Eplontersen in transthyretin amyloid cardiomyopathy: results from the randomised, double-blind, placebo-controlled CARDIO-TTRansform trial

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HOT LINE 1: August 28, 11:00

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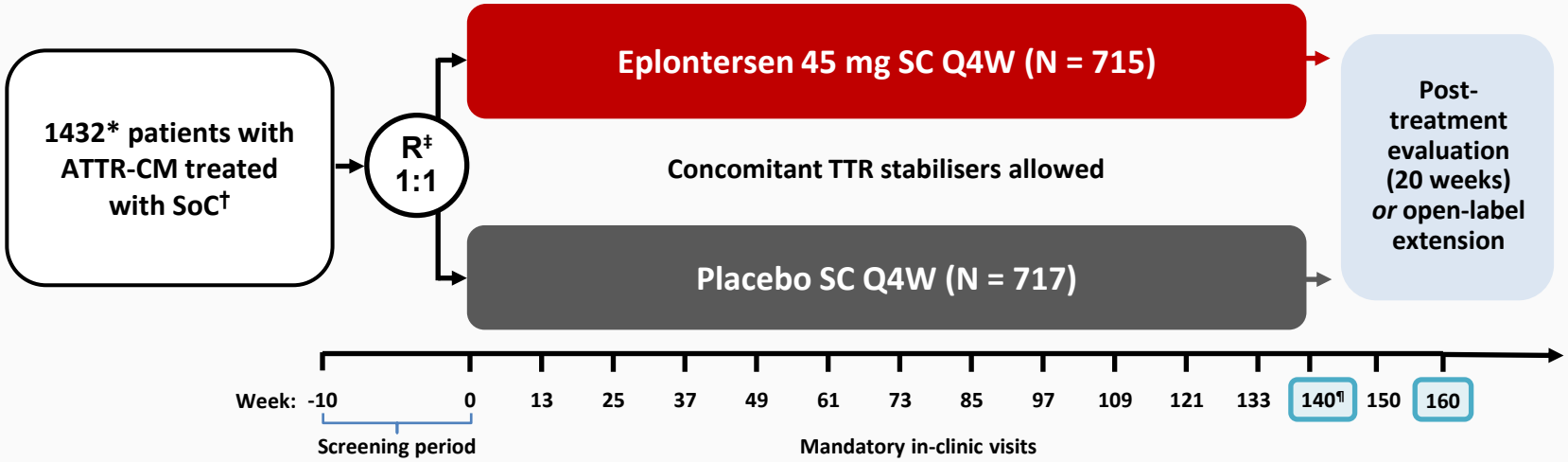
Background

- ATTR-CM is characterised by the extracellular deposition of TTR fibrils within the myocardium, causing progressive, fatal cardiac dysfunction[1–3]
- TTR misfolding occurs either due to a pathogenic gene variant (ATTRv) or an age-related process in patients with wild-type TTR (ATTRwt)[2,4]
- Despite existing therapies, a considerable unmet need remains for patients with ATTR-CM with respect to mortality and morbidity[4]
- CARDIO-TTRansform, the largest trial in patients with ATTR-CM to date, was prospectively designed to evaluate eplontersen versus placebo in the contemporary treatment landscape, where TTR stabilisers are standard of care

ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv, variant/hereditary ATTR; ATTRwt, wild-type ATTR; TTR, transthyretin.

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. Fontana M, et al. *J Cardiac Failure* 2025;31:318; 5. Maurer MS, et al. *N Engl J Med* 2018; 379:1007–1016; 6. Gilmore JD, et al. *N Engl J Med* 2024;390:132–142; 7. Griffin JM, et al. *J Am Coll Cardio HF* 2025;13:685–694; 8. Coelho T, et al. *JAMA* 2023;330:1448–58.

