Outcomes of the HELIOS-B Monotherapy Population: A Post Hoc Analysis Censoring Data Following Tafamidis Initiation

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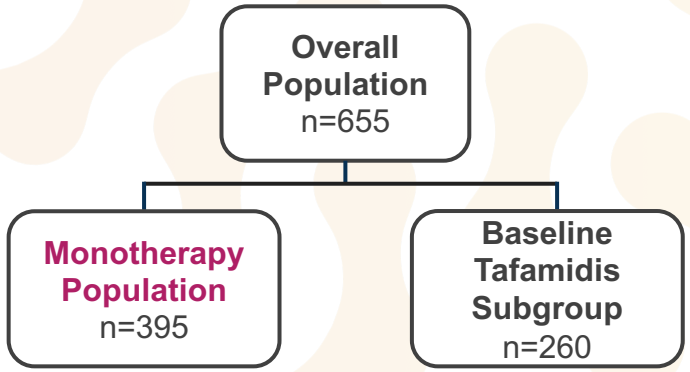
Introduction and Methods

Transthyretin Amyloidosis with Cardiomyopathy (ATTR-CM)

- ATTR-CM is a progressive, fatal disease caused by misfolded TTR depositing as amyloid fibrils in the heart[1–3]
- In the Phase 3 HELIOS-B study (NCT04153149), vutrisiran significantly reduced ACM and recurrent CV events versus placebo in patients with ATTR-CM[4]

Study Populations

- All key HELIOS-B endpoints were prespecified for evaluation separately in the **overall** and **monotherapy populations**
- The **monotherapy population** included patients **not on tafamidis at baseline**
  - Patients could initiate tafamidis during the study at the investigator's discretion
  - 21.5% of monotherapy patients initiated tafamidis after randomization[4] in a median (IQR) of 18 (12–28) months



Objective: **Post-hoc analysis to assess the efficacy and safety of vutrisiran in the monotherapy population with observations censored after tafamidis initiation**

Methods

- Results **with** and **without** censoring of observations after tafamidis initiation are compared for all key HELIOS-B endpoints
  - As 21.5% of patients in the **monotherapy population** initiated tafamidis after randomization[4], censoring data allows for the evaluation of vutrisiran in **patients not receiving tafamidis**

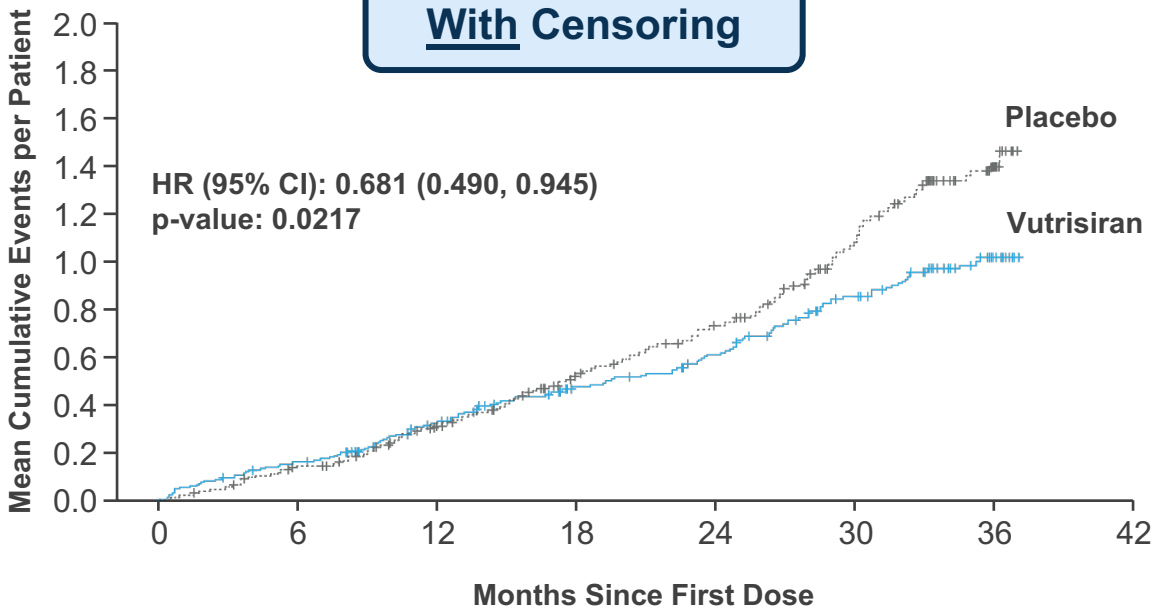
Abbreviations: ACM, all-cause mortality; ATTR-CM, ATTR with cardiomyopathy; CV, cardiovascular; IQR, interquartile range; TTR, transthyretin.

