ORIGINAL ARTICLE

Eplontersen for Transthyretin Amyloid Cardiomyopathy

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ABSTRACT

BACKGROUND

Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a progressive, life-threatening disease caused by deposition of misfolded transthyretin (TTR). Eplontersen, an antisense oligonucleotide, reduces the production of hepatic TTR. The effect of eplontersen on ATTR-CM is unclear.

METHODS

In this phase 3, international, double-blind trial, we randomly assigned, in a 1:1 ratio, patients with ATTR-CM to receive subcutaneous eplontersen (45 mg) or placebo every 4 weeks for 140 weeks, in addition to standard treatment. The primary end point was a cumulative composite of death from cardiovascular causes and recurrent cardiovascular clinical events up to week 140. The effect of death from non-cardiovascular causes on the primary analysis was assessed with a cumulative composite of death from any cause and cardiovascular events up to week 140.

RESULTS

A total of 1432 patients underwent randomization and received at least one dose of the assigned intervention (715 patients in the eplontersen group and 717 in the placebo group). The mean age of the patients was 76.4 years, and 90.6% were men. A total of 381 primary end-point events occurred in 210 patients (29.4%) receiving eplontersen, and 392 events occurred in 231 patients (32.2%) receiving placebo (rate ratio, 0.89; 95% confidence interval [CI], 0.73 to 1.09; P=0.28). Death from cardiovascular causes, as a component of the primary end point, occurred in 74 patients in the eplontersen group and in 70 in the placebo group; there were 307 cardiovascular clinical events in the eplontersen group and 322 in the placebo group. The rate ratio for the composite of death from any cause and cardiovascular events was 0.86 (95% CI, 0.71 to 1.04). Serious adverse events occurred in 413 patients (57.8%) in the eplontersen group and in 426 (59.4%) in the placebo group.

CONCLUSIONS

Among patients with ATTR-CM, eplontersen therapy did not lead to a lower risk of a composite of death from cardiovascular causes and recurrent cardiovascular events than placebo up to 140 weeks. (Funded by Ionis Pharmaceuticals and AstraZeneca; CARDIO-TTRansform ClinicalTrials.gov number, NCT04136171.)

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*A list of the CARDIO-TTRansform investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a progressive and life-threatening disease characterized by extracellular deposition of misfolded transthyretin (TTR) fibrils within the myocardium.[1] Misfolding of TTR occurs as a result of a pathogenic gene variant (variant, also called hereditary, ATTR [ATTRv]) or as an acquired age-related process in the absence of a predisposing gene variant (wild-type ATTR [ATTRwt]) and can manifest as amyloid cardiomyopathy, polyneuropathy, or both.[2-4] ATTR-CM is characterized by restrictive cardiomyopathy with progressive diastolic and systolic dysfunction, conduction disease, and arrhythmias.[4-6] Although the clinical presentation of patients with ATTR-CM varies, substantial impairment in functional status and health-related quality of life typically develops, and these patients have progressively worsening symptoms of heart failure and reduced survival.[3,6,7] Despite treatment with TTR stabilizers or gene-silencing therapies, including tafamidis,[8] acoramidis,[9] and vutrisiran,[10] mortality and morbidity remain high.[3,11]

Eplontersen is a 2′-*O*-methoxyethyl–modified antisense oligonucleotide that degrades TTR messenger RNA, resulting in rapid knockdown of TTR and minimizing the tetramer available for dissociation into amyloidogenic monomers and subsequent misfolding and tissue deposition.[12] Because circulating TTR is produced in the liver, eplontersen is conjugated to a liver-specific triantennary *N*-acetylgalactosamine (GalNAc) ligand, leading to potency that is approximately 30 times as high as that with unconjugated antisense oligonucleotides, with marked reductions in both wild-type and variant TTR serum levels.[12-15] Eplontersen is approved for the treatment of ATTRv with polyneuropathy on the basis of the phase 3 NEURO-TTRansform trial, which showed that eplontersen slowed progression of neuropathic impairment and improved health-related quality of life as compared with a historical placebo group.[15,16] The CARDIO-TTRansform trial was designed to assess the efficacy and safety of eplontersen as compared with placebo in patients with ATTR-CM who also received standard treatment.

METHODS

TRIAL DESIGN, OVERSIGHT, AND AUTHOR RESPONSIBILITIES

We conducted this phase 3, double-blind, randomized, placebo-controlled trial involving patients with ATTRwt or ATTRv cardiomyopathy at 130 sites across 20 countries. The trial design (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), including details on the statistical testing hierarchy,[17] as well as baseline demographic and clinical data,[11] have been described previously. The trial protocol, including the statistical analysis plan, is available at NEJM.org.

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference for Harmonisation, and all applicable laws and regulations. The trial was designed by a scientific advisory committee and representatives of the sponsor, Ionis Pharmaceuticals, and representatives of both AstraZeneca and Ionis Pharmaceuticals contributed to the protocol amendment process. The trial protocol was approved by institutional review boards or ethics committees at each participating site. All the patients provided written informed consent.

