Vutrisiran: Concomitant Use with Tafamidis

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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]
  - Patients were excluded from the study if they were currently taking tafamidis; if previously on tafamidis, the patient must have completed a 14-day wash-out prior to dosing.[2]
- 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.[3]
  - Patients who received tafamidis at baseline were eligible to be included in the study (baseline tafamidis subgroup). Concomitant tafamidis use at baseline was 40% and 39% in the vutrisiran and placebo groups, respectively.[3]
  - During the double-blind period, tafamidis drop-in on the monotherapy population (defined as patients who did not receive tafamidis at baseline) was 22% and 21% for the vutrisiran and placebo groups, respectively.[3]
  - Study participants were not randomized by baseline tafamidis use; therefore, a randomized comparison of vutrisiran monotherapy versus tafamidis monotherapy cannot be made.[3]
  - In a prespecified analysis of the baseline tafamidis subgroup, treatment with vutrisiran resulted in a HR of 0.79 (95% CI 0.51, 1.21) for the primary composite endpoint of all-cause mortality and recurrent CV events during the double-blind exposure period and a HR of 0.59 (95% CI 0.32, 1.08) for the secondary endpoint of all-cause mortality through 42 months.[3]
    - Additional analyses of all-cause mortality and CV mortality were conducted through 42 months using an updated data cut (November 22, 2024). [4]
  - Additional endpoints assessed in the baseline tafamidis subgroup included the change from baseline in 6-MWT, KCCQ-OS, NT-proBNP, troponin I, and echocardiographic parameters at 30 months.[5–7]
  - In the overall population, the proportion of patients with at least one AE was similar between treatment groups, and the majority of AEs with vutrisiran were mild or moderate. Cardiac AEs occurred at similar or lower rates with vutrisiran compared with placebo.[8]

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HELIOS-B 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.[3]

Select Inclusion Criteria

Patients were eligible to be included in the study if all inclusion criteria applied, including patients meeting one of the following criteria[9]:

- Tafamidis-naïve and not actively planning to commence treatment with tafamidis during the first 12 months following randomization (in addition to patients who have never taken tafamidis, those who have previously been on tafamidis and have not received any tafamidis for at least 30 days before the screening visit will be considered tafamidis-naïve for purposes of this study)
- On tafamidis (must be on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use)

Patients who were on tafamidis at baseline (per the inclusion criteria listed above) were permitted, if medically appropriate in the opinion of the Investigator, to remain on tafamidis throughout the study.[9]

Select Exclusion Criteria

Patients were excluded from the study if the following criteria applied[9]:

- Tafamidis-naïve patients for whom the Investigator actively plans or anticipates commencing treatment with tafamidis either during the Screening Period or the first 12 months following randomization, taking into consideration clinical status, patient preference, and/or commercial availability of tafamidis

Randomization was stratified according to tafamidis use at baseline (yes vs. no). 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 treatment period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline).[3]

After study enrollment, patients who were not receiving tafamidis at baseline could initiate tafamidis (tafamidis drop-in) if considered to be necessary by the Investigator, per the study protocol.[9]

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Clinical characteristics of the baseline tafamidis subgroup are summarized in **Table 1**.[6]

Table 1. Baseline Characteristics of the Overall Population and Baseline Tafamidis Subgroup.[6]

Characteristic	Overall Population		Baseline Tafamidis Subgroup	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=130)	Placebo (n=129)
Age at randomization, years	77.0 (45-85)	76.0 (46-85)	77.0 (45-85)	75.0 (46-85)
Wild-type ATTR-CM[a]	289 (88.7)	289 (88.1)	116 (89.2)	115 (89.1)
Time since diagnosis, years	0.9 (0-11.1)	1.0 (0.0-10.8)	1.3 (0.0-11.1)	1.53 (0.1-10.8)
LVEF, %	55.6±12.7	55.9±12.4	56.9±12.8	56.3±12.8
Global longitudinal strain, %	14.0±3.5	14.0±3.5	13.9±3.5	13.5±3.4
LV wall thickness, cm	1.82±0.26	1.82±0.27	1.82±0.26	1.80±0.24
NT-proBNP, pg/mL (IQR)	2021 (1138-3312)	1801 (1042-3082)	1760 (1085-2685)	1746 (968-2906)
Troponin I, pg/mL (IQR)	71.9 (44.9-115.9)	65.2 (41.1-105.5)	64.9 (42.9-93.2)	68.3 (44.8-104.6)

Abbreviations: ATTR-CM = transthyretin amyloidosis with cardiomyopathy; IQR = interquartile range; LV = left ventricle; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; SD = standard deviation; TTR = transthyretin.

