Alzheon to Present Baseline Imaging Characteristics from Ongoing APOLLOE4 Phase 3 Trial of Oral Tablet ALZ-801 (Valiltramiprosate) and Positive Biomarker/Clinical Correlations from Phase 2 Biomarker Study at Alzheimer's Association International Conference in Amsterdam

Alzheimer's Disease (AD) Patients with APOE4/4 Homozygous Genotype Show High Prevalence of Cerebral Amyloid Angiopathy (CAA) Lesions at Baseline

CAA Pathology Increases Risk of Treatment-Induced Brain Edema and Hemorrhage with Anti-Amyloid Antibodies in AD Patients with APOE4 Genotype

Reduction of Hippocampal Atrophy and Lateral Ventricle Enlargement Correlates with Clinical Benefit of ALZ-801 in APOE4 Carriers with Early AD

Data Further Supports Differentiated Profile and Unique Mechanism of Action of ALZ-801 as Potentially First Oral Disease Modifying Therapy in Alzheimer's

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

FRAMINGHAM, Mass., July 11, 2023 — 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 that it will be presenting baseline imaging characteristics from its ongoing APOLLOE4 Phase 3 clinical trial and new correlation analyses from the Phase 2 biomarker study evaluating ALZ-801 oral tablet at the upcoming Alzheimer's Association International Conference, to be held from July 16 – 20, 2023 in Amsterdam, Netherlands.

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 potential for robust clinical efficacy in the highest-risk Alzheimer's

population – patients with two copies of the apolipoprotein ε4 allele (APOE4/4 homozygotes), and favorable safety with no increased risk of brain vasogenic edema. This population is the focus of Alzheon's pivotal Phase 3 APOLLOE4 trial, which is now fully enrolled and will be completed in in the third quarter of 2024.

"ALZ-801 is potentially two years from a U.S. commercial launch as 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," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon. "With our pioneering development program, we have set out to first address the urgent need in the most fragile APOE4/4 population, and the recent Phase 3 results from trials evaluating anti-amyloid antibodies further highlight the safety risks in patients carrying the APOE4 genotype. This limitation was also emphasized by the Black Box Warning for this class of drugs, showing how prescient our development focus has been. New data and analyses continue to support our precision medicine approach that has the potential to remarkably simplify the patient journey with the well-differentiated efficacy profile of our ALZ-801 tablet, combined with favorable safety, showing no increase in vasogenic edema."

Alzheon Chief Medical Officer, Susan Abushakra, MD, is the lead author on a poster that will be presented on Sunday, July 16, 2023, from 8:45 a.m. to 4:15 p.m. CEST, during P1-18 Developing Topics: Drug Development session, titled: *Prevalence of Cerebral Microhemorrhages and Cortical Superficial Siderosis in APOE4/4 Homozygotes with Early Alzheimer's Disease: Baseline Findings from APOLLOE4 Phase 3 Trial of Oral ALZ-801 in APOE4/4 Homozygotes*.

Imaging findings of subjects enrolled in the APOLLOE4 Phase 3 trial showed that APOE4/4 homozygotes with Early AD exhibit a high rate of cerebral amyloid angiopathy (CAA)-related lesions at baseline, making them more susceptible to treatment-induced brain edema and microhemorrhage shown on the magnetic resonance imaging (MRI) as amyloid related imaging abnormalities (ARIA). Approximately 32% of subjects presented with at least one lobar microhemorrhage (MH), including 9% with greater than four MH and 9% with superficial siderosis. Occipital and frontal lobes were the most common locations of these CAA lesions.

"High prevalence of CAA-related lesions in APOE4/4 Alzheimer's patients is consistent with the emerging safety risks of plaque-clearing antibodies in large pivotal AD trials, showing how helpful oral ALZ-801 treatment could be even just from the safety standpoint in APOE4 patients, who represent 65-70% of Alzheimer's population," said Dr. Abushakra. "APOE4/4 individuals have a high burden of aggregated amyloid plaque in brain vessels, which leads to the CAA lesions seen on MRI scans, and this pathology contributes to an increased risk of developing brain edema and bleeds when treated with anti-amyloid antibodies. The unique upstream mechanism of action of ALZ-801 has demonstrated the ability to prevent the formation of the soluble neurotoxic oligomers, while avoiding the breakdown of amyloid plaque in blood vessels, and ongoing safety surveillance in our clinical trials continues to show no increase in brain edema and bleeds in APOE4/4 homozygous AD patients, who are at the highest risk of symptomatic ARIA with anti-amyloid antibodies."

