



## Update on CARDIO-TTRansform Phase 3 trial of eplontersen in adults with transthyretin-mediated amyloid cardiomyopathy

July 9, 2026

*– Study missed primary endpoint of composite outcome of cardiovascular (CV) mortality and recurrent CV events; in a pre-specified subgroup analysis, a nominally significant result was observed with eplontersen monotherapy –*

*– Favorable safety profile consistent with previous results –*

CARLSBAD, Calif.--(BUSINESS WIRE)--Jul. 9, 2026-- [Ionis Pharmaceuticals, Inc.](#) (Nasdaq: IONS) and partner AstraZeneca today announced that the CARDIO-TTRansform Phase 3 trial for eplontersen in patients with transthyretin-mediated amyloid cardiomyopathy (ATTR-CM) did not meet the primary efficacy endpoint of the composite outcome of cardiovascular (CV) mortality and recurrent CV clinical events up to Week 140 compared with placebo. In this contemporary patient population treated with standard of care, including a majority on a stabilizer, adding eplontersen did not provide a statistically significant benefit.

In a prespecified subgroup analysis of patients treated with eplontersen monotherapy compared to placebo, a nominally significant hazard ratio of 0.71 was observed on the composite outcome of CV mortality and recurrent CV events. In patients who were on stabilizer therapy at baseline, no treatment effect was observed.

In the overall population, multiple secondary, imaging and biomarker analyses favored eplontersen versus placebo. Large and sustained reductions in transthyretin (TTR) were observed, consistent with the silencer class for ATTR. Eplontersen was well tolerated, with a favorable safety profile consistent with previous results.

“We believe these findings reflect the rapidly evolving treatment landscape, in which contemporary ATTR-CM patients are widely treated with stabilizers,” said Brett P. Monia, Ph.D., chief executive officer, Ionis. “Although we are disappointed that the study did not meet the primary endpoint, these results have the potential to guide the treatment landscape for ATTR-CM and contribute to advancing future care for patients. We extend our sincere gratitude to the patients, families and investigators whose participation helped progress the science of ATTR-CM treatment.”

CARDIO-TTRansform is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study to evaluate the safety and efficacy of eplontersen compared to placebo in participants with ATTR-CM receiving available standard of care: 57% of patients in each arm received a stabilizer treatment at baseline, and a further 24% in each arm initiated a stabilizer during the trial.

“Ionis continues to be well positioned to create substantial value in both the near and long term, driven primarily by the strength of our wholly owned portfolio,” said Monia. “We have multiple successful independent launches underway, including TRYNGOLZA, our first in a prevalent population, and we continue to advance a robust pipeline of potentially transformational medicines. We remain on track to deliver a steady cadence of new medicines to patients and achieve cash flow breakeven by 2028.”

“Over the last decade, multiple advances and increased awareness of ATTR-CM have driven earlier diagnosis, improved management and better outcomes for patients,” said Mathew Maurer, M.D., primary investigator, Arnold and Arlene Goldstein professor of cardiology, Columbia University Irving Medical Center. “These data from the largest enrolled study of a contemporary ATTR-CM patient population provide important clarity for the field that will help inform future treatment decisions in ATTR-CM.”

Ionis and AstraZeneca will continue to analyze the full data set, and results will be shared with the scientific community at the European Society of Cardiology (ESC) Congress in August 2026.

### **Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM)**

ATTR-CM is a systemic, progressive, debilitating and fatal disease that predominantly affects the heart and is an underrecognized cause of heart failure (HF). ATTR-CM, which can be inherited (hereditary, ATTRv) or develop with age (wild-type, ATTRwt), and occurs when amyloid fibrils consisting of misfolded TTR protein build up in the heart, disrupting cardiac structure and function and making it harder for the heart to pump blood throughout the body. Patients commonly present with non-specific symptoms such as shortness of breath, swelling, heart palpitations, dizziness, weakness and fatigue, which can contribute to misdiagnosis and delays in care. With an estimated 300,000 to 500,000 people living with ATTR-CM worldwide, greater awareness, earlier diagnosis and appropriate targeted treatment are critical to improving outcomes and quality of life for patients.

### **About the CARDIO-TTRansform Trial**

CARDIO-TTRansform is a global, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy and safety of eplontersen in adults with wild-type or hereditary ATTR-CM who are receiving available standard of care therapy. As the largest enrolled ATTR-CM trial to date, CARDIO-TTRansform enrolled 1,432 participants across 130 study sites in 20 countries, who were randomized 1:1 to receive eplontersen 45 mg or placebo by subcutaneous injection every four weeks. The primary endpoint is a composite of CV mortality and recurrent CV clinical events through Week 140. Secondary endpoints include changes from baseline in the 6-Minute Walk Test and Kansas City Cardiomyopathy Questionnaire overall summary score at Week 140, total recurrent CV clinical events up to Week 140, all-cause mortality up to Weeks 140 and 160, the primary endpoint in the subgroup of patients receiving a TTR stabilizer at baseline and CV mortality through Weeks 140 and 160.

### **About Eplontersen**

Eplontersen is a once-monthly RNA-targeted silencer that can be self-administered via an autoinjector or as a pre-filled syringe by healthcare professional administration in the U.S. It reduces production of TTR protein at its source in the liver. WAINUA® (eplontersen) has now been approved for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults, commonly referred to as hATTR-PN or ATTRv-PN in over 20 countries, including in the EU as Wainzua.

As part of a global development and commercialization agreement, AstraZeneca and Ionis are jointly developing and commercializing eplontersen in the US. Outside the US, AstraZeneca has exclusive rest of world commercialization and development rights.

### **About Ionis Pharmaceuticals, Inc.**

For three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has marketed medicines and a leading pipeline in neurology, cardiometabolic disease and select 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](https://www.ionis.com) and follow us on [X \(Twitter\)](#), [LinkedIn](#) and [Instagram](#).

### **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 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 December 31, 2025, and most recent Form 10-Q, 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.

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