



Peer-Reviewed Scientific Publication Demonstrates Central Role of Neurotoxic Soluble Amyloid Oligomers in Driving Alzheimer’s Pathogenesis

Inhibition of Amyloid Toxicity Represents the Only Clinically Validated Approach for Slowing Progression of Alzheimer’s Disease

All Anti-Amyloid Agents with Positive Clinical Data Engage Amyloid Oligomers, Including Three Antibody Infusions and Oral Tablet ALZ-801

FRAMINGHAM, Mass., June 23, 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 the publication of a peer-reviewed research paper, “Neurotoxic Soluble Amyloid Oligomers Drive Alzheimer’s Pathogenesis and Represent a Clinically Validated Target for Slowing Disease Progression,” in the Special Issue [Alzheimer’s Disease: Role and Structure of Soluble Oligomers](#) of the *International Journal of Molecular Sciences*, available through open access at: <https://doi.org/10.3390/ijms22126355>.

“We have entered a new era of drug development for Alzheimer’s disease with the recent approval of aducanumab, the first treatment that targets toxic forms of amyloid. The degree of amyloid oligomer selectivity appears to be the key factor that, together with pharmacokinetic properties, determines the magnitude of the benefit and risk profile for each anti-amyloid agent,” said Martin Tolar, MD, PhD, Alzheon Founder, President and Chief Executive Officer, and the lead author of the publication. “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. Accelerated approval of anti-amyloid antibody aducanumab based on biomarker data validates our development approach in running a Phase 2 biomarker trial concurrently with a Phase 3 trial of our oral drug ALZ-801, which began dosing patients earlier this month. 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.”

The publication provides an up-to-date summary of longitudinal clinical data elucidating the chronology of amyloid and tau biomarkers in AD, and review of non-clinical studies and clinical trials supporting the upstream pathogenic role of amyloid oligomers in AD. In summary, the authors:

- Present analyses showing that only agents that target soluble amyloid oligomers show clinical efficacy in AD patients, while agents that predominantly target amyloid monomers or plaque failed to demonstrate clinical effects.
- Analyze data on clearance of amyloid plaques in amyloid antibody trials showing that even complete plaque removal does not correlate with clinical efficacy.
- Explain why in positive trials, clinical efficacy is greater in carriers of the $\epsilon 4$ allele of apolipoprotein E gene (APOE4), who are known to have a higher burden of amyloid oligomers in the brain.
- Review data from recent positive trials, where inhibition of amyloid neurotoxicity leads to a reduction in tau pathology, showing that amyloid toxicity drives increased tau phosphorylation and tau deposition in neurofibrillary tangles.
- The review highlights the superior selectivity of ALZ-801 for amyloid oligomers and the pioneering precision medicine approach of the APOLLOE4 Phase 3 trial evaluating ALZ-801 tablet in APOE4/4 homozygous AD patients.

“This publication is very timely since the FDA’s recent accelerated approval of aducanumab is based on its effects on toxic amyloid, underscoring the importance of amyloid as an upstream trigger of Alzheimer’s pathogenesis, and establishing the central role of biomarkers in Alzheimer’s drug approvals,” said senior author Susan Abushakra, MD, Chief Medical Officer at Alzheon. “Our analysis shows that the biomarker that best correlates with clinical benefit is reduction of phosphorylated tau in cerebral spinal fluid, and tau hyperphosphorylation is driven by soluble toxic amyloid oligomers rather than plaque. We believe that plaque reduction is an indirect association since its correlation with clinical efficacy seems to be mediated by drug effects on phosphorylated tau biomarker.”

The FDA’s accelerated approval of Biogen’s anti-amyloid therapy aducanumab (Aduhelm) validates ALZ-801’s mechanism of action and confirms a regulatory path for a clinical study that provides strong biomarker data to support clinical outcomes. Anti-amyloid antibody treatments present logistical challenges since they are administered by intravenous infusions and require serial magnetic resonance imaging scans to monitor for brain edema and hemorrhage, while ALZ-801 is an oral drug with a robust safety profile among AD patients.

“In our paper, we demonstrate that while effects on soluble toxic amyloid oligomers correlate with clinical benefit, clearance of insoluble amyloid plaque from vessel walls by antibodies comes with the side effects of vasogenic edema and brain bleeds due to small vessel injury at the clinically efficacious dose,” said John Hey, PhD, Chief Scientific Officer of Alzheon, and co-author of the paper. “ALZ-801 is an oral drug that does not interact with amyloid plaque and, therefore, is not associated with the risk of vasogenic edema, making the ALZ-801 treatment much more accessible to patients, with the potential to have a significant impact around the world. In its first indication for Alzheimer’s patients with two copies of the APOE4 gene, ALZ-801 may be able to serve 1.35 million patients, which can scale up to 15 million patients in additional indications.”

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 brain⁷ 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 \$\epsilon\$ 4/ \$\epsilon\$ 4 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 A \$\beta\$ 42 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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