Vutrisiran: Survival and Mortality

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SUMMARY

- HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN.[1]
  - All-cause mortality and survival were not evaluated as endpoints in HELIOS-A.[1]
- 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.[2]
  - Vutrisiran reduced the risk of the primary composite of all-cause mortality and recurrent CV events through the double-blind period 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).[2]
  - Analyses of all-cause mortality and CV mortality were conducted through 42 months using an updated data cut (November 22, 2024). As compared to 42.4% of patients from the primary data cut (May 8, 2024), 96.3% of patients had follow-up through 42 months with the updated data cut. These analyses were not controlled for multiplicity.[3]
    - Vutrisiran reduced the risk of all-cause mortality through 42 months (double-blind period and up to 6 months in the OLE) in both the overall population (HR 0.64; 95% CI 0.46, 0.88; nominal P=0.01) and monotherapy population (HR 0.61; 95% CI 0.42, 0.90; nominal P=0.02).[3]
    - Vutrisiran reduced the risk of CV mortality through 42 months (double-blind period and up to 6 months in the OLE) in both the overall population (HR 0.67; 95% CI 0.47, 0.96; nominal P=0.04) and monotherapy population (HR 0.64; 95% CI 0.41, 0.98; nominal P=0.05).[3]
  - In the overall population, the proportion of patients with at least one AE was similar between treatment arms, and the majority of AEs with vutrisiran were mild or moderate. Cardiac AEs occurred at similar or lower rates with vutrisiran compared with placebo.[4]

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STUDY DESIGN

HELIOS-B Study

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.[2]

Primary and Key Secondary Endpoints

The primary endpoint was the composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) at the end of the double-blind period (up to 33–36 months) in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). A secondary endpoint was all-cause mortality through 42 months. For the analyses that included death from any cause, heart transplantation and implantation of a left ventricular assist device were treated as deaths.[2]

Predefined subgroups were stratified according to tafamidis use at baseline (yes vs. no), NT-proBNP at baseline (≤2,000 pg/mL vs. >2,000 pg/ml), ATTR disease type (wtATTR vs. hATTR), NYHA class (I or II vs. III), and age at baseline (<75 years vs. ≥75 years).[2]

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

A total of 655 patients were enrolled and were randomly assigned to receive vutrisiran (n=326) or placebo (n=329). The median age of study participants was 77 years, 93% were male, 88% had wtATTR, and 78% had NYHA Class II heart failure. The patient demographic and clinical characteristics at baseline were similar between the vutrisiran and placebo groups, except that NT-proBNP and troponin I levels were higher in the vutrisiran group than the placebo group in the monotherapy population.[2]

At baseline, concomitant tafamidis use was 40% and 39% in the vutrisiran and placebo groups, respectively. Baseline use of SGLT2 inhibitors was 3% in both treatment groups; and baseline use of diuretics was 80% and 79% in the vutrisiran and placebo groups, respectively.[5]

EFFICACY RESULTS

Primary Endpoint: All-Cause Mortality and Recurrent CV Events

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) (**Table 1**).[2]

Table 1. Primary Endpoint and Patients With At Least One Event.[2]

Endpoint	Overall Population			Monotherapy Population		
	Vutrisiran (n=326)	Placebo (n=328)	Measure of Effect	Vutrisiran (n=196)	Placebo (n=199)	Measure of Effect
Death from any cause and recurrent CV events, HR (95% CI), P-value	-	-	0.72 (0.56–0.93), P=0.01	-	-	0.67 (0.49–0.93), P=0.02

Endpoint	Overall Population			Monotherapy Population		
	Vutrisiran (n=326)	Placebo (n=328)	Measure of Effect	Vutrisiran (n=196)	Placebo (n=199)	Measure of Effect
Death from any cause, HR (95% CI), P-value	-	-	0.69 (0.49–0.98), P=0.04	-	-	0.71 (0.47–1.06), P=0.12
Recurrent CV events, relative rate ratio (95% CI), P-value	-	-	0.73 (0.61–0.88), P=0.001	-	-	0.68 (0.53–0.86), P=0.001
Patients with at least one event, n (%)	125 (38)	159 (48)	-	76 (39)	105 (53)	-
Death from any cause[a]	51 (16)	69 (21)	-	36 (18)	46 (23)	-
Recurrent CV events	112 (34)	133 (41)	-	66 (34)	87 (44)	-

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio.

