Effects of Vutrisiran on Echocardiographic Cardiac Structure and Function: The HELIOS-B Trial

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Declaration of Interests for Karola Jering

Conflicts of interest: None

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Introduction

Transthyretin Amyloidosis with Cardiomyopathy (ATTR-CM)

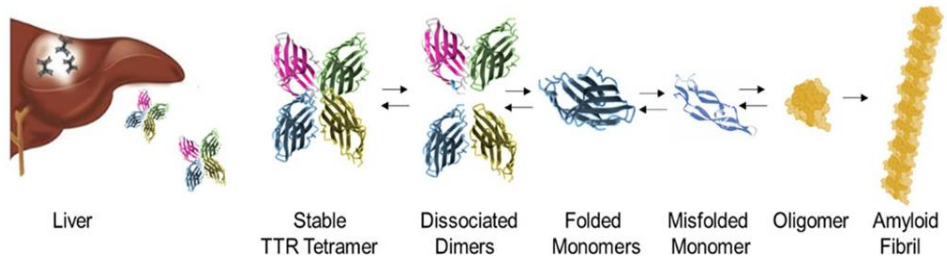
- ATTR-CM is an increasingly diagnosed cause of heart failure associated with high burden of morbidity and mortality[1–3]
- Contemporary patients have less advanced disease because of earlier diagnosis and improved heart failure management. Many receive tafamidis, SGLT2 inhibitors, and diuretics[2]
- Extracellular deposition of amyloid fibrils in the heart leads to restrictive physiology, arrhythmias, and conduction disease[1–4]
- Echocardiography is frequently the initial diagnostic modality and is also used to monitor for disease progression, often defined as increases in wall thickness, declines in LVEF or LV peak longitudinal strain, or deterioration in diastolic function[1,5,6]

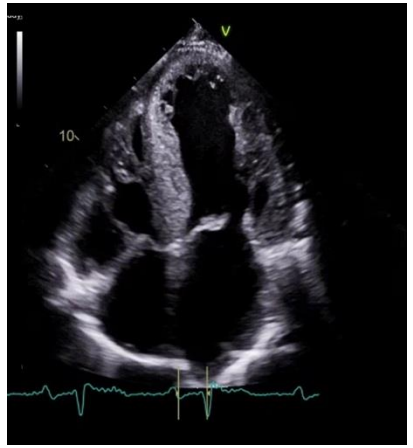
HELIOS-B Study

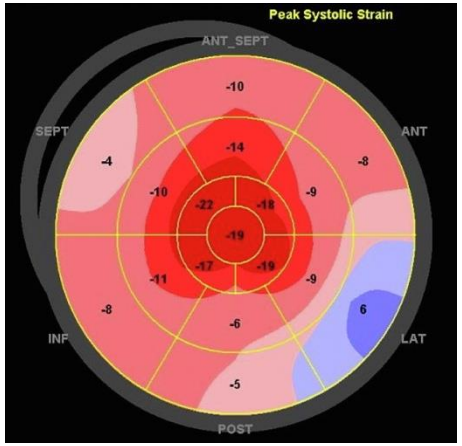
- Evaluated vutrisiran, a SC-administered RNAi therapeutic (quarterly dosing), in patients with ATTR-CM in a Phase 3, randomized, placebo-controlled trial[7]

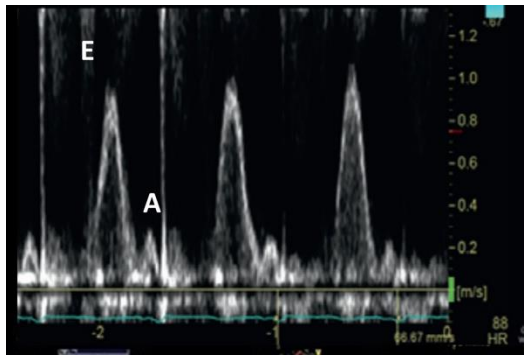
Objective

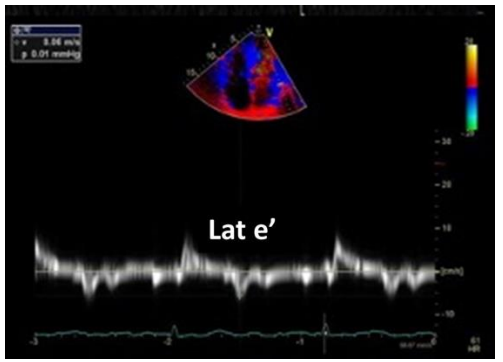
- Determine effects of vutrisiran on echocardiographic measures of cardiac structure and function in patients with ATTR-CM











Abbreviations: LV, left ventricular; LVEF LV ejection fraction; SC, subcutaneous; RNAi, RNA interference.

References: 1. Porcari et al. *Cardiovasc Res* 2022;118:3517–35; 2. Garcia-Pavia et al. *Eur J Heart Fail* 2021;23:512–26; 3. Ruberg et al. *JAMA* 2024;331:778–91; 4. Kittleson et al. *Circulation* 2020;142:e7–e22; 5. Dorbala et al. *J Am Coll Img* 2020;13:1368–83; 6. Cuddy S et al. *Journal of the American Society of Echocardiography*. 2022;35(9):A31-A40 7. Fontana et al. *N Eng J Med* 2024; DOI: 10.1056/NEJMoa2409134. Epub ahead of print.

