Ionis announces eplontersen met co-primary and secondary endpoints in interim analysis of the Phase 3 NEURO-TTRansform study for hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN)

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- *Eplontersen showed statistically significant and clinically meaningful improvements in mNIS+7 and Norfolk QoL-DN*
- *Eplontersen demonstrated a favorable safety profile*
- *Ionis and AstraZeneca expect to file a New Drug Application this year*

CARLSBAD, Calif., June 21, 2022 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive topline results from a 35-week interim analysis of the Phase 3 NEURO-TTRansform study of Ionis and AstraZeneca's eplontersen in patients with hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN). Eplontersen demonstrated a statistically significant and clinically meaningful change from baseline for the co-primary endpoints of percent change in serum transthyretin (TTR) concentration and the modified Neuropathy Impairment Score +7 (mNIS+7), a measure of neuropathic disease progression, versus the historical placebo group. Eplontersen also met its key secondary endpoint of change from baseline in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN), showing treatment with eplontersen significantly improved patient-reported quality of life versus the historical placebo group.

In the study, eplontersen demonstrated a favorable safety and tolerability profile with no specific concerns. The study data are consistent with the clinical profile seen across Ionis' other LICA programs, further validating how advancements in the company's **LI**gand-**C**onjugated **A**ntisense technology position Ionis to deliver potentially transformative treatments for a range of unmet medical needs.

Based on these study results, the companies will seek regulatory approval for eplontersen for ATTRv-PN and plan to file a new drug application with the U.S. Food and Drug Administration this year.

"These encouraging data reinforce the safety profile of eplontersen and demonstrate clear evidence of its potential to provide much needed therapeutic benefit to patients living with hereditary transthyretin-mediated amyloid polyneuropathy," said Teresa Coelho, M.D., a neurologist and neurophysiologist at Hospital Santo António, Centro Hospitalar Universitário do Porto, Portugal and an investigator for the NEURO-TTRansform study.

"We are pleased that the data in the NEURO-TTRansform study demonstrate eplontersen had a positive impact on disease progression, including improvement in neuropathy impairment and quality of life in a substantial number of patients. These highly statistically significant and clinically meaningful results put us on the cusp of providing a new therapeutic option for polyneuropathy patients living with this debilitating and fatal disease," said Eugene Schneider, M.D., Ionis' executive vice president and chief clinical development officer. "We are grateful to the patients, families and clinicians who are participating in NEURO-TTRansform. Without their commitment the eplontersen program would not have progressed as successfully as it has."

The data from the 35-week interim analysis will be presented at an upcoming medical meeting later this year.

As part of a global development and commercialization agreement between Ionis and AstraZeneca, 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).

Eplontersen was granted Orphan Drug Designation in the U.S. It is also currently being evaluated in the Phase 3 CARDIO-

TTRansform study for amyloid transthyretin cardiomyopathy (ATTR-CM), a systemic, progressive and fatal condition that leads to progressive heart failure and death within four years from diagnosis.

For more information on the NEURO-TTRansform study, please visit: https://clinicaltrials.gov/ct2/show/NCT04136184.

About the NEURO-TTRansform Study

NEURO-TTRansform is a global, open-label, randomized study evaluating the efficacy and safety of eplontersen in patients with hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN). The study has enrolled adult patients with stage 1 or stage 2 polyneuropathy and will compare efficacy of eplontersen to the historical placebo arm from the TEGSEDI® (inotersen) NEURO-TTR registrational study that Ionis completed in 2017. The final primary endpoint analysis will be completed at week 66 and all patients will be followed until week 85 when they will have the option to transition into the open label extension study.

The co-primary efficacy endpoints at week 66 are:

- Percent change from baseline in serum TTR concentration
- Change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7), a measure of neuropathic disease progression
- Change from baseline in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN)

About Eplontersen

Eplontersen is an investigational antisense medicine that uses Ionis' advanced **LI**gand-**C**onjugated **A**ntisense, or LICA, technology designed to inhibit the production of the transthyretin (TTR) protein at its source. Eplontersen, which is planned to be delivered to patients via an autoinjector, is in development to treat all types of ATTR, a systemic, progressive and fatal disease.

About Hereditary Transthyretin Amyloidosis (ATTRv)

Hereditary transthyretin amyloidosis (ATTRv) is a severe, progressive, and life-threatening disease caused by the abnormal formation of the TTR protein and aggregation of TTR amyloid deposits in various tissues and organs throughout the body, including in peripheral nerves, the heart and intestinal tract. The progressive accumulation of TTR amyloid deposits in these organs often leads to intractable peripheral sensorimotor neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations. Hereditary transthyretin amyloidosis causes significant morbidity and progressive decline in quality of life, severely impacting activities of daily living. The disease often progresses rapidly and can lead to premature death. The median survival is 4.7 years following diagnosis.

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been the 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 premier late-stage pipeline highlighted by industry-leading cardiovascular and neurological franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming a leading, fully integrated biotechnology company.

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 those related to the impact COVID-19 could have on our business, and 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, 2021, and the most recent Form 10-Q quarterly filing, 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.

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