Alzheon Announces Early Completion of Enrollment of APOLLOE4 Phase 3 Clinical Trial Evaluating Oral ALZ-801 (Valiltramiprosate) in APOE4/4 Homozygotes with Early Alzheimer's Disease

Pivotal Phase 3 Trial Completed Enrollment Ahead of Schedule Enabling Topline Data Readout and NDA Filing in 2024

Safety Profile in ALZ-801 Studies Remains Favorable and Consistent with Prior Data in Over 2,000 AD Patients, with no Evidence of Vasogenic Brain Edema

ALZ-801 Tablet Inhibits Formation of Soluble Toxic Amyloid Aggregates in Brain and Acts Upstream from All Late-Stage Amyloid Targeting Treatments

ALZ-801 Has Potential to Become the First Oral Agent to Slow and Prevent Alzheimer's Pathology in Patients and Healthy Individuals at Risk for the Disease

FRAMINGHAM, Mass., December 6, 2022 — 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 has achieved the enrollment target of 325 patients in its pivotal APOLLOE4 Phase 3 trial evaluating oral ALZ-801 in Early AD patients, who carry two copies of the ε4 allele of apolipoprotein E gene (APOE4/4 homozygotes). These patients represent approximately 15% of all AD patients, have an earlier onset of AD and higher risk of rapid disease progression, and carry a high burden of neurotoxic soluble beta amyloid oligomers.

ALZ-801 (valiltramiprosate) is an oral investigational agent in Phase 3 development as a potentially disease modifying treatment for AD that blocks formation of the neurotoxic soluble beta amyloid oligomers causing cognitive decline in Alzheimer's patients. In mechanism of action studies, ALZ-801 fully inhibited the formation of amyloid oligomers at the Phase 3 clinical dose. ALZ-801 has shown potential for robust efficacy in the highest-risk Alzheimer's population of APOE4/4 homozygotes, and favorable safety with no events of the brain vasogenic edema seen in trials with plaque-clearing antibodies.

"The APOLLOE4 study will support potential commercial launch of ALZ-801 tablet in 2025, and our ability to complete enrollment in a groundbreaking Phase 3 trial ahead of schedule reflects the desire among Alzheimer's patients and their caregivers for a safe, effective, and convenient oral treatment," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon. "The recent announcement of industry-leading disease modifying effects from our Phase 2 biomarker trial of oral ALZ-801 in Alzheimer's patients provided further validation of Alzheon's approach in blocking formation of amyloid oligomers and attracted enthusiastic investor support. This important milestone will accelerate development of ALZ-801 to potentially become the first oral agent that can slow and prevent Alzheimer's pathology in all patients and healthy individuals at risk for the disease."

Alzheon has pioneered precision medicine in AD by targeting neurotoxic amyloid oligomers and has developed a well-differentiated solution to both treatment and prevention of Alzheimer's with a broad platform of small molecules, which act upstream on the same pathway as anti-amyloid antibodies. These oral agents prevent the formation of neurotoxic soluble amyloid oligomers without disrupting the insoluble plaque deposits in brain tissue and small vessels, thereby avoiding the vascular complications of brain edema and microbleeds seen with infusions of plaque-clearing antibodies. Alzheon's lead investigational product, ALZ-801, is a first-in-class oral drug with a favorable safety profile that may not only slow, but also arrest the progression of Alzheimer's.

"The Alzheon team and our clinical trial sites worked incredibly hard and effectively to initiate and find subjects for the APOLLOE4 study," said Aidan Power, MB, MSc, MRCPsych, Chief Development Officer of Alzheon. "Despite all the challenges during the COVID pandemic, we were able to beat our target date for full enrollment and exceed the initial enrollment target size of the study. Trials with plaque-clearing antibodies continue to support Alzheon science of targeting neurotoxic soluble aggregates of beta amyloid, and our recent positive Phase 2 results represent the latest evidence confirming the promise of ALZ-801. We are excited to announce this important milestone for our ALZ-801 development program and would like to thank the patients and caregivers who are participating in the trial. Future studies by Alzheon will broaden our target patient population to include Early AD subjects with just one copy of the APOE4 gene and pursue prevention of Alzheimer's disease in carriers of the APOE4 risk gene."

With support from the National Institute on Aging in the form of a $47M grant to fund the APOLLOE4 Phase 3 study with ALZ-801, Alzheon's drug candidate is well positioned to become one of the first disease-modifying treatments approved for slowing and even preventing cognitive decline in Alzheimer's patients. The APOLLOE4 Phase 3 trial has recruited the homozygous APOE4/4 AD patients at 93 clinical sites across the US, Canada, UK, Iceland, France, Spain, Germany, Czech Republic, and Netherlands. This pivotal Phase 3 study incorporates the gold-standard primary clinical endpoint, ADAS-Cog 13 (Alzheimer's Disease Assessment Scale – Cognitive Subscale), along with CDR-SB (Clinical Dementia Rating Scale – Sum of Boxes), the latest biomarker and volumetric MRI measures to track patient benefit, including plasma levels of p-tau$_{181}$ and beta amyloid isoforms, as well as hippocampal volume, and other volumetric brain measures.

“Trials with plaque-clearing antibodies continue to support Alzheon science of targeting neurotoxic soluble aggregates of beta amyloid and I am proud of the Alzheon team, our investigators, and the participants who are contributing to such important data,” said Susan Abushakra, MD, Chief Medical Officer of Alzheon. “Our recent positive results from Phase 2 represent the latest evidence confirming the promise of ALZ-801, extending other key discoveries made by Alzheon scientists over the past 9 years. If the results from our Phase 3 replicate the robust efficacy we have observed in prior studies of APOE4/4 homozygotes with Early AD, then this data, in combination with the large safety database we have in over 2,000 patients, has the potential to enable approval and commercial launch of ALZ-801 in 2025, offering a simplified patient journey towards an effective treatment.”

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 Alzheimer's pathology in subjects with Early AD, who have either the APOE4/4 or APOE3/4 genotypes, who together 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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