Vutrisiran: HELIOS-B Study

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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]
- Vutrisiran reduced the risk of the primary composite of all-cause mortality and recurrent CV events compared with placebo through the double-blind period in 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 study met all secondary endpoints with vutrisiran demonstrating statistically significant differences compared with placebo in all-cause mortality through Month 42 (i.e., double-blind period and up to 6 months in the OLE) and 6-MWT, KCCQ-OS, and NYHA class at Month 30.[1,2]
- The median (95% CI) percent reduction from baseline in serum TTR trough level at Month 30 was 86.8% (83.7%, 88.2%) in the vutrisiran group of the overall population.[3]
- There were improvements in exploratory endpoints with vutrisiran compared with placebo for NT-proBNP, troponin I, peak longitudinal strain, and EuroQoL-5D-5L at Month 30.[1]
- The majority of AEs in the study were mild or moderate and similar between treatment groups.[4]

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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 treatment period, all remaining eligible patients were allowed to receive vutrisiran in an OLE.[1]

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 Month 33–36) in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline).[1]

This endpoint was tested in parallel between the overall population and the monotherapy population and was analyzed using a modified Andersen-Gill model with a robust variance estimator (LWYY model). Heart transplantation or implantation of a left ventricular assist device, or both, were treated as deaths from any cause. Sensitivity analysis was performed using a Mantel-Haenszel-type stratified win ratio method, stratified by baseline NT-proBNP. Predefined subgroups were stratified according to age at baseline, tafamidis use at baseline, ATTR disease type (hATTR vs wtATTR), and NYHA class.[1,5]

The secondary endpoints assessed mortality, functional capacity, patient-reported health status and health-related quality of life, and the severity of clinical HF symptoms, including[1]:

- All-cause mortality up to Month 42 (double-blind period and up to 6 months of OLE data)
- Change from baseline in 6 MWT at Month 30
- Change from baseline in KCCQ-OS at Month 30
- Change from baseline in NYHA class at Month 30

The exploratory endpoints included[1]:

- Cardiac biomarkers (NT-proBNP level and troponin I level)
- Peak longitudinal strain, assessed with echocardiograms performed at Months 12, 18, 24, and 30
- Quality of life, assessed with the EuroQol-5D-5L questionnaire

The pharmacodynamic endpoint was the change from baseline in serum TTR levels at Month 30.[1]

Safety was monitored throughout the study, including assessments of[1,6]:

- AEs
- Clinical laboratory measures
- Vital signs

Inclusion and Exclusion Criteria

Select inclusion and exclusion criteria for HELIOS-B are presented in **Table 1**.[1]

Table 1. HELIOS-B Key Inclusion and Exclusion Criteria.[1]

Inclusion Criteria	Exclusion Criteria

• Age 18-85 years
• Documented diagnosis of ATTR-CM (either hATTR or wtATTR)
• Medical history of HF with at least 1 prior hospitalization for HF or clinical evidence of HF
• Patient meets one of the following criteria:
  ○ Tafamidis-naïve and not actively planning to commence treatment with tafamidis during the first 12 months following randomization; or
  ○ On tafamidis (Note: must be on-label use of commercial tafamidis per the approved indication and dose in the country of use)
• NT-proBNP >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation)
• Ability to complete ≥150 m on the 6-MWT
	• NYHA Class IV heart failure
	• NYHA Class III with NAC ATTR Stage 3
	• PND Score IIIa, IIIb, or IV
	• eGFR <30 mL/min/1.73 m^2
	• Cardiomyopathy not associated with ATTR

Abbreviations: 6-MWT = 6-minute walk test; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CV = cardiovascular; eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; wtATTR= wild-type transthyretin amyloidosis.

