New Peer-Reviewed Scientific Publication Describes Study Design and Baseline Characteristics from APOLLOE4 Phase 3 Trial of Oral ALZ-801/Valiltramiprosate in APOE4/4 Homozygous Individuals with Early Alzheimer's Disease

APOLLOE4 is the first interventional AD drug trial focused on APOE4/4 homozygotes, a population enriched with amyloid pathology in brain parenchyma and small vessels – a condition called cerebral amyloid angiopathy

Current FDA approved anti-amyloid antibody AD therapies increase risk of brain edema and microbleeds, which is greatest in APOE4/4 homozygotes – a population with major unmet medical need for an effective and safe treatment

FRAMINGHAM, Mass., Sept., 18 2024 — 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 a new scientific publication describing its APOLLOE4 Phase 3 study, the first Phase 3 trial focused on AD patients carrying two copies of apolipoprotein ε4 allele (APOE4/4 homozygotes), a population with pressing unmet medical need for effective and safe treatments.

The research paper, "APOLLOE4 Phase 3 Study of Oral ALZ-801/Valiltramiprosate in APOE ε4/ε4 Homozygotes with Early Alzheimer's Disease: Trial Design & Baseline Characteristics," was published in the scientific journal *Alzheimer's Dementia Translational Research & Clinical Interventions* and is available at:
https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.12498

"We have taken a precision medicine approach with the design of the APOLLOE4 Phase 3 trial, focusing on the most vulnerable Alzheimer's population – APOE4/4 homozygotes, who have up to 14-fold higher risk of Alzheimer's disease and a decade earlier onset of the symptomatic disease," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon, and the senior author of the publication. "APOE4/4 homozygotes represent approximately 15% of people with Alzheimer's worldwide and there are currently no treatment options for them that can slow the progression of the disease without serious safety concerns. This is our 13th publication, which adds to the growing body of pioneering research from Alzheon in the pursuit of effective and safe treatments for people living with Alzheimer's disease."

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 oligomers at the Phase 3 clinical dose. ALZ-801 has shown both potential for clinical efficacy in the highest-risk and most fragile 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 the pivotal 78-week APOLLOE4 Phase 3 trial, with topline data expected in late 2024.

According to current diagnostic criteria, AD is categorized into preclinical, mild cognitive impairment (MCI), and dementia stages. APOLLOE4 is a Phase 3 randomized, double-blind, placebo-controlled, parallel-arm, multicenter study of 78-week duration, enrolling APOE4/4 individuals at the early symptomatic stages of AD, which include MCI and Mild AD dementia per Alzheimer's Association clinical criteria. After two stages of screening, patients aged 50-80 years, with Mini-Mental State Examination score ≥22, CDR-G=0.5 or 1 and RBANS-delayed memory ≤85, with stable medical conditions and no exclusionary findings on brain MRI were enrolled. A total of 325 subjects were eligible and randomized into either placebo or active arm at 265 mg ALZ-801 administered orally twice daily. There was a dedicated effort in the United States to enroll subjects from underrepresented populations to maximize the diversity, equity, and inclusiveness of the study. Importantly, the study allowed inclusion of subjects with any number of microbleeds and up to 2 siderosis lesions on MRI, markers of underlying cerebral amyloid angiopathy (CAA) that is common in APOE4/4 individuals. Individuals with more than four microbleeds are typically excluded from trials of anti-amyloid antibodies.

The occurrence of neurovascular injuries, termed amyloid-related imaging abnormalities (ARIA), has been observed in patients with FDA-approved anti-amyloid antibody treatments. APOE4/4 homozygous AD patients are at the highest risk of symptomatic and serious ARIA when treated with the approved anti-amyloid antibodies and, therefore, the occurrence of ARIA is an important focus of the APOLLOE4 study.

"With recently published results from the Phase 2 single-arm study of oral ALZ-801 in biomarker-confirmed Early AD subjects that showed significant plasma biomarker effects and no increased ARIA risk in APOE4 carriers over 2 years, the Phase 3 trial is an important next step in evaluating the efficacy and safety profile of ALZ-801", said Susan Abushakra, MD, Chief Medical Officer at Alzheon and the lead author of the publication. "APOE4/4 homozygous AD patients have a pressing need for an effective and safe treatment that avoids the increased risk of serious ARIA and its challenging and burdensome clinical management. An effective and safe oral agent with a simple screening and treatment regimen would be optimal for these patients and their caregivers."

