Primary Results from HELIOS-B, a Phase 3 Study of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

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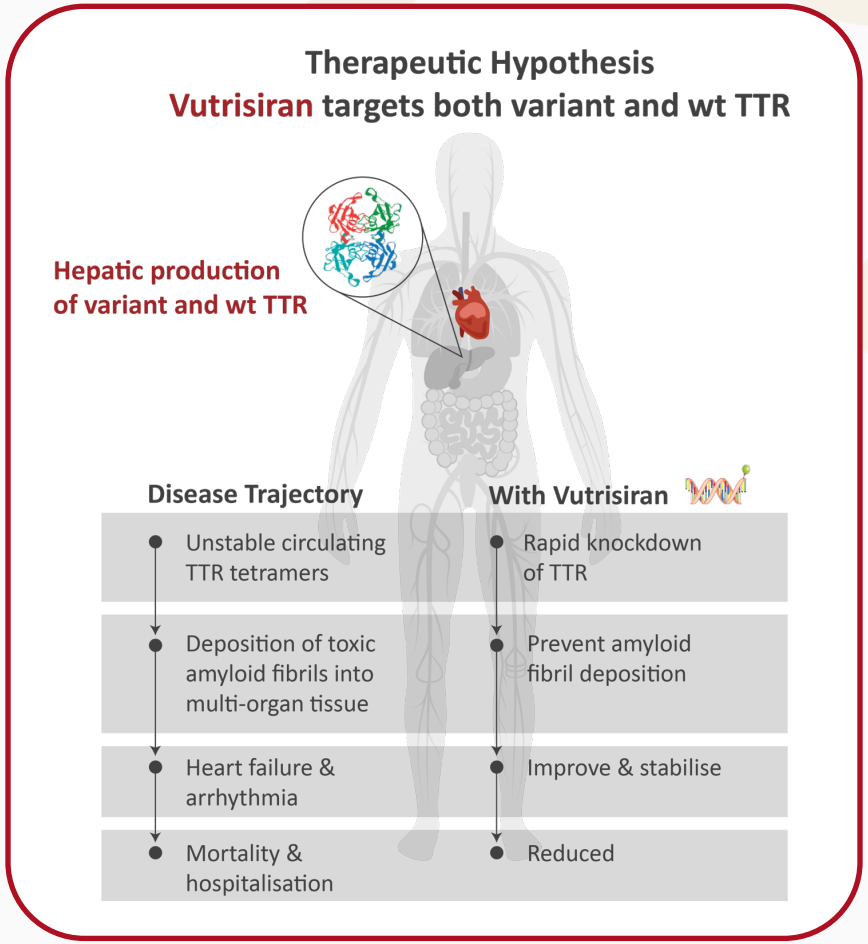
Introduction

ATTR Cardiomyopathy

- Results from accumulation of wild type or variant TTR amyloid fibrils in the heart[1-5]
- Leads to progressive heart failure, arrhythmias, declines in functional status and QOL, increased hospitalisations and reduced survival[6–10]
- Evolution toward earlier diagnosis and improved HF management; contemporary patients have less advanced disease, and are managed with tafamidis, SGLT2 inhibitors, and diuretics

HELIOS-B study

- Evaluated vutrisiran, a SC-administered RNAi therapeutic (quarterly dosing)
- Objective: Establish efficacy and safety in a contemporary ATTR-CM patient population



References: 1. Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 4. Živković et al. *Amyloid* 2020;27:142–3; 5. Sipe et al. *Amyloid* 2014;21:221–4; 6. Castano et al. *Heart Fail Rev* 2015;20:163–78; 7. Swiecicki et al. *Amyloid* 2015;22:123–31; 8. Ruberg et al. *Am Heart J* 2012;164:222–8.e1; 9. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 10. Gertz et al. *Mayo Clin Proc* 1992;67:428–40.
Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; HF, heart failure; QOL, quality of life; RNAi, RNA interference; SC, subcutaneous; SGLT2, sodium-glucose cotransporter 2; TTR, transthyretin; wt TTR, wild-type transthyretin.

HELIOS-B Study Design

A randomised, double-blind outcomes study in ATTR amyloidosis patients with cardiomyopathy

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[a] 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

1:1 RANDOMISATION[b]

Vutrisiran SC q3M 25 mg

or

Placebo SC q3M

Primary Endpoints

- Composite outcome of all-cause mortality and recurrent CV events during double-blind (DB) period (**Month 33-36**) in:
  - Overall population
  - Monotherapy population (patients not on tafamidis at baseline)

Secondary Endpoints[c]

- Change from BL to **Month 30** in 6-MWT distance
- Change from BL to **Month 30** in KCCQ-OS
- All-cause mortality through **42 Months**
- Change from BL to **Month 30** in NYHA class

Vutrisiran SC q3M 25 mg

Vital status was ascertained for 99.8% of patients

[a]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation).
[b]Randomisation was stratified according to the use of tafamidis at baseline (yes versus no), ATTR disease type (hATTR or wtATTR), and NYHA class and age at baseline (NYHA class I or II and age <75 years versus all others).
[c]Assessed in the overall population and monotherapy population as separate endpoints.

