Vutrisiran: HELIOS-B OLE

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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]
- After the double-blind period (33 to 36 months), all remaining eligible patients were allowed to receive vutrisiran in an OLE for up to 24 months.[2]
  - Through Month 12 of the OLE, treatment with vutrisiran compared with placebo reduced the risk in time to first CV event or all-cause mortality by 37% in the overall population (time-to-first: HR = 0.631, 95% CI: 0.506, 0.788; P=0.0001) and 42% in the monotherapy population (time-to-first: HR = 0.577, 95% CI: 0.436, 0.762; P=0.0002).[2]
  - Additional endpoints assessed at Month 12 of the OLE included ACM and changes from baseline in KCCQ-OS, NYHA class, NT-proBNP, and troponin I in the overall and monotherapy populations.[2]
  - As of Month 12 of the OLE, the median exposure to vutrisiran was 47.5 months (range 0.6-60.5) for the vutrisiran/vutrisiran group and 13.7 months (range 0.6-22.1) for the placebo/vutrisiran group. The safety of vutrisiran treatment in the OLE was consistent with results from the double-blind period.[2]

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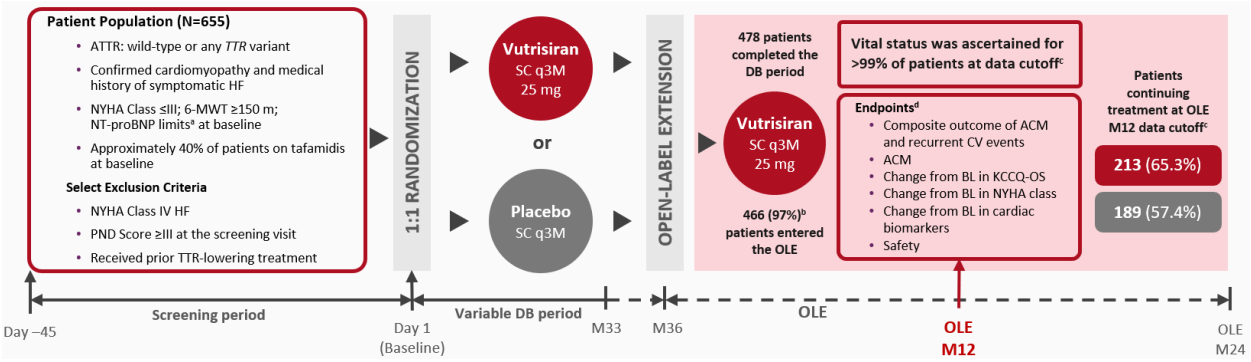
STUDY DESIGN

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).[1]

After the double-blind period, all remaining eligible patients were allowed to receive vutrisiran in an OLE for up to 24 months (**Figure 1**). Of the 478 patients who completed the double-blind period, 466 patients (97%) entered the OLE. As of the data cutoff for Month 12 of the OLE, 213 patients who initially received vutrisiran and 189 patients who initially received placebo in the double-blind period have continued treatment.[2]

Figure 1. HELIOS-B Double-Blind Period and OLE Study Design.[2]



Abbreviations: 6-MWT = 6-minute walk test; ACM = all-cause mortality; ATTR = transthyretin amyloidosis; BL = baseline; CV = cardiovascular; DB = double-blind; HF = heart failure: KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; M = month; NT-proBNP = *N*-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; PND = polyneuropathy disability; q3M = every 3 months; SC = subcutaneous; TTR = transthyretin.

[a]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or > 600 pg/mL and <8500 pg/mL for patients with atrial fibrillation).

[b]259 patients (55.6%) were in the monotherapy population.

[c]Month 12 OLE data cutoff as of April 9, 2025.

[d]6-MWT and echocardiography measures were not analyzed in the OLE.

