Vutrisiran: Echocardiographic Assessments 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. Echocardiograms were performed at 12, 18, 24, and 30 months.[1,2]
- Measures of cardiac structure, diastolic function, and systolic function were assessed over 30 months in the vutrisiran and placebo arms in the overall population. Consistent treatment effects were observed in select echocardiographic assessments in the monotherapy population (patients not receiving tafamidis at baseline).[2]
- In the overall population, the incidence of AEs and cardiac AEs were similar between the treatment arms. There were no clinically relevant changes in laboratory measures, vital signs, or electrocardiograms in either treatment arm.[1,3]

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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).[1]

Echocardiograms were performed at 12, 18, 24, and 30 months. Exploratory endpoints included change from baseline in mean LV wall thickness and peak longitudinal strain at 30 months in the overall population and monotherapy population. The changes from baseline to 30 months were analyzed with MMRM. Fixed effect terms were baseline value, treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group.[2]

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Select baseline characteristics of echocardiographic measures in the overall study population are presented in **Table 1.**[2] In the overall population, concomitant tafamidis use at baseline was 40% and 39% in the vutrisiran and placebo arms, respectively. The monotherapy population was defined as patients who did not receive tafamidis at baseline and comprised a total of 395 patients (196 patients [60%] in the vutrisiran arm and 199 patients [60%] in the placebo arm).[1]

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

Table 1. Baseline Echocardiographic Parameters in HELIOS-B.[2]

Baseline Characteristic	Overall Population	
	Placebo (N=328)[a]	Vutrisiran (N=326)
LV ejection fraction (%), mean (SD)	55.9 (12.3)	55.6 (12.7)
Peak longitudinal strain (%), mean (SD)	-14.0 (3.5)	-14.0 (3.5)
Stroke volume (mL), mean (SD)	53.8 (19.0)	50.7 (16.3)
Mean LV wall thickness (mm), mean (SD)	18.2 (3.0)	18.2 (3.0)
Relative wall thickness, mean (SD)	0.8 (0.2)	0.8 (0.2)
LV mass index (g/m^2), mean (SD)	180.8 (46.1)	182.1 (44.2)
E/A ratio, mean (SD)	1.9 (1.0)	2.1 (1.1)
Lateral E/e' ratio, mean (SD)	15.3 (6.3)	14.8 (6.7)

Abbreviations: 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; LV = left ventricular.
[a]329 patients were randomized to receive placebo. One patient withdrew from the study and was not dosed.

EFFICACY RESULTS

The study met the 10 primary and secondary endpoints in the overall and monotherapy populations. 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).[1]

Cardiac Structure

Changes in cardiac structure, as assessed by mean LV wall thickness and LV mass index, were evaluated in the vutrisiran and placebo arms at 30 months (**Table 2**).[2]

Table 2. Change in Cardiac Structure at 30 Months.[2]

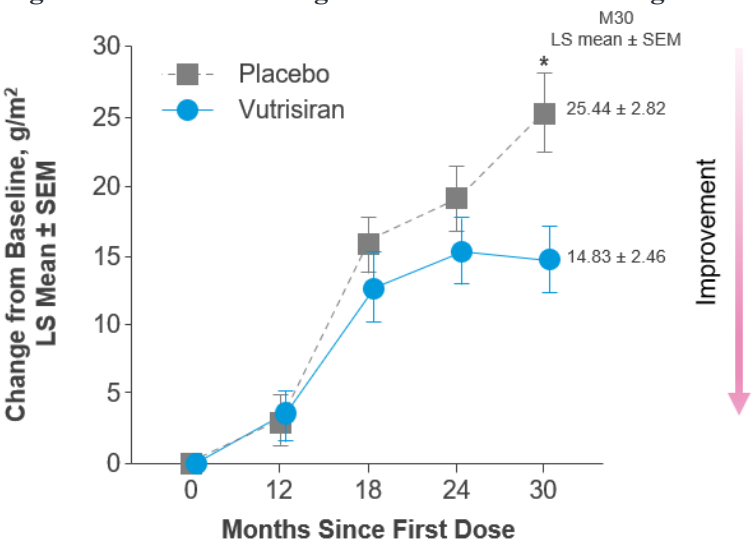
Parameter	Overall Population	
	Vutrisiran – Placebo (LS Mean Difference, 95% CI)	Nominal p-value
Mean LV wall thickness (mm)	-0.43 (-0.82, -0.03)	0.0343
LV mass index (g/m^2)	-10.6 (-18.0, -3.3)	0.0047

Abbreviations: CI = confidence interval; LS = least squares; LV = left ventricular.

