Vutrisiran: Cardiac Biomarkers in HELIOS-B

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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 including both hATTR and wtATTR.[1]
- The study met the primary endpoint and vutrisiran reduced the risk of all-cause mortality and recurrent CV events compared with placebo during the double-blind period (up to 36 months). The HR was 0.72 (95% CI 0.56, 0.93; P=0.01) in the overall population and 0.67 (95% CI 0.49, 0.93; P=0.02) in the monotherapy population.[1]
- In the overall population, the ratio of geometric mean fold-changes from baseline favored vutrisiran for NT-proBNP (ratio 0.68; 95% CI: 0.61-0.76) and for troponin I (ratio 0.68; 95% CI: 0.62-0.75). In the monotherapy population, the geometric mean fold-change ratio for NT-proBNP was 0.57 (95% CI: 0.49-0.66) and 0.55 (95% CI: 0.48-0.63) for troponin I. In the baseline tafamidis subgroup, the geometric mean fold change ratio for NT-proBNP was 0.82 (95% CI: 0.71-0.94) and 0.90 (95% CI: 0.80-1.01) for troponin I.[2]
- In the overall population, the median change from baseline in the vutrisiran arm for NT-proBNP at month 30 was 118 pg/mL (Q1-Q3: -419 to 911 pg/mL) and for troponin I was -5.8 pg/mL (Q1-Q3: -25.0 to 10.0 pg/mL).[2]
- The ratio of adjusted geometric mean fold-change from baseline (95% CI) for NT-proBNP and troponin I at month 30 favored vutrisiran over placebo across all subgroups.[2]
- The majority of AEs in the trial were mild or moderate and similar between treatment groups.[3]

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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).[1] After the double-blind period, all remaining eligible patients were allowed to receive vutrisiran in an OLE for up to 24 months.[4]

Study Endpoints

The primary endpoint was the composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) at month 33 or 36, which was analyzed using a modified Andersen-Gill model with a robust variance estimator (LWYY model). The primary endpoint was analyzed in both the overall study population and the vutrisiran monotherapy population (patients who were not on tafamidis at baseline). These endpoints were tested in parallel. 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 tafamidis use at baseline, ATTR disease type (wtATTR versus hATTR), NYHA class, and age at baseline.[1,5]

Select exploratory endpoints included levels of cardiac biomarkers NT-proBNP and troponin I. These were measured using validated assays at a central laboratory in blood samples taken from patients at baseline and months 3, 6, 12, 18, 24, and 30. Associations between levels of NT-proBNP or troponin I and the primary endpoint and the secondary endpoint were explored. Change in levels of NT-proBNP and troponin I from baseline to month 30 were also assessed, which were the pre-specified exploratory endpoints in HELIOS-B.[2]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

There were 326 patients randomly assigned to the vutrisiran group and 329 patients to the placebo group in the overall population. Of the patients from the overall population, 60% (196 of 326 patients) in the vutrisiran group and 60% (199 of 329 patients) in the placebo group were not taking tafamidis at baseline (monotherapy population). Patient baseline characteristics were comparable between the groups, except for higher NT-proBNP and troponin I values in the vutrisiran group than the placebo group in the monotherapy population as shown in **Table 1**. Baseline demographics and clinical characteristics were not substantially different between the monotherapy population and overall population. Forty-four of 196 (22%) patients in the vutrisiran group and 41 of 199 (21%) patients in the placebo group started tafamidis after randomization in the monotherapy population.[1] In the overall population, 3% of patients in both treatment arms were receiving SGLT2 inhibitors at baseline. Eighty percent of patients in the vutrisiran arm and 79% of patients in the placebo arm had use of diuretics at baseline.[5] Of the 478 patients who completed the double-blind period, 466 patients (97%) entered the OLE.[4]

Table 1. Baseline Characteristics in HELIOS-B.[2]