Investigators collected the data reported here, an independent data and safety monitoring board evaluated unblinded data during the trial, and an independent clinical-event committee, whose members were unaware of the trial-group assignments, adjudicated all deaths and cardiovascular events (see the Supplementary Appendix). Data analysis was conducted by the sponsor in collaboration with the investigators and independently verified at an academic core laboratory (Brigham and Women's Hospital). The first two authors and the last author drafted the initial version of the manuscript, and the final version was approved by all the authors, who made the decision to submit the manuscript for publication. Editorial assistance with the development of the manuscript was provided by medical writers funded by AstraZeneca. Two authors who had access to the data vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. There were no agreements restricting authors' access or concerning the confidentiality of the data, including restrictions on publication, among Ionis Pharmaceuticals, AstraZeneca, the authors, or named institutions.

PATIENTS

Eligible patients were adults 18 to 90 years of age who had an interventricular septum thickness of at least 12 mm; a New York Heart Association

(NYHA) functional class of I, II, or III; a history of heart failure; and an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of at least 600 pg per milliliter (or ≥1200 pg per milliliter in patients with atrial fibrillation). Full eligibility criteria are listed in the Supplementary Appendix.

TRIAL PROCEDURES

Patients were randomly assigned in a 1:1 ratio to receive either subcutaneous eplontersen (45 mg) or placebo every 4 weeks for 140 weeks (the double-blind period). An interactive voice- and Web-response system (Almac Clinical Technologies) was used for randomization, which was stratified according to the baseline NYHA functional class (I or II vs. III), TTR genotype (wild-type vs. variant), the 6-minute walk distance (≤350 m vs. >350 m), and TTR stabilizer use at baseline (yes vs. no).

The use of prescribed, approved therapies such as TTR stabilizers (local standard-of-care therapy) was permitted throughout the trial. Patients were instructed to take the recommended daily allowance of vitamin A to mitigate potential effects related to reduction of TTR-mediated retinol transport.[18] After 140 weeks, patients could opt to either enroll in an open-label extension study (ClinicalTrials.gov number, NCT05667493) or complete a 20-week follow-up period (up to week 160), during which they received no additional doses of eplontersen or placebo.

END POINTS

The primary end point was a cumulative composite of death from cardiovascular causes and recurrent cardiovascular clinical events up to week 140. Death from a cardiovascular or undetermined cause and events of heart transplantation or intermediate- or long-term cardiac mechanical circulatory support, such as implantation of a left ventricular assist device, were counted as deaths in analyses of death from cardiovascular causes. Cardiovascular clinical events included hospitalization for heart failure, myocardial infarction, stroke, transient ischemic attack, or arrhythmia and urgent visits for heart failure to the emergency department or heart-failure clinic that led to the use of intravenous diuretics.

Secondary end points were planned to be tested in the following hierarchical order: the change from baseline to week 140 in the 6-minute walk distance; the change from baseline to week 140 in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score (range, 0 to 100, with higher values indicating better health-related quality of life); cumulative recurrent cardiovascular events up to week 140; death from any cause up to week 160; death from any cause up to week 140; primary end-point events in patients receiving TTR stabilizers at baseline; death from cardiovascular causes up to week 160; and death from cardiovascular causes up to week 140. Trial-group assignments remained concealed throughout the trial for all the primary and secondary end points. Details of selected prespecified exploratory end points, which included the change from baseline to week 140 in the serum TTR level and the NT-proBNP level, are provided in the Supplementary Appendix.

Sensitivity analyses were also performed for the primary end point and some secondary end points. To assess the effect of death from noncardiovascular causes as a competing event, we evaluated a Fine–Gray model using a time-to-first-event version of the primary composite end point. To assess the potential effect of informative censoring for terminal events such as death from noncardiovascular causes, we used an inverse-probability-weighting model for censoring using the same covariates as the primary Lin–Wei–Yang–Ying model. An analysis of the secondary end point of recurrent cardiovascular events up to week 140 that was based on inverse probability of censoring weighting was performed in which death from any cause was treated as an informative censoring event. In addition, sensitivity analyses were performed that assumed the worst-case values for the 6-minute walk distance and KCCQ-OS score in patients who had died. To assess the effect of death from noncardiovascular causes on the primary end point, we also evaluated a cumulative composite end point of death from any cause and cardiovascular events up to week 140.

For safety assessments, adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 28.1. Adverse events of special interest included a platelet count of less than 50×10^9 per liter accompanied by a major bleeding event or a clinically relevant, nonmajor bleeding event, as well as a platelet count of less than 25×10^9 per liter independent of a major bleeding or clinically relevant, nonmajor bleeding event.

STATISTICAL ANALYSIS

We estimated that a sample size of 1432 would provide the trial with 85% power to detect a 20% lower risk of the primary composite end point at a two-sided alpha level of 0.05, assuming that 15% of the patients would withdraw, the overall cardiovascular mortality would be 8.7%, and there would be 0.476 cardiovascular clinical events per patient in the placebo group.[18] Primary, secondary, and exploratory efficacy end points and safety were assessed in all the patients who received at least one dose of eplontersen or placebo as assigned. The primary end point was analyzed with the use of a modified Andersen–Gill method with a robust variance estimator — specifically, a Lin–Wei–Yang–Ying model, which accounts for the total event burden associated with recurrent events.[19] The four randomization stratification factors and log-transformed baseline NT-proBNP level were incorporated as covariates. Patients had their data censored for the primary analysis if ascertainment of either component (death from cardiovascular causes or recurrent cardiovascular events) was not possible.

