Design and baseline characteristics of the CARDIO-TTRansform phase 3 randomised controlled trial of eplontersen for participants with transthyretin amyloidosis with cardiomyopathy (ATTR-CM)

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Disclosures

Mathew Maurer reports

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Background

ATTR-CM is a progressive, life-threatening disease caused by the destabilisation of transthyretin (TTR), which dissociates into misfolded monomers or oligomers that aggregate into amyloid fibril deposits in the myocardium[1–3]

Concentric wall thickening and progressive systolic and diastolic dysfunction[2,3] result in declining cardiac performance, reduced quality of life, frequent hospitalisations and high mortality among patients with ATTR-CM[2,4,5]

ATTR-CM can either be hereditary (ATTRv-CM) or occur via a sporadic age-related pathogenic process (ATTRwt-CM)[2]

Despite existing therapies, considerable unmet clinical need remains for patients with ATTR-CM with respect to mortality and morbidity[6]

1. Kelly JW, et al. *Adv Protein Chem* 1997;50:161–81; 2. Ruberg FL, et al. *JAMA* 2024;331:778–91; 3. Griffin JM, et al. *Circ Res* 2021;128:1554–75; 4. Lane T, et al. *Circulation* 2019;140:16–26; 5. Meier-Ewert HK, et al. *Curr Treat Options Cardiovasc Med* 2011;13:528–42; 6. Fontana M, et al. *J Cardiac Failure* 2025;31:318
ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-CM, hereditary/variant ATTR-CM; ATTRwt-CM, wild-type ATTR-CM; QoL, quality of life; TTR, transthyretin

Eplontersen in ATTR-CM

Eplontersen is a GalNAc-conjugated antisense oligonucleotide designed for targeted hepatic delivery,[1] where it binds *TTR* mRNA to reduce production of circulating TTR

Eplontersen is approved for the treatment of ATTRv-PN[2]

The ongoing phase 3, international, multicentre, double-blind, randomised, placebo-controlled CARDIO-TTRansform* trial is evaluating eplontersen in ATTR-CM

Purpose

Here, we present the CARDIO-TTRansform trial design and baseline characteristics of participants

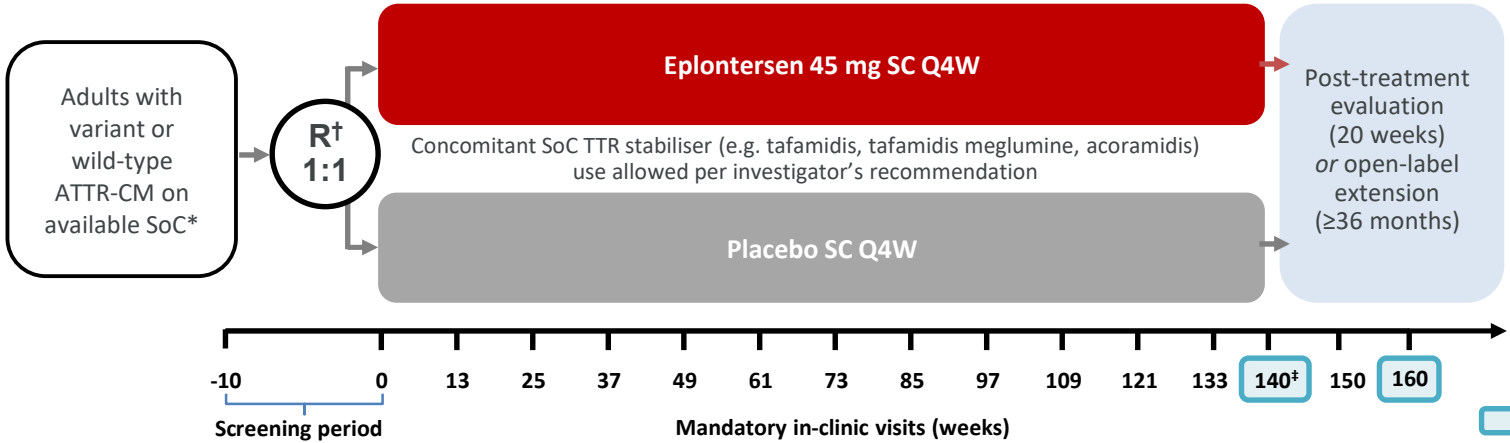
*CARDIO-TTRansform is registered on clinicaltrials.gov as NCT04136171

