HELIOS-B: 12-Month Results from the Open-Label Extension Period of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

HELIOS·B

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Rationale and Study Design

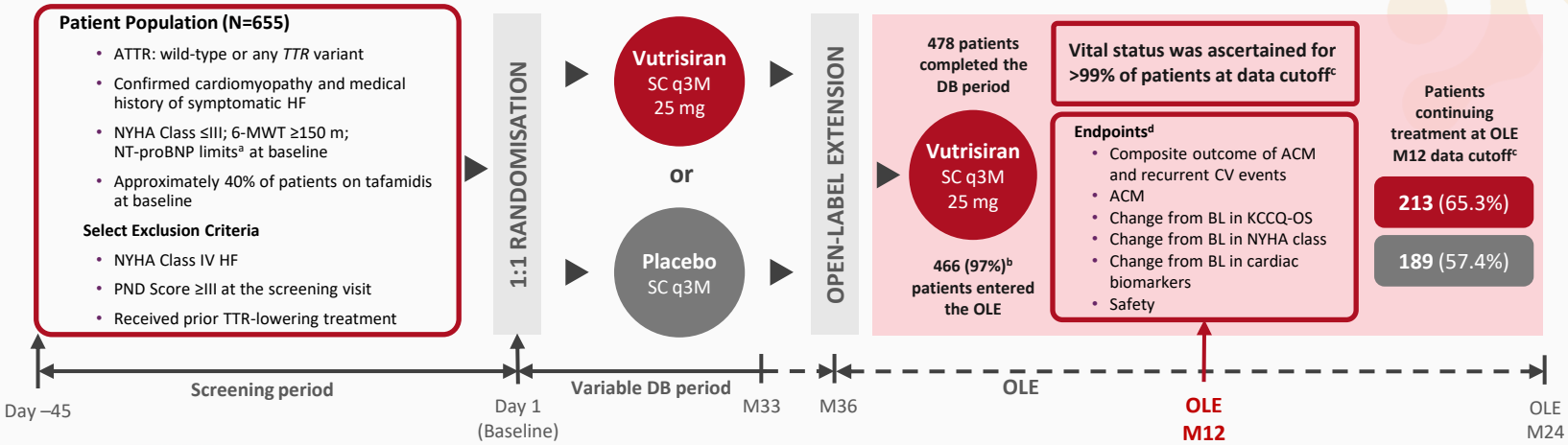
Background

- ATTR-CM is a progressive, fatal disease caused by accumulation of TTR amyloid fibrils in the heart[1]
- Over the HELIOS-B DB period, the RNAi therapeutic vutrisiran lowered the risk of ACM and recurrent CV events vs placebo in patients with ATTR-CM[2]

Objectives

- To present efficacy data through Month 12 of the OLE and all available safety data from HELIOS-B in the overall and monotherapy populations (patients not on tafamidis at baseline)

HELIOS-B Study Design: A Double-Blind, Randomised, Placebo-Controlled Trial



[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 data cutoff: 9 April 2025. [d]6-MWT and echocardiography measures were not analyzed in the OLE. **References:** 1. Ruberg et al. *J Am Coll Cardiol.* 2019;73:2872–92; 2. Fontana M et al. *N Engl J Med*. 2025;392:33–44.

Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; 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; RNAi, RNA interference; SC, subcutaneous; TTR, transthyretin.

Long-Term Vutrisiran Treatment Significantly Reduced the Risk of the Composite Endpoint of ACM and CV Events

Risk reduction of 37% and 42% in the overall and monotherapy populations

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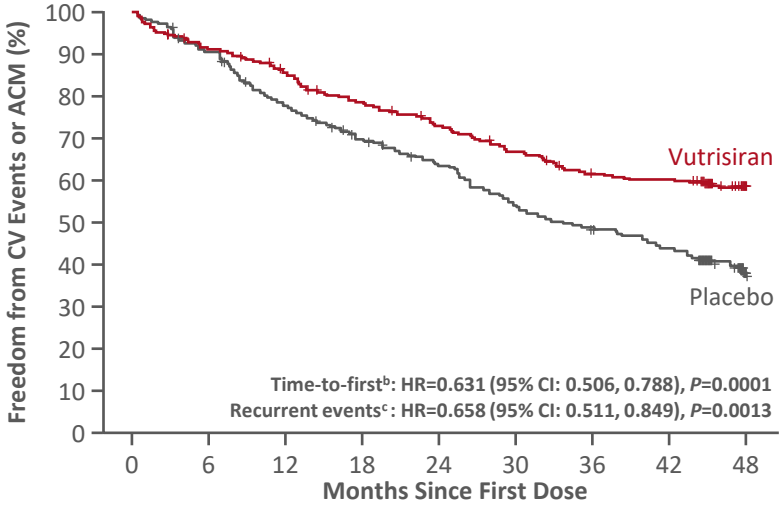
Time-to-First CV Event or ACM[a]