CARDIO-TTRansform: phase 3 trial of eplontersen vs placebo in ATTR-CM



Key inclusion/exclusion criteria

- ✓ Adult age 18-90 years
- ✓ TTR amyloid deposits via biopsy, or grade 2-3 Tc99 cardiac uptake
- ✓ Intraventricular wall thickness >12 mm
- ✓ ≥1 HF hospitalisation, or HF requiring loop diuretic therapy
- ✓ NYHA functional class I–III
- ✓ NT-proBNP ≥600 pg/mL (≥1200 with atrial fibrillation)
- ✓ 6MWT ≥100 m
- X eGFR <30 mL/min/1.73m^2

CARDIO-TTRansform was a rigorously conducted trial; discontinuation rates were lower in the eplontersen arm, with minimal loss to follow-up

*1438 patients were randomised; 6 did not receive treatment. †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 (≤350 m vs >350 m), and treatment at baseline with TTR stabiliser (yes vs no); ¶Primary endpoint at Week 140.

Hierarchical testing of primary and secondary 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 patients receiving TTR stabiliser at baseline up to Week 140
6. CV mortality up to weeks 160 and 140†

All deaths and CV events were adjudicated by an independent Clinical Adjudication Committee

*CV clinical events include hospitalisation for myocardial infarction, HF, stroke/transient ischaemic attacks, HF urgent visits to emergency department or HF clinics requiring administration of intravenous diuretics for improvement, and unscheduled hospitalisation or emergency department stay >24 hours for arrhythmia-related events; †All-cause and CV mortality tested first up to week 160, and then up to week 140, in the formal testing hierarchy.
KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary.

Baseline characteristics were generally balanced across arms

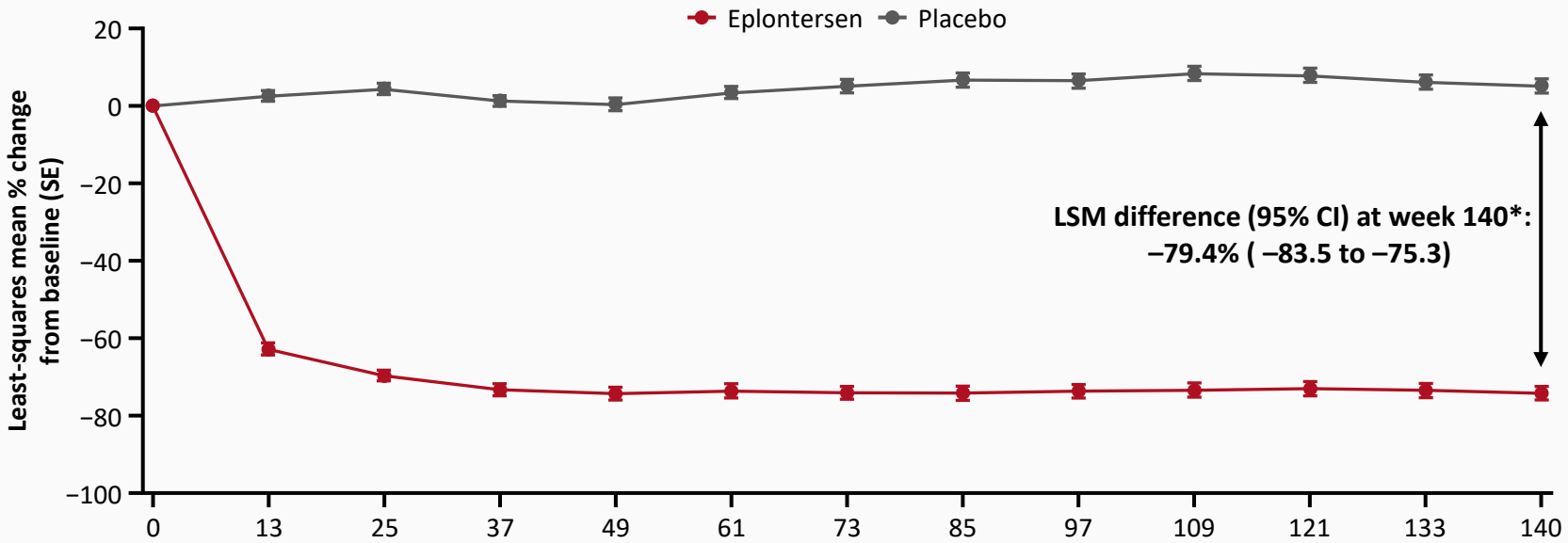
	Eplontersen (N=715)	Placebo (N=717)
Age, years, mean ± SD	76.2 ± 7.2	76.6 ± 7.0
Male sex, n (%)	636 (89.0)	661 (92.2)
Race , n (%)		
White	634 (88.7)	637 (88.8)
Black	54 (7.6)	57 (7.9)
Asian	20 (2.8)	15 (2.1)
Multiple/Other	7 (1.0)	8 (1.1)
TTR genotype, n (%)		
Wild-type	608 (85.0)	613 (85.5)
Variant (hereditary)	107 (15.0)	104 (14.5)
6-minute walk test (m), mean ± SD	350.5 ± 95.2	354.0 ± 97.3
KCCQ-OS score, mean ± SD	72.5 ± 19.8	72.7 ± 20.0

