Ionis and AstraZeneca to develop and commercialize eplontersen

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- Collaboration expected to enable faster and deeper market penetration into growing global TTR amyloidosis market
- The companies will jointly develop and commercialize eplontersen in the U.S., AstraZeneca has exclusive rights to commercialize in rest of the world
- Bolsters Ionis' commercial organization as it prepares for multiple product launches
- Ionis to hold webcast Dec. 7, 2021, at 10 a.m. Eastern Time

CARLSBAD, Calif., Dec. 7, 2021 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), the leader in RNA-targeted therapies, today announced it has entered into a strategic collaboration agreement with AstraZeneca to develop and commercialize eplontersen, Ionis' investigational antisense medicine for the treatment of transthyretin amyloidosis (ATTR).

Eplontersen, formerly known as IONIS-TTR-L_{Rx}, is designed to reduce the production of transthyretin, or TTR protein, to treat ATTR, a systemic, progressive and fatal disease. It uses Ionis' advanced **LI**gand-**C**onjugated **A**ntisense (LICA) technology.

The companies will develop a global strategy for developing, manufacturing and commercializing eplontersen. A breakdown of responsibilities of the collaboration includes, but is not limited to:

- Ionis will continue to lead the conduct of the global Phase 3 clinical trials in patients with hereditary ATTR amyloidosis (hATTR) with polyneuropathy (NEURO-TTRansform) and cardiomyopathy (CARDIO-TTRansform).
- Ionis will manufacture and supply eplontersen for the ongoing clinical trials and process qualifications. AstraZeneca will be responsible for commercial supply, with transition timing to be agreed by both companies.
- Ionis and AstraZeneca will have shared responsibility for medical affairs and commercial activities in the U.S.
- AstraZeneca will have an exclusive license for eplontersen outside the U.S. except certain countries in Latin America.

"We believe that bringing together Ionis' industry-leading experience in RNA-targeted therapeutics and deep knowledge of the TTR amyloidosis market with AstraZeneca's global scale and leadership in cardiovascular drug development and commercialization will enable faster and deeper market penetration for the benefit of patients," said Brett P. Monia, Ph.D., chief executive officer of Ionis. "In addition to being the best strategy to maximize patient and shareholder value for eplontersen, this agreement also represents a key step in bolstering our commercial organization as we prepare to launch multiple products."

Hereditary ATTR amyloidosis (hATTR) with polyneuropathy is expected to be the first indication for which the companies will seek regulatory approval for eplontersen, with the potential to file a new drug application (NDA) with the U.S. Food and Drug Administration by the end of 2022.

Under the terms of the agreement, Ionis will receive a $200 million upfront payment, up to $485 million in development and approval milestones, and up to $2.9 billion in sales-related milestone payments. The collaboration includes territory-specific development, commercial and medical affairs cost-sharing provisions. Ionis is also eligible to earn royalties in the range of low double-digit to mid-20s percentage depending on region.

The agreement is expected to become effective by the end of 2021, subject to the satisfaction of requirements of the Hart-Scott-Rodino Antitrust Improvements Act of 1976.

Webcast

Ionis will conduct a webcast on Dec. 7 at 10 a.m. Eastern Time to discuss this announcement and related activities. Interested parties may access the webcast here. A webcast replay will be available for a limited time at the same address.

About eplontersen

Eplontersen (formerly known as IONIS-TTR-L_{Rx}) is an investigational antisense medicine developed with Ionis' **LI**gand-**C**onjugated **A**ntisense (LICA) technology that is designed to reduce the production of transthyretin, or TTR protein, to treat all types of TTR amyloidosis (ATTR), a systemic, progressive, and fatal disease. In patients with ATTR, both the mutant and wild type (wt) TTR protein builds up as fibrils in tissues, such as the peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone marrow. The presence of TTR fibrils interferes with the normal functions of these tissues. As the TTR protein fibrils enlarge, more tissue damage occurs and the disease worsens, resulting in poor quality of life and eventually death. Ionis is currently evaluating eplontersen through its CARDIO-TTRansform Phase 3 study for the treatment of patients with hereditary and wild-type cardiomyopathy (ATTR-CM) and its NEURO-TTRansform Phase 3 study for the treatment of patients with hereditary transthyretin-mediated amyloid polyneuropathy (hATTR-PN).

About TTR Amyloidosis (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.

Polyneuropathy due to hATTR is caused by the accumulation of misfolded mutated TTR protein in the peripheral nerves. Patients with polyneuropathy due to hATTR 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 compromise their function and eventually leading to death within five to fifteen years of disease onset.

ATTR cardiomyopathy is caused by the accumulation of misfolded TTR protein in the cardiac muscle. Patients experience ongoing debilitating heart damage resulting in progressive heart failure, which results in death within 3 to 5 years from disease onset. ATTR cardiomyopathy includes both the genetic and wild-type form of the disease.

Worldwide, there are an estimated 300,000 – 500,000[1,2] patients with ATTR.

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.

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 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.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

[1] Mohamed-Salem L, et al. Prevalence of wild type ATTR assessed as myocardial uptake in bone scan in the elderly population. Int J Cardiol. 2018 Nov 1;270:192-196. doi: 10.1016/j.ijcard.2018.06.006.
[2] Cuscaden C, et al. Estimation of prevalence of transthyretin (ATTR) cardiac amyloidosis in an Australian subpopulation using bone scans with echocardiography and clinical correlation. J Nucl Cardiol. 2020 May 8. doi: 10.1007/s12350-020-02152-x.

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