[a]Three patients in the vutrisiran group and four in the placebo group had a heart transplantation. No patients had implantation of a left ventricular assist device.

Similar effects were observed in all-cause mortality and recurrent CV events across all prespecified subgroups in the overall population and in the monotherapy population.[2]

Secondary Endpoint: All-Cause Mortality

Treatment with vutrisiran reduced the risk of all-cause mortality through 42 months in both the overall population (HR 0.65; 95% CI 0.46, 0.90; P=0.01; **Figure 1**) and monotherapy population (HR 0.66, 95% CI 0.44, 0.97; P=0.045; **Figure 2**) (**Table 2**).[2]

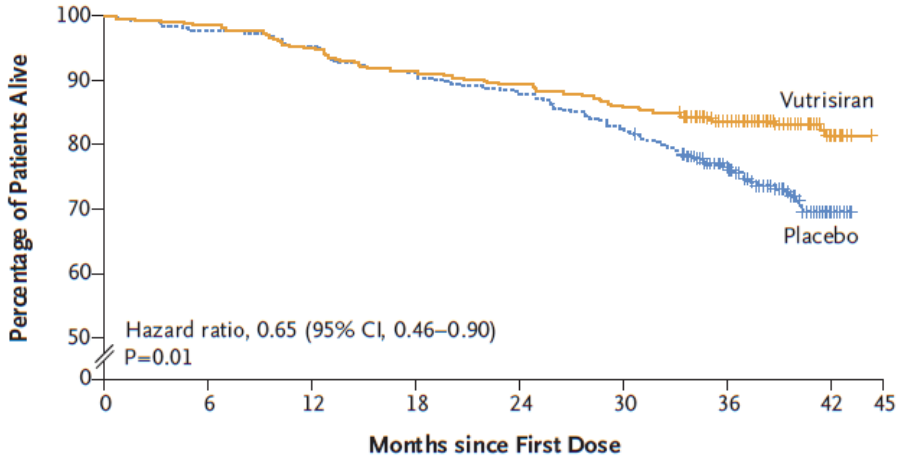
Table 2. Secondary Endpoint and Patients Who Died.[2]

Endpoint	Overall Population			Monotherapy Population		
	Vutrisiran (n=326)	Placebo (n=328)	Measure of Effect	Vutrisiran (n=196)	Placebo (n=199)	Measure of Effect
Death from any cause through 42 months, HR (95% CI), P-value	-	-	0.65 (0.46–0.9), P=0.01	-	-	0.66 (0.44–0.97), P=0.045
Patients who died, n (%)	60 (18)	85 (26)	-	43 (22)	58 (29)	-

Abbreviations: CI = confidence interval; HR = hazard ratio.

Data as of May 8, 2024.

Figure 1. Overall Population: Death from Any Cause.[2]