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

A total of 655 patients were enrolled and 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; and they were not substantially different between the overall and monotherapy populations (**Table 2**).[1]

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]

Table 2. Baseline Patient Demographics and Clinical Characteristics.[1]

Baseline Characteristics	Overall Population		Monotherapy Population	
	Vutrisiran (n=326)	Placebo (n=328)[a]	Vutrisiran (n=196)	Placebo (n=199)
Age at randomization, years, median (range)	77.0 (45-85)	76.0 (46-85)	77.5 (46-85)	76.0 (53-85)
Male sex, n (%)	299 (92)	306 (93)	178 (91)	183 (92)
Race, n (%)[b]				
White	277 (85)	275 (84)	169 (86)	169 (85)
Asian	18 (6)	19 (6)	12 (6)	15 (8)
Black/African American	23 (7)	24 (7)	10 (5)	11 (6)

Baseline Characteristics	Overall Population		Monotherapy Population	
	Vutrisiran (n=326)	Placebo (n=328)[a]	Vutrisiran (n=196)	Placebo (n=199)
Other/Not reported	8 (2)	10 (3)	5 (3)	4 (2)
wtATTR, n (%)	289 (89)	289 (88)	173 (88)	174 (87)
Time since diagnosis of ATTR, years, median (range)	0.86 (0-11.1)	1.03 (0-10.8)	0.50 (0-8.3)	0.63 (0-6.2)
Tafamidis use at baseline, n (%)	130 (40)	129 (39)	-	-
Time on tafamidis prior to trial start, months, median (range)	9.2 (1.1-65.3)	11.3 (1.1-65.5)	-	-
NYHA Class, n (%)				
I	49 (15)	35 (11)	15 (8)	12 (6)
II	250 (77)	258 (79)	172 (88)	169 (85)
III	27 (8)	35 (11)	9 (5)	18 (9)
NAC[c] ATTR stage, n (%)				
1	208 (64)	229 (70)	113 (58)	138 (69)
2	100 (31)	87 (27)	68 (35)	55 (28)
3	18 (6)	12 (4)	15 (8)	6 (3)
Laboratory parameters, median (IQR)				
NT-proBNP, pg/mL	2021 (1138-3312)	1801 (1042-3082)	2402 (1322-3868)	1865 (1067-3099)
High-sensitivity troponin I level, pg/mL	71.9 (44.9-115.9)	65.2 (41.1-105.5)	76.3 (48.4-138.8)	62.2 (39.2-105.6)

Abbreviations: ATTR = transthyretin amyloidosis; IQR = interquartile range; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; wtATTR = wild-type transthyretin amyloidosis.

[a]One patient withdrew and did not receive study drug.[5]

[b]Race was reported by the patients.

[c]NAC stages are determined on the basis of the levels of the serum biomarkers NT-proBNP and estimated glomerular filtration rate.

PRIMARY ENDPOINT

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 3**).[1]

Table 3. Primary Endpoint and Patients With At Least One Event.[1]

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
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

Endpoint	Overall Population			Monotherapy Population		
	Vutrisiran (n=326)	Placebo (n=328)	Measure of Effect	Vutrisiran (n=196)	Placebo (n=199)	Measure of Effect
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 patients in the placebo group had a heart transplantation. No patients had implantation of a left ventricular assist device.

In both the overall population and monotherapy population, similar effects were observed in all-cause mortality and recurrent CV events across all prespecified subgroups: age at baseline (<75 years vs ≥75 years), tafamidis use at baseline (yes vs no), ATTR disease type (hATTR vs wtATTR), NYHA class (I or II vs III), and baseline NT-proBNP level (≤2000 pg/ml vs >2000 pg/ml).[1]

