Vutrisiran: HELIOS-B Results by Baseline Heart Failure Disease Severity

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SUMMARY

- In exploratory subgroup analyses of the HELIOS-B study, the effect of vutrisiran on patients with different heart failure severities was assessed by baseline NYHA class (I, II, or III) and NT-proBNP levels (≤2,000 ng/L or >2,000 ng/L).[1]
  - Patients were excluded from the study if they had NYHA class IV or NYHA class III with NAC ATTR Stage 3 (defined as NT-proBNP > 3,000 ng/L and eGFR < 45 mL/min/1.73m^2).[1]
  - Results are descriptive in nature; there were no statistical comparisons between subgroups and randomization in the study was not stratified by the subgroups.[1]
- In the overall population, the HRs (95% CI) for the composite of all-cause mortality and recurrent CV events in patients treated with vutrisiran compared with placebo were 0.54 (0.27, 1.10), 0.77 (0.57, 1.03), and 0.68 (0.33, 1.41) in the baseline NYHA class I, II, and III groups, respectively; and 0.53 (0.35-0.79) and 0.80 (0.56-1.13) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]
- Treatment with vutrisiran demonstrated similar effects in the monotherapy population and across additional endpoints of all-cause mortality, functional assessments, and cardiac biomarkers. A greater benefit was observed in earlier, less severe disease.[1]
- In the overall population of the HELIOS-B study, the incidence of AEs was similar between treatment arms.[2]

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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). After the double-blind period, all eligible patients remaining in the study were allowed to receive vutrisiran in an OLE.[2]

Patients aged 18 to 85 years with a diagnosis of ATTR-CM and NT-proBNP levels of >300 ng/L and <8,500 ng/L were eligible to be included in the study. Patients were excluded from the study if they had NYHA class IV or NYHA class III with NAC ATTR Stage 3 (defined as NT-proBNP >3,000 ng/L and eGFR <45 mL/min/1.73m^2).[1]

Exploratory subgroup analyses of the HELIOS-B study were conducted to evaluate the efficacy and safety of vutrisiran compared with placebo in patients with different heart failure severities at baseline including patients with NYHA class I (no symptoms with ordinary physical activity), class II (symptoms with ordinary physical activity), or class III (symptoms with less than ordinary physical activity) and with NT-proBNP levels of >300 ng/L to ≤2,000 ng/L (referred to as the ≤2,000 ng/L group) or >2,000 ng/L to <8,500 ng/L (referred to as the >2,000 ng/L group). Baseline disease severity group analyses were conducted in the overall population and in the monotherapy population.[1]

Treatment effects for the primary composite endpoint and secondary endpoint of all-cause mortality were also evaluated across subgroups defined by other measures of disease severity, including NAC stage 1 or 2/3, Columbia early stage (score 1-3) or intermediate/late stage (score 4-9), and baseline NT-proBNP tertiles (<1,368 ng/L, ≥1,368 and <2,691 ng/L, and ≥2,691 ng/L).[1]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

A total of 654 patients with ATTR-CM who received vutrisiran (n=326) or placebo (n=328) were assessed in groups by NYHA class I, II, and III and NT-proBNP ≤2,000 ng/L and >2,000 ng/L. In the overall population, 84 patients (12.8%) were NYHA class I, 508 patients (77.7%) were NYHA class II, and 62 patients (9.5%) were NYHA class III; 342 patients (52.3%) had NT-proBNP levels ≤2,000 ng/L and 312 patients (47.7%) had NT-proBNP levels >2,000 ng/L. A summary of the baseline demographics and disease characteristics in the overall population are shown in **Tables 1 and 2**.[1]

In both the overall and monotherapy populations, baseline demographics were generally similar between the vutrisiran and placebo arms across the NYHA functional class and NT-proBNP groups, although there were some differences in tafamidis use between the groups in the overall population and more patients had a baseline NT-proBNP >2,000 ng/L in the vutrisiran arm in the monotherapy population. Baseline 6-MWT and KCCQ-OS decreased with increasing baseline NYHA class, and NT-proBNP levels were generally higher with increasing baseline NYHA class.[1]