For the primary end point and all secondary end points, the discontinuation of eplontersen or placebo and the initiation of a TTR stabilizer were handled with a treatment-policy strategy (i.e., events were counted regardless) in the full analysis population. The primary estimand was the treatment effect of eplontersen as compared with placebo, in addition to standard therapy, on the total burden of recurrent cardiovascular clinical events and death from cardiovascular causes up to week 140 in the full analysis population, expressed as a rate ratio, for which a hypothetical strategy for intercurrent events (i.e., censoring) was used for deaths from noncardiovascular causes.

Details of the secondary end-point estimands are provided in the Supplementary Appendix. In brief, the estimands for 6-minute walk distance and KCCQ-OS score were expressed as the difference in means, whereas death was handled as a negative outcome with the use of a composite strategy in accordance with the multiple imputation framework (see the Supplementary Appendix); missing data that were caused by intercurrent events were also handled within the multiple imputation framework. The estimand for recurrent cardiovascular events through week 140 was equivalent to the estimand for the primary end point except that censoring was used for death from any cause. The estimands for death from cardiovascular causes and death from any cause at weeks 160 and 140 were expressed as hazard ratios; in the case of the former, censoring was used for death from noncardiovascular causes.

Changes in the 6-minute walk distance and the KCCQ-OS score at week 140 were analyzed with analysis-of-covariance models that were adjusted for baseline values and the four stratification factors. Missing data for the 6-minute walk distance and the KCCQ-OS score were considered to be missing not at random for death and discontinuation of treatment due to an adverse event or disease progression, and all other missing data were considered to be missing at random; all missing data were addressed with imputation from a pattern-mixture model (see the Supplementary Appendix). Cardiovascular events up to week 140 were analyzed by a Lin–Wei–Yang–Ying model in the same manner as the primary end point. All time-to-first-event analyses of all-cause and cardiovascular mortality were performed with Cox proportional-hazards models[20] incorporating the same covariates as the primary analysis. There was no evidence of proportional-hazards violations for the treatment effect of eplontersen for all mortality end points reported as assessed by means of Schoenfeld residuals and visual inspection of the log–log survival plot. Primary end-point events were analyzed in patients receiving TTR stabilizers at baseline with the use of methods identical to those for the primary end-point analysis but with the exclusion of the stratification factor of baseline TTR stabilizer use as a covariate.

The pharmacodynamic effects of eplontersen were assessed according to the changes from baseline in serum TTR level and serum NT-proBNP level up to week 140. Both analyses used mixed models for repeated measures that included fixed effects for trial group, visit, stratification factors, a trial group–by–visit interaction, and baseline value. Adverse events and adverse events of special interest were compared descriptively. Details regarding multiplicity control for subgroup analyses and prespecified exploratory end points and statistical model spec-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Eplontersen (N=715)	Placebo (N=717)
Age — yr	76.2±7.2	76.6±7.0
Male sex — no. (%)	636 (89.0)	661 (92.2)
Race — no. (%)†		
White	634 (88.7)	637 (88.8)
Black	54 (7.6)	57 (7.9)
Asian	20 (2.8)	15 (2.1)
Other or multiple	7 (1.0)	8 (1.1)
Hispanic or Latino ethnic group — no. (%)†	54 (7.6)	43 (6.0)
Variant TTR genotype — no. (%)	107 (15.0)	104 (14.5)
Median time since diagnosis of ATTR-CM (IQR) — mo	9.9 (4.8–23.4)	9.3 (4.6–21.2)
Median duration between ATTR-CM symptom onset and enrollment (IQR) — mo	20.1 (9.2–37.3)	18.6 (9.6–36.8)
NYHA functional class — no. (%)		
I	84 (11.7)	108 (15.1)
II	509 (71.2)	488 (68.1)
III	122 (17.1)	121 (16.9)
NAC disease stage — no. (%)‡		
1	434 (60.7)	462 (64.4)
2	209 (29.2)	192 (26.8)
3	72 (10.1)	63 (8.8)
6-Min walk distance — m	350.5±95.2	354.0±97.3
KCCQ-OS score§	72.5±19.8	72.7±20.0
TTR stabilizer use — no. (%)	410 (57.3)	409 (57.0)
Median duration of TTR stabilizer use before randomization (IQR) — mo	9.6 (4.1–19.0)	8.4 (3.7–16.6)
Estimated GFR — ml/min/1.73 m^2	60.7±16.3	62.4±16.2
NT-proBNP		
Median (IQR) — pg/ml	2068 (1323–3563)	1965 (1284–3422)
>8500 pg/ml — no. (%)	32 (4.5)	19 (2.6)
Median high-sensitivity cardiac troponin T level (IQR) — pg/ml	49 (34–67)	50 (37–71)

* Plus–minus values are means ±SD. Data were missing for the following variables: the duration between symptom onset and enrollment (for 28 patients in the eplontersen group and for 36 in the placebo group); the distance walked in the 6-minute walk test (for 2 in the placebo group); the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score (for 3 in each group); and the high-sensitivity cardiac troponin T level (for 6 in the eplontersen group and for 5 in the placebo group). Percentages may not total 100 due to rounding. ATTR-CM denotes transthyretin amyloid cardiomyopathy, GFR glomerular filtration rate, IQR interquartile range, NT-proBNP N-terminal pro–B-type natriuretic peptide, NYHA New York Heart Association, and TTR transthyretin.