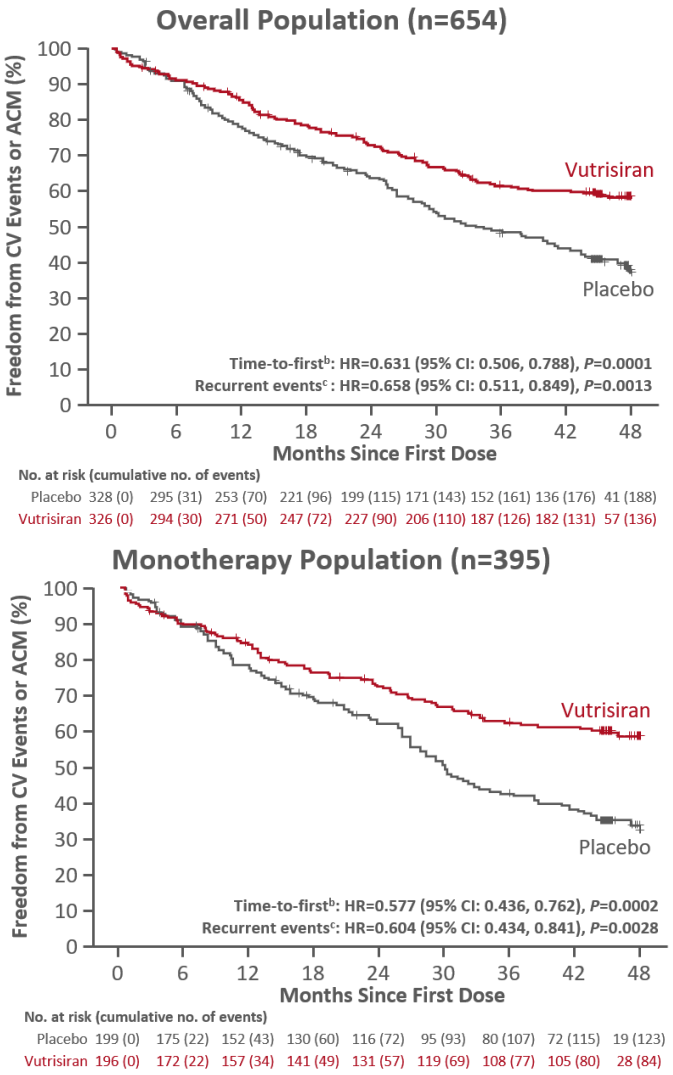
From Garcia-Pavia et al.[2]

EFFICACY RESULTS

Composite of All-Cause Mortality and Recurrent CV Events

Treatment with vutrisiran compared with placebo reduced the risk in time to first CV event or all-cause mortality through Month 48 (Month 12 of the OLE) by 37% in the overall population (time-to-first: HR = 0.631, 95% CI: 0.506, 0.788; P=0.0001) and 42% in the monotherapy population (time-to-first: HR = 0.577, 95% CI: 0.436, 0.762; P=0.0002) (**Figure 2**).[2]

Figure 2. Time to First CV Event or All-Cause Mortality Through Month 12 of the OLE.[2,a]



Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; IPTW = inverse probability of treatment weighting; LWYY = Lin, Wei, Yang, and Ying; NT-proBNP = *N*-terminal prohormone of B-type natriuretic peptide; OLE = open-label extension.

[a]All-cause mortality includes heart transplantation and left ventricular assist device placement. CV events include CV-related hospitalizations and urgent heart failure visits.

[b]Survival probability based on IPTW-adjusted Kaplan-Meier curves. The HR is derived from Cox proportional hazards model.

[c]Recurrent events analysis based on the modified Andersen-Gill model, also known as LWYY.

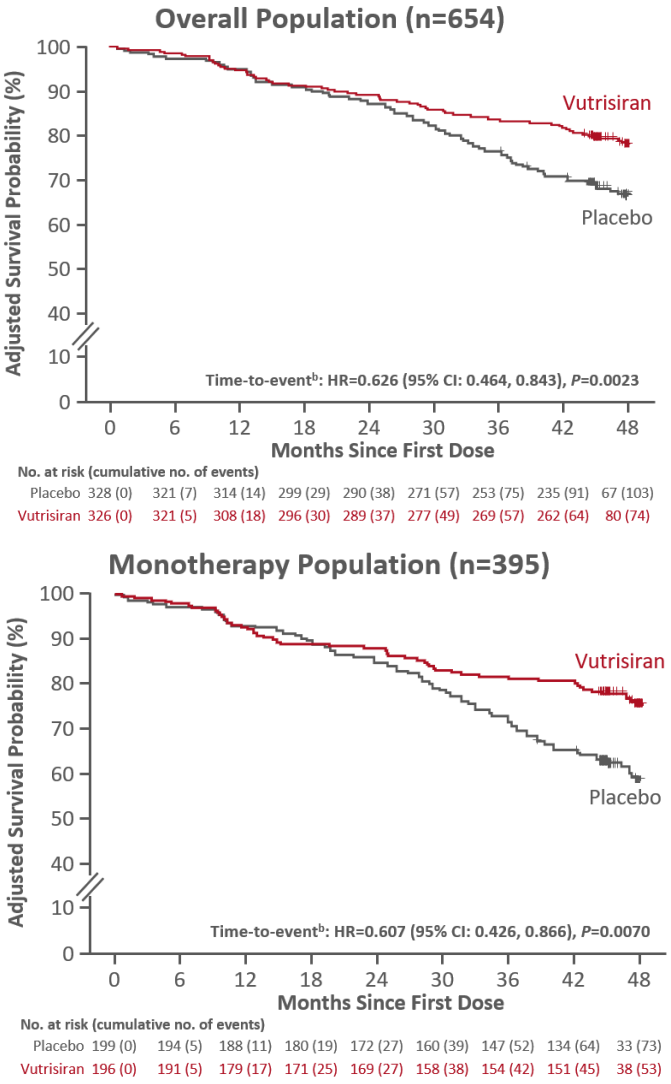
Given significant NT-proBNP baseline imbalance, IPTW-adjusted Kaplan-Meier curves are shown for a balanced visualization consistent with the prespecified NT-proBNP adjusted Cox analysis.

