Impact of Vutrisiran on Outpatient Worsening Heart Failure in Patients with Transthyretin Amyloidosis with Cardiomyopathy in the HELIOS-B Trial

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November 16–18, 2024 || American Heart Association Scientific Sessions 2024

Disclosure for Dr. Marianna Fontana, MD, PhD

Conflict	Disclosure—if conflict of interest exists
Research Support	AstraZeneca
Meeting Attendance	Alnylam Pharmaceuticals, AstraZeneca, and Attralus
Shareholder	Lexeo Therapeutics and Mycardium
Consultant/Advisory Board	Alexion, Alnylam Pharmaceuticals, Attralus, Caelum Biosciences, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Lexeo Therapeutics, Novo Nordisk, Pfizer, and Prothena

Introduction

Transthyretin Amyloidosis with Cardiomyopathy (ATTR-CM)

- Results from accumulation of wild-type or variant TTR amyloid fibrils in the heart,[1–5] causing worsening HF, increased hospitalizations, and reduced survival[6–10]
- Intensification or initiation of oral diuretics, a common sign of disease progression and worsening HF in the outpatient setting,[11–14] is common in patients with ATTR-CM and is associated with mortality[15–17]

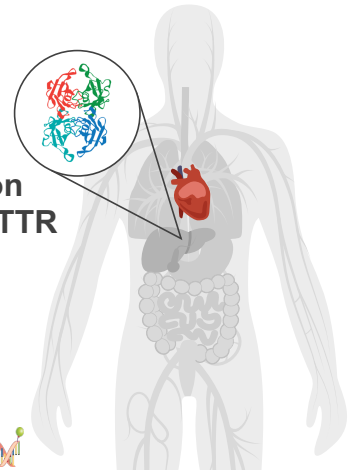
HELIOS-B Study

- Evaluated vutrisiran, a SC-administered (quarterly dosing) RNAi therapeutic, in patients with ATTR-CM in a Phase 3, randomized, placebo-controlled trial[18]

Objective

- Investigate the prognostic value of and the effect of vutrisiran on outpatient worsening HF, defined by oral diuretic initiation or intensification in ATTR-CM

Therapeutic Hypothesis:
Vutrisiran Targets Both Variant and wt TTR



With vutrisiran

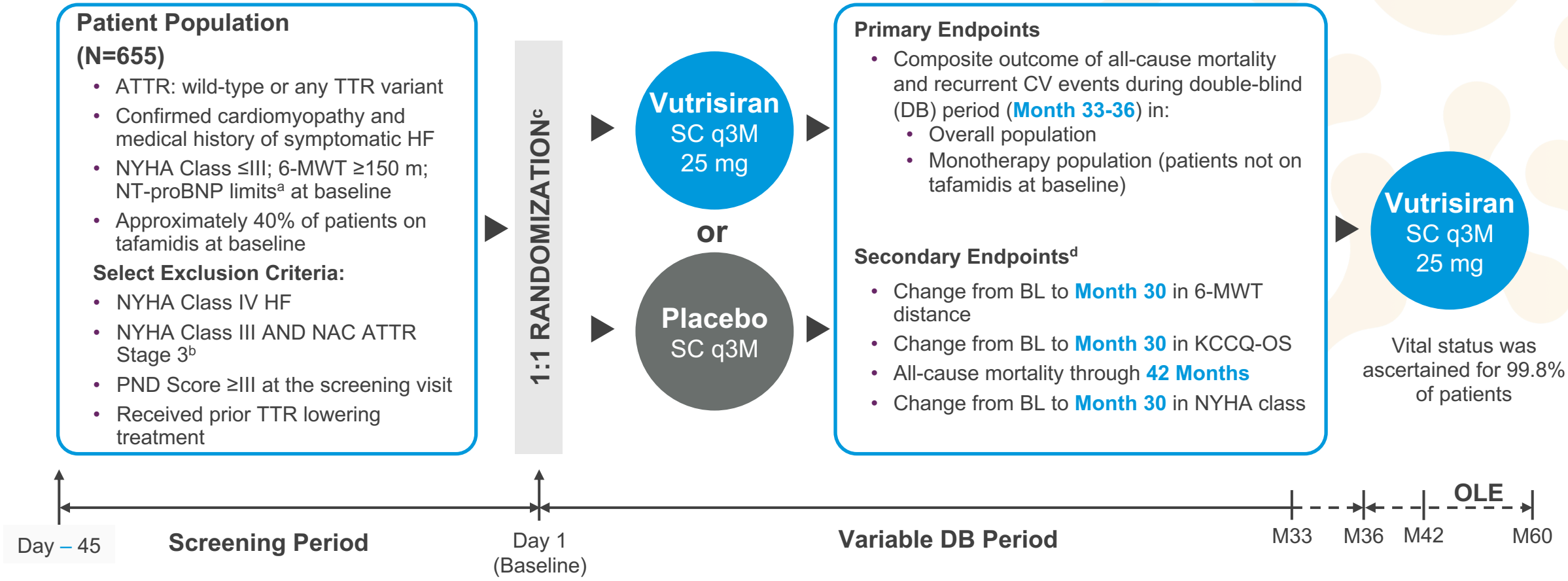
- Rapid knockdown of circulating TTR tetramers
- Prevents amyloid fibril deposition in multi-organ tissues
- Improves cardiac outcomes and reduced mortality and hospitalization

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; HF, heart failure; RNAi, RNA interference; SC, subcutaneous; TTR, transthyretin; wt, wild-type.

