Alzheon Partners with Czech Institute of Organic Chemistry and Biochemistry to Develop First Alzheimer's Diagnostic Assay for Measuring Neurotoxic Beta Amyloid Oligomers in Human Brain

Assay Builds on Alzheon's Research to Detect and Quantify Soluble Oligomers, and Enhances Phase 2 and Phase 3 Alzheimer's Studies with Oral ALZ-801

Quantitative Assay to Monitor Alzheimer's Disease Onset and Progression will Provide Insights into Pathogenesis and Accelerate Development of Treatments

FRAMINGHAM, Mass., May 4, 2021 — Alzheon, Inc., a clinical-stage biopharmaceutical company focused on developing new medicines for patients suffering from Alzheimer's disease (AD) and other neurodegenerative disorders, today announced that it has entered into a collaboration and license agreement with the Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences (IOCB) to develop the first clinical assay to measure neurotoxic beta amyloid (amyloid, Aβ) oligomers in human cerebrospinal fluid (CSF). Under the collaboration agreement, IOCB will apply Alzheon's technology for detecting oligomers into a customized clinical assay in human CSF, to be developed by the IOCB and commercialized by Alzheon. This initiative builds on successfully completed feasibility studies performed over the past year by the two organizations.

The assay developed by the Alzheon-IOCB collaboration will be sensitive to the full spectrum of soluble oligomer species in CSF and will be able to quantify the amyloid oligomer burden in the brain. The new diagnostic is designed to address the limitations of current assays used to detect amyloid oligomers, such as enzyme-linked immunosorbent assays, that can be sensitive to oligomer levels, but are non-specific, as they do not distinguish individual species of Aβ oligomers.

"In just the last year, we have seen clinical validation and consensus around the importance of targeting soluble amyloid oligomers to effectively treat Alzheimer's patients, however, these oligomers are extremely challenging to track," said Martin Tolar, MD, PhD, Alzheon Founder, President and Chief Executive Officer. "Working with IOCB, we will apply state-of-the-art analytical chemistry technologies to develop an assay that can provide a key missing piece of the puzzle – detecting and measuring neurotoxic amyloid oligomers, the underlying 'fire in the brain' that drives Alzheimer's pathology. Such a tool is not only valuable as a diagnostic for patients with Alzheimer's disease, but also offers a way to monitor response of patients to therapy. Using

genetics-based precision medicine, we are advancing our oral tablet ALZ-801 into Phase 3, and in our studies, we will now have an opportunity to determine how reduction in oligomer toxicity correlates with clinical benefit."

The collaboration between Alzheon and IOCB will leverage Alzheon's discoveries and scientific expertise in AD, particularly the insights into the role of Aβ oligomers in disease biology. Alzheon will provide biospecimens from AD patients including samples from patients treated with ALZ-801. The IOCB will be primarily responsible for the development and validation of an assay to detect amyloid oligomers and to measure the change in amyloid levels in biological samples following treatment with Alzheon's anti-oligomer agents, such as ALZ-801.

"Beyond its diagnostic and theragnostic potential, this assay will provide researchers and clinicians with the ability to profile anti-amyloid antibodies and other Alzheimer's drugs with different selectivity for amyloid oligomers relative to fibrils and plaque, which can improve therapeutic paradigms for patients," said Prof. Ing. Martin Fusek, CSc., Vice-Director for Strategic Development of IOCB. "We are excited to enter this partnership with Alzheon, the market leader of small molecule anti-amyloid agents, in developing a novel approach to measuring the toxic products of amyloid aggregation. This new assay can have a far-reaching impact on Alzheimer's research and treatment by illuminating new aspects of the disease mechanism and by informing interventions to stop or even prevent the disease process."

Recent findings from AD studies and clinical trials provide strong evidence that soluble amyloid oligomers are directly neurotoxic upstream drivers of AD pathology, leading to progressive increase in phosphorylated tau protein and markers of neuronal injury in CSF and plasma of AD patients. Amyloid oligomers are a key target of several promising Phase 3 antibodies for Early AD including aducanumab, lecanemab/BAN2401 and donanemab, as well as Alzheon's lead clinical candidate, ALZ-801, an oral treatment that fully blocks formation of neurotoxic oligomers in the brain at clinical dose.

"We are excited to join forces with researchers from IOCB to develop a sensitive and specific assay that will enable us to track the levels of toxic amyloid fragments that have eluded detection in brains of Alzheimer's patients. Such an assay will provide the opportunity for earlier diagnosis and better therapeutic treatments tailored to each patient, a precision medicine approach to Alzheimer's disease that we have pioneered at Alzheon" said John Hey, PhD, Chief Scientific Officer of Alzheon. "This collaboration builds on the discovery of mechanism of action of ALZ-801 and numerous studies by Alzheon scientists, and leverages IOCB's world-class expertise in analytical science and technologies. Combined with data from our ongoing Phase 2 study evaluating ALZ-801 effects on fluid and imaging biomarkers, this theragnostic will allow us to gain critical insights into the links between neurotoxic amyloid oligomers, disease progression, and response to treatment."

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,[6,8] and has a novel anti-amyloid oligomer

mechanism of action.[4,7] 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.[4,6,8] ALZ-801 acts through a novel enveloping molecular mechanism of action to fully block formation of neurotoxic soluble amyloid oligomers[6] associated with the onset of cognitive symptoms and progression of AD.[2,3] 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 in the human brain discovered by Alzheon scientists that, like tramiprosate, inhibits formation of toxic amyloid oligomers.[4] 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. 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.[4,5] 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.[1,2,3]

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 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 using a precision medicine approach based on individual genetic and biological information to advance therapies with the greatest impact for patients.

About Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences

The Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences in Prague is a leading scientific institution in the Czech Republic, recognized internationally. Its primary mission is basic research in the fields of chemical biology and medicinal chemistry, organic and material-oriented chemistry, chemistry of natural compounds, biochemistry and molecular biology, physical chemistry, theoretical chemistry, and analytical chemistry. The Institute has a long tradition and expertise in medicinal chemistry and drug development together with the pharma industry. Antivirals discovered by Antonín Holý and developed further by Gilead Sciences revolutionized the treatment of AIDS and hepatitis B and have significantly improved lives of millions of people around the globe.

Alzheon Scientific Publications

[1] 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.

[2] 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.

[3] Tolar M, et al: *The Path Forward in Alzheimer's Disease Therapeutics: Reevaluating the Amyloid Cascade Hypothesis,* **Alzheimer's & Dementia,** 2019; 1-8.

[4] 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.

[5] 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.

[6] 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.

[7] 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.

[8] 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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