New data presented at AD/PD™2023 show IONIS-MAPT Rx (BIIB080) substantially reduced tau protein in patients with early-stage Alzheimer's disease

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- *Phase 1b study showed dose-dependent and sustained reduction of tau protein in cerebrospinal fluid through open-label long-term extension (LTE)*
- *IONIS-MAPT$_{Rx}$ reduced aggregated tau pathology across all brain composites assessed starting as early as week 25 through week 100*

CARLSBAD, Calif., March 29, 2023 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today reported that its partner Biogen presented new Phase 1b clinical data showing that IONIS-MAPT$_{Rx}$ (BIIB080) reduced soluble tau protein in cerebrospinal fluid (CSF) in a dose-dependent and sustained manner in patients with early-stage Alzheimer's disease (AD). IONIS-MAPT$_{Rx}$ also reduced aggregated tau pathology, as measured by positron emission tomography (PET) in all brain composites assessed. The primary endpoint of the Phase 1b study (25 weeks) and open-label long-term extension study (through week 100) was safety and tolerability, with biomarker data as an exploratory endpoint. The results were presented today at the International Conference on Alzheimer's and Parkinson's Diseases (AD/PD™ 2023).

In patients with AD, tau protein can form "tangles" that progressively accumulate in brain regions involved in cognition. The accumulation of pathological tau tangles has been shown to promote neuronal damage and death. IONIS-MAPT$_{Rx}$ is an investigational antisense medicine discovered by Ionis that is being developed by Biogen. It is designed to target microtubule-associated protein tau (MAPT) mRNA and prevent production of tau protein.

"This Phase 1b clinical study of IONIS-MAPT$_{Rx}$ is the first to demonstrate this magnitude of a reduction of tau pathology across important brain regions. These encouraging findings are the latest example of the potential of the Ionis RNA-targeting platform to selectively modulate proteins linked to CNS disease," said Eugene Schneider, M.D., executive vice president and chief clinical development officer at Ionis. "Ionis is pioneering potential therapies for serious neurological diseases with high unmet need. In addition to Alzheimer's disease, our clinical stage neurology programs include ATTR polyneuropathy, ALS, Alexander disease, Parkinson's disease and Angelman syndrome."

The Phase 1b trial and its open-label long-term extension (LTE) were designed to evaluate the safety and tolerability of multiple dose levels of IONIS-MAPT$_{Rx}$ in patients with mild AD (n=46). In this study, the majority of adverse events were mild or moderate in severity, of which the most common were headache, back pain, and post-lumbar puncture syndrome (PLPS). The results showed that IONIS-MAPT$_{Rx}$ reduced biomarkers of soluble tau in CSF (t-tau and p-tau181) in a dose-dependent and sustained manner, with all dose groups showing approximately a 60% reduction from baseline CSF tau levels by the end of the LTE. IONIS-MAPT$_{Rx}$ impacted aggregated tau pathology as measured by PET as early as week 25 and up to the end of the LTE at week 100, including in patients who began on placebo and received IONIS-MAPT$_{Rx}$ treatment starting at week 25 in the LTE. By the end of the LTE, IONIS-MAPT$_{Rx}$ reduced tau pathology relative to baseline in all dose groups across all brain composites assessed.

The Phase 2 CELIA study of IONIS-MAPT$_{Rx}$ (NCT05399888) is in progress and currently recruiting participants in the U.S.

About Ionis' Neurology Franchise

Ionis' neurology franchise addresses all major brain regions and central nervous system cell types and currently has three Phase 3 studies ongoing with 12 therapies in clinical development, several of which Ionis plans to commercialize directly. Ionis is discovering and developing potential treatments for many neurological diseases for which there are few or no disease modifying treatments, including common diseases like Alzheimer's and Parkinson's as well as rare diseases such as amyotrophic lateral sclerosis (ALS) and Alexander disease. Ionis' marketed neurological disease medicines include SPINRAZA®, a global foundation of care for spinal muscular atrophy (SMA), commercialized by Biogen, and TEGSEDI®, for hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN).

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been a leader in RNA-targeted therapy, pioneering new markets and changing standards of care. Ionis currently has three marketed medicines and a promising late-stage pipeline highlighted by cardiovascular and neurological franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision to become the leader in genetic medicine, utilizing a multi-platform approach to discover, develop and deliver life-transforming therapies.

To learn more about Ionis visit www.ionispharma.com and follow us on Twitter @ionispharma.

Ionis' Forward-looking Statements

This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of Ionis' technologies, IONIS-MAPT$_{Rx}$ and other products in development. 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, including but not limited to, those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. 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 Dec. 31, 2022, which is on file with the Securities

and Exchange Commission. Copies of this 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.

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Ionis Investor Contact: D. Wade Walke, Ph.D., info@ionisph.com, 760-603-2331, or Ionis Media Contact: David Polk, J.D., ionis_ca@ionisph.com, 760-603-4679