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. Chacko et al. *Eur J Heart Fail* 2022;24:1700–12; 8. Lane et al. *Circulation* 2019;140:16–26; 9. Nativi-Nicolau et al. *ESC Heart Fail* 2021;8:3875–84; 10. Gillmore et al. *Eur Heart J* 2018;39:2799–806; 11. Okumura et al. *Circulation* 2016;133:2254–62; 12. Chatur et al. *Circulation* 2023;148:1735–45; 13. Ferreira et al. *Eur J Heart Fail* 2022;24:378–84; 14. Khan et al.. *Circ Heart Fail* 2021;14:e008351; 15. Law et al. *Eur Heart J* 2022;43:2622–32; 16. Cheng et al. *JACC CardioOncol* 2020;2:414–24; 17. Ioannou et al. *J Am Coll Cardiol* 2024;83:1276–91; 18. Fontana et al. *N Engl J Med* 2024. DOI: 10.1056/NEJMoa2409134. Epub ahead of print.

HELIOS-B Study Design

A randomized, double-blind outcomes study to evaluate vutrisiran in patients with ATTR-CM



[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]NAC ATTR stage 3 defined as NT-proBNP levels >3000 pg/mL and an eGFR of <45 mL/min/1.73 m^2 of body-surface area. [c]Randomization 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). [d]Assessed in the overall population and monotherapy population as separate endpoints.

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; CV, cardiovascular; DB, double-blind; eGFR, estimated glomerular filtration rate; hATTR, hereditary ATTR; HF, heart failure; M, Month; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; PND, polyneuropathy disability; q3M, every 3 months; SC, subcutaneous; TTR, transthyretin; wtATTR, wild-type ATTR. **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)

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

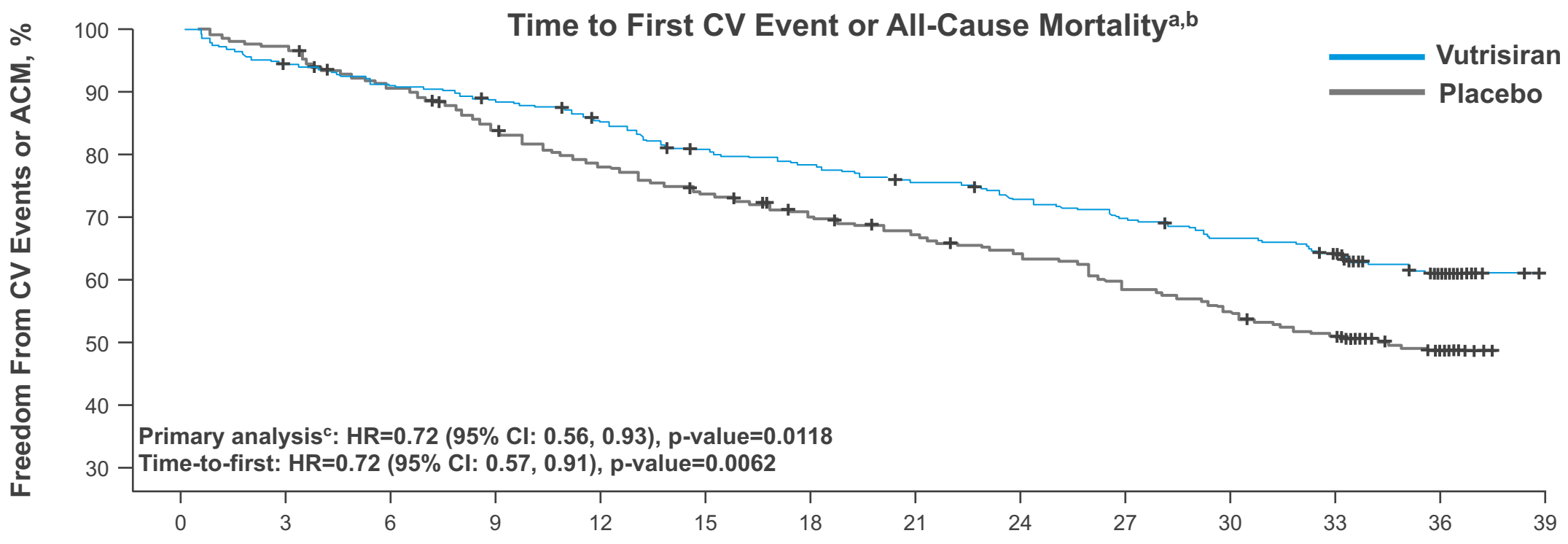
Patients were not randomized to baseline tafamidis; patients on baseline tafamidis were generally healthier based on NYHA class, NT-proBNP, 6-MWT, and KCCQ-OS score

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.

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

HELIOS-B

Achieved 28% reduction in the overall population



Cumulative No. of Events														
Placebo	0	11	31	53	70	84	96	105	115	131	142	154	159	159
Vutrisiran	0	19	30	39	50	65	72	81	90	101	110	118	125	125

[a]Based on inverse probability of treatment weighting-adjusted Kaplan–Meier curves. [b]HR derived from Cox proportional hazards model, p-value derived from log-rank test. [c]Primary analysis based on the modified Andersen–Gill model, also known as LWYY.

Abbreviations: ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LWYY, Lin, Wei, Yang , and Ying.