From Garcia-Pavia et al.[2]

All-Cause Mortality

Treatment with vutrisiran compared with placebo reduced the risk of all-cause mortality through Month 48 (Month 12 of the OLE) by 37% in the overall population (time-to-event: HR = 0.626, 95% CI: 0.464, 0.843; P=0.0023) and 39% in the monotherapy population (time-to-event: HR = 0.607, 95% CI: 0.426, 0.866; P=0.0070) (**Figure 3**).[2]

Figure 3. Time to All-Cause Mortality Through Month 12 of the OLE.[2,a]



Abbreviations: CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; NT-proBNP = *N*-terminal prohormone of B-type natriuretic peptide; OLE = open-label extension.

[a]All-cause mortality includes heart transplantation and left ventricular assist device placement.

[b]Survival probability based on IPTW-adjusted Kaplan-Meier curves. The HR is derived from Cox proportional hazards model. P-value derived from log-rank test.

Given significant NT-proBNP baseline imbalance, IPTW-adjusted Kaplan-Meier curves are shown for a balanced visualization consistent with the prespecified NT-proBNP adjusted Cox analysis.

From Garcia-Pavia et al.[2]

KCCQ-OS

The changes from baseline in KCCQ-OS at Month 12 of the OLE in the overall and monotherapy populations are summarized in **Table 1**. The median (95% CI) changes from baseline in KCCQ-OS in the overall and monotherapy populations are presented in **Figure 4.**[2]

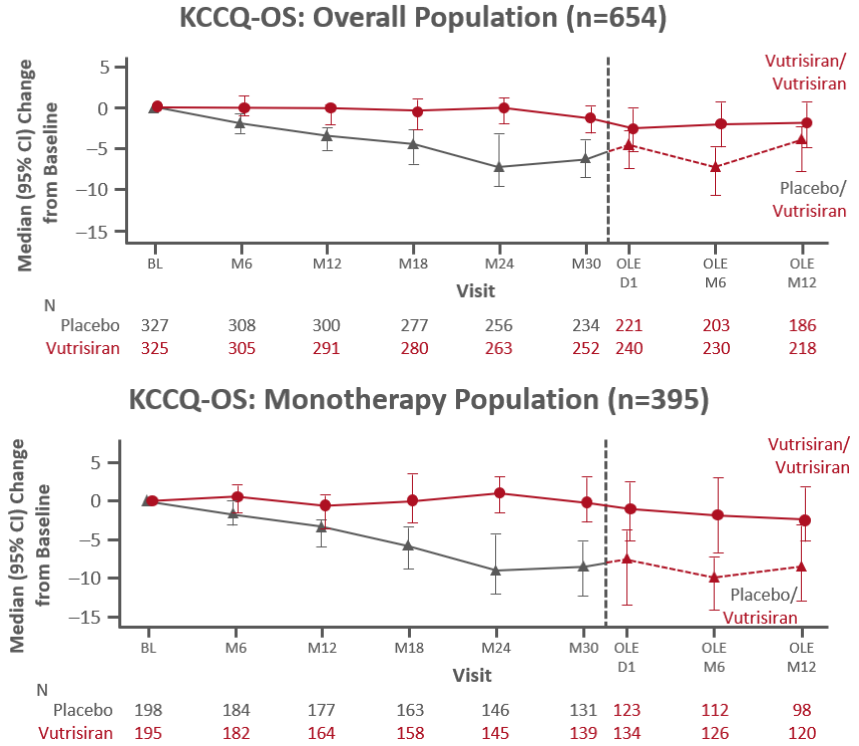
Table 1. Change from Baseline in KCCQ-OS at Month 12 of the OLE.[2]