Baseline characteristics were generally balanced across arms

	Eplontersen (N=715)	Placebo (N=717)
NYHA functional class, n (%)		
Class I	84 (11.7)	108 (15.1)
Class II	509 (71.2)	488 (68.1)
Class III	122 (17.1)	121 (16.9)
NAC disease stage, n (%)		
Stage 1	434 (60.7)	462 (64.4)
Stage 2	209 (29.2)	192 (26.8)
Stage 3	72 (10.1)	63 (8.8)
NT-proBNP, ng/mL, median (IQR)	2068 (1323–3563)	1965 (1284–3422)
Baseline TTR stabiliser use, n (%)	410 (57.3)	409 (57.0)
Baseline SGLT2i use, n (%)	135 (18.9)	130 (18.1)
Baseline MRA use, n (%)	303 (42.4)	315 (43.9)

MRA, mineralocorticoid receptor antagonist.

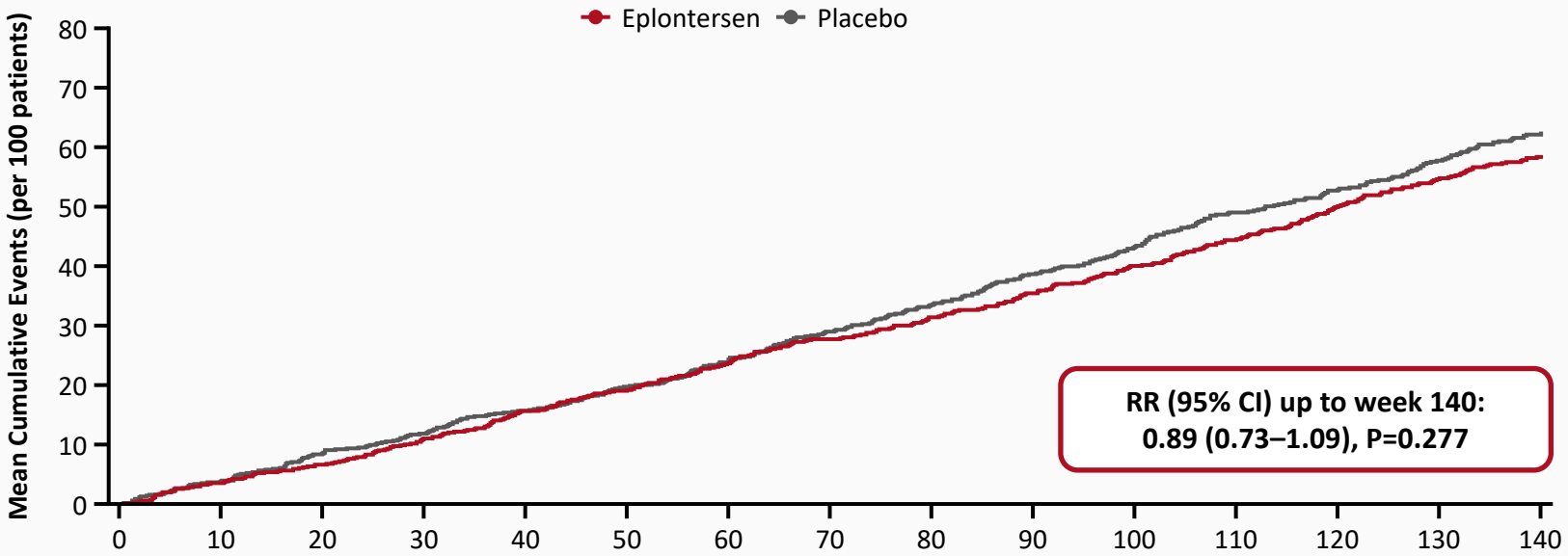
Eplontersen led to rapid, deep and sustained decrease in serum TTR



