Circulation: Heart Failure

METHODS PAPER

Rationale and Design of CARDIO-TTRansform, a Phase 3 Trial of Eplontersen in Transthyretin Amyloid Cardiomyopathy

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BACKGROUND: Transthyretin amyloidosis with cardiomyopathy is a progressive, fatal disease characterized by deposition of extracellular misfolded transthyretin (TTR) in the myocardium. Eplontersen is an N-acetylgalactosamine ligand–conjugated antisense oligonucleotide targeting hepatocyte *TTR* messenger RNA to reduce the production of circulating TTR.

METHODS: CARDIO-TTRansform is a Phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of eplontersen in transthyretin amyloidosis with cardiomyopathy. Key inclusion criteria include histological evidence of amyloid deposits or grade 2 to 3 cardiac uptake on cardiac scintigraphy in the absence of plasma cell dyscrasia, New York Heart Association class I–III, and end-diastolic interventricular septum thickness >12 millimeters. Participants were randomized 1:1 to receive eplontersen 45 mg or placebo, administered subcutaneously every 4 weeks for up to 140 weeks, followed by a 20-week post-treatment evaluation period or open-label extension. Participants received locally available standard of care, including unrestricted use of TTR stabilizers. The primary end point is a composite of cardiovascular mortality and recurrent clinical cardiovascular events through 140 weeks. Secondary end points, in order of testing hierarchy, include changes from baseline in 6-minute walk distance and Kansas City Cardiomyopathy Questionnaire overall summary score, recurrent cardiovascular events, all-cause mortality, the primary end point in the patient subgroup receiving stabilizers at baseline, and cardiovascular mortality. Echocardiography was performed in all participants, with cardiovascular magnetic resonance imaging and technetium scintigraphy in a subset.

CONCLUSIONS: CARDIO-TTRansform is fully enrolled, with 1432 randomized participants who were dosed with study drug or placebo. As the largest transthyretin amyloidosis with cardiomyopathy study to date, it will evaluate whether eplontersen improves cardiovascular outcomes in patients receiving locally available standard of care, including TTR stabilizers.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04136171. URL: http://ClinicalTrialsRegister.eu; Unique identifier: EudraCT number 2019-002835-27.

Key Words: amyloidosis ■ cardiomyopathies ■ eplontersen ■ heart failure ■ transthyretin

Transthyretin amyloidosis (ATTR) is a systemic, progressive, irreversible, and life-threatening disease.[1–4] It is caused by the destabilization of the tetrameric structure of transthyretin (TTR), which dissociates into monomers or oligomers, that misfold and aggregate into insoluble amyloid fibril deposits causing organ

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This work was presented as an oral presentation and abstract at the European Society of Cardiology Heart Failure (ESC-HF) Congress, Barcelona, Spain, May 9-12, 2026.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.126.014205.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- CARDIO-TTRansform is a Phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of eplontersen in variant or wild-type transthyretin amyloidosis with cardiomyopathy, a potentially fatal disease characterized by misfolded transthyretin amyloid deposits in the heart.
- CARDIO-TTRansform is the largest trial to date in transthyretin amyloidosis with cardiomyopathy and was conducted in a contemporary real-world setting with unrestricted use of background stabilizer therapy.
- Eplontersen is an N-acetylgalactosamine–conjugated antisense oligonucleotide designed for targeted delivery to the liver to reduce production of transthyretin.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Results from CARDIO-TTRansform will demonstrate whether eplontersen improves outcomes in patients receiving standard-of-care therapy for transthyretin amyloidosis with cardiomyopathy, including cardiovascular mortality, cardiovascular events (including hospitalization for myocardial infarction, heart failure, arrhythmia, or stroke; and heart failure-related urgent visits to the emergency department or heart failure clinics requiring administration of intravenous diuretics for improvement), exercise function, and health status.
- Changes in cardiac structure and function will be evaluated using echocardiography in all patients, and with cardiovascular magnetic resonance imaging and scintigraphy in separate substudies.
- If successful, the results of CARDIO-TTRansform could support eplontersen as an important novel treatment option for patients with transthyretin amyloidosis with cardiomyopathy.

Nonstandard Abbreviations and Acronyms

6MWT	6-Minute Walk Test
ASO	antisense oligonucleotide
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin amyloidosis with cardiomyopathy
ATTRv-PN	variant transthyretin amyloid polyneuropathy
CK-MB	creatine kinase-muscle/brain fraction
hs-cTnT	high-sensitivity cardiac troponin T
KCCQ	Kansas City Cardiomyopathy Questionnaire
LWYY	Lin, Wei, Yang, and Ying
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
sST2	soluble suppression of tumorigenicity-2
TTR	transthyretin

dysfunction.[5] Circulating TTR is synthesized in the liver and is a physiological transport protein for retinol and thyroxine.[6] ATTR amyloidosis is classified as either variant (ATTRv, previously known as hereditary), which is inherited in an autosomal dominant fashion, or wild-type, which occurs secondary to an acquired. but as yet undefined, pathogenic process associated with aging.[3,4] ATTRv amyloidosis can present with peripheral polyneuropathy (ATTRv-PN), cardiomyopathy (ATTRv-CM), or both, with the combination described as a mixed phenotype.[7,8] Wild-type ATTR cardiomyopathy is typically a disease of older individuals who predominantly have cardiac involvement, where neurological manifestations are uncommon or mild.[3] Amyloid fibrils deposit in the extracellular space of the myocardium, leading to progressive increases in wall thickness and impaired relaxation that cause declines in cardiac function, physical activity, worsening symptoms of heart failure (HF), and impaired quality of life that can ultimately lead to recurrent cardiovascular events and, ultimately, death.[9] Although classically described as a form of restrictive HF with preserved ejection fraction, development of systolic dysfunction is not uncommon.[10] While historically considered rare, diagnosis rates have increased worldwide, and it is evident that ATTR with cardiomyopathy (ATTR-CM) is far more common than previously believed.[9,11]