† Race and ethnic group were reported by the patient.

‡ National Amyloidosis Centre (NAC) stages were defined as follows[21]: stage 1 as an NT-proBNP level of 3000 pg per milliliter or less and an estimated GFR of at least 45 ml per minute per 1.73 m^2 of body-surface area, stage 2 as an NT-proBNP level of more than 3000 pg per milliliter and an estimated GFR of at least 45 ml per minute per 1.73 m^2 or as an NT-proBNP level of 3000 pg per milliliter or less and an estimated GFR of less than 45 ml per minute per 1.73 m^2, and stage 3 as an NT-proBNP level of more than 3000 pg per milliliter and an estimated GFR of less than 45 ml per minute per 1.73 m^2.

§ KCCQ-OS scores range from 0 to 100, with higher scores indicating better health-related quality of life.

ifications are presented in the Supplementary Appendix. Statistical analyses were performed with SAS software, version 9.3 or higher (SAS Institute), and Stata software, version 19 (StataCorp).

RESULTS

CHARACTERISTICS OF THE PATIENTS

From March 2020 through July 2023, a total of 2337 patients were screened; 1438 patients under-

Table 2. End Points and Adverse Events.

Variable	Eplontersen (N=715)	Placebo (N=717)	Efficacy vs. Placebo (95% CI)*
End points			
Primary end point: composite of death from cardiovascular causes and recurrent cardiovascular clinical events up to wk 140†			
No. of patients with events (%)	210 (29.4)	231 (32.2)	
No. of events	381	392	Rate ratio: 0.89 (0.73–1.09)‡
Death from cardiovascular causes	74	70	
Cardiovascular clinical event	307	322	
Secondary end points, in order of testing hierarchy			
LSM change from baseline in 6-min walk distance at wk 140 — m§	–27.5	–47.3	Difference: 19.7 (9.9–29.6)
LSM change from baseline in KCCQ-OS score at wk 140§	–5.4	–9.4	Difference: 4.0 (2.0–6.0)
Cardiovascular events up to wk 140			
No. of patients with events (%)	180 (25.2)	204 (28.5)	
No. of events¶	307	323	Rate ratio: 0.88 (0.71–1.10)
Death from any cause up to wk 160 — no. (%)	126 (17.6)	147 (20.5)	Hazard ratio: 0.78 (0.61–0.99)
Death from any cause up to wk 140 — no. (%)	111 (15.5)	130 (18.1)	Hazard ratio: 0.77 (0.60–0.99)
Primary end-point event among patients receiving a TTR stabilizer at baseline			
No. of patients with events/total no. (%)	105/410 (25.6)	107/409 (26.2)	
No. of events	209	171	Rate ratio: 1.14 (0.85–1.53)
Death from cardiovascular causes up to wk 160 — no. (%)	97 (13.6)	101 (14.1)	Hazard ratio: 0.86 (0.65–1.14)
Death from cardiovascular causes up to wk 140 — no. (%)‖	85 (11.9)	86 (12.0)	Hazard ratio: 0.88 (0.65–1.18)
Adverse events**			
Any adverse event			
No. of patients with event (%)	708 (99.0)	705 (98.3)	
No. of events	10,173	9979	
Any serious adverse event			
No. of patients with event (%)	413 (57.8)	426 (59.4)	
No. of events	1200	1380	
Any serious adverse event deemed related to eplontersen or placebo			
No. of patients with event (%)	4 (0.6)	2 (0.3)	
No. of events	6	2	
Any adverse event leading to discontinuation			
No. of patients with event (%)	46 (6.4)	53 (7.4)	
No. of events	47	53	

Table 2. (Continued.)

Variable	Eplontersen (N=715)	Placebo (N=717)	Efficacy vs. Placebo (95% CI)*
Any adverse event of special interest — no. of patients with event (%)††	1 (0.1)	4 (0.6)	
Platelet count <25×10⁹/liter, independent of a major bleeding event or clinically relevant, nonmajor bleeding event	1 (0.1)	4 (0.6)	

* Rate ratios for primary end-point events and cardiovascular events were calculated with the use of the Lin–Wei–Yang–Ying model. Hazard ratios for death from cardiovascular causes and death from any cause were calculated with the use of the Cox proportional-hazards model. Confidence intervals for all end-point differences other than the primary end point have not been adjusted for multiplicity and the intervals should not be used to infer treatment effect. LSM denotes least-squares mean.

† Deaths from a cardiovascular or undetermined cause and events of heart transplantation or intermediate- or long-term cardiac mechanical circulatory support (i.e., implantation of a left ventricular assist device) were counted as deaths in analyses of death from cardiovascular causes. Cardiovascular events included hospitalization for heart failure, urgent visit for heart failure that led to the use of intravenous diuretics, myocardial infarction, stroke, transient ischemic attack, and arrhythmia. Events were counted cumulatively.