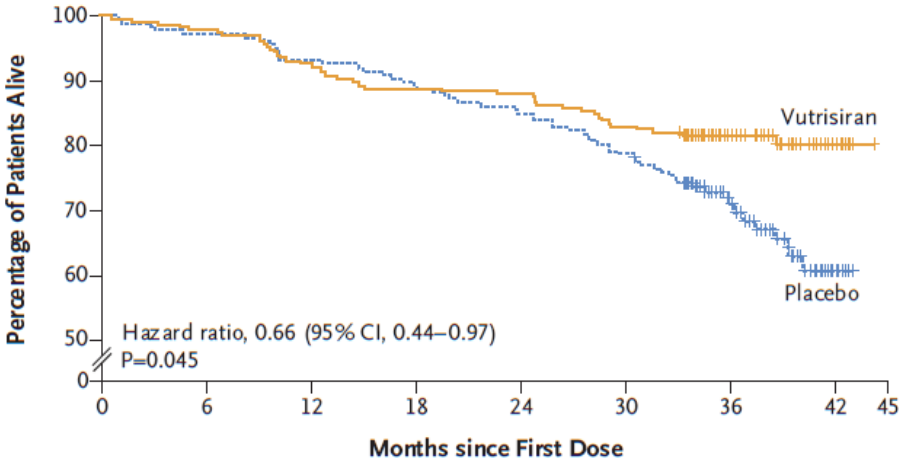


No. at Risk (cumulative no. of events)

Vutrisiran	326 (0)	321 (5)	308 (18)	296 (30)	289 (37)	277 (49)	198 (56)	33 (60) 0 (60)
Placebo	328 (0)	321 (7)	314 (14)	299 (29)	290 (38)	271 (57)	180 (74)	24 (85) 0 (85)

Abbreviations: CI = confidence interval.
Data as of May 8, 2024.
From Fontana et al.[2]

Figure 2. Monotherapy Population: Death from Any Cause.[2]



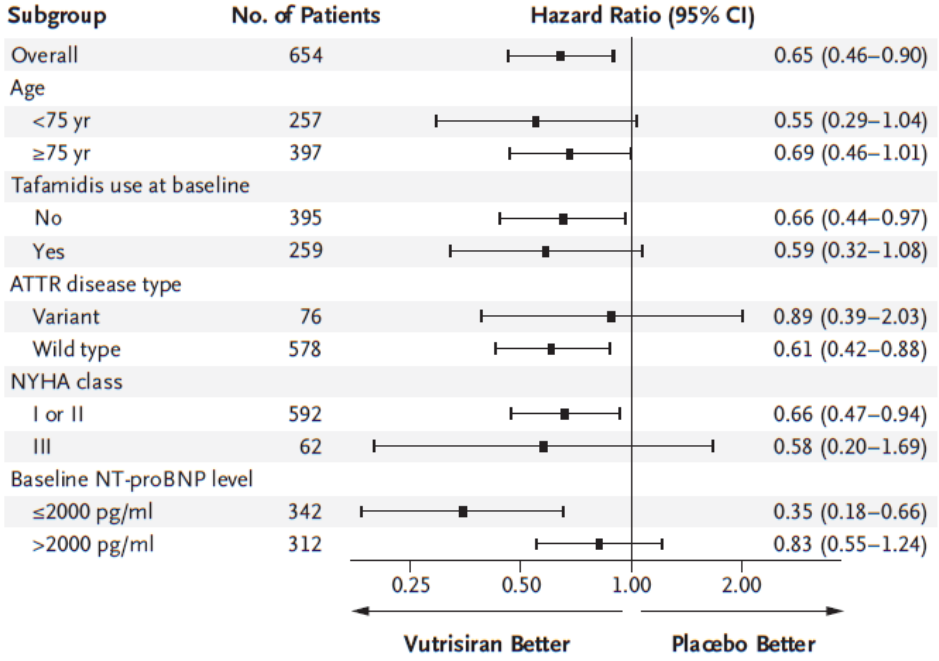
No. at Risk (cumulative no. of events)

Vutrisiran	196 (0)	191 (5)	179 (17)	171 (25)	169 (27)	158 (38)	86 (41)	17 (43) 0 (43)
Placebo	199 (0)	194 (5)	188 (11)	180 (19)	172 (27)	160 (39)	79 (51)	16 (58) 0 (58)

Abbreviations: CI = confidence interval.
Data as of May 8, 2024.
From Fontana et al.[2]