HELIOS-B Study Design

A phase 3 study to evaluate vutrisiran in patients with ATTR-CM

Patient Population (n=655)

- ATTR: Wild-type or any TTR variant
- Confirmed cardiomyopathy and medical history of symptomatic HF
- NYHA Class ≤III; 6-MWT ≥150 m; NT-proBNP limits[b] at baseline
- Approximately 40% of patients on tafamidis at baseline

Select Exclusion Criteria:

- NYHA Class IV HF
- PND score ≥III at the screening visit
- Received prior TTR-lowering treatment

➢ *All endpoints were prespecified for analysis separately in the **Overall** and **Monotherapy** populations*

Primary Endpoint: Composite outcome of all-cause mortality and recurrent CV events during double blind (DB) period (Month 33–36)

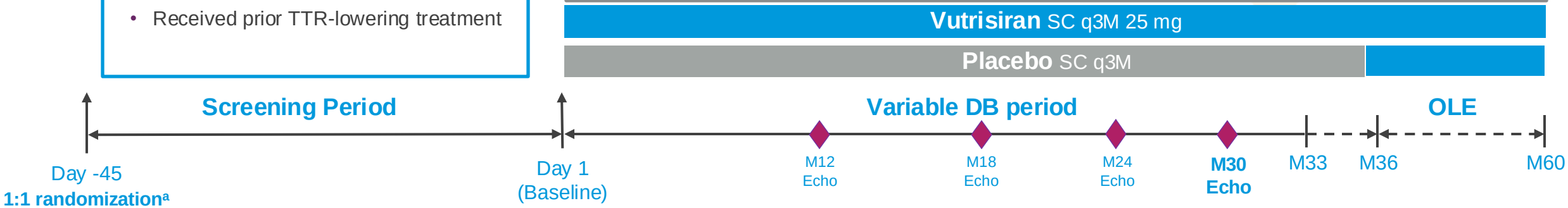
Secondary Endpoints: Change from baseline in 6-minute walk test, KCCQ-OS, all-cause mortality through 42 months, NYHA Functional Class

Select Exploratory Endpoints: Change from baseline in mean left ventricular wall thickness and peak longitudinal strain at M30

- Echocardiographic assessments performed at months 12, 18, 24 and 30

Statistical Analysis for Echo Endpoints

- Changes from baseline to month 30 were analyzed with mixed models for repeated measures
- Fixed effect terms were baseline value, treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis and age group



[a]Randomization was stratified according to the use of tafamidis at baseline (yes vs no), ATTR disease type (hATTR or wtATTR), and NYHA class and age at baseline (NYHA class I or II and age <75 years vs all others).
[b]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation). **Abbreviations:** ATTR-CM; transthyretin amyloidosis with cardiomyopathy; FC, functional class; TTR, transthyretin; NYHA, New York Heart Association, 6-MWT, 6-minute walk test, HF, heart failure, PND, polyneuropathy disability score. **Reference:** Clinicaltrials.gov identifier: NCT04153149.

Contemporary Population with Baseline Characteristics Balanced Across Arms

Parameter		Overall Population	
		Placebo (N=328)	Vutrisiran (N=326)
Age (years), median (range)		76 (46, 85)	77 (45, 85)
Male sex, n (%)		306 (93.3)	299 (91.7)
hATTR amyloidosis, n (%)		39 (11.9)	37 (11.3)
NYHA class, n (%)	I	35 (10.7)	49 (15.0)
	II	258 (78.7)	250 (76.7)
	III	35 (10.7)	27 (8.3)
ATTR disease stage, n (%)	1	229 (69.8)	208 (63.8)
	2	87 (26.5)	100 (30.7)
	3	12 (3.7)	18 (5.5)
Baseline 6-MWT, meters, mean (SD)		377 (96)	372 (104)
Baseline KCCQ-OS, points, mean (SD)		72.26 (19.92)	72.96 (19.44)
Baseline NT-proBNP, ng/L, median (IQR)		1801 (1042, 3082)	2021 (1138, 3312)
Baseline Troponin I, ng/L, median (IQR)		65.2 (41.1, 105.5)	71.9 (44.9, 115.9)

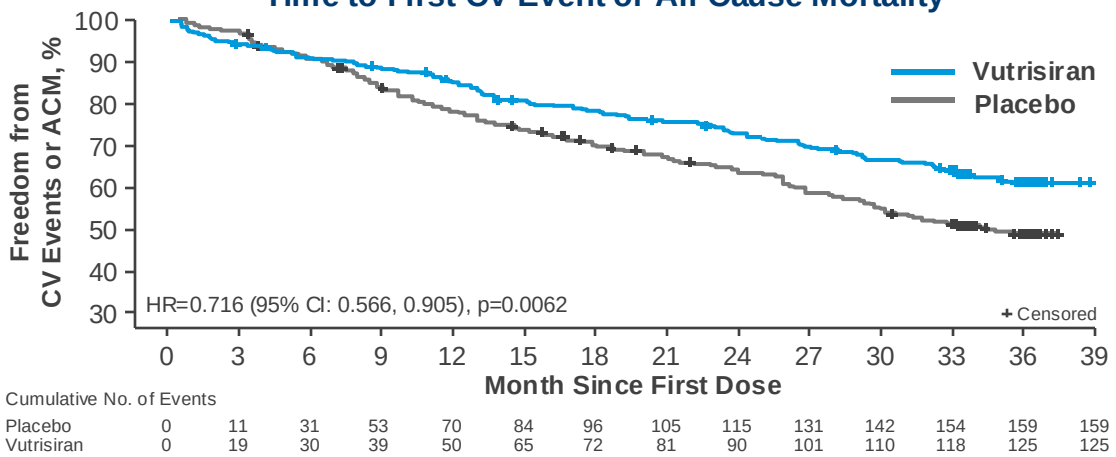
Echo Characteristics	Placebo (N=328)	Vutrisiran (N=326)
LV ejection fraction (%), mean (SD)	**55.9 (12.3)**	**55.6 (12.7)**
Peak longitudinal strain (%), mean (SD)	-14.0 (3.5)	-14.0 (3.5)
Stroke volume (mL), mean (SD)	53.8 (19.0)	50.7 (16.3)
Mean LV wall thickness (mm), mean (SD)	18.2 (3.0)	18.2 (3.0)
Relative wall thickness, mean (SD)	0.8 (0.2)	0.8 (0.2)
LV mass index (g/m^2), mean (SD)	180.8 (46.1)	182.1 (44.2)
E/A ratio, mean (SD)	1.9 (1.0)	2.1 (1.1)
Lateral E/e' ratio, mean (SD)	15.3 (6.3)	14.8 (6.7)