Outpatient Worsening Heart Failure

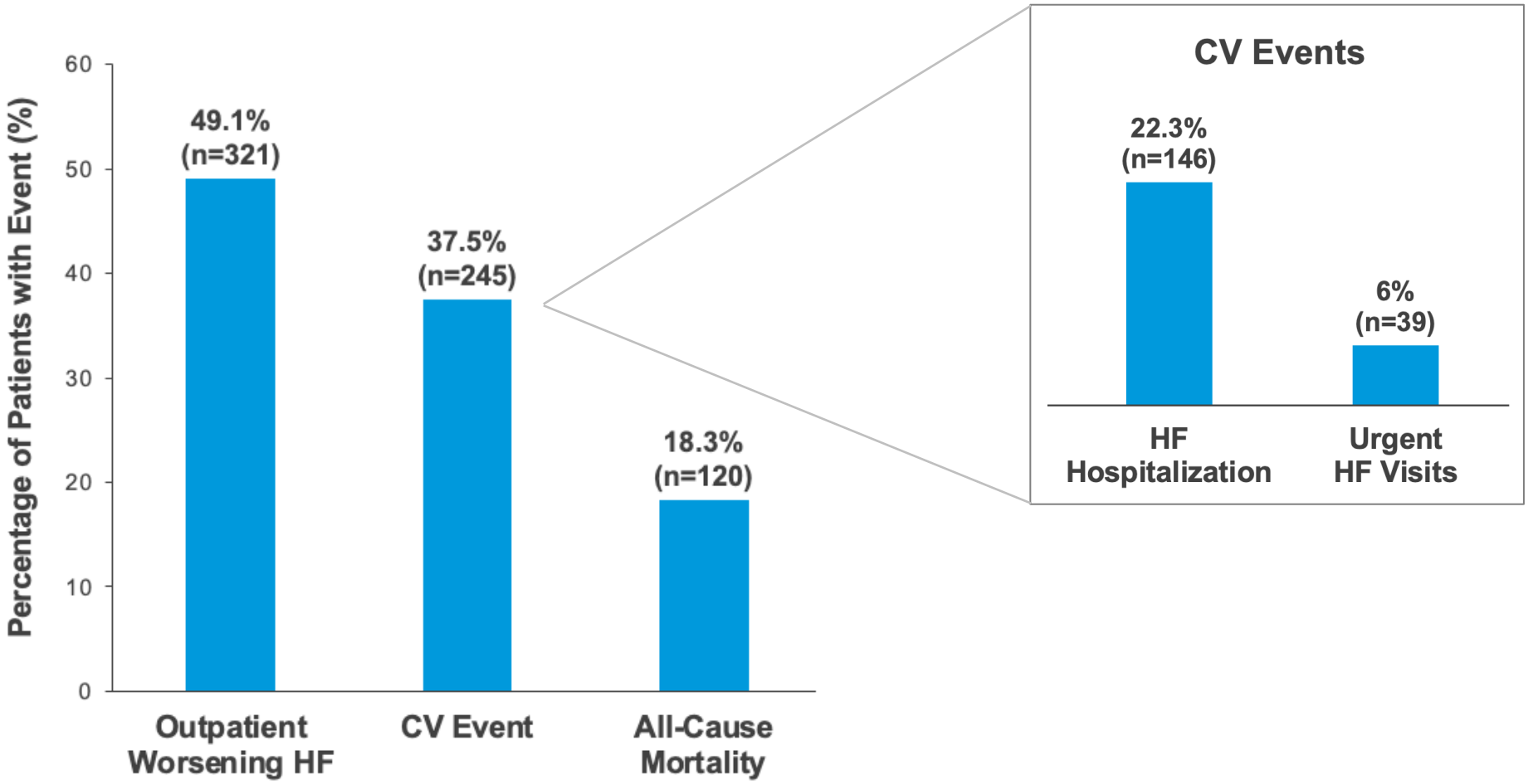
- Reduction in HF hospitalization or urgent HF visits have been used as markers of efficacy for testing HF therapies. However, worsening HF can also manifest in the outpatient setting with initiation or intensification of loop diuretic therapy, which has been shown to be prognostic for mortality and discriminatory for therapies in HF

- Outpatient oral diuretic intensification is frequent in ATTR-CM and has strong prognostic significance, and such events represent a potential opportunity for intervention to prevent downstream hospitalization and mortality events

- Because outpatient oral diuretic initiation or intensification may occur more frequently and earlier than HF hospitalizations and may be more modifiable by treatment, inclusion of these events in a composite endpoint could provide more complete capture of HF events

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; HF, heart failure.