1. Crooke ST, et al. *Nucleic Acid Ther* 2019;29:16–32; 2.Wainzua Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/wainzua-epar-product-information_en.pdf (accessed March 2026)

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary/variant ATTR with polyneuropathy; GalNAc, N-acetylgalactosamine; mRNA, messenger RNA; TTR, transthyretin

Participants enrolled at 130 sites across 20 countries

CARDIO-TTRansform trial design



Key inclusion/exclusion criteria

- ✓ TTR amyloid deposits on endomyocardial/extracardiac biopsy, or grade 2–3 cardiac uptake on scintigraphy without plasma evidence of monoclonal proteins
- ✓ End-diastolic interventricular septum thickness >12 mm
- ✓ ≥1 HF hospitalisations, or HF signs and symptoms requiring loop diuretic therapy
- ✓ NT-proBNP ≥600 pg/mL or ≥1200 pg/mL if patient has atrial fibrillation (no upper limit)
- ✓ NYHA class I to III and 6MWT ≥100 m
- X eGFR <30 mL/min/1.73 m^2 (<45 mL/min/1.73 m^2 in France, Spain and Denmark)

*Locally approved and available treatments for ATTR-CM;†Participants 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 stabiliser (yes vs no); ‡Primary endpoint at Week 140
6MWT, 6-minute walk test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; eGFR, estimated glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Q4W, every 4 weeks; R, randomisation; SoC, standard of care; SC, subcutaneous; TTR, transthyretin

CARDIO-TTRansform trial endpoints

Primary endpoint

Composite of **CV mortality** and recurrent CV clinical events*

Secondary endpoints (in hierarchical order)

1. Change in 6MWT distance at Week 140
2. Change in KCCQ-OS score at Week 140
3. Total recurrent CV clinical events* up to Week 140
4. All-cause mortality up to Weeks 160 and 140†
5. 1º endpoint in participants receiving TTR stabiliser at baseline up to Week 140
6. CV mortality up to Weeks 160 and 140†

Exploratory endpoints include:

- Echocardiographic assessments
- Cardiac biomarkers (NT-proBNP, hs-cTnT)
- Renal function (eGFR)
- Change in cardiac uptake by Tc99 cardiac scintigraphy‡
- Change in amyloid myocardial burden assessed by ECV by CMR‡

*CV clinical events include hospitalisation for myocardial infarction, HF, arrhythmia or stroke/transient ischaemic attacks, HF urgent visits to emergency department or HF clinics requiring administration of intravenous diuretics for improvement; †All-cause and CV mortality will be tested first up to Week 160, and then up to Week 140, in the formal testing hierarchy; ‡Assessed in optional imaging sub-studies
6MWT, 6-minute walk test; CMR, cardiovascular magnetic resonance; CV, cardiovascular; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-cTnT, high sensitivity cardiac troponin T; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Tc99, Technitium-99; TTR, transthyretin

CARDIO-TTRansform vs other phase 3 ATTR-CM trials: Trial design

	CARDIO-TTRansform eplontersen vs placebo	HELIOS-B[1] vutrisiran vs placebo	ATTRibute-CM[2] acoramidis vs placebo	ATTR-ACT[3] tafamidis vs placebo
Patient population	**N = 1432**	N = 655*	N = 632	N = 441
Enrolment dates	Mar 2020–Jul 2023	Dec 2019–Aug 2021	Apr 2019–Oct 2020	Dec 2013–Aug 2015
Location	20 countries, 130 sites	26 countries, 87 sites	18 countries, 104 sites	13 countries, 48 sites
NT-proBNP criteria (pg/mL)	≥600 (≥1200 if patient has atrial fibrillation); **no upper limit**	>300 (>600 if patient has atrial fibrillation) to <8500	≥300 to <8500	≥600; no upper limit
Open-label concomitant TTR stabiliser use	**No restrictions**	Restricted unless permitted by investigator†	Tafamidis permitted after 12 months	N/A
Primary endpoint	Composite of **CV death** and recurrent CV events	Composite of all-cause death and recurrent CV events	Any-cause death, CV-related hospitalisations, change from baseline in NT-proBNP and 6MWT distance‡	All-cause mortality and CV-related hospitalisations‡

