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Overview of the preclinical program for OLX-07010 - a novel inhibitor of tau self-association

New therapies and clinical trials

Biographies (1 for poster/oral communications & 4 for the symposium) / 200 words per bio
James Moe, Ph.D., MBA, CEO, Head of Discovery & Strategy - Co-Founder, Director, PI, Oligomerix, Inc.: Dr. Moe has over 29 years of industrial experience having held senior management positions in product development working on international teams in both early and late-stage diagnostic, biotechnology and biopharmaceutical companies including Gene-Trak/Amoco Technology Group/Vysis, bioMerieux, and Mosaic Technologies. Prior to founding Oligomerix in 2006, he was Director of Product Development at Pyrosequencing, Senior Molecular Biologist at Spire Biomedical, and Director of Product Development at Q-RNA; Inc. He received his Ph.D. degree in molecular biology and biochemistry with a focus on molecular biophysics from Wesleyan University, did his postdoctoral studies at Vanderbilt University in the Center for Molecular Toxicology where he was jointly appointed in the Biochemistry Department in the Medical School, and the Chemistry Department in the College of Arts and Sciences, and has an MBA degree with a concentration in entrepreneurial studies from Boston University. His current research focuses on developing the tau self-association target for drug discovery and development for Alzheimer's disease and related tauopathies. This has led to the development of a lead molecule that completed pre-clinical development and an IND submission.

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Abstract:

Background: Tau has been implicated in the pathogenesis of multiple neurodegenerative diseases associated with the accumulation of abnormal species of tau, collectively called tauopathies. Mutations in MAPT can cause a range of rare inherited tauopathies to develop due to overproduction of specific tau isoforms or changes in the structure of tau, both of which can cause tau to aggregate. In AD, tau

pathology is driven by numerous posttranslational modifications that lead to loss of normal function and/or gain of toxic function. Neurofibrillary tangles, composed primarily of tau, accumulate in a highly reproducible spatiotemporal order starting in the transentorhinal/entorhinal regions and spreading through the hippocampal structure to the neocortex demonstrating a close association between tau aggregation and AD progression. Tau prion-like propagation through neuronal communication pathways uses a seeding mechanism of templated misfolding and is accelerated by the presence of brain Aβ. Multiple studies have shown that tau oligomers, not fibrils or tangles, are closely correlated with neuronal loss and memory impairment.

We have shown that tau oligomers cause disruption of neuronal signaling and inhibit the formation of memory in mice (Fá M et al., 2016). Memory formation was impaired following administration of oligomeric tau to hippocampi, areas of the brain involved in short-term memory formation. But similar treatment with tau monomer (tau that did not self-associate) did not have an effect. This impairment of memory was also found using oligomers formed from hyperphosphorylated tau purified from human AD brain specimens. Memory-specific mechanisms involved in gene regulation were shown to be disrupted by these extracellular tau oligomers. We have found that certain forms of tau oligomers are toxic when applied to cultured neurons, whereas tau monomer was not toxic at the same concentrations (Tian H et al., 2013). Our in vivo efficacy studies were carried out in two different transgenic mouse models, the htau model that expresses all 6 human isoforms with no mutations, and the JNPL3 model that has 4R0N tau with a P301L mutation. Treatment with the lead caused significant reduction in tau aggregates in blinded preventive studies (Davidowitz EJ et. al., 2020) in the htau model and also showed efficacy in both preventive and therapeutic studies in JNPL3 mice modeling 4R tau aggregation in tauopathies. Taken together these studies support the development of OLX-07010.

Objectives: The overall goal of this program is to develop a small molecule therapeutic targeting tau self-association for Alzheimer's disease and related tauopathies. The aim of this preclinical development program was to perform the studies needed for an IND application for a first-in-human clinical study for the safety and pharmacokinetics of OLX-07010. To achieve this aim, studies were required to evaluate the pharmacodynamics, pharmacokinetics, metabolism and toxicity of the candidate. Process development and manufacture of the drug substance (DS) for the non-clinical studies (non-GMP) and for the GMP manufacture of drug product (DP) were needed to perform the safety studies and to evaluate the stability of the DS and DP.

Methods: All toxicology, metabolism, and transporter studies, as well as DS and DP manufacture and testing were performed at CROs. The 14-day toxicity studies (non-GLP) had once daily oral gavage to rats at dose levels of 100, 300, and 1,000 mg/kg/day, and once daily oral gavage to Beagle dogs at dose levels of 50 and 150 mg/kg/day. The dose levels in the 28-day toxicity studies (GLP) were 30, 100 and 300 mg/kg/day in rats and 15, 50 and 150 mg/kg/day in dogs. The Functional Observational Battery was performed as part of the 28-day rat study to evaluate CNS effects.

Results: OLX-07010 demonstrated: pharmacologic activity in two mouse models of tauopathy; reasonable pharmacokinetic characteristics; minimal DDI potential; lack of genotoxicity; minimal off-target activity in safety pharmacology profiling with tier 1 and 3 safety panels; lack of/minimal effects on cardiovascular, pulmonary and CNS systems; relatively modest findings which were not considered adverse were

observed in 28-day rat and dog GLP toxicity studies; the drug substance showed high purity and stability, and the drug product showed good stability.
Conclusion: The preclinical development program demonstrated that OLX-07010 is an excellent candidate for clinical development. Long-term treatment for chronic diseases such as AD requires safe, effective, and economically feasible approaches. This small molecule, CNS drug-like lead substantially fulfills these requirements based on our preliminary results and the fact that it would not need cold-storage nor expensive infusion centers for administration for ease of treatment to address the unmet global health crisis.
References: Fá M et al., Sci Rep. 2016 Jan 20;6:19393. PMC4726138; Tian H, et. al., Int J Cell Biol. 2013, 260787. PMC3789488; Davidowitz EJ et al., J Alzheimers Dis. 2020; 73(1):147-161. PMC6957711.