Outpatient Worsening HF was Common in HELIOS-B

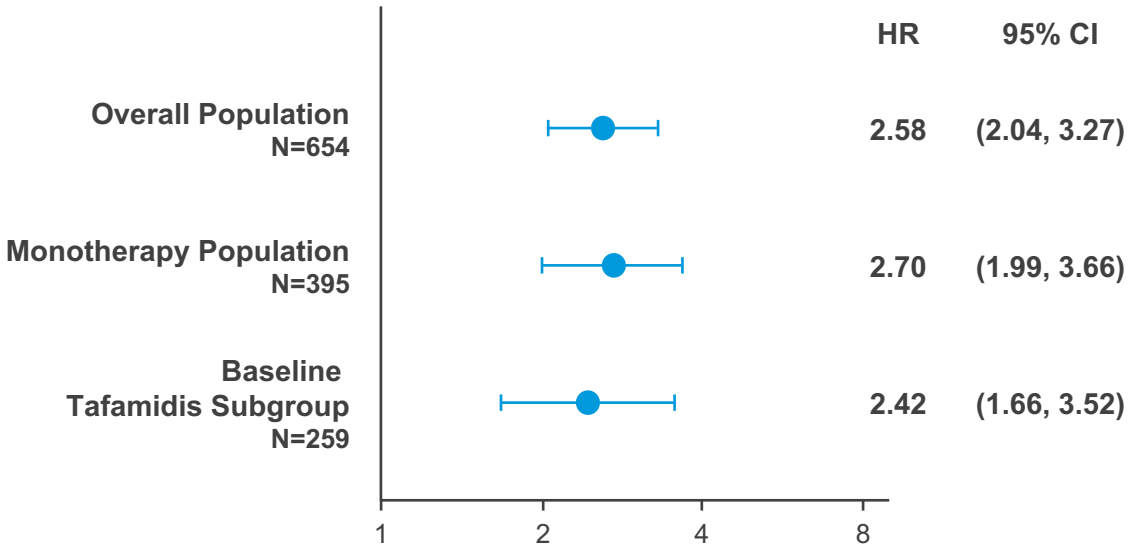


Abbreviations: CV, cardiovascular; HF, heart failure.

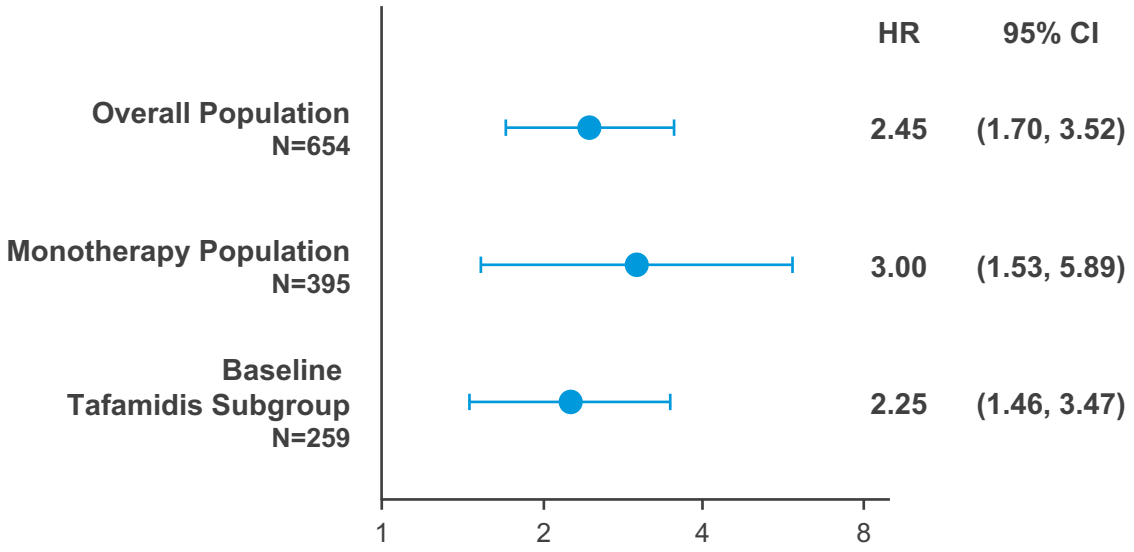
Outpatient Worsening HF Is Associated with Risk of CV Events and All-Cause Mortality

Outpatient worsening HF more than doubles the risk

Association of Outpatient Worsening HF with the Composite of All-Cause Mortality and Recurrent CV Events[a]



Association of Outpatient Worsening HF with All-Cause Mortality[b]



- The risks were similar in the overall and monotherapy populations and the baseline tafamidis subgroup

[a]The HR for the association between outpatient worsening HF and the composite of all-cause mortality and recurrent CV events was analyzed using a modified Andersen–Gill model with a robust variance estimator stratified by randomized treatment. [b]The HR for the association between outpatient worsening HF events and all-cause mortality was analyzed using a Cox regression model stratified by randomized treatment. Outpatient worsening HF events were included as time-varying covariates and in the overall population, all models were stratified by baseline tafamidis use. An HR >1 indicates greater risk with outpatient worsening HF. **Abbreviations:** ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio.

