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Update on CARDIO-TTRansform Phase III trial for *Wainua* (eplontersen) in adults with transthyretin-mediated amyloid cardiomyopathy

The CARDIO-TTRansform Phase III trial[1] for AstraZeneca and Ionis' *Wainua* (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 140 weeks compared with placebo. *Wainua* was generally well tolerated, with a safety profile consistent with previous results.[2]

In this contemporary patient population treated with standard of care, including a majority on a stabiliser,[3,4] adding *Wainua* did not provide a statistically significant benefit on the composite outcome of CV mortality and recurrent CV events. In a prespecified subgroup analysis of patients treated with *Wainua* monotherapy as compared to placebo, fewer primary composite events (CV mortality and recurrent CV events) were observed and this result was nominally significant. In patients who were on stabiliser therapy at baseline, no treatment effect was observed.

Sharon Barr, Executive Vice President, BioPharmaceuticals R&D, said: "The CARDIO-TTRansform trial was designed to examine the role of *Wainua*, a gene silencer treatment, on top of today's standard of care in reducing recurring cardiovascular events and mortality. Although the trial did not meet its primary objective, we believe the results support greater scientific understanding of treatment approaches for the hundreds of thousands of patients worldwide suffering from this progressive and often fatal condition."

CARDIO-TTRansform is a Phase III, multicentre, randomised, double-blinded, placebo-controlled trial[1] to evaluate the safety and efficacy of *Wainua* compared to placebo in participants with ATTR-CM receiving available standard of care: 57% of patients in each arm received a stabiliser treatment at baseline, and a further 24% in each arm initiated a stabiliser during the trial.[3]

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

Notes

Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM)

ATTR-CM is a systemic, progressive, debilitating and fatal disease that predominantly affects the heart and is an underrecognised cause of HF.[5,6] ATTR-CM, which can be inherited (hereditary, ATTRv) or develop with age (wild-type, ATTRwt), 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.[5-7] 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.[5,7] With an estimated 300,000 to 500,000 people living with ATTR-CM worldwide,[9] greater awareness, earlier diagnosis and appropriate targeted treatment are critical to improving outcomes and quality of life for patients.[10,11]

CARDIO-TTRansform Trial

CARDIO-TTRansform is a global, randomised, double-blind, placebo-controlled Phase III trial evaluating the efficacy and safety of *Wainua* (eplontersen) in adults with wild-type or hereditary ATTR-CM who are receiving available standard of care.[1,3,4] As the largest enrolled ATTR-CM trial to date, CARDIO-TTRansform enrolled 1,432 participants across 130 study sites in 20 countries, who were randomised 1:1 to receive eplontersen 45 mg or placebo by subcutaneous injection every four weeks.[3] The primary endpoint is a composite of CV mortality and recurrent CV clinical events through Week 140.[4] 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 stabiliser at baseline and CV mortality through Weeks 140 and 160.[4]

***Wainua* (eplontersen)**
Wainua 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 US.[12-14] It provides upstream suppression of serum TTR production at its source in the liver.[12,13] *Wainua* 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*.[15]

As part of a global development and commercialisation agreement, AstraZeneca and Ionis are jointly developing and commercialising *Wainua* in the US. Outside the US, AstraZeneca has exclusive rest of world commercialisation and development rights.

AstraZeneca in CVRM
Cardiovascular, Renal and Metabolism (CVRM), part of BioPharmaceuticals, forms one of AstraZeneca's main disease areas and is a key growth driver for the Company. By following the science to understand more clearly the underlying links between the heart, kidneys, liver and pancreas, AstraZeneca is investing in a portfolio of medicines for organ protection by slowing or stopping disease progression and ultimately paving the way towards regenerative therapies. The Company's ambition is to improve and save the lives of millions of people, by better understanding the interconnections between CVRM diseases and targeting the mechanisms that drive them, so we can detect, diagnose and treat people earlier and more effectively.

AstraZeneca
AstraZeneca (LSE/STO/NYSE: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Disease, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca's innovative medicines are sold in more than 125 countries and used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Social Media @AstraZeneca.

Contacts
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