Vutrisiran: Post-Hoc Analysis of the HELIOS-B Monotherapy Population with Observations Following Tafamidis Initiation Censored

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SUMMARY

- HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM.[1]
  - Endpoints in the HELIOS-B study were prespecified for assessment in both the overall population and the monotherapy population (defined as patients not receiving tafamidis at baseline).[1]
  - In the monotherapy population, 21.5% of patients initiated tafamidis after randomization.[2]
  - Treatment with vutrisiran reduced the risk of the primary composite of all-cause mortality and recurrent CV events in both the overall population (HR 0.72; 95% CI 0.56, 0.93; P=0.01) and monotherapy population (HR 0.67, 95% CI 0.49, 0.93; P=0.02).[1]
  - The incidence of AEs were similar in both treatment groups.[1]
- In a post-hoc analysis of the HELIOS-B monotherapy population with data after patients initiated tafamidis censored, the efficacy and safety of vutrisiran monotherapy was consistent with results observed from the primary analysis.[2]

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STUDY DESIGN

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. After the double-blind period, all remaining eligible patients were allowed to receive vutrisiran in an OLE.[1]

Endpoints were prespecified for assessment in both the overall population and the monotherapy population (patients not receiving tafamidis at baseline). The primary endpoint was the composite

endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind period.[1]

A total of 395 patients were not on tafamidis at baseline and comprised the monotherapy population. Patients that were not receiving tafamidis at baseline could initiate tafamidis at the discretion of the investigator. In the monotherapy population, a total of 21.5% of patients initiated tafamidis after randomization in a median (IQR) of 18 (12-28 months), which included 44 out of 196 patients (22%) in the vutrisiran group and 41 out of 199 patients (21%) in the placebo group.[1,2]

Post-Hoc Analysis

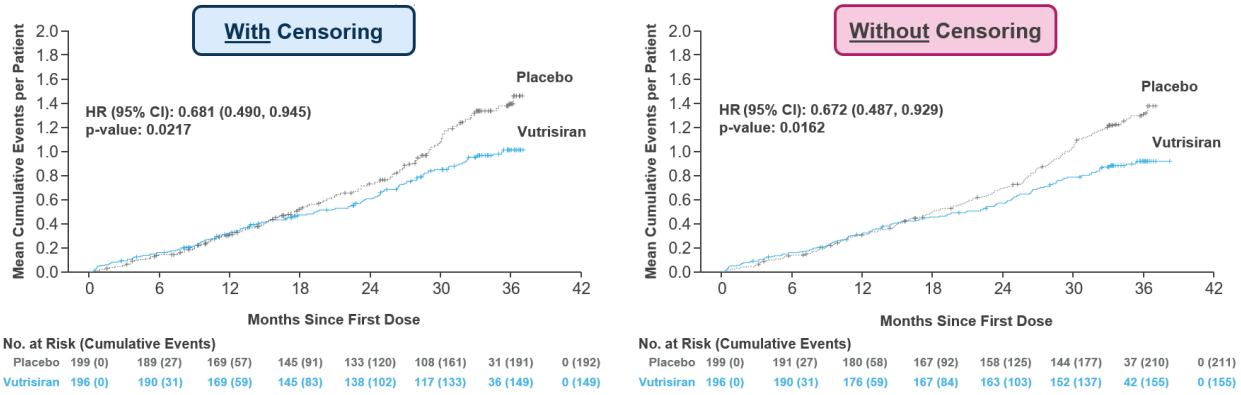
A post-hoc analysis of data from the monotherapy population with observations after tafamidis initiation censored was conducted to further assess the monotherapy population in the HELIOS-B study.[2]

EFFICACY RESULTS

Primary Endpoint: Composite of All-Cause Mortality and Recurrent CV Events Through the Double-Blind Period

With censoring of observations after tafamidis initiation in the monotherapy population, treatment with vutrisiran compared with placebo resulted in a HR of 0.68 (95% CI 0.49, 0.95) in the composite of all-cause mortality and recurrent CV events (**Figure 1**). The reduction in risk of the composite of all-cause mortality and recurrent events was consistent with the result observed from the primary analysis without censoring (HR 0.67, 95% CI 0.49, 0.93; P=0.02).[2]

Figure 1. All-Cause Mortality and Recurrent CV Events in the Monotherapy Population With and Without Censoring of Observations After Tafamidis Initiation.[2]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.
HR derived using the modified Andersen-Gill model stratified by baseline tafamidis use, with treatment group, log-transformed NT-proBNP, type of ATTR, NYHA class, and age group as covariates.
Primary analysis at May 2024 data cut.
From Witteles et al.[2]

Secondary Endpoints

A summary of the secondary endpoints assessed in the monotherapy population with and without censoring of observations after tafamidis initiation are presented in **Table 1**.[2]

Table 1. Secondary Endpoints Assessed in the Monotherapy Population.[2]

Endpoint	Monotherapy Population with Censoring (n=395)		Monotherapy Population without Censoring (n=395)	
	Treatment Effect	p-value	Treatment Effect	p-value
All-cause mortality up to 42 months, HR (95% CI)[a]	0.59 (0.39, 0.89)	0.012	0.61 (0.42, 0.90)	0.016
Change from baseline in 6-MWT at Month 30, LS mean difference (95% CI)	28.67 (9.35, 47.99)	0.004	32.09 (14.03, 50.15)	<0.001
Change from baseline in KCCQ-OS at Month 30, LS mean difference (95% CI)	9.32 (4.43, 14.21)	<0.001	8.69 (3.98, 13.40)	<0.001
Change from baseline in NYHA class at Month 30: % stable or improved, adjusted % difference (95% CI)	13.6 (2.6, 24.5)	0.015	12.5 (2.7, 22.5)	0.010

Abbreviations: 6-MWT = 6-minute walk test; CI = confidence interval; HR = hazard ratio; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; NYHA = New York Heart Association.

[a]HR is derived from a Cox proportional hazards model at November 2024 data cut, incorporating inverse probability of censoring weights to adjust for informative censoring.

SAFETY RESULTS

A summary of the safety results observed during the double-blind period in the monotherapy population with and without censoring of observations after tafamidis initiation are presented in **Table 2**.[2]

Table 2. Safety Results in the Monotherapy Population During the Double-Blind Period.[2]

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

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

ABBREVIATIONS

6-MWT = 6-minute walk test; AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; HR = hazard ratio; IQR = interquartile range; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; SAE = serious adverse event; wtATTR = wild-type transthyretin amyloidosis.

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REFERENCES

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2. Witteles R, Kristen A, Habib G, et al. Outcomes of the HELIOS-B monotherapy population: a post hoc analysis censoring data following tafamidis initiation. Presented at: Heart Failure Society of America (HFSA) Annual Scientific Meeting; September 26-29, 2025; Minneapolis, MN, USA.