

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

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Rationale and Study Design

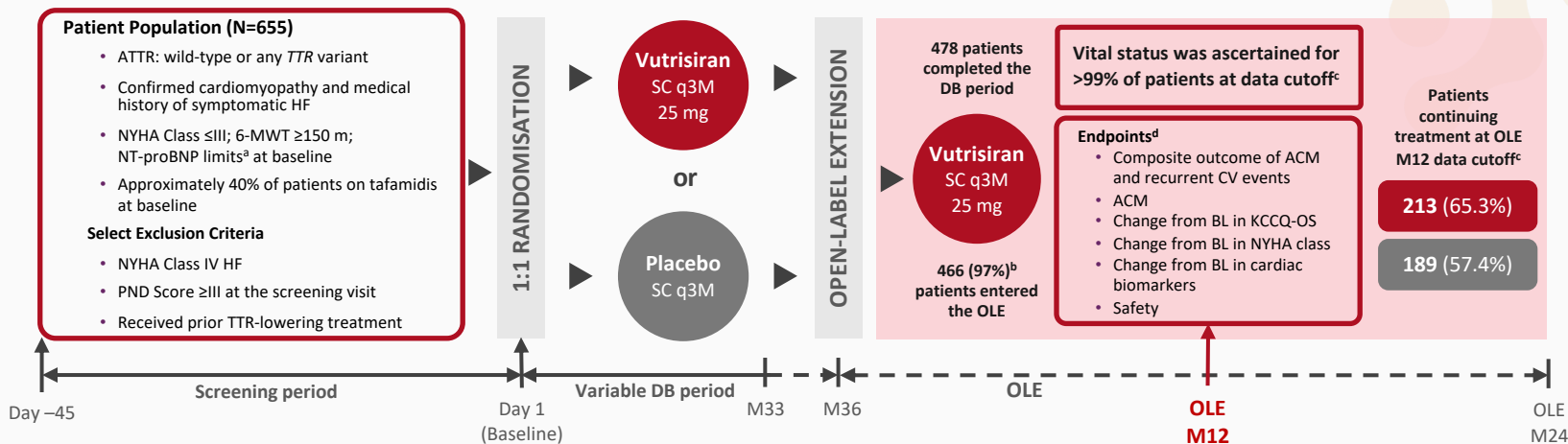
Background

- ATTR-CM is a progressive, fatal disease caused by accumulation of TTR amyloid fibrils in the heart¹
- 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-CM²

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

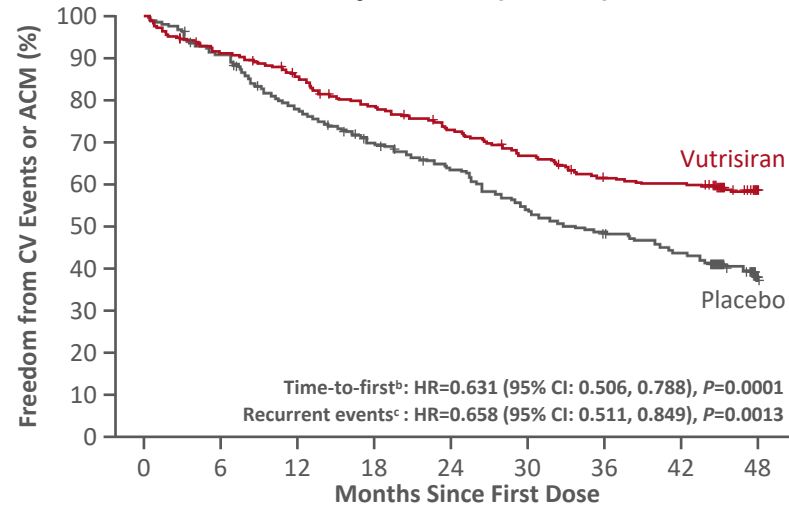


Long-Term Vutrisiran Treatment Significantly Reduced the Risk of the Composite Endpoint of ACM and CV Events