No. of patients													
Eplontersen	715	704	688	667	651	639	625	614	597	579	563	546	531
Placebo	717	695	668	640	624	614	591	577	563	542	522	499	486

*On-treatment analysis

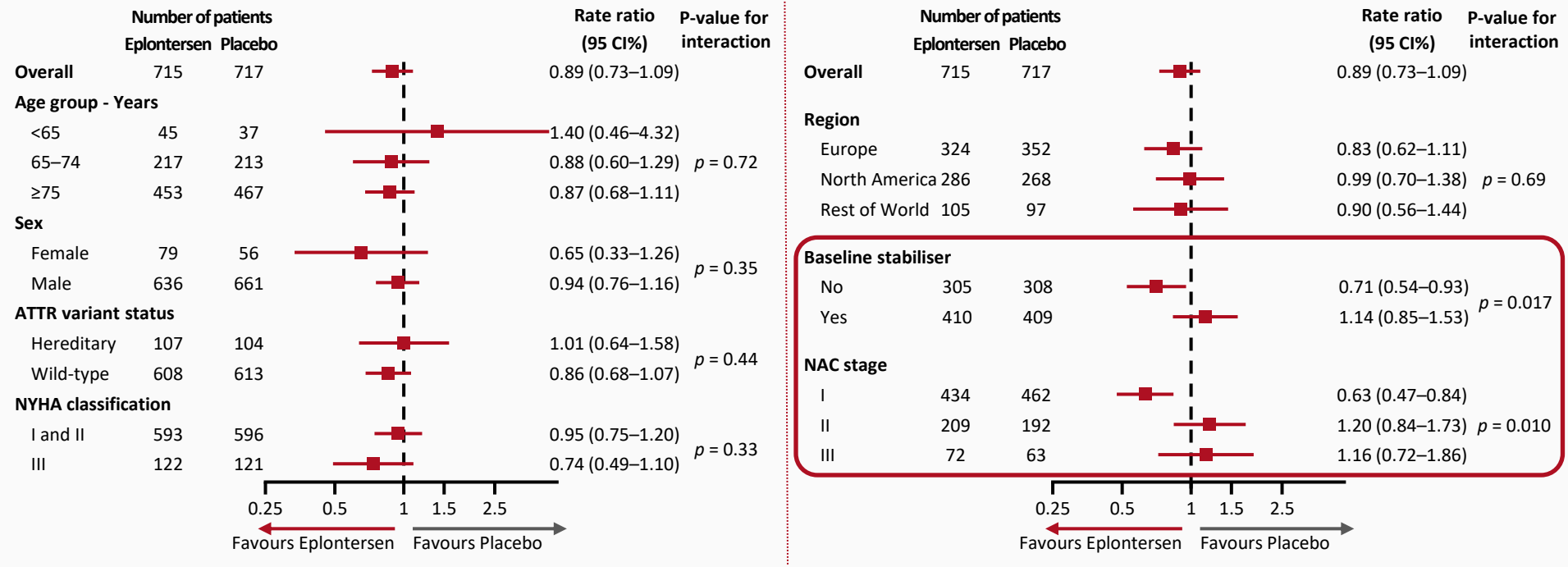
Primary composite endpoint of CV death and recurrent CV events



