Ionis completes enrollment in landmark Phase 3 CARDIO-TTRansform study in patients with TTR-mediated amyloid cardiomyopathy

July 31, 2023

- *CARDIO-TTRansform is the largest, most comprehensive ATTR-CM study with more than 1,400 patients enrolled*
- *Eplontersen is currently under U.S. FDA review for ATTRv-polyneuropathy, with ATTR-CM representing a second, larger potential patient population*

CARLSBAD, Calif., July 31, 2023 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced the completion of enrollment in the Phase 3 CARDIO-TTRansform cardiovascular outcomes study of eplontersen in patients with transthyretin-mediated amyloid cardiomyopathy (ATTR-CM), a large and growing patient population at risk of life-threatening cardiovascular (CV) events. The study enrolled more than 1,400 patients.

Eplontersen is an investigational antisense medicine designed to inhibit the production of transthyretin and slow the progression of cardiomyopathy for people living with hereditary or wild-type ATTR-CM.

"CARDIO-TTRansform is the largest and most comprehensive ATTR-CM study ever conducted. The evaluation of eplontersen in this broad, diverse patient population will enable robust and clinically meaningful analysis of the composite endpoint of CV mortality and recurrent CV events," said Eugene Schneider, M.D., executive vice president and chief clinical development officer for Ionis. "It will also allow us to gather data from important patient subsets, including patients with or without stabilizer therapy and those with or without hereditary disease within the evolving ATTR-CM landscape. We look forward to reporting results as early as the first half of 2025."

As part of a global development and commercialization agreement, Ionis and AstraZeneca are seeking regulatory approval for eplontersen for the treatment of transthyretin-mediated amyloid polyneuropathy (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 Dec. 22, 2023. Eplontersen was granted Orphan Drug Designation in the U.S.

For more information on the CARDIO-TTRansform study, please visit www.clinicaltrials.gov (NCT04136171).

About the CARDIO-TTRansform Study

CARDIO-TTRansform is a global, double-blind, randomized, placebo-controlled Phase 3 cardiovascular outcome study in more than 1,400 patients with ATTR cardiomyopathy (ATTR-CM). It is designed to compare eplontersen to placebo in patients with both wild-type ATTRwt-CM and hereditary ATTRv-CM who are either naïve to treatment or on a currently available standard of care. The primary composite endpoint is cardiovascular (CV) mortality and recurrent CV clinical events comparing the two study arms up to week 140. Secondary endpoints include the change from baseline in the 6-minute walk test (6MWT) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores at week 121, as well as the rates of CV mortality, CV clinical events and all-cause mortality at week 140.

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 Transthyretin-mediated Amyloid Cardiomyopathy (ATTR-CM)

Transthyretin-mediated amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed and potentially fatal disease. It 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 three to five years from disease onset. ATTR-CM 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-CM.

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.

Ionis Pharmaceuticals® is a registered trademark of Ionis Pharmaceuticals, Inc.

[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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