Characteristic	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Vutrisiran (N=326)	Placebo (N=328)	Vutrisiran (n=196)	Placebo (n=199)	Vutrisiran (n=130)	Placebo (n=129)
Age at randomization, years	77.0 (45-85)	76.0 (46-85)	77.5 (46-85)	76.0 (53-85)	77.0 (45–85)	75.0 (46-85)
Male	299 (91.7)	306 (93.3)	178 (90.8)	183 (92.0)	121 (93.1)	123 (95.3)
Wild-type ATTR-CM[a]	289 (88.7)	289 (81.1)	173 (88.3)	174 (87.4)	116 (89.2)	115 (89.1)
Time since diagnosis, years	0.9 (0-11.1)	1.0 (0-10.8)	0.5 (0-8.3)	0.6 (0-6.2)	1.3 (0-11.1)	1.53 (0.1-10.8)
LVEF, %	55.6±12.7	55.9±12.4	54.8±12.6	55.7±12.1	56.9±12.8	56.3±12.8
Global longitudinal strain, %	14.0±3.5	14.0±3.5	14.04±3.4	14.3±3.5	13.9±3.5	13.5±3.4
LV wall thickness, cm	1.82±0.26	1.82±0.27	1.82±0.27	1.83±0.29	1.82±0.26	1.80±0.24
NT-proBNP, pg/mL	2021 [1138-3312]	1801 [1042-3082]	2402 [1322-3868]	1865 [1067-3099]	1760 [1085-2685]	1746 [968-2906]
Range	322-8,892	317-7988	370-8892	335-7988	322-7541	317-6530
Troponin I, 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]	64.9 [42.9-93.2]	68.3 [44.8-104.6]
Range	10.0-8712.0	10.0-30827.7	10.0-2304.2	10.0-30827.7	11.2-8712	10.0-631.5

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.

Values are median (minimum-maximum range), n (%), mean ± SD, or median [Q1-Q3]. [a]Patients with hereditary or variant ATTR-CM had 13 TTR variants, with the most common being V122I (64%), T60A (11%), and V30M (8%).

EFFICACY RESULTS

Primary Endpoint: All-Cause Mortality and Recurrent CV Events

Treatment with vutrisiran reduced the risk of all-cause mortality and recurrent CV events; HR 0.72 (95% CI 0.56, 0.93; P=0.01) in the overall population and HR 0.67 (95% CI 0.49, 0.93; P=0.02) in the monotherapy population. Prespecified win ratio sensitivity analyses in both populations were consistent with the results of the primary analysis.[1]

Exploratory Cardiac Biomarker Analyses

Change Ratio During 30-Month Period

In the overall population, the ratio in geometric mean fold-changes from baseline (95% CI) at month 6 between those who received vutrisiran and those who received placebo for NT-proBNP was 0.92 (95% CI: 0.87-0.98; nominal P = 0.0127) and for troponin I was 0.91 (95% CI: 0.86-0.98; nominal P = 0.0098).[2] **Table 2** provides results for additional exploratory endpoints.[5]

Table 2. Change from Baseline at 30 Months for Select Exploratory Endpoints.[5]

End Point	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 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 fold-change ratio (95% CI)	0.68 (0.62, 0.75)		0.55 (0.48, 0.63)	

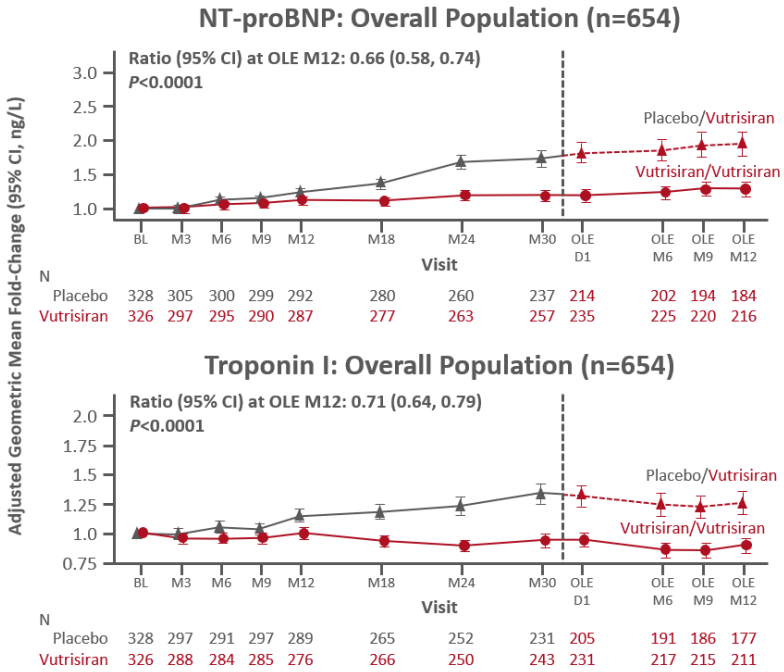
Abbreviations: CI = confidence interval; LS = least squares; NT-proBNP = N-terminal pro-brain natriuretic peptide.

