Alzheon to Present Results from Pivotal APOLLOE4 Phase 3 Trial of Oral Valiltramiprosate/ALZ-801 at Dedicated Symposium at ADPD Conference in Vienna on April 1st, 2025

First Interventional Alzheimer's Drug Trial Focused on High-Risk APOE4/4 Homozygotes with Major Unmet Medical Need for an Effective and Safe Treatment

Valiltramiprosate Tablet Inhibits Formation of Soluble Toxic Amyloid Aggregates and Acts Upstream from All Late-Stage Amyloid Targeting Treatments

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

FRAMINGHAM, Mass., March 18, 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 topline results from the pivotal APOLLOE4 Phase 3 trial of oral valiltramiprosate/ALZ-801 in patients with early AD who carry two copies of the ε4 allele of the apolipoprotein E gene (APOE4/4 homozygotes). The first-of-its-kind data will be presented in a symposium during the International Conference on Alzheimer's and Parkinson's Disease and Related Neurological Disorders (ADPD) in Vienna, Austria.

"Results from the APOLLOE4 Phase 3 trial show promising clinical and biomarker effects for Alzheimer's patients with the APOE4/4 genotype. APOLLOE4 is the largest clinical trial conducted to date in these patients with a desperate need of new effective, safe, and accessible treatment options," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon. "Serious hurdles remain with currently available anti-amyloid disease modifying treatments, including appropriate patient identification, safety monitoring, access, and cost effectiveness. Due to safety concerns and restrictions, these therapies are not optimal for APOE4/4 homozygotes, the most vulnerable Alzheimer's patient population. At Alzheon we strive to address these challenges with our investigational oral molecule, valiltramiprosate, which could become the first oral agent to slow Alzheimer's pathology in patients."

The APOLLOE4 study was a first-of-its-kind Phase 3 trial focusing on APOE4/4 homozygotes and included 325 patients in the early stages of AD. 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 severe stages of disease. Furthermore, the approved disease modifying therapies for AD have a boxed warning for treating APOE4/4 homozygotes, as they are more likely to develop brain swelling and bleeding.

Valiltramiprosate is an investigational oral AD treatment in Phase 3 clinical development with an upstream mechanism of action that prevents formation of neurotoxic amyloid oligomers. The 78-week APOLLOE4 trial included 325 APOE4/4 homozygotes from study sites throughout North America and Europe, and enrolled 51% females, 50-80 years old, with the majority being mild cognitive impairment (MCI) and Mild Alzheimer's disease subjects. APOLLOE4 primary outcome was the 13-item Alzheimer's Disease Assessment Scale Cognitive subscale, with two functional measures as key secondary outcomes (Clinical Dementia Rating–Sum of Boxes, Amsterdam-Instrumental Activities of Daily Living), hippocampal volume as the main imaging outcome and fluid biomarkers as additional outcomes.

Details of Symposium at ADPD 2025
The symposium will be held on the opening morning of ADPD 2025 and will be available to all conference attendees, both in person at the Austria Center Vienna and virtually via the following link: https://cslide.ctimeetingtech.com/adpd25/attendee.

Title: *Inhibition of Beta Amyloid Oligomer Neurotoxicity with Oral Valiltramiprosate in APOE ε4/ε4 Homozygotes with Early Alzheimer's Disease: Results of APOLLOE4 Phase 3 Trial*
Date and Time: Tuesday, April 1, 9:45 a.m. local Vienna time (CET)
Location: Hall A

Moderator:
- Philip Scheltens, M.D., Ph.D., Professor of Cognitive Neurology and Director of the Alzheimer Center at the VU University Medical Center in Amsterdam, Netherlands

Presenters*:*
- Susan Abushakra, M.D., Chief Medical Officer, Alzheon, Inc., Framingham, MA, USA
- Murali Doraiswamy, MBBS, FRCP, Professor of Psychiatry and Professor of Medicine at Duke University School of Medicine, Durham, NC, USA
- Anton Porsteinsson, M.D., Director of the University of Rochester Alzheimer's Disease Care, Research and Education Program (AD-CARE), Rochester, NY, USA
- David Watson, Psy.D., CPI, CEO and Principal Investigator, Alzheimer's Research and Treatment Center, Wellington, FL, USA

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 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 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]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.

[7]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.

[8]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.

[9]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.

[10]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.

[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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