SECONDARY ENDPOINT: ALL-CAUSE MORTALITY

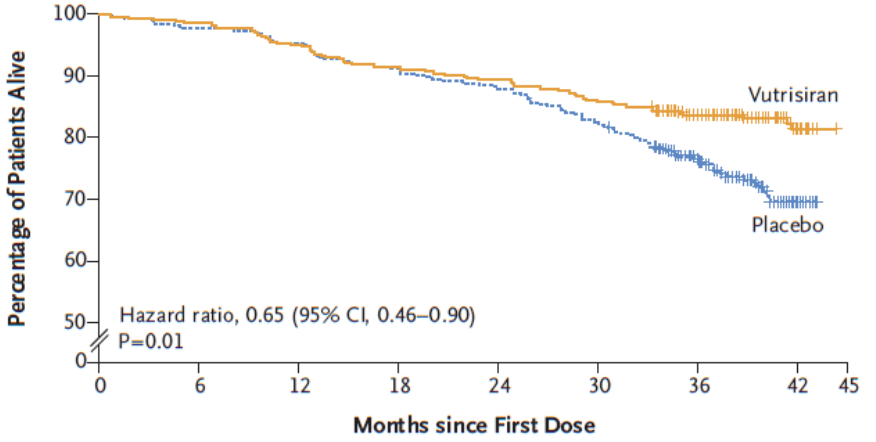
Treatment with vutrisiran reduced the risk of all-cause mortality through Month 42, as shown in **Table 4**, in both the overall population (HR 0.65; 95% CI 0.46, 0.90; P=0.01; **Figure 1**) and monotherapy population (HR 0.66, 95% CI 0.44, 0.97; P=0.045; **Figure 2**).[1]

Table 4. Secondary End Point and Patients Who Died.[1]

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 Month 42 – 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.

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

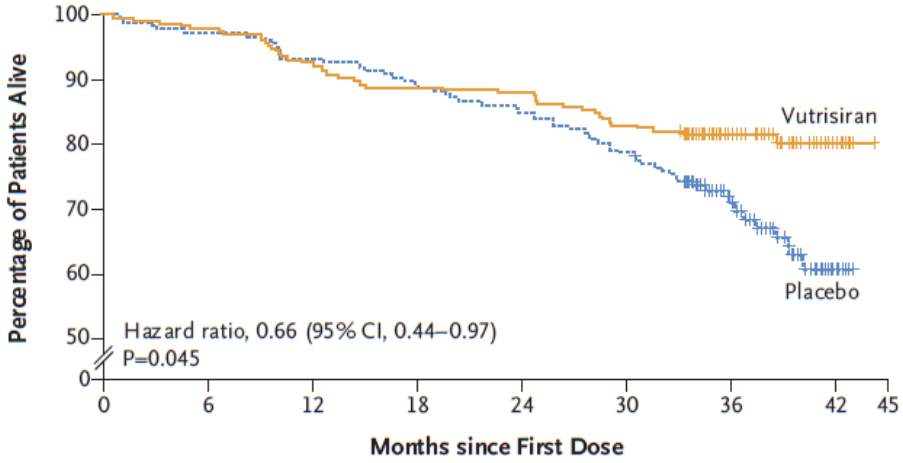


No. at Risk (cumulative no. of events)

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.
From Fontana et al.[1]

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



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.
From Fontana et al.[1]

In both the overall population and monotherapy population, similar effects were observed in all-cause mortality across all prespecified subgroups: age at baseline (<75 years vs ≥75 years), tafamidis use at baseline (yes vs no), ATTR disease type (hATTR vs wtATTR), NYHA class (I or II vs III), and baseline NT-proBNP level (≤2000 pg/ml vs >2000 pg/ml). Sensitivity analyses of the secondary endpoint were consistent with the secondary endpoint analysis.[1]

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

Analyses of all-cause mortality and CV mortality were conducted through Month 42 (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 Month 42 with the updated data cut.[2]

Treatment with vutrisiran reduced the risk of all-cause mortality through Month 42 in both the overall population (HR 0.64; 95% CI 0.46, 0.88; nominal P=0.01; event rates at Month 42 [SE]: placebo 28.95 [2.55], vutrisiran 18.36 [2.21]) and monotherapy population (HR 0.61; 95% CI 0.42, 0.90; nominal P=0.02).[2]

Treatment with vutrisiran reduced the risk of CV mortality through Month 42 in both the overall population (HR 0.67; 95% CI 0.47, 0.96; nominal P=0.04; event rates at Month 42 [SE]: placebo 22.70 [2.40], vutrisiran 14.96 [2.07]) and monotherapy population (HR 0.64; 95% CI 0.41, 0.98; nominal P=0.05).[2]