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

Time-to-First CV Event or ACM^a

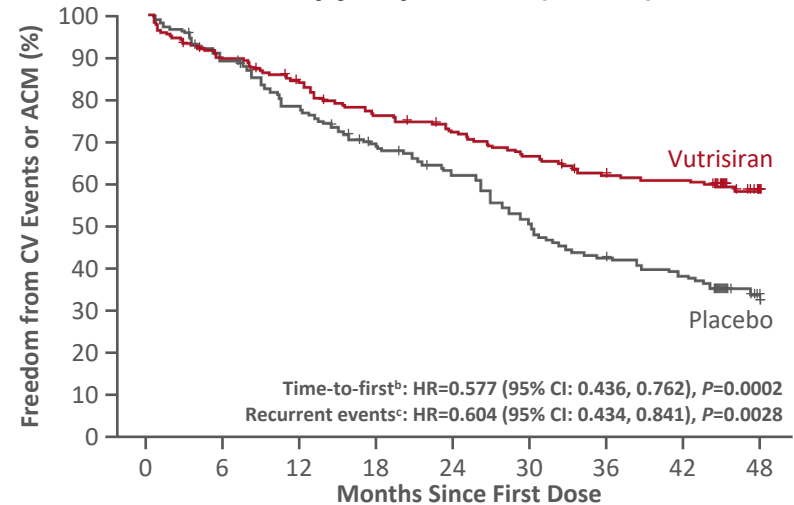
Overall Population (n=654)



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)

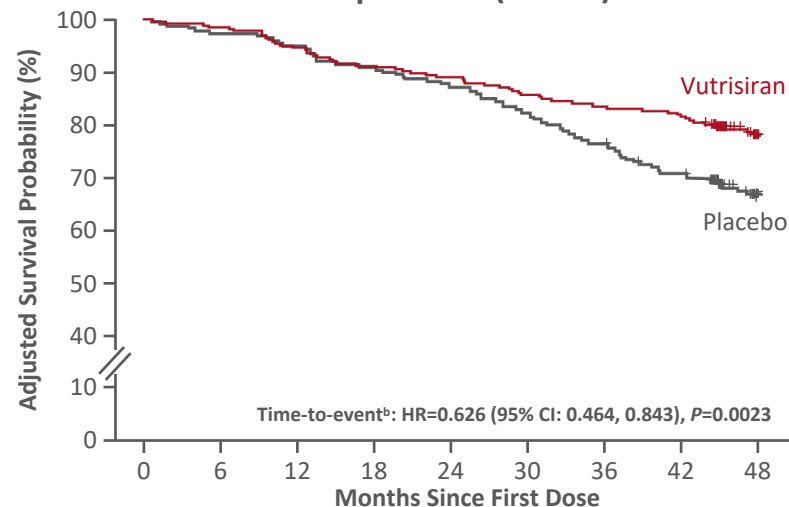
Given significant NT-proBNP baseline imbalance, IPTW-adjusted Kaplan-Meier curves are shown for a balanced visualisation consistent with the pre-specified NT-proBNP adjusted Cox analysis.

Long-Term Vutrisiran Treatment Significantly Reduced the Risk of ACM

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

Time to ACM^a

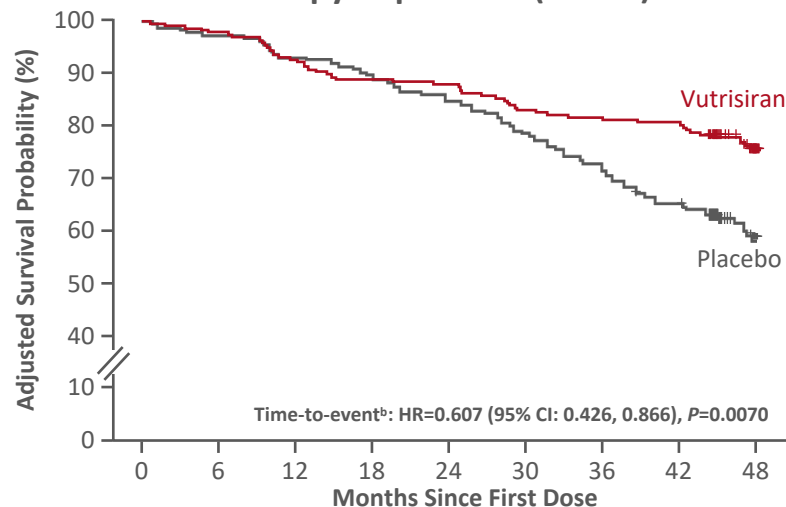
Overall Population (n=654)



No. at risk (cumulative no. of events)

Placebo	328 (0)	321 (7)	314 (14)	299 (29)	290 (38)	271 (57)	253 (75)	235 (91)	67 (103)
Vutrisiran	326 (0)	321 (5)	308 (18)	296 (30)	289 (37)	277 (49)	269 (57)	262 (64)	80 (74)