‡ P=0.28.

§ For the 6-minute walk distance and KCCQ-OS assessments, values that were missing because of death, heart transplantation, or implantation of a left ventricular assist device were imputed on the basis of the bottom 20% of observed values at the same trial visit in the same group. Differences are LSM differences.

¶ One additional cardiovascular event occurred in the placebo group after censoring for the primary end-point analysis.

‖ After censoring for the primary end-point analysis, there were 11 deaths from cardiovascular causes in the eplontersen group and 16 such deaths in the placebo group. Deaths were ascertained in patients who discontinued the trial by means of survival follow-up only or data from public records.

** Adverse events were recorded at any time on or after the date of the administration of the first dose. Numbers of events are shown when they differ from the numbers of patients with an event.

†† Adverse events of special interest included a platelet count of less than 50×10⁹ per liter accompanied by a major bleeding event or a clinically relevant, nonmajor bleeding event and a platelet count of less than 25×10⁹ per liter independent of a major bleeding event or a clinically relevant, nonmajor bleeding event.

went randomization, with 719 patients assigned to each of the eplontersen and placebo groups. A total of 1432 patients (715 in the eplontersen group and 717 in the placebo group) received at least one dose of eplontersen or placebo, as assigned, and were included in the analyses of the primary and secondary end points (Fig. S2, and see the Supplementary Appendix). The median exposure up to 140 weeks was 136.1 weeks (interquartile range, 134.7 to 136.3) in the eplontersen group and 136.0 weeks (interquartile range, 112.3 to 136.1) in the placebo group.

The demographic and clinical characteristics of the patients at baseline were similar across the two trial groups (Table 1 and Table S1). The patients who were included in the trial were generally representative of the broader population of patients with ATTR-CM (Table S2). The mean age of the patients was 76.4 years, 90.6% were men, 17.0% had symptoms of NYHA functional class III disease, and 14.7% had a variant TTR genotype, with a representative distribution of TTR variants. At baseline, TTR stabilizer use was reported in 819 patients (57.2%), with 410 patients in the eplontersen group and 409 in the placebo group; 765 patients (53.4%) received tafamidis at a dose of 61 mg or 80 mg, and 54 patients (3.8%) received other tafamidis doses. In addition, 174 patients in each trial group who were not receiving TTR stabilizer therapy at baseline initiated TTR stabilizer therapy during the trial up to week 160. Mineralocorticoid receptor antagonist use was reported in 303 patients in the eplontersen group and in 315 patients in the placebo group; sodium–glucose cotransporter 2 inhibitor use was reported in 135 and 130 patients, respectively.

EFFICACY

Up to week 140, a total of 381 primary end-point events occurred in 210 patients (29.4%) receiving eplontersen, and 392 primary end-point events occurred in 231 patients (32.2%) receiving placebo (rate ratio, 0.89; 95% confidence interval [CI], 0.73 to 1.09; P=0.28) (Table 2 and Fig. 1). Death from cardiovascular causes, as a component of the primary end point, occurred in 74 patients in the eplontersen group and in 70 in the placebo group; 307 cardiovascular events occurred in the eplontersen group and 322 cardiovascular events in

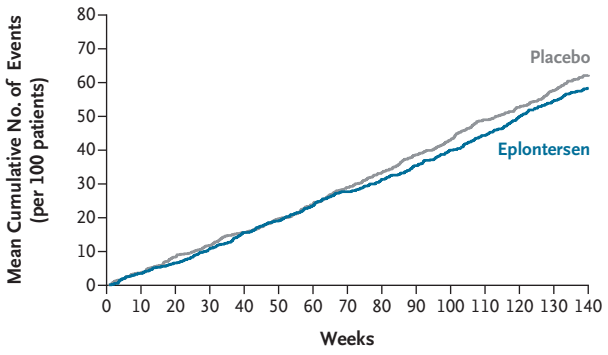

Figure 1. Death from Cardiovascular Causes and Cardiovascular Events up to Week 140.

Shown is the mean cumulative event rate (per 100 patients) for primary end-point events (death from cardiovascular causes and recurrent cardiovascular events) up to week 140.

the placebo group. The results of the primary analysis were consistent when death from noncardiovascular causes was considered as a competing event according to the Fine–Gray model (subdistribution hazard ratio, 0.83; 95% CI, 0.69 to 1.00). Results were also consistent in an analysis that used inverse probability of censoring weighting in the informative censoring model that accounted for the potential effect of informative terminal events (rate ratio, 0.91; 95% CI, 0.74 to 1.11). A subgroup analysis for the primary end point is shown in Figure 2. The rate ratio for death from any cause and cardiovascular events up to week 140 was 0.86 (95% CI, 0.71 to 1.04).