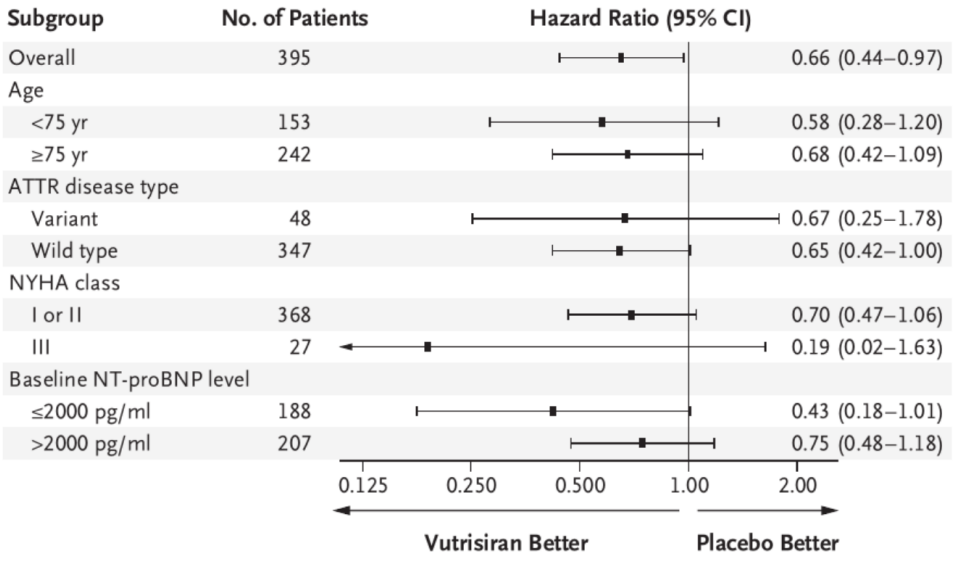
Similar effects were observed in all-cause mortality across all prespecified subgroups in both the overall population (**Figure 3**) and monotherapy population (**Figure 4**). Sensitivity analyses of the secondary endpoint were consistent with the secondary endpoint analysis.[2]

Figure 3. Overall Population: All-Cause Mortality in Prespecified Subgroups.[2]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.
From Fontana et al.[2]

Figure 4. Monotherapy Population: All-Cause Mortality in Prespecified Subgroups.[2]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.
From Fontana et al.[2]

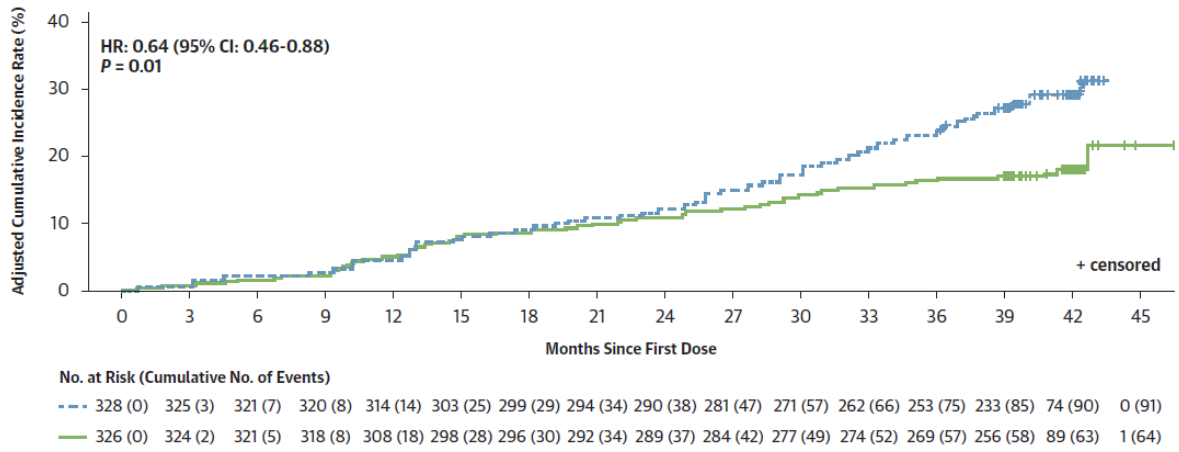
Analyses of All-Cause Mortality and CV Mortality Through 42 Months