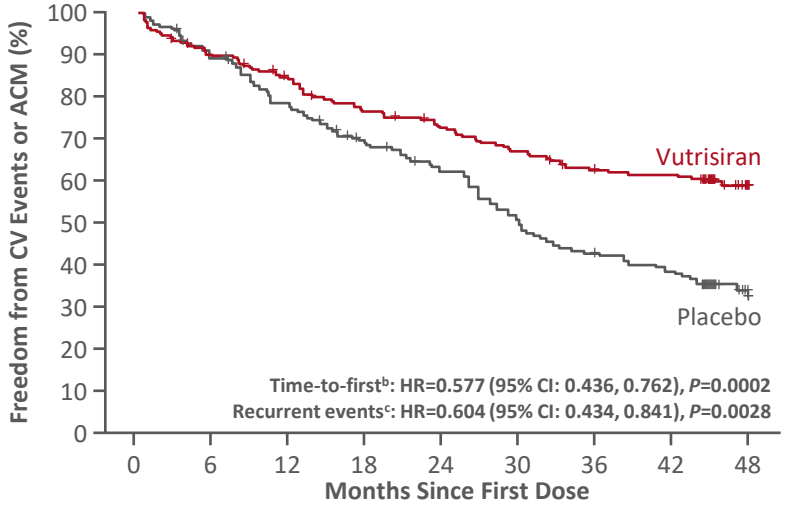
Overall Population (n=654)



No. at risk (cumulative no. of events)

Placebo	328 (0)	295 (31)	253 (70)	221 (96)	199 (115)	171 (143)	152 (161)	136 (176)	41 (188)
Vutrisiran	326 (0)	294 (30)	271 (50)	247 (72)	227 (90)	206 (110)	187 (126)	182 (131)	57 (136)

Monotherapy Population (n=395)



No. at risk (cumulative no. of events)

Placebo	199 (0)	175 (22)	152 (43)	130 (60)	116 (72)	95 (93)	80 (107)	72 (115)	19 (123)
Vutrisiran	196 (0)	172 (22)	157 (34)	141 (49)	131 (57)	119 (69)	108 (77)	105 (80)	28 (84)

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

[a]All-cause mortality includes heart transplantation and left ventricular assist device placement, and CV events include CV-related hospitalisations 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.

Abbreviations: ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LWYY, Lin, Wei, Yang , and Ying; OLE, open-label extension.