A sensitivity analysis that included data after tafamidis treatment initiation during the double-blind period was conducted and the geometric mean fold-change ratio for NT-proBNP was 0.68 (95% CI: 0.62-0.75) and 0.70 (95% CI: 0.64-0.76) for troponin I. In the baseline tafamidis subgroup, the geometric mean fold-change ratio for NT-proBNP was 0.82 (95% CI: 0.71-0.94) and 0.90 (95% CI: 0.80-1.01) for troponin I.[2]

Change Ratio Through 12-Month OLE

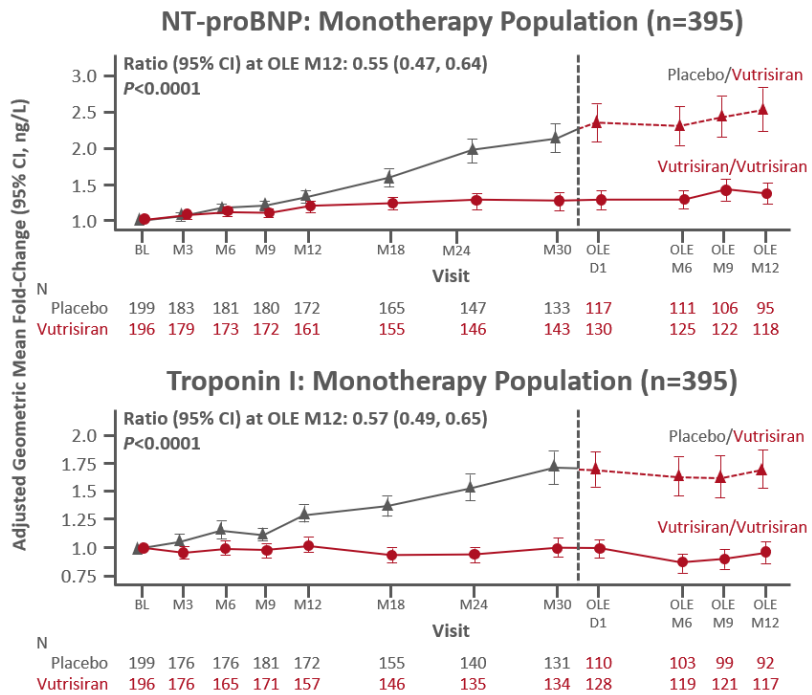
The results of the adjusted geometric mean fold-change ratio were maintained through month 12 of the OLE. Treatment with vutrisiran compared with placebo resulted in an adjusted geometric mean fold-change ratio of 0.66 (95% CI: 0.58, 0.74) for NT-proBNP and 0.71 (95% CI: 0.64, 0.79) for troponin I in the overall population (**Figure 1**). In the monotherapy population, treatment with vutrisiran compared with placebo resulted in an adjusted geometric mean fold-change ratio of 0.55 (95% CI: 0.47, 0.64) for NT-proBNP and 0.57 (95% CI: 0.49, 0.65) for troponin I (**Figure 2**).[4]

Figure 1. Change Ratio in NT-proBNP and Troponin I in the Overall Population.[4]



Abbreviations: BL = baseline; CI = confidence interval; NT-proBNP = *N*-terminal prohormone of B-type natriuretic peptide; OLE = open-label extension.
From Garcia-Pavia et al.[4]

Figure 2. Change Ratio in NT-proBNP and Troponin I in the Monotherapy Population.[4]

