Alzheon to Present New Data from Ongoing Phase 2 Biomarker Trial of ALZ-801 Oral Tablet at Clinical Trials in Alzheimer's Disease (CTAD) Conference

Baseline Data in Early Alzheimer's Disease Shows Significant Differences in CSF Biomarker Profiles Between APOE4/4 Homozygotes and APOE3/4 Heterozygotes Validating Patient Selection for APOLLOE4 Phase 3 Study with ALZ-801 Tablet

Distinct Patterns of Hippocampal Atrophy and Cortical Thinning with Advanced Disease and Age Observed in APOE4/4 Homozygotes and APOE3/4 Heterozygotes

FRAMINGHAM, Mass., November 1, 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 will be presenting two scientific posters at the 14th Annual Clinical Trials on Alzheimer's Disease (CTAD) conference to be held on November 9-12, 2021 in Boston, MA, USA.

At the CTAD conference, Alzheon will provide the first presentation of baseline data from the ongoing Phase 2 biomarker study of oral drug candidate 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). APOE4 genotype, the most important risk factor for Alzheimer's after aging, is associated with a several-fold higher brain burden of amyloid oligomers. ALZ-801 is an oral agent being evaluated in Alzheon's APOLLOE4 Phase 3 trial as a 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.

"The Alzheimer's space has seen tremendous progress over the past year and the CTAD conference comes at the perfect time to reflect on these advancements. At this conference, Alzheon scientists will report novel biomarker data and insights from our Phase 2 study with oral tablet ALZ-801, demonstrating the clear distinction between homozygous and heterozygous APOE4 patients with Early AD. This data helps explain the differential efficacy and safety outcomes in these populations in clinical studies with anti-amyloid agents and validates the selection of homozygous APOE4/4 patient population for the ongoing ALZ-801 APOLLOE4 Phase 3 study," said Martin Tolar, MD, PhD, Alzheon Founder, President and Chief Executive Officer. "Importantly, the Alzheimer's community must also address the two "elephants in our living room"; these are controversial and unanswered issues that are critical to our success as a field:

1) the lack of correlation of amyloid plaque clearance with clinical efficacy, and 2) the impact of apolipoprotein E4 genotype on safety and efficacy of anti-amyloid agents."

Alzheon presentations are included in the poster session theme, Clinical Trials: Biomarkers Including Plasma:

1) Scientific poster #LP8: Hey et al. *Cerebrospinal Fluid Biomarkers in Early Alzheimer's Disease Subjects with APOE4/4 and APOE3/4 Genotypes: Baseline Data from Phase 2 Biomarker Study with Oral Anti-Amyloid Agent ALZ-801*
2) Scientific poster #LP9: Abushakra et al. *Brain Hippocampal Volume and Cortical Thickness in Early Alzheimer's Disease Subjects with APOE4/4 and APOE3/4 Genotypes: Baseline Data from Phase 2 Biomarker Study with Oral Anti-Amyloid Agent ALZ-801*

The Phase 2 study completed enrollment earlier this year and 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 of oral tablet ALZ-801 in APOE4/4 and APOE3/4 patients with Early AD, by assessing its effects on cerebrospinal fluid (CSF) and plasma biomarkers of beta amyloid (Aβ), phosphorylated tau (p-tau), neuronal injury and neuroinflammation. The study also evaluates drug effects on brain hippocampal volume using magnetic resonance imaging (MRI), and on cognitive and functional outcomes.

Alzheon's scientists analyzed baseline CSF, MRI, and clinical data from 131 screened subjects enrolled in the Phase 2 biomarker study evaluating ALZ-801 oral tablet, of which 108 provided baseline CSF samples and 110 provided baseline MRI data included in this analysis.

"Our new biomarker analyses provide important insights into the biology of Alzheimer's and decisively support Alzheon's precision medicine approach for the treatment of Alzheimer's disease," said John A. Hey, PhD, Chief Scientific Officer of Alzheon. "Alzheon's oral tablet ALZ-801 acts on the same pathway as leading anti-amyloid antibodies but works upstream to prevent the formation of toxic amyloid oligomers, without impacting the insoluble plaque. ALZ-801 is, therefore, in a class of its own as a small-molecule oral drug that has shown potential for robust efficacy with a favorable safety profile, by avoiding the vascular complications of brain edema and microbleeds seen with infusions of plaque-clearing anti-amyloid antibodies. The Phase 2 study will bring additional biomarker data readouts in 2022, and the rapidly advancing APOLLOE4 Phase 3 trial positions ALZ-801 tablet to potentially become the first oral, disease-modifying agent for Alzheimer's patients and healthy individuals at risk for the disease."

Analysis of 108 Early AD subjects with one or two copies of the APOE4 gene enrolled in Phase 2 study showed significant baseline differences in CSF biomarker profiles between APOE4/4 homozygotes and APOE3/4 heterozygotes. Almost all homozygotes (>97%) had abnormal p-tau/Aβ42 levels, thereby validating the selection of this patient population for the ALZ-801 APOLLOE4 Phase 3 study focused on the subjects with APOE4/4 genotype. In contrast, one third of APOE3/4 heterozygotes had negative CSF biomarkers, indicating the necessity for PET imaging or fluid biomarkers to identify subjects with AD. These data support the selection of a genetically

defined APOE4/4 AD population enriched in Aβ pathology for the pivotal APOLLOE4 Phase 3 trial of ALZ-801 in Alzheimer's disease.

In cross-sectional analyses of baseline MRI data in 110 Early AD patients, a comparison of APOE4/4 homozygotes versus APOE3/4 heterozygotes showed distinct profiles of hippocampal atrophy and cortical thinning with advanced disease and age. In APOE3/4 heterozygotes, both volumetric measures showed significant and strong correlations with clinical measure Mini-Mental Status Examination, while in APOE4/4 homozygotes this correlation was significant but modest. In addition, in APOE3/4 heterozygotes, cortical thinning appears to be more prominent with advanced disease.

"Baseline CSF and MRI analyses from the ongoing Phase 2 biomarker study with ALZ-801 further support the distinct biological phenotype of Alzheimer's subjects with the APOE4/4 genotype," said Susan Abushakra, MD, Chief Medical Officer of Alzheon. "These data confirm and validate Alzheon's precision medicine approach in the ongoing APOLLOE4 Phase 3 trial with ALZ-801 tablet, which focuses on APOE4/4 homozygotes, who show the highest levels of amyloid pathology and a tight range of phosphorylated tau and beta amyloid ratio. In addition, Phase 2 will inform the selection of imaging and fluid biomarkers for our next Phase 3 trial, in APOE3/4 heterozygotes. We look forward to future Phase 2 readouts to support the product profile of ALZ-801 as a first-in-class drug, which can provide several advantages over the late-stage antibody treatments, in particular the convenience and wide accessibility of an oral tablet, and the favorable safety profile."

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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