Ionis completes enrollment in pivotal NEURO-TTRansform study of eplontersen

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- Results from interim analysis expected by mid-2022
- NDA filing to potentially follow by year-end 2022

CARLSBAD, Calif., July 29, 2021 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), the leader in RNA-targeted therapies, today announced it has completed enrollment of NEURO-TTRansform, the company's Phase 3 study of eplontersen, formerly AKCEA-TTR-L_{Rx}, for people with hereditary transthyretin-mediated amyloid polyneuropathy (hATTR-PN). The company has exceeded the enrollment target in NEURO-TTRansform and expects to register more than 160 patients in the study.

Eplontersen is an investigational antisense medicine designed to inhibit production of transthyretin (TTR), a protein that forms the amyloid deposits that cause debilitating nerve damage throughout the body. Eplontersen utilizes Ionis' advanced **LI**gand **C**onjugated **A**ntisense (LICA) technology. In a Phase 1 clinical trial, patients treated with eplontersen experienced reductions in TTR of up to 94 percent.

"The speed of enrollment in our pivotal NEURO-TTRansform study speaks to the urgent need for new treatment options for people living with hATTR amyloidosis," said Brett P. Monia, Ph.D., Ionis' chief executive officer. "Because eplontersen utilizes Ionis' LICA technology, it offers the advantages of high potency, convenient, infrequent dosing and an attractive safety and tolerability profile. We remain dedicated to advancing eplontersen as rapidly as possible and look forward to announcing results from a formal interim analysis by mid-year 2022, with NDA filing to potentially follow by year-end 2022."

Ionis is also studying eplontersen in the CARDIO-TTRansform Phase 3 study in patients with hereditary and wild-type cardiomyopathy (ATTR-CM).

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 polyneuropathy due to hATTR amyloidosis. The study has enrolled adult patients with stage 1 or stage 2 polyneuropathy and will be compared to the historical placebo arm from the TEGSEDI® (inotersen) NEURO-TTR registrational study that Ionis completed in 2017. There will be a formal interim analysis at week 35 analyzing the co-primary efficacy endpoints of percent change from baseline in serum TTR concentration and change from baseline in mNIS+7.

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 antisense drug 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 is in development to treat a broad population of patients with both hereditary and wild-type forms of transthyretin amyloidosis, or ATTR amyloidosis.

About Hereditary Transthyretin (hATTR) Amyloidosis

hATTR amyloidosis 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. hATTR 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 neurological and cardiometabolic franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming one of the most successful biotechnology companies.

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

Ionis' Forward-looking Statement

This press release includes forward-looking statements regarding Ionis' business, 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 December 31, 2020, 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.

View original content to download multimedia:https://www.prnewswire.com/news-releases/ionis-completes-enrollment-in-pivotal-neuro-ttransform-study-of-eplontersen-301343941.html

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