Approved ATTR therapies are broadly categorized into 2 main groups: TTR stabilizers and silencers.[11–13] Stabilizers such as tafamidis[14] and acoramidis[15] reduce TTR dissociation by stabilizing the tetrameric structure of the TTR protein, preventing amyloid accumulation.[13] Both drugs are approved for the treatment of ATTR-CM.[16,17] Silencers suppress TTR production by binding to and degrading TTR messenger RNA, thereby reducing production of circulating TTR.[13] Currently 4 TTR silencers are approved to treat ATTRv-PN, including the antisense oligonucleotides (ASOs) inotersen[18] and eplontersen,[19] and the small interfering RNAs patisiran[20] and vutrisiran;[21] vutrisiran has also been recently approved for ATTR-CM.[21] While no head-to-head trials have directly compared stabilizers and silencers, current clinical consensus is that silencers are the preferred agents for those with ATTRv and a mixed phenotype given their benefit on polyneuropathy.[11] Other therapeutic approaches under investigation include medications that deplete amyloid fibrils and CRISPR-Cas9–based gene-editing therapy,[22,23] but these have yet to demonstrate clinical benefit in a Phase 3 trial and are not currently approved by regulatory bodies.

Despite the recent advances in care, several unanswered questions remain regarding the clinical

management of ATTR-CM. First, whether silencers provide additional clinical benefits in the setting of contemporary use of background stabilizer therapy has not been definitively established; in the HELIOS-B trial of vutrisiran patients not receiving stabilizer therapy at baseline were not permitted to initiate it within the first 12 months of the study, and the subgroup analysis of patients on a background of stabilizers was underpowered.[24] Second, while ASO silencers are approved for ATTRv-PN, the efficacy of ASOs for ATTR-CM has not been determined. Finally, there is a need for a mechanistic understanding of the impact of TTR reduction on new amyloid load and its relationship to cardiac structure and function. These questions will be addressed by the CARDIO-TTRansform trial evaluating eplontersen, which also includes 2 substudies to investigate the use of scintigraphy and cardiovascular magnetic resonance imaging for the longitudinal assessment of amyloid myocardial burden.

Eplontersen is a novel 2′-*O*-methoxyethyl-modified ASO that is conjugated to a triantennary N-acetylgalactosamine ligand for liver-specific targeting via asialoglycoprotein receptor-mediated uptake (Figure S1).[25] A Phase 3 study, NEURO-TTRansform (NCT04136184), demonstrated that eplontersen produced sustained decreases in plasma TTR which halted neuropathic impairment and improved quality of life for patients with ATTRv-PN compared with a historical placebo group.[26] Eplontersen was approved by the FDA for the treatment of ATTRv-PN in December 2023,[19] and by the European Medicines Agency in March 2025,[27] and can be self-administered at-home with an autoinjector. An exploratory analysis of NEURO-TTRansform participants who had evidence of cardiac involvement suggested favorable changes in echocardiographic parameters associated with eplontersen treatment.[28]

This article discusses the design and rationale of the ongoing CARDIO-TTRansform trial evaluating eplontersen as a therapy for ATTR-CM. Several unique features of the trial have the potential to advance our understanding of ATTR-CM prognosis and treatment; most importantly, CARDIO-TTRansform is the largest trial to date in ATTR-CM and was conducted in a contemporary real-world setting with unrestricted use of background stabilizer therapy.

METHODS

Data requests from qualified researchers will be considered once all 3 of the following criteria are met: (1) 12 months from marketing approval of the study drug in both the United States and the European Union; (2) 18 months from conclusion of the study; and (3) 6 months from the publication of this article. For additional information, visit https://vivli.org/ourmembers/ionis.

Study Design

CARDIO-TTRansform (NCT04136171) is a Phase 3, international, multicenter, double-blind, randomized, placebo-controlled trial consisting of a screening period of up to 10 weeks, followed by randomization with a 140-week double-blind study period, and a 20-week post-treatment evaluation period (Figure 1). The trial is being conducted at 130 sites across 20 countries in North and South America, Europe, and Asia (Figure 2). Participants were randomized to receive eplontersen 45 mg or matching placebo by subcutaneous injection once every 4 weeks for 140 weeks. This eplontersen dose was selected based on pharmacodynamic and safety analyses of the Phase 1 study in healthy volunteers.[29] Randomization (1:1) was stratified by New York Heart Association (NYHA) functional class (I/II versus III), *TTR* variant status (variant versus wild-type), 6-Minute Walk Test (6MWT) distance (≤350 m versus >350 m), and treatment with TTR stabilizer at the time of randomization (yes versus no). Following completion of the 140-week double-blind treatment period, participants may either elect to enroll in an open-label extension study (NCT05667493) or end their participation with a 20-week post-treatment evaluation period (during which no study drug is administered).