Table 1. Baseline Characteristics by Baseline NYHA Class in the Overall Population.[1,a]

Characteristic	NYHA Class I		NYHA Class II		NYHA Class III	
	Vutrisiran (n=49)	Placebo (n=35)	Vutrisiran (n=250)	Placebo (n=258)	Vutrisiran (n=27)	Placebo (n=35)
Age, y	77.0 (72.0-80.0)	76.0 (70.0-80.0)	77.0 (72.0-81.0)	76.0 (72.0-80.0)	77.0 (71.0-81.0)	76.0 (71.0-80.0)
Male	49 (100.0)	33 (94.3)	226 (90.4)	241 (93.4)	24 (88.9)	32 (91.4)
Race						
White	44 (89.8)	31 (88.6)	208 (83.2)	214 (82.9)	25 (92.6)	30 (85.7)

Characteristic	NYHA Class I		NYHA Class II		NYHA Class III	
	Vutrisiran (n=49)	Placebo (n=35)	Vutrisiran (n=250)	Placebo (n=258)	Vutrisiran (n=27)	Placebo (n=35)
Asian	2 (4.1)	0 (0)	15 (6.0)	18 (7.0)	1 (3.7)	1 (2.9)
Black	3 (6.1)	4 (11.4)	19 (7.6)	18 (7.0)	1 (3.7)	2 (5.7)
Other	0 (0)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	0 (0)
Not reported	0 (0)	0 (0)	6 (2.4)	6 (2.3)	0 (0)	2 (5.7)
Time since diagnosis of ATTR, y	1.1 (0.6-1.7)	1.1 (0.6-2.4)	0.7 (0.2-1.8)	1.0 (0.3-2.1)	0.7 (0.3-2.2)	0.8 (0.5-2.3)
wtATTR	44 (89.8)	30 (85.7)	220 (88.0)	229 (88.8)	25 (92.6)	30 (85.7)
Tafamidis use at baseline	34 (69.4)	23 (65.7)	78 (31.2)	89 (34.5)	18 (66.7)	17 (48.6)
NAC stage						
1	40 (81.6)	30 (85.7)	154 (61.6)	180 (69.8)	14 (51.9)	19 (54.3)
2	8 (16.3)	4 (11.4)	79 (31.6)	68 (26.4)	13 (48.1)	15 (42.9)
3	1 (2.0)	1 (2.9)	17 (6.8)	10 (3.9)	0 (0)	1 (2.9)
6-MWT, m	422.3 (375.0-485.4)	421.8 (358.9-480.0)	360.0 (298.7-435.3)[b]	383.0 (323.4-450.0)	318.5 (256.0-429.4)	295.0 (244.7-345.0)
KCCQ-OS, points	85.4 ± 12.7	83.7 ± 15.1	72.0 ± 19.2[b]	73.2 ± 19.3[c]	58.8 ± 20.2	54.2 ± 17.0
NT-proBNP, ng/L	1,458 (838-2,703)	1,285 (776-2,045)	2,159 (1,227-3,455)	1,814 (1,080-3,080)	2,468 (1,760-3,796)	2,563 (1,401-3,885)
Troponin I, ng/L	65.0 (38.0-99.3)	68.6 (30.3-130.0)	73.8 (48.4-117.8)	63.6 (40.4-104.8)	48.6 (33.6-140.8)	71.4 (47.7-121.6)
eGFR, mL/min/1.73 m^2	70.8 ± 21.3	70.7 ± 25.1	67.0 ± 21.7	69.5 ± 20.2	60.9 ± 17.2	59.2 ± 16.7
Concomitant SGLT2i use	0 (0)	0 (0)	5 (2.0)	9 (3.5)	2 (7.4)	1 (2.9)
Oral loop diuretic dose, furosemide equivalent dose, mg/d[d]	20.0 (0-40.0)	20.0 (0-60.0)	40.0 (10.0-60.0)	40.0 (10.0-80.0)	40.0 (10.0-120.0)	40.0 (20.0-60.0)

