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]
- Vutrisiran maintained stability of NT-proBNP and troponin I compared with placebo.[2]
- Results from NT-proBNP and troponin I were consistent across all prespecified subgroups.[2]
- The majority of AEs in the trial were mild or moderate and similar between treatment arms.[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 treatment period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all eligible patients remaining on the study were allowed to receive vutrisiran in an ongoing OLE.[1]

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 to 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.[1,4]

Exploratory endpoints included levels of cardiac biomarkers NT-proBNP and troponin I.[1]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Baseline Characteristics

In the overall population, there were 326 patients randomized to receive vutrisiran and 329 patients randomized to receive placebo. 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 and demographics were comparable between 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.[1] Three percent of patients in both treatment arms were receiving SGLT2 inhibitors at baseline. Thirty-one percent of patients in the vutrisiran group and 35% in the placebo group started SGLT2 inhibitors during the DB period. Approximately 80% of patients in both treatment arms had substantial use of diuretics at baseline. Forty eight percent of patients in the vutrisiran arm and 56% in the placebo group required outpatient initiation or intensification of diuretics during the DB period.[2]

Table 1. 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)
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.[4]

[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.

Baseline levels of NT-proBNP and troponin I were associated with risk of adverse outcomes, as seen in **Table 2.**[2]

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

	NT-proBNP		Troponin I	
	HR for Event	**95% CI**	**HR for Event**	**95% CI**
CV Events and All-Cause Mortality	1.584	1.405, 1.785	1.286	1.186, 1.394
All-Cause Mortality	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.

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. The time to first CV event or all-cause mortality in the overall population and monotherapy population is provided in **Table 3**.[1]

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

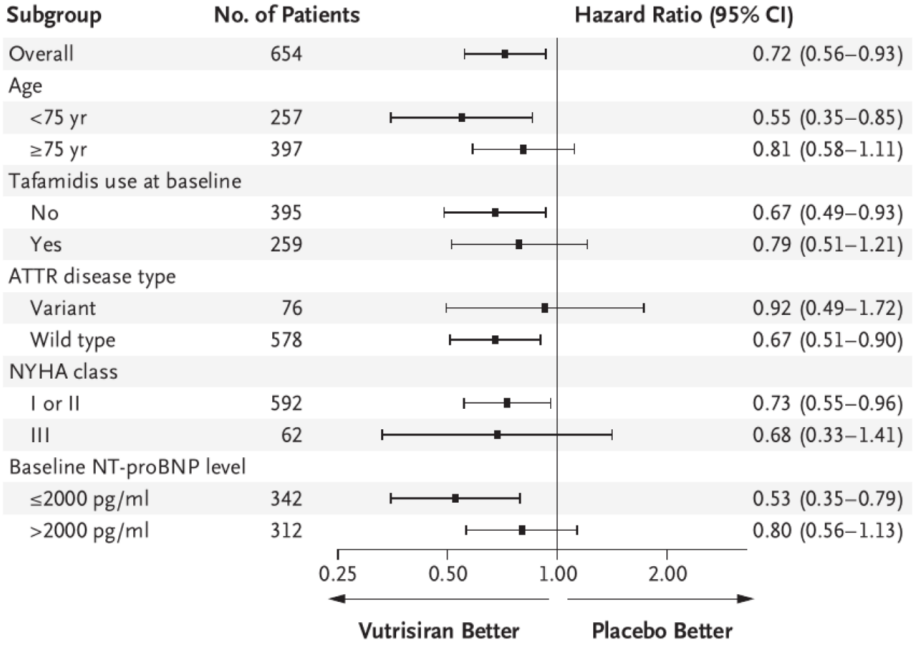
	Overall Population			Monotherapy Population		
End Point	**Vutrisiran (n=326)**	**Placebo (n=328)**	**Measure of Effect**	**Vutrisiran (n=196)**	**Placebo (n=199)**	**Measure of Effect**
Death from any cause and recurrent CV events – HR (95% CI), P-value			0.72 (0.56 to 0.93), P=0.01			0.67 (0.49 to 0.93), P=0.02
Death from any cause – HR (95% CI), P-value			0.69 (0.49 to 0.98), P=0.04			0.71 (0.47 to 1.06), P=0.12
Recurrent CV events – relative rate ratio (95% CI), P-value			0.73 (0.61 to 0.88), P=0.001			0.68 (0.53 to 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.