Long-Term Vutrisiran Treatment Significantly Reduced the Risk of ACM

Risk reduction of 37% and 39% in the overall and monotherapy populations

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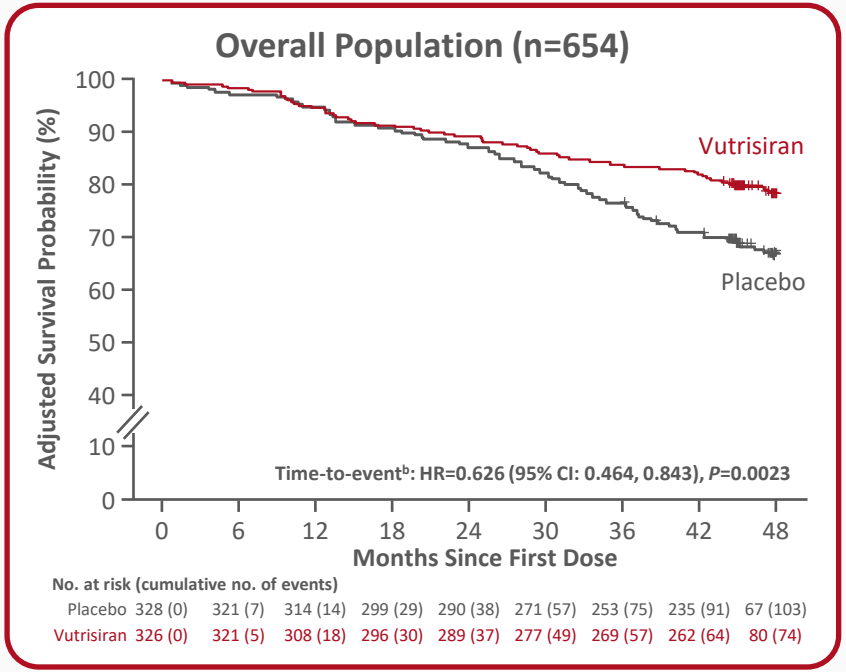
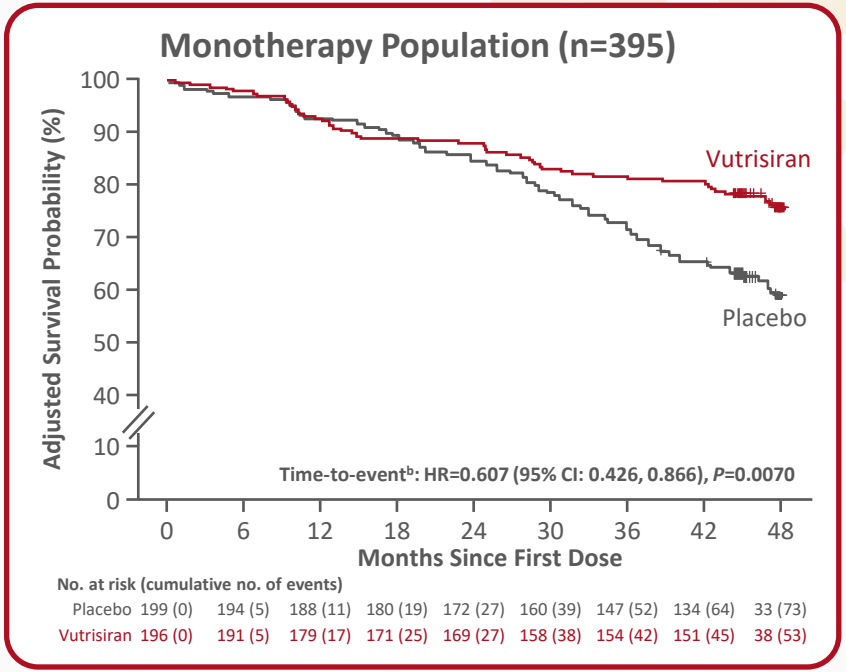
Time to ACM[a]





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

[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.

Abbreviations: ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting.

Favourable Impact with Long-Term Vutrisiran Treatment

Benefit on multiple measures of disease progression maintained relative to placebo

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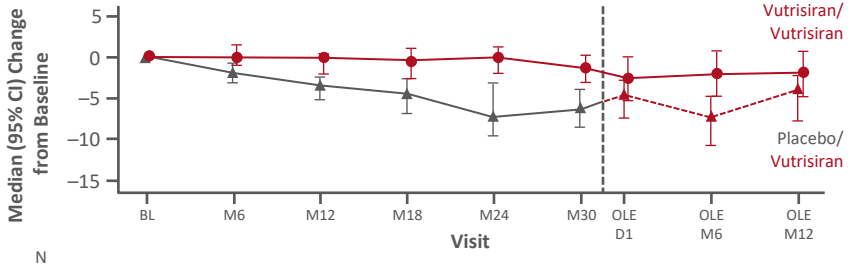
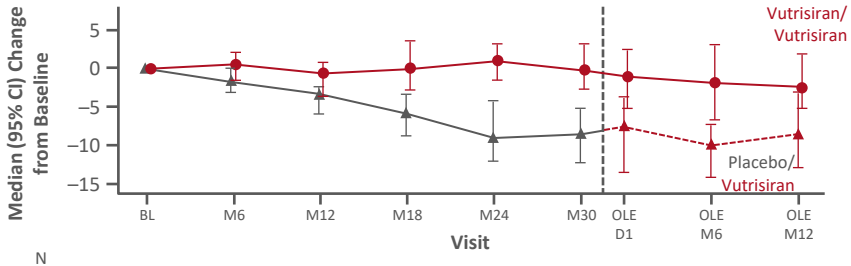
Endpoint	Overall Population		Monotherapy Population	
	Placebo (n=328)	Vutrisiran (n=326)	Placebo (n=199)	Vutrisiran (n=196)
KCCQ-OS, change from baseline at M12 of OLE				
n	186	218	98	120
Median	–3.9	–1.9	–8.5	–2.5
LS mean (SEM)	–21.32 (1.33)	–12.37 (1.29)	–26.68 (1.79)	–15.29 (1.87)
LS mean difference (95% CI)[a]	**8.95 (5.31, 12.59)**		**11.40 (6.31, 16.48)**	
P-value	<0.001		<0.001	
NYHA Class stable/improved from baseline at M12 of OLE				
n (%)	150 (45.7)	176 (54.0)	78 (39.2)	98 (50.0)
Adjusted difference in % patients stable/improved (95% CI)	**10.3 (2.6, 17.9)**		**13.7 (4.0, 23.4)**	
OR of being stable/improved (95% CI)[b]	1.6 (1.1, 2.2)		1.9 (1.2, 2.9)	
P-value	<0.01		<0.01	