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; BL, baseline; CV, cardiovascular; DB, double-blind; HF, heart failure; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NYHA, New York Heart Association; OLE, open label extension; PND, polyneuropathy disability; q3M, every 3 months; SC, subcutaneous; TTR, transthyretin.

References: Clinicaltrials.gov identifier: NCT04153149

Contemporary Population with Baseline Characteristics Balanced Across Arms

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Overall Population

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)

Substantial use of effective background medications

- **Tafamidis**
  - Baseline ~40% in both treatment arms
  - Drop-in on monotherapy population during DB period ~21% and ~22% for placebo and vutrisiran, respectively
- **SGLT2 inhibitors**
  - Baseline ~3% in both treatment arms
  - Drop-in during DB period ~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

Patients were not randomised to baseline tafamidis; patients on baseline tafamidis were generally healthier based on NYHA class, NT-proBNP, 6-MWT, and KCCQ-OS score

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 Endpoints in Overall Population and Monotherapy Population

Vutrisiran met all 10 primary and secondary endpoints

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

Abbreviations: 6-MWT, 6-minute walk test; CV, cardiovascular; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS, least squares; NYHA, New York Heart Association.
References: Clinicaltrials.gov identifier: NCT04153149

Primary Endpoint: Statistically Significant Reduction in the Composite of All-Cause Mortality and Recurrent CV Events

Achieved 28% reduction in the overall population

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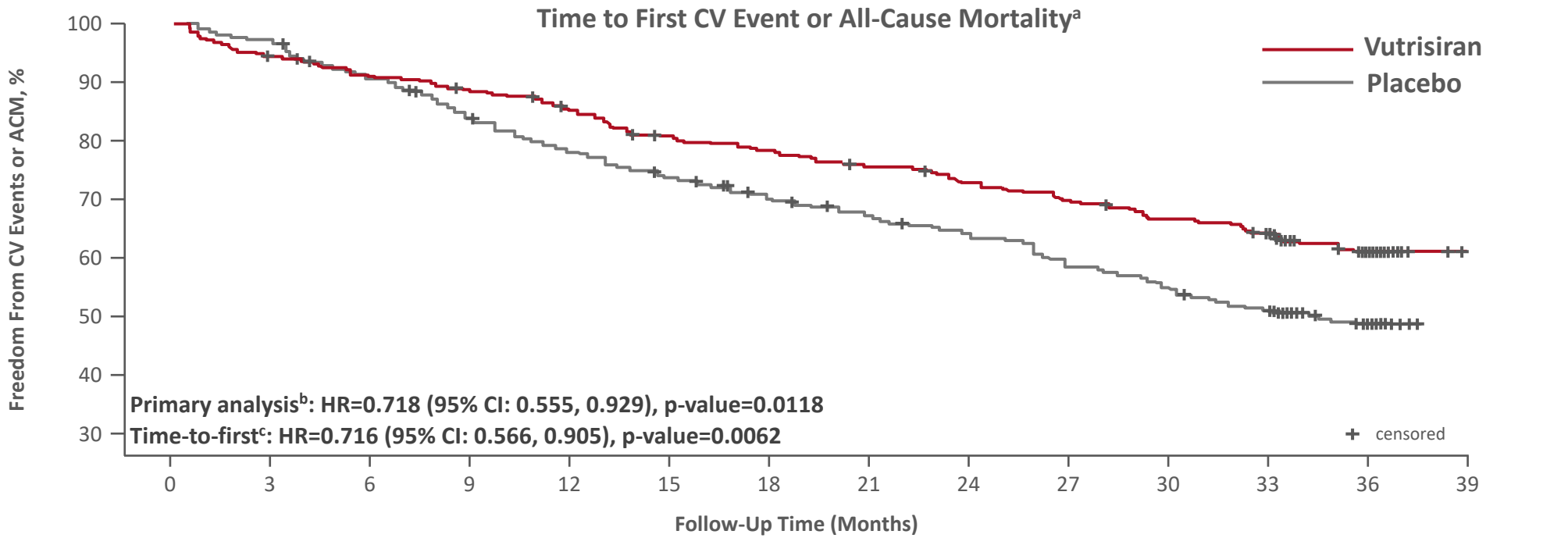
OVERALL POPULATION



- Results consistent across multiple sensitivity analyses, including win ratio

All-cause mortality includes heart transplantation and left ventricular assist device placement. [a]Based on IPTW-adjusted Kaplan-Meier curves; [b]Primary analysis based on the modified Andersen-Gill model, also known as LWYY; [c]Time to first event HR derived from Cox PH model, p-value derived from Log-rank test. **Abbreviations:** ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LWYY, Lin, Wei, Yang , and Ying; PH, proportional hazard.

Nominally Significant Effect on Both Components of Composite Outcome During Double-Blind Period (Month 33-36)

Similar effect on all-cause mortality and recurrent CV events components of the primary endpoint

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OVERALL POPULATION

	Overall population (N = 654)
Primary endpoint: all-cause mortality and recurrent CV events (LWYY)	
HR (95% CI)	**0.718** (0.555, 0.929)
p-value	**0.0118**
Components	
All-cause mortality (DB period)	
HR (95% CI)[a]	**0.694** (0.490, 0.982)
Log-rank p-value	**0.0389**
Recurrent CV events (Poisson regression)	
Relative rate ratio (95% CI)	**0.733** (0.610, 0.882)
p-value	**0.0010**

[a]HR based on Cox PH model

All-cause mortality includes heart transplantation and left ventricular assist device placement.