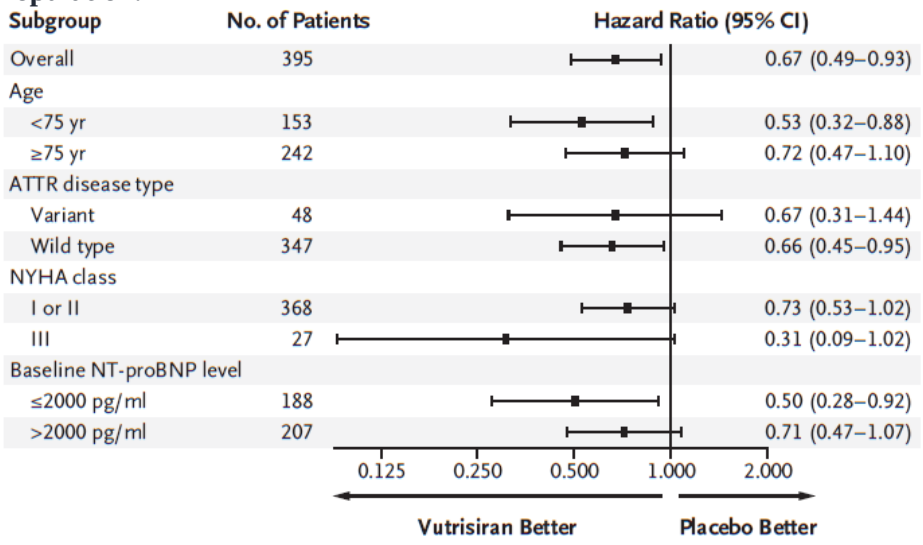
Similar effects were observed in all-cause mortality and recurrent CV events across all prespecified subgroups shown in **Figure 1** and **Figure 2**.[1]

Figure 1. All-Cause Mortality and CV Events in Prespecified Subgroups in the Overall Population.[1]



From Fontana et al[1]
Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association

Figure 2. All-Cause Mortality and CV Events in Prespecified Subgroups in the Monotherapy Population.[1]



From Fontana et al[1]
Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association

Exploratory Cardiac Biomarker Analyses

Table 4 provides results for select exploratory endpoints.[4]

Table 4. Select Exploratory Endpoints.[4]

End Point	Overall Population		Monotherapy Population	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
NT-proBNP fold-change from baseline at 30 months				
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 from baseline at 30 months				
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; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Changes in NT-proBNP and troponin I levels from baseline were associated with risk of adverse outcomes at 6 months, as seen in **Table 5**.[2]

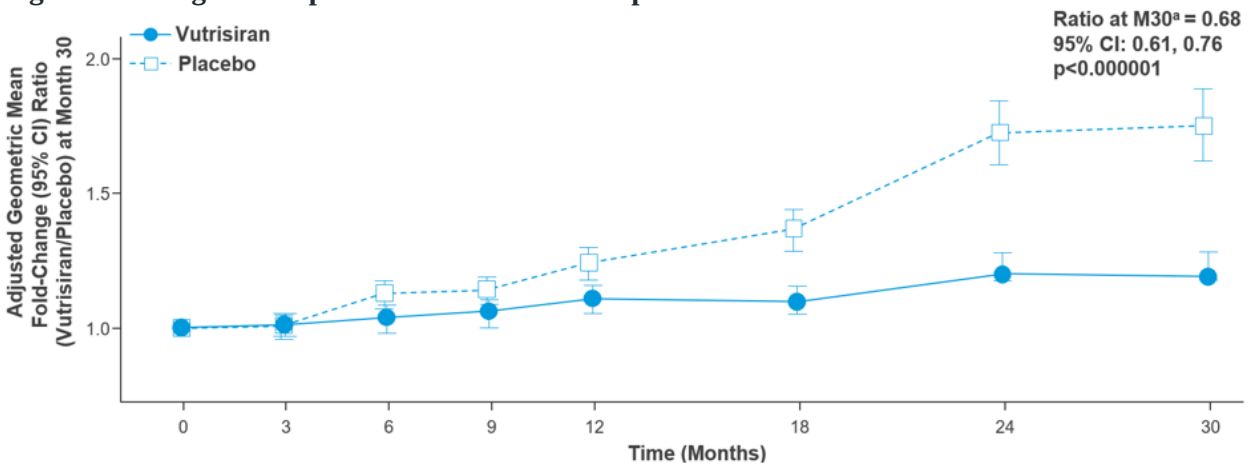
Table 5. HR per 2-Fold Increase in Fold-Change from Baseline in Cardiac Biomarkers at 6 Months.[2]

