Alzheon Reports Industry-Leading Biomarker, Brain Preservation and Clinical Benefits Following 24 Months of Treatment in Phase 2 Trial of Oral ALZ-801 (Valiltramiprosate) in Patients with Early Alzheimer's Disease

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

Unprecedented 28% Preservation of Hippocampal Volume Compared to External Control of Matched Subjects from Alzheimer's Disease Neuroimaging Initiative Supports 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

Cognitive Improvements Show Statistically Significant Correlations with Decreased Hippocampal Atrophy and Cortical Thinning on Volumetric MRI Measurements

Safety Profile of ALZ-801 Remains Favorable & Consistent with Prior Data in Over 2,800 AD Patients, with no Increased Risk of Vasogenic Brain Edema

FRAMINGHAM, Mass., September 13, 2023 — Alzheon, Inc., a clinical-stage biopharmaceutical company developing a portfolio of product candidates and diagnostic assays for patients suffering from Alzheimer's disease (AD) and related neurodegenerative disorders, today announced 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 agent ALZ-801 in the Phase 2 biomarker trial.

"We are pleased with the growing body of evidence that supports ALZ-801's potential as the first oral disease modifying therapy for Alzheimer's disease. The magnitude of p-tau$_{181}$ biomarker

reduction in plasma compared to plaque-clearing anti-amyloid antibodies, combined with preservation of brain hippocampal volume and its strong positive correlations with cognitive benefits, reinforces our conviction that ALZ-801 has the potential to disrupt the Alzheimer's treatment paradigm by halting the progression of this relentless and debilitating disease," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon. "These efficacy data combined with a favorable safety profile with no events of vasogenic edema underscore the differentiated clinical profile of ALZ-801 oral tablet, and we look forward to further validation of these findings from our ongoing Phase 3 APOLLOE4 trial in APOE4/4 homozygotes that is expected to read out 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. Oral ALZ-801 has shown potential for robust clinical efficacy in the highest-risk and most fragile late-onset 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 Alzheon's pivotal 78-week APOLLOE4 Phase 3 trial, which is now fully enrolled and topline data is expected in the third quarter of 2024.

The open-label, multicenter, single-arm Phase 2 biomarker trial evaluated biomarker effects, clinical efficacy, and safety of ALZ-801 tablet in 84 Early AD patients, who carry either one or two copies of the ε4 allele of 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 brain burden of neurotoxic amyloid oligomers, and APOE4 carriers represent two thirds of the Alzheimer's patient population.

Elevation of phosphorylated tau (p-tau) levels in plasma is a sensitive and specific marker of neuronal stress and brain injury in AD and is considered a highly reliable core biomarker of disease pathology. P-tau is produced by neurons as a reaction to formation of neurotoxic beta amyloid oligomers, the key driver of AD pathology and neurodegeneration. P-tau$_{181}$ levels rise with onset of AD symptoms and with the clinical deterioration of patients and have been shown to fall in response to clinically effective anti-amyloid disease modifying treatments in Alzheimer's.

Study subjects were treated with ALZ-801 265 mg tablet once daily for two weeks and twice daily thereafter over a 104-week treatment period. At baseline, study subjects were 52% female, with mean age 69 years, MMSE 26 (range 22-30), and 70% having mild cognitive impairment (MCI). In November 2022, Alzheon reported positive study results from a pre-specified analysis following 52 weeks of treatment with ALZ-801. An ongoing long-term extension of the trial evaluates ALZ-801 for an additional 52 weeks of treatment for a total of 156 weeks. The current analysis at 104 weeks is the study's primary completion date, with plasma p-tau$_{181}$ being the primary outcome and hippocampal volume the primary imaging outcome.