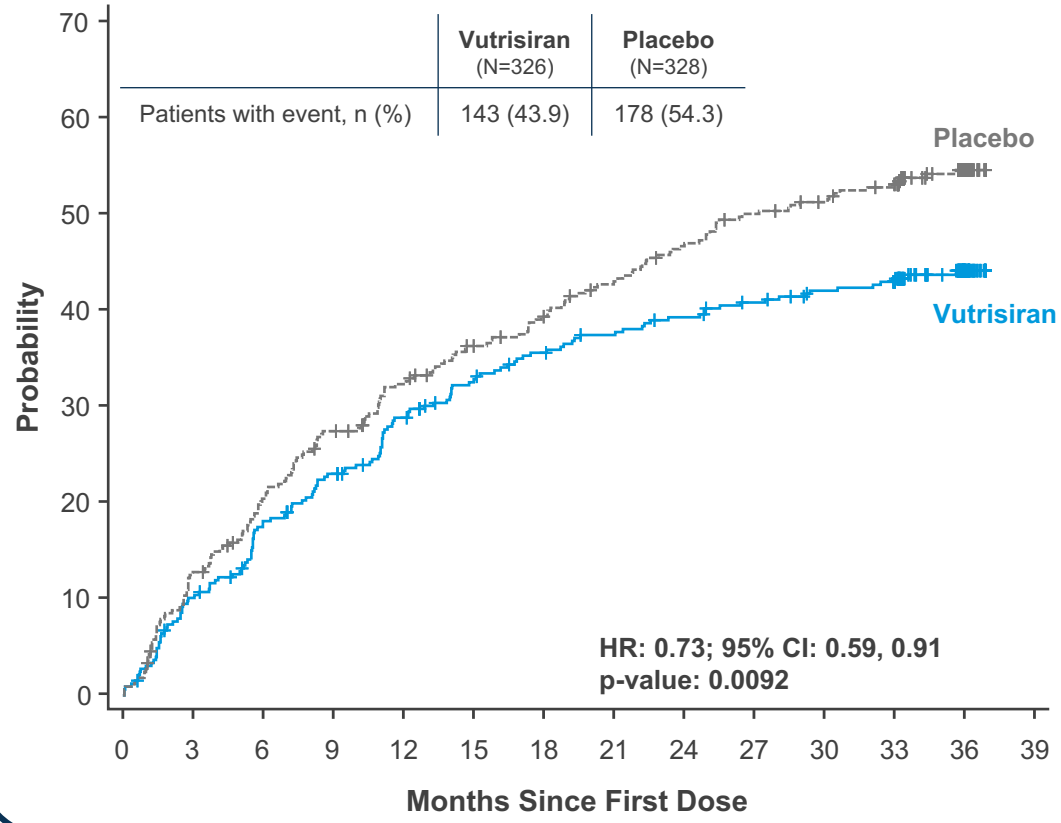
Vutrisiran Reduces the Risk of Outpatient Worsening HF

Decreased risks of both a first outpatient worsening HF and of recurrent outpatient worsening HF

HELIOS-B

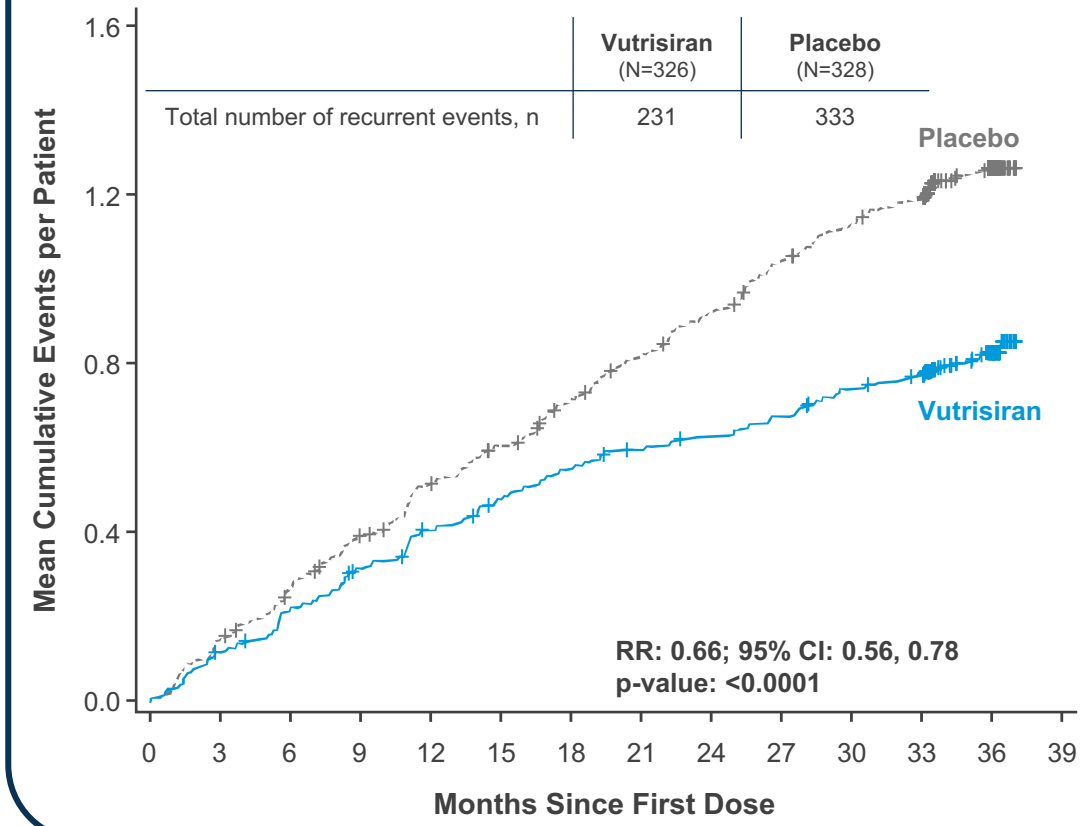
Impact of Vutrisiran on Time to First Outpatient Worsening HF[a]

	Vutrisiran (N=326)	Placebo (N=328)
Patients with event, n (%)	143 (43.9)	178 (54.3)



Impact of Vutrisiran on Recurrent Outpatient Worsening HF[b]