- **Tafamidis:** Baseline ~40% in both treatment arms; drop-in during DB ~21% and ~22% for placebo and vutrisiran, respectively
- **SGLT2 inhibitors:** Baseline ~3% in both treatment arms; drop-in during DB ~35% and ~31% for placebo and vutrisiran, respectively
- **Substantial use of diuretics:** Baseline ~80% in both treatment arms; Outpatient initiation or intensification of diuretics after first dose was ~56% and ~48% for placebo and vutrisiran, respectively

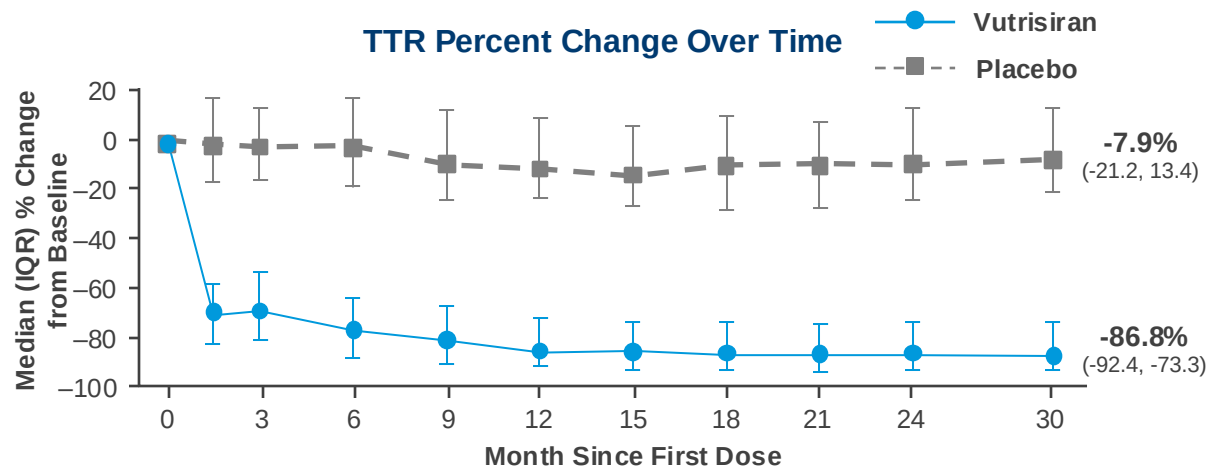
Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; DB, double-blind; hATTR, hereditary transthyretin amyloidosis; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2.

HELIOS-B Met All 10 Primary and Secondary Endpoints in the Overall and Monotherapy Populations

Time to First CV Event or All-Cause Mortality[a,b]



TTR Percent Change Over Time



TTR % change at Month 30: Mean (SD): placebo -1.98 (35.4); vutrisiran -80.98 (16.1)

Endpoint	Treatment Effect Estimation	Overall Population (N=654)		Monotherapy Population (N=395)	
		Treatment Effect	p-value	Treatment Effect	p-value
Primary endpoint Composite outcome of all-cause mortality and recurrent CV events[c,d]	Hazard ratio	**0.718**	**0.0118**	**0.672**	**0.0162**
Secondary endpoints					
6-MWT change at Month 30[e]	LS Mean difference	**26.46**	**0.00008**	**32.09**	**0.0005**
KCCQ-OS change at Month 30[e]	LS Mean difference	**5.80**	**0.0008**	**8.69**	**0.0003**
All-cause mortality through Month 42[b]	Hazard ratio	**0.645**	**0.0098**	**0.655**	**0.0454**
NYHA class: % stable or improved at Month 30[f]	Adjusted % difference	**8.7%**	**0.0217**	**12.5%**	**0.0121**

- **Vutrisiran met all 10 primary and secondary endpoints**
- **Rapid and durable TTR knockdown through Month 30**
- **Knockdown comparable to prior studies with vutrisiran**

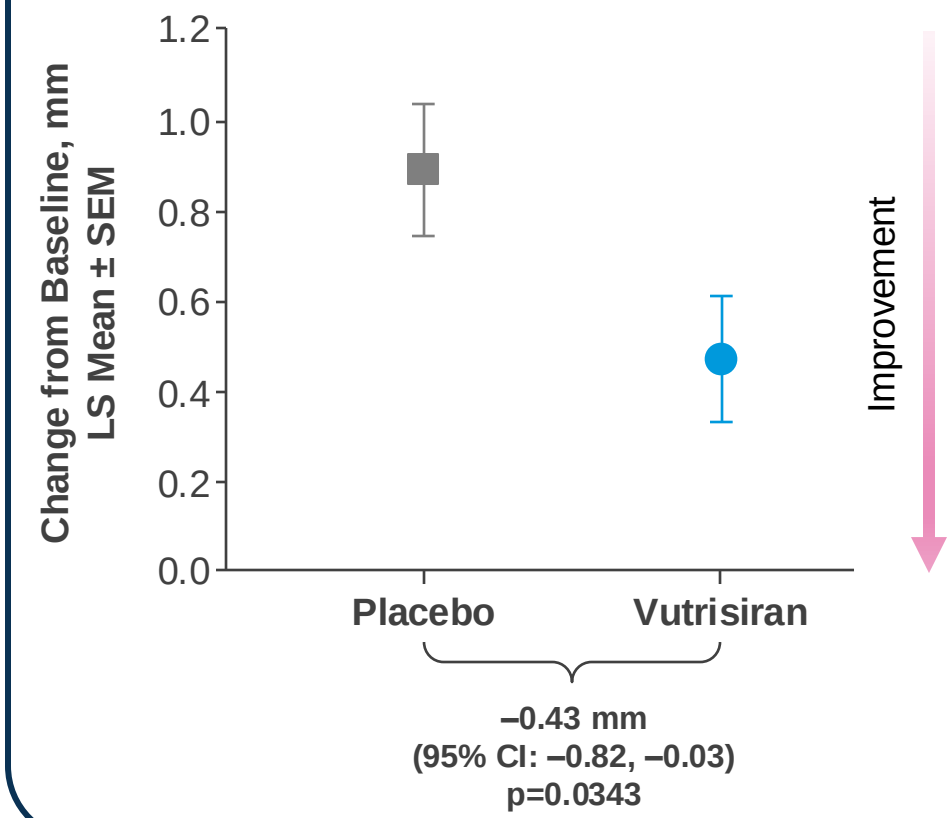
[a]Based on IPTW-adjusted Kaplan-Meier curves. [b]HR derived from Cox PH model, p-value derived from log-rank test. [c]Primary analysis based on the modified Andersen-Gill model, also known as LWYY. [d]Assessed at 33-36 months. [e]Based on a MMRM model. [f]Based on CMH method. From N Engl J Med, Fontana et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. DOI: 10.1056/NEJMoa2409134. Epub ahead of print. Copyright © (2024). Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society. **Abbreviations**: CV, cardiovascular; 6-MWT, 6-minute walk test; IQR, interquartile range; KCCQ-OS, Kansas City cardiomyopathy questionnaire – Overall Summary; LS, least squares; NYHA, New York Heart Association. **Reference**: Fontana et al. N Eng J Med 2024. DOI: 10.1056/NEJMoa2409134. Epub ahead of print.