No. of patients															
Eplontersen	715	714	707	699	685	676	667	656	649	637	624	619	605	594	572
Placebo	717	711	697	681	671	662	650	632	621	612	601	582	561	551	535

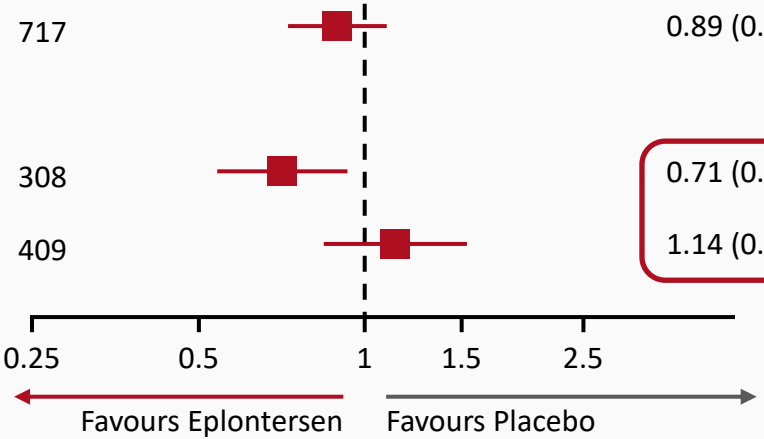
RR, rate ratio.

Consistent effects across subgroups except by baseline stabiliser use and NAC stage



Strong interaction between baseline stabiliser use and eplontersen effect

	Number of patients		Rate ratio (95 CI%)	P-value for interaction
	Eplontersen	Placebo		
Overall	715	717	0.89 (0.73–1.09)	
Baseline stabiliser				
No	305	308	0.71 (0.54–0.93)	$p = 0.017$
Yes	410	409	1.14 (0.85–1.53)	