Analyses of all-cause mortality and CV mortality were conducted through 42 months (i.e., 33–36 months of the double-blind period and up to 6 additional months of follow-up in the OLE, resulting in 39-42 months total) using a data cut of November 22, 2024. The analyses were not controlled for multiplicity,

and as such, p-values are nominal. The endpoint of all-cause mortality from the primary analysis was conducted based on a data cut of May 8, 2024. As compared to 42.4% of patients from the primary data cut, 96.3% of patients had follow-up through 42 months with the updated data cut.[3]

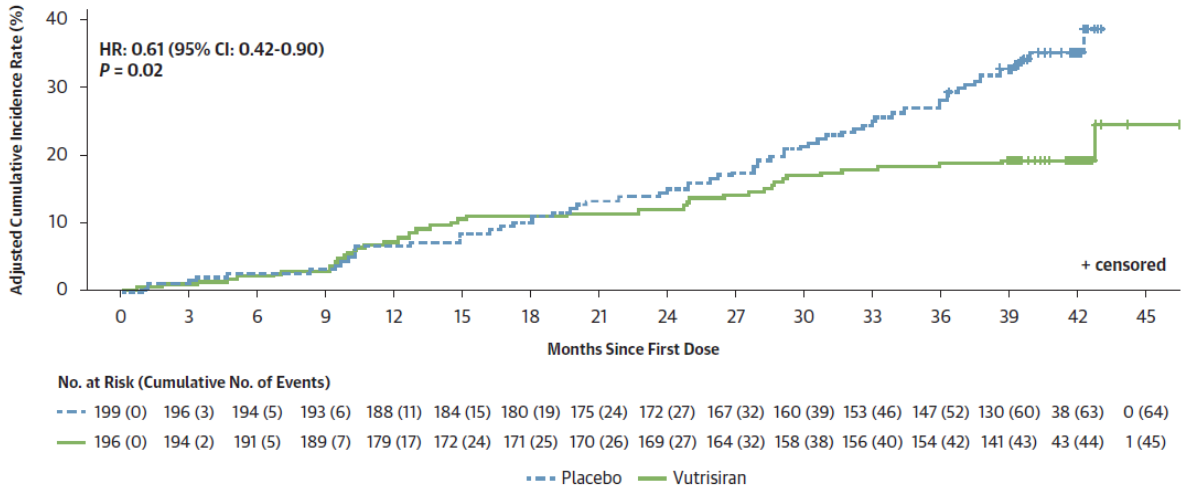
Treatment with vutrisiran reduced the risk of all-cause mortality through 42 months in both the overall population (HR 0.64; 95% CI 0.46, 0.88; nominal P=0.01; event rates at 42 months [SE]: placebo 28.95 [2.55], vutrisiran 18.36 [2.21]; **Figure 5**) and monotherapy population (HR 0.61; 95% CI 0.42, 0.90; nominal P=0.02; **Figure 6**).[3]

Figure 5. Overall Population: Cumulative Rate of All-Cause Mortality Through 42 Months.[3]



Abbreviations: CI = confidence interval; HR = hazard ratio.
Deaths after the end of the study were included in the analysis. Data as of November 22, 2024.
From Witteles et al.[3]

Figure 6. Monotherapy Population: Cumulative Rate of All-Cause Mortality Through 42 Months.[3]