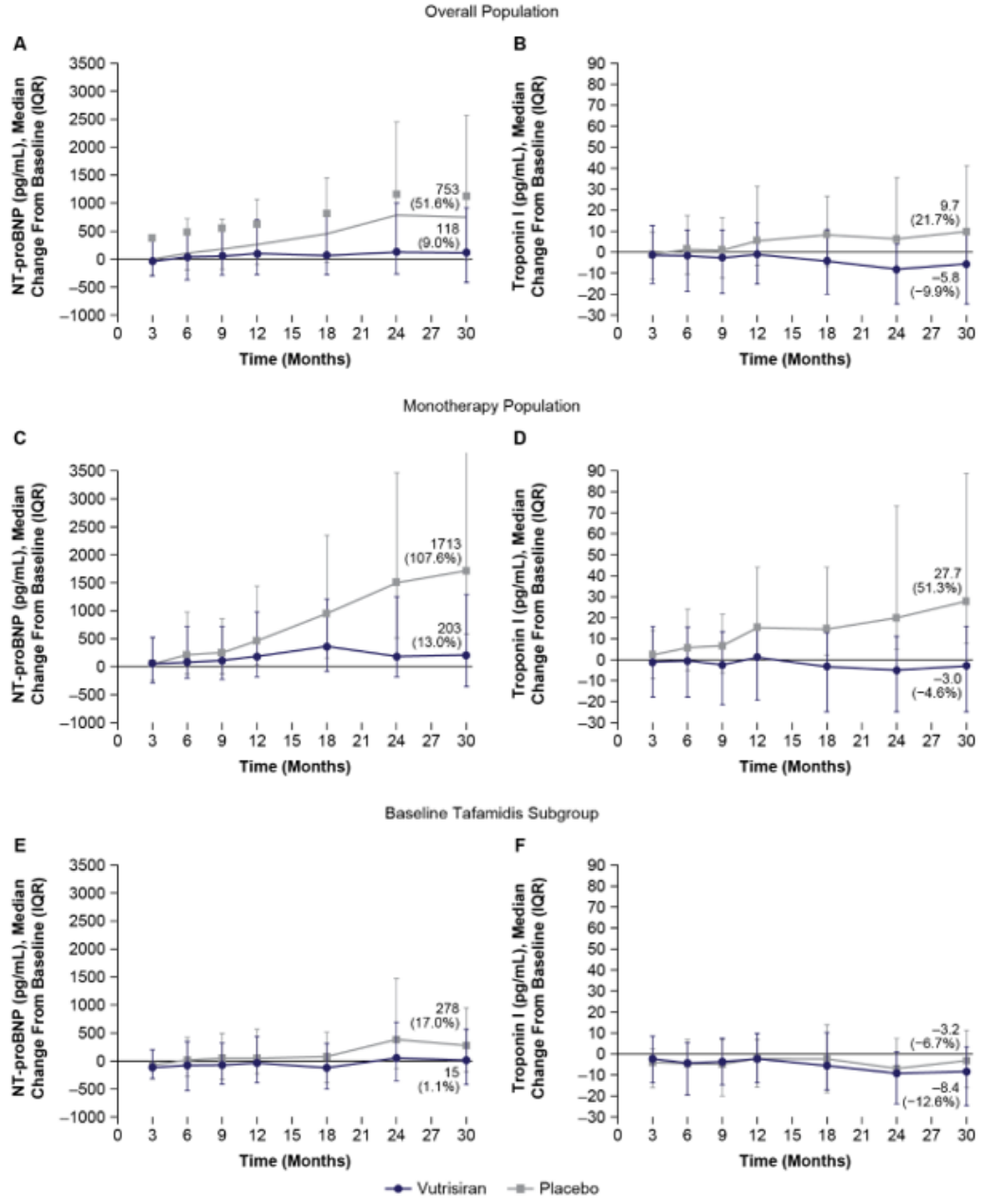


Abbreviations: BL = baseline; CI = confidence interval; D = day; M = month; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; OLE = open-label extension.
From Garcia-Pavia et al.[4]