Abbreviations: CI, confidence interval; CV, cardiovascular; DB, double-blind; HR, hazard ratio; LWYY, Lin, Wei, Yang , and Ying; PH, proportional hazard.

Secondary Endpoint: Statistically Significant Reduction in All-Cause Mortality Through 42 Months

Achieved 36% reduction in the overall population

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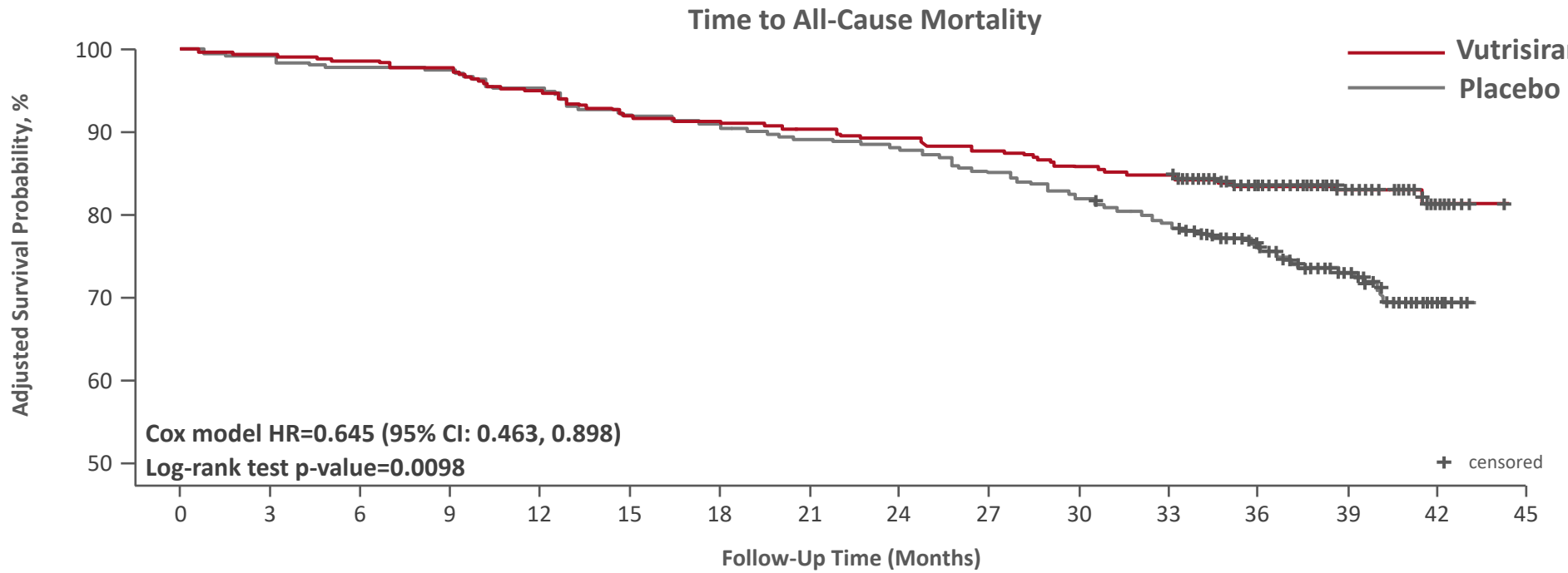
OVERALL POPULATION



All-cause mortality includes heart transplantation and left ventricular assist device placement; deaths after end of study are included in the analysis. Includes data from the double-blind period and up to 6 months in the OLE.

Based on IPTW-adjusted Kaplan-Meier curves. The HR is derived from Cox proportional hazards model.

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OLE, open label extension.