Abbreviations: 6-MWT = 6-minute walk test; ATTR = transthyretin amyloidosis; eGFR = estimated glomerular filtration rate; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; SGLT2i = sodium-glucose co-transporter-2 inhibitor; wtATTR = wild-type transthyretin amyloidosis.

[a]Values are median (Q1-Q3), n (%), or mean ± SD.

[b]n=249

[c]n=257

[d]Patients who were in the study but did not take any oral loop diuretic agents during a specific period are included in the summary, with daily dose as 0 mg/day.

Table 2. Baseline Characteristics by Baseline NT-proBNP Levels in the Overall Population.[1,a]

Characteristic	NT-proBNP ≤2,000 ng/L		NT-proBNP >2,000 ng/L	
	Vutrisiran (n=161)	Placebo (n=181)	Vutrisiran (n=165)	Placebo (n=147)
Age, y	76.0 (70.0-79.0)	75.0 (70.0-79.0)	78.0 (74.0-81.0)	77.0 (73.0-80.0)
Male	148 (91.9)	166 (91.7)	151 (91.5)	140 (95.2)
Race				

Characteristic	NT-proBNP ≤2,000 ng/L		NT-proBNP >2,000 ng/L	
	Vutrisiran (n=161)	Placebo (n=181)	Vutrisiran (n=165)	Placebo (n=147)
White	135 (83.9)	142 (78.5)	142 (86.1)	133 (90.5)
Asian	10 (6.2)	12 (6.6)	8 (4.8)	7 (4.8)
Black	14 (8.7)	20 (11.0)	9 (5.5)	4 (2.7)
Other	0 (0)	2 (1.1)	2 (1.2)	0 (0)
Not reported	2 (1.2)	5 (2.8)	4 (2.4)	3 (2.0)
Time since diagnosis of ATTR, y	0.8 (0.3-1.7)	1.0 (0.3-1.9)	0.9 (0.3-1.9)	1.1 (0.4-2.6)
wtATTR	140 (87.0)	159 (87.8)	149 (90.3)	130 (88.4)
Tafamidis use at baseline	80 (49.7)	74 (40.9)	50 (30.3)	55 (37.4)
NAC stage				
1	149 (92.5)	172 (95.0)	59 (35.8)	57 (38.8)
2	12 (7.5)	9 (5.0)	88 (53.3)	78 (53.1)
3	0 (0)	0 (0)	18 (10.9)	12 (8.2)
6-MWT, m	406.2 (339.9-472.0)[b]	405.0 (340.7-467.5)	332.1 (264.4-410.5)	360.0 (291.0-411.6)
KCCQ-OS, points	75.4 ± 19.1	74.4 ± 19.1	70.6 ± 19.6[c]	69.6 ± 20.6[d]
NT-proBNP, ng/L	1,126 (807-1,599)	1,110 (776-1,479)	3,294 (2,589-4,579)	3,323 (2,576-4,424)
Troponin I, ng/L	53.6 (34.5-81.2)	55.1 (33.6-81.0)	89.4 (59.6-143.7)	81.8 (53.0-121.9)
eGFR, mL/min/1.73 m^2	74.4 ± 23.5	73.9 ± 22.1	59.9 ± 16.2	61.9 ± 16.6
Concomitant SGLT2i use	3 (1.9)	5 (2.8)	4 (2.4)	5 (3.4)
Oral loop diuretic dose, furosemide equivalent dose, mg/d[e]	20.0 (0-40.0)	20.0 (0-40.0)	40.0 (20.0-80.0)	40.0 (20.0-80.0)

Abbreviations: 6-MWT = 6-minute walk test; ATTR = transthyretin amyloidosis; eGFR = estimated glomerular filtration rate; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SD = standard deviation; SGLT2i = sodium-glucose co-transporter-2 inhibitor; wtATTR = wild-type transthyretin amyloidosis.