*HELIOS-B recruited N=655 patients: reported baseline and mortality data omit one patient in the placebo group who was randomized but withdrew before dosing; †Tafamidis-naïve participants were required to have no plans to initiate tafamidis within 1 year of enrolment, but could start treatment if deemed necessary by the investigator; ‡Endpoints are presented in hierarchical order

1. Fontana M, et al. *N Engl J Med* 2025;392:33–44; 2. Gillmore JD, et al. *N Engl J Med* 2024;390:132–42; 3. Maurer MS, et al. *N Engl J Med* 2018;379:1007–16

6MWT, 6-minute walk test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; NT-proBNP, N-terminal pro–B-type natriuretic peptide; TTR, transthyretin

CARDIO-TTRansform vs other phase 3 ATTR-CM trials: Baseline characteristics

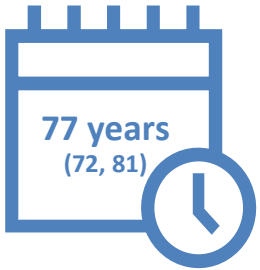
	CARDIO-TTRansform eplontersen vs placebo	HELIOS-B[1] vutrisiran vs placebo*	ATTRibute-CM[2] acoramidis vs placebo*	ATTR-ACT[3] tafamidis vs placebo*
	N = 1432	N = 654†	N = 632	N = 441
Age, median years	77	77 vs 76	77 (mean)	75 vs 74
Female, n (%)	135 (9%)	49 (7%)	62 (10%)	43 (10%)
Race White, n (%)	1271 (89%)	552 (84%)	555 (88%)	357 (81%)
Race Black, n (%)	112 (8%)	37 (6%)	30 (5%)	63 (14%)
NYHA class, n (%) I	192 (13%)	84 (13%)	68 (11%)	37 (8%)
NYHA class, n (%) II	997 (70%)	508 (78%)	455 (72%)	263 (60%)
NYHA class, n (%) III	243 (17%)	62 (9%)	109 (17%)	141 (32%)
UK NAC Stage, n (%) 1	895 (63%)	437 (67%)	361 (57%)	190 (43%)[4]
UK NAC Stage, n (%) 2	400 (28%)	187 (29%)	203 (32%)	167 (38%)[4]
UK NAC Stage, n (%) 3	135 (9%)	30 (5%)	68 (11%)	84 (19%)[4]
ATTRv-CM, n (%)	211 (15%)	76 (12%)	61 (10%)	106 (24%)
NT-proBNP, median pg/mL (IQR range)	2025 (1296–3465)	2021 vs 1801 (1138–3312 vs 1042–3082)	2326 vs 2306 (1332–4019 vs 1128–3754)	2996 vs 3161 (1752–4862 vs 1864–4825)
eGFR, mean ml/min/1.73m²	61.5	64 vs 65 (median)	61	57.5 vs 56[4]

*Data has been extracted from published sources. Where only available by treatment group, data is presented by group (age, NT-proBNP and eGFR) or total n numbers have been calculated and the average taken;†HELIOS-B recruited N=655 patients: reported baseline and mortality data omit one patient in the placebo group who was randomized but withdrew before dosing

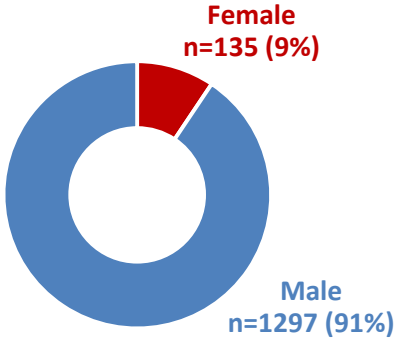
1. Fontana M, et al. *N Engl J Med* 2025;392:33–44; 2. Gillmore JD, et al. *N Engl J Med* 2024;390:132–42; 3. Maurer MS, et al. *N Engl J Med* 2018;379:1007–16; 4. Sperry BW, et al. *JACC CardioOncol* 2024;6:300–6