KCCQ-OS[c]: Overall Population (n=654)



N	BL	M6	M12	M18	M24	M30	OLE D1	OLE M6	OLE M12
Placebo	327	308	300	277	256	234	221	203	186
Vutrisiran	325	305	291	280	263	252	240	230	218

KCCQ-OS[c]: Monotherapy Population (n=395)



N	BL	M6	M12	M18	M24	M30	OLE D1	OLE M6	OLE M12
Placebo	198	184	177	163	146	131	123	112	98
Vutrisiran	195	182	164	158	145	139	134	126	120

[a]Derived from MMRM model. [b]Derived from logistic regression model. [c]95% CIs for median change are calculated from the distribution-free method of order statistics (ranks).
Abbreviations: BL, baseline; CI, confidence interval; D, day; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS, least squares; M, month; MMRM, mixed model with repeated measures; NYHA, New York Heart Association; OLE, open-label extension; OR, odds ratio; SEM, standard error of the mean.

Favourable Impact of Vutrisiran on Established Cardiac Biomarkers

Relative stability maintained with long-term vutrisiran

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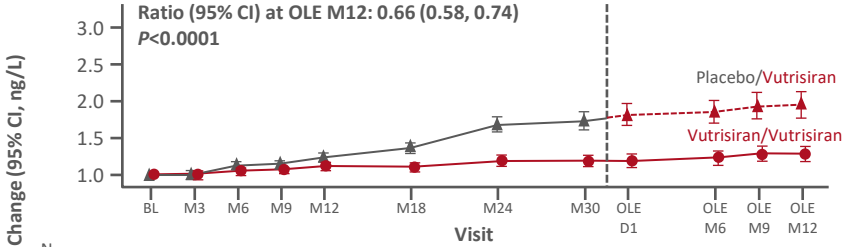
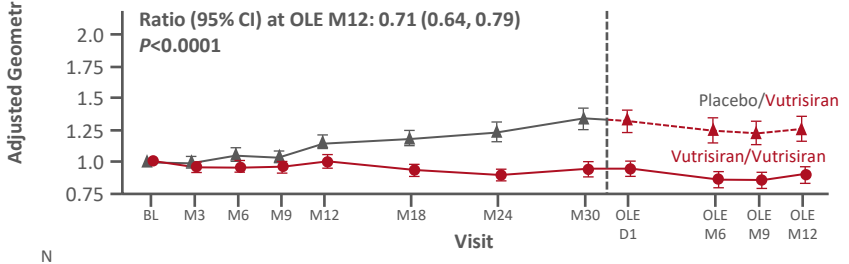
NT-proBNP: Overall Population (n=654)