At week 140, the least-squares mean change in the 6-minute walk distance was –27.5 m in the eplontersen group and –47.3 m in the placebo group (least-squares mean difference, 19.7 m [based on unrounded data]; 95% CI, 9.9 to 29.6) (Table 2 and Fig. 3A). The least-squares mean change in health-related quality of life, as measured by the KCCQ-OS score, was –5.4 in the eplontersen group and –9.4 in the placebo group (least-squares mean difference, 4.0; 95% CI, 2.0 to 6.0) (Table 2 and Fig. 3B). Sensitivity analyses that assumed the worst-case values for the 6-minute walk distance and the KCCQ-OS score for death (i.e., zero) were performed and yielded results similar to those of the main analysis; for the 6-minute walk distance, the least-squares mean difference was 23.5 m (95% CI, 9.5 to 37.5), and for the KCCQ-OS score, the least-squares mean difference was 4.1 (95% CI, 1.2 to 7.0).

A total of 180 patients (25.2%) in the eplontersen group and 204 (28.5%) in the placebo group had recurrent cardiovascular events up to week 140 (rate ratio, 0.88; 95% CI, 0.71 to 1.10) (Table 2 and Fig. S3A). Death from any cause up to week 160 occurred in 126 patients (17.6%) in the eplontersen group and in 147 (20.5%) in the placebo group (hazard ratio, 0.78; 95% CI, 0.61 to 0.99) and up to week 140 in 111 patients (15.5%) in the eplontersen group and in 130 (18.1%) in the placebo group (hazard ratio, 0.77; 95% CI, 0.60 to 0.99) (Table 2 and Fig. S3B and S3C).

Among patients who were being treated with TTR stabilizers at baseline, 105 of 410 patients (25.6%) who received eplontersen had 209 primary end-point events and 107 of 409 patients (26.2%) who received placebo had 171 events (rate ratio, 1.14; 95% CI, 0.85 to 1.53) (Table 2 and Fig. S3D). In a prespecified analysis of the subgroup of patients not receiving TTR stabilizers at baseline, the rate ratio was 0.71 (95% CI, 0.54 to 0.93) (Fig. 2). All deaths from cardiovascular causes up to week 160 and up to week 140 are shown in Table 2 and Figure S3E and S3F, regardless of whether they were counted for the primary end point.

Serum TTR levels decreased over time in patients treated with eplontersen, with a 60.0% reduction in the observed mean trough level seen as early as the first postbaseline assessment at week 13. At week 140, the observed mean change from baseline in serum TTR among patients in the eplontersen group was –69.7%, with a least-squares mean placebo-corrected percent change from baseline of –77.2% (95% CI, –81.4 to –72.9) (Fig. S4A). Results of post hoc analysis of the observed median percent change and least-squares mean percent change in serum TTR levels from baseline to week 140 according to whether patients received a dose of of eplontersen or placebo at each time point (on-treatment analysis) are shown in Table S3. At week 140, the observed geometric mean change in the NT-proBNP level was 14.8% (95% CI, 8.3 to 21.7) in the eplontersen group, with a least-squares mean placebo-corrected percent change from baseline of –15.7% (95% CI, –21.6 to –9.4) (Fig. S4B).

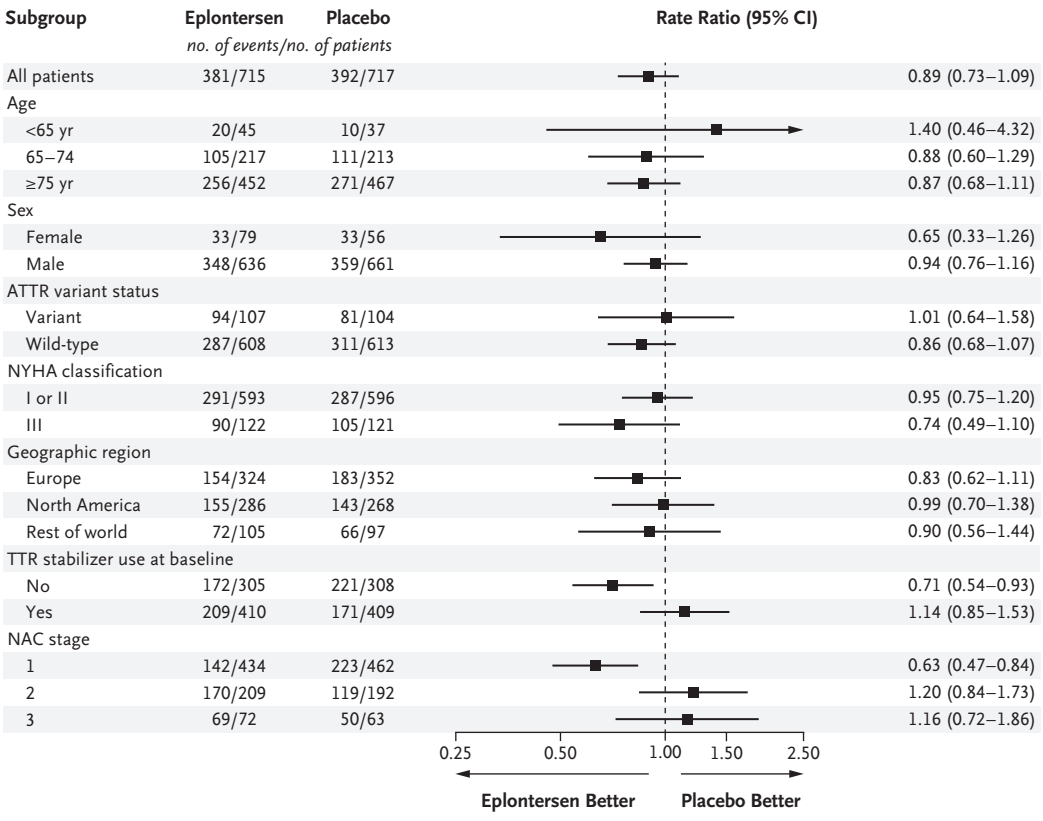

Figure 2. Subgroup Analysis of the Primary End Point.