Consistent Benefits across All Prespecified Subgroups

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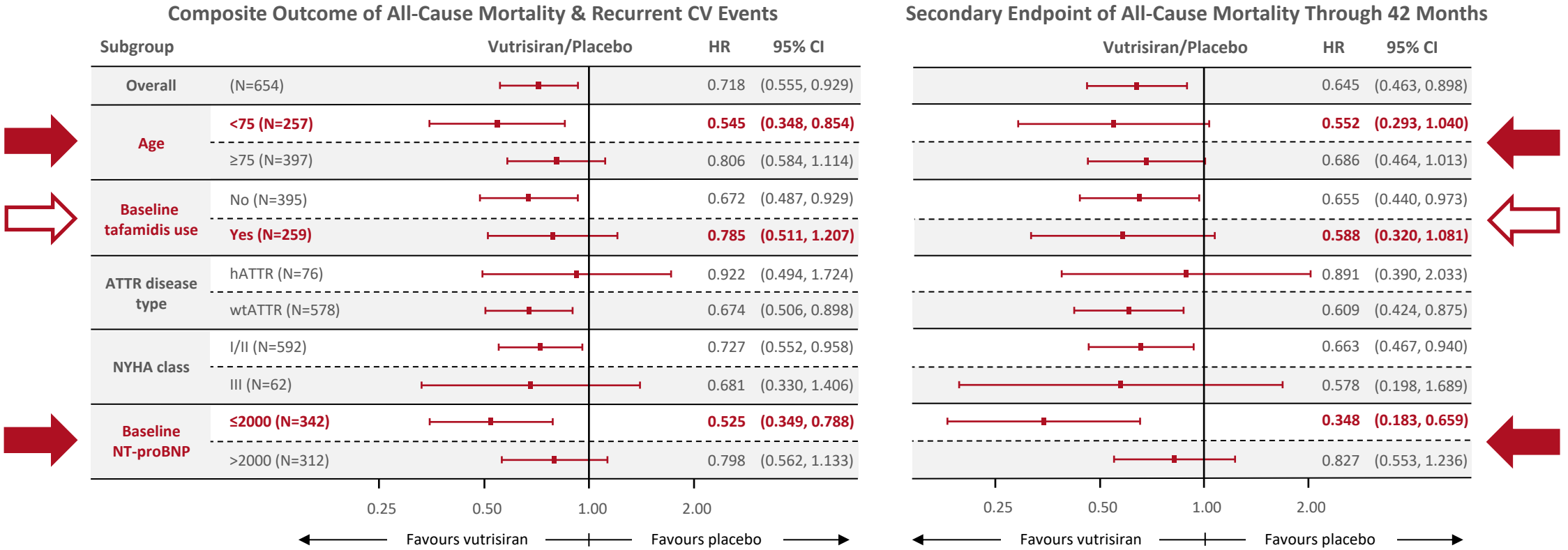
OVERALL POPULATION



- Greater benefits seen in patients with earlier disease (i.e., age <75 years and NT-proBNP ≤2000 ng/L), with 46% and 48% reduction, respectively, in primary composite endpoint, and 45% and 65% reduction, respectively, in all-cause mortality
- Consistent benefit in patients with or without baseline tafamidis

All-cause mortality includes heart transplantation and left ventricular assist device placement.
Abbreviations: ATTR, transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; hATTR, hereditary transthyretin amyloidosis; HR, hazard ratio; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; wtATTR, wild-type transthyretin amyloidosis.

Statistically Significant Outcomes Benefit with Vutrisiran Monotherapy

33% reduction in the primary composite endpoint and 35% reduction in all-cause mortality

MONOTHERAPY POPULATION

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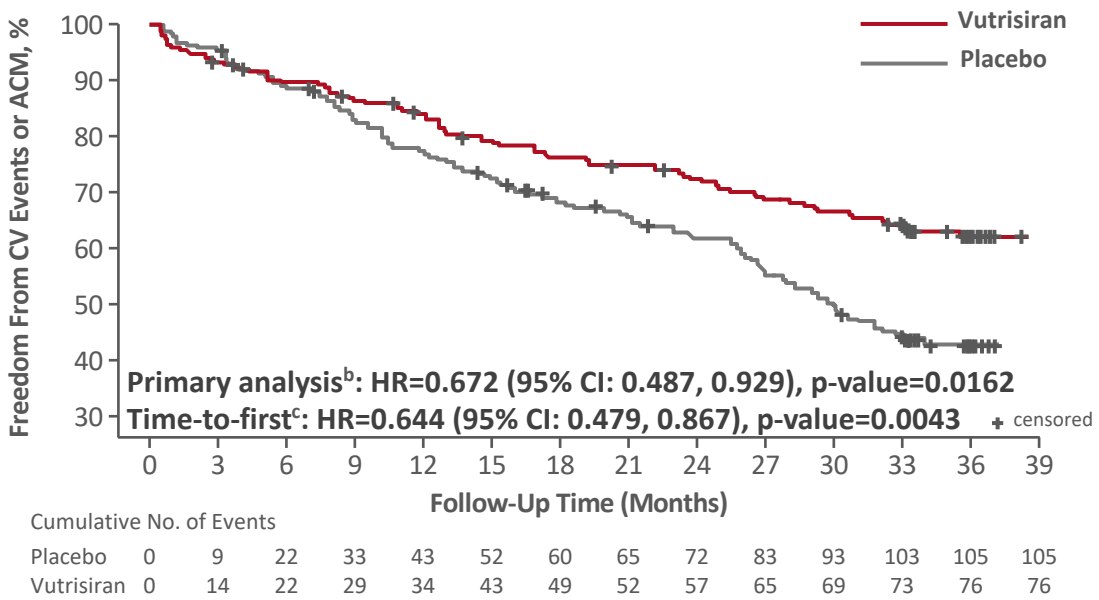
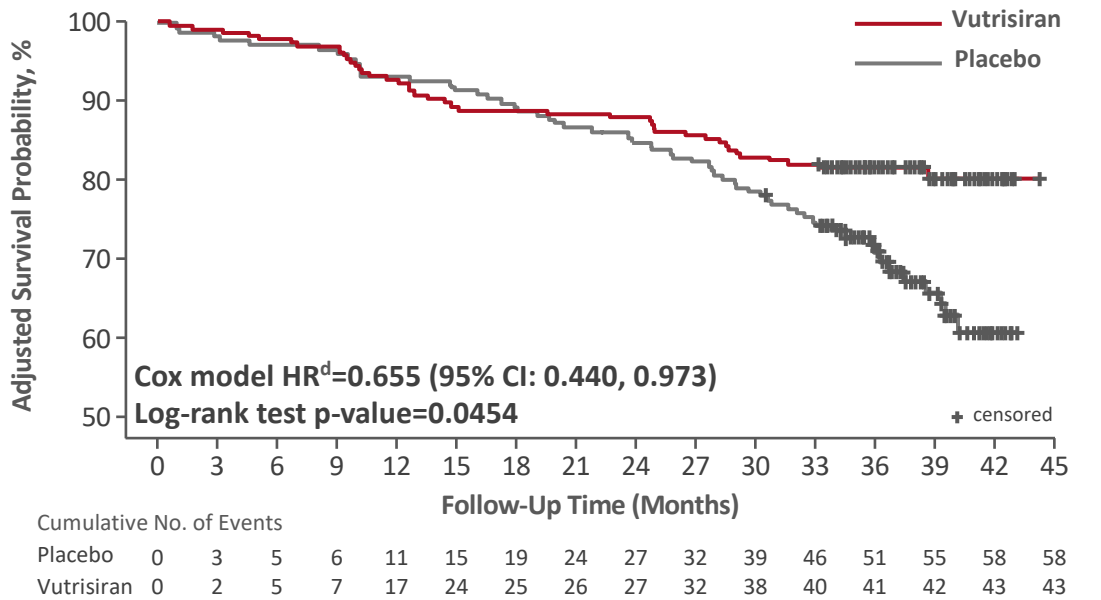
Time to First CV Event or All-Cause Mortality[a]