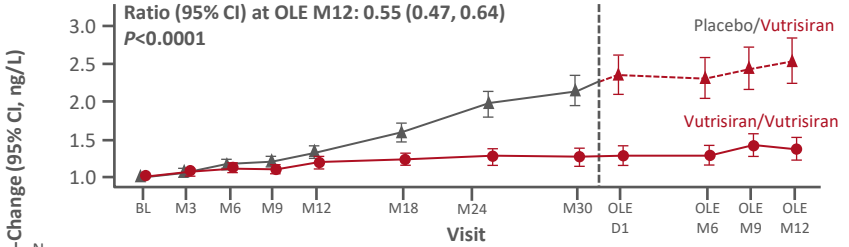
N	BL	M3	M6	M9	M12	M18	M24	M30	OLE D1	OLE M6	OLE M9	OLE M12
Placebo	328	305	300	299	292	280	260	237	214	202	194	184
Vutrisiran	326	297	295	290	287	277	263	257	235	225	220	216

Troponin I: Overall Population (n=654)



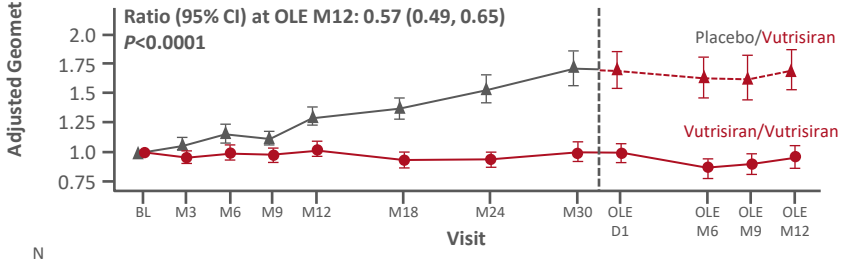
N	BL	M3	M6	M9	M12	M18	M24	M30	OLE D1	OLE M6	OLE M9	OLE M12
Placebo	328	297	291	297	289	265	252	231	205	191	186	177
Vutrisiran	326	288	284	285	276	266	250	243	231	217	215	211

NT-proBNP: Monotherapy Population (n=395)



N	BL	M3	M6	M9	M12	M18	M24	M30	OLE D1	OLE M6	OLE M9	OLE M12
Placebo	199	183	181	180	172	165	147	133	117	111	106	95
Vutrisiran	196	179	173	172	161	155	146	143	130	125	122	118

Troponin I: Monotherapy Population (n=395)



N	BL	M3	M6	M9	M12	M18	M24	M30	OLE D1	OLE M6	OLE M9	OLE M12
Placebo	199	176	176	181	172	155	140	131	110	103	99	92
Vutrisiran	196	176	165	171	157	146	135	134	128	119	121	117

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; BL, baseline; CI, confidence interval; D, day; M, month; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; OLE, open-label extension.

Safety Profile During Vutrisiran Exposure Period

Long-term treatment with vutrisiran was well tolerated

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	Exposure-adjusted event rate per 100 PY	
	Placebo/vutrisiran during the OLE (n=223; 252.8 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

- Median vutrisiran exposure 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
- Safety data for long-term vutrisiran treatment through 1 year of the OLE were consistent with those reported for the double-blind period
  - The rate of AEs, including cardiac events, did not increase with longer treatment
- Higher event rates for SAEs and severe AEs for the placebo/vutrisiran group compared with the vutrisiran/vutrisiran group are consistent with more advanced disease following placebo treatment during the double-blind period

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

Conclusions

The significant clinical benefits of vutrisiran versus placebo were maintained with long-term treatment

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- Reduced ACM and CV events with vutrisiran vs placebo persisted through 1-year of OLE treatment
  - Risk reduction of 37% (overall population) and 42% (monotherapy population) in time to first CV event or ACM
  - Risk reduction of 37% (overall population) and 39% (monotherapy population) in ACM
- Vutrisiran demonstrated continued benefit on clinical measures of disease progression including QoL and cardiac biomarkers
  - In long-term vutrisiran patients, relative stability in QoL and cardiac biomarkers was maintained through 12 months of the OLE, demonstrating durable benefits
  - Loss of QoL in the placebo group during the DB period may not be fully reversable after starting vutrisiran, highlighting the importance of early treatment
- The long-term safety and tolerability profile was consistent with the established profile of vutrisiran
- These data add to the primary analysis of the study in further suggesting that vutrisiran has the potential to become a standard of care for newly diagnosed patients and those progressing on other therapies

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the HELIOS-B study

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Abbreviations: ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; DB, double-blind; OLE, open-label extension; QoL, quality of life.