References: 1. Ruberg and Maurer. *JAMA* 2024;331:778–791; 2. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 3. Nativi-Nicolau et al. *ESC Heart Fail* 2021;8:3875-3884; 4. Fontana et al. *N Engl J Med* 2025;392:33–44.

Similar Reductions in the Risk of ACM and Recurrent CV Events Were Observed with Vutrisiran vs Placebo, Irrespective of Censoring

ACM and Recurrent CV Events in the Monotherapy Population with and without Censoring of Observations after Tafamidis Initiation

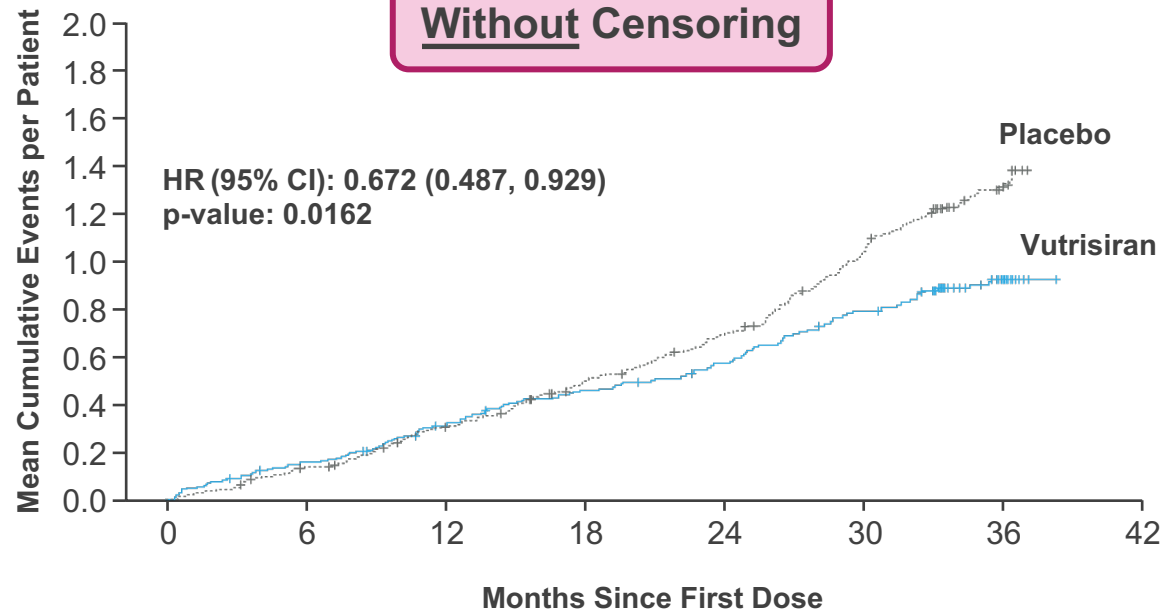
With Censoring



No. at Risk (Cumulative Events)

Placebo	199 (0)	189 (27)	169 (57)	145 (91)	133 (120)	108 (161)	31 (191)	0 (192)
Vutrisiran	196 (0)	190 (31)	169 (59)	145 (83)	138 (102)	117 (133)	36 (149)	0 (149)

Without Censoring



No. at Risk (Cumulative Events)

Placebo	199 (0)	191 (27)	180 (58)	167 (92)	158 (125)	144 (177)	37 (210)	0 (211)
Vutrisiran	196 (0)	190 (31)	176 (59)	167 (84)	163 (103)	152 (137)	42 (155)	0 (155)

HR derived using the modified Andersen–Gill model stratified by baseline tafamidis use, with treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class, and age group as covariates.