Cumulative No. of Events

Placebo	0	9	22	33	43	52	60	65	72	83	93	103	105	105
Vutrisiran	0	14	22	29	34	43	49	52	57	65	69	73	76	76

Time to All-Cause Mortality[a]



Cumulative No. of Events

Placebo	0	3	5	6	11	15	19	24	27	32	39	46	51	55	58	58
Vutrisiran	0	2	5	7	17	24	25	26	27	32	38	40	41	42	43	43

All-cause mortality includes heart transplantation and left ventricular assist device placement. [a]Based on IPTW-adjusted Kaplan-Meier curves; [b]Primary analysis based on the modified Andersen-Gill model, also known as LWYY; [c]Time to first event HR derived from Cox PH model, p-value derived from Log-rank test; [d]Time to all-cause mortality includes data from the double-blind period and up to 6 months in the OLE, deaths after end of study are included in the analysis, HR derived from Cox PH model. **Abbreviations:** CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LWYY, Lin, Wei, Yang , and Ying; PH, proportional hazard.

Evidence of Added Benefit on Top of Tafamidis

Favourable trends in baseline tafamidis subgroup on both primary composite (22% reduction) and all-cause mortality (41% reduction)

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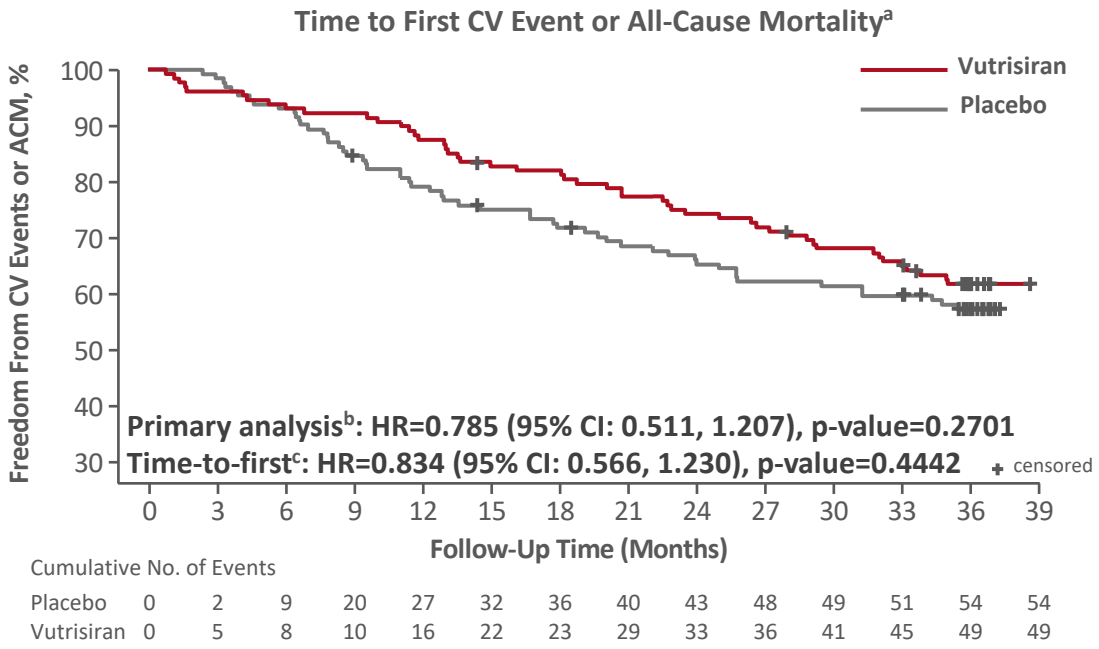
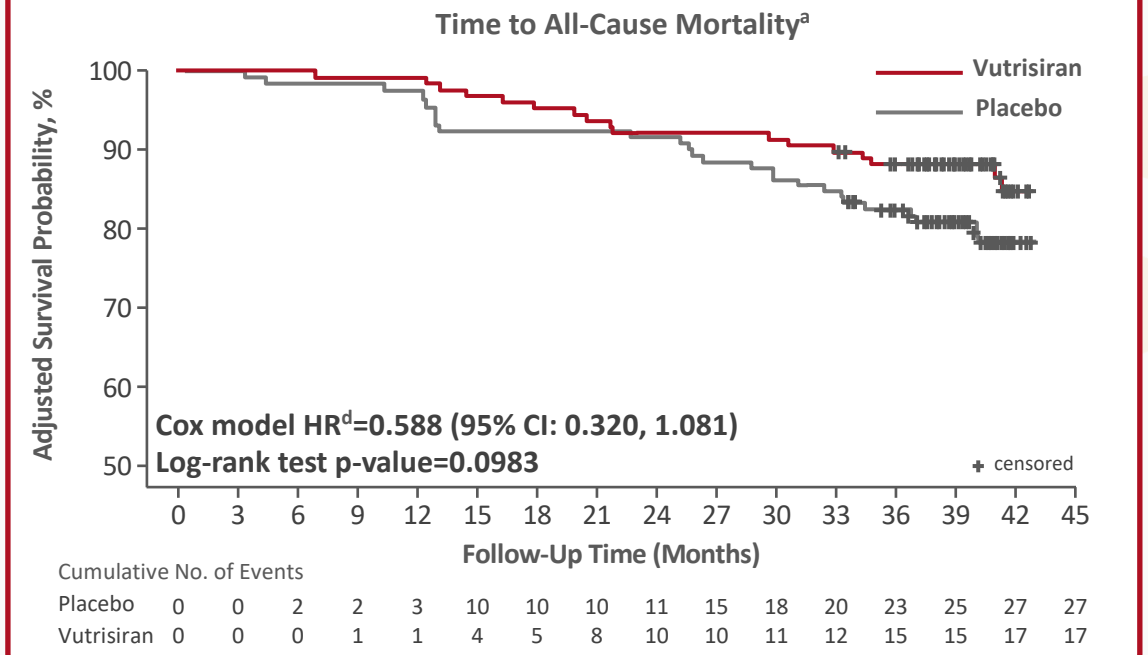
TAFAMIDIS SUBGROUP





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Favourable Impact on Multiple Measures of Disease Progression

Maintains functional capacity, health status, and quality of life; statistically significant impact relative to placebo

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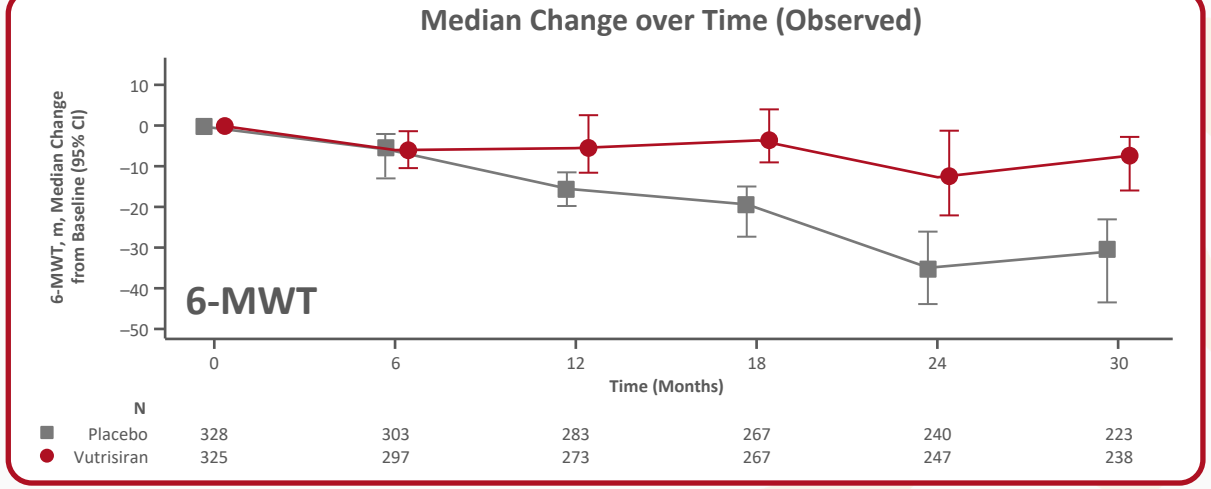
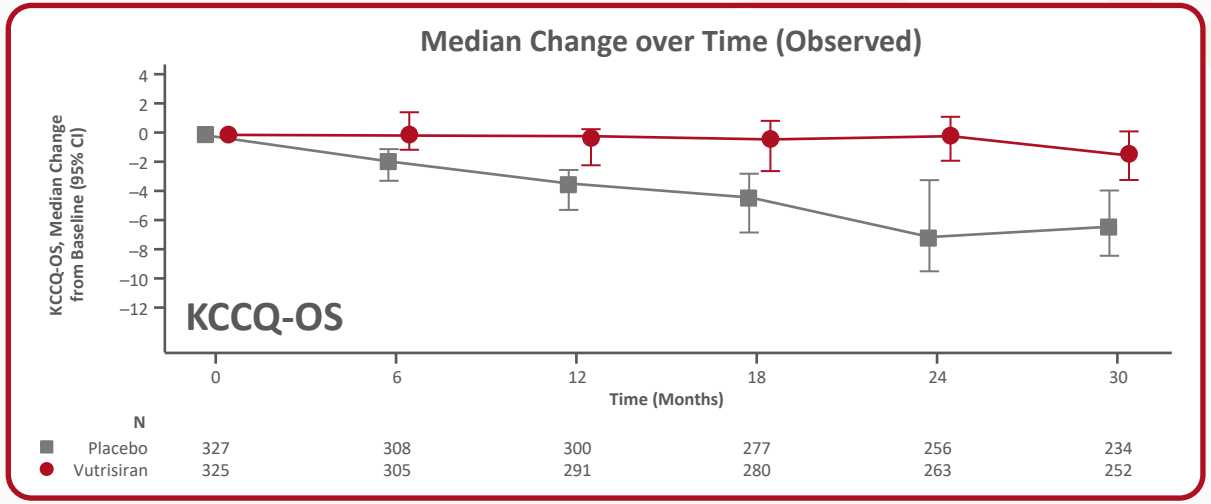
OVERALL POPULATION