In the overall population, the LS mean difference (95% CI) in change in LV mean wall thickness at 30 months between the vutrisiran and placebo arms was -0.43 mm (-0.82, -0.03). In the monotherapy population, the LS mean difference (95% CI) in change in mean LV wall thickness at 30 months between the vutrisiran and placebo arms was -0.8 mm (-0.14, -0.02).[2]

Changes over time in LV mass index between the treatment arms in the overall population are shown in **Figure 1**. At 30 months, the LS mean (±SEM) change from baseline in LV mass index was 14.83 g/m^2 (±2.46) and 25.44 g/m^2 (±2.82) in the vutrisiran and placebo arms, respectively.[2]

Figure 1. LS Mean Change in LV Mass Index through 30 Months.[2]



Abbreviations: ATTR = transthyretin amyloidosis; LS = least squares; LV = left ventricular; MMRM = mixed models for repeated measures; SEM = standard error of the mean.
Footnotes: *p<0.05. Results are from a MMRM with baseline 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.
From Jering et al.[2]

LV Diastolic Function

Changes in LV diastolic function, as assessed by E/A ratio, E/e' ratio, and TDI lateral e', were evaluated in the vutrisiran and placebo arms at 30 months (**Table 3**).[2]

Table 3. Change in LV Diastolic Function at 30 Months.[2]

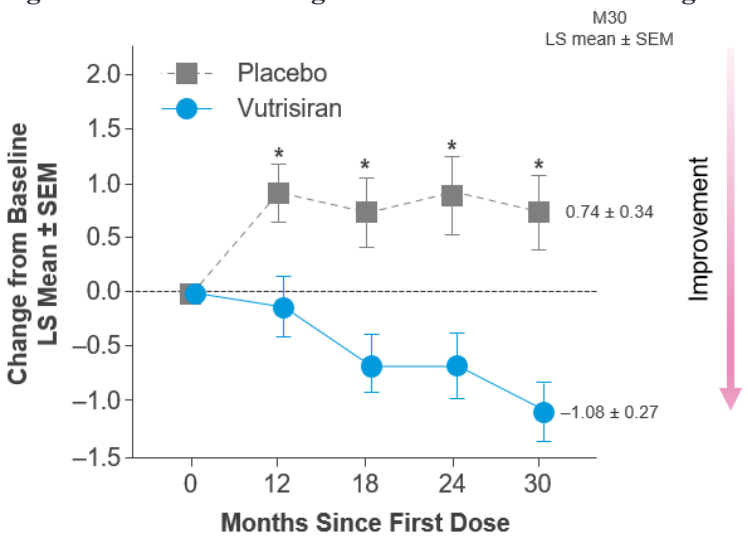
Parameter	Overall Population	
	Vutrisiran – Placebo (LS Mean Difference, 95% CI)	Nominal p-value
E/A ratio	-0.29 (-0.57, -0.01)	0.0434
E/e' ratio	-1.82 (-2.67, -0.97)	<0.0001
TDI lateral e' (cm/s)	0.55 (0.24, 0.85)	0.0005

Abbreviations: 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; TDI lateral e' = lateral peak early diastolic mitral annular tissue velocity.

In the overall population, the LS mean difference (95%) in change in E/e' ratio at 30 months between the vutrisiran and placebo arms was -1.82 (-2.67, -0.97). In the monotherapy population, the LS mean difference (95% CI) in change in E/e' ratio at 30 months between the vutrisiran and placebo arms was -2.73 (-3.90, -1.56).[2]

Changes over time in lateral E/e' ratio between the treatment arms in the overall population are shown in **Figure 2**. At 30 months, the LS mean (±SEM) change from baseline in E/e' ratio was -1.08 (±0.27) and 0.74 (±0.34) in the vutrisiran and placebo arms, respectively.[2]

Figure 2. LS Mean Change in Lateral E/e' Ratio through 30 Months.[2]



Abbreviations: ATTR = transthyretin amyloidosis; E/e' = ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; LS = least squares; MMRM = mixed models for repeated measures; SEM = standard error of the mean.
Footnotes: *p<0.05. Results are from a MMRM with baseline 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.
From Jering et al.[2]

LV Systolic Function

Changes in LV systolic function, as assessed by LV ejection fraction, absolute peak longitudinal strain, and LV stroke volume, were evaluated in the vutrisiran and placebo arms at 30 months (**Table 4**).[2]

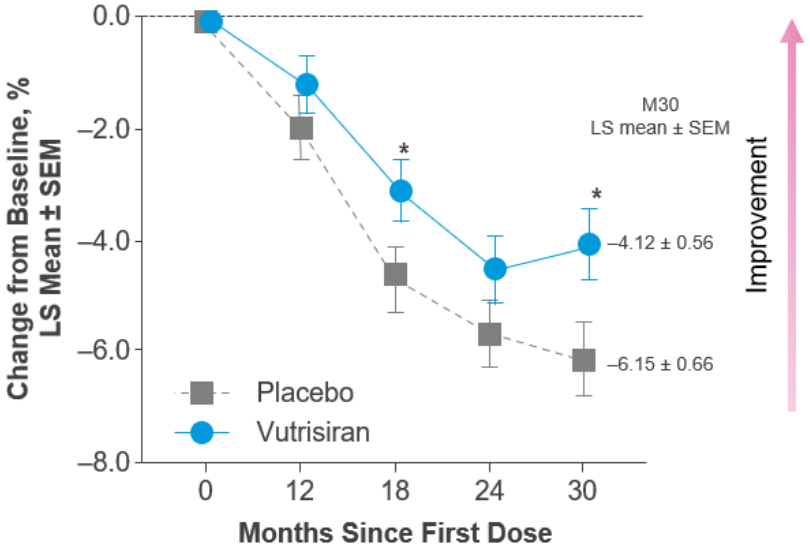
Table 4. Change in LV Systolic Function at 30 Months.[2]