A total of 70 subjects completed the Week 104 visit and 68 subjects provided evaluable plasma for biomarker assays and were included in this primary analysis. In this population, ALZ-801 achieved a statistically significant 27% reduction from baseline in plasma p-tau$_{181}$ (p=0.015) at Week 13 that was sustained and significant through the remainder of the treatment period. At Week 52, ALZ-801 achieved a statistically significant 43% reduction in plasma p-tau$_{181}$ (p<0.009) and at Week 104 a 31% reduction was observed (p<0.045). Plasma Aβ42 levels decreased throughout the treatment period, reaching a statistically significant 4% reduction from baseline (p<0.042) at Week 104, while the reduction in plasma Aβ40 levels stabilized at 52 weeks at a new homeostatic level. All analyses of plasma biomarkers were performed at the laboratory of Professor Kaj Blennow at the University of Gothenburg in Molndal, Sweden, and audited according to Good Laboratory Practice.

"Alzheon has pioneered an oral precision medicine in Alzheimer's disease targeting neurotoxic amyloid oligomers, and now very promising biomarker, imaging and clinical data with ALZ-801 provide further support for this approach," said Kaj Blennow, MD, PhD, Professor of Clinical Neurochemistry at the University of Gothenburg, Sweden, a member of Alzheon's Scientific Advisory Board and developer of the p-tau$_{181}$ assay. "Across many trials of anti-amyloid treatments, p-tau$_{181}$ has emerged as a consistent plasma biomarker that appears to correlate with clinical benefit. Upon analysis of the plasma p-tau$_{181}$ data in our laboratory, we have observed a sustained reduction in this leading biomarker of Alzheimer's pathology in patients taking ALZ-801 tablet for 24 months. This suggests a downstream effect on neuronal function and supports the potential for clinical efficacy of this novel treatment."

On measurements of hippocampal volume (HV), subjects treated with ALZ-801 demonstrated a statistically significant 28% reduction of hippocampal atrophy at Week 104 (p<0.015) compared to the external control of matched Early AD subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI is a longitudinal observational multicenter study of MCI, AD, and healthy individuals. Real-world evidence analyses were performed against matched ADNI controls based on APOE4 genotype, age, gender, and disease stage, following the recent FDA guidance from August 2023 on the use of real-world data and real-world evidence to support regulatory decision-making for drugs and biological products.

On cognitive scales, Rey Auditory Verbal Learning Test (RAVLT) and Digit Symbol Substitution Test (DSST), patients treated with ALZ-801 demonstrated a consistent improvement at Week 26 and remained stable and above baseline through the 104-week treatment period. On the RAVLT Total Score, which combines effects on immediate and delayed recall tests, patients treated with ALZ-801 demonstrated a statistically significant 24% improvement (p<0.0001) at Week 104 compared to matched ADNI subjects.

"The sustained reduction in plasma p-tau$_{181}$ combined with the decrease in rate of hippocampal atrophy as well as the stabilization of cognition over 2 years is consistent with a disease modifying action in Alzheimer's patients. These early p-tau$_{181}$ effects are enabled by the robust 40% brain penetration of ALZ-801 compared to an approximately 1% brain penetration of plaque-clearing anti-amyloid antibodies. As p-tau$_{181}$ is primarily of brain origin and is actively cleared from brain

into plasma, the significant lowering of p-tau$_{181}$ in response to ALZ-801 treatment validates the drug's target engagement and mechanism of action in the brain," said John Hey, PhD, Chief Scientific Officer of Alzheon. "To put these effects into context, trials with currently approved anti-amyloid antibodies showed a 24-32% reduction in cognitive decline over 1.5 years, while patients treated with ALZ-801 demonstrated cognitive gain from baseline status and maintained their cognitive skills through and beyond same time period. These well-differentiated results position ALZ-801 to potentially become the first oral agent that can slow or even stop and prevent Alzheimer's pathology in patients and healthy individuals at risk for the disease."

ALZ-801 treatment demonstrated significant correlations at Week 104 between effects on volumetric MRI outcomes and 3 cognitive scales, including the Mini-Mental Status Examination (MMSE), suggesting that cognitive gain from baseline status and maintenance of cognitive skills are a result of preservation of brain structures from neurodegeneration and atrophy:

- Hippocampal volume versus RAVLT Total Score: r=0.44, p=0.0002
- Hippocampal volume versus MMSE: r=0.43, p=0.0003
- Hippocampal volume versus DSST: r=0.38, p=0.002
- Cortical thickness versus RAVLT Total Score: r=0.35, p=0.004
- Cortical thickness versus MMSE: r=0.58, p<0.0001
- Cortical thickness versus DSST: r=0.55, p<0.0001

Consistent with the prior safety database of over 2,800 AD patients, ALZ-801 demonstrated a favorable safety profile in the Phase 2 trial, showing no events of vasogenic brain edema (amyloid-related imaging abnormalities, or ARIA) in APOE4 carriers. Common adverse events experienced in more than 10% of participants were COVID infection, mild nausea, and decreased appetite.