[a]Values are median (Q1-Q3), n (%), or mean ± SD.

[b]n=160

[c]n=164

[d]n=146

[e]Patients who were in the study but did not take any oral loop diuretic agents during a specific period are included in the summary, with daily dose as 0 mg/day.

EFFICACY RESULTS

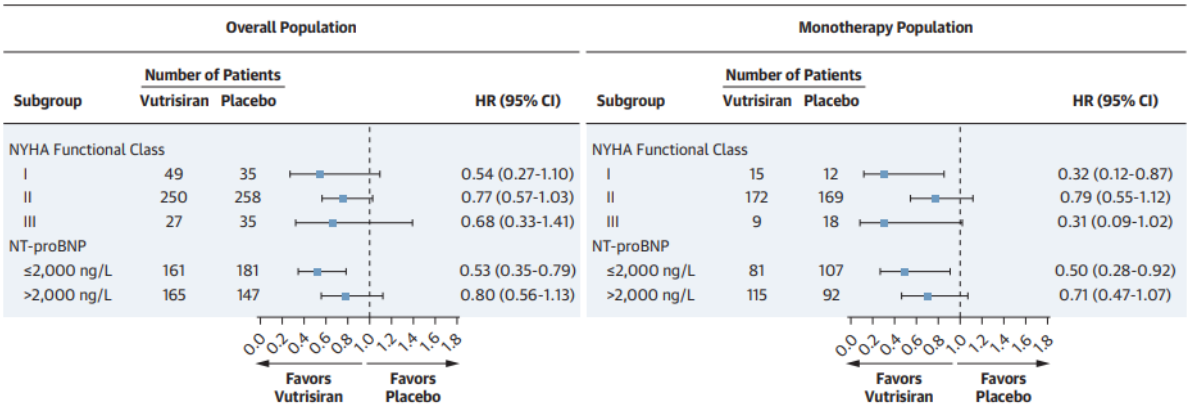
Composite of All-Cause Mortality and Recurrent CV Events During the Double-Blind Period

In the overall population, the HRs (95% CI) for the composite of all-cause mortality and recurrent CV events in patients treated with vutrisiran compared with placebo were 0.54 (0.27, 1.10), 0.77 (0.57, 1.03), and 0.68 (0.33, 1.41) in the baseline NYHA class I, II, and III groups, respectively; and 0.53 (0.35-0.79) and 0.80 (0.56-1.13) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 1**).[1]

In the monotherapy population, the HRs (95% CI) for the composite of all-cause mortality and recurrent CV events in patients treated with vutrisiran compared with placebo were 0.32 (0.12, 0.87), 0.79 (0.55,

1.12), and 0.31 (0.09, 1.02) in the baseline NYHA class I, II, and III groups, respectively; and 0.50 (0.28-0.92) and 0.71 (0.47-1.07) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 1**).[1]

Figure 1. Composite Endpoint of All-Cause Mortality and Recurrent CV Events by Baseline Heart Failure Severity.[1,a]



Abbreviations: CI = confidence interval; CV = cardiovascular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

[a]The primary composite endpoint of all-cause mortality and recurrent CV events was analyzed using a modified Andersen–Gill model with robust variance estimator stratified by baseline tafamidis use (overall population only) and adjusted for baseline log-transformed NT-proBNP, following the prespecified analysis approach for groups. All-cause mortality included heart transplantation and left ventricular assist device placement.