Change in NT-proBNP and Troponin I During 30 Month Period

In the overall population, the median change from baseline in the vutrisiran arm for NT-proBNP at month 30 was 118 pg/mL (Q1-Q3: -419 to 911 pg/mL) and for troponin I was -5.8 pg/mL (Q1-Q3: -25.0 to 10.0 pg/mL). The median change from baseline in the placebo arm was 753 pg/mL (Q1-Q3: -8 to 2,573 pg/mL) and 9.7 pg/mL (Q1-Q3: -6.3 to 41.2 pg/mL) for NT-proBNP and troponin I, respectively (**Figure 3A and 3B**). Results for the median change from baseline in NT-proBNP and troponin I for the monotherapy population and baseline tafamidis subgroup are provided in **Figures 3C, 3D, 3E, and 3F**.[2]

Figure 3. Median (IQR) Change From Baseline in NT-proBNP and Troponin I.[6]



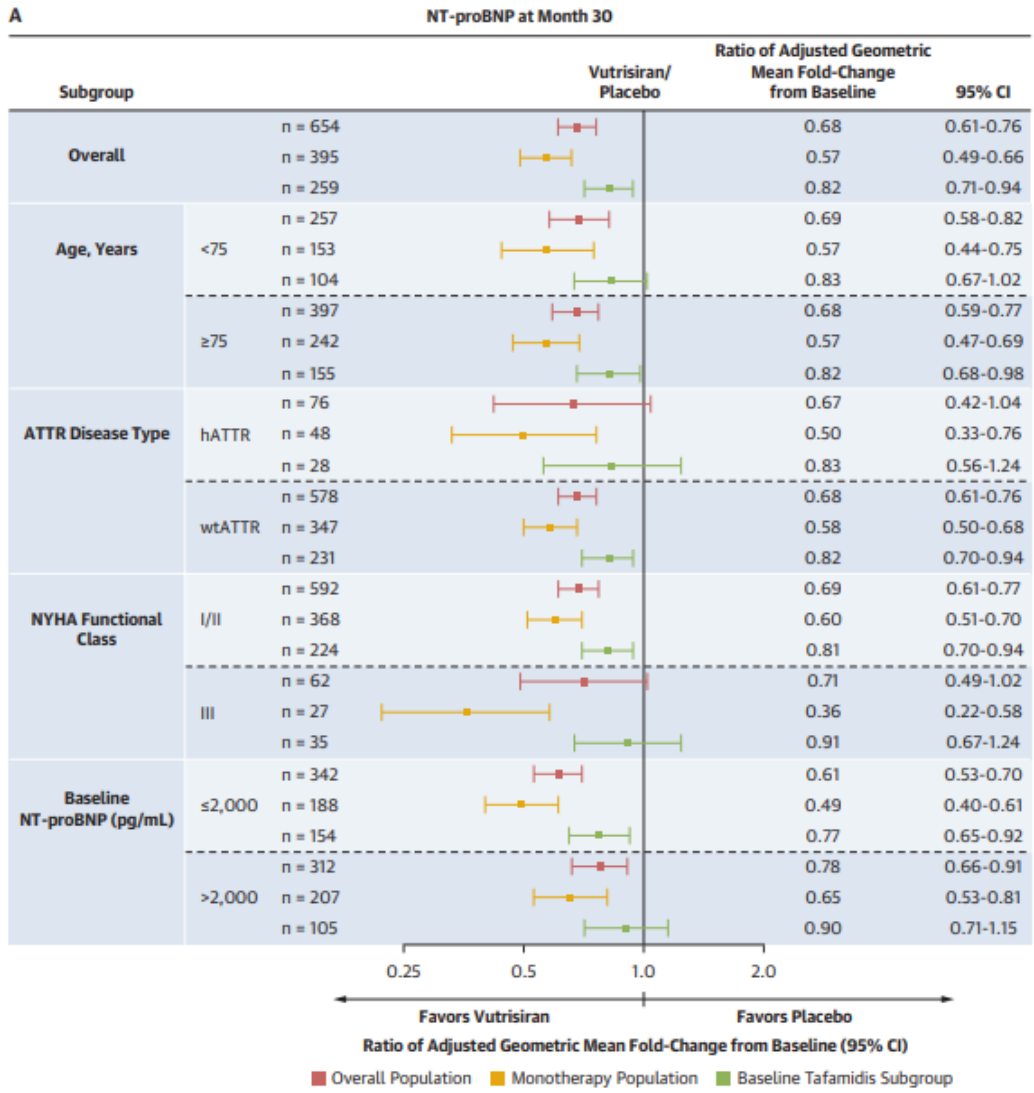
Abbreviations: CI = confidence interval; IQR = interquartile range; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.
From Maurer et al.[6]