Vutrisiran Significantly Attenuated Increases in LV Wall Thickness and LV Mass Index at Month 30 vs Placebo

HELIOS-B

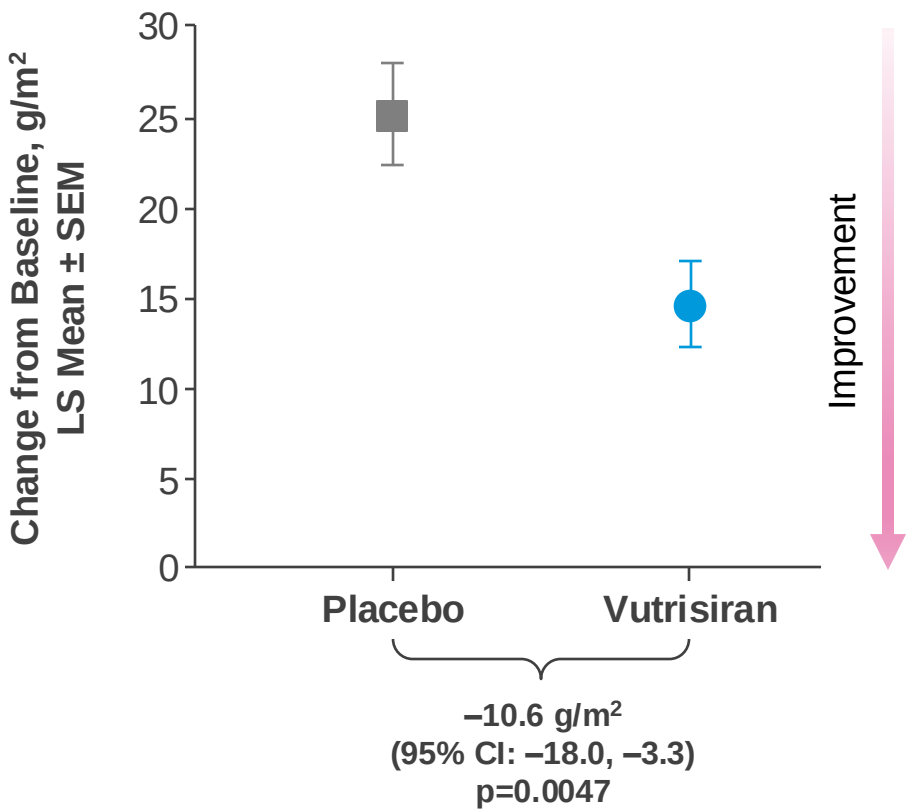
Overall Population

Mean LV Wall Thickness



–0.43 mm
(95% CI: –0.82, –0.03)
p=0.0343

LV Mass Index



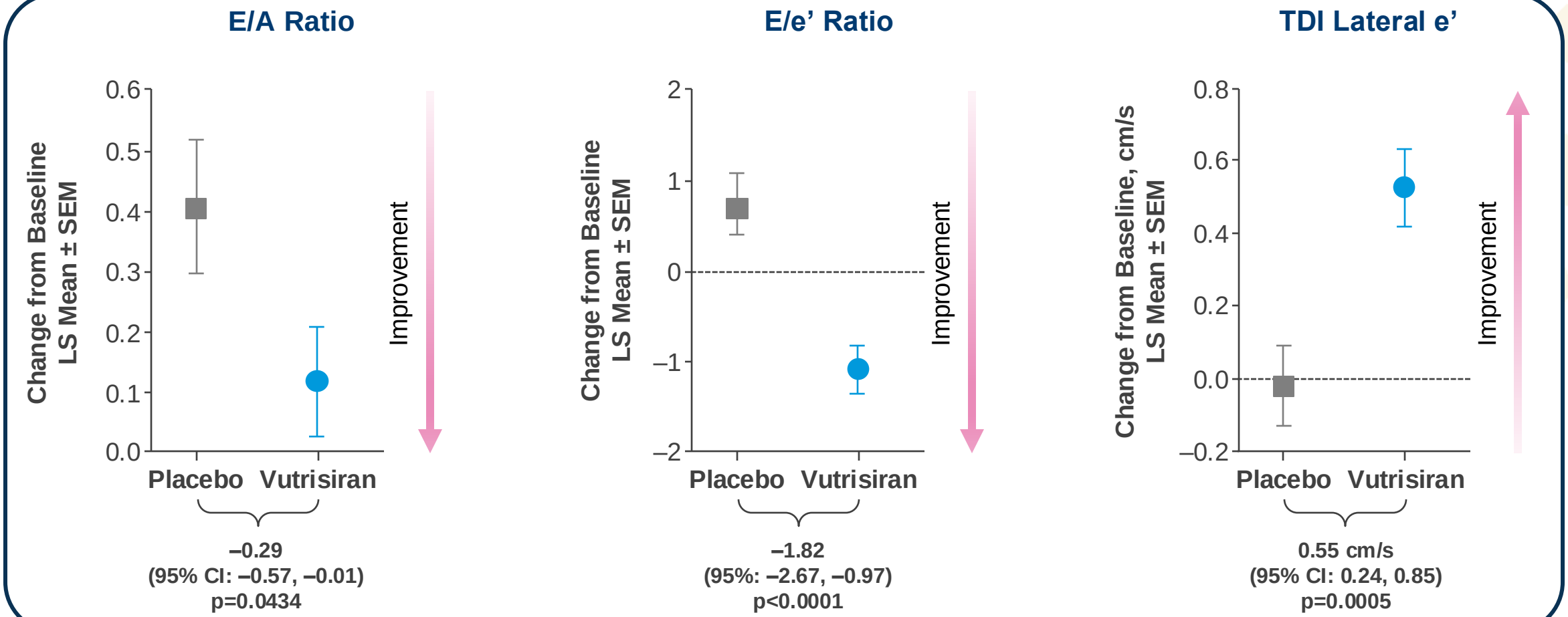
–10.6 g/m²
(95% CI: –18.0, –3.3)
p=0.0047

