WAINZUA (eplontersen) recommended for approval in the EU by CHMP for the treatment of adults with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis

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- Recommendation based on NEURO-TTRansform Phase 3 results showing WAINZUA demonstrated consistent and sustained benefit improving neuropathy impairment and quality of life versus placebo

CARLSBAD, Calif., Oct. 21, 2024 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) announced today that Ionis' and AstraZeneca's WAINZUA (eplontersen) has been recommended for approval by the Committee for Medicinal Products for Human Use (CHMP) in the European Union (EU) for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, commonly referred to as hATTR-PN or ATTRv-PN. If approved by the European Commission, WAINZUA will be the only approved medicine in the EU for the treatment of ATTRv-PN that can be self-administered monthly via an auto-injector.

The CHMP based its opinion on the positive NEURO-TTRansform Phase 3 trial which showed that through 66 weeks, patients treated with WAINZUA demonstrated consistent and sustained benefit on the co-primary endpoints of serum transthyretin (TTR) concentration and neuropathy impairment measured by modified Neuropathy Impairment Score +7 (mNIS+7), and key secondary endpoint of quality of life (QoL) on the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) versus external placebo. WAINZUA continued to demonstrate a favorable safety and tolerability profile throughout the NEURO-TTRansform trial.

ATTRv-PN is a debilitating disease that leads to peripheral nerve damage with motor disability within five years of diagnosis and, without treatment, is generally fatal within a decade. WAINZUA is a once-monthly RNA-targeted medicine designed to reduce the production of TTR protein at its source.

"Hereditary transthyretin-mediated amyloidosis with polyneuropathy remains a progressive and debilitating disease in Europe and other parts of the world, despite currently available medicines," said Brett P. Monia, Ph.D., chief executive officer, Ionis. "The CHMP recommendation is an important step toward making WAINZUA available in Europe, which, if approved, will be the only medicine in the EU for the treatment of transthyretin-mediated amyloidosis with polyneuropathy that can be self-administered monthly via an auto-injector. We are proud to partner with AstraZeneca whose global leadership and expertise positions our alliance to rapidly and effectively bring WAINZUA to many people living with hereditary transthyretin-mediated amyloidosis with polyneuropathy in Europe, pending the EMA's decision."

In December 2023, eplontersen was approved in the U.S. for the treatment of ATTRv-PN, under the brand name WAINUA™ (eplontersen). WAINUA is now gaining approvals in additional countries worldwide, including Canada. As part of a global development and commercialization agreement, AstraZeneca and Ionis are commercializing WAINUA in the U.S. The companies are seeking regulatory approval in Europe and other parts of the world where AstraZeneca has exclusive rest of world commercialization and development rights. Eplontersen has also been granted Orphan Drug Designation in the U.S. and in the EU for the treatment of transthyretin-mediated amyloidosis (ATTR).

Eplontersen is also currently being evaluated in the global CARDIO-TTRansform Phase 3 study for the treatment of adults with ATTR-CM. The trial is fully enrolled with more than 1,400 patients – making it the largest, most comprehensive study to date in this patient population. More information on the CARDIO-TTRansform study (NCT04136171) is available at www.clinicaltrials.gov.

About TTR Amyloidosis

ATTR is caused by the accumulation of liver-derived misfolded TTR protein in tissues, such as the heart and the peripheral

nerves, causing organ damage and failure. ATTR then causes complications, leading to cardiovascular, neurological and renal diseases such as heart failure and chronic kidney disease. There are both hereditary (ATTRv) and non-hereditary (wild-type) forms of ATTR. ATTR is a rapidly progressive and fatal disease that requires timely recognition of symptoms. ATTR has several phenotypes including ATTR-cardiomyopathy (CM), which predominantly impacts the heart, potentially leading to heart failure, ATTR-polyneuropathy (PN), which predominantly affects the peripheral nervous system and mixed phenotype, where patients experience symptoms of both. Worldwide, there are an estimated 300,000 – 500,000 patients with ATTR-CM and about 10,000 – 40,000 patients with ATTRv-PN.

About NEURO-TTRansform

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, which is still ongoing. Full results from the NEURO-TTRansform trial were published in *The Journal of the American Medical Association (JAMA)* demonstrating the benefit of eplontersen across the spectrum of ATTRv-PN at 35, 66 and 85 weeks of treatment.

About WAINZUA / WAINUA™ (eplontersen)

Eplontersen is a once-monthly RNA-targeted medicine that provides upstream suppression of transthyretin (TTR) production and is designed to precisely target and reduce the production of TTR protein at its source in the liver.

WAINZUA has been approved in the U.S. and Canada under the brand name WAINUA™ (eplontersen) for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults, commonly referred to as hATTR-PN or ATTRv-PN. Please see link for full U.S. Prescribing Information. WAINZUA is not yet approved for any indication in Europe.

U.S. INDICATION for WAINUA™ (eplontersen)

WAINUA injection for subcutaneous use 45 mg is indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

IMPORTANT SAFETY INFORMATION for WAINUA™ (eplontersen)

WARNINGS AND PRECAUTIONS

Reduced Serum Vitamin A Levels and Recommended Supplementation WAINUA leads to a decrease in serum vitamin A levels. Supplement with recommended daily allowance of vitamin A. Refer patient to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

ADVERSE REACTIONS

Most common adverse reactions (≥9% in WAINUA-treated patients) were vitamin A decreased (15%) and vomiting (9%).

Please see link to U.S. Full Prescribing Information for WAINUA.

About Ionis Pharmaceuticals, Inc.

For three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has five marketed medicines and a leading pipeline in neurology, cardiology, and other areas of high patient need. As the pioneer in RNA-targeted medicines, Ionis continues to drive innovation in RNA therapies in addition to advancing new approaches in gene editing. A deep understanding of disease biology and industry-leading technology propels our work, coupled with a passion and urgency to deliver life-changing advances for patients. To learn more about Ionis, visit Ionis.com and follow us on X (Twitter) and LinkedIn.

Ionis Forward-looking Statements

This press release includes forward-looking statements regarding eplontersen, Ionis' business, and the therapeutic and commercial potential of Ionis' commercial medicines, additional medicines in development and technologies. 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. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. 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, 2023, and most recent Form 10-Q, which are on file with the SEC. Copies of these and other documents are available at www.Ionis.com.

Ionis Pharmaceuticals® is a registered trademark of Ionis Pharmaceuticals, Inc. WAINUA™ is a trademark of AstraZeneca plc.

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