Concomitant administration of local standard-of-care TTR stabilizer therapy for ATTR-CM (eg, tafamidis, tafamidis meglumine, acoramidis) is allowed per the investigator's recommendation, if approved, available, and consistent with local clinical practice. Concomitant treatment with other ATTR-CM therapies (ASOs, small interfering RNAs, diflunisal, or doxycycline) or medications typically contraindicated in ATTR-CM (including nondihydropyridine calcium-channel blockers, such as verapamil and diltiazem) is prohibited. Participants are receiving supplemental doses of the recommended daily allowance of vitamin A, given the potential for disruption of vitamin A transport, as transthyretin is a carrier of retinol.[6,30] Periodic assessment of symptomatic vitamin A deficiency using an ocular questionnaire is being conducted for all patients during the trial.

Cardiac imaging is performed locally and interpreted by central core imaging laboratories (see Table S1 for further details). Echocardiography is performed in all study participants within the main trial, and participants are also offered both optional 99m-technetium scintigraphy (99mTc-DPD, 99mTc-PYP, or 99mTc-HMDP) and cardiovascular magnetic resonance imaging as part of substudies NCT06073587 (CARDIO-TTRansform Scintigraphy Sub-study) and NCT06073574 (CARDIO-TTRansform Magnetic Resonance Imaging Substudy), respectively.

This study is being conducted according to the guidelines of the International Conference on Harmonization and in accordance with all applicable regulatory requirements. All participants provided written consent before assessment of eligibility. The study protocol and any protocol amendments are subject to approval by the local institutional review boards and ethics committees. An independent Data Safety Monitoring Board has access to unblinded data. An independent Clinical Adjudication Committee, blinded to treatment allocation, is adjudicating deaths and cardiovascular clinical events.

Study Population

Inclusion/exclusion criteria are summarized in Table S2. The trial enrolled adults (≥18 years of age) who have mild or moderate HF (NYHA functional class I–III) due to variant or wild-type ATTR-CM, as evidenced by a history of at least 1 HF hospitalization or HF signs and symptoms requiring loop diuretic therapy.

