Alzheon Reports Industry-Leading Disease Modifying Effects from Phase 2 Biomarker Trial of Oral Tablet ALZ-801 (Valiltramiprosate) in Patients with Early Alzheimer's Disease

29% Reduction in Plasma P-tau$_{181}$, Core Biomarker of Alzheimer's Pathology, Observed after 6 Months Treatment in Carriers of One or Two Copies of APOE4 Gene who Represent Two Thirds of Patients with Disease

Several-Fold Greater Reduction on P-tau$_{181}$ Compared to Anti-Amyloid Antibodies Validates Superior Clinical Benefit from Prior Studies in Alzheimer's Patients

Significant Improvement on Memory Tests Consistent with P-tau$_{181}$ Biomarker Effects to be Further Confirmed in Ongoing APOLLOE4 Phase 3 Trial

Safety Profile in ALZ-801 Studies Remains Favorable and Consistent with Prior Safety Data in 2,000 Patients with No Evidence of Vasogenic Brain Edema

FRAMINGHAM, Mass., February 8, 2022 — 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 reported a clinically relevant and statistically significant plasma biomarker reduction and memory improvement in Alzheimer's patients following 6 months of treatment with oral tablet ALZ-801 (valiltramiprosate) in its Phase 2 biomarker trial.

ALZ-801 is an oral agent in Phase 3 development as a potentially disease modifying treatment for AD that blocks the formation of neurotoxic soluble amyloid oligomers that lead to cognitive decline in Alzheimer's patients. In mechanism of action studies, ALZ-801 has been shown to fully inhibit the formation of amyloid oligomers at the Phase 3 clinical dose. ALZ-801 has shown potential for robust efficacy and favorable safety in the highest-risk Alzheimer's population – patients with two copies of the apolipoprotein ε4 allele (APOE4/4). This population is the focus of Alzheon's pivotal Phase 3 APOLLOE4 trial and has the highest likelihood of demonstrating a successful outcome.

The ongoing, fully enrolled Phase 2 biomarker study is evaluating 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 leading risk factor for Alzheimer's after aging, is associated with a several-fold higher brain burden of neurotoxic amyloid oligomers.

Phosphorylated tau (p-tau) levels in plasma and CSF are sensitive and specific markers of brain injury and neurodegeneration in AD. P-tau is produced as a reaction to toxic beta amyloid (Aβ) oligomers. P-tau$_{181}$ levels rise with AD progression and clinical deterioration, and have been shown to fall in response to clinically effective disease modifying treatments in Alzheimer's.

"The several-fold greater reduction on p-tau$_{181}$ biomarker compared to anti-amyloid antibodies provides further support for superior clinical benefit observed in Alzheon's prior Alzheimer's studies. Combined with a favorable safety profile and no events of vasogenic edema, these new biomarker data and their positive correlations with cognitive benefits further validate the disease modifying effect of ALZ-801 in Alzheimer's patients," said Martin Tolar, MD, PhD, Founder, President, and CEO of Alzheon. "Importantly, rather than slowing the cognitive decline of patients as seen in trials with other agents, subjects treated with ALZ-801 demonstrated significant cognitive gain from baseline status on memory tests, showing improvement over the course of treatment. These well-differentiated results position ALZ-801 to potentially become the first oral agent that can slow or even stop and prevent Alzheimer's pathology in patients and healthy individuals at risk for the disease."

Alzheon's Phase 2 AD biomarker study (NCT04693520) enrolled 84 patients with Early AD, who carry the APOE4/4 or APOE3/4 genotype and received oral ALZ-801 265 mg twice daily. The primary outcome for this interim analysis was change from baseline in plasma p-tau$_{181}$. All analyses of plasma biomarkers were performed at the laboratory of Professor Kaj Blennow at University of Gothenburg in Molndal, Sweden. A total of 80 patients (mean age 69 years, 51% female) completed the Week 26 visit and were included in this analysis. In this population, ALZ-801 demonstrated a significant 29% reduction in plasma p-tau$_{181}$ (p=0.028) at 26 weeks, and 18% reduction at 13 weeks (p=0.038). ALZ-801 also significantly reduced the plasma p-tau$_{181}$/Aβ42 ratio by 30% at 26 weeks (p=0.022), and by 21% at 13 weeks (p=0.018). Given the importance of p-tau$_{181}$ and Aβ42 as biomarkers of core AD pathology, these results support a disease modifying effect of ALZ-801 in Alzheimer's.