OTHER SECONDARY ENDPOINTS

A summary of the other secondary endpoints related to the effect of vutrisiran on functional capacity, patient-reported health status and health-related quality of life, and severity of clinical HF symptoms are presented in **Table 5**.[1] There was a significantly greater proportion of patients receiving vutrisiran who had maintained or improved 6-MWT, as well as KCCQ-OS, compared with placebo at Month 30.[7]

Table 5. Other Secondary Endpoints: 6-MWT, KCCQ-OS, and NYHA Class.[1]

Endpoint	Overall Population		Monotherapy Population	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
Change in 6-MWT at Month 30, meters				
LS mean change from baseline (95% CI)	-45.4 (-54.5, -36.3)	-71.9 (-81.3, -62.4)	-59.7 (-72.7, -46.7)	-91.8 (-104.4, -79.2)
LS mean difference (95% CI), P value	26.5 (13.4, 39.6), P<0.001		32.1 (14.0, 50.2), P<0.001	
Change in KCCQ-OS at Month 30, points				
LS mean change from baseline (95% CI)	-9.7 (-12.0, -7.4)	-15.5 (-18.0, -13.0)	-10.8 (-14.1, -7.5)	-19.5 (-22.9, -16.1)
LS mean difference (95% CI), P value	5.8 (2.4, 9.2), P<0.001		8.7 (4.0, 13.4), P<0.001	
Change in NYHA class at Month 30				
Stable or improved, %	68	61	66	56
Adjusted % difference (95% CI), P value	8.7 (1.3, 16.1), P=0.02		12.5 (2.7, 22.2), P=0.01	

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

Analyses of 6-MWT and KCCQ-OS

6-MWT

At Month 30, the proportion of patients who had maintained or improved 6-MWT distance (i.e., did not have a decrease from baseline of more than the cutoff values of >7 m, >15 m, or >35 m) was significantly greater compared with placebo across the cutoff values in both the overall population (7 m [49.6%

vs 33.2%], 15 m [55.5% vs 38.6%], and 35 m [68.5% vs 51.6%]) and monotherapy population (7 m [46.9% vs 28.2%], 15 m [53.1% vs 31.5%], and 35 m [62.3% vs 42.7%]).[7]

KCCQ-OS

At Month 30, the proportion of patients who had maintained or improved KCCQ-OS (i.e., did not have a decrease from baseline of more than the cutoff values of >5 points or >10 points) was significantly greater compared with placebo across the cutoff values in both the overall population (>5 points [63.5% vs 46.6%] and >10 points [74.6% vs 60.7%]) and monotherapy population (>5 points [64.7% vs 38.2%] and >10 points [73.4% vs 51.9%]).[7]

SELECT EXPLORATORY ENDPOINTS

Select exploratory endpoints included levels of cardiac biomarkers NT-proBNP and troponin I, echocardiographic parameters, and quality of life assessed with the EuroQoL-5D-5L questionnaire.[5,6,8]

Cardiac Biomarkers

Treatment with vutrisiran led to a 32% relative reduction from baseline in NT-proBNP and troponin I (geometric mean fold-change ratio: 0.68) to Month 30 when compared with placebo in the overall population (**Table 6**). The treatment effect of vutrisiran on NT-proBNP and troponin I was observed at Month 6 and increased over time. NT-proBNP and troponin I results were consistent across all prespecified subgroups in both the overall population and monotherapy population.[8]

Echocardiographic Parameters

Between-group differences were observed at Month 12 in LV diastolic function (as measured by LS mean change from baseline in E/e' ratio) and at Month 18 in LV systolic function (as measured by LS mean change from baseline in LV ejection fraction, GLS, and LV stroke volume) and RV S', with continued improvement in the vutrisiran group compared with the placebo group through Month 30 in the overall population.[9]

At Month 30, the LS mean change from baseline in LV wall thickness and LV mass index were improved in the vutrisiran group compared with the placebo group in the overall population (**Table 6**).[9]

Table 6. Change from Baseline in Select Exploratory Endpoints at Month 30.[5,8,9]