Values are median (minimum-maximum range), n (%), mean ±SD, or median (Q1-Q3), unless otherwise indicated.

[a]Patients with hereditary ATTR-CM had 13 TTR variants, with the most common being V122I (64%), T60A (11%), and V30M (8%).

Concomitant Medications

At baseline, 130 of 326 patients (40%) in the vutrisiran arm and 129 of 328 patients (39%) in the placebo arm were on tafamidis.[3] The monotherapy population comprised 196 patients (60%) in the vutrisiran arm and 199 patients (60%) in the placebo arm who were not on tafamidis at baseline.[3] Tafamidis drop-in on the monotherapy population during the double-blind period is shown in **Table 2**.[8]

Table 2. Concomitant Tafamidis Use During the Double-Blind Period.[8,a]

Tafamidis, n (%)	Vutrisiran (n=326)	Placebo (n=328)[b]
Use at baseline	130 (40)	129 (39)
Drop-in on monotherapy population	44/196 (22)	41/199 (21)
Time from study start to initial drop-in dose, months, median (range)	17.7 (6.6-39.1)	17.0 (1.5-33.8)

[a]Double-blind period consisted of a variable follow-up of 33 to 36 months.

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

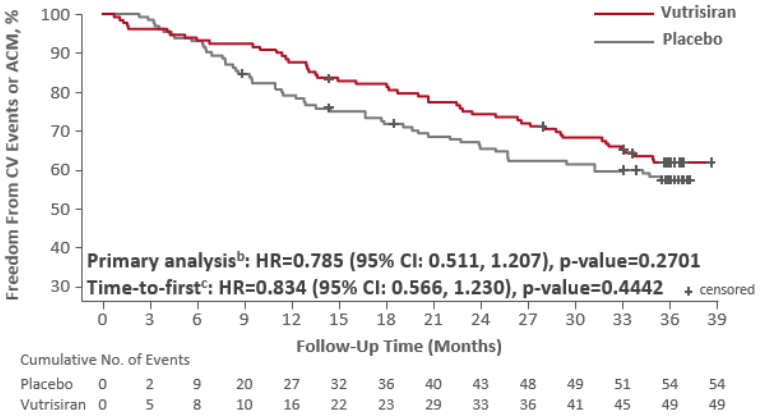
In the overall population, baseline use of SGLT2 inhibitors was 3% in both treatment groups; and baseline use of diuretics was 80% and 79% in the vutrisiran and placebo groups, respectively.[8]

PRIMARY ENDPOINT

Study participants were not randomized by baseline tafamidis use; therefore, a randomized comparison of vutrisiran monotherapy versus tafamidis monotherapy cannot be made.[3]

Treatment with vutrisiran reduced the risk of the primary composite endpoint of all-cause mortality and recurrent CV events when compared with placebo in the overall population (HR 0.72; 95% CI 0.56, 0.93; P=0.01). In a prespecified analysis of the baseline tafamidis subgroup, treatment with vutrisiran compared with placebo resulted in a HR of 0.79 (95% CI 0.51, 1.21; P=0.4) in all-cause mortality and recurrent CV events (**Figure 1**).[3,10]

Figure 1. Time to First CV Event or All-Cause Mortality in the Baseline Tafamidis Subgroup.[10,a]