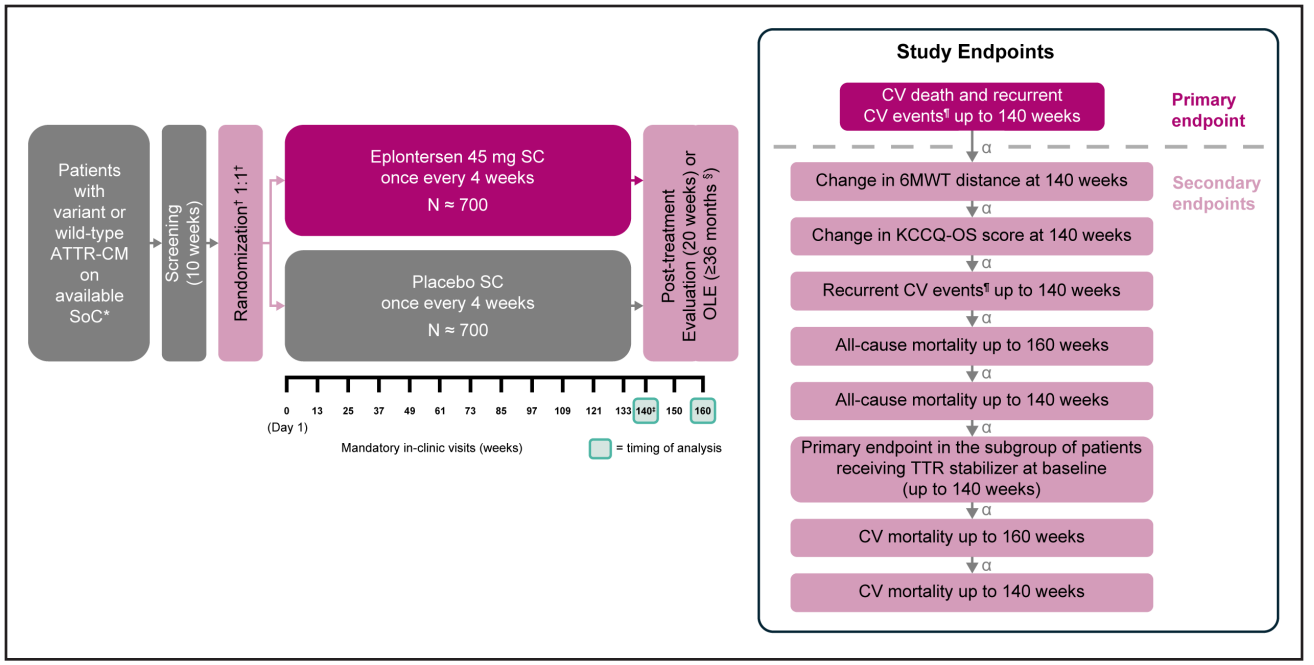

Figure 1. Study design of the CARDIO-TTRansform trial.
*Locally approved and available treatments for ATTR-CM (e.g., tafamidis, tafamidis meglumine, acoramidis). †Patients stratified by New York Heart Association Functional Classification (I and II vs. III), TTR status (variant vs wild-type), 6MWT distance (≤350 m vs >350 m), and treatment at baseline with TTR stabilizer (Yes vs No). ‡Primary endpoint at Week 140. §Up to 36 months or until after eplontersen is approved and available in the site's country. If eplontersen is not yet available after 36 months, the participant may continue to participate in the study (under an abbreviated monitoring schedule) until they complete an additional 36 months or eplontersen becomes commercially available in the site's country or the last participant completes 36 months. ¶CV clinical events include hospitalization for myocardial infarction, hospitalization for heart failure (HF), hospitalization for arrhythmia, hospitalization for stroke/transient ischemic attacks, HF urgent visits to emergency department or HF clinics requiring administration of intravenous diuretics for improvement. KCCQ-OS indicates Kansas City Cardiomyopathy Questionnaire-Overall Summary; OLE, open-label extension; SoC, standard of care; and SC, subcutaneous.

The diagnosis of ATTR-CM was established by the presence of ATTR amyloid deposits in cardiac or noncardiac tissue confirmed by Congo Red (or equivalent) staining OR technetium scintigraphy with Grade 2 or 3 cardiac uptake in the absence of an abnormal light chain ratio, centrally confirmed. Patients were excluded if they had monoclonal gammopathy of undetermined significance and alterations in immunoglobulin free light chain ratio (after accounting for renal function), unless fat, bone marrow, or heart biopsy confirmed the absence of light chain and the presence of TTR protein by mass spectrometry or immunoelectron microscopy. Eligible participants must have had confirmed cardiac involvement based on left ventricular end-diastolic interventricular septum thickness of >12 mm on a screening echocardiogram, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration of ≥600 pg/mL (or ≥1200 pg/mL if the patient is in atrial fibrillation), and demonstrated the ability to walk ≥100 meters on the 6MWT. Other inclusion criteria consisted of a willingness to undergo genetic testing for *TTR* gene variants during screening if not previously performed, and, if being treated with HF medications, participants must have received stable doses for 2 weeks before randomization. Individuals with alanine aminotransferase or aspartate aminotransferase >2.0× the upper limit of normal, total bilirubin ≥2.0× the upper limit of normal, platelet count below 125 × 10^9/L, estimated glomerular filtration rate <30 mL/min per 1.73 m^2 (<45 mL/min per 1.73 m^2 in France, Spain, and Denmark), and urine protein creatinine ratio ≥750 mg/g at screening were not eligible for enrollment. Recipients of liver or heart transplant and left ventricular assist device (or if transplantation or left ventricular assist device were planned within 1 year after randomization) were excluded.

Analytical Data Sets

Efficacy end points are evaluated using the Full Analysis Set, defined as all randomized patients who received at least 1 dose of blinded study drug and who had at least 1 post-baseline primary efficacy assessment or 1 post-baseline study visit. Safety is evaluated using the Safety Analysis Set, defined as all patients who were randomized and received at least 1 dose of blinded study drug.

Trial End Points

The primary end point is a composite of cardiovascular mortality and recurrent cardiovascular clinical events assessed up to Week 140. Cardiovascular clinical events in the composite end point include hospitalization for any of the following: HF exacerbation, myocardial infarction, stroke, transient ischemic attack, and arrhythmia; and HF-related urgent, nonscheduled visits to emergency departments or outpatient HF clinics requiring administration of intravenous diuretics for management according to standardized definitions.[31]

Secondary end points, in order of formal testing hierarchy, are: (1) changes from baseline in the 6MWT distance (to assess exercise function) and (2) Kansas City Cardiomyopathy Questionnaire (KCCQ)-Overall Summary Score (to assess