Results are from a MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group. **Abbreviations:** CI, confidence interval; LS, least squares; LV, left ventricular; SEM, standard error of the mean.

Vutrisiran Significantly Improved LV Diastolic Function at Month 30 vs Placebo

HELIOS-B

Overall Population



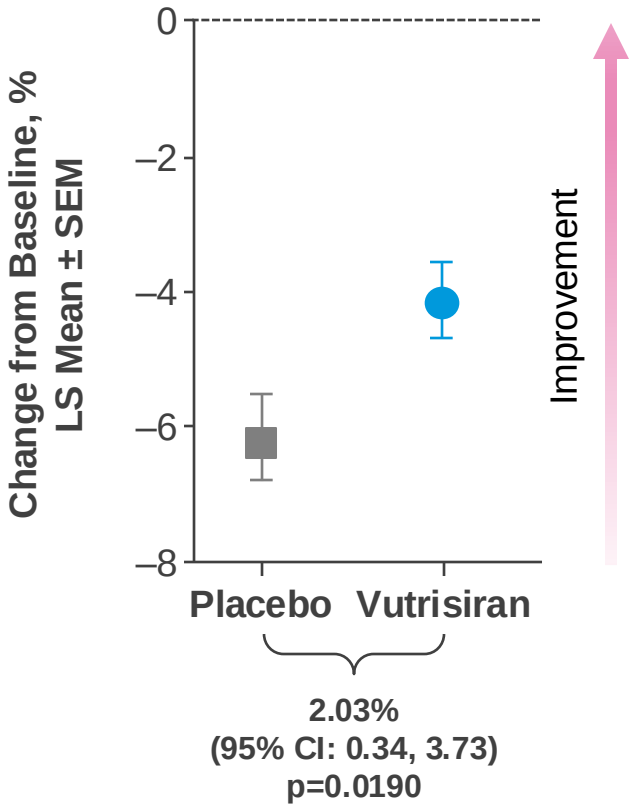
Results are from a MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group. **Abbreviations**: CI, confidence interval; E/A, ratio of early to late diastolic transmitral inflow velocities; E/e', ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; LS, least squares; SEM, standard error of the mean; TDI lateral e', lateral peak early diastolic mitral annular tissue velocity.

Vutrisiran Significantly Attenuated Decline in LV Systolic Function at Month 30 vs Placebo