KCCQ-OS, change from baseline at M12 of the OLE	Overall Population		Monotherapy Population	
	Placebo (n=328)	Vutrisiran (n=326)	Placebo (n=199)	Vutrisiran (n=196)
n	186	218	98	120
Median	-3.9	-1.9	-8.5	-2.5
LS mean (SEM)	-21.32 (1.33)	-12.37 (1.29)	-26.68 (1.79)	-15.29 (1.87)
LSMD (95% CI)[a]	8.95 (5.31, 12.59)		11.40 (6.31, 16.48)	
P-value	<0.001		<0.001	

Abbreviations: CI = confidence interval; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; LSMD = least squares mean difference; M = month; MMRM = mixed models with repeated measures; OLE = open-label extension; SEM = standard error of the mean.

[a]Derived from MMRM model.

Figure 4. Median Change from Baseline in KCCQ-OS Through Month 12 of the OLE.[2]



Abbreviations: BL = baseline; CI = confidence interval; D = day; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; M = month; OLE = open-label extension.

95% CIs for median change are calculated from the distribution-free method of order statistics (ranks).

From Garcia-Pavia et al.[2]

NYHA Class

The proportion of patients with stable or improved NYHA class from baseline at Month 12 of the OLE are summarized in **Table 2**.[2]

Table 2. Proportion of Patients with Stable or Improved NYHA Class from Baseline at Month 12 of the OLE.[2]

NYHA Class, stable/improved from baseline at M12 of the OLE	Overall Population		Monotherapy Population	
	Placebo (n=328)	Vutrisiran (n=326)	Placebo (n=199)	Vutrisiran (n=196)
n (%)	150 (45.7)	176 (54.0)	78 (39.2)	98 (50.0)
Adjusted difference in % of patients stable/improved (95% CI)	10.3 (2.6, 17.9)		13.7 (4.0, 23.4)	
OR of being stable/improved (95% CI)[a]	1.6 (1.1, 2.2)		1.9 (1.2, 2.9)	
P-value	<0.01		<0.01	

Abbreviations: CI = confidence interval; M = month; OLE = open-label extension; OR = odds ratio.
[a]Derived from logistic regression model.

Cardiac Biomarkers

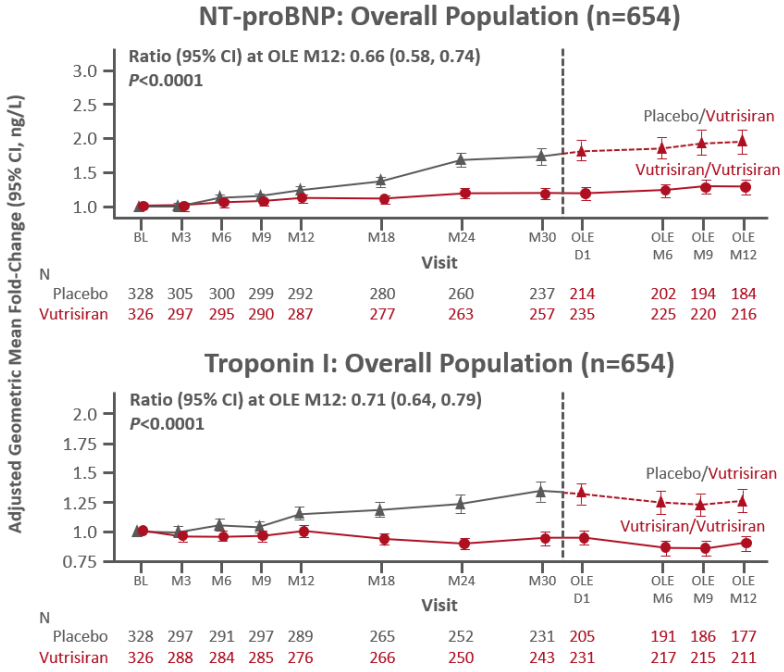
NT-proBNP

Treatment with vutrisiran compared with placebo resulted in an adjusted geometric mean fold-change ratio of 0.66 (95% CI: 0.58, 0.74) and 0.55 (95% CI: 0.47, 0.64) for NT-proBNP from baseline to Month 12 of the OLE in the overall and monotherapy populations, respectively (**Figures 5 and 6**).[2]