"These positive results represent the latest evidence supporting the promise of ALZ-801, expanding upon other key discoveries made by Alzheon scientists over the past decade. The significant effect on plasma p-tau$_{181}$, combined with hippocampus volume preservation and clinical stabilization after 24 months of treatment, supports the disease modifying action of ALZ-801 in patients with Alzheimer's disease," said Susan Abushakra, MD, Chief Medical Officer of Alzheon. "We have developed a differentiated agent in terms of its mechanism of action, which acts upstream on the same pathway as the currently approved anti-amyloid antibodies and that translates to promising and meaningful efficacy, as well as decrease in brain atrophy, easy oral administration and a favorable safety profile that obviates the need for frequent monitoring for brain edema and microhemorrhage. ALZ-801 tablet is well positioned to become the first oral disease-modifying AD treatment approved for slowing and even halting cognitive decline, and we are very encouraged by these results and the potential for a life-changing impact on the lives of Alzheimer's patients and their families."

Alzheon is pioneering a precision medicine approach in Alzheimer's with the APOLLOE4 Phase 3 trial evaluating ALZ-801 effects in homozygous APOE4/4 AD patients with Early AD. Trial incorporates neurodegeneration biomarkers to track patient benefit – levels of p-tau$_{181}$ and beta

amyloid in plasma and cerebrospinal fluid, hippocampal volume, and other volumetric brain measures, along with the gold-standard primary clinical endpoint, ADAS-Cog13 (Alzheimer's Disease Assessment Scale-Cognitive Subscale). The fully enrolled trial with 325 participants is supported by the National Institute on Aging in the form of a $51M grant, and topline data is expected in the third quarter of 2024.

About ALZ-801

ALZ-801 (valiltramiprosate) is an investigational oral agent in Phase 3 development as a potentially disease modifying treatment for AD.[1,3] It blocks the formation of neurotoxic soluble beta amyloid oligomers causing cognitive decline in Alzheimer's patients. In mechanism of action studies, ALZ-801 has been shown to fully inhibit the formation of neurotoxic soluble beta amyloid oligomers at the Phase 3 clinical dose.[5,6] ALZ-801 acts through a novel enveloping molecular mechanism of action to fully block formation of neurotoxic soluble amyloid oligomers in the human brain[7] associated with the onset of cognitive symptoms and progression of AD.[1–4] ALZ-801 received Fast Track designation from the U.S. Food and Drug Administration in 2017. The clinical data for ALZ-801 and Alzheon's safety database indicate a favorable safety profile.[5–7,9] The initial Phase 3 program for ALZ-801 is focusing on Early AD patients with the APOE4/4 genotype, with future expansion to AD treatment and prevention in patients carrying one copy of the APOE4 gene and noncarriers.[1–4]

ALZ-801 Phase 2 Biomarker Trial

Biomarker Effects of ALZ-801 in APOE4 Carriers With Early Alzheimer's Disease (NCT04693520): This ongoing trial is 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 includes evaluation of clinical efficacy, safety, tolerability, and pharmacokinetic profile of ALZ-801 over 104 weeks of treatment. An ongoing long-term extension of the trial evaluates ALZ-801 for an additional 52 weeks of treatment for a total of 156 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.

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 an oral agent in Phase 3 development as a potentially

disease modifying treatment for AD. ALZ-801 is an oral small molecule that fully blocks formation of neurotoxic soluble amyloid oligomers in the brain. 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: *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.

[2] 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.

[3] 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.

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

[5] 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.

[6] 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.

[7] 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.

[8] 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.

[9] 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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