Two Peer-Reviewed Scientific Publications Describe Fluid Biomarker, Brain Preservation and Clinical Benefits Following 2 Years of Treatment in Phase 2 Trial Evaluating Oral ALZ-801/Valiltramiprosate in APOE4 Carriers with Early Alzheimer's Disease

Early, Sustained and Statistically Significant Reduction in Plasma P-tau$_{181}$ Reaching 31% at 24 Months Observed in Carriers of One or Two Copies of APOE4 Gene, who Represent Two Thirds of Alzheimer's Patients

Preservation of Hippocampal Volume Compared to External Control of Matched Subjects from Alzheimer's Disease Neuroimaging Initiative Suggests Neuroprotective Effects on Brain Structures

Improvement on Cognitive Tests at 6 Months and Sustained Stabilization of Cognition Above Baseline for 24 Months Consistent with Biomarker & Brain Imaging Effects on Core Alzheimer's Pathologies

Quantitative Systems Pharmacology Analysis of Amyloid Fluid Biomarkers and Cognitive Benefits Supports ALZ-801/Valiltramiprosate Target Engagement, and Potential for Disease Modification and Clinical Efficacy

Topline Data from Pivotal APOLLOE4 Phase 3 Trial and Initiation of Regulatory Filings for Valiltramiprosate Expected in 2H 2024

FRAMINGHAM, Mass., June 25, 2024 — Alzheon, Inc., a clinical-stage biopharmaceutical company developing a broad portfolio of product candidates and diagnostic assays for patients suffering from Alzheimer's disease (AD) and other neurodegenerative disorders, today announced two scientific publications of results from the Phase 2 biomarker trial showing statistically significant and clinically relevant reduction in plasma biomarkers of neurodegeneration, preservation of brain volume, and positive cognitive effects in Early AD patients who are carriers of apolipoprotein ε4 allele (APOE4) following 24 months of treatment with investigational oral agent ALZ-801/valiltramiprosate.

The research papers, "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" and "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" were published in the scientific journal *Drugs*, and are available through open access at: https://doi.org/10.1007/s40265-024-02067-8 and https://doi.org/10.1007/s40265-024-02068-7, respectively.

"The two new seminal papers showcase Alzheon's scientific leadership in understanding of the pathogenesis of Alzheimer's disease and provide support for the single toxin theory of brain neurodegeneration, our thesis that the aggregation of misfolded native proteins initiates and drives the pathogenic cascade that leads to Alzheimer's disease and other age-related neurodegenerative disorders. In addition, our new analyses further strengthen the growing body of evidence for ALZ-801's potential as the first oral disease-modifying therapy," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon, and the senior author of both publications. "Valiltramiprosate is the most advanced of the next generation of highly selective anti-oligomer agents in development and these efficacy data, combined with a favorable safety profile showing no increased risk of vasogenic edema, underscore the differentiated clinical profile of our lead agent. We look forward to further validation of these findings from the ongoing pivotal APOLLOE4 Phase 3 trial in APOE4/4 homozygotes that is expected to report in the third quarter of 2024."

ALZ-801/valiltramiprosate is an investigational oral disease-modifying therapy in Phase 3 development for the treatment of Early AD. In mechanism of action studies, ALZ-801 fully blocked the formation of neurotoxic soluble beta amyloid (Aβ) oligomers at the Phase 3 clinical dose. ALZ-801 has shown both potential for clinical efficacy in the highest-risk and most fragile Alzheimer's population – patients with two copies of the apolipoprotein ε4 allele (APOE4/4 homozygotes) and favorable safety with no increased risk of vasogenic brain edema. This population is the focus of the pivotal 78-week APOLLOE4 Phase 3 trial, which is fully enrolled with topline data expected in the third quarter of 2024.