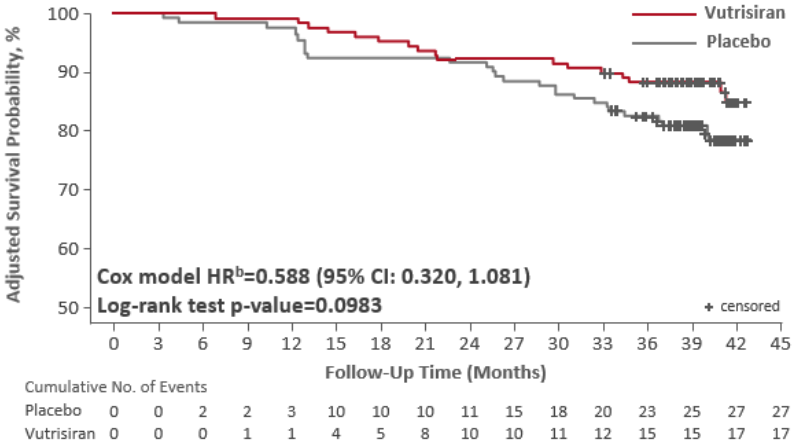


Abbreviations: ACM = all-cause mortality; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; IPTW = inverse probability of treatment weighting; LWYY = Lin, Wei, Yang, Ying; PH = proportional hazard.
All-cause mortality includes heart transplantation and left ventricular assist device placement.
[a]Based on IPTW-adjusted Kaplan-Meier curves.
[b]Primary analysis based on modified Andersen-Gill model, also known as LWYY.
[c]Time to first event HR derived from Cox PH model, p-value derived from Log-rank test.
From Fontana et al.[10]

SECONDARY ENDPOINT: ALL CAUSE MORTALITY

In the overall population, 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).[3] In the baseline tafamidis subgroup, treatment with vutrisiran compared with placebo resulted in a HR of 0.59 (95% CI 0.32, 1.08; P=0.1) in all-cause mortality through 42 months (**Figure 2**).[10]

Figure 2. Time to All-Cause Mortality in the Baseline Tafamidis Subgroup.[10,a]



Abbreviations: CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; OLE = open-label extension; PH = proportional hazard.
[a]Based on IPTW-adjusted Kaplan-Meier curves.
[b]Time to all-cause mortality included data from the double-blind period and up to 6 months in the OLE; Deaths after end of the study were included in the analysis. HR derived from Cox PH model.
Data cutoff: May 8, 2024.
From Fontana et al.[10]

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.[4]

In the overall population, treatment with vutrisiran reduced the risk of all-cause mortality (HR 0.64; 95% CI 0.46, 0.88; P=0.01) and the risk of CV mortality (HR 0.67; 95% CI 0.47, 0.96; P=0.04). The baseline tafamidis subgroup was not powered for statistical analysis. In the baseline tafamidis subgroup, treatment with vutrisiran compared with placebo resulted in a HR of 0.66 (95% CI 0.37, 1.20) in all-cause mortality and a HR of 0.75 (95% CI 0.38, 1.47) in CV mortality through 42 months.[4]

OTHER SECONDARY ENDPOINTS

Post-Hoc Analysis of 6-MWT at 30 Months

In the overall population, the LS mean change from baseline in the secondary endpoint of 6-MWT was -45.4 m in the vutrisiran arm and -71.9 m in the placebo arm at 30 months. The LSMD in change from baseline in 6-MWT (vutrisiran vs. placebo) was 26.5 m (95% CI 13.4, 39.6; P<0.001).[3] In the baseline tafamidis subgroup, the LSMD in change from baseline in 6-MWT (vutrisiran vs. placebo) at 30 months was 18.44 m (95% CI 0.42, 36.47). The baseline tafamidis subgroup analysis for 6-MWT was not powered for statistical significance.[5]

A post-hoc analysis was conducted to evaluate the proportion of patients with a maintenance or improvement in 6-MWT from baseline to 30 months. Maintenance or improvement was defined as not having a decrease from baseline in 6-MWT by cutoff values of greater than 7 m, 15 m, or 35 m.[5]

In the overall population, the following proportion of patients treated with vutrisiran had maintained or improved 6-MWT distance at 30 months compared with placebo across the cutoffs applied: 7 m (49.6% vs. 33.2%), 15 m (55.5% vs. 38.6%), and 35 m (68.4% vs. 51.6%; nominal P<0.001 for all).[5]