Parameter	Overall Population	
	Vutrisiran – Placebo (LS Mean Difference, 95% CI)	Nominal p-value
LV ejection fraction (%)	2.03 (0.34, 3.73)	0.0190
Absolute peak longitudinal strain (%)	1.23 (0.73, 1.73)	<0.0001
LV stroke volume (mL)	4.05 (1.72, 6.38)	0.0007

Abbreviations: CI = confidence interval; LS = least squares; LV = left ventricular.

In the overall population, the LS mean (±SEM) change from baseline in LV ejection fraction at 30 months was -4.12% (±0.56) and -6.15% (±0.66) in the vutrisiran and placebo arms, respectively, resulting in a LS mean difference (95% CI) of 2.03% (0.34, 3.73) (**Figure 3**). In the monotherapy population, the LS mean difference (95% CI) in change in LV ejection fraction at 30 months between the vutrisiran and placebo arms was 2.27% (-0.07, 4.61).[2]

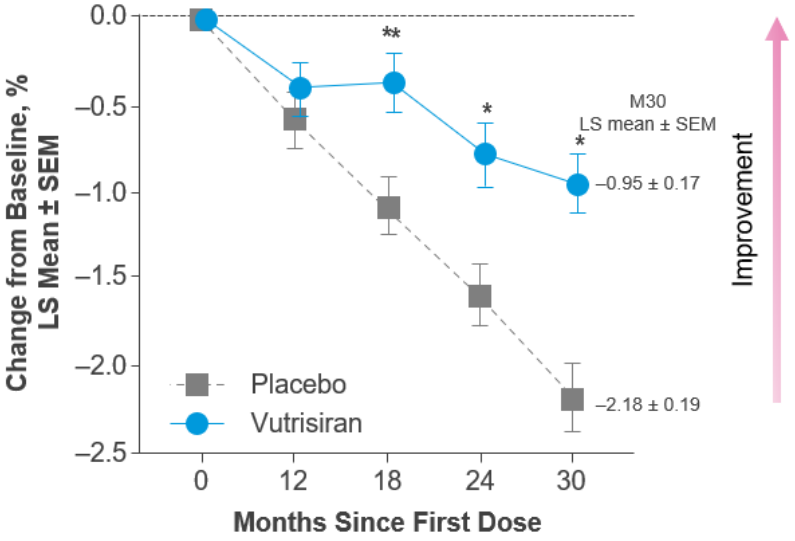
Figure 3. LS Mean Change in LV Ejection Fraction through 30 Months.[2]



Abbreviations: ATTR = transthyretin amyloidosis; LS = least squares; LV = left ventricular; MMRM = mixed models for repeated measures; SEM = standard error of the mean.
Footnotes: *p<0.05. Results are from a MMRM with baseline 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.
From Jering et al.[2]

In the overall population, the LS mean (±SEM) change from baseline in absolute peak longitudinal strain at 30 months was -0.95% (±0.17) and -2.18% (±0.19) in the vutrisiran and placebo arms, respectively, resulting in a LS mean difference (95% CI) of 1.23% (0.73, 1.73) (**Figure 4**). In the monotherapy population, the LS mean difference (95% CI) in change in absolute peak longitudinal strain at 30 months between the vutrisiran and placebo arms was 1.30% (0.59, 2.01).[2]

Figure 4. LS Mean Change in Absolute Peak Longitudinal Strain through 30 Months.[2]



Abbreviations: ATTR = transthyretin amyloidosis; LS = least squares; MMRM = mixed models for repeated measures; SEM = standard error of the mean.
Footnotes: *p<0.05. Results are from a MMRM with baseline 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.
From Jering et al.[2]

SAFETY RESULTS

In the overall population, the incidence of AEs and cardiac AEs were similar between the treatment arms. A summary of the safety results during the double-blind period are presented in **Table 5.**[1,3]

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.

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]

ABBREVIATIONS

AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; 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; hATTR = hereditary transthyretin amyloidosis; HR = hazard ratio; LS = least squares; LV = left ventricular; MMRM = mixed models for repeated measures; SAE = serious adverse event; SEM = standard error of the mean; SGLT2 = sodium-glucose cotransporter-2; TDI lateral e' = lateral peak early diastolic mitral annular tissue velocity; wtATTR = wild-type transthyretin amyloidosis.

Updated 30 September 2024

REFERENCES

1. 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
2. Jering K, Fontana M, Skali H, et al. Effects of vutrisiran on echocardiographic cardiac structure and function: The HELIOS-B trial. Presented at: Heart Failure Society of America (HFSA) Annual Scientific Meeting; September 27-30, 2024; Atlanta, GA, USA.
3. 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