

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

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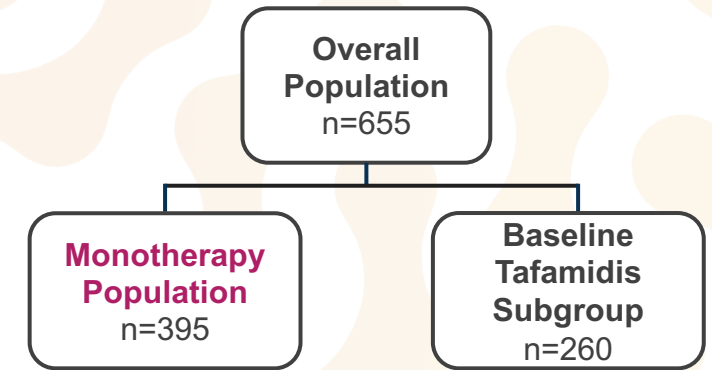
Introduction and Methods

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-CM⁴

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 randomization⁴ 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

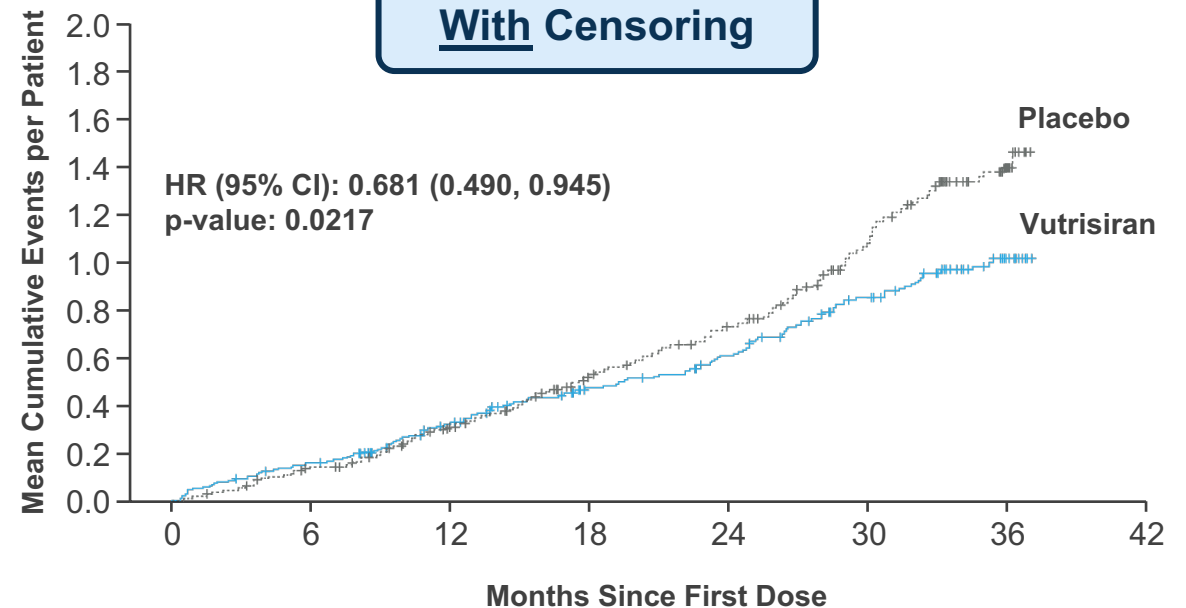
Methods

- 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 randomization⁴, censoring data allows for the evaluation of vutrisiran in **patients not receiving tafamidis**

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

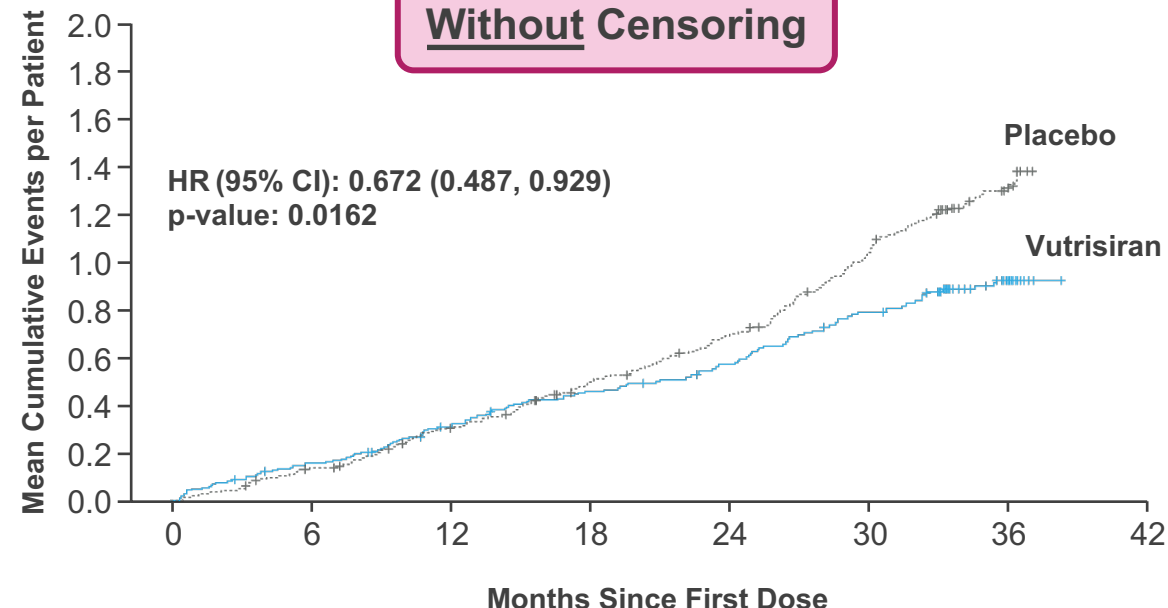
With Censoring



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.

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

Endpoint	Monotherapy Population <u>with</u> Censoring (n=395)		Monotherapy Population <u>without</u> 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

^aPrimary 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.

^bHR 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.

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



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)



For US HCPs only

Summary

- 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**

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