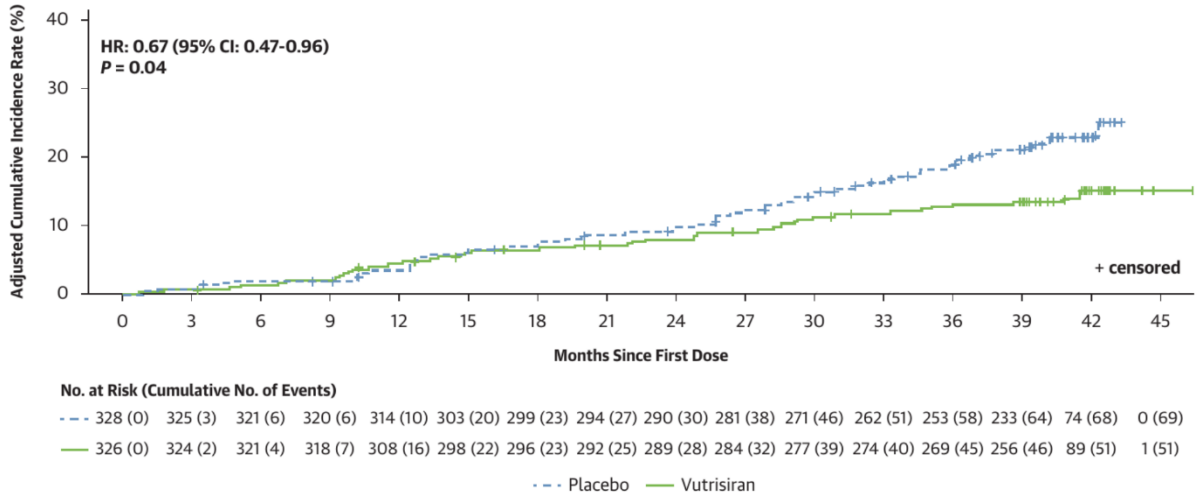


Abbreviations: CI = confidence interval; HR = hazard ratio.
Deaths after the end of the study were included in the analysis. Data as of November 22, 2024.
From Witteles et al.[3]

Treatment with vutrisiran reduced the risk of CV mortality through 42 months in both the overall population (HR 0.67; 95% CI 0.47, 0.96; nominal P=0.04; event rates at 42 months [SE]: placebo 22.70

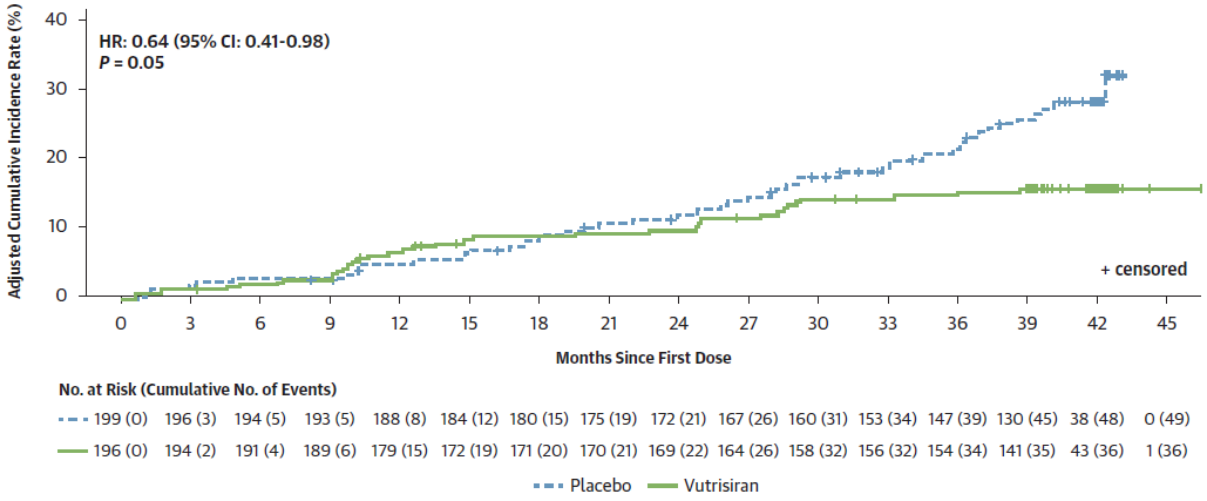
[2.40], vutrisiran 14.96 [2.07]; **Figure 7**) and monotherapy population (HR 0.64; 95% CI 0.41, 0.98; nominal P=0.05; **Figure 8**).[3]