	NT-proBNP		Troponin I	
	HR for Event	95% CI	HR for Event	95% CI
CV Events and All-Cause Mortality	1.695	1.310, 2.193	1.372	1.150, 1.635
All-Cause Mortality	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.

Vutrisiran maintained relative stability of NT-proBNP compared with placebo as seen in **Figure 3**.[2]

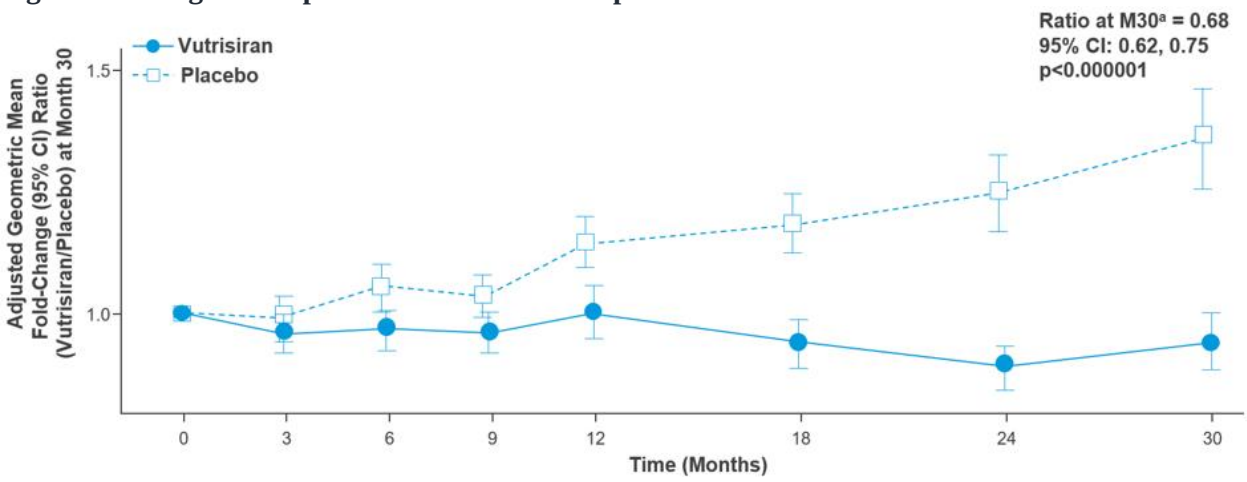
Figure 3. Change in NT-proBNP in the Overall Population.[2]



From Maurer et al[2]
Abbreviations: BL = baseline; CI = confidence interval; LS = least squares; M = month; MMRM = mixed models for repeated measures.
[a]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, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group.

Vutrisiran maintained relative stability of troponin I compared with placebo as seen in **Figure 4**.[2]