Change from Baseline at Month 30	Overall Population	
	Placebo (N=328)	Vutrisiran (N=326)
6-MWT, n	285	294
Median	-30.65	-7.50
LS mean (SEM)	-71.88 (4.79)	-45.42 (4.62)
LS mean difference (95% CI)	—	26.46 (13.38, 39.55)
p-value	—	0.00008
KCCQ-OS, n	298	306
Median	-6.25	-1.30
LS mean (SEM)	-15.49 (1.26)	-9.68 (1.19)
LS mean difference (95% CI)	—	5.80 (2.40, 9.20)
p-value	—	0.0008
NYHA Class, n	328	326
Stable or improved %	61	68
Difference in % patients stable or improved (95% CI)	—	8.7 (1.3, 16.1)
p-value	—	0.0217





LS mean accounts for missing data due to death or HT/LVAD, unable to walk due to disease progression (only for 6-MWT) that were imputed from resampling of worst 10%. Median representation is based on observed data only, no imputations due to death/unable to walk due to disease progression.

Abbreviations: 6-MWT, 6-minute walk test; CI, confidence interval; HT, heart transplant; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS, least squares; LVAD, left ventricular assist device; NYHA, New York Heart Association; SEM, standard error of the mean.

Impact of Vutrisiran on NT-proBNP, a Well-Established Cardiac Biomarker Prognostic of Mortality in ATTR-CM