From Maurer et al.[1]

Additional analyses on all-cause mortality and recurrent CV events were conducted based on additional measures of baseline heart failure severity including Columbia stage, NAC stage, and NT-proBNP tertile at baseline, as shown in **Table 3**.[1]

Table 3. All-Cause Mortality and Recurrent CV Events by Additional Measures of Baseline Heart Failure Severity.[1,a]

	Columbia Stage		NAC Stage		NT-proBNP		
	Early	Intermediate/ Late	1	2/3	<1,368 ng/L	≥1,368 to <2,691 ng/L	≥2,691 ng/L
Overall Population	n=312	n=342	n=437	n=217	n=217	n=218	n=219
	0.69 (0.45-1.07)	0.74 (0.53-1.02)	0.49 (0.34-0.72)	1.08 (0.74-1.56)	0.52 (0.30-0.88)	0.61 (0.37-1.00)	0.93 (0.64-1.35)
Monotherapy Population	n=179	n=216	n=251	n=144	n=120	n=128	n=147
	0.69 (0.37-1.28)	0.66 (0.45-0.97)	0.48 (0.29-0.82)	0.90 (0.58-1.38)	0.56 (0.25-1.26)	0.56 (0.29-1.08)	0.82 (0.54-1.22)

Abbreviations: CI = confidence interval; HR = hazard ratio; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-brain natriuretic peptide.

[a]Values are HR (95% CI). The primary composite endpoint of all-cause mortality and recurrent CV events was analyzed using a modified Andersen–Gill model with robust variance estimator stratified by baseline tafamidis use (overall population only) and adjusted for baseline log-transformed NT-proBNP, following the prespecified analysis approach for groups.

All-Cause Mortality Through 42 Months

In the overall population, the HRs (95% CI) for all-cause mortality through 42 months in patients treated with vutrisiran compared with placebo were 0.32 (0.11, 0.94), 0.73 (0.50, 1.06), and 0.58 (0.20, 1.69) in

the baseline NYHA class I, II, and III groups, respectively; and 0.35 (0.18-0.66) and 0.83 (0.55-1.24) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

In the monotherapy population, the HRs (95% CI) for all-cause mortality through 42 months in patients treated with vutrisiran compared with placebo were 0.43 (0.10, 1.82), 0.73 (0.48, 1.12), and 0.19 (0.02, 1.63) in the baseline NYHA class I, II, and III groups, respectively; and 0.43 (0.18-1.01) and 0.75 (0.48-1.18) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

Additional analyses on all-cause mortality were conducted based on additional measures of baseline heart failure severity including Columbia stage, NAC stage, and NT-proBNP tertile at baseline, as shown in **Table 4.**[1]

Table 4. All-Cause Mortality by Additional Measures of Baseline Heart Failure Severity.[1,a]

	Columbia Stage		NAC Stage		NT-proBNP		
	Early (n=312)	**Intermediate/ Late (n=342)**	**1 (n=437)**	**2/3 (n=217)**	**<1,368 ng/L (n=217)**	**≥1,368 to <2,691 ng/L (n=218)**	**≥2,691 ng/L (n=219)**
Overall Population	n=312	n=342	n=437	n=217	n=217	n=218	n=219
	0.58 (0.30-1.12)	0.70 (0.48-1.03)	0.42 (0.25-0.69)	0.91 (0.58-1.43)	0.38 (0.15-0.95)	0.48 (0.26-0.91)	0.85 (0.54-1.33)
Monotherapy Population	n=179	n=216	n=251	n=144	n=120	n=128	n=147
	0.60 (0.27-1.36)	0.69 (0.44-1.09)	0.44 (0.22-0.86)	0.83 (0.50-1.37)	0.39 (0.11-1.39)	0.57 (0.25-1.28)	0.77 (0.46-1.27)

Abbreviations: CI = confidence interval; HR = hazard ratio; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-brain natriuretic peptide.

[a]Values are HR (95% CI). The secondary endpoint of all-cause mortality through 42 months was analyzed using a Cox proportional hazards model stratified by baseline tafamidis use (for the overall population only) and adjusted for baseline log-transformed NT-proBNP, following the prespecified analysis approach for groups.