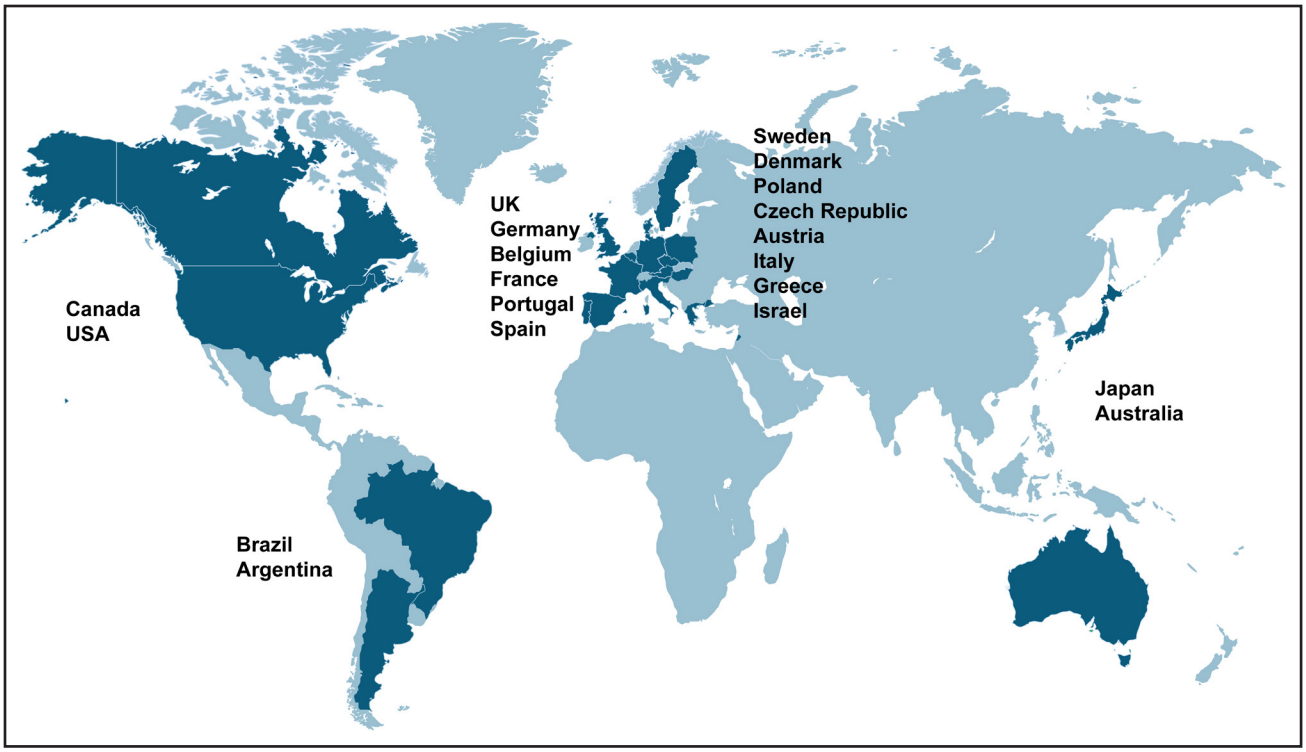

Figure 2. Countries enrolling in CARDIO-TTRansform.
Countries colored dark blue are those enrolling in CARDIO-TTRansform. UK indicates United Kingdom; and USA, United States of America.

patient-reported health status and health-related quality of life) at Week 140, (3) recurrent cardiovascular clinical events up to Week 140, (4) all-cause mortality, (5) effect on the primary end point up to Week 140 within the subgroup of participants who received TTR stabilizer at baseline, and (6) cardiovascular mortality. All-cause and cardiovascular mortality end points are tested first up to Week 160, and then up to Week 140; the former timepoint was selected to allow more events to be included to improve the power and precision of the treatment effect estimates. Ascertainment of vital status up to Week 140 is obtained from the double-blind period, and vital status between Week 140 and Week 160 is obtained from fatal events in either the open-label extension study or the 20-week post-treatment evaluation period. Exploratory end points include echocardiographic assessments of cardiac structure and function, cardiac biomarkers (NT-proBNP, high-sensitivity cardiac troponin T [hs-cTnT], creatine kinase-muscle/brain fraction [CK-MB], galectin-3, and soluble suppression of tumorigenicity-2 [sST2]), renal function (estimated glomerular filtration rate), NYHA functional class, patient-reported and quality-of-life outcomes, and eplontersen pharmacokinetics and immunogenicity. In patients with hereditary ATTR-CM, exploratory end points include lower-limb function and the 10-meter walk test. Changes in amyloid myocardial burden assessed by extracellular volume by cardiovascular magnetic resonance and changes in cardiac uptake by technetium-99 bone scintigraphy (99mTc-DPD, 99mTc-PYP, or 99mTc-HMDP) will be assessed in optional imaging substudies.

Safety assessments include adverse events, clinical laboratory measures (eg, blood and urine), vital signs, and electrocardiographic changes.

Statistical Analysis

The primary end point is a composite of cardiovascular mortality and recurrent cardiovascular clinical events over a 140-week treatment period. The treatment effect is estimated using the semiparametric proportional rates method (Lin, Wei, Yang, and Ying [LWYY]),[32] which is equivalent to the stratified Anderson-Gill model using a robust variance estimator to account for within-participant correlations.[33] The primary end point model includes treatment group with the 4 randomization stratification factors (NYHA functional class, TTR variant status, 6MWT distance, treatment with TTR stabilizer at baseline) and log NT-proBNP as covariates. Time-to-first event analyses for the primary composite end point will also be conducted as sensitivity analyses using Cox proportional hazards models[34] with the same covariates, and displayed by treatment group using Kaplan-Meier survival curves.

Organ transplantation (ie, heart) or implantation of a non-temporary mechanical circulatory support (ie, ventricular assist device, total artificial heart) is considered as cardiovascular death in the primary efficacy analysis. Events adjudicated by the Clinical Adjudication Committee as undetermined or indeterminate causes of death are categorized as cardiovascular death in the primary efficacy analysis, similar to other trials,[15,24] as the majority of deaths in patients with ATTR-CM are due to a cardiovascular etiology.[35]

If the null hypothesis is rejected for the primary composite end point, then formal prespecified testing of secondary end points will occur sequentially at an α level of 0.05 in the order described in Figure 1.