Troponin I

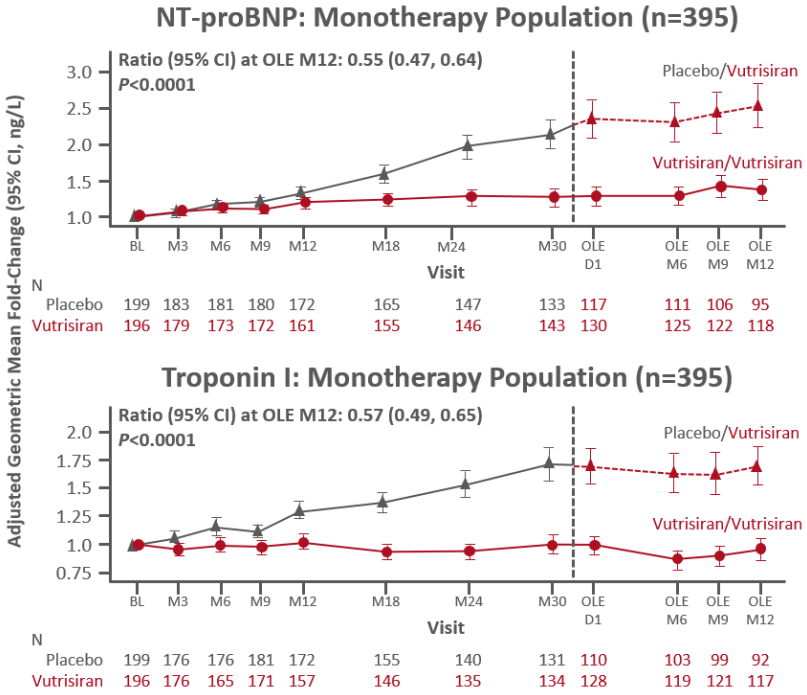
Treatment with vutrisiran compared with placebo resulted in an adjusted geometric mean fold-change ratio of 0.71 (95% CI: 0.64, 0.79) and 0.57 (95% CI: 0.49, 0.65) for troponin I from baseline to Month 12 of the OLE in the overall and monotherapy populations, respectively (**Figures 5 and 6**).[2]

Figure 5. NT-proBNP and Troponin I Through Month 12 of the OLE in the Overall Population.[2]



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.[2]

Figure 6. NT-proBNP and Troponin I Through Month 12 of the OLE in the Monotherapy Population.[2]



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.[2]

SAFETY RESULTS

The median exposure to vutrisiran was 47.5 months (range 0.6-60.5) for the vutrisiran/vutrisiran group and 13.7 months (range 0.6-22.1) for the placebo/vutrisiran group. The exposure-adjusted event rates per 100 PY of the placebo/vutrisiran and vutrisiran/vutrisiran groups are summarized in **Table 3**.[2]

The safety data for long-term treatment with vutrisiran through Month 12 of the OLE were consistent with those reported for the double-blind period. The rates of AEs did not increase with longer treatment. Higher event rates for SAEs and severe AEs in the placebo/vutrisiran group compared with the vutrisiran/vutrisiran group were consistent with more advanced disease following placebo treatment during the double-blind period.[2]

Table 3. Safety Results During the Vutrisiran Exposure Period.[2,a]

	Exposure-adjusted event rate per 100 PY	
	Placebo/vutrisiran during the OLE (n=233; 252.7 PY[a])	Vutrisiran/vutrisiran during the study (n=326; 1123.1 PY[a])
AEs	600.5	427.8
SAEs	110.8	62.9
Severe AEs	76.7	43.9
AEs leading to treatment discontinuation	2.0	0.8

Abbreviations: AE = adverse event; OLE = open-label extension; PY = patient-years; SAE = serious adverse event.
[a]Exposure to study drug during vutrisiran treatment.

ABBREVIATIONS

6-MWT = 6-minute walk test; ACM = all-cause mortality; AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; BL = baseline; CI = confidence interval; CV = cardiovascular; D = day; DB = double-blind; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; HR = hazard ratio; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; LSMD = least squares mean difference; M = month; MMRM = mixed models with repeated measures; NT-proBNP = *N*-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; OR = odds ratio; PND = polyneuropathy disability; PY = patient-years; q3M = every 3 months; SAE = serious adverse event; SC = subcutaneous; SEM = standard error of the mean; 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*. 2025;392(1):33-44. doi:10.1056/NEJMoa2409134
2. Garcia-Pavia P, Witteles R, Morbach C, et al. HELIOS-B: 12-month results from the open-label extension period of vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. Presented at: European Society of Cardiology (ESC); August 29-September 1, 2025; Madrid, Spain.