In the overall population, 28.0% of vutrisiran-treated patients had reductions in both NT-proBNP and troponin I compared with 15.6% of patients receiving placebo (nominal P = 0.0011). In the monotherapy population, 21.6% of vutrisiran-treated patients had reductions in both NT-proBNP and troponin I compared with 3.8% of patients receiving placebo (nominal P < 0.0001).[2]

Subgroup Analyses During 30 Month Period

The ratio of adjusted geometric mean fold-change from baseline (95% CI) for NT-proBNP and troponin I at month 30 favored vutrisiran over placebo across all subgroups (**Figures 4 and 5**).[2]

Figure 4. Effect of Vutrisiran on NT-proBNP in Prespecified Subgroups.[2]

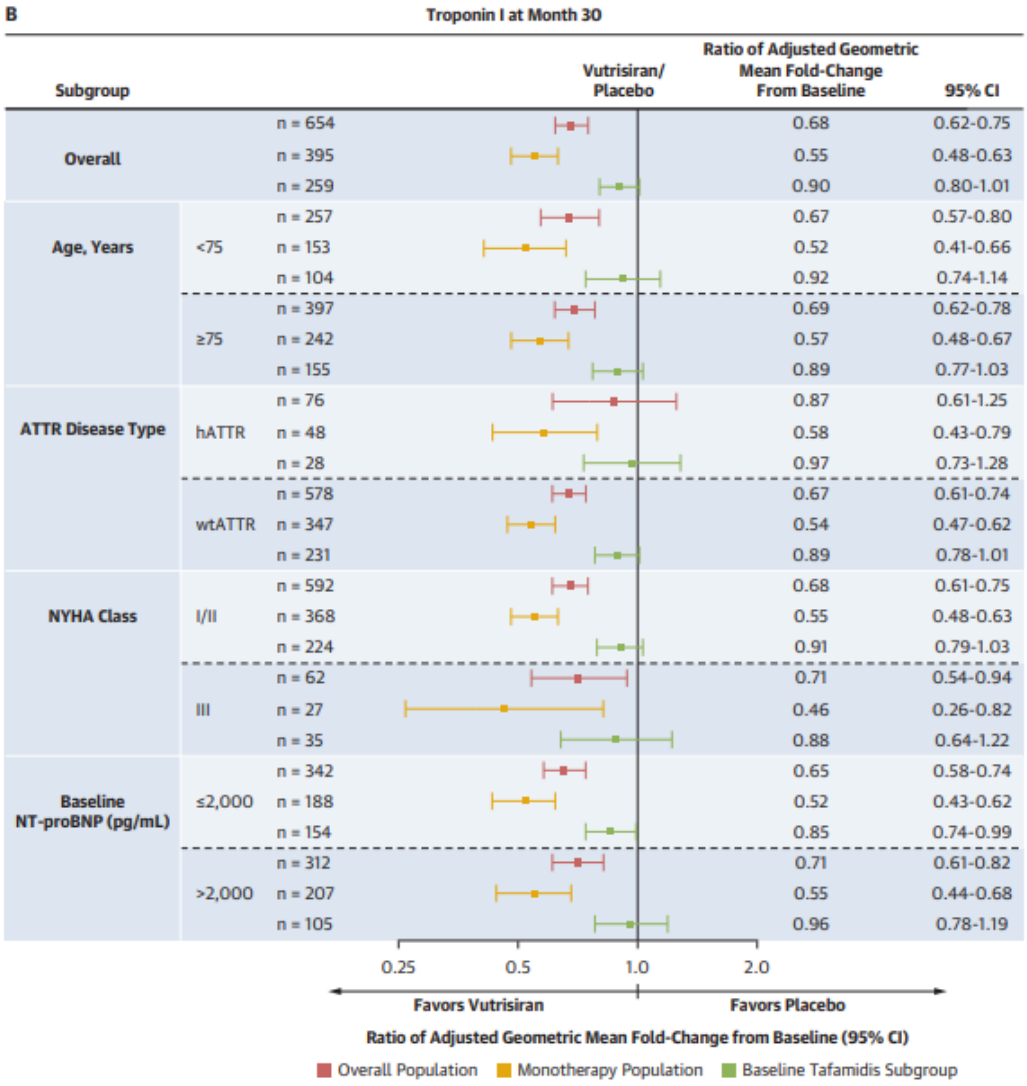


Abbreviations: ATTR = transthyretin amyloidosis; hATTR = hereditary transthyretin amyloidosis; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association; wtATTR = wild-type transthyretin amyloidosis.

For all subgroups, results are based on subgroup data only from MMRM with change from baseline in log-transformed biomarker as the outcome, log-transformed baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use. For baseline tafamidis subgroup, the model also includes type of ATTR and age group but excludes baseline tafamidis use term. For patients in the vutrisiran monotherapy group with tafamidis drop-in during the study, data collected after tafamidis drop-in are excluded from analysis.

From Maurer et al.[2]

Figure 5. Effect of Vutrisiran on Troponin I in Prespecified Subgroups.[2]



Abbreviations: ATTR = transthyretin amyloidosis; hATTR = hereditary transthyretin amyloidosis; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association; wtATTR = wild-type transthyretin amyloidosis.
For all subgroups, results are based on subgroup data only from MMRM with change from baseline in log-transformed biomarker as the outcome, log-transformed baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use. For baseline tafamidis subgroup, the model also includes type of ATTR and age group but excludes baseline tafamidis use term. For patients in the vutrisiran monotherapy group with tafamidis drop-in during the study, data collected after tafamidis drop-in are excluded from analysis.