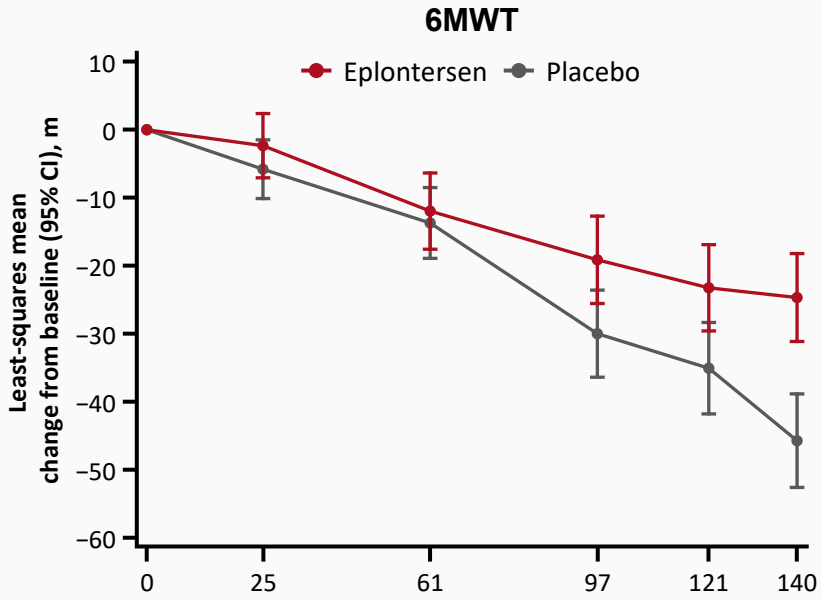


Significant for several secondary endpoints

Endpoint	Eplontersen (N=715)	Placebo (N=717)	Efficacy vs placebo (95% CI)	Nominal P-value
Δ 6MWT (m), LSM (SE)	−27.5 (3.6)	−47.3 (3.6)	19.7 (9.9–29.6)	**<0.001**
Δ KCCQ-OS, LSM (SE)	−5.4 (0.7)	−9.4 (0.7)	4.0 (2.0–6.0)	**<0.001**
Recurrent CV events up to 140 weeks, n*	307	323	RR: 0.88 (0.71–1.10)	0.26
All-cause death up to 160 weeks, n (%)	126 (17.6%)	147 (20.5%)	HR: 0.78 (0.61–0.99)	**0.039**
All-cause death up to 140 weeks, n (%)	111 (15.5%)	130 (18.1%)	HR: 0.77 (0.60–0.99)	**0.043**
Primary endpoint events in stabiliser subgroup, n*	209	171	RR: 1.14 (0.85–1.53)	0.39
CV death up to 160 weeks, n (%)	97 (13.6%)	101 (14.1%)	HR: 0.86 (0.65–1.14)	0.29
CV death up to 140 weeks, n (%)	85 (11.9%)	86 (12.0%)	HR: 0.88 (0.65–1.18)	0.39

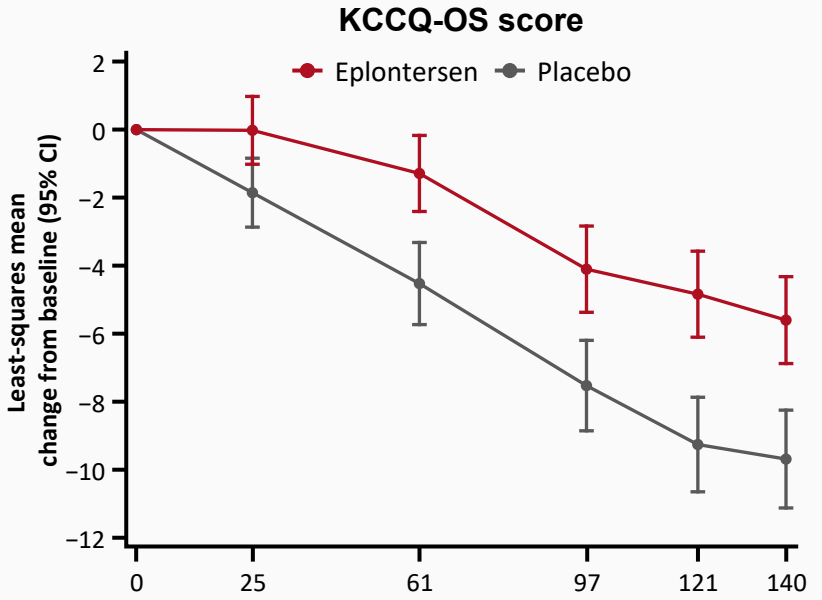
*Number of events.

Benefit on functional capacity and quality of life



No. of patients						
Week	0	25	61	97	121	140
Eplontersen	715	715	715	715	715	715
Placebo	717	717	717	717	717	717

LSMD (95% CI) at week 140:
19.7 m (9.9–29.6), P <0.001*



No. of patients						
Week	0	25	61	97	121	140
Eplontersen	715	715	715	715	715	715
Placebo	717	717	717	717	717	717

LSMD (95% CI) at week 140:
4.0 points (2.0–6.0), P <0.001*

Error bars indicate 95% confidence intervals. *Nominal P-value <0.05

Eplontersen was well tolerated with no new safety signals

	Eplontersen (N=715)		Placebo (N=717)	
	Patients with event, n (%)	Events, n	Patients with event, n (%)	Events, n
Any adverse event	708 (99.0)	10 173	705 (98.3)	9979
Any serious adverse event	413 (57.8)	1200	426 (59.4)	1380
Any serious adverse event deemed related to study intervention	4 (0.6)	6	2 (0.3)	2
Any adverse event leading to discontinuation	46 (6.4)	47	53 (7.4)	53
Any adverse event of special interest	1 (0.1)	1	4 (0.6)	4
Platelet count <25 x 10^9/l independent of a major bleeding or CRNMB event	1 (0.1)	1	4 (0.6)	4
Glomerulonephritis	0	0	0	0

CRNMB, clinically relevant, non-major bleeding.