The statistical approaches used to evaluate secondary end points are as follows:

- The change from baseline to the Week 140 study visit in 6MWT distance and KCCQ Overall Summary Score is analyzed using an ANCOVA model that includes the 4 randomization stratification factors as covariates for KCCQ Overall Summary Score but excludes the baseline 6MWT distance stratification factor for analysis of 6MWT distance change, with the addition of the baseline value of 6MWT distance or KCCQ Overall Summary Score, and an interaction term of TTR stabilizer treatment at baseline with the treatment group.
- Recurrent cardiovascular clinical events are analyzed using an LWYY model identical to the model analyzing the primary end point.
- The analysis of the primary end point in the subgroup of patients using TTR stabilizer at baseline uses an LWYY model with 3 randomization stratification factors (NYHA functional class, TTR variant status, 6MWT distance) and log-transformed NT-proBNP as covariates.
- All-cause and cardiovascular mortality up to 160 weeks and 140 weeks are analyzed using Cox proportional hazards models[34] with the 4 randomization stratification factors and log-transformed NT-proBNP as covariates and displayed by treatment group using Kaplan-Meier survival curves.

Prespecified subgroup analyses for primary and secondary efficacy end points include NYHA functional classification, variant versus wild-type TTR status, baseline treatment with TTR stabilizer, region (North America, Europe, and the rest of the world), age (<65 years, 65–74 years, ≥75 years), and sex.

Amendments to the original study protocol increased the sample size from the initial 700 participants to 1000 participants, and extended the treatment period from 120 weeks to 140 weeks, due to emerging evidence that event rates appeared to be declining in contemporary populations of patients with ATTR-CM.[36] The minimum 6MWT distance at screening was decreased from 150 to 100 meters to include more participants with severe disease.

A subsequent protocol amendment increased the sample size from 1000 to 1400 participants due to updated projected event rates based on blinded events from the ongoing trial. The power calculation assumed a cardiovascular death rate of 8.7% for the placebo group during the 140-week period and 0.476 cardiovascular clinical events per patient for the placebo group during the 140-week period. A sample size of 1400 participants is expected to provide ≈85% power to test a 20% reduction in the primary composite end point with eplontersen treatment compared with placebo at a significance level (α) of 0.05 (2-sided test) with a treatment duration of 140 weeks, accounting for a 5% to 10% dropout rate.[14] In the final protocol, the secondary end points were revised to include all-cause and cardiovascular death up to Week 160, to provide a more precise estimate of eplontersen treatment effect, and formal testing of the primary composite end point in the subgroup of patients who received TTR stabilizer at baseline, to specifically examine the effect of eplontersen in the patient population receiving standard-of-care TTR stabilizer.

DISCUSSION

The CARDIO-TTRansform trial is the first randomized, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of an ASO-based TTR silencer for patients with ATTR-CM. Several key features of the trial position it as a landmark contribution to the field and need to be highlighted. First, 1432 patients have been randomized and received study drug, making it the largest trial in ATTR-CM to date, and it is also expected to have enrolled the highest number of patients with ATTRv-CM. Second, CARDIO-TTRansform allows for the enrollment of older patients up to 90 years of age, which is of particular relevance given the established association of wild-type ATTR with cardiomyopathy with advanced age. Third, given both the size of the trial and the time period during which it is being conducted, CARDIO-TTRansform will provide the most comprehensive evaluation of TTR silencer therapy on top of contemporary standard of care, including unrestricted use of TTR stabilizers. This will allow for estimates of treatment effect in the population receiving standard-of- care stabilizer therapy, unlike other silencer trials of ATTR-CM that limited the use of open-label stabilizers during the study and thus may be less representative of current clinical practice.[24,37] Fourth, the trial, by nature of its lack of restriction on NT-proBNP upper limits and by allowing National Amyloidosis Center stage 3 patients with NYHA class III, includes a wider range of disease severity than other recent trials. Fifth, another strength of the trial is the inclusion of cardiovascular mortality, rather than all-cause mortality, in the composite primary end point, unlike other ATTR-CM trials.[14,15,24] By excluding deaths from polyneuropathy-related causes in patients with ATTR-mixed disease phenotypes,[38] this end point more optimally assesses the cardiovascular-specific benefit of eplontersen. Finally, an additional feature of note is the longitudinal assessment with cardiovascular magnetic resonance imaging and 99m technetium scintigraphy.

Including urgent HF visits (ie, urgent visits to the emergency room or unscheduled outpatient HF clinics requiring administration of intravenous diuretics), in addition to cardiovascular hospitalizations, in the composite end point in the CARDIO-TTRansform trial will result in a broad assessment of cardiovascular efficacy. Urgent HF visits represent an important marker of disease progression upstream of an HF hospitalization, and focusing only on hospital admissions likely underestimates the actual burden of worsening disease. Inclusion of urgent HF visits captures a wider spectrum of clinically meaningful events that is agnostic to location of care, especially as many health care systems increasingly transfer acute HF care to outpatient settings due to nonbiological reasons such as economic factors or availability.[39]

Due to the heterogeneity of ATTR-CM, randomization in the trial was stratified on several well-established prognostic factors: variant *TTR* status, NYHA functional class, 6MWT distance, and baseline TTR stabilizer treatment.