In the baseline tafamidis subgroup, the following proportion of patients treated with vutrisiran had maintained or improved 6-MWT distance at 30 months compared with placebo across the cutoffs applied: 7 m (52.8% vs 39.4%), 15 m (58.3% vs. 47.5%), and 35 m (75.9% vs. 62.6%; nominal P<0.05).[5]

Post-Hoc Analysis of KCCQ-OS at 30 Months

In the overall population, the LS mean change from baseline in the secondary endpoint of KCCQ-OS was -9.7 points in the vutrisiran arm and -15.5 points in the placebo arm. The LSMD in change from baseline in KCCQ-OS (vutrisiran vs. placebo) was 5.8 points (95% CI 2.4, 9.2; nominal P<0.001).[3] In the baseline tafamidis subgroup, the LSMD in change from baseline in KCCQ-OS at 30 months between the vutrisiran and placebo groups was 1.75 points (95% CI -2.85, 6.35). The baseline tafamidis subgroup analysis for KCCQ-OS was not powered for statistical significance.[5]

A post-hoc analysis was conducted to evaluate the proportion of patients with a maintenance or improvement in KCCQ-OS from baseline to 30 months. Maintenance or improvement was defined as not having a decrease from baseline in KCCQ-OS by cutoff values of greater than 5 points or 10 points.[5]

In the overall population, the following proportion of patients treated with vutrisiran had maintained or improved KCCQ-OS at 30 months compared with placebo across the cutoffs applied: 5 points (63.5% vs. 46.6%; nominal P<0.001) and 10 points (74.6% vs. 60.7%; nominal P<0.01).[5]

In the baseline tafamidis subgroup, the following proportion of patients treated with vutrisiran had maintained or improved KCCQ-OS at 30 months compared with placebo across the cutoffs applied: 5 points (61.9% vs. 57.3%) and 10 points (76.1% vs. 71.8%).[5]

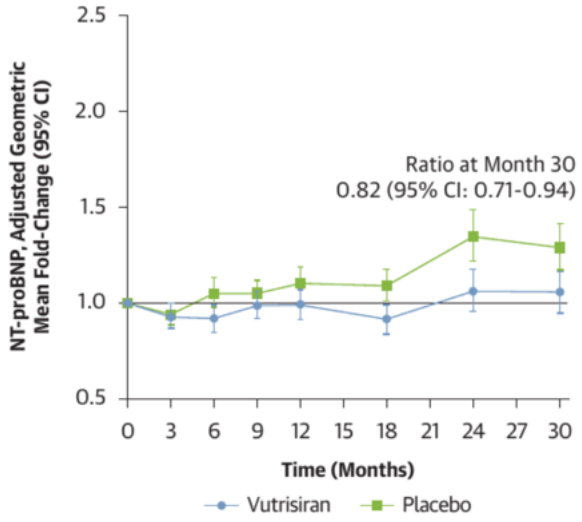
SELECT EXPLORATORY ENDPOINTS

Cardiac Biomarkers: NT-proBNP and Troponin I at 30 Months

Select exploratory endpoints assessed in the baseline tafamidis subgroup included the adjusted geometric mean fold-change from baseline in NT-proBNP and troponin I at 30 months.[6]

In the overall population, treatment with vutrisiran when compared with placebo resulted in an adjusted geometric mean-fold change ratio of 0.68 (95% CI 0.61, 0.76; P<0.0001) for NT-proBNP from baseline to 30 months. In the baseline tafamidis subgroup, treatment with vutrisiran compared with placebo resulted in an adjusted geometric mean fold-change ratio of 0.82 (95% CI 0.71, 0.94; P=0.0045) for NT-proBNP from baseline to 30 months (**Figure 3**).[6]