Figure 7. Overall Population: Cumulative Rate of CV Mortality Through 42 Months.[3]



Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio.
Deaths after the end of the study were included in the analysis. Data as of November 22, 2024.
From Witteles et al.[3]

Figure 8. Monotherapy Population: Cumulative Rate of CV Mortality Through 42 Months.[3]

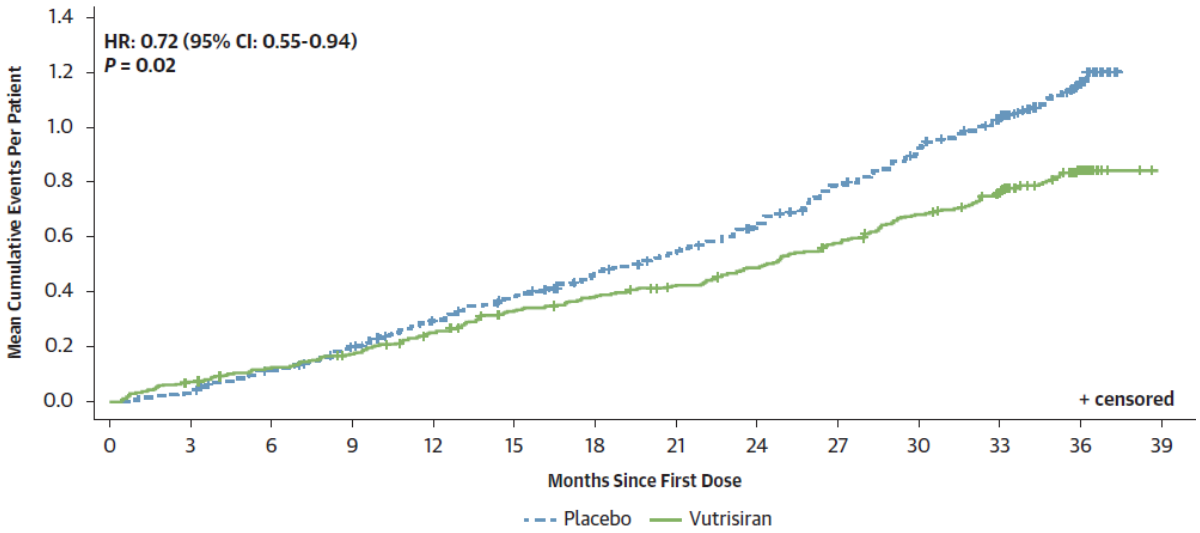


Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio.
Deaths after the end of the study were included in the analysis. Data as of November 22, 2024.
From Witteles et al.[3]

Additional Analyses of CV Mortality and CV Events Through the Double-Blind Period

