Eplontersen Phase 3 results published in JAMA show consistent and sustained benefit

September 28, 2023

- *Publication of NEURO-TTRansform study in patients with hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN) showed eplontersen halted disease progression and continuously improved quality of life at 35-, 66- and 85-week analyses*

- *Data demonstrates consistent and sustained benefit on all co-primary and secondary endpoints*

CARLSBAD, Calif., Sept. 28, 2023 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced that *The Journal of the American Medical Association* (JAMA) published positive results from the Phase 3 NEURO-TTRansform study of eplontersen, an investigational treatment for hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN).

Results from the week 66 primary analysis showed that eplontersen-treated patients demonstrated improvement across all co-primary and secondary endpoints, including serum transthyretin (TTR) concentration, neuropathy impairment and quality of life, compared to the external placebo group. An end-of-treatment analysis also showed eplontersen continued to demonstrate sustained improvements through 85 weeks.

"The totality of positive, consistent eplontersen data position this therapy, which can be self-administered, to be an important and empowering potential new medicine for treating hereditary transthyretin-mediated amyloid polyneuropathy," said Sami Khella, M.D., chief, department of neurology at Penn Presbyterian Medical Center, professor of clinical neurology at the Perelman School of Medicine at the University of Pennsylvania School of Medicine and a principal investigator on the NEURO-TTRansform trial. "Without treatment, hereditary transthyretin-mediated amyloid polyneuropathy is a debilitating and devasting disease that can ultimately result in death. The JAMA publication reinforces the growing body of evidence showing that eplontersen significantly reduces serum transthyretin concentration, may halt progression of neuropathy impairment, and improves overall patient quality of life, providing hope to this community."

"These data reinforce the ability of eplontersen to halt disease progression and improve quality of life throughout the 19-month treatment period," said Eugene Schneider, M.D., executive vice president and chief clinical development and operations officer for Ionis. "We look forward to the upcoming FDA action date in December and bringing eplontersen to this underserved patient community in the U.S. and around the world."

In the NEURO-TTRansform Phase 3 study, patients treated with eplontersen demonstrated consistent and sustained benefit on the three co-primary endpoints of serum transthyretin (TTR) concentration, neuropathy impairment measured by modified Neuropathy Impairment Score +7 (mNIS+7) and quality of life (QoL) on the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN):

- Eplontersen achieved a least squares (LS) mean reduction of 82% in TTR serum concentration from baseline at 65 weeks compared to an 11% reduction from baseline in the external placebo group ($p<0.001$).
- Eplontersen demonstrated statistically significant benefits on both mNIS+7 and Norfolk QoL-DN at 35 weeks versus the external placebo group, which were further improved at 66 weeks. Eplontersen halted disease progression as measured by modified Neuropathy Impairment Score +7 (by modified mNIS+7), resulting in a 0.3 point LS mean increase at week 66 compared to a 25.1 point increase for the external placebo group from baseline (24.8 point LS mean improvement; $p<0.001$). Overall, 47% of treated patients showed improvements in neuropathy at 66 weeks compared to baseline versus 17% in the external placebo group. Among study completers, 53% of treated patients showed improvements in neuropathy at 66 weeks compared to baseline versus 19% in the external placebo group.
- In addition, eplontersen improved QoL (on Norfolk QoL-DN), demonstrating a 5.5 point LS mean decrease at 66 weeks (improvement) on the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN), compared to a 14.2 point increase (worsening) in the external placebo group (19.7 point LS mean improvement; $p<0.001$). Overall, 58% of treated patients showed improvements in QoL at 66 weeks compared to baseline versus 20% in the external placebo group. Among study completers, 65% of treated patients showed improvements in QoL at 66 weeks compared to baseline versus 23% in the external placebo group.
- Eplontersen also achieved statistically significant improvements in all secondary endpoints versus the external placebo group through 66 weeks and continued to demonstrate a favorable safety and tolerability profile. The rate of treatment-emergent adverse events in the eplontersen group was comparable to the external placebo group across all major categories. There were no adverse events of special interest that led to study drug discontinuation.

Results from the end-of-treatment analysis showed eplontersen provided sustained improvements through 85 weeks. Eplontersen continued to demonstrate a sustained reduction in serum TTR concentration, continued to halt disease progression as measured by the mNIS+7, and demonstrated continued improvement in QoL as measured by the Norfolk QoL-DN, all compared to baseline.

Ionis and AstraZeneca presented the results from the 35- and 66-week analyses as an Emerging Science presentation at the American Academy of Neurology Annual Meeting in April. The results from the 85-week end-of-treatment analysis of the trial will be submitted to an upcoming medical meeting.

As part of a global development and commercialization agreement, Ionis and AstraZeneca are seeking regulatory approval for eplontersen for the treatment of ATTRv-PN in the U.S. and plan to seek regulatory approval in Europe and other parts of the world. This agreement was recently expanded to include exclusive rights for AstraZeneca to commercialize eplontersen in Latin America and all other countries outside the U.S. Eplontersen was granted Orphan Drug Designation in the U.S. The U.S. Food and Drug Administration (FDA) granted a PDUFA action date of Dec.

22, 2023.

Eplontersen is currently being evaluated in the CARDIO-TTRansform Phase 3 study for transthyretin-mediated amyloid cardiomyopathy (ATTR-CM), a systemic, progressive and fatal condition that typically leads to progressive heart failure and often 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 Hereditary Transthyretin-Mediated Amyloid Polyneuropathy (ATTRv-PN)

ATTRv-PN is caused by the accumulation of misfolded mutated TTR protein in the peripheral nerves. Patients with ATTRv-PN experience ongoing debilitating nerve damage throughout their body resulting in the progressive loss of motor functions, such as walking. These patients also accumulate TTR in other major organs, which progressively compromises their function. The damage from misfolded TTR protein accumulation leads to disability within five years of diagnosis and is generally fatal within a decade.

About the NEURO-TTRansform Study

NEURO-TTRansform is a global, open-label, randomized trial evaluating the efficacy and safety of eplontersen in patients with ATTRv-PN at week 35, week 66 and week 85. The final analysis comparing eplontersen to an external placebo group was completed at week 66. All patients were then followed on treatment until week 85 and evaluated four weeks after the last dose in an end-of-trial assessment. Following treatment and the end-of-trial assessments, patients were eligible to enter an open-label extension study to continue receiving eplontersen once every four weeks or enter a 20-week post-treatment evaluation period. For more information on the NEURO-TTRansform study, please visit: https://clinicaltrials.gov/ct2/show/NCT04136184

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 four 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 eplontersen, Ionis' technologies 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 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, and the most recent Form 10-Q quarterly filing, which are on file with the Securities and Exchange Commission. 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" all refer to Ionis Pharmaceuticals and its subsidiaries.

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