ALZ-801 shows early and robust plasma p-tau$_{181}$ reductions at 13 and 26 weeks with improvements in memory. These early p-tau$_{181}$ effects are likely enabled by the robust 40% brain penetration of ALZ-801 compared to approximately 1% brain penetration of antibodies. As p-tau$_{181}$ is primarily of brain origin and actively clears from brain into plasma, the significant lowering of p-tau$_{181}$ in response to ALZ-801 treatment validates the drug's target engagement and action in the AD brain.

"Alzheon has pioneered precision medicine in Alzheimer's disease targeting neurotoxic amyloid oligomers, and now very promising biomarker data with ALZ-801 provide further support for this

approach," said Kaj Blennow, MD, PhD, Professor of Clinical Neurochemistry at the University of Gothenburg, Sweden, a member of Alzheon's Scientific Advisory Board and developer of the p-tau$_{181}$ assay. "Across many trials of anti-amyloid antibodies, p-tau$_{181}$ has emerged as a consistent biomarker that correlates with amyloid reduction and clinical benefit. Upon analysis of the plasma p-tau$_{181}$ data in our laboratory, we have observed an unprecedented reduction in this leading biomarker of Alzheimer's pathology in patients taking ALZ-801 tablet for 6 months. This suggests a downstream effect on neuronal function and the potential for clinical efficacy of this novel treatment."

In addition to the biomarker outcomes, the Phase 2 study included a standard learning and memory test, Rey Auditory Verbal Learning Test (RAVLT), as a secondary outcome. Analysis of RAVLT total memory scores, which included both immediate and delayed recall, showed a significant improvement from baseline to Week 26 (p=0.002). In the overall 84 subjects who received ALZ-801, the most common adverse event was mild nausea. There was no evidence of vasogenic edema and no drug-related serious events. The safety and tolerability profile was favorable and consistent with prior data from more than 2,000 AD patients in Alzheon's safety database.

"These positive results represent the latest evidence confirming the promise of our disease-modifying mechanism and favorable brain penetration of ALZ-801, extending other key discoveries made by Alzheon scientists over the last 8 years. The significant effect on p-tau$_{181}$/Aβ42 ratio supports the anti-amyloid oligomer action of ALZ-801 in brains of patients with Alzheimer's disease. Specifically, the reduction in p-tau$_{181}$/Aβ42 ratio is consistent with the mechanism of action of ALZ-801, which inhibits the formation of neurotoxic soluble amyloid aggregates that cause neuronal damage," said John Hey, PhD, Chief Scientific Officer of Alzheon. "Alzheon has developed a well-differentiated approach to both treatment and prevention of Alzheimer's disease with the small molecule oral tablet, ALZ-801 (valiltramiprosate), which acts on the same pathway as anti-amyloid antibodies but works upstream to prevent the formation of neurotoxic soluble amyloid oligomers, without disrupting the insoluble plaque deposits. ALZ-801 is, therefore, in a class of its own as an easy to administer oral tablet that has shown the potential for robust efficacy with a favorable safety profile, avoiding the vascular complications of brain edema and microbleeds seen with infusions of plaque-clearing anti-amyloid antibodies."

With support from the National Institute on Aging in the form of a $47M grant to fund the APOLLOE4 Phase 3 study with ALZ-801, Alzheon's drug candidate is well positioned to become one of the first disease-modifying treatments approved for slowing and even preventing cognitive decline in Alzheimer's patients. Pioneering a precision medicine approach in Alzheimer's, the APOLLOE4 Phase 3 trial is enrolling the highest-risk APOE4/4 AD patients and incorporates the latest biomarkers to track patient benefit – p-tau$_{181}$ in cerebrospinal fluid and blood, synaptic and inflammatory biomarkers, hippocampal volume, and cortical thickness measures, along with the gold-standard primary clinical endpoint, ADAS-Cog 13 (Alzheimer's Disease Assessment Scale-Cognitive Subscale).

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 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] ALZ-801 received Fast Track designation from the U.S. Food and Drug Administration in 2017. The clinical data for ALZ-801 and Alzheon's safety database indicate a favorable safety profile.[5–7,9] 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 and noncarriers.[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 that fully blocks formation of neurotoxic soluble amyloid oligomers in the brain. 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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