Conclusions

- Overall, CARDIO-TTRansform was rigorously executed and designed to test an important hypothesis in a broad spectrum of contemporary patients with ATTR-CM receiving SoC including TTR stabilisers
- In the overall study population, eplontersen did not significantly reduce the primary composite endpoint, despite rapid, deep and sustained suppression of circulating serum TTR levels
- Primary results appear influenced by baseline stabiliser use in this contemporary population
  - In the stabiliser subgroup, there was no benefit observed in the primary endpoint
  - In the non-stabiliser subgroup, fewer primary endpoint events were observed with eplontersen compared with placebo
- Eplontersen preserved functional capacity and health-related quality of life compared with placebo
- Eplontersen was well tolerated with no new safety concerns

Acknowledgements

Funding

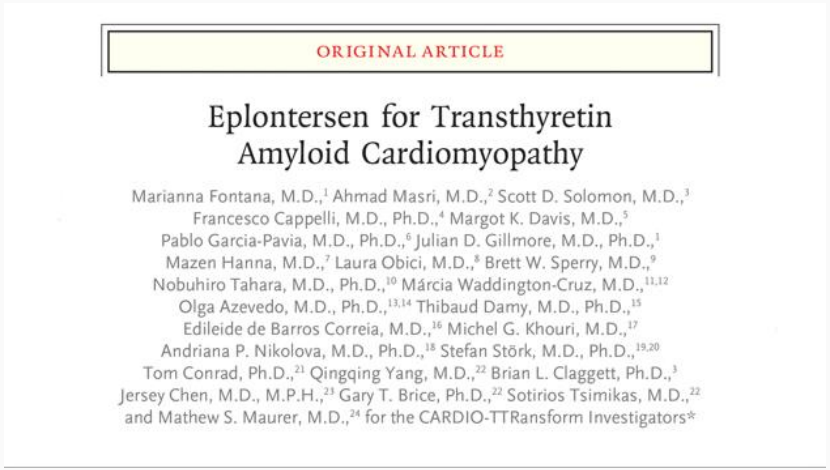
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ORIGINAL ARTICLE

Eplontersen for Transthyretin Amyloid Cardiomyopathy

Marianna Fontana, M.D.,[1] Ahmad Masri, M.D.,[2] Scott D. Solomon, M.D.,[3] Francesco Cappelli, M.D., Ph.D.,[4] Margot K. Davis, M.D.,[5] Pablo Garcia-Pavia, M.D., Ph.D.,[6] Julian D. Gillmore, M.D., Ph.D.,[1] Mazen Hanna, M.D.,[7] Laura Obici, M.D.,[8] Brett W. Sperry, M.D.,[9] Nobuhiro Tahara, M.D., Ph.D.,[10] Márcia Waddington-Cruz, M.D.,[11,12] Olga Azevedo, M.D., Ph.D.,[13,14] Thibaud Damy, M.D., Ph.D.,[15] Edileide de Barros Correia, M.D.,[16] Michel G. Khouri, M.D.,[17] Andriana P. Nikolova, M.D., Ph.D.,[18] Stefan Störk, M.D., Ph.D.,[19,20] Tom Conrad, Ph.D.,[21] Qingqing Yang, M.D.,[22] Brian L. Claggett, Ph.D.,[3] Jersey Chen, M.D., M.P.H.,[23] Gary T. Brice, Ph.D.,[22] Sotirios Tsimikas, M.D.,[22] and Mathew S. Maurer, M.D.,[24] for the CARDIO-TTRansform Investigators*

For a deep dive on CARDIO-TTRansform trial results stratified by baseline TTR stabiliser use:

Late-Breaking Clinical Science: Cardiac Amyloidosis
Sunday 30 August, 13.45–15.00

Efficacy and safety of transthyretin gene silencer eplontersen in patients with transthyretin amyloid cardiomyopathy receiving stabiliser therapy in the CARDIO-TTRansform trial

Presenter: Pablo García-Pavía