The Phase 2 biomarker study was designed to inform the development of ALZ-801 in the broader population of APOE4 carriers, which represents ~65% of all patients with AD. The open-label, multicenter, single-arm Phase 2 trial evaluated the effects of ALZ-801 265 mg administered orally twice daily on plasma AD biomarkers, hippocampal volume (HV) as measured by magnetic resonance imaging (MRI), and clinical tests of learning and memory, as well as safety and tolerability, over 104 weeks. The trial enrolled 84 patients ages 50 to 80 years with early AD (MMSE 22-30), who carry either one or two copies of the ε4 allele of the apolipoprotein E gene (APOE3/4 heterozygotes and APOE4/4 homozygotes, respectively), and showed positivity for amyloid and tau biomarkers in cerebrospinal fluid (CSF). APOE4 genotype, the leading risk factor for AD after aging, is associated with a several-fold higher risk of symptomatic AD and higher brain burden of neurotoxic amyloid oligomers and of aggregated amyloid in cerebral

microvasculature (cerebral amyloid angiopathy, CAA). The study was designed to provide evidence of target engagement to support initiation of a pivotal Phase 3 trial in APOE4 carriers.

"The published data from our Phase 2 study reinforce the potential benefits of ALZ-801 in patients with early symptomatic Alzheimer's disease who are APOE4 carriers. Study participants experienced a significant positive impact on core biomarkers of AD pathology, hippocampal brain atrophy and cognitive decline over two years of treatment with ALZ-801," said John Hey, PhD, Chief Scientific Officer of Alzheon and the lead author of both publications. "In addition, the quantitative systems pharmacology biomarker analysis supports ALZ-801 target engagement and suggests potential for disease modification and meaningful clinical efficacy in Alzheimer's patients with APOE4 genotype. These are encouraging results, given that this high-risk AD patient population typically experiences rapid cognitive decline and disease progression. Our goal is to bring valiltramiprosate to these patients as the first potential oral disease-modifying therapy, and we look forward to sharing the topline data from our pivotal APOLLOE4 Phase 3 trial and initiating a New Drug Application to the FDA later this year."

This positive Phase 2 study evaluating oral ALZ-801 in APOE4 patients with early AD achieved its primary efficacy endpoint of reduction in plasma p-tau$_{181}$ over two years, suggesting a robust decrease in amyloid-induced brain neurodegeneration and target engagement. A significant 31% reduction (p=0.045) in plasma p-tau$_{181}$ from baseline to 104 weeks started at 13 weeks and was sustained at every visit through 104 weeks. HV atrophy was significantly reduced by 25% (p=0.0014) compared to a matched external control from ADNI-1, an observational AD study. Memory scores showed improvement from baseline at 26 weeks and thereafter showed minimal decline from baseline at 104 weeks. These cognitive effects correlated significantly with decreased HV atrophy (p=0.002). The most common treatment-emergent adverse events were nausea and urinary tract infections, and no drug-related serious adverse events were reported. Of 14 early withdrawals, six were due to non-serious treatment-emergent adverse events and there was one death due to COVID-19 (not related to study drug). No vasogenic brain edema (amyloid-related imaging abnormalities with brain edema, ARIA-E) was observed on MRI over 104 weeks. After completion of the core study, a long-term extension of an additional 104 weeks was initiated and is in progress to allow long-term assessment of plasma biomarkers, hippocampal volume, cognitive tests, and safety over four years of treatment.

"Well-tolerated disease-modifying treatments are needed for patients with Alzheimer's disease, particularly those who are APOE4 carriers, since these patients are at increased risk of vascular complications known as amyloid-related imaging abnormalities. The Phase 2 biomarker trial generated compelling data demonstrating that treatment with oral ALZ-801 leads to a sustained reduction in p-tau$_{181}$, a key measure of brain neurodegeneration, as well as slowing of hippocampal atrophy compared to a matched external control arm, and stabilization of cognition for two years," said Susan Abushakra, MD, Chief Medical Officer at Alzheon. "A well-tolerated oral agent with a simple dosing regimen would be optimal for presymptomatic individuals who may require life-long treatment. This study adds to the body of data for ALZ-801, a well-differentiated investigational oral therapeutic with a favorable safety profile with no increased

risk of vasogenic brain edema that has the potential to transform the treatment of Alzheimer's disease and reduce its burden on patients, their loved ones and society as a whole."