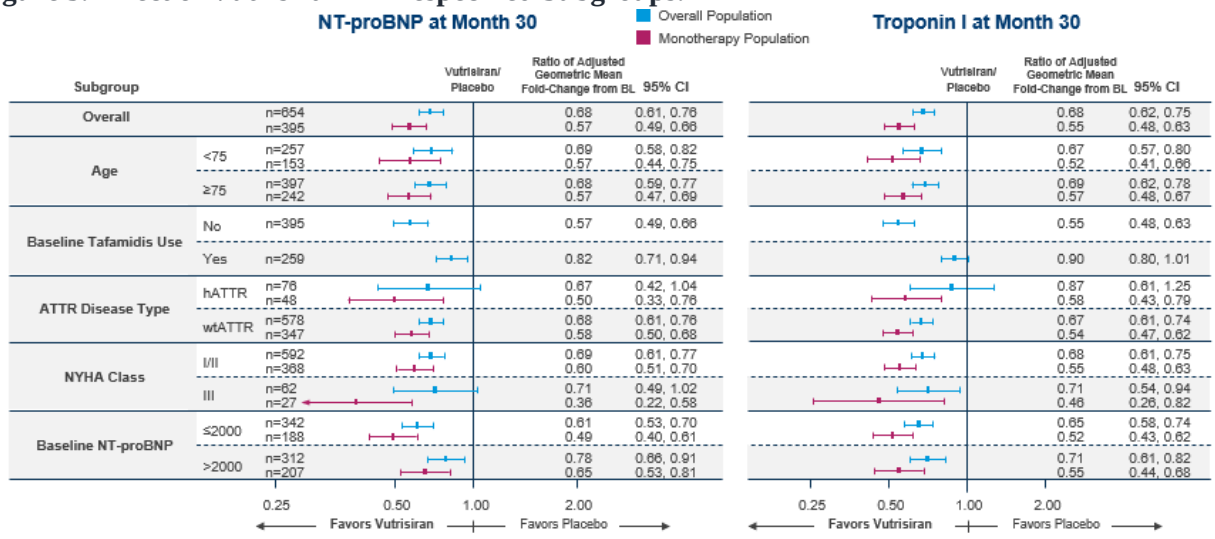
Figure 4. Change in Troponin I in the Overall Population.[2]



From Maurer et al[2]
Abbreviations: BL= baseline; CI = confidence interval; LS = least squares; M = Month; MMRM = mixed models for repeated measures.
[a]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, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group.

There were beneficial effects of vutrisiran on NT-proBNP and troponin I in all prespecified subgroups as seen in in **Figure 5**.[2]

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



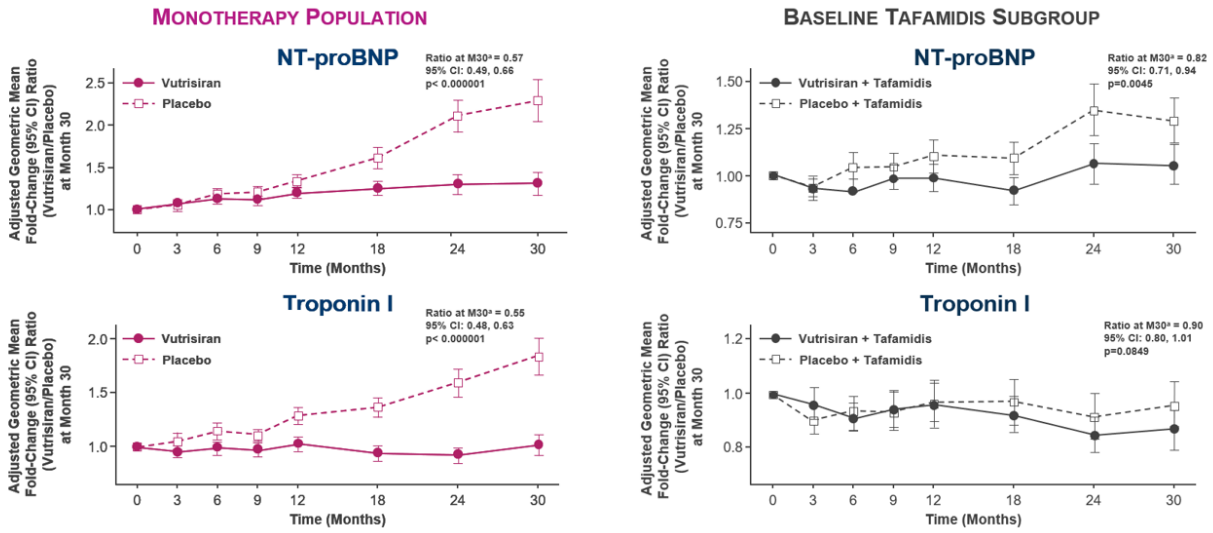
From Maurer et al[2]
Abbreviations: ATTR = transthyretin amyloidosis; BL = baseline; CI = confidence interval; hATTR = hereditary transthyretin amyloidosis; MMRM = mixed models for repeated measures; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association; wtATTR = 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.

