Alzheon Announces Dosing of First Patient in ALZ-801 Phase 2 Biomarker Study in APOE4 Carriers with Early Alzheimer's Disease

Study to Evaluate ALZ-801 Effects on Alzheimer's Biomarkers Associated with Clinical Benefit

Includes Comprehensive Biomarker Assessment to Accelerate Development of ALZ-801 for Alzheimer's Disease Prevention

Facilitates Biomarker-Enabled Indication Expansion for ALZ-801 to Two Thirds of all Alzheimer's Patients Carrying APOE4 Gene

FRAMINGHAM, Mass., October 27, 2020 – 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 initiation of a Phase 2 study evaluating biomarker effects of ALZ-801, an oral treatment blocking formation of neurotoxic soluble amyloid oligomers, in Early AD patients carrying one or two copies of the ε4 allele of the apolipoprotein E (APOE4) gene. AD patients with this genetic profile have a higher risk of rapid disease progression and are responsive to drug agents targeting pathogenic amyloid oligomers.

The primary objective of Phase 2 biomarker study is to assess the effects of 265 mg oral tablet of ALZ-801, administered twice daily for two years, on fluid and imaging biomarkers shown to be sensitive early markers of AD progression. The biomarkers selected for this study have been shown to correlate with clinical benefit in AD patients in trials with amyloid-targeted antibody therapies. This Phase 2 study is the first AD biomarker trial to prospectively evaluate APOE4 carriers using leading-edge cerebrospinal fluid (CSF) and plasma biomarkers, as well as volumetric magnetic resonance imaging (MRI) evaluating brain atrophy. Study evaluations will include a battery of biomarkers that reflect amyloid pathology (beta amyloid 42 and 40), tau pathology (phosphorylated tau protein, or p-tau) and neuronal injury (neurofilament light chain protein, or NfL).

A Biomarker Steering Committee comprised of world-leading AD experts advised on the design of the trial and will oversee its conduct. Committee members include: Kaj Blennow, MD, PhD, Professor and Head of Research on Neurochemical Pathogenesis and Diagnostics at the University of Gothenburg in Sweden; Eric Reiman, MD, PhD, Executive Director of the Banner Alzheimer's Institute and Clinical Director of the Neurogenomics Division at the Translational Genomics Research Institute in Phoenix, Arizona; and Philip Scheltens, MD, Professor of Cognitive Neurology and Director of the Alzheimer Center at Amsterdam University Medical Centers in Netherlands.

"This study will provide important insights into the effects of treatment with oral ALZ-801 in APOE4 carriers, using an extensive set of cutting-edge biomarkers shown to indicate a clinically relevant benefit to patients. Positive biomarker changes would confirm disease modifying effects of ALZ-801 anti-amyloid oligomer therapy and enable the use of plasma biomarkers, such as p-tau and NfL, as surrogate outcome measures for registration trials for ALZ-801, in particular in prevention of Alzheimer's disease," said Dr. Kaj Blennow.

"Recent findings in the Alzheimer's field have shown that soluble amyloid oligomers are directly neurotoxic upstream drivers of the disease and lead to early increases in p-tau and other markers of neuronal injury. Furthermore, APOE4 carriers have been shown to have up to three-fold higher brain levels of soluble amyloid oligomers compared to non-carriers. These factors provide a strong biological rationale for using an anti-oligomer agent, such as ALZ-801, for treatment and prevention in APOE4 carriers, who represent the majority of patients with Alzheimer's disease," said Dr. Philip Scheltens.

Phase 2 Biomarker Study Expands NIA-Backed ALZ-801 Pivotal Phase 3 Program

Recently, Alzheon was awarded a $47 million grant from the National Institute on Aging (NIA) to advance the Phase 3 study of ALZ-801 in high risk APOE4/4 homozygous AD patients, starting in 1Q 2021. The addition of this Phase 2 biomarker trial will provide first-ever insights into the biomarker profile of a broader population of APOE4 carriers who receive ALZ-801 treatment, and thereby expand the potential indications for ALZ-801 to approximately two thirds of all Alzheimer's patients.

The Phase 2 biomarker trial is designed to accelerate development of ALZ-801 for prevention of AD in asymptomatic individuals with risk factors, based on their genetic and biomarker profile. ALZ-801 is an oral small molecule, with a favorable safety and tolerability profile more suitable for long-term use in AD treatment and prevention than amyloid-targeted antibodies that require burdensome 1-3 hour bi-weekly or monthly intravenous infusions or subcutaneous injections, as well as MRI safety monitoring for serious adverse events such as brain edema and microbleeds.

"This biomarker study is a key element of our overall Alzheimer's clinical development program for ALZ-801," said Susan Abushakra, MD, Alzheon Chief Medical Officer. "With the urgent need to advance new treatments for a broad population of Alzheimer's patients, a positive biomarker readout will confirm the clinical effects of ALZ-801 in APOE4 carriers. It also opens the exciting possibility of preventive treatment for Alzheimer's, and enables expedited, biomarker-based development of ALZ-801 as a convenient oral pill for patients."

The Phase 2 biomarker trial will initially enroll 40 Early AD patients with one or two copies of the APOE4 gene, at leading clinical research sites in the Czech Republic and the Netherlands. All patients will receive ALZ-801 in 265 mg oral tablets twice daily for two years. Frequent fluid biomarker assessments, volumetric MRI imaging, and cognitive tests will be performed throughout the duration of the trial.

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,[5,7] and has a novel anti-amyloid oligomer mechanism of action.[3,6] 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.[3,5,7] ALZ-801 acts through a novel enveloping molecular mechanism of action to fully block formation of neurotoxic soluble amyloid oligomers[5] associated with the onset of cognitive symptoms and progression of AD.[1,2] 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.[3] 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.[3,4] 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]

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] Tolar 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.

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

[3] Hey 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.

[4] Hey 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.

[5] Abushakra 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.

[6] Kocis 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.

[7] Abushakra 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.

Contact

Kathryn Morris
The Yates Network
914-204-6412
kathryn@theyatesnetwork.com