ATTRv-CM, variant transthyretin amyloidosis with cardiomyopathy; eGFR, estimated glomerular filtration rate; IQR, Interquartile range; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NAC, National Amyloidosis Centre; NYHA, New York Heart Association; TTR, transthyretin

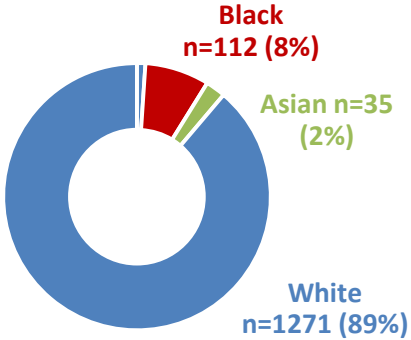
Demographics and characteristics



Median age (IQR)

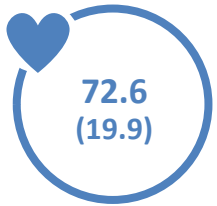


Sex



Race

Mean 6MWT distance, m (SD)



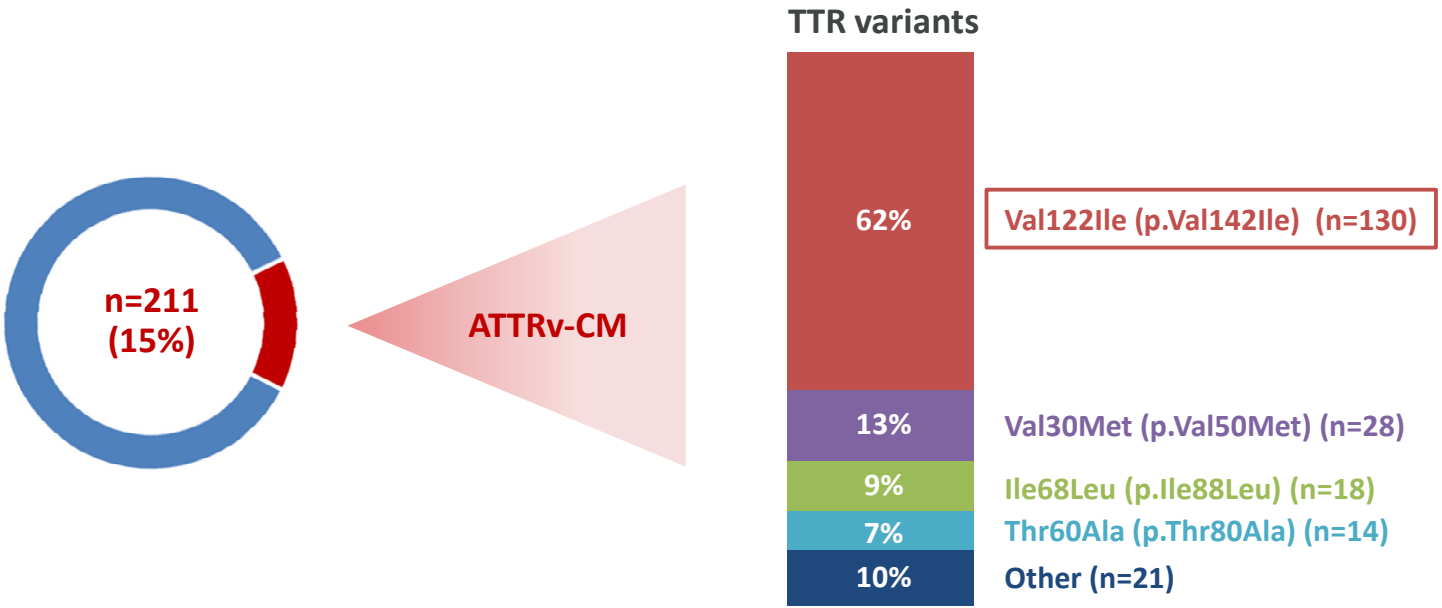
Mean KCCQ-OS score (SD)