	Vutrisiran (N=326)	Placebo (N=328)
Total number of recurrent events, n	231	333



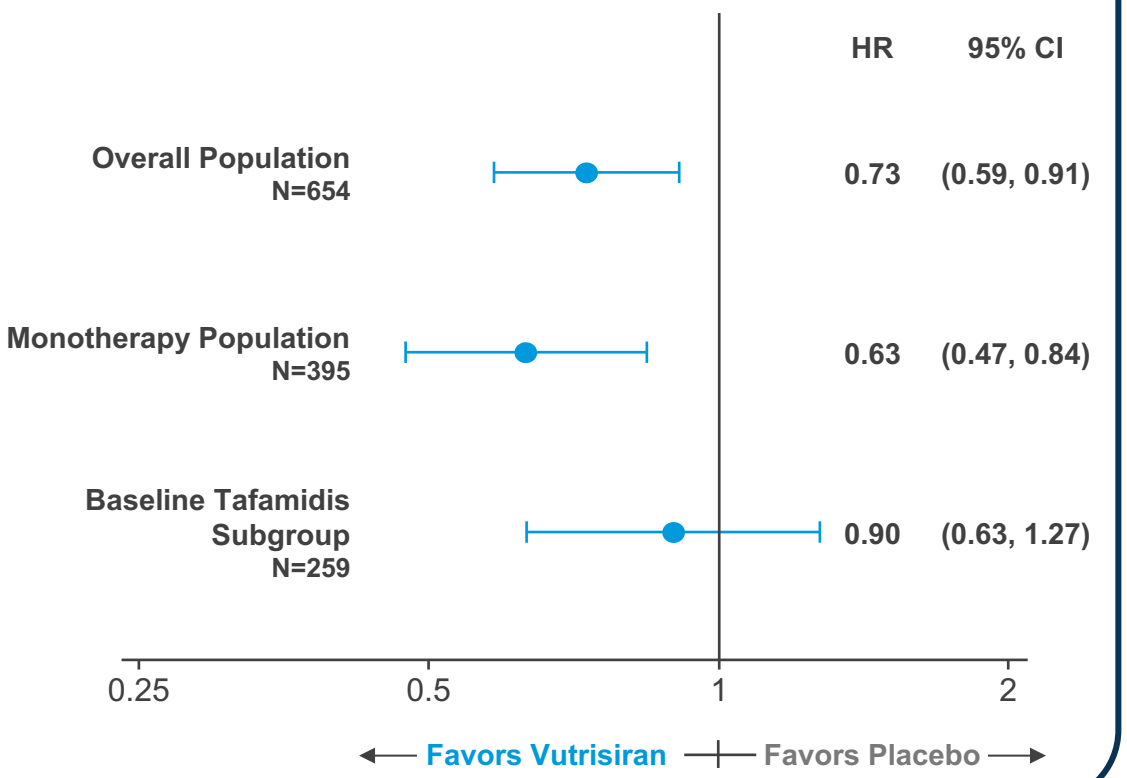
[a]Probabilities are estimated from the cumulative incidence function.HR was derived from a Cox proportional hazards model stratified by baseline tafamidis use, with treatment group, log-transformed baseline NT-proBNP, ATTR amyloidosis type, NYHA class, and age group as covariates, and with death treated as a competing risk. [b]Mean cumulative events are estimated from the mean cumulative function. RR was derived using the Poisson regression model including treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class, age group, baseline tafamidis use, and treatment-by-baseline tafamidis use interaction as covariates, with the logarithm of the follow-up time as an offset variable. Data are truncated when the at-risk population reaches five patients.

Abbreviations: ATTR, transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio, NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; PH, proportional hazards; RR, rate ratio.

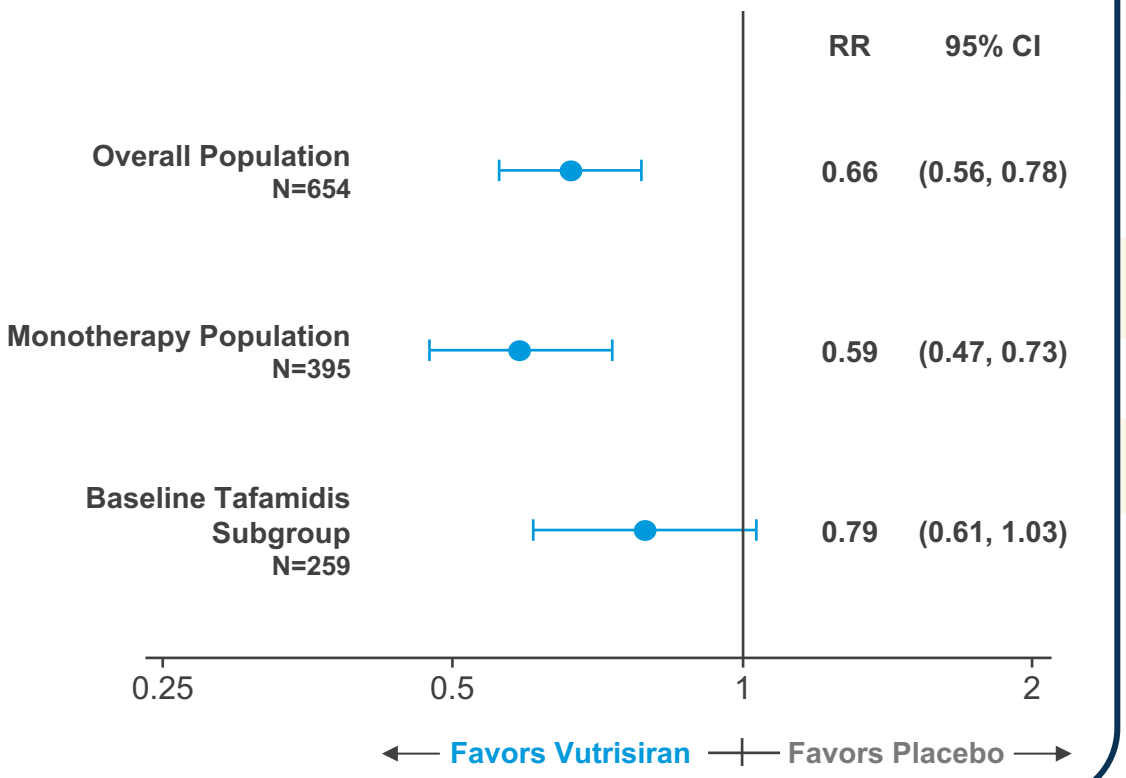
The Benefit of Vutrisiran Is Consistent across Study Populations

