Ionis announces FDA acceptance of New Drug Application for eplontersen for the treatment of hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN)

March 7, 2023

- *35-week data included in the filing demonstrated a statistically significant and clinically meaningful change from baseline for co-primary and secondary endpoints compared to external placebo group*
- *Eplontersen previously granted Orphan Drug Designation for transthyretin-mediated amyloidosis*
- *FDA assigns PDUFA action date of Dec. 22, 2023*

CARLSBAD, Calif., March 7, 2023 /PRNewswire/ -- Ionis Pharmaceuticals (Nasdaq: IONS) today announced that the U.S. Food and Drug Administration (FDA) has accepted for review a New Drug Application (NDA) for eplontersen, an investigational antisense medicine for the treatment of people living with hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN). The application has been given a Prescription Drug User Fee Act (PDUFA) action date of Dec. 22, 2023.

In its acceptance letter, the FDA stated that it has not identified any review issues and did not make any additional data requests. The FDA also noted that it is not planning to hold an advisory committee meeting to discuss the application.

Patients with ATTRv-PN experience ongoing debilitating nerve damage throughout their body resulting in the progressive loss of motor function. These patients accumulate TTR in other major organs, which progressively compromises their function and eventually leads to death within five to fifteen years of disease onset.

"We are excited by today's FDA acceptance of our NDA filing as it brings Ionis and our partner, AstraZeneca, one step closer to making eplontersen available to patients with ATTR polyneuropathy," said Eugene Schneider, M.D., executive vice president and chief clinical development officer at Ionis. "Significant reductions in TTR protein levels were observed during the NEURO-TTRansform 35-week interim analysis. Overall, the interim analysis demonstrated eplontersen has the potential to make a positive impact on disease progression and improve quality of life in a substantial number of patients."

The NDA is based on results from the global Phase 3 NEURO-TTRansform study presented at the International Symposium on Amyloidosis (ISA). In the 35-week interim analysis, eplontersen demonstrated a statistically significant and clinically meaningful change from baseline for its co-primary and key secondary endpoints compared to the external placebo group. In the study, eplontersen achieved a significant mean reduction ($p<0.0001$) in the co-primary endpoint of serum transthyretin (TTR) concentration compared to baseline. Eplontersen also demonstrated a significant treatment effect on the co-primary endpoint of modified Neuropathy Impairment Score +7 (mNIS+7), a measure of neuropathic disease progression, with a statistically significant difference in mean change from baseline versus the external placebo group ($p<0.0001$). The study met its key secondary endpoint of change from baseline in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN), showing that treatment with eplontersen significantly improved patient-reported quality of life compared to the external placebo group

(p<0.0001). Eplontersen also demonstrated a favorable safety and tolerability profile.

Eplontersen is an investigational medicine designed to reduce the production of transthyretin (TTR) protein to treat both hereditary and non-hereditary forms of ATTR amyloidosis (ATTR). In December 2021, Ionis and AstraZeneca entered into a strategic collaboration to develop and commercialize eplontersen. Eplontersen is being jointly developed and commercialized by both companies in the U.S. and will be developed and commercialized in the rest of the world by AstraZeneca, with the exception of Latin America. In January 2022, eplontersen was granted Orphan Drug Designation in the U.S. by the FDA.

In addition to the NEURO-TTRansform study, eplontersen is also currently being evaluated in the global Phase 3 CARDIO-TTRansform study for transthyretin amyloid cardiomyopathy (ATTR-CM), a systemic, progressive and fatal condition that leads to progressive heart failure and death within three to five years from disease onset.

About Eplontersen

Eplontersen is an investigational **LI**gand-**C**onjugated **A**ntisense (LICA) medicine designed to inhibit the production of TTR protein. Eplontersen is being developed as a monthly self-administered subcutaneous injection to treat all types of ATTR. ATTR amyloidosis is a systemic, progressive and fatal disease in which patients experience multiple overlapping clinical manifestations caused by the inappropriate formation and aggregation of TTR amyloid deposits in various tissues and organs, including peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone marrow. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to organ failure and eventually death.

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 with its novel antisense technology. 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, eplontersen 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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