

Ionis Pharmaceuticals Initiates Clinical Study of IONIS-MAPT Rx in Patients with Alzheimer's Disease

October 13, 2017

Antisense drug designed to reduce tau protein in the CNS Ionis earns \$10 million milestone payment from Biogen

CARLSBAD, Calif., Oct. 13, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today announced that it has initiated a Phase 1/2a clinical study of IONIS-MAPT_{Rx} in patients with mild Alzheimer's disease (AD). Ionis earned a \$10 million milestone payment from Biogen related to the initiation of this study.



IONIS-MAPT_{Rx} is an antisense drug designed to selectively reduce the production of microtubule-associated protein tau (MAPT), or tau protein, in the brain. Tau misfolding leads to the accumulation of neurofibrillary tangles inside brain cells. These tangles are a hallmark feature of a spectrum of neurodegenerative diseases known as tauopathies, which include AD and some forms of frontotemporal dementia (FTD). AD is the most common form of dementia, accounting for an estimated 70% of cases. FTD is a rare form of early-onset dementia resulting from neuronal damage in the frontal and temporal lobes of the brain.

"In contrast to amyloid plaques that may begin to deposit in the brain for up to 20 years before the onset of AD, tau deposits are spatially and temporally associated with the brain regions where atrophy occurs and neurocognitive deficits originate. IONIS-MAPT_{Rx} is designed to reduce the production of all of the many forms of tau in all regions of the brain," said C. Frank Bennett, Ph.D., senior vice president of research at Ionis Pharmaceuticals.

The three-month randomized, placebo-controlled, dose escalation Phase 1/2a clinical study will evaluate the safety and activity of IONIS-MAPT_{Rx} in approximately 44 patients with mild AD. In the study, IONIS-MAPT_{Rx} is administered as a once-monthly intrathecal injection directly into the cerebral spinal fluid, similar to the way SPINRAZA[®] (nusinersen) is administered. Biogen has an option to develop and commercialize IONIS-MAPT_{Rx}.

"IONIS-MAPT_{Rx} is another exciting program within our strategic collaboration with Biogen," said B. Lynne Parshall, chief operating officer of Ionis Pharmaceuticals. "Targeting MAPT represents a unique opportunity to address the unmet need in both rare and more prevalent tauopathies. The first clinical study with IONIS-MAPT_{Rx} is in patients with AD, however, in parallel, we also plan to develop IONIS-MAPT_{Rx} for patients with FTD, a rare disease population. This strategy has the potential to accelerate the drug's path to market."

ABOUT IONIS AND BIOGEN

Ionis and Biogen have a broad strategic collaboration combining Biogen's expertise in neurology with Ionis' leadership in antisense technology to develop novel therapies to treat neurological disorders. SPINRAZA, an antisense drug developed with Ionis Pharmaceuticals' proprietary antisense technology is the first commercial drug from this collaboration. SPINRAZA is approved in global markets for the treatment of patients with spinal muscular atrophy (SMA). Biogen is responsible for commercialization of SPINRAZA. Also under this collaboration, Ionis and Biogen are developing IONIS-SOD1_{Rx} for amyotrophic lateral sclerosis (ALS), and IONIS-BIIB5_{Rx}, IONIS-BIIB6_{Rx}, and IONIS-BIIB7_{Rx} to treat undisclosed neurodegenerative diseases.

ABOUT IONIS PHARMACEUTICALS, INC.

Ionis is the leading company in RNA-targeted drug discovery and development focused on developing drugs for patients who have the highest unmet medical needs, such as those patients with severe and rare diseases. Using its proprietary antisense technology, Ionis has created a large pipeline of first-in-class or best-in-class drugs, with over three dozen drugs in development. SPINRAZA[®] (nusinersen) has been approved in global markets for the treatment of spinal muscular atrophy (SMA). Biogen is responsible for commercializing SPINRAZA. Drugs that have successfully completed Phase 3 studies include inotersen, an antisense drug Ionis is developing to treat patients with TTR amyloidosis, and volanesorsen, an antisense drug discovered by Ionis and co-developed by Ionis and Akcea Therapeutics to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy. Akcea, an affiliate of Ionis, is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. If approved, volanesorsen will be commercialized through Ionis' affiliate, Akcea. Volanesorsen filings for marketing approval have been submitted in the U.S., EU and Canada. Inotersen is progressing toward regulatory filings for marketing authorization. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

IONIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Ionis' strategic relationship with Biogen and the development, activity, therapeutic potential, commercial potential and safety of IONIS-MAPT_{Rx}.

Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect

the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2016, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

Ionis Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark of Ionis Pharmaceuticals, Inc. SPINRAZA® is a registered trademark of Biogen.

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