Patients with variant ATTR cardiomyopathy are known to have worse survival compared with those with wild-type disease, despite their younger age.[3] Because functional capacity is associated with poorer outcomes in ATTR-CM, stratification included both NYHA class (as a clinical assessment of functional status)[40] and 6MWT distance (as a reproducible, objective assessment of functional capacity).[41] The 350-meter threshold for 6MWT distance was selected, as it was the mean baseline distance observed in the tafamidis arm of the ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) trial;[14] this value is confirmed by recent data demonstrating that a 6MWT distance of <350 meters is independently associated with an increased risk of mortality that is consistent across different genotypes and disease stages.[42] In addition, since 6MWT distance is an important secondary end point—and could be affected by neuropathic manifestations of ATTR—it was critical to ensure that the treatment and placebo groups were balanced at baseline. To adequately assess changes in 6MWT distance over time, only patients who were able to walk at least 100 meters at baseline were eligible for inclusion; this minimum distance ensured there was sufficient potential for measurable change in walking capacity during the study.

Cardiac biomarkers (NT-proBNP, troponin) were measured at baseline and throughout the trial and represent important exploratory end points. Notably, in contrast to other trials,[15,24] there is no upper limit of cardiac biomarkers (eg, NT-proBNP) or National Amyloidosis Center stage used to exclude patients from CARDIO-TTRansform (and ATTR-ACT),[14] and thus this trial will be able to assess the impact of eplontersen across a wide range of disease severity, including patients with advanced cardiac disease who are at the highest risk of early mortality.[43]

Statistical design features are intended to optimize study interpretability and clinical relevance. The composite end point of cardiovascular mortality and recurrent cardiovascular clinical events will be estimated using the LWYY method, an extension of Cox proportional hazards regression to evaluate the effect of treatment on recurrent events that has an advantage over the time-to-first event method in capturing how treatment affects total disease burden.[33] This approach allows for the accommodation of the total burden of recurrent events that are important to both patients and clinicians.[33] Since a lower mortality rate is expected than observed in the ATTR-ACT study,[14] the LWYY method will consider the contemporary clinical scenario where recurrent cardiovascular hospitalizations likely play a more prominent role.[14,15,44]

Cardiovascular-related and all-cause deaths will be formally tested at the end of the double-blind period (at 140 weeks). The observation that deaths appeared to accrue nonlinearly led to end point extension to 160 weeks as a separate secondary end point, allowing more events to be included in the analyses of mortality end points and thereby likely improving the precision of treatment effect estimates. Prior ATTR-CM trials suggest that the benefit from ATTR therapy on mortality would be delayed,[14,15,24] and it would be unlikely that a substantial mortality benefit would be observed during the first 20 weeks in patients who were originally randomized to receive placebo and subsequently received eplontersen in the open-label extension period. A similar approach to incorporating open-label extension data to assess mortality was used in the HELIOS-B trial.[24]

Eplontersen is well tolerated, as demonstrated by its safety profile in the Phase 1 program[29] and Phase 3 NEURO-TTRansform study.[26] As a class, N-acetylgalactosamine–linked 2′-*O*-methoxyethyl-modified ASOs have excellent tolerability, as observed in both Phase 1[45] and Phase 2 studies,[46,47] with no adverse liver, kidney, or hematologic findings.[45,47–49] The main difference in safety and tolerability between ASOs with and without N-acetylgalactosamine conjugation is due to the ability to use lower doses of conjugated ASOs to achieve comparable pharmacology, thereby reducing systemic exposure and potential safety issues.[29,45,48]

Eplontersen is the only TTR silencer available via autoinjector, enabling convenient at-home dosing by patients or caregivers and reducing reliance on in-clinic visits. This delivery approach is designed to lower treatment burden and support adherence. The pivotal trial and open-label extension will provide evidence on study drug adherence and successful autoinjector use in patients with ATTR-CM.

In conclusion, CARDIO-TTRansform is expected to provide definitive evidence as to the clinical benefits of silencing TTR production with eplontersen therapy in a contemporary population of patients with ATTR-CM who receive locally available standard-of-care therapy, including real-world use of TTR stabilizers. The design elements of the trial, including its distinction as the largest ATTR-CM trial conducted thus far and the common use of stabilizers at baseline, are anticipated to generate new insights into the clinical impact of a novel TTR-silencing therapy for both variant and wild-type ATTR cardiomyopathy.

ARTICLE INFORMATION

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Acknowledgments

The authors would like to thank the patients, their families, and the CARDIO-TTRansform investigators for their invaluable contributions. The authors acknowledge the following individuals for their technical and intellectual contributions to the study: Gustavo Buchele MD, PhD; Michela Brambatti, MD, MS; Li-Jung Tai, MD, PhD, an employee of Ionis Pharmaceuticals, Inc., at the time of this work; Cecilia Monteiro, MD, PhD, an employee of Ionis Pharmaceuticals, Inc., at the time of this work; Ewa Karwatowska-Prokopczuk, MD, PhD; Eugene Schneider, MD; Richard S. Geary, MD; and Brett P. Monia, PhD, of Ionis Pharmaceuticals, Inc, Carlsbad CA, USA; and Louis St. L. O'Dea, MB, BCh, an employee of Akcea Therapeutics at the time of this work, Boston, MA, USA. In particular, the authors acknowledge Merrill Benson, MD (deceased), of the Indiana University School of Medicine for his substantial input into the design of this trial.

