Alzheon Publication Defines New Path for 2nd Generation Anti-Amyloid Drugs for Alzheimer's Disease, Supporting Launch of Phase 3 Study with ALZ-801 Oral Tablet

Publication in Alzheimer's & Dementia, The Journal of the Alzheimer's Association, Details Scientific Underpinnings for ALZ-801 to Slow or Stop Disease Course

Publication Outlines Therapeutic Characteristics that Overcome Limitations Seen with Anti-Amyloid Drug Candidates to Date

FRAMINGHAM, Mass., November 6, 2019 – Alzheon, Inc., a clinical-stage biopharmaceutical company focused on developing new medicines for patients suffering from Alzheimer's disease and other neurodegenerative disorders, today announced the publication of a peer-reviewed research paper "The Path Forward in Alzheimer's Disease Therapeutics: Reevaluating the Amyloid Cascade Hypothesis," in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association,* available through open access at link: https://doi.org/10.1016/j.jalz.2019.09.075

The publication, authored by Alzheon experts, offers six key insights about therapeutic strategies for Alzheimer's disease (AD), at a time when few drugs remain in advanced clinical trials. The key properties of 2nd generation anti-amyloid drugs that address the limitations seen with treatments to date are: simple oral dosing; high brain penetration; selectivity for soluble amyloid oligomers, the most toxic form of amyloid; and favorable safety, avoiding the risk of brain edema and microhemorrhage associated with plaque-clearing treatments. This improved pharmacological profile will enable anti-amyloid drugs to achieve robust and meaningful clinical efficacy, and to realize the full potential of this most promising class of Alzheimer's medicines. These insights have also guided Alzheon strategy in developing ALZ-801, which is the only remaining Phase 3 candidate with the attributes required for the next generation of anti-amyloid therapies.

The review builds upon learnings from genetic, biomarker, and clinical studies, as well as from new discoveries made by Alzheon scientists elucidating the novel mechanism of targeting toxic soluble amyloid oligomers, and provides the following insights:

- *The inability of therapies to selectively and fully block oligomer formation or to clear them from the brain, has led to trial failures:* Soluble amyloid oligomers, rather than insoluble fibrils and plaques, are the neurotoxic forms of amyloid responsible for the onset and progression of AD.
- *Limitations of anti-amyloid antibodies include poor brain penetration and lack of selectivity for oligomers:* Modest effects, or even failures, of antibody programs are the result of their inherent inability to reach and sustain brain concentrations that enable effective removal of oligomers. Furthermore, the lack of selectivity leads to clearance of amyloid plaques that may contribute to vascular injury resulting in brain edema and microhemorrhages.
- *A precision medicine approach is necessary to address specific pathologies in well-defined patient populations:* Alzheon has pioneered the focus on genetically-defined AD populations – such as APOE4 carriers and other patients with an increased risk of AD due to a high burden of amyloid oligomers – who are most likely to show a robust drug response.[1,2]

The publication also highlights a series of discoveries that the Alzheon team has made and published:

- *Discovery of a novel mechanism of action and therapeutic approach to block the formation of toxic amyloid oligomers:* ALZ-801 fully inhibits the formation of oligomers in the brain and can be dosed as a simple oral tablet with a wide safety margin.[3]
- *ALZ-801 prodrug design improves brain penetration, efficacy and safety profile:* The design of ALZ-801 optimizes oral delivery and enables the achievement of sustained high brain concentrations that assure full inhibition of the formation of toxic oligomers. High selectivity of ALZ-801 for oligomers also supports a favorable safety profile compared to other anti-amyloid approaches.[4]
- *Discovery that the active metabolite of ALZ-801 is an endogenous molecule with amyloid anti-aggregation effects:* During clinical studies, the Alzheon team discovered that the primary metabolite of ALZ-801 (known as 3-SPA) is produced endogenously in the human brain and blocks aggregation of amyloid, further supporting the biological relevance of this mechanism and its role in naturally protecting the human brain against oligomer toxicity.[5]

"We have a historic opportunity to bring to patients and their families the first safe, oral treatment, with the potential to slow, or even stop, disease progression in Alzheimer's. ALZ-801 augments the body's natural mechanism for blocking the formation of toxic amyloid oligomers that can lead to memory loss, and drive the onset and progression of Alzheimer's symptoms," said Martin Tolar, MD, PhD, Founder, President and Chief Executive Officer of Alzheon. "Based on our insights, we are poised to initiate a pivotal Phase 3 trial with ALZ-801 – the only oral anti-amyloid drug remaining in the late-stage trials for Alzheimer's. Our ultimate goal with ALZ-801 is to prevent the onset of clinical symptoms in the aging population, and to preserve their independence and dignity."

"This review offers an important blueprint for Alzheimer's drug developers, because it builds on the key learnings of the research community and capitalizes on the convergence of new science around synaptotoxic amyloid oligomers as triggers of disease progression" said Marwan Sabbagh, MD, Director of Cleveland Clinic Lou Ruvo Center for Brain Health, scientific advisor to Alzheon and co-author of the publication. "Recent validation of amyloid targeting by aducanumab brought up the necessity to prevent the formation of amyloid aggregates and the onset of the clinical symptoms of Alzheimer's – and this is what we hope the new therapeutic approach will accomplish."

About ALZ-801

Alzheon's lead product candidate, ALZ-801, is an oral anti-amyloid drug candidate that is an optimized prodrug of tramiprosate, which has shown promising results in analyses of clinical data[1,2] and a novel therapeutic mechanism of action.[3] ALZ-801 received Fast Track designation from the U.S. Food and Drug Administration. The clinical data for ALZ-801[4] and its active agent, tramiprosate, suggest long-term clinical efficacy in AD patients with the apolipoprotein ε4 (APOE4) genotype and a favorable safety profile.[1,2] ALZ-801 acts through a novel molecular mechanism of action blocking the formation of toxic amyloid oligomers[3] associated with the development and progression of AD. The cognitive improvements observed in AD patients in the tramiprosate Phase 3 studies may 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 inhibits the formation of neurotoxic beta amyloid oligomers.[5] 3-SPA is

the primary metabolite of ALZ-801 in humans and its discovery elucidates the beneficial pharmaceutical attributes of ALZ-801, including a favorable safety profile, selectivity against beta amyloid oligomers, and excellent brain penetration. ALZ-801 increases levels of 3-SPA in the brain and augments the body's natural mechanism for blocking the formation of toxic amyloid oligomers.[5] The initial Phase 3 program for ALZ-801 will focus on patients with the homozygous APOE4/4 genotype at the Mild stage of AD, with the potential for future expansion to additional Alzheimer's populations.

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 a Phase 3-ready, first-in-class, small molecule oral inhibitor of beta amyloid aggregation and neurotoxicity – hallmarks of Alzheimer's disease. ALZ-801 is a novel 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 Publications

[1] Abushakra et al. *Journal of Prevention of Alzheimer's Disease*, 2016
[2] Abushakra et al. *Journal of Prevention of Alzheimer's Disease*, 2017
[3] Kocis et al. *CNS Drugs*, 2017
[4] Hey et al. *Clinical Pharmacokinetics*, 2018
[5] Hey et al. *CNS Drugs*, 2018

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