ALZ-801 tablet is currently being evaluated in two clinical trials in Early AD subjects: the 84-patient Phase 2 biomarker study in APOE4 carriers, including 31 APOE4/4 homozygotes, and the fully enrolled pivotal APOLLOE4 Phase 3 study in 325 APOE4/4 homozygotes. The 24-month Phase 2 biomarker trial will be completed in the third quarter of 2023, and the topline of 18-month APOLLOE4 Phase 3 trial is expected in the third quarter of 2024, with planned NDA filing shortly thereafter and commercial launch in 2025.

Alzheon Chief Scientific Officer, John Hey, PhD, will give a poster presentation, on Sunday, July 16, 2023, from 8:45 a.m. to 4:15 p.m. CEST during P1-18 Developing Topics: Drug Development session, titled: *Reduction of Hippocampal Atrophy and Lateral Ventricle Enlargement Correlate with Clinical Benefits in APOE4 Carriers with Early AD: 1-Year Results from a Phase 2 Biomarker Study with Oral Anti-Amyloid Oligomer Inhibitor ALZ-801/Valiltramiprosate*.

The modified intent to treat population of Phase 2 trial included 84 subjects, with 75 completing 12 months of treatment. The mean age was 69 years, with 51% female, and a mean MMSE of 26.0. Approximately 70% of patients were in the MCI stage and 30% were in the Mild AD stage. Significant plasma p-tau$_{181}$ reduction started at 13 weeks of treatment and reached 41% at 52 weeks (p=0.016), with a significant reduction in plasma Aβ42 and Aβ40 at 52 weeks (-5%, p=0.002, p=0.005 respectively). Hippocampal atrophy was reduced by approximately 20% following 12 months of treatment compared to matched Alzheimer's Disease Neuroimaging Initiative external controls. Composite cognitive Z-score improved significantly at 13 and 26 weeks, remaining above baseline at 52 weeks. Common adverse events were mild nausea and COVID infection, with no drug-related serious events or ARIA-E.

"Phase 2 study results provide compelling support for the disease modifying effect of ALZ-801 tablet in APOE4 carriers, as well as the unique molecular mechanism of action that blocks misfolding of beta amyloid monomers and the subsequent aggregation into neurotoxic amyloid oligomers. By preventing this key initial key step in the amyloid aggregation cascade, ALZ-801 significantly attenuates brain neurodegeneration," said Dr. Hey. "This beneficial action is manifested by the significant reduction in brain atrophy, as well as the rapid and sustained reduction in plasma p-tau$_{181}$, the leading biomarker of AD neurodegeneration. The greater reduction on the p-tau$_{181}$ biomarker in plasma compared to plaque-clearing anti-amyloid antibodies, combined with the preservation of brain hippocampal volume and positive correlations of these biomarkers with cognitive benefits, highlight the potential for efficacy of ALZ-801 in APOE4 carriers, who represent two thirds of Alzheimer's patients. We look forward to communicating the final 24-month data from our Phase 2 study later in 2023."

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] 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 APOLLOE4 Phase 3 Study

An Efficacy and Safety Study of ALZ-801 in APOE4/4 Early Alzheimer's Disease Subjects (NCT04770220): This ongoing study 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 the APOE4/4 genotype, 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 Phase 2 Biomarker Study

Biomarker Effects of ALZ-801 in APOE4 Carriers With Early Alzheimer's Disease (NCT04693520): This ongoing study 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 study also includes evaluation of clinical efficacy, safety, tolerability, and pharmacokinetic profile of ALZ-801 over 104 weeks of treatment.

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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