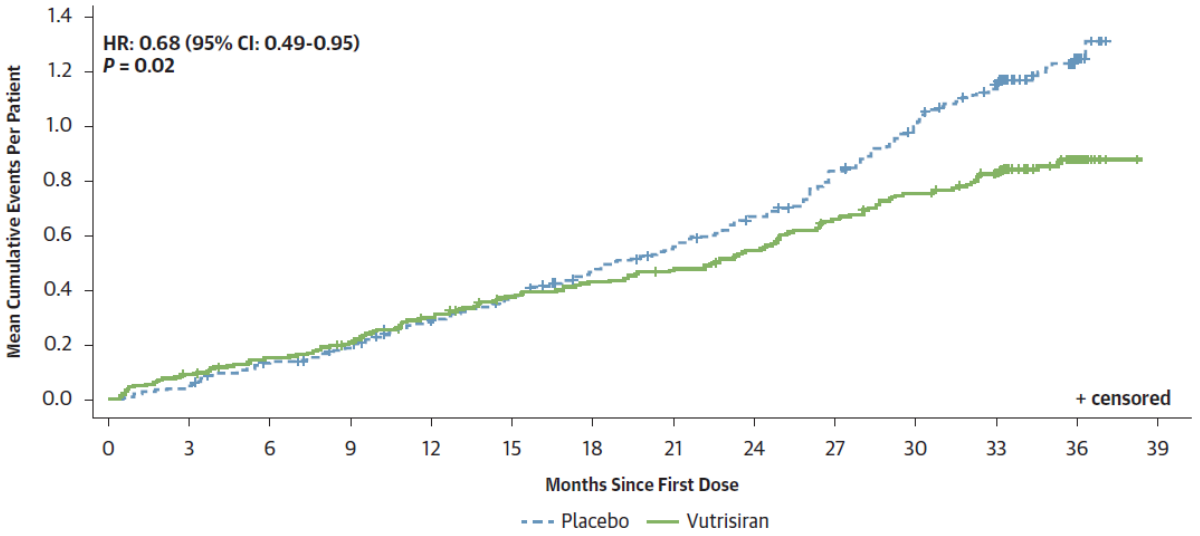
Analyses of the composite of CV mortality and CV events were analyzed using data from the double-blind period of 33-36 months (data cut of May 8, 2024). Treatment with vutrisiran reduced the risk of the composite of CV mortality and CV events through the double-blind period in both the overall population (HR 0.72; 95% CI 0.55, 0.94; nominal P=0.02; events per 100 PYs [SE]: placebo 34.18 [5.96], vutrisiran 24.77 [6.77]; **Figure 9**) and monotherapy population (HR 0.68, 95% CI 0.49, 0.95; nominal P=0.02; **Figure 10**).[3]

Figure 9. Overall Population: Mean Cumulative CV Mortality and CV Events Per Patient.[3]



Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio.
Deaths after the end of the study were included in the analysis.
From Witteles et al.[3]

Figure 10. Monotherapy Population: Mean Cumulative CV Mortality and CV Events Per Patient.[3]



Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio.
Deaths after the end of the study were included in the analysis.
From Witteles et al.[3]

SAFETY RESULTS

In the overall population, the incidence of AEs and cardiac AEs were similar between the treatment arms, and the majority of AEs with vutrisiran were mild or moderate.[2,4] A summary of the safety results during the double-blind period is presented in **Table 3**.[5]

Table 3. HELIOS-B Safety Summary.[5]

Event, n (%)	Overall Population	
	Vutrisiran (n=326)	Placebo (n=328)[a]
At least 1 AE	322 (99)	323 (98)
Any SAE[b]	201 (62)	220 (67)
Any severe AE[c]	158 (48)	194 (59)
Cardiac AEs	227 (70)	242 (74)
Cardiac SAEs	116 (36)	124 (38)
Any AE leading to treatment discontinuation	10 (3)	13 (4)
Any AE leading to death[d]	49 (15)	63 (19)

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

[a]Of the 329 patients randomized to receive placebo, 1 patient withdrew from the study and was not dosed.

[b]SAEs were defined as AEs that resulted in death, were life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators.

[c]Severe AEs were defined as AEs for which more than minimal, local, or noninvasive intervention was received; which had a severe effect on limiting self-care activities of daily living; or which had the potential for life-threatening consequences or death.

[d]Deaths that occurred after the end of study visit or after the data cut-off date were not included.

There were no clinically relevant changes in laboratory measures (including hematologic measures, blood chemistry measures, liver function tests, and renal function tests), vital signs, or electrocardiograms in either treatment arm.[2]

ABBREVIATIONS

AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; HF = heart failure; HR = hazard ratio; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; PY = person-year; SAE = serious adverse event; SE = standard error; SGLT2 = sodium-glucose co-transporter 2; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

Updated 11 September 2025

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