The confidence intervals in the subgroup analysis have not been adjusted for multiplicity and therefore should not be interpreted as representing hypothesis tests of effects within the subgroups. The National Amyloidosis Centre (NAC) stages were defined as follows[21]: stage 1 as an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of 3000 pg per milliliter or less and an estimated glomerular filtration rate (GFR) of at least 45 ml per minute per 1.73 m^2 of body-surface area, stage 2 as an NT-proBNP level of more than 3000 pg per milliliter and an estimated GFR of at least 45 ml per minute per 1.73 m^2 or as an NT-proBNP level of 3000 pg per milliliter or less and an estimated GFR of less than 45 ml per minute per 1.73 m^2, and stage 3 as an NT-proBNP level of more than 3000 pg per milliliter and an estimated GFR of less than 45 ml per minute per 1.73 m^2. The arrow indicates that the boundary for the confidence interval extends outside the graphed area. ATTR denotes transthyretin amyloidosis, NYHA New York Heart Association, and TTR transthyretin.

SAFETY

Adverse events, serious adverse events, and adverse events of special interest are summarized in Table 2. Overall, 708 patients (99.0%) in the eplontersen group and 705 (98.3%) in the placebo group had at least one adverse event; the most common adverse events during the treatment period are summarized in Table S4. At least one serious adverse event was reported in 413 patients (57.8%) in the eplontersen group and in 426 (59.4%) in the placebo group. Adverse events leading to the discontinuation of eplontersen or placebo were reported in 46 patients (6.4%) who received eplontersen and in 53 (7.4%) who received placebo. Adverse events of special interest were reported in 1 patient (0.1%) who received eplontersen and in 4 (0.6%) who received placebo.

DISCUSSION

In this phase 3 trial comparing eplontersen with placebo in patients with ATTR-CM, eplontersen therapy did not lead to a significantly lower risk of the primary composite end point, death from

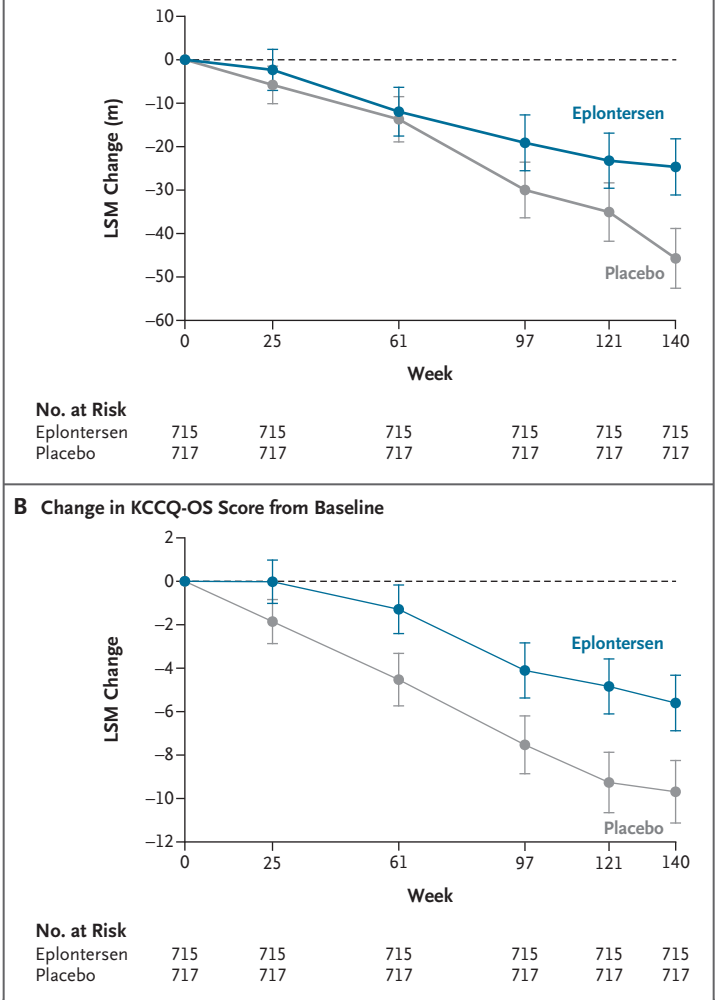

Figure 3. Change in Functional and Health-Related Quality-of-Life Assessments up to Week 140.