HELIOS-B

Time to First Outpatient Worsening HF[a]



Recurrent Outpatient Worsening HF[b]



- Results are consistent with data from APOLLO-B,[1] where patisiran significantly reduced the risk of:
  - Time to first outpatient worsening HF, HR: 0.70; 95% CI: 0.51, 0.96
  - Recurrent outpatient worsening HF, HR: 0.71; 95% CI: 0.53, 0.95

[a]HR was analyzed with a Cox proportional hazards model including treatment, ATTR disease type, NYHA class, age group, and log-transformed baseline NT-proBNP as covariates, with mortality treated as a competing risk. In the overall population, the model was stratified by baseline tafamidis use; [b]Poisson regression model includes treatment group, log-transformed NT-proBNP, type of ATTR, NYHA class and age group as covariates, and the logarithm of the follow-up time as an offset variable. For subgroups, the analysis is based on the subgroup data only. For overall population, the model includes baseline tafamidis use and treatment-by-baseline tafamidis use interaction. **Abbreviations**: ATTR, transthyretin amyloidosis; CI, confidence interval; HF, heart failure; HR, hazard ratio; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association RR, rate ratio. **Reference:** 1. Fontana et al. *J Am Coll Cardiol* 2024 Apr, 83 (13_Supplement) 511. https://doi.org/10.1016/S0735-1097(24)02501-4. (Manuscript In Press).

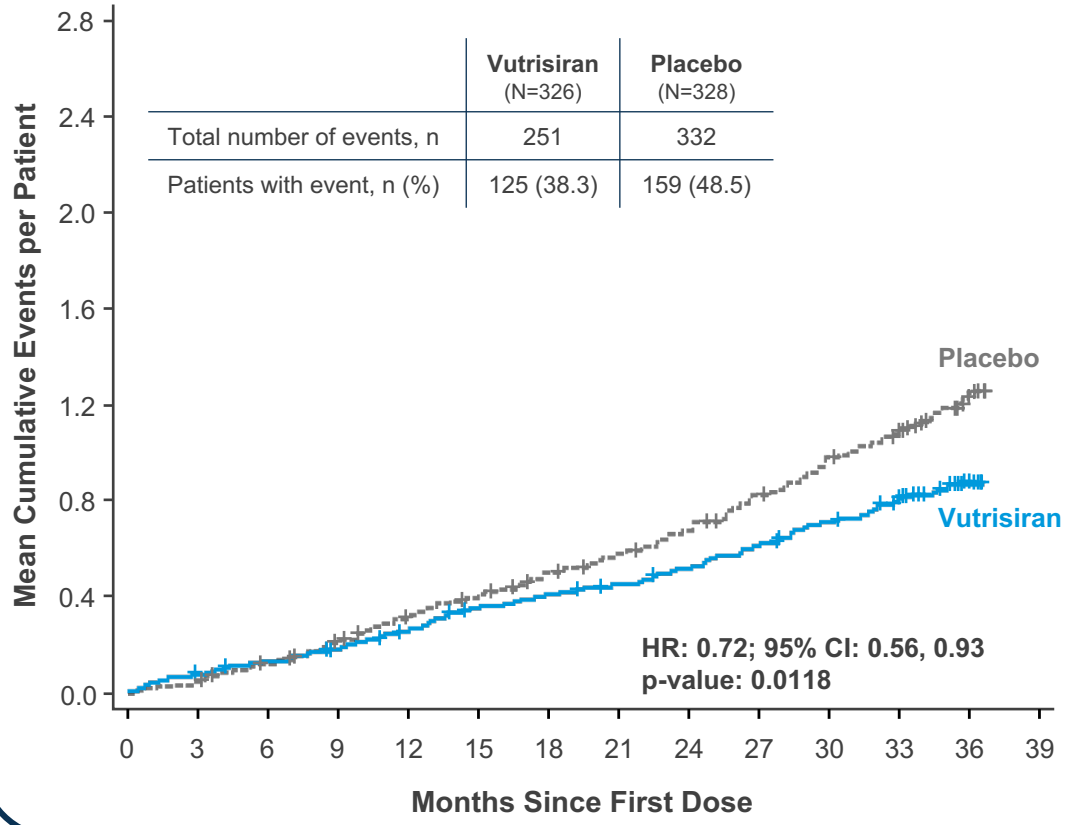
Vutrisiran Reduces the Risk of Outpatient Worsening HF, Recurrent CV Events, and All-Cause Mortality