Maintained relative stability in NT-proBNP levels compared to placebo

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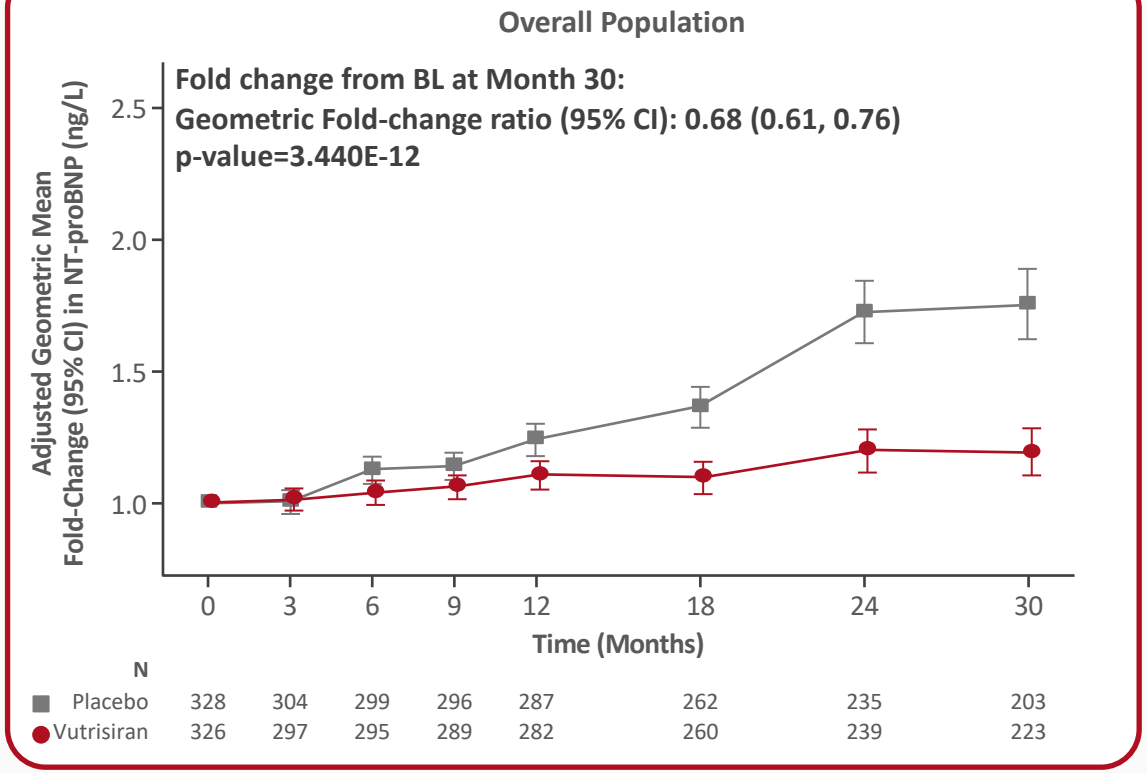
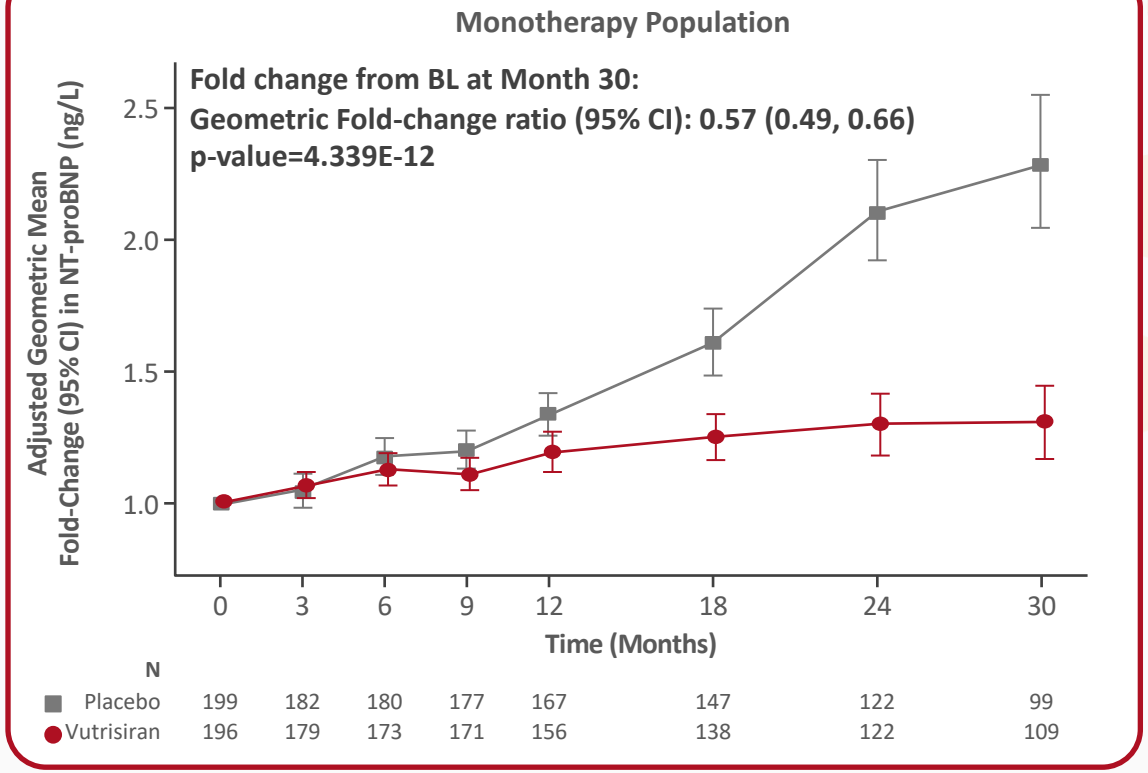
OVERALL & MONOTHERAPY POPULATIONS





Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; BL, baseline; CI, confidence interval; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide.

Safety Profile

Vutrisiran was well tolerated

HELIOS-B

OVERALL POPULATION

AE Category, n (%)	Overall Population	
	Placebo (N=328)	Vutrisiran (N=326)
AEs	323 (98.5)	322 (98.8)
SAEs	220 (67.1)	201 (61.7)
Severe AEs	194 (59.1)	158 (48.5)
AE leading to treatment discontinuation	13 (4.0)	10 (3.1)
Deaths[a]	63 (19.2)	49 (15.0)

- The majority of AEs were mild or moderate
- No AEs seen ≥3% more frequently with vutrisiran compared with placebo
- Cardiac AEs were similar or lower with vutrisiran compared with placebo

[a]Deaths after study discontinuation are not included
Treatment emergent AEs are presented.

Abbreviations: AE, adverse event; SAE, serious adverse event.

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Conclusions

Vutrisiran achieved statistical significance on primary and all secondary endpoints

- Reduced all-cause mortality and recurrent CV events in a contemporary population with ATTR CM, including substantial use of background therapy
- Demonstrated significant benefit on multiple clinical measures of disease progression, as well as NT-proBNP
- Results consistent across all prespecified subgroups, including patients on vutrisiran monotherapy and those on background tafamidis
- Acceptable safety and tolerability profiles, as previously established
- If approved, vutrisiran has the potential to become a standard of care for newly diagnosed patients and those progressing on stabilising therapies

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the HELIOS-B study

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ORIGINAL ARTICLE

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