Exercise tolerance and health status

A total of **1432** participants were randomised and received ≥1 dose of study drug*

*The CARDIO-TTRansform trial is currently ongoing. The baseline characteristics data presented are near final. Baseline characteristics are presented for the full analysis set (all randomised patients who received at least one injection of study drug and who had at least one post-baseline primary efficacy assessment or one post baseline study visit)
6MWT, 6-minute walk test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; SD, standard deviation

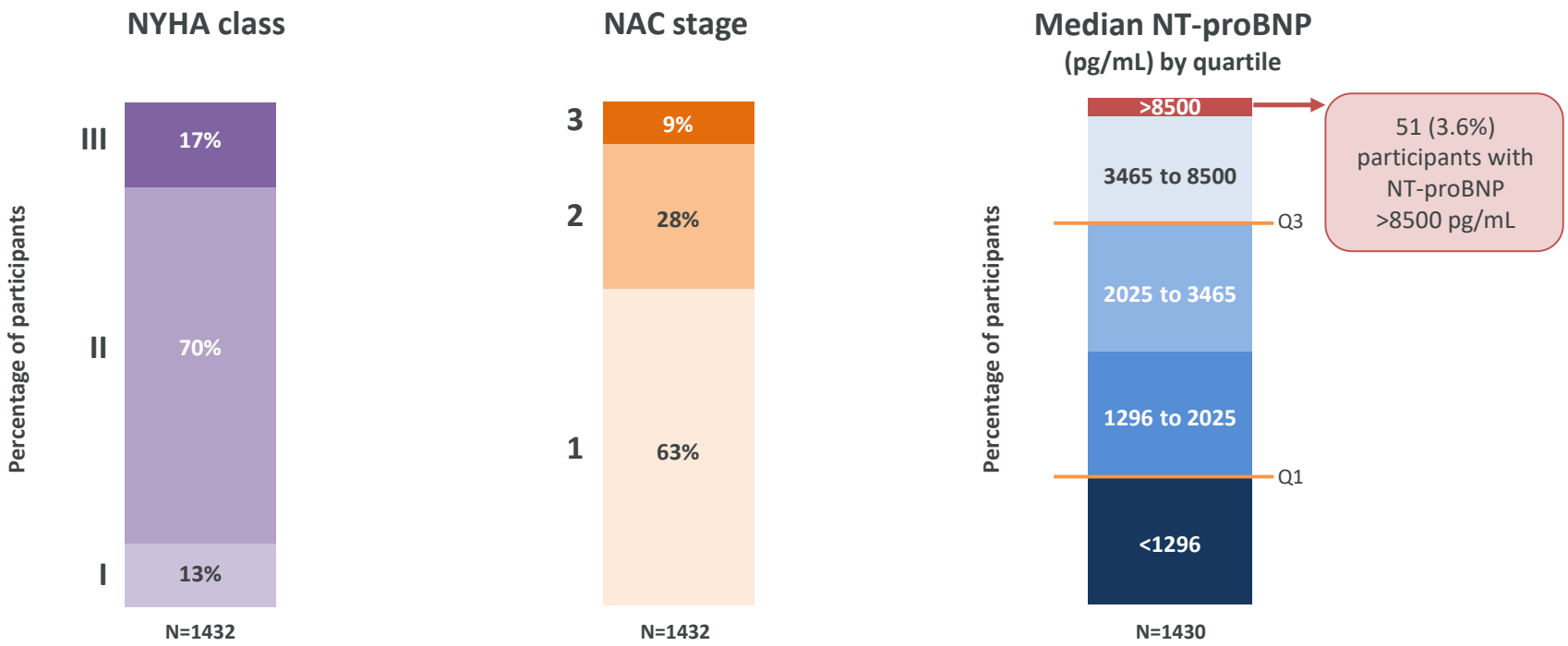
Largest number of participants with V122I variant in an ATTR-CM trial to date