Endpoint	Overall Population		Monotherapy Population	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
NT-proBNP fold-change				
Geometric mean (95% CI)	1.19 (1.11, 1.28)	1.75 (1.62, 1.89)	1.30 (1.17, 1.45)	2.28 (2.04, 2.55)
Geometric mean fold-change ratio (95% CI)	0.68 (0.61, 0.76)		0.57 (0.49, 0.66)	
Troponin I fold-change				
Geometric mean (95% CI)	0.94 (0.88, 1.00)	1.37 (1.28, 1.47)	1.01 (0.92, 1.12)	1.85 (1.68, 2.03)
Geometric mean fold-change ratio (95% CI)	0.68 (0.62, 0.75)		0.55 (0.48, 0.63)	
Measures of LV structure				
Mean LV wall thickness, mm				

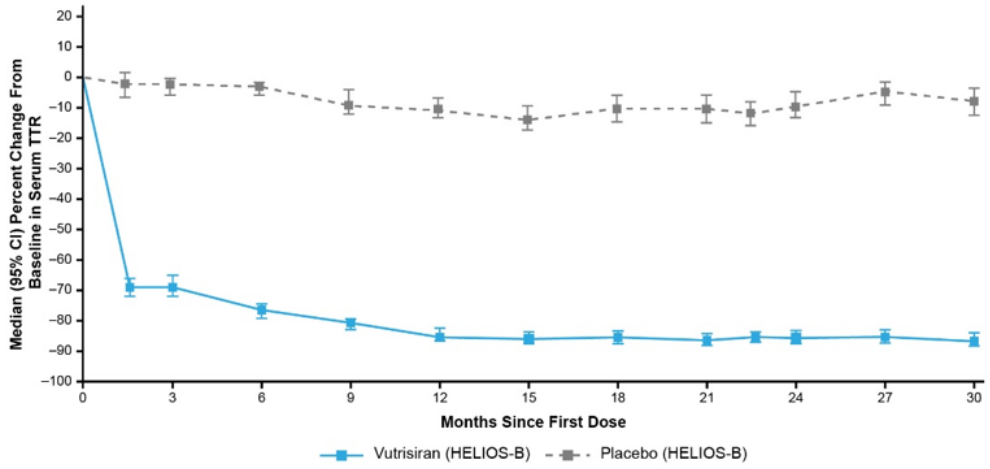
Endpoint	Overall Population		Monotherapy Population	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
LS mean (SEM)	0.5 (0.1)	0.9 (0.1)	0.4 (0.2)	1.1 (0.2)
LS mean difference (95% CI)	-0.4 (-0.8, 0.0)		-0.8 (-1.4, -0.2)	
LV mass index, g/m^2				
LS mean (SEM)	14.8 (2.5)	25.4 (2.8)	11.8 (3.7)	29.8 (4.2)
LS mean difference (95% CI)	-10.6 (-18.0, -3.3)		-18.0 (-28.9, -7.1)	
Measures of LV diastolic function				
TDI lateral e', mm/s				
LS mean (SEM)	5.3 (1.1)	-0.2 (1.1)	4.3 (1.4)	-4.5 (1.4)
LS mean difference (95% CI)	5.5 (2.4, 8.5)		8.7 (4.8, 12.6)	
Lateral E/e'				
LS mean (SEM)	-1.08 (0.3)	0.7 (0.3)	-1.0 (0.4)	1.7 (0.5)
LS mean difference (95% CI)	-1.8 (-2.7, -1.0)		-2.7 (-3.9, -1.6)	
Measures of LV systolic function				
LV ejection fraction, %				
LS mean (SEM)	-4.1 (0.6)	-6.2 (0.7)	-3.6 (0.8)	-5.9 (0.9)
LS mean difference (95% CI)	2.0 (0.3, 3.7)		2.3 (-0.1, 4.6)	
Absolute GLS, %				
LS mean (SEM)	-1.0 (0.2)	-2.2 (0.2)	-1.1 (0.3)	-2.4 (0.3)
LS mean difference (95% CI)	1.2 (0.7, 1.7)		1.3 (0.6, 2.0)	
LV stroke volume, mL				
LS mean (SEM)	-2.4 (0.9)	-6.5 (0.8)	-2.2 (1.2)	-6.4 (1.2)
LS mean difference (95% CI)	4.1 (1.7, 6.4)		4.2 (0.9, 7.4)	
Measures of RV and pulmonary pressure				
RV S', mm/s				
LS mean (SEM)	-2.6 (1.5)	-9.6 (1.5)	-6.3 (2.0)	-13.4 (2.0)
LS mean difference (95% CI)	7.0 (2.8, 11.2)		7.1 (1.5, 12.7)	
EuroQoL-5D-5L index change from baseline at Month 30				
LS mean (SEM)	-0.03 (0.008)	-0.06 (0.008)	-0.03 (0.011)	-0.08 (0.011)
LS mean difference (95% CI)	0.03 (0.01, 0.05)		0.05 (0.02, 0.08)	

