Alzheon Completes Patient Enrollment in Phase 2 Biomarker Trial of ALZ-801 Oral Tablet in APOE4 Carriers with Alzheimer's Disease

Study Evaluates Biomarker Evidence of Disease Modification in APOE4 Carriers, Who Comprise Two-Thirds of All Alzheimer's Patients

Applies State-of-the-Art Fluid Biomarkers and Array of Clinical Measures to Accelerate Expansion of ALZ-801 Phase 3 Program to All APOE4 Carriers

FRAMINGHAM, Mass., June 23, 2021 — 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 enrollment target of 80 patients for its Phase 2 biomarker study of ALZ-801 in Early AD patients, who carry either one or two copies of the ε4 allele of apolipoprotein E gene (APOE3/4 heterozygotes and APOE4/4 homozygotes, respectively). These patients represent two-thirds 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 is an oral agent in Phase 3 development as a potentially disease modifying treatment for AD. In mechanism of action studies, ALZ-801 has been shown to fully inhibit the formation of neurotoxic soluble amyloid oligomers at the Phase 3 clinical dose. This therapeutic approach has been validated by the FDA's recent accelerated approval of Biogen's anti-amyloid antibody infusion Aduhelm (aducanumab) that established toxic amyloid species as an effective therapeutic target in AD.

The ongoing APOLLOE4 Phase 3 trial (NCT04770220), which began dosing patients earlier this month, is supported by a $47 million grant from the National Institute on Aging. The APOLLOE4 Phase 3 trial is focused on APOE4/4 homozygotes, who constitute approximately 15% of AD patients. The Phase 2 biomarker data will guide the design of future Phase 3 trials in APOE3/4 heterozygotes, increasing the potential patient population of ALZ-801 tablet to include 65-70% of all AD patients.

Originally targeting an enrollment of 40 patients, the Phase 2 study size was doubled to 80 patients to strengthen the statistical power in each of the two APOE4 genotypes for the primary outcome of change from baseline of phosphorylated-tau (p-tau$_{181}$), a key biomarker of AD pathology. The study enlargement has been facilitated by a high demand from patients and

clinicians to participate in the trial, allowing accelerated enrollment across 7 clinical sites in the Czech Republic and Netherlands.

"Our ability to not only meet but double the patient enrollment target in the Phase 2 biomarker trial, and complete enrollment 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, Alzheon Founder, President and Chief Executive Officer. "This ground-breaking biomarker study focusing on a well-defined genetic population is a first of its type — enabling us to apply the newest advances in Alzheimer's fluid biomarkers, and to correlate them with clinical and imaging endpoints, as we build the strongest data package to confirm the disease modifying profile of ALZ-801 and support regulatory approval. In addition, by expanding ALZ-801's target patient population beyond APOE4/4 homozygotes, we have the unique opportunity to go from helping 1.35 million patients in ALZ-801's first indication to potentially benefiting more than 15 million Alzheimer's patients globally. ALZ-801 is a first-in-class Phase 3 oral drug with a favorable safety profile that may not only slow, but also arrest the progression of Alzheimer's, with the advantage of an oral tablet compared to the infusions required for antibody treatments."

The Phase 2 biomarker study (NCT04693520) is evaluating the effects of 265 mg twice daily oral dose of ALZ-801 on fluid biomarkers, imaging, and clinical outcomes over two years of treatment. The study objective is to confirm the disease modifying potential for ALZ-801 in both APOE4/4 and APOE3/4 AD patients by assessing its effects on cerebrospinal fluid and plasma biomarkers of amyloid, tau, neuronal injury and neuroinflammation. The study also evaluates drug effects on brain hippocampal volume using magnetic resonance imaging, and on cognitive and functional outcomes. The first interim data readout is expected in 2022.

"We are excited to announce this important milestone for our ALZ-801 development program. This cutting-edge study is designed to investigate an extensive battery of leading-edge fluid and imaging biomarkers, which can provide critical insights on how these biomarkers are temporally linked to the hallmarks of Alzheimer's disease progression," said John Hey, PhD, Chief Scientific Officer of Alzheon. "The knowledge gained from this study is expected to unveil a new understanding on how we can use plasma or cerebrospinal fluid biomarkers to tailor treatment for individual patients based on their genetic and biomarker profiles. Importantly, this study also provides an opportunity to test our amyloid oligomer assay, and correlate effects on amyloid oligomers to clinical benefit, which will confirm the anti-oligomer action of oral ALZ-801 in Alzheimer's patients."

About ALZ-801

ALZ-801 is an 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 amyloid oligomers at the Phase 3 clinical dose.[5,6] ALZ-801 is an optimized prodrug of tramiprosate that has shown promising results in analyses of Phase 3 clinical data,[7,9] and has a novel anti-amyloid oligomer mechanism of action.[5,8] 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.[5–7,9] 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] 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 found in the human brain discovered by Alzheon scientists that, like tramiprosate, inhibits formation of toxic amyloid oligomers.[5] 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.[3,5,6] 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.[5,6] 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.[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 one dose of 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 constitute 65-70% of Alzheimer's patients. The study also includes evaluation of clinical efficacy, safety, and tolerability of ALZ-801 over 104 weeks of treatment and will evaluate the extended pharmacokinetic profile of ALZ-801 over 8 hours in 24 subjects after 65 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 devastating neurodegenerative disorders. Our lead Alzheimer's clinical candidate, ALZ-801, is an oral agent in Phase 3 development as a potentially disease modifying treatment for AD. 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 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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