



Alzheon Announces First Patient Dosed in APOLLOE4 Phase 3 Trial of Oral ALZ-801 in Patients with Early Alzheimer’s Disease

Study to Confirm ALZ-801 Effects on Cognition and Function in High-Risk Patients with APOE4/4 Genotype

Unprecedented Array of Cutting-Edge Fluid and Imaging Biomarkers to Assess Impact of ALZ-801 on Alzheimer’s Pathology

FRAMINGHAM, Mass., June 4, 2021 — [Alzheon, Inc.](#), a clinical-stage biopharmaceutical company focused on developing new medicines for patients suffering from Alzheimer’s disease (AD) and other neurodegenerative disorders, today announced the dosing of the first patient in its APOLLOE4 Phase 3 study evaluating the efficacy and safety of ALZ-801 in Early AD patients carrying two copies of the $\epsilon 4$ allele of the apolipoprotein E gene (APOE4/4 homozygotes). AD patients with this genetic profile present with an early onset and rapid progression of the disease and are responsive to drug agents that remove or inhibit pathogenic amyloid oligomers. ALZ-801 is an oral treatment that has been shown in preclinical mechanistic studies to fully inhibit the formation of neurotoxic soluble beta amyloid oligomers at the Phase 3 clinical dose.

APOLLOE4 is the only Phase 3 trial evaluating an oral anti-amyloid treatment and applying a precision medicine approach to disease-modification in AD. The APOLLOE4 study is supported by a \$47 million [grant from the National Institute on Aging](#) (NIA). The primary objective of the APOLLOE4 study is to measure the impact of ALZ-801 on cognition using the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog). Secondary endpoints include assessments of function, ability to perform daily activities, and neuropsychiatric symptoms. The study will also evaluate ALZ-801’s effects on fluid and imaging biomarkers shown to be sensitive early markers of AD progression and neuroinflammation.

“We have designed this confirmatory Phase 3 trial in an unprecedented way by applying a precision medicine approach, focusing initially on high-risk patients with the APOE4/4 genotype shown to respond to anti-amyloid agents, and incorporating state-of-the-art fluid and imaging biomarkers. By fully blocking the formation of neurotoxic amyloid oligomers in brain, but without interaction with amyloid plaques, the APOLLOE4 trial may also provide definitive proof of the central role of amyloid oligomers in the initiation and progression of AD,” said Martin Tolar, MD, PhD, Alzheon Founder, President and Chief Executive Officer. “Our goal is to build the strongest data package to evaluate the therapeutic profile of ALZ-801 and support regulatory approval. In

this first indication alone, we have an opportunity to provide a safe and effective treatment to more than a million Alzheimer's patients, and open a path to treatment for the remaining Alzheimer's populations, as well as healthy people at high risk for the disease."

The APOLLOE4 randomized, double-blind, placebo-controlled trial will enroll 300 APOE4/4 homozygotes with Early AD at approximately 85 sites in the United States, Canada, and Europe. Recent findings from clinical trials with anti-amyloid agents provide strong evidence that soluble amyloid oligomers are neurotoxic upstream drivers of AD pathology, leading to progressive worsening in tau pathology and neuronal injury markers in cerebrospinal fluid (CSF) of AD patients.

"The APOLLOE4 trial, combined with the data from Alzheon's ALZ-801 Phase 2 biomarker study that is currently underway, will provide important insights into the pathogenesis of Alzheimer's disease and offer a new treatment paradigm in Alzheimer's therapeutics," said Anton Porsteinsson, MD, the William B. and Sheila Konar Professor of Psychiatry, Neurology, Neuroscience, and Medicine, Director of Alzheimer's Disease Care, Research and Education Program at the University of Rochester School of Medicine and Dentistry, and member of Alzheon's Clinical Steering Committee. "Because ALZ-801 is an oral treatment that has been shown to fully block formation of neurotoxic amyloid oligomers, it could be used as a monotherapy or as a long-term maintenance treatment in combination with, or following, a treatment with monoclonal antibodies, which remove amyloid plaques from the brain."

