Alzheon Announces New Research Showing Accelerated Hippocampus Atrophy in APOE4/4 Patients with Early Alzheimer's Disease

Hippocampus Atrophy and Cortical Thinning Correlate with Cognitive Decline and Show Promise as Biomarkers in Alzheimer's Treatment and Prevention Clinical Trials

Hippocampal Volume Included as Key Imaging Endpoint in Ongoing ALZ-801 Biomarker Study and Pivotal Phase 3 Trial of ALZ-801 Starting in 2021

FRAMINGHAM, Mass., December 8, 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 publication of a research paper, "APOE4/4 Homozygotes with Early Alzheimer's Disease Show Accelerated Hippocampal Atrophy and Cortical Thinning that Correlates with Cognitive Decline," in *Alzheimer's & Dementia: Translational Research and Clinical Interventions* journal, available through open access at: https://doi.org/10.1002/trc2.12117.

This publication is the first report of longitudinal hippocampus atrophy rates in AD patients homozygous for the ε4 allele of apolipoprotein E gene (APOE4/4), and their correlation with cognitive decline. The APOE4 gene is the strongest genetic risk factor for sporadic AD, and APOE4/4 homozygotes are at high risk of early onset and faster disease progression. The hippocampus is affected by amyloid oligomer-mediated neurodegeneration early in AD, resulting in atrophy detectable on volumetric magnetic resonance imaging (MRI) scans.

This study provides quantitative analysis of hippocampal volume and cortical thickness in APOE4/4 and APOE3/3 subjects with either Mild Cognitive Impairment (MCI) or Mild AD. Two datasets were analyzed: the Alzheimer's Disease Neuroimaging Initiative, Cohort 1 (ADNI-1) and the placebo arm of the tramiprosate North American Phase 3 trial. Dr. Susan Abushakra, Chief Medical Officer of Alzheon, and the imaging experts from Bioclinica calculated the rates of hippocampal atrophy and cortical thinning over 12 and 24 months, and correlated them to changes in cognitive and functional scores.

Key findings from the study include:

- At baseline, APOE4/4 subjects with MCI were approximately 5 years younger, and had significantly smaller hippocampal volumes and worse cognitive scores than APOE3/3 subjects.
- APOE4/4 subjects with MCI and Mild AD (collectively called Early AD) showed significantly faster hippocampus atrophy and cortical thinning over 2 years compared to APOE3/3 subjects.

- Atrophy rates of hippocampal volume and cortical thinning were significantly correlated with cognitive decline in MCI subjects, but not in Mild AD.
- Hippocampus atrophy and cortical thinning seem to contribute to cognitive impairments early in the disease process, and may be a harbinger for future cognitive decline.

Among the drug candidates in late stage development for AD, only ALZ-801/tramiprosate has shown significant protection from hippocampal atrophy in Alzheimer's patients. Quantitative analysis of hippocampal volume in the MRI substudy of the tramiprosate North American Phase 3 trial, which included 312 subjects treated for 18 months, showed that that tramiprosate slows hippocampal atrophy in a dose-dependent manner (Gauthier S, et al, 2009).

"Protection of hippocampus against neurodegeneration and atrophy is of particular importance in APOE4/4 individuals, who are at high risk of early disease onset and faster progression," said Dr. Abushakra, the lead author of the publication. "Because these volumetric MRI measures correlate with cognitive decline, they will be used as primary imaging outcomes in the upcoming pivotal Phase 3 trial of ALZ-801. Hippocampal volume measurements may also have utility in AD prevention clinical trials for drug treatments as surrogate outcomes allowing earlier detection of therapeutic efficacy."

Several AD studies have shown that neurotoxic soluble amyloid oligomers are direct upstream drivers of Alzheimer's pathology and trigger early increases in phosphorylated tau protein and other markers of neuronal injury.[1,2] APOE4/4 patients are known to have approximately three-fold higher brain levels of amyloid oligomers compared to APOE4 non-carriers. These factors provide a strong biological rationale for using an anti-oligomer agent, such as oral ALZ-801, to protect against cognitive decline and hippocampal atrophy in APOE4/4 patients at high risk of early disease progression.[4]

Two clinical trials evaluating ALZ-801 in Early AD will assess hippocampal volume and cortical thickness as key imaging outcomes. The first trial is an ongoing Phase 2 biomarker study that will provide first-ever insights into the fluid biomarker profile of a broad population of APOE4 carriers and their response to ALZ-801 treatment. This will support expansion of the potential indications for ALZ-801 to all APOE4 carriers, representing two thirds of all AD patients. The second trial is a Phase 3 study of ALZ-801 in high risk APOE4/4 AD patients that will start in early 2021, supported by a $47 million grant from the National Institute on Aging (NIA) awarded to Alzheon.

"Structural imaging biomarkers, in particular hippocampus volume and cortical thickness, are key elements in the clinical development of our anti-oligomer treatment ALZ-801," said Martin Tolar, MD, PhD, Founder, President and Chief Executive Officer of Alzheon. "With the urgent need for new treatments for a broad population of Alzheimer's patients, data showing preservation of hippocampal volume can support the clinical efficacy of ALZ-801. In addition, because these data allow biomarker-driven development, they can unlock the exciting opportunity for preventive treatment of AD with ALZ-801. As an oral drug, ALZ-801 can become a convenient treatment for healthy individuals at high risk for developing AD symptoms."

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 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.

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

[3] 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.

[4] 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.

[5] 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.

[6] 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.

[7] 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.

Gauthier S, et al: *"Effect of Tramiprosate in Patients with Mild-to-Moderate Alzheimer's Disease: Exploratory Analyses of the MRI Sub-Group of the Alphase Study*." **The Journal of Nutrition, Health & Aging,** 2009; 13(6): 550-557

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