In the monotherapy population, relative reductions of 43% in NT-proBNP and 45% in troponin I with vutrisiran compared with placebo were observed at 30 months. In the baseline tafamidis subgroup, relative

reductions of 18% in NT-proBNP and 10% in troponin I with vutrisiran compared with placebo were observed at 30 months, as seen in **Figure 6**.[2]

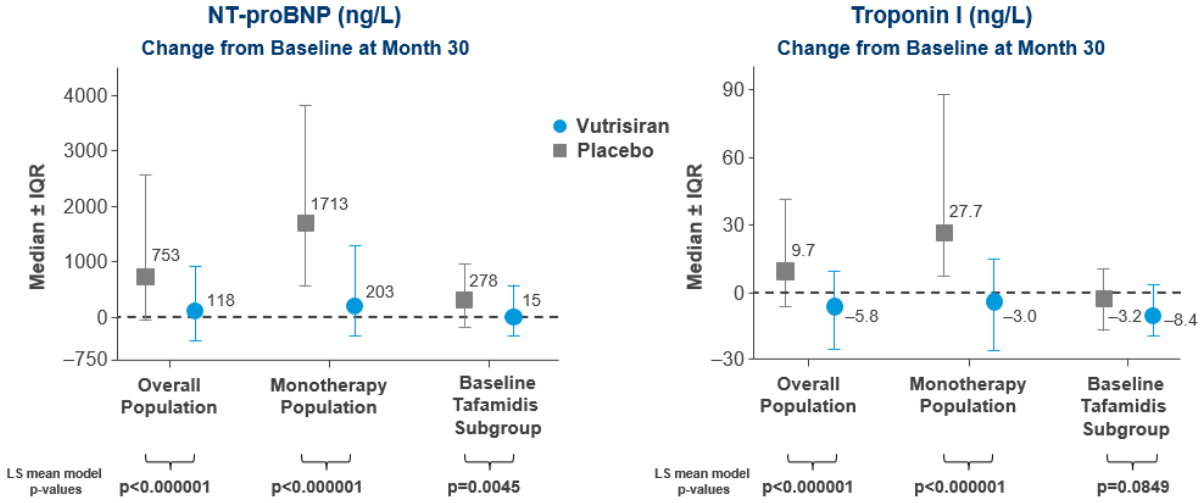
Figure 6. Change Ratio in NT-proBNP and Troponin I.[2]



From Maurer et al[2]
Abbreviations: BL = baseline; CI = confidence interval; LS = least squares; M = Month; MMRM = mixed models for repeated measures; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.
[a]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP or troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP or troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group. In the vutrisiran monotherapy subgroup, terms related to baseline tafamidis use are removed from the model.

Vutrisiran maintained long-term stability of NT-proBNP and troponin I at 30 months, as seen in **Figure 7**, consistent with improvements relative to placebo in CV events and all-cause mortality.[2]

Figure 7. NT-proBNP and Troponin I Change From Baseline.[2]



From Maurer et al[2]
Abbreviations: CV = cardiovascular; IQR = interquartile range; 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 or troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP or troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group. In the vutrisiran monotherapy subgroup, terms related to baseline tafamidis use are removed from the model.

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 6.**[4] 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 6. Safety Summary.[4]

Event, n (%)	Overall Population	
	Vutrisiran (N=326)	Placebo (N=328)
At least 1 AE	322 (99)	323 (98)
Any SAE[a]	201 (62)	220 (67)
Any severe AE[b]	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[c]	49 (15)	63 (19)

Abbreviations: AE = adverse event; SAE = serious adverse event.
[a]Serious AEs 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.
[b]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.
[c]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; DB = double blind; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; HR = hazard ratio; IQR= interquartile range; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LWYY = Lin-Wei-Yang-Ying; MMRM = mixed models for repeated measures; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2; TTR = transthyretin; wtATTR= wild-type transthyretin amyloidosis.

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REFERENCES

1. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. *N Engl J Med*. August 2024. doi:10.1056/NEJMoa2409134
2. Maurer MS, Berk JL, Damy T, et al. Exploratory biomarker analyses from HELIOS-B, a phase 3 study of vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. Presented at: Heart Failure Society of America (HFSA) Annual Scientific Meeting; September 27-30, 2024; Virtual.
3. Fontana M, Berk JL, Gillmore JD, et al. Primary results from HELIOS-B, a phase 3 study of vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. Presented at: European Society of Cardiology (ESC) Congress; August 30-September 2, 2024; London, UK.
4. Supplement to: Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2024. doi:10.1056/NEJMoa2409134