AD patients with the APOE4/4 genotype will be enrolled in the APOLLOE4 Phase 3 trial into either placebo or active treatment arms, each including 150 patients. Patients will receive 265 mg of ALZ-801 or matching placebo tablets twice daily for 78 weeks. Frequent cognitive tests, functional assessments, and volumetric magnetic resonance imaging will be performed, and all patients will have plasma biomarker assessments. A subgroup of patients will also provide CSF samples for biomarker testing at three timepoints during the trial. Correlation of clinical efficacy to biomarker effects may allow the use of these biomarkers as surrogate outcomes in future studies in other AD populations, and in prevention studies in pre-symptomatic patients.

"The APOLLOE4 trial will evaluate the efficacy and long-term safety of ALZ-801, and we expect it to confirm the previously reported efficacy in APOE4/4 homozygous AD patients and add to the large safety database from the previous tramiprosate AD trials. Tramiprosate, the active agent in ALZ-801, showed favorable safety in more than 3,000 patients, with no cases of vasogenic edema reported in AD studies. This profile provides an advantage over other late-stage amyloid antibodies, which are associated with increased risks of brain edema and small bleeds and are administered as intravenous infusions that present logistical challenges," said Susan Abushakra, MD, Alzheon's Chief Medical Officer and the Principal Investigator for the NIA grant supporting the APOLLOE4 study.

To learn more about the Phase 3 trial, please visit clinicaltrials.gov. Individuals interested in enrolling in the study can inquire by contacting clinicaltrialsinfo@alzheon.com.

About ALZ-801

An oral anti-amyloid drug, [ALZ-801](#) is an optimized prodrug of tramiprosate that has shown promising results in analyses of Phase 3 clinical data,^{6,8} and has a novel anti-amyloid oligomer mechanism of action.^{4,7} ALZ-801 received Fast Track designation from the U.S. Food and Drug Administration in 2017. The clinical data for ALZ-801 and its active agent, tramiprosate, indicate long-term clinical efficacy in AD patients with the APOE4 genotype and a favorable safety profile.^{4,6,8} ALZ-801 acts through a novel [enveloping molecular mechanism of action](#) to fully block formation of neurotoxic soluble amyloid oligomers⁶ associated with the onset of cognitive symptoms and progression of AD.^{2,3} The cognitive improvements observed in the tramiprosate Phase 3 studies may also be attributed in part to the therapeutic effects of 3-sulfopropanoic acid (3-SPA), [an endogenous anti-oligomer substance in the human brain discovered by Alzheon scientists](#) that, like tramiprosate, inhibits formation of toxic amyloid oligomers.⁴ 3-SPA is the primary metabolite of ALZ-801 and its discovery helps explain the beneficial pharmaceutical attributes of ALZ-801, including favorable safety profile, high selectivity for amyloid, and excellent brain penetration. ALZ-801 treatment increases levels of 3-SPA in the brain and augments the body's natural mechanism to inhibit formation of toxic amyloid oligomers.^{4,5} The initial [Phase 3 program for ALZ-801](#) will focus on Early AD patients with the APOE4/4 genotype, with future expansion to investigate ALZ-801 for prevention of Alzheimer's onset and in patients carrying only one copy of the APOE4 gene.^{1,2,3}

About Alzheon

[Alzheon, Inc.](#) is committed to developing innovative medicines by directly addressing the underlying pathology of devastating neurodegenerative disorders. Our lead Alzheimer's clinical candidate, [ALZ-801](#), is an oral small molecule prodrug of tramiprosate that fully blocks formation of neurotoxic soluble amyloid oligomers in the brain. ALZ-801 is an easy-to-take tablet that builds on the safety and efficacy profile of its active compound tramiprosate, which has been evaluated in clinical trials involving over 2,000 Alzheimer's patients. Our clinical expertise and technology platform are focused on developing drug candidates using a [precision medicine approach](#) based on individual genetic and biological information to advance therapies with the greatest impact for patients.

Alzheon Scientific Publications

¹ 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.

² 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.

³ Tolar M, et al: [The Path Forward in Alzheimer's Disease Therapeutics: Reevaluating the Amyloid Cascade Hypothesis, *Alzheimer's & Dementia*](#), 2019; 1-8.

⁴ 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.

⁵ 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.

⁶ 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.

⁷ Kocis P, et al: [Elucidating the A642 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.

⁸ 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.

Media Contact

Zoia Alexanian

Tager & Co.

609.454.1674

zalex@tagerco.com