Eplontersen halted ATTRv-PN disease progression and improved neuropathy impairment and quality of life in Phase 3 study through 66 weeks

April 24, 2023

- *NEURO-TTRansform study met all co-primary and secondary endpoints*
- *Positive results to be presented today at AAN 2023 demonstrate eplontersen efficacy, safety and administration profile may provide an important new treatment option in this fatal disease with significant unmet need*
- *Ionis to host webcast on Tuesday, April 25 at 1 p.m. ET*

CARLSBAD, Calif., April 24, 2023 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced that the Phase 3 NEURO-TTRansform study for AstraZeneca and Ionis' eplontersen in patients with hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN) met all co-primary endpoints and secondary endpoints at 66 weeks versus an external placebo group. The positive results are being presented today in an Emerging Science Session at the American Academy of Neurology (AAN) 2023 Annual Meeting in Boston. ATTRv-PN is a debilitating disease driven by the progressive accumulation of TTR amyloid deposits, which causes progressive nerve damage and leads to organ failure and eventually death.

At 66 weeks, patients treated with eplontersen demonstrated consistent and sustained benefit on the three co-primary endpoints measuring serum transthyretin (TTR) concentration, neuropathy impairment and quality of life:

- Eplontersen achieved a least squares (LS) mean reduction of 82% in serum TTR concentration from baseline, compared to an 11% reduction from baseline in the external placebo group ($p<0.0001$).
- Eplontersen halted disease progression as measured by modified Neuropathy Impairment Score +7 (mNIS+7), resulting in a 0.28 point LS mean increase compared to a 25.06 point increase for the external placebo group from baseline (24.8 point LS mean improvement; $p<0.0001$).
    - 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.
- Eplontersen improved quality of life demonstrating a 5.5 point LS mean decrease (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; $p<0.0001$).
    - 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 demonstrated statistically significant benefits on both mNIS+7 and Norfolk QoL-DN at 35 weeks versus the external placebo, which were further improved at 66 weeks.

Eplontersen achieved statistically significant improvements in all secondary endpoints versus the external placebo group.

Eplontersen 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.

"In the past, patients with hereditary transthyretin amyloid polyneuropathy usually deteriorated given the limited available treatments. This new study shows eplontersen can halt progression of neuropathy and improve quality of life at 66 weeks when compared to placebo," 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 study. "Today's important results demonstrate that eplontersen has a consistent and sustained treatment effect and reinforces its potential as an important medicine for the thousands of patients living with this debilitating and fatal disease."

"In the NEURO-TTRansform study, we were encouraged to see a substantial number of patients treated with eplontersen improved in measures of neuropathy impairment and quality of life at both the interim and final analyses," said Eugene Schneider, M.D., executive vice president and chief clinical development officer for Ionis. "We and our partners at AstraZeneca are especially grateful to the patients who participated in this study. With our potential approval in the U.S. in December and plans to file for regulatory approval in the EU and other countries, we are looking forward to potentially bringing eplontersen to ATTRv-PN patients in this largely underrecognized global patient population."

The NEURO-TTRansform Emerging Science presentation and poster at AAN can be found on Ionis' website after today's AAN presentation at 11:57 a.m. ET.

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. The U.S. Food and Drug Administration accepted the New Drug Application for eplontersen for the treatment of ATTRv-PN with a PDUFA action date of December 22, 2023. Eplontersen was granted Orphan Drug Designation in the U.S.

Eplontersen is currently being evaluated in the Phase 3 CARDIO-TTRansform 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.

Webcast

Ionis will host a webcast to discuss the detailed 66-week results from the NEURO-TTRansform study on Tuesday, April 25 at 1 p.m. ET. Interested parties may access the webcast here. A webcast replay will be available for a limited time.

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)

Hereditary transthyretin-mediated amyloid polyneuropathy (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. The trial enrolled 168 adult patients with ATTRv-PN Stage 1 or Stage 2 and up to week 66 eplontersen is being compared to the external placebo group from the NEURO-TTR registrational trial for inotersen that Ionis completed in 2017. The final analysis comparing eplontersen to external placebo was completed at week 66 and all patients will be followed on treatment until week 85, when they will have the option to transition into an open-label extension study. 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 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.

Editor's Note: The NEURO-TTRansform study was funded by AstraZeneca and Ionis. Dr. Khella reports research support from and scientific advisory board participation with AstraZeneca, and compensation for serving as a consultant for Ionis.

View original content to download multimedia:https://www.prnewswire.com/news-releases/eplontersen-halted-attrv-pn-disease-progression-and-improved-neuropathy-impairment-and-quality-of-life-in-phase-3-study-through-66-weeks-301804971.html

SOURCE Ionis Pharmaceuticals, Inc.

Ionis Investor Contact: D. Wade Walke, Ph.D., info@ionisph.com, 760-603-2331; Ionis Media Contact: Sophia Patel, ionis_ca@ionisph.com, 760-603-4679