to all conference attendees, both in person at the Westin Harbor Castle in Toronto and virtually via the following link: https://aaic.alz.org/program/schedule.asp#a06

Title: *Inhibition of Beta Amyloid Oligomer Neurotoxicity with Oral Valiltramiprosate*
Date and Time: Wednesday, July 30, 12:30 p.m. local Toronto time (ET)
Location: Westin Harbor Castle, Frontenac Ballroom

Symposium Chair & Moderator:

- Sharon Cohen, M.D., FRCPC, Medical Director, Toronto Memory Program, Toronto, ON, Canada

Presenters*:*

- Samuel Gandy, M.D., Ph.D., Professor of Neurology and Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
- Kenjiro Ono, M.D., Ph.D., Department of Neuropathology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
- Huge Geerts, M.D., Ph.D., Head of Neuroscience Modeling, Quantitative Systems Pharmacology, Certara, Berwyn, PA, USA
- John Hey, Ph.D., Chief Scientific Officer, Alzheon, Inc. Framingham, MA, USA

In addition, Alzheon scientists will be provide clinical and imaging analyses from the APOLLOE4 Phase 3 study of valiltramiprosate in APOE4/4 homozygotes in eight poster presentations at the conference:

Poster: *"Quantitative Systems Pharmacology Analysis of Hippocampal Volume Trajectory by APOE Genotype and Neuroprotective Effects of Valiltramiprosate/ALZ-801 in Early AD"*

- **Presenter:** Dr. Hugo Geerts, Head of Neuroscience Modeling, Quantitative Systems Pharmacology, Certara, Berwyn, PA, USA
- **Poster #108550**

Poster: *"Efficacy and Safety of Oral Valiltramiprosate in APOE4/4 Homozygotes with Early AD: Topline Results from the APOLLOE4 Phase 3 Trial"*

- **Presenter:** Dr. Aidan Power, Chief Development Officer, Alzheon, Inc.
- **Poster #108821**

Poster: *"Safety and ARIA Results of the Oral Anti-Amyloid Agent Valiltramiprosate from the Phase 3 APOLLOE4 Trial in APOE4/4 Homozygotes with Early AD"*

- **Presenter:** Dr. Patrick Kesslak, Senior Research Fellow, Alzheon, Inc.
- **Poster #108685**

Poster: *"Correlations of Valiltramiprosate Effects on Hippocampal Volume and Cortical Thickness with Clinical Outcomes in the Pre-Specified MCI Group: Subgroup Analysis from the 78-Week APOLLOE4 Phase 3 Trial in APOE4/4 Homozygotes"*

- **Presenter:** Dr. Susan Abushakra, Chief Medical Officer, Alzheon, Inc.
- **Poster #108827**

Poster: *"Valiltramiprosate Effects on Microstructural Integrity of Grey and White Matter in APOE4/4 Homozygotes with Early AD and their Correlations to Clinical Outcomes: MRI Mean Diffusivity Results from the 78-Week APOLLOE4 Phase 3 Trial"*

- **Presenter:** Dr. Earvin Liang, Vice President of Clinical Development, Alzheon, Inc.

- **Poster #108716**

Poster: *"Quantitative Systems Pharmacology Analysis of Oral Valiltramiprosate/ALZ-801 Predicts Slowing of Alzheimer's Disease Progression by Anti-Amyloid Oligomer and APOE4 Structural Corrector Modes of Action"*

- **Presenter:** Jean Schaefer, Vice President of CMC & Project Management, Alzheon, Inc.
- **Poster #108561**

Poster: *"Valiltramiprosate/ALZ-801 Prevents Hippocampal Atrophy and Clinical Decline in a Stage 2 AD Subpopulation in APOLLOE4 Phase 3 Study"*

- **Presenter:** Dr. Jeremy Yu, Senior Clinical Research Fellow, Alzheon, Inc.
- **Poster #108565**

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 has fully inhibited the formation of neurotoxic soluble beta amyloid oligomers at the Phase 3 clinical trial 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 clinical trials, valiltramiprosate has shown potential for robust clinical efficacy and favorable safety results with no increased risk of brain vasogenic edema.[3-8,11,13] 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 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 (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 is 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[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]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.

[2]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.

[3]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.

[4]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.

[5]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.

[6]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.

[7]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.
[8]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.
[9]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.
[10]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.
[11]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.
[12]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.
[13]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.
[14]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.
[15]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.
[16]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, Alzheon, Inc.
508.808.2301
yasemin.khakian@alzheon.com

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