Abbreviations: ACM, all-cause mortality; ATTR, transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LWYY, Lin, Wei, Yang, and Ying; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Benefits Were Observed with Vutrisiran vs Placebo in the Monotherapy Population across All Efficacy Endpoints, Irrespective of Censoring

Endpoint	Monotherapy Population with Censoring (n=395)		Monotherapy Population without Censoring (n=395)	
	Treatment Effect	p-value	Treatment Effect	p-value
Primary endpoint				
Composite ACM and recurrent CV events through 36 months, HR (95% CI)[a]	0.68 (0.49, 0.95)	0.022	0.67 (0.49, 0.93)	0.016
Secondary endpoints				
ACM up to 42 months, HR (95% CI)[b]	0.59 (0.39, 0.89)	0.012	0.61 (0.42, 0.90)	0.016
6-MWT change from baseline at Month 30, LS mean difference (95% CI)	28.67 (9.35, 47.99)	0.004	32.09 (14.03, 50.15)	<0.001
KCCQ-OS change from baseline at Month 30, LS mean difference (95% CI)	9.32 (4.43, 14.21)	<0.001	8.69 (3.98, 13.40)	<0.001
NYHA class change from baseline: % stable or improved at Month 30, adjusted % difference (95% CI)	13.6 (2.6, 24.5)	0.015	12.5 (2.7, 22.5)	0.010

[a]Primary analysis at the May 2024 data-cut based on the modified Andersen–Gill model, (also known as LWYY), incorporating inverse probability of censoring weights to adjust for informative censoring.
[b]HR is derived from a Cox proportional hazards model at the Nov 2024 data-cut, incorporating inverse probability of censoring weights to adjust for informative censoring.

Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; IPCW, inverse probability censoring weights; LS, least squares; LWYY, Lin, Wei, Yang, and Ying; NYHA, New York Heart Association.

Safety Profile of Vutrisiran Was Consistent in the Monotherapy Population, Irrespective of Censoring

HELIOS-B

AEs during Double-Blind Period	Monotherapy Population with Censoring, n (%)		Monotherapy Population without Censoring, n (%)	
	Vutrisiran (n=196)	Placebo (n=199)	Vutrisiran (n=196)	Placebo (n=199)
Any AE Treatment-related	**191 (97.4)** 17 (8.7)	**190 (95.5)** 22 (11.1)	**192 (98.0)** 18 (9.2)	**194 (97.5)** 23 (11.6)
SAEs Treatment-related	**104 (53.1)** 1 (0.5)	**127 (63.8)** 1 (0.5)	**112 (57.1)** 1 (0.5)	**135 (67.8)** 1 (0.5)
Severe AEs Treatment-related	**86 (43.9)** 0	**119 (59.8)** 1 (0.5)	**93 (47.4)** 0	**126 (63.3)** 1 (0.5)
AEs leading to study drug interruption Treatment-related	**6 (3.1)** 1 (0.5)	**5 (2.5)** 0	**6 (3.1)** 1 (0.5)	**5 (2.5)** 0
AEs leading to study drug discontinuation Treatment-related	**6 (3.1)** 0	**10 (5.0)** 0	**6 (3.1)** 0	**10 (5.0)** 0
AEs leading to study withdrawal Treatment-related	**1 (0.5)** 0	**4 (2.0)** 0	**1 (0.5)** 0	**4 (2.0)** 0
Deaths	**36 (18.4)**	**42 (21.1)**	**37 (18.9)**	**43 (21.6)**

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

Summary

For US HCPs only

- In HELIOS-B, the efficacy and safety of vutrisiran monotherapy in patients with ATTR-CM were **consistent with the established profile when data after tafamidis initiation were censored**
  - Vutrisiran monotherapy conferred significant benefit across key endpoints, including survival, CV events, functional outcomes (6-MWT), NYHA class, and QoL versus placebo
- These **results further demonstrate the efficacy and safety of vutrisiran as a monotherapy in patients with ATTR-CM**

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Abbreviations: 6-MWT, 6-minute walk test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; HCP, healthcare professional; NYHA, New York Heart Association; QoL, quality of life.