Early benefit of vutrisiran on the expanded composite endpoint

HELIOS-B

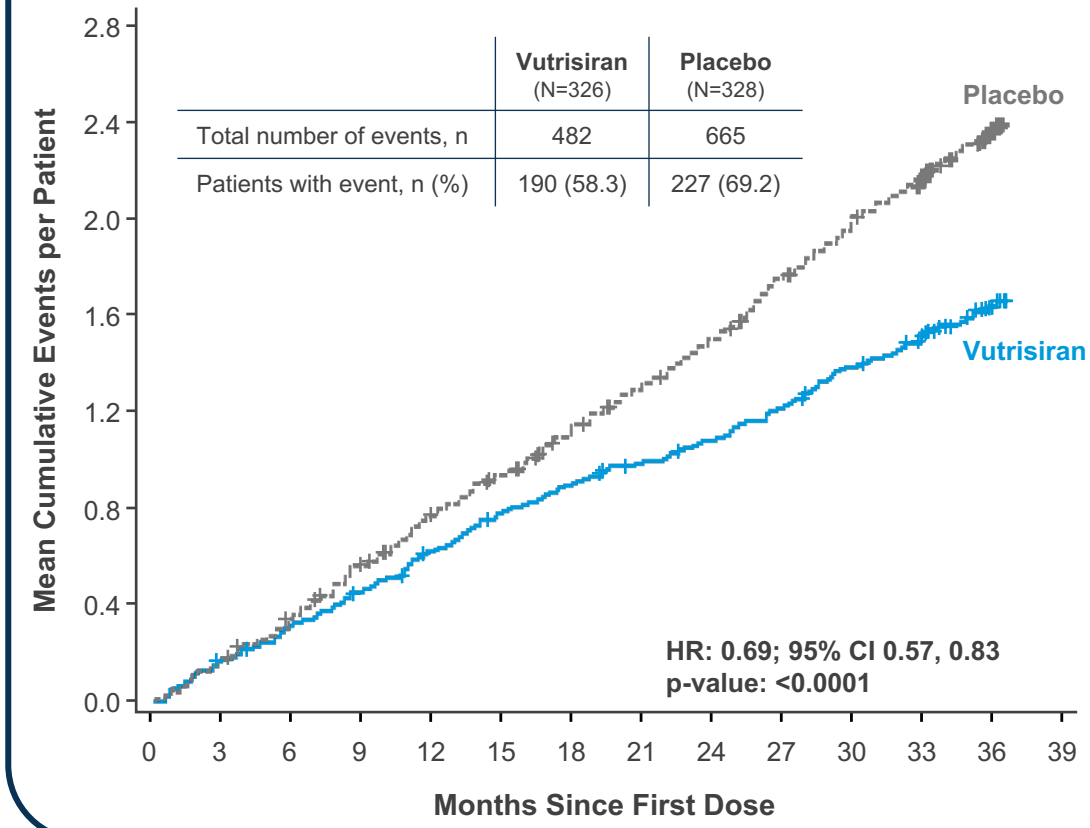
Composite of All-Cause Mortality or Recurrent CV Events[a,b]

	Vutrisiran (N=326)	Placebo (N=328)
Total number of events, n	251	332
Patients with event, n (%)	125 (38.3)	159 (48.5)



Composite of All-Cause Mortality, Recurrent CV Events[a], or Recurrent Outpatient Worsening HF Events[b]

	Vutrisiran (N=326)	Placebo (N=328)
Total number of events, n	482	665
Patients with event, n (%)	190 (58.3)	227 (69.2)



[a]CV events defined as CV hospitalizations or urgent HF visits. [b]Mean cumulative events are estimated from the mean cumulative function. HRs were derived using the modified Andersen–Gill model with robust variance estimator stratified by baseline tafamidis use, with treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class, and age group as covariates. Data are truncated when the at-risk population reaches five patients.

Abbreviations: ATTR, transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Summary

For US HCPs Only

- In HELIOS-B, vutrisiran rapidly knocked down TTR, lowered risk of all-cause mortality and CV events, and preserved functional capacity and quality of life, compared with placebo, in a population reflective of today's patients with ATTR-CM that had substantial use of background therapy
- In this prespecified analysis of HELIOS-B, outpatient worsening HF was common, occurring in 49% of patients with ATTR-CM during the 36-month double-blind period
- Outpatient worsening HF was associated with an increased risk of all-cause mortality and recurrent CV events, all-cause mortality alone
- Vutrisiran reduced the risk of outpatient worsening HF and the composite of outpatient worsening HF, all-cause mortality, and recurrent CV events compared with placebo
- Compared with placebo, the benefit of vutrisiran on the risk of worsening HF is observed early after treatment initiation

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

This study was funded by Alnylam Pharmaceuticals. Medical writing assistance was provided by Kristen Brown, PhD, of Adelphi Communications Ltd, UK, and funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice guidelines. If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; HF, heart failure; TTR, transthyretin.

Outpatient Worsening Heart Failure in Patients with Transthyretin Amyloidosis with Cardiomyopathy in the HELIOS-B Trial

Simultaneously published in *JACC*

Outpatient Worsening Heart Failure in Patients with ATTR-CM from the APOLLO-B Trial also accepted for publication in *JACC*