Alzheon to Present Baseline Imaging Characteristics from Ongoing APOLLOE4 Phase 3 Trial of Oral Tablet ALZ-801 (Valiltramiprosate) and Results of Phase 2 Biomarker Study at American Academy of Neurology Conference in Boston

Alzheimer's Disease (AD) Patients with APOE4/4 Homozygous Genotype Show More Frequent 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

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

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

FRAMINGHAM, Mass., April 18, 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 ongoing APOLLOE4 Phase 3 clinical trial and 12-month results from the Phase 2 biomarker study evaluating ALZ-801 oral tablet at the upcoming American Academy of Neurology (AAN) Conference to be held from April 22 – April 27, 2023 in Boston, Massachusetts.

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 mid-2024.

"Preventing oligomer formation with an oral tablet is a simplified approach to disease modification in Alzheimer's and we are potentially two years from a commercial launch of ALZ-801 in the U.S.," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon. "Our well-differentiated efficacy results combined with a favorable safety profile, showing no events of vasogenic edema, 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."

Alzheon Chief Medical Officer, Susan Abushakra, MD, will give a poster presentation at the AAN conference titled: *Prevalence of Amyloid-Related Imaging Abnormalities in APOE4/4 Homozygotes with Early Alzheimer's Disease: Baseline Findings from Ongoing Clinical Trials of Oral Anti-Amyloid Agent ALZ-801 (Valiltramiprosate)*, on April 24, 2023, from 11:45 a.m. to 12:45 p.m. EST during Poster Session 5.

Imaging findings of subjects enrolled in pivotal APOLLOE4 Phase 3 trial showed that this patient population exhibits a high rate of cerebral amyloid angiopathy (CAA)-related lesions at baseline, making them more susceptible to treatment-induced amyloid related imaging abnormalities (ARIA) lesions that represent brain edema and microhemorrhage. 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 CAA-related lesions.

"Our findings are consistent with the evolving scientific understanding of Alzheimer's pathology in APOE4 carriers. These individuals frequently present with CAA-like lesions and have a high burden of aggregated amyloid in the vessel walls. When treated with anti-amyloid antibodies that activate microglia and breakdown amyloid plaque, these subjects can develop inflammation in these small vessels, which leads to brain swelling and small bleeds," said Dr. Abushakra. "In contrast, the unique upstream mechanism of ALZ-801 has demonstrated the ability to prevent formation of the neurotoxic oligomers early in the amyloid cascade, without actively breaking down amyloid plaque or inducing inflammation in blood vessels. Our ongoing safety surveillance continues to show no increased risk for brain edema and bleeds in the ongoing Phase 2 and 3 studies in Alzheimer's disease subjects treated with oral ALZ-801."

ALZ-801 is currently being evaluated in two clinical trials in early AD subjects: an 84-patient Phase 2 biomarker study comprising APOE4 carriers, including 31 APOE4/4 homozygotes, and a 325-patient pivotal Phase 3 study comprising APOE4/4 homozygotes. The Phase 2 biomarker trial will be completed in mid-2023, and the APOLLOE4 trial will read out in mid-2024 with a planned NDA filing the same year and expected commercial launch in 2025.

Alzheon Chief Scientific Officer, John Hey, PhD, will give a podium presentation at the AAN conference titled: *Effects of ALZ-801, an Oral Amyloid Oligomer Inhibitor, on Biomarkers of Alzheimer's Disease (AD): 12-Month Results of Phase 2 Biomarker Study in Early AD*, on April 25, 2023, from 2:12 - 2:24 p.m. EST during Session S26.

The modified intent to treat (mITT) population of Phase 2 trial included 84 subjects, with 75 completing 12 months of treatment. The mean age of the subjects was 69 years, with 51% female, having a mean MMSE of 26.0. Approximately 70% of patients were in MCI stage and 30% were in 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 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 (ADNI) 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.

"The 12-month results of our Phase 2 trial support the finding that ALZ-801 blocks misfolding of amyloid monomers and subsequent formation of neurotoxic amyloid oligomers, the key initial step in the amyloid aggregation cascade that leads to a rapid and sustained reduction of brain neurodegeneration as measured by plasma p-tau$_{181}$. The several-fold greater reduction on the p-tau$_{181}$ biomarker in plasma compared to plaque-clearing anti-amyloid antibodies, combined with preservation of brain hippocampal volume and their positive correlations with cognitive benefits, further validate the disease modifying effects of ALZ-801 in Alzheimer's patients," said Dr. Hey. "Phase 2 study results provide compelling evidence for potential efficacy of ALZ-801 in APOE4 carriers with Alzheimer's disease, who represent two thirds of Alzheimer's patients. These data also highlight the potential safety and efficacy advantages of ALZ-801 compared to plaque-clearing antibodies, while offering a simplified patient journey towards an effective treatment. 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 $47 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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