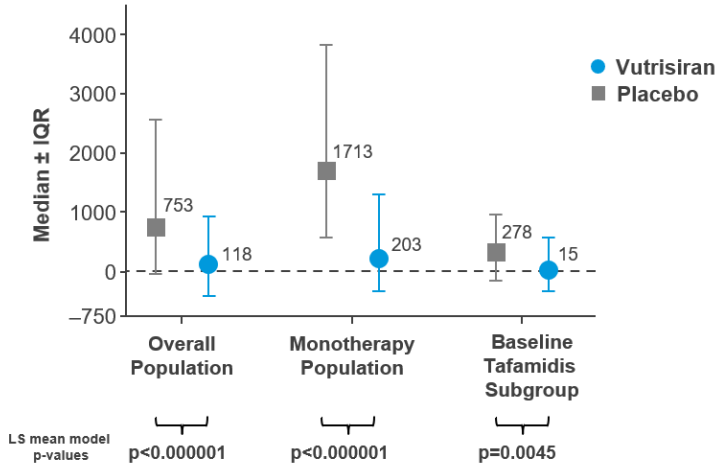
Figure 3. NT-proBNP at 30 Months in the Baseline Tafamidis Subgroup.[6]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; LS = least squares; MMRM = mixed models for repeated measures; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.
Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, type of ATTR, and age group.
From Maurer et al.[6]

In the baseline tafamidis subgroup, the median change from baseline in NT-proBNP at 30 months was 15 ng/L in the vutrisiran arm and 278 ng/L in the placebo arm (**Figure 4**).[11]

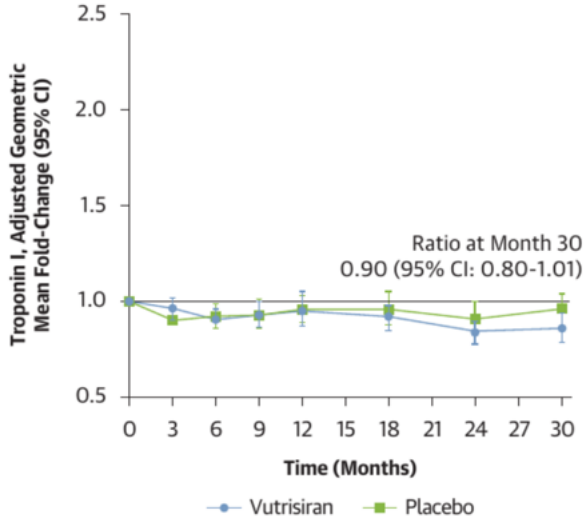
Figure 4. Median Change from Baseline in NT-ProBNP at 30 Months in the Baseline Tafamidis Subgroup.[11]



Abbreviations: IQR = interquartile range; LS = least squares; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.
From Maurer et al.[11]

In the overall population, treatment with vutrisiran compared with placebo resulted in an adjusted geometric mean fold-change ratio of 0.68 (95% CI 0.62, 0.75; P<0.0001) for troponin I from baseline at 30 months. In the baseline tafamidis subgroup, treatment with vutrisiran compared with placebo resulted in an adjusted geometric mean fold-change ratio of 0.90 (95% CI 0.80, 1.01; P=0.0849) in troponin I from baseline at 30 months (**Figure 5**).[6]

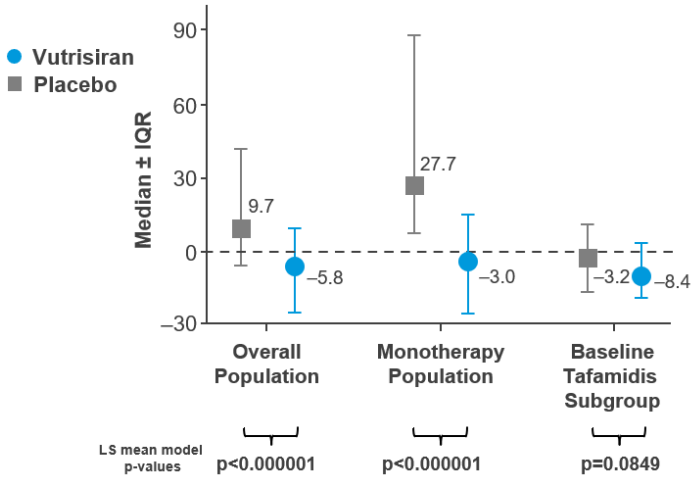
Figure 5. Troponin I at 30 Months in the Baseline Tafamidis Subgroup.[6]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; LS = least squares; MMRM = mixed models for repeated measures.
Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, type of ATTR, and age group.
From Maurer et al.[6]