Panel A shows the least-squares mean (LSM) change from baseline up to week 140 in the distance (in meters) that patients walked in the 6-minute walk test. Panel B shows the LSM change from baseline up to week 140 in the scores in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS). KCCQ-OS scores range from 0 to 100, with higher scores indicating better health-related quality of life. For the 6-minute walk distance and KCCQ-OS score assessments, values that were missing because of death or heart transplantation were imputed on the basis of the bottom 20% of observed values at the same trial visit in the same group. In both panels, I bars indicate 95% confidence intervals. Confidence intervals for all end points other than the primary end point have not been adjusted for multiplicity and should not be used to infer a treatment effect.

cardiovascular causes and recurrent cardiovascular clinical events, despite substantially suppressing circulating levels of TTR. Eplontersen-treated patients appeared to have a lesser decline in exercise capacity and health-related quality of life than patients who received placebo. No additional treatment effect was apparent among patients who were receiving TTR stabilizers at trial entry. The incidence of adverse events was similar in the two trial groups.

TTR silencers and stabilizers act at different points within the same biologic pathway, the amyloidogenic cascade.[22] TTR stabilizers reduce amyloid formation by preventing tetramer dissociation, whereas gene silencers act upstream by reducing hepatic production of TTR, thereby lowering the circulating substrate available for aggregation.[22] Both reduce but do not completely stop amyloid formation, a factor that raises the possibility of benefit in combination.[22,23] Such benefit might be appealing given the high residual risk even among patients receiving TTR stabilizer therapy. With unrestricted use of TTR stabilizers permitted at enrollment, more than half the patients in the CARDIO-TTRansform trial were already receiving the first TTR stabilizer to be approved for ATTR-CM, tafamidis, at baseline, and additional patients initiated TTR stabilizer therapy during the trial. Of note, this trial incorporated testing of the subgroup of patients receiving a TTR stabilizer at baseline in the prespecified testing hierarchy. Nevertheless, the findings of the trial, which appeared to show a benefit in patients not receiving TTR stabilizer therapy at baseline but no benefit in patients receiving TTR stabilizer therapy, suggest no additional clinical benefit of eplontersen therapy once suppression of amyloid formation had already been achieved through stabilization.

The primary end-point results that were observed in the subgroup of patients not receiving TTR stabilizers at baseline (Fig. 2) were directionally consistent with what was observed in the HELIOS-B trial,[10] which compared vutrisiran with placebo in a similar population of patients with ATTR-CM. The degree of TTR reduction that we observed in this trial is on par with what was seen in NEURO-TTRansform, the polyneuropathy trial of eplontersen — a finding that indicated the anticipated level of pharmacodynamic effect.[15] However, direct comparisons of TTR reduction in this trial with that in the HELIOS-B trial are challenging because of differences in the assays used, assessment time points, enrolled populations, and baseline TTR stabilizer use, which increases TTR levels.[10] Whether therapies that offer even more profound TTR reduction would show

incremental benefit on a background of TTR stabilizer therapy requires further investigation.

The findings from our trial should also be interpreted in the context of evolving standards of care and the broad spectrum of disease severity represented in the trial population, as compared with that in the HELIOS-B trial.[10] First, contemporary management of heart failure evolved during the conduct of this trial, with increasing use of TTR stabilizers, as well as other therapies such as sodium–glucose cotransporter 2 inhibitors and mineralocorticoid receptor antagonists[24]; use of these therapies, which was greater than in the HELIOS-B[10] and ATTRibute-CM[9] trials, may have reduced residual cardiovascular risk. Second, the broad inclusion criteria captured patients across the full spectrum of ATTR-CM, including those with advanced disease (e.g., those with an NT-proBNP level >8500 pg per milliliter, a 6-minute walk distance <150 m, or both National Amyloidosis Centre [NAC] stage 3 disease [defined as an NT-proBNP level of >3000 pg per milliliter and an estimated glomerular filtration rate of <45 ml per minute per 1.73 m^2] and symptoms of NYHA functional class III disease). In such patients, treatments that reduce new amyloid production, such as eplontersen, may be less likely to be beneficial, as was observed in this trial in patients with more advanced NAC disease stage,[21] whereas there was an apparent benefit in patients with NAC stage 1 disease (defined as an NT-proBNP level of ≤3000 pg per milliliter and an estimated glomerular filtration rate of ≥45 ml per minute per 1.73 m^2 of body-surface area). Accordingly, in addition to the high baseline use of TTR stabilizers, it is possible that differences in disease stage, evolving background therapy, or a combination of these factors could also have contributed to the overall trial findings.

The trial has potential limitations. The proportions of patients who were enrolled in the CARDIO-TTRansform trial and were non-White, were women, or had the ATTRv genotype were low. In addition, because TTR stabilizers were allowed as background therapy at baseline but were not randomly assigned, this trial design does not allow for a randomized comparison of the effects of eplontersen alone as compared with TTR stabilizers alone. Also, tafamidis was the most prevalent concomitant TTR stabilizer therapy used, which may potentially limit conclusions regarding acoramidis.

In this trial involving patients with ATTR-CM, eplontersen therapy did not lead to a significantly lower risk of the primary composite end point of death from cardiovascular causes and recurrent cardiovascular events than placebo up to 140 weeks.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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