Peer-Reviewed Scientific Publication Profiles First Wave of Disease-Modifying Alzheimer's Treatments with Potential for Near Term Approval: Aducanumab, Gantenerumab, BAN2401 and ALZ-801

Anti-Amyloid Agents that Block Toxicity of Soluble Amyloid Oligomers – A Key Driver of Alzheimer's Disease – Show Positive Clinical Effects and Consistent Biomarker Results

Selectivity for Amyloid Oligomers and Pharmacological Profiles Define Magnitude of Clinical Benefit & Risk and Ease of Administration

FRAMINGHAM, Mass., August 17, 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, announced today the publication of a peer-reviewed research paper, "Aducanumab, Gantenerumab, BAN2401 and ALZ-801 – the First Wave of Amyloid-Targeting Drugs for Alzheimer's Disease with Potential for Near Term Approval," in *Alzheimer's Research & Therapy* journal, available through open access at: https://doi.org/10.1186/s13195-020-00663-w.

"We are entering a new era of drug development for Alzheimer's disease, with high probability of meeting the goal of bringing effective treatments to patients before the United States NIH's National Alzheimer's Plan target date of 2025," said Martin Tolar, MD, PhD, Founder, President and Chief Executive Officer of Alzheon. "The groundbreaking work by Biogen and BioArctic/Eisai to develop injectable anti-amyloid antibodies with enhanced specificity for neurotoxic soluble amyloid oligomers has resulted in late-stage clinical candidates with promising efficacy signals and potential for near term approval. The research team at Alzheon has built upon this work to demonstrate that our lead oral drug candidate, ALZ-801, works by inhibiting the oligomerization of beta amyloid protein that drives the downstream pathology and cognitive decline in Alzheimer's disease. This positions ALZ-801 to potentially become the first oral disease-modifying agent for patients and healthy people at high risk for Alzheimer's disease."

"This review offers a timely analysis of the benefit and risk profiles of the four leading anti-amyloid agents in late-stage development, and synthesizes the clinical and scientific evidence supporting amyloid oligomers as the most promising therapeutic target in Alzheimer's disease," said Marwan Sabbagh, MD, advisor to Alzheon and co-author of the publication. "With the need for disease-modifying treatments for Alzheimer's patients greater than ever, we are optimistic that one or more of these agents will become available to patients in the near future."

The publication profiles four anti-amyloid treatments that have progressed to late-stage clinical trials for Alzheimer's disease, in spite of clinical trial failures across the class of amyloid-targeted drugs in AD. The four agents are the injectable antibodies aducanumab, gantenerumab, and BAN2401, and a small molecule oral tablet, ALZ-801.

- The paper synthesizes the clinical and biomarker evidence for each of the four agents, which engage neurotoxic amyloid oligomers to various degrees, a mechanism shown to be a key driver of AD pathology and clinical progression.

- The authors present analysis of pharmacological properties of each of the anti-amyloid treatments, including selectivity for amyloid oligomers, plasma half-life, brain penetration, and time to peak brain exposure.
- The authors define the magnitude of clinical efficacy, biomarker effects, benefit and risk profile, and ease of administration for each of the agents.
- The review highlights the superior selectivity for amyloid oligomers of ALZ-801 and the pioneering precision medicine approach of the clinical development of this oral agent in a genetically defined population of AD patients.

"The degree of amyloid oligomer selectivity appears to be the key factor that, together with the pharmacokinetic properties, determines the magnitude of the benefit and risk profile for each anti-amyloid agent," said John Hey, PhD, Chief Scientific Officer of Alzheon. "Alzheon's ALZ-801 provides advantages over injectable antibodies as an oral agent that efficiently crosses the blood brain barrier, selectively interacts with amyloid monomers to inhibit their misfolding, and blocks the formation of neurotoxic soluble amyloid oligomers in a concentration-dependent manner, without affecting insoluble amyloid plaques or fibrils. Given these superior anti-oligomer characteristics, ALZ-801 is the most advanced of the next generation of highly selective anti-oligomer agents in development, with potential for use as a preventive treatment of healthy individuals with high risk for Alzheimer's."

Clinical Development Path for ALZ-801

Initial clinical development of ALZ-801 is for a genetically defined Alzheimer's population at high risk for early onset of the disease and rapid progression – Early AD patients homozygous for the ε4 allele of apolipoprotein E (APOE4/4 genotype) – with the Phase 3 trial to evaluate ALZ-801 in this patient population scheduled to begin in early 2021. Based on the results from ALZ-801 Phase 2 AD biomarker study, subsequent development will extend to: (i) ALZ-801 for prevention of onset of Alzheimer's in healthy, high risk people without any symptoms of AD, and (ii) ALZ-801 for Alzheimer's patients with only one copy of the APOE4 gene, a group that constitutes 50% of AD patients.

Dr. Tolar added, "Alzheon's ultimate vision for ALZ-801 is to provide an effective oral, well-tolerated at-home treatment for individuals at risk for Alzheimer's that can maintain their cognitive abilities, preserve functional independence, and reduce the societal burden of Alzheimer's disease worldwide."

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-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 inhibit formation of toxic 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 substance in the human brain discovered by Alzheon scientists that, like tramiprosate, inhibits formation of neurotoxic 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, selectivity against amyloid oligomer formation, and excellent brain penetration. ALZ-801 treatment increases levels of 3-SPA in the brain and augments the body's natural mechanism to inhibit toxic oligomer formation.[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 that fully blocks formation of neurotoxic amyloid oligomers in the brain. ALZ-801 is a new chemical entity prodrug that builds on the safety and efficacy profile of the 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.

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