HELIOS-B

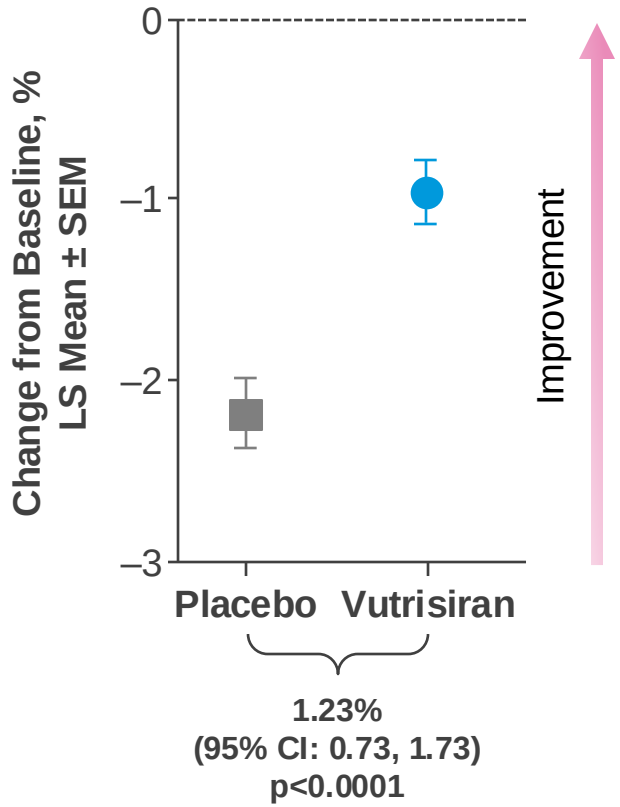
Overall Population

LV Ejection Fraction



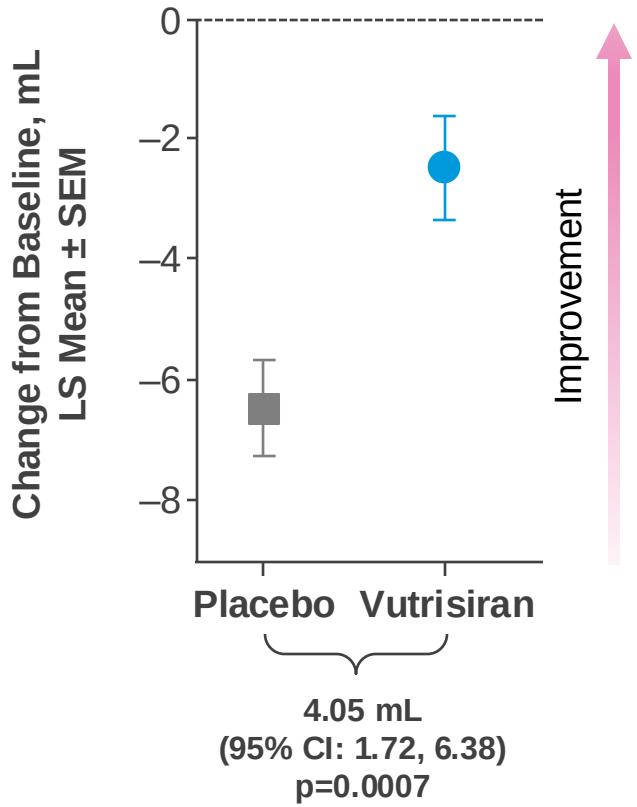
2.03%
(95% CI: 0.34, 3.73)
p=0.0190

Absolute Peak Longitudinal Strain



1.23%
(95% CI: 0.73, 1.73)
p<0.0001

LV Stroke Volume



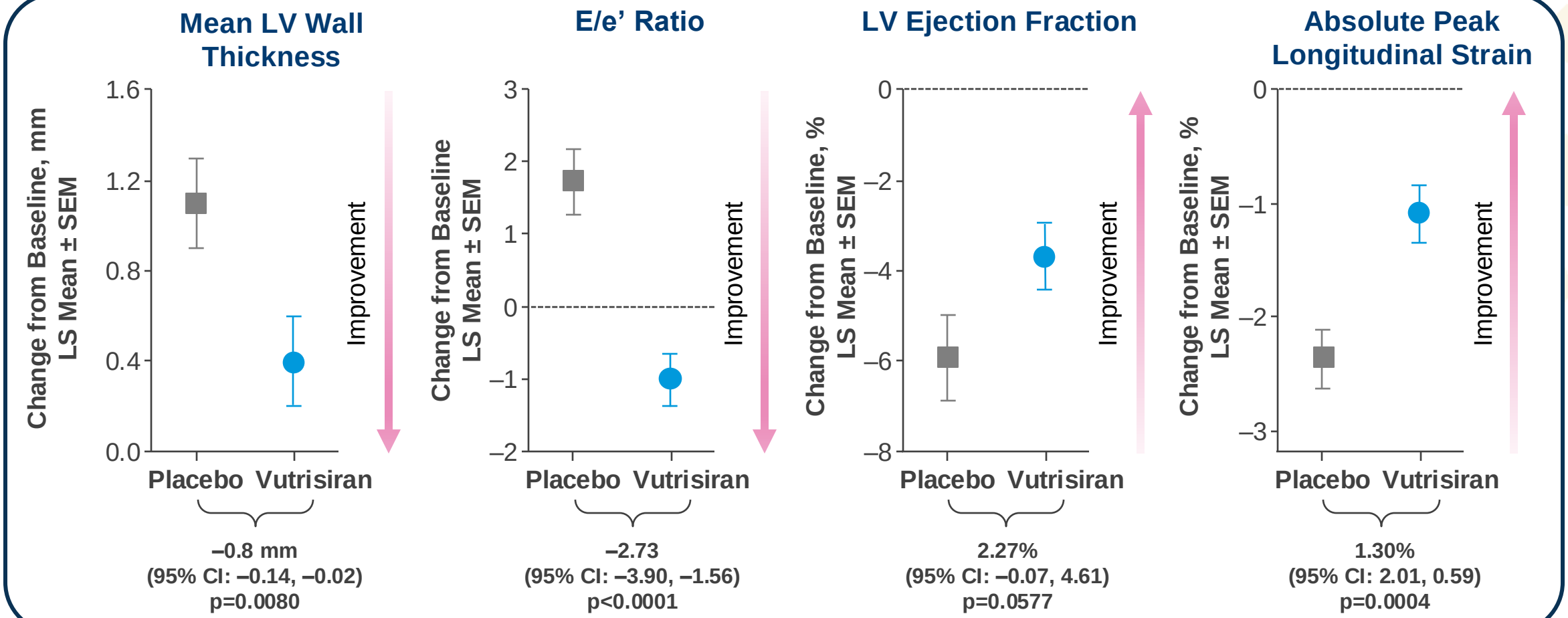
4.05 mL
(95% CI: 1.72, 6.38)
p=0.0007

Results are from a MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group. **Abbreviations:** CI, confidence interval; LS, least squares; LV, left ventricular; SEM, standard error of the mean.

The Benefits of Vutrisiran on Cardiac Structure and Function were Similar or Larger in the Monotherapy Population

HELIOS-B

Monotherapy Population



Results are from MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, type of ATTR amyloidosis, and age group.