In the Phase 2 trial, oral ALZ-801 showed early and sustained significant reduction of plasma p-tau$_{181}$ and plasma Aβ42 levels over 2 years, suggesting alleviation of neurodegeneration due to toxic effects of soluble amyloid oligomers. The quantitative systems pharmacology (QSP) biomarker analysis supports the positive therapeutic effect of ALZ-801, with evidence of arresting the natural decline of monomeric CSF and plasma amyloid biomarkers, consistent with the target engagement to prevent aggregation of amyloid monomers into soluble neurotoxic oligomers. Accompanying the amyloid biomarker changes, ALZ-801 also stabilized the natural trajectory of memory decline, suggesting that the clinical benefits are consistent with its mechanism of action. The QSP analysis provides supportive amyloid fluid biomarker and clinical evidence for ALZ-801 as a potential first-in-class, oral small-molecule anti-Aβ oligomer agent with disease modification potential in AD.

About ALZ-801/Valiltramiprosate

ALZ-801/valiltramiprosate is a potential first-in-class, investigational oral agent in Phase 3 development as a potentially disease modifying treatment for AD.[1-4,6,9] ALZ-801 is designed to block the formation of neurotoxic soluble beta amyloid oligomers implicated in cognitive decline in Alzheimer's patients.[1-4,6,11] In mechanism of action studies, ALZ-801 has fully inhibited the formation of neurotoxic soluble beta amyloid oligomers at the Phase 3 clinical dose.[6,9,11] ALZ-801 acts through a novel enveloping molecular mechanism of action to block formation of neurotoxic soluble amyloid oligomers in the human brain[11] associated with the onset and progression of cognitive decline in AD patients.[1,4,6,7] ALZ-801 received Fast Track designation from the U.S. Food and Drug Administration in 2017 for Alzheimer's disease. In clinical trials, ALZ-801 has shown potential for robust clinical efficacy and favorable safety results with no increased risk of brain vasogenic edema.[2-7,10,12] The initial Phase 3 program for ALZ-801 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.[1–7]

ALZ-801 Phase 2 Biomarker Trial

Biomarker Effects of ALZ-801 in APOE4 Carriers With Early Alzheimer's Disease (NCT04693520): This ongoing trial was designed to evaluate the effects of 265 mg twice daily oral dose of ALZ-801 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 ALZ-801 over 104 weeks of treatment (primary endpoint). An ongoing long-term extension of the trial evaluates ALZ-801 for an additional 104 weeks of treatment for a total of 208 weeks.

ALZ-801 APOLLOE4 Phase 3 Trial

An Efficacy and Safety Study of ALZ-801 in APOE4/4 Early Alzheimer's Disease Subjects (NCT04770220): This ongoing trial is designed to evaluate the efficacy, safety, biomarker and imaging effects of 265 mg twice daily oral dose of ALZ-801 in Early AD subjects with two copies

of the apolipoprotein ε4 allele (APOE4/4 homozygotes), who constitute approximately 15% of Alzheimer's patients. This is a double-blind, randomized trial comparing oral ALZ-801 to placebo treatment over 78 weeks. The APOLLOE4 trial is supported by a $51 million grant from the National Institute on Aging.

ALZ-801 APOLLOE4 Long Term Extension Trial

An ongoing long-term extension of the trial, APOLLOE4-LTE, evaluates ALZ-801 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 (NCT06304883).

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, ALZ-801/valiltramiprosate, is a first-in-class oral agent in Phase 3 development as a potentially disease modifying treatment for AD. ALZ-801 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] 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, 2727.

[2] Hey J, 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.

[3] Hey J, 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.

[4] 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, 6355.

[5] 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: e12117.

[6] 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: 95.

[7] Tolar M, et al: *The Path Forward in Alzheimer's Disease Therapeutics: Reevaluating the Amyloid Cascade Hypothesis*, **Alzheimer's & Dementia**, 2019; 1-8.

[8] 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.
[9] 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.
[10] 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.
[11] 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.
[12] 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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