Percentages do not add up to 100% due to rounding

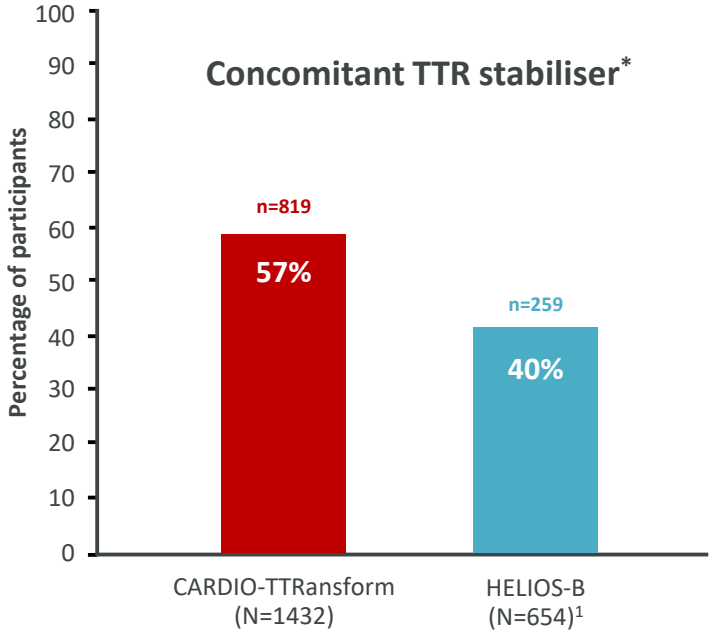
A, alanine; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-CM, hereditary/variant transthyretin amyloidosis with cardiomyopathy; I, isoleucine; L, leucine; M, methionine; T, threonine; TTR, transthyretin; V, valine

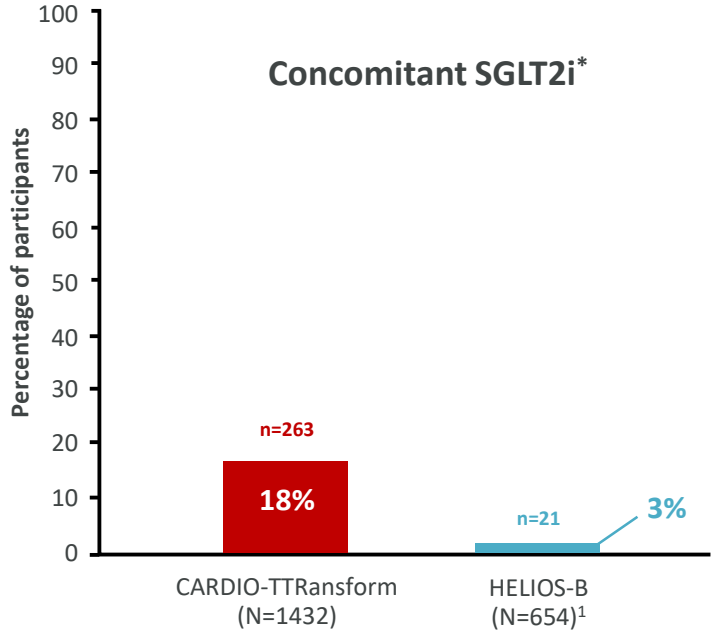
Wide range of heart failure and ATTR-CM severity



ATTR-CM, transthyretin amyloidosis with cardiomyopathy; NAC, National Amyloidosis Centre; NYHA, New York Heart Association; NT-proBNP, N-terminal pro–B-type natriuretic peptide; Q, quartile

Contemporary use of concomitant medications at baseline





*Open label

1. Fontana M, et al. *N Engl J Med* 2025;392:33–44

SGLT2i, sodium-glucose co-transporter 2 inhibitor; TTR, transthyretin

Conclusions

CARDIO-TTRansform includes the largest number of patients enrolled in an ATTR-CM trial to date

CARDIO-TTRansform has enrolled a well-treated patient population spanning a wide range of disease severity and reflecting current standard of care management for ATTR-CM, including widespread use of TTR stabilisers

The study design provides a unique opportunity to determine the clinical benefits of eplontersen in a contemporary setting and in clinically relevant subgroups of patients with ATTR-CM

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; TTR, transthyretin

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Circulation:
Heart Failure

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

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