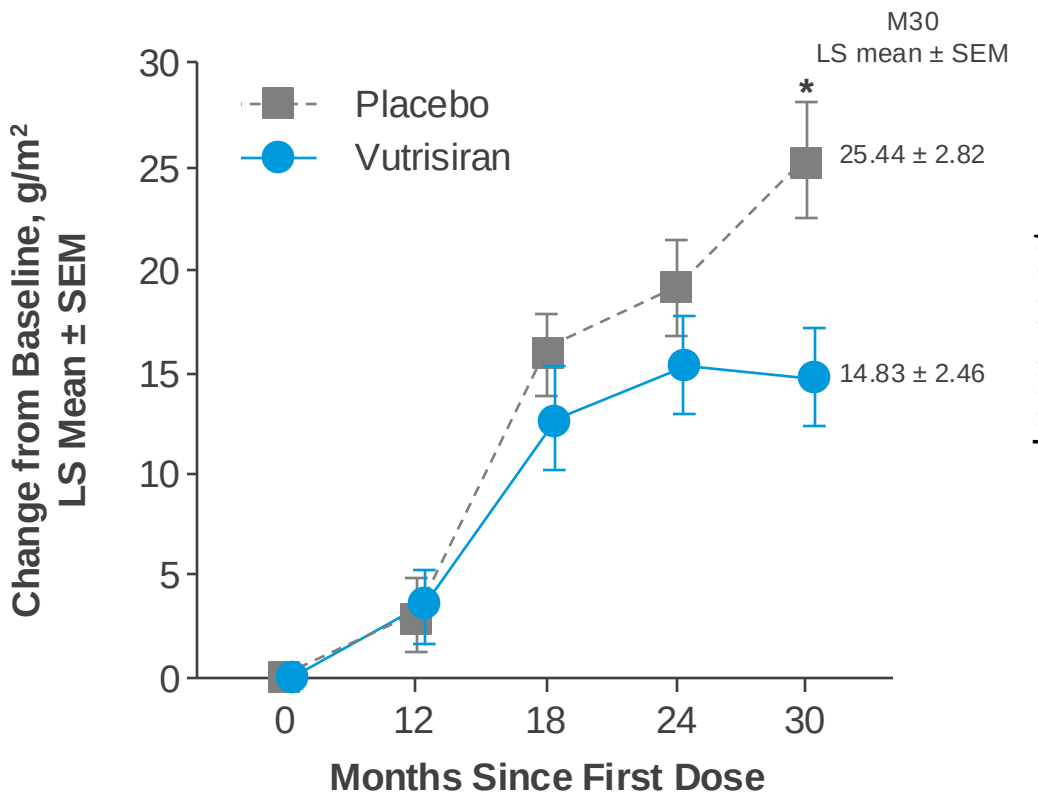
Abbreviations: CI, confidence interval; E/e', ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; LS, least squares; NS, non-significant; SEM, standard error of the mean.

Significant Between-Group Differences in LV Diastolic Function Emerged as Early as 12 Months