In the baseline tafamidis subgroup, the median change from baseline in troponin I at 30 months was -8.4 ng/L in the vutrisiran arm and -3.2 ng/L in the placebo arm (**Figure 6**).[11]

Figure 6. Median Change from Baseline in Troponin I at 30 Months.[11]



Abbreviations: IQR = interquartile range; LS = least squares.
From Maurer et al.[11]

Echocardiographic Parameters at 30 Months

Changes from baseline in mean LV wall thickness and GLS at 30 months were prespecified exploratory endpoints in the HELIOS-B study and other echocardiographic parameters are considered exploratory. Missing data were not imputed. The analyses were not powered to evaluate treatment differences in the baseline tafamidis subgroup.[7]

In the baseline tafamidis subgroup, changes from baseline in select echocardiographic parameters at 30 months are summarized in **Table 3**.[7]

Table 3. LS Mean Changes from Baseline in Select Echocardiographic Parameters at 30 Months in the Baseline Tafamidis Subgroup.[7]

Echocardiographic Parameter	Baseline Tafamidis Subgroup			
	n	Vutrisiran (n=130)	Placebo (n=129)	Placebo-corrected treatment difference (95% CI)
LV structure				
LV wall thickness, mm	257	0.6 (0.2)	0.5 (0.2)	0.1 (-0.1, 0.6)
LV mass index, g/m^2	255	18.6 (3.2)	19.9 (3.6)	-1.3 (-10.8, 8.3)
LV diastolic function				
TDI lateral *e'*, mm/s	247	6.6 (1.7)	5.9 (1.7)	0.7 (-4.1, 5.5)
Lateral *E/e'*	246	-1.1 (0.4)	-0.6 (0.5)	-0.5 (-1.7, 0.7)
LV systolic function				
LVEF, %	253	−4.8 (0.8)	−6.4 (0.9)	1.5 (−0.9, 4.0)
Absolute GLS, %	259	−0.8 (0.2)	−1.9 (0.3)	1.1 (0.4, 1.8)
Stroke volume, mL	243	−2.6 (1.3)	−6.3 (1.1)	3.7 (0.4, 7.1)
RV and pulmonary pressure				
RV *S'*, mm/s	251	2.8 (2.3)	−4.0 (2.4)	6.8 (0.3, 13.3)

Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; E/e' = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; LS = least squares; LV = left ventricle; LVEF = left ventricular ejection fraction; RV = right ventricular; RV S' = right ventricular systolic myocardial velocity; SEM = standard error of the mean. Results are reported as the LS mean difference (SEM) derived from repeated measures models with baseline as a covariate and fixed-effect terms including the treatment group, visit, treatment-by-visit interaction, ATTR disease type, and age group.

SAFETY RESULTS

In the overall population, the incidence of AEs and cardiac AEs were similar between the treatment groups, and the majority of AEs with vutrisiran were mild or moderate.[3,10] A summary of the safety results during the double-blind period is presented in **Table 4**.[8]

Table 4. HELIOS-B Safety Summary.[8]

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.

ABBREVIATIONS

6-MWT = 6-minute walk test; ACM = all-cause mortality; AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; E/e' = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; hATTR = hereditary transthyretin amyloidosis; GLS = global longitudinal strain; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; HR = hazard ratio; IPTW = inverse probability of treatment weighting; IQR = interquartile range; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least-squares; LSMD = least squares mean difference; LV = left ventricle; LVEF = left ventricular ejection fraction; LWYY = Lin, Wei, Yang, Ying; MMRM = mixed models for repeated measures; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; OLE = open-label extension; PH = proportional hazard; RV = right ventricular; RV S' = right ventricular systolic myocardial velocity; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; SGLT2 = sodium-glucose cotransporter-2; TDI = tissue Doppler imaging; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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