Sources of Funding

This study was supported by Ionis Pharmaceuticals, Inc and AstraZeneca. Medical writing and editing support for the development of this article, under the direction and guidance of the authors, was provided by Karen Yee, PhD, of Ashfield MedComms (London, UK), an Inizio Company, in accordance with Good Publication Practice (GPP) guidelines (http://www.ismpp.org/gpp-2022), and funded by AstraZeneca.

Disclosures

Dr Masri reports consulting fees from Cytokinetics, BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Alnylam, Haya, Alexion, Akros, Edgewise, Rocket, Lexeo, Prothena, BioMarin, AstraZeneca, Avidity, and Neurimmune; and grants/funds from Pfizer, Attralus, Cytokinetics, and Janssen. Dr Cappelli reports consultancy fees from Alnylam, Bayer, BridgeBio Pharma, AstraZeneca, Novo Nordisk, Bristol Myers Squibb, and Pfizer. Dr Davis reports honoraria from Alnylam, AstraZeneca, Bayer, Novo Nordisk, and Pfizer; consulting fees from Alnylam, Anthos, AstraZeneca, Bayer, BridgeBio, Novo Nordisk, and Pfizer; and research funding from Pfizer. Dr Fontana reports consulting fees for Alnylam, Alexion/Caelum Biosciences, AstraZeneca, BridgeBio/Eidos, Prothena, Attralus, Intellia Therapeutics, Ionis Pharmaceuticals, Cardior, Lexeo Therapeutics, Janssen Pharmaceuticals, Prothena, Pfizer, Novo Nordisk, Bayer and MyCardium AI; research grants from Alnylam, BridgeBio, AstraZeneca, and Pfizer; and share options in Lexeo Therapeutics and shares in MyCardium AI. Dr Garcia-Pavia reports honoraria from Alnylam Pharmaceuticals, AstraZeneca, Bayer, BridgeBio, Intellia, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer; consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio, Intellia, Ionis Pharmaceuticals, Life Molecular Imaging, Pfizer, Neuroimmune, and Novo Nordisk; and research/educational support to his institution from Alnylam Pharmaceuticals, AstraZeneca, Bayer, BridgeBio, Intellia, Novo Nordisk, and Pfizer. Dr Gillmore reports consultancy fees from Alnylam, AstraZeneca, Alexion, Attralus, BridgeBio, Bayer, Ionis, Intellia, and Pfizer; and institutional grants from Alnylam and AstraZeneca. Dr Hanna reports consulting fees from Pfizer, Ionis, BridgeBio, Alnylam, Alexion, and Novo Nordisk. Dr Obici reports speaker honoraria from Alnylam, AstraZeneca, Bayer, BridgeBio, Novo Nordisk, Intellia, Medison, Purpose Pharma, and Pfizer; and consulting fees from Alnylam, AstraZeneca, Bayer, BridgeBio, Novo Nordisk, Intellia, Purpose Pharma, and Pfizer. Dr Solomon reports research grants from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, BMS, Cytokinetics, Eidos, Gossamer, GSK, Ionis, Lilly, MyoKardia, National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI), Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, and Theracos; and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, MyoKardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo. Dr. Sperry reports professional fees from AstraZeneca, Pfizer, Alnylam, and BridgeBio. Dr Tahara reports honoraria and consulting fees from Pfizer, Alnylam and Alexion; and serves as an advisor for AstraZeneca. Dr Waddington–Cruz reports consulting fees from Pfizer, AstraZeneca, Alnylam, Intellia, Ionis, and PTC Therapeutics; and serves as an advisor for Pfizer, AstraZeneca, Alnylam, Ionis, and Novo Nordisk. Dr Falk is a consultant for Alexion, Alnylam, and Pfizer; and a member of the Data and Safety Monitoring Committee for Novo Nordisk. Dr Shah reports consulting fees from Pfizer, Alnylam, BridgeBio, Ionis, and Novo Nordisk; and grants and funds from Alnylam, BridgeBio, and Amyloid Research Consortium. Dr Nativi-Nicolau reports research grants and funds from Pfizer, BridgeBio, Ionis, Alnylam, Alexion, and Intellia. Dr Tsimikas, N.J. Viney, and Dr Yang are employees of, and hold stock/stock options in Ionis Pharmaceuticals. Dr Chen is an employee of, and holds stock/stock options in AstraZeneca. Dr Maurer reports consulting fees for Alnylam, AstraZeneca, Bayer, BridgeBio, Novo Nordisk, Intellia, Purpose Pharma, and Pfizer; has received grants/funds from the NIH (R01HL177670 and R01AG081582), Alnylam Pharmaceuticals, Attralus, BridgeBio, Intellia Therapeutics, Ionis Pharmaceuticals, and Pfizer; and serves as an advisor for Alnylam, AstraZeneca, Attralus, Bayer, BridgeBio, Intellia, Ionis, Novo Nordisk, and Pfizer. The other author reports no conflicts.

Supplemental Material

Tables S1–S2
Figure S1

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