Functional Assessments

6-MWT at 30 Months

In the overall population, the LS mean differences (95% CI) between vutrisiran compared with placebo in change from baseline to Month 30 in 6-MWT were 34.8 m (–1.6, 71.2), 22.6 m (7.5, 37.6), and 28.4 m (-12.1, 68.9) in the baseline NYHA class I, II, and III groups, respectively; and 35.2 m (17.6-52.8) and 21.7 m (2.8-40.6) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

In the monotherapy population, the LS mean differences (95% CI) between vutrisiran compared with placebo in change from baseline to Month 30 in 6-MWT were 62.9 m (–31.3, 157.2), 29.0 m (9.5, 48.5), and 72.2 m (2.7, 141.7) in the baseline NYHA class I, II, and III groups, respectively; and 44.0 m (17.5-70.6) and 32.1 m (8.6-55.5) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

KCCQ-OS at 30 Months

In the overall population, the LS mean differences (95% CI) between vutrisiran compared with placebo in change from baseline to Month 30 in KCCQ-OS were 6.6 (–2.5, 15.7), 5.9 (2.0, 9.8), and 3.5 (–9.2, 16.3) in the baseline NYHA class I, II, and III groups, respectively; and 8.6 (4.3-12.8) and 3.8 (-1.5, 9.0) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

In the monotherapy population, the LS mean differences (95% CI) between vutrisiran compared with placebo in change from baseline to Month 30 in KCCQ-OS were 7.9 (–13.7, 29.4), 8.3 (3.2, 13.3), and

17.5 (–3.0, 37.9) in the baseline NYHA class I, II, and III groups, respectively; and 12.1 (5.9, 18.3) and 7.8 (1.1-14.5) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

Cardiac Biomarkers

NT-proBNP at 30 Months

In the overall population, the adjusted geometric mean fold-change ratios (95% CI) from baseline to Month 30 in NT-proBNP between vutrisiran and placebo were 0.74 (0.55, 0.98), 0.68 (0.60, 0.76), and 0.71 (0.49, 1.02) in the baseline NYHA class I, II, and III groups, respectively; and 0.61 (0.53, 0.70) and 0.78 (0.66-0.91) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

In the monotherapy population, the adjusted geometric mean fold-change ratios (95% CI) from baseline to Month 30 in NT-proBNP between vutrisiran and placebo were 0.45 (0.28, 0.72), 0.60 (0.51, 0.71), and 0.36 (0.22, 0.58) in the baseline NYHA class I, II, and III groups, respectively; and 0.49 (0.40-0.61) and 0.65 (0.53, 0.81) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

Troponin I at 30 Months

In the overall population, the adjusted geometric mean fold-change ratios (95% CI) from baseline to Month 30 in troponin I between vutrisiran and placebo were 0.81 (0.64, 1.02), 0.67 (0.59, 0.75), and 0.71 (0.54, 0.94) in the baseline NYHA class I, II, and III groups, respectively; and 0.65 (0.58, 0.74) and 0.71 (0.61, 0.82) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

In the monotherapy population, the adjusted geometric mean fold-change ratios (95% CI) from baseline to Month 30 in troponin I between vutrisiran and placebo were 0.57 (0.36, 0.89), 0.55 (0.48, 0.64), and 0.46 (0.26, 0.82) in the baseline NYHA class I, II, and III groups, respectively; and 0.52 (0.43, 0.62) and 0.55 (0.44, 0.68) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively.[1]

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 with vutrisiran were mild or moderate. A summary of the safety results during the double-blind period are presented in **Table 5.**[2,3]

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

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]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.
[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; AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; HR = hazard ratio; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; SAE = serious adverse event; SD = standard deviation; SGLT2i = sodium-glucose co-transporter-2 inhibitor; wtATTR = wild-type transthyretin amyloidosis.

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