Abbreviations: CI = confidence interval; E/A = ratio of early to late diastolic transmitral inflow velocities; E/e' = ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; EuroQoL-5D-5L = EuroQoL 5-dimensions-5 levels; GLS = global longitudinal strain; LS = least squares; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide; RV = right ventricular; RV S' = right ventricular systolic myocardial velocity; SEM = standard error of the mean; TDI lateral e' = lateral peak early diastolic mitral annular tissue velocity.

PHARMACODYNAMIC ENDPOINTS

In the overall population, the median (95% CI) percent reduction from baseline in serum TTR trough level at Month 30 was 86.8% (83.7%, 88.2%) in the vutrisiran group and 7.9% (3.2%, 12.2%) in the placebo group (**Figure 3**).[3]

Figure 3. Median Percent Change from Baseline in Serum TTR Level Through Month 30.[3]



Abbreviations: CI = confidence interval; TTR = transthyretin.
Data on file [3]

SAFETY RESULTS

In the overall population, the proportion of patients with at least one AE and the incidence of AEs and cardiac AEs was similar between treatment groups. The majority of AEs were mild or moderate in severity.[4] A summary of the safety results during the double-blind period are presented in **Table 7**.[5]

Table 7. Safety Summary.[5]

Event, n (%)	Overall Population	
	Vutrisiran (n=326)	Placebo (n=328)[a]
At least 1 AE	322 (99)	323 (98)
AEs occurring in ≥15% of patients in either treatment group		
Cardiac failure	101 (31)	128 (39)
COVID-19	87 (27)	99 (30)
Atrial fibrillation	69 (21)	68 (21)
Gout	48 (15)	51 (16)
Dyspnea	43 (13)	51 (16)
Fall	42 (13)	69 (21)
Any SAE[b]	201 (62)	220 (67)
Any severe AE[c]	158 (48)	194 (59)
SAEs occurring in ≥5% of patients in either treatment group		
Cardiac failure	38 (12)	57 (17)
Atrial fibrillation	26 (8)	20 (6)
Cardiac failure acute	13 (4)	18 (5)
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; COVID-19 = coronavirus disease 2019; 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 group.[1]

ABBREVIATIONS

6-MWT = 6-minute walk test; AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; COVID-19 = coronavirus disease 2019; CV = cardiovascular; E/A = ratio of early to late diastolic transmitral inflow velocities; E/e' = ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; eGFR = estimated glomerular filtration rate; EuroQoL-5D-5L = EuroQoL 5-dimensions-5 levels; GLS = global longitudinal strain; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; HR = hazard ratio; IQR = interquartile range; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; LV = left ventricular; LWYY = Lin-Wei-Yang-Ying; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; PND = polyneuropathy disability; RV = right ventricular; RV S' = right ventricular systolic myocardial velocity; SAE = safety adverse event; SE = standard error; SEM = standard error of the mean; SGLT2 = sodium-glucose cotransporter-2; TDI lateral e' = lateral peak early diastolic mitral annular tissue velocity; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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