About ALZ-801

ALZ-801/valiltramiprosate is a potential first-in-class, investigational oral agent in Phase 3 development as a potentially disease modifying treatment for AD.[1-5,7,10] ALZ-801 is designed to block the formation of neurotoxic soluble beta amyloid oligomers implicated in cognitive decline

in Alzheimer's patients.[1-5,7,12] In mechanism of action studies, ALZ-801 has fully inhibited the formation of neurotoxic soluble beta amyloid oligomers at the Phase 3 clinical dose.[1,7,10,12] ALZ-801 acts through a novel enveloping molecular mechanism of action to block formation of neurotoxic soluble amyloid oligomers in the human brain[12] associated with the onset and progression of cognitive decline in AD patients.[1,2,5,7,8] ALZ-801 received Fast Track designation from the U.S. Food and Drug Administration in 2017 for Alzheimer's disease. In clinical trials, ALZ-801 has shown potential for robust clinical efficacy and favorable safety results with no increased risk of brain vasogenic edema.[3-8,11,13] The initial Phase 3 program for ALZ-801 is focusing on Early AD patients with two copies of the apolipoprotein ε4 allele (APOE4/4 homozygotes), with potential future program expansion to AD treatment and prevention in patients carrying one copy of the APOE4 gene and noncarriers.[1–8]

ALZ-801 Phase 2 Biomarker Trial

Biomarker Effects of ALZ-801 in APOE4 Carriers with Early Alzheimer's Disease (NCT04693520): This trial was 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 included evaluation of clinical efficacy, safety, tolerability, and pharmacokinetic profile of ALZ-801 over 104 weeks of treatment (primary endpoint). An ongoing long-term extension of the trial evaluates the same dose of ALZ-801 for an additional 104 weeks of treatment for a total of 208 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 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 to Alzheon, with Susan Abushakra as the principal investigator.

ALZ-801 APOLLOE4 Long Term Extension Trial (LTE)

An ongoing long-term extension of the trial, APOLLOE4-LTE, evaluates ALZ-801 in subjects who complete the core APOLLOE4 study for an additional 52 weeks of treatment for a total of 130 weeks or 2.5 years over the core and LTE study. This LTE study is currently ongoing in the US, UK and Canada (NCT06304883).

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 a first-in-class oral agent in Phase 3 development as a potentially disease modifying treatment for AD. ALZ-801 is an oral small molecule that has been observed to fully block the formation of neurotoxic soluble amyloid oligomers in preclinical tests.

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]Abushakra S, et al: *APOLLOE4 Phase 3 Study of Oral ALZ-801/Valiltramiprosate in APOE ε4/ε4 Homozygotes with Early Alzheimer's Disease: Trial Design and Baseline Characteristics,* ***Alzheimer's & Dementia*** 2024; 10: e12498

[2]Tolar M, et al: *The Single Toxin Origin of Alzheimer's Disease and Other Neurodegenerative Disorders Enables Targeted Approach to Treatment and Prevention,* **International Journal of Molecular Sciences,** 2024; 25, 2727.

[3]Hey J, et al: *Analysis of Cerebrospinal Fluid, Plasma βAmyloid Biomarkers, and Cognition from a 2Year Phase 2 Trial Evaluating Oral ALZ801/Valiltramiprosate in APOE4 Carriers with Early Alzheimer's Disease Using Quantitative Systems Pharmacology Model,* **Drugs** 2024.

[4]Hey J, et al: *Effects of Oral ALZ801/Valiltramiprosate on Plasma Biomarkers, Brain Hippocampal Volume, and Cognition: Results of 2-Year Single Arm, Open Label, Phase 2 Trial in APOE4 Carriers with Early Alzheimer's Disease,* **Drugs** 2024. 2024.

[5]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.

[6]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.

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[11]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.

[12]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.

[13]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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