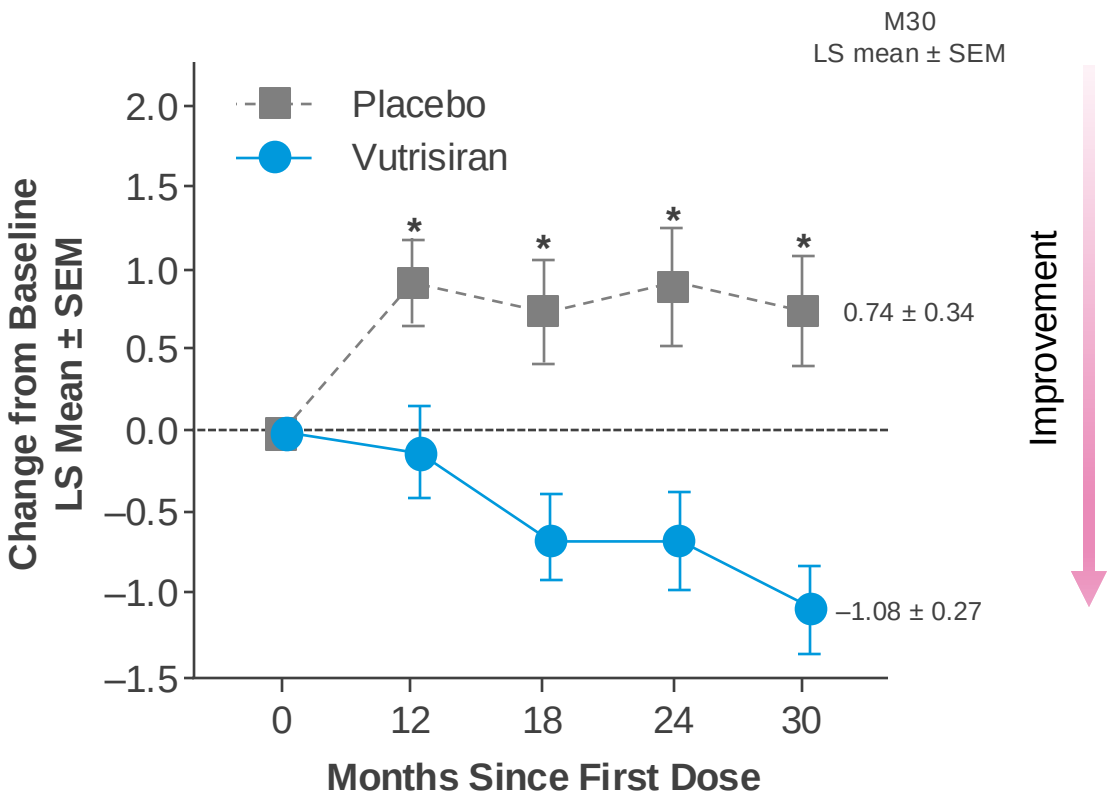
HELIOS-B

Overall Population

Left Ventricular Mass Index



E/e' Ratio



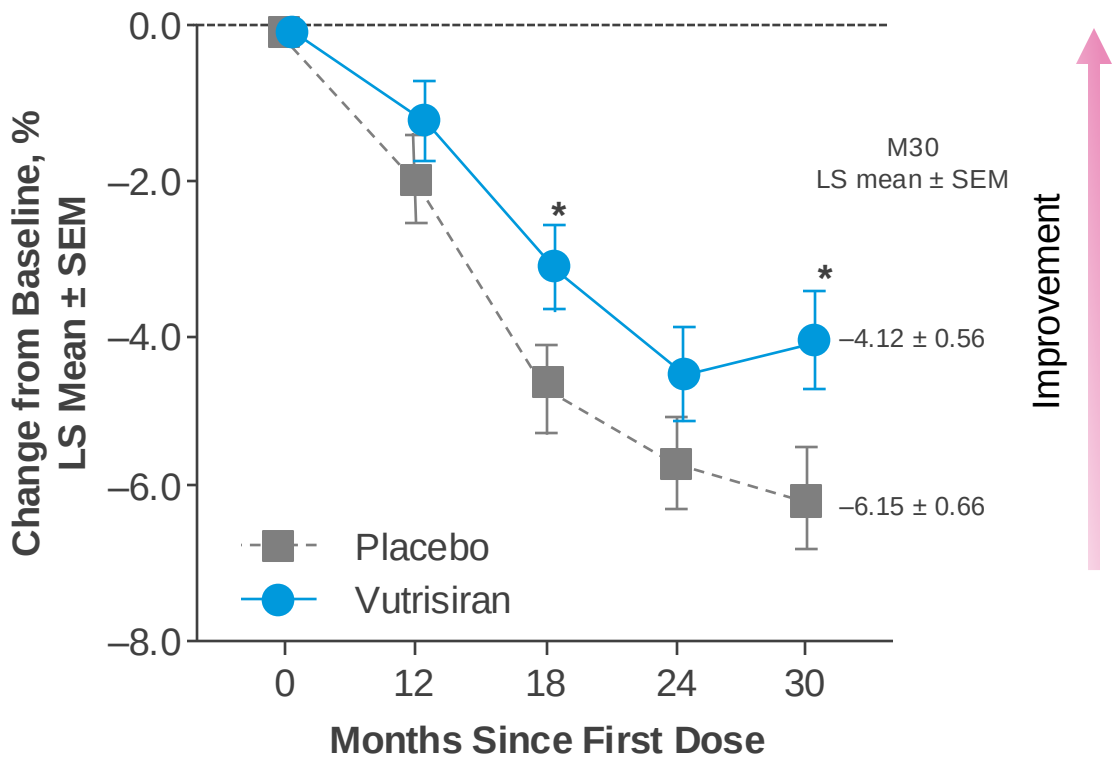
*p<0.05. Results are from a MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group. **Abbreviations:** E/e', ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; LS, least squares; LV, left ventricular; SEM, standard error of the mean.

Significant Between-Group Differences in LV Systolic Function Emerged as Early as 18 Months

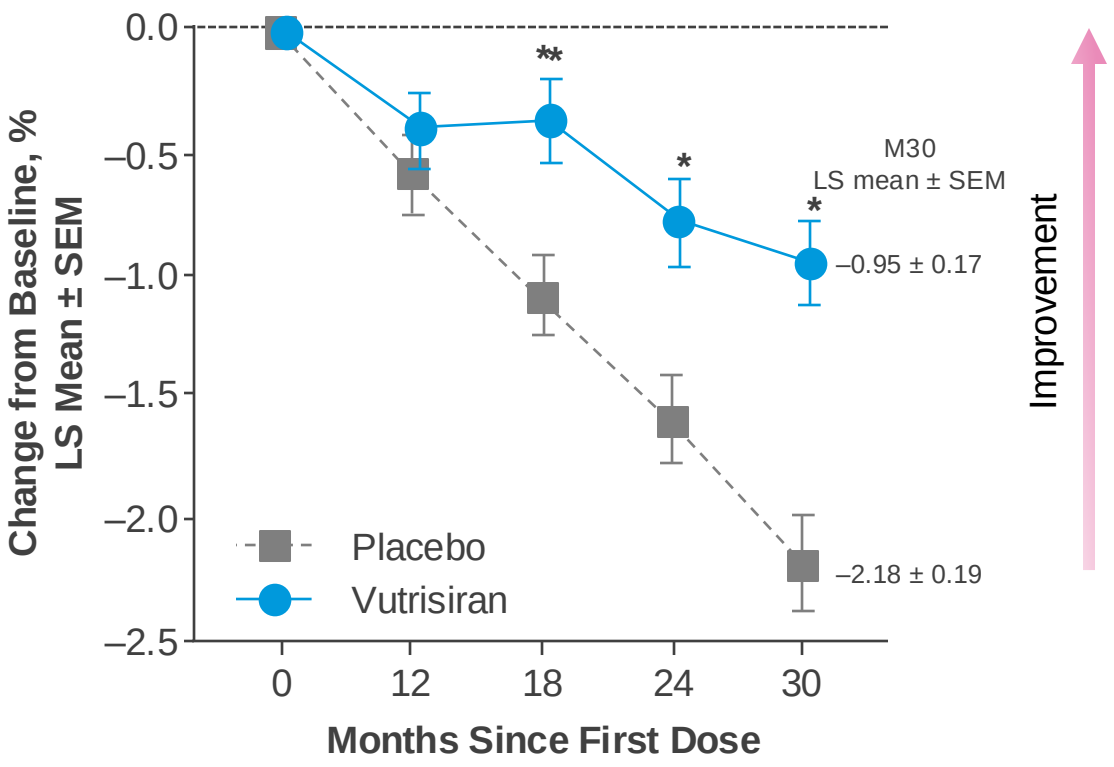
HELIOS-B

Overall Population

Left Ventricular Ejection Fraction



Absolute Peak Longitudinal Strain



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Summary

HELIOS-B

For US HCPs Only

- In this contemporary population, compared with placebo, vutrisiran had beneficial impact across all measures of cardiac structure, systolic, and diastolic function, providing further evidence of the disease-modifying effect of vutrisiran treatment.
- These echocardiographic findings were consistent with the benefit observed with vutrisiran on clinical outcomes, biomarkers, and health status.
- The magnitude of the treatment effects with vutrisiran compared to placebo were similar or greater in the monotherapy population.
- Significant improvement in diastolic function with vutrisiran was observed early, followed by significant favorable effects on cardiac structure and systolic function.
- If approved, vutrisiran has the potential to become a standard of care for newly diagnosed patients with ATTR-CM and those progressing on stabilizing therapies.

We thank the patients, their families, investigators, staff, and collaborators for their participation in HELIOS-B

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy.