Vutrisiran: Results in Patients who had Progressed on Tafamidis in HELIOS-B

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SUMMARY

- A post-hoc analysis of the HELIOS-B study was conducted to evaluate the impact of vutrisiran on all-cause mortality and recurrent CV events among patients who were identified by investigators at baseline as having manifested disease progression while on tafamidis (i.e., "tafamidis progressors").[1]
- Of the 259 patients who received tafamidis at baseline, 61 patients (28 patients in the vutrisiran arm; 33 patients in the placebo arm) were identified as having disease progression by the investigators.[1]
- In the tafamidis progressors subgroup, treatment with vutrisiran compared with placebo resulted in a HR of 0.59 (95% CI 0.22, 1.58) for the composite endpoint of all-cause mortality and recurrent CV events during the double blind period and a HR of 0.44 (95% CI 0.13, 1.48) for all-cause mortality through 42 months.[1]
- All patients in the tafamidis progressors subgroup experienced at least 1 AE. The safety profile of vutrisiran in tafamidis progressors was similar to that observed in the overall population of HELIOS-B.[1]

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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. 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 in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind period, all eligible patients remaining in the study were allowed to receive vutrisiran in an OLE.[2]

A post-hoc analysis was conducted to evaluate the impact of vutrisiran on all-cause mortality and recurrent CV events among patients who were identified by investigators at baseline as having manifested disease progression while on tafamidis (i.e., "tafamidis progressors") in the HELIOS-B study.[1]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Of the 259 patients who received tafamidis at baseline, 61 patients were identified as having disease progression by the investigators. The baseline demographics and disease characteristics of tafamidis progressors compared with the overall population and baseline tafamidis subgroup are summarized in **Table 1**.[1]

Table 1. Baseline Characteristics of Tafamidis Progressors in HELIOS-B.[1]

Characteristic	Tafamidis Progressors			HELIOS-B Overall Population	Baseline Tafamidis Subgroup
	Total (n=61)	Vutrisiran (n=28)	Placebo (n=33)	Total (N=654)	Total (n=259)
Age, years, median (range)	77.0 (64-85)	77.0 (64-85)	77.0 (64-85)	77.0 (45-85)	76.0 (45-85)
Male sex, n (%)	60 (98.4)	28 (100.0)	32 (97.0)	605 (92.5)	244 (94.2)
wtATTR, n (%)	56 (91.8)	26 (92.9)	30 (90.9)	578 (88.4)	231 (89.2)
Time from start of tafamidis therapy, months, median (range)	13.2 (1.1-65.5)	12.2 (1.1-58.8)	13.6 (2.6-65.5)	10.8 (1.1-65.5)	10.8 (1.1-65.5)
Previous HF hospitalization, n (%)	24 (39.3)	10 (35.7)	14 (42.4)	221 (33.8)	88 (34.0)
NYHA Class, n (%)					
I	19 (31.1)	11 (39.3)	8 (24.2)	84 (12.8)	57 (22.0)
II	37 (60.7)	13 (46.4)	24 (72.7)	508 (77.7)	167 (64.5)
III	5 (8.2)	4 (14.3)	1 (3.0)	62 (9.5)	35 (13.5)
6-MWT distance, m, mean (SD)	393.0 (85.9)	374.9 (90.4)	408.4 (80.0)	374.6 (100.0)	384.9 (98.7)
KCCQ-OS, points, mean (SD)	75.6 (19.1)	75.7 (19.4)	75.4 (19.2)	72.6 (19.7)	76.4 (17.7)
NT-proBNP >3000 ng/L, n (%)	16 (26.2)	9 (32.1)	7 (21.2)	185 (28.3)	58 (22.4)

Abbreviations: 6-MWT = 6-minute walk test; HF = heart failure; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; wtATTR = wild-type transthyretin amyloidosis.

EFFICACY RESULTS

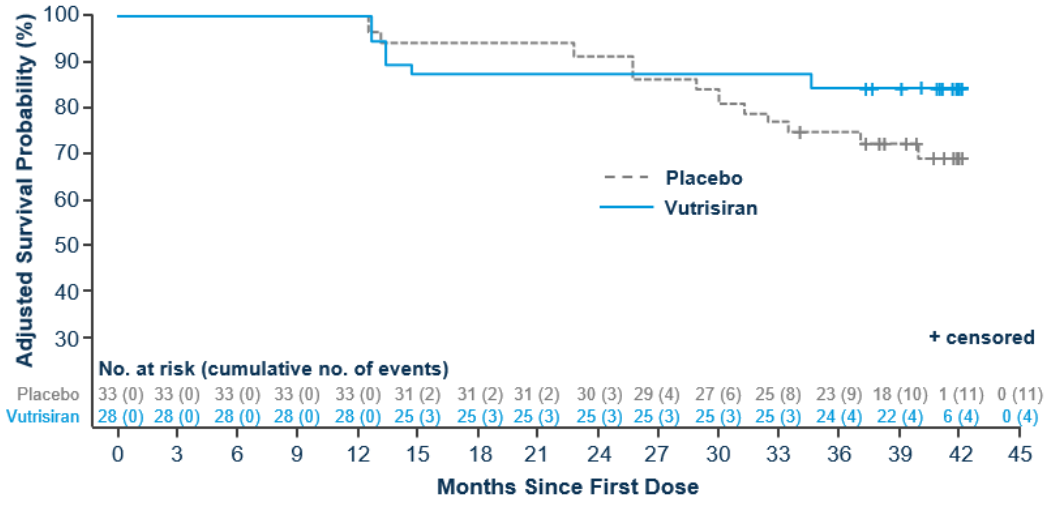
All-Cause Mortality and Recurrent CV Events During the Double-Blind Period

In the overall population (N=654), treatment with vutrisiran reduced the risk of the primary composite endpoint of all-cause mortality and recurrent CV events when compared with placebo (HR of 0.72; 95% CI 0.56, 0.93; p=0.01). The HR for time to first event was 0.72 (95% CI 0.57, 0.91; p=0.006).[2]

In the tafamidis progressors subgroup (n=61), a total of 29 events for the composite endpoint of all-cause mortality and CV events were observed in the vutrisiran arm (n=28), and 45 events were observed in the placebo arm (n=33). Twelve patients in the vutrisiran arm (42.9%) and 18 patients in the placebo arm (54.5%) had ≥1 event. Among tafamidis progressors, treatment with vutrisiran compared with placebo resulted in a HR of 0.59 (95% CI 0.22, 1.58) for the composite of all-cause mortality and recurrent CV events. The HR for time to first event was 0.56 (95% CI 0.25, 1.29) (**Figure 1**).[1]

In the baseline tafamidis subgroup (n=259), treatment with vutrisiran compared with placebo resulted in a HR of 0.79 (95% CI 0.51, 1.21) in all-cause mortality and recurrent CV events. The HR for time to first event was 0.83 (95% CI 0.57, 1.23).[1]

Figure 1. Composite All-Cause Mortality and CV Events During the Double-Blind Period in Tafamidis Progressors.[1,a]



Abbreviations: CV = cardiovascular.
[a]Adjusted probabilities were estimated using the Kaplan-Meier method with the Inverse Probability of Treatment Weighting applied.
From Gonzalez-Costello et al.[1]

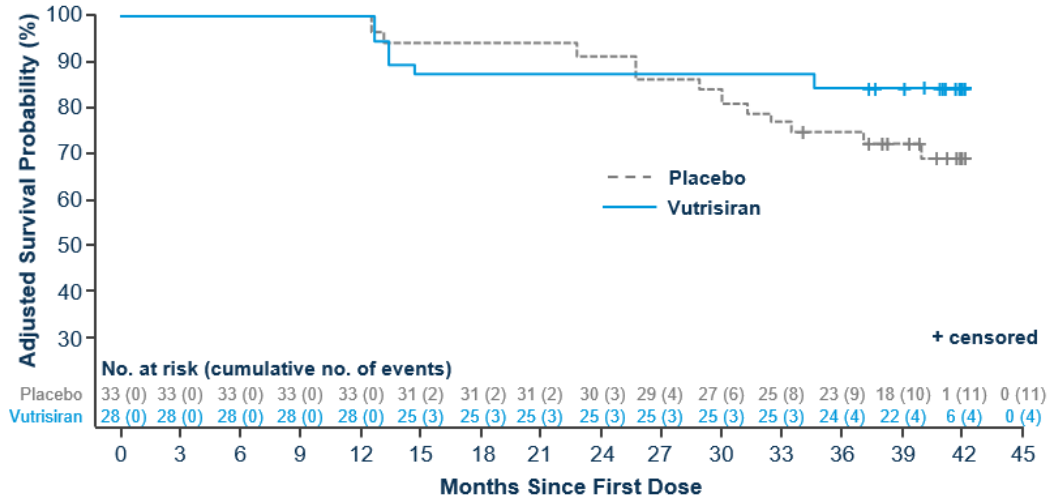
All-Cause Mortality Through 42 Months (Double-Blind Period and 6 Months OLE)

In the overall population (N=654), treatment with vutrisiran reduced the risk of the secondary endpoint of all-cause mortality through 42 months when compared with placebo (HR of 0.65; 95% CI 0.46, 0.90; p=0.01).[2]

In the tafamidis progressors subgroup (n=61), there were 4 deaths (14.3%) in the vutrisiran arm and 11 deaths (33.3%) in the placebo arm through 42 months. Treatment with vutrisiran compared with placebo resulted in a HR of 0.44 (95% CI 0.13, 1.48) for all-cause mortality through 42 months (**Figure 2**).[1]

In the baseline tafamidis subgroup (n=259), treatment with vutrisiran compared with placebo resulted in a HR of 0.59 (95% CI 0.32, 1.08) for all-cause mortality through 42 months.[1]

Figure 2. All-Cause Mortality Through 42 Months in Tafamidis Progressors.[1,a]



[a]Adjusted probabilities were estimated using the Kaplan-Meier method with the Inverse Probability of Treatment Weighting applied.
From Gonzalez-Costello et al.[1]

SAFETY RESULTS

A summary of the safety results observed in tafamidis progressors is presented in **Table 2**. The safety profile of vutrisiran in tafamidis progressors was similar to that observed in the overall population of HELIOS-B.[1]

Table 2. Safety Summary of Tafamidis Progressors in HELIOS-B.[1]

AE Category, n (%)	Tafamidis Progressors		HELIOS-B Overall Population	
	Vutrisiran (n=28)	Placebo (n=33)	Vutrisiran (n=326)	Placebo (n=328)
Any AE	28 (100)	33 (100)	322 (99)	323 (98)
Any SAE	21 (75)	23 (70)	201 (62)	220 (67)
Any AE leading to discontinuation	0	1 (3)	10 (3)	13 (4)
Any AE leading to death	4 (14)	9 (27)	49 (15)	63 (19)
Most common AEs occurring in ≥20% in either tafamidis progressors treatment group				
COVID-19	16 (57)	12 (36)	87 (27)	99 (30)
Atrial fibrillation	8 (29)	9 (27)	69 (21)	68 (21)
Acute kidney injury	6 (21)	7 (21)	32 (10)	27 (8)
Atrial flutter	6 (21)	1 (3)	30 (9)	23 (7)
Dizziness	6 (21)	3 (9)	32 (10)	43 (13)
Hypervolemia	6 (21)	6 (18)	17 (5)	21 (6)
Cardiac failure	5 (18)	8 (24)	101 (31)	128 (39)
Dyspnea	4 (14)	10 (30)	43 (13)	51 (16)
Fatigue	4 (14)	11 (33)	28 (9)	45 (14)
Fall	2 (7)	9 (27)	42 (13)	69 (21)

Abbreviations: AE = adverse event; COVID-19 = coronavirus-19; SAE = serious adverse event.

ABBREVIATIONS

6-MWT = 6-minute walk test; AE = adverse event; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; COVID-19 = coronavirus-19; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; HR = hazard ratio; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; SAE = serious adverse event; SD = standard deviation; wtATTR = wild-type transthyretin amyloidosis.

Updated 20 May 2025

REFERENCES

1. Gonzalez-Costello J, Khouri M, Sarswat N, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy in HELIOS-B who had progressed on tafamidis. Presented at: Heart Failure Association (HFA); May 17-20, 2025; Belgrade, Serbia.
2. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2025;392(1):33-44. doi:10.1056/NEJMoa2409134