Alzheon Announces First Patient Dosed in Long-Term Extension of APOLLOE4 Phase 3 Trial of Oral ALZ-801/Valiltramiprosate and Launches 52-Week Extension of Phase 2 Biomarker Trial in Patients with Early Alzheimer's Disease

APOLLOE4 Phase 3 Trial Subjects Who Completed 78 Weeks of Treatment Offered Enrollment in Long-Term Extension Study to Provide Insights into Effect of ALZ-801 on Disease Progression and Additional Safety and Tolerability Data

Phase 2 Biomarker Trial Subjects Who Completed 156 Weeks of Treatment Offered Enrollment in 52-Week Extension to Support Biomarker-Enabled Indication Expansion to Two Thirds of all AD Patients Carrying APOE4 Gene

Array of Cutting-Edge Fluid and Imaging Biomarkers Deployed to Assess Impact of ALZ-801 Tablet on Alzheimer's Pathology

Fully Enrolled Pivotal APOLLOE4 Phase 3 Trial in Early Alzheimer's Disease Patients on Track for Topline Data Readout and Initiation of NDA Submission in 2024

FRAMINGHAM, Mass., April 30, 2024 — 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 the dosing of the first patient in a long-term extension of the ongoing pivotal APOLLOE4 Phase 3 trial of 265 mg oral tablet of ALZ-801/valiltramiprosate, administered twice daily, in Early AD subjects carrying two copies of the ε4 allele of the apolipoprotein E gene (APOE4/4 homozygotes). Early AD includes patients with mild cognitive impairment due to AD (MCI) and mild AD.

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. Oral ALZ-801 has shown both potential for robust clinical efficacy in the highest-risk and most fragile late-onset 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 Alzheon's pivotal 78-week APOLLOE4 Phase 3 trial, which is now fully enrolled with topline data expected in the third quarter of 2024.

"At Alzheon, we always put patients first, so we are pleased to offer subjects in our Alzheimer's studies who have completed the APOLLOE4 Phase 3 trial or the Phase 2 biomarker trial an option to continue ALZ-801 treatment for an extended period of time," said Susan Abushakra, MD, Chief Medical Officer of Alzheon. "Alzheimer's disease is a devastating, fatal illness with limited treatment options, especially for patients with APOE4 genotype, and we recognize the urgent need to provide continued access to ALZ-801 therapy. We are grateful to subjects who have participated in our clinical trials and look forward to generating additional insights into ALZ-801's effects from these long-term extension studies."

The long-term open label extension of the APOLLOE4 Phase 3 trial will continue to evaluate safety and efficacy of ALZ-801 tablet in APOE4/4 homozygous subjects with Early AD. Participants in the APOLLOE4 Phase 3 trial who completed Week 78 of the study and who are still eligible, are offered enrollment in the long-term extension and will be treated with ALZ-801 for 52 weeks, followed by a four-week safety visit after the last dose of ALZ-801. The primary objective of the APOLLOE4 trial 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 look forward to the topline data from the 78-week, randomized, placebo-controlled portion of the APOLLOE4 Phase 3 trial in the second half of this year. We have designed this confirmatory study in an unprecedented way by applying a precision-medicine approach, focusing initially on the high-risk patients with the APOE4/4 genotype, and incorporating state-of-the-art fluid and imaging biomarkers," said Aidan Power, MB, MSc, MRCPsych, Chief Development Officer of Alzheon. "Following the completion of the trial, participants who choose to continue into the long-term extension where all subjects receive active treatment, will help us evaluate long-term effects of ALZ-801/valiltramiprosate on the progression of Alzheimer's disease, as well as generate additional safety and tolerability data."

The Phase 2 biomarker trial in Early AD subjects who have the APOE4/4 or APOE3/4 genotype and test positive for amyloid and tau biomarkers in cerebrospinal fluid (CSF) was designed as a 104-week study, where all subjects receive active treatment of 265 mg oral tablet of ALZ-801, administered twice daily. The objective of the trial is to assess the effects on leading-edge CSF and plasma biomarkers, as well as volumetric magnetic resonance imaging evaluating brain atrophy, shown to be sensitive early markers of AD progression. The study's primary outcome was achieved, showing statistically significant 31% reduction from baseline of plasma p-tau$_{181}$ at 104 weeks. A 52-week long-term extension was initiated last year, and now an additional 52-week extension is enrolling subjects. In addition to safety, assessments of plasma biomarkers

hippocampal volume, cortical thickness, and cognitive effects will be performed at Week 156 and Week 208 in the long-term extension phase.

"The Phase 2 biomarker trial generated compelling data demonstrating that treatment with oral ALZ-801 leads to a sustained reduction in p-tau$_{181}$, a key measure of brain neurodegeneration, as well as slowing of hippocampal atrophy compared to a matched external control arm, and stabilization of cognition for two years," said John Hey, PhD, Chief Scientific Officer of Alzheon. "Given these encouraging results, we are compelled to extend the trial for an additional year, bringing the treatment period to four years for these patients. We believe this extension phase will offer meaningful insights into the correlation of fluid and imaging biomarkers with the progression of Alzheimer's disease, help evaluate disease modifying effects of ALZ-801 tablet and provide further evidence for expanding our treatment to APOE4 carriers representing 65-70% of Alzheimer's patients in a planned Phase 3 trial."

About ALZ-801

ALZ-801/valiltramiprosate is a potential first-in-class, investigational oral disease-modifying therapy in Phase 3 development for the treatment of early Alzheimer's disease. 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 AD 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.

ALZ-801 Phase 2 Biomarker Trial

Biomarker Effects of ALZ-801 in APOE4 Carriers With Early Alzheimer's Disease (NCT04693520): This ongoing 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. An ongoing long-term extension of the trial evaluates 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 ongoing 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. An ongoing long-term extension of the trial evaluates ALZ-801 for an additional 52 weeks of treatment for a total of 130 weeks.

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

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[2] 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.

[3] 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: Translational Research & Clinical Interventions**, 2020; 6: e12117.

[4] 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.

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[6] 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.

[7] 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.

[8] 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.

[9] 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.

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