From Maurer et al.[2]

BASELINE CARDIAC BIOMARKER CORRELATION

Baseline levels of NT-proBNP and troponin I were associated with risk of adverse outcomes (**Table 3**).[2,7]

Table 3. HR per 2-Fold Increase in Baseline Value of Cardiac Biomarkers.[7]

	NT-proBNP		Troponin I	
	HR for Event	95% CI	HR for Event	95% CI
CV Events and All-Cause Mortality (primary endpoint)	1.584	1.405, 1.785	1.286	1.186, 1.394
All-Cause Mortality (secondary endpoint)	1.903	1.585, 2.286	1.443	1.301, 1.602

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Changes in NT-proBNP and troponin I levels from baseline at 6 months were associated with risk of adverse outcomes (**Table 4**).[2,7]

Table 4. HR per 2-Fold Increase in Fold-Change from Baseline in Cardiac Biomarkers at 6 Months.[7]

	NT-proBNP		Troponin I	
	HR for Event	95% CI	HR for Event	95% CI
CV Events and All-Cause Mortality (primary endpoint)	1.695	1.310, 2.193	1.372	1.150, 1.635
All-Cause Mortality (secondary endpoint)	2.330	1.619, 3.354	1.451	1.082, 1.946

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; NT-proBNP = N-terminal pro-brain natriuretic peptide.

SAFETY RESULTS

In the overall population, the proportion of patients with at least one AE was similar between treatment arms, and the majority of AEs were mild or moderate. Cardiac AEs occurred at similar or lower rates with vutrisiran than placebo.[3] A summary of the safety results during the double-blind period are presented in **Table 5**.[5] 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.[1]

Table 5. 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.

ABBREVIATIONS

AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; HR = hazard ratio; LWYY = Lin-Wei-Yang-Ying; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; Q1-Q3 = interquartile range; SGLT2 = sodium-glucose cotransporter-2; wtATTR = wild-type transthyretin amyloidosis.

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