Monotherapy Population (n=395)



No. at risk (cumulative no. of events)

Placebo	199 (0)	194 (5)	188 (11)	180 (19)	172 (27)	160 (39)	147 (52)	134 (64)	33 (73)
Vutrisiran	196 (0)	191 (5)	179 (17)	171 (25)	169 (27)	158 (38)	154 (42)	151 (45)	38 (53)

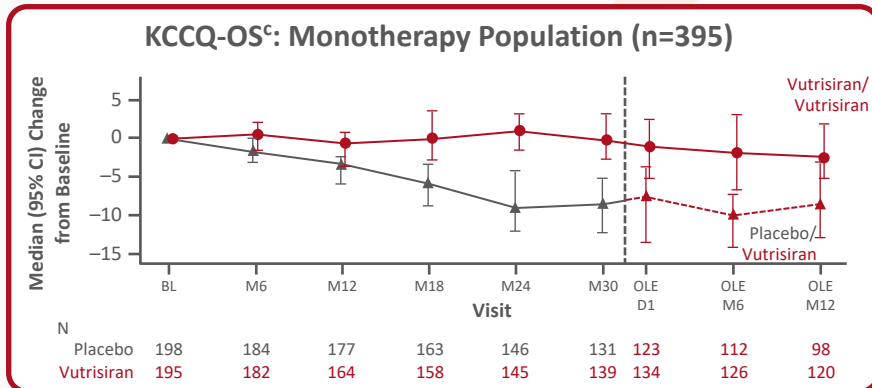
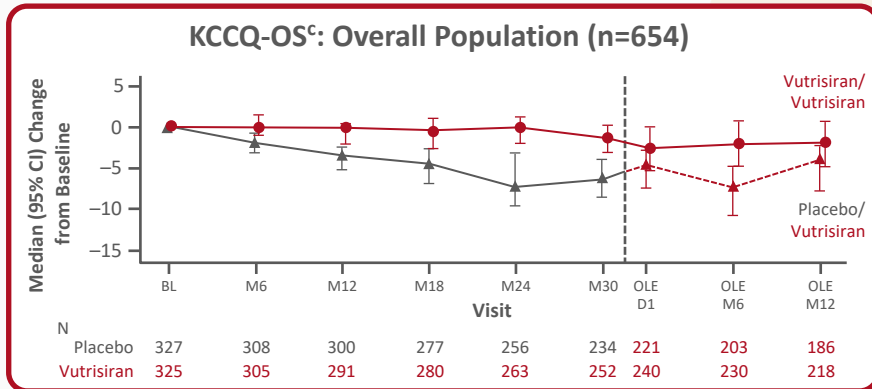
Given significant NT-proBNP baseline imbalance, IPTW-adjusted Kaplan-Meier curves are shown for a balanced visualisation consistent with the pre-specified NT-proBNP adjusted Cox analysis.

^aAll-cause mortality includes heart transplantation and left ventricular assist device placement. ^bSurvival 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

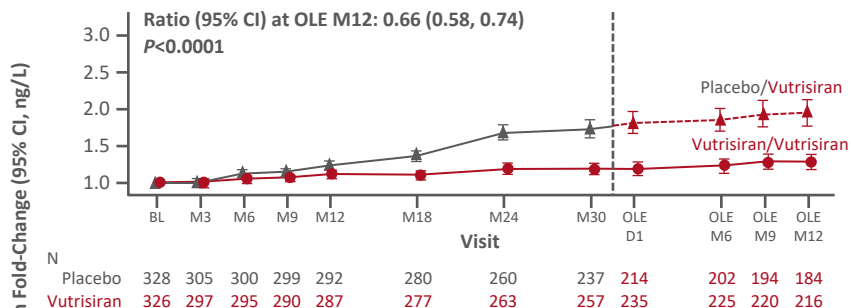
Endpoint	Overall Population		Monotherapy Population	
	Placebo (n=328)	Vutrisiran (n=326)	Placebo (n=199)	Vutrisiran (n=196)
KCCQ-OS, change from baseline at M12 of OLE				
n	186	218	98	120
Median	−3.9	−1.9	−8.5	−2.5
LS mean (SEM)	−21.32 (1.33)	−12.37 (1.29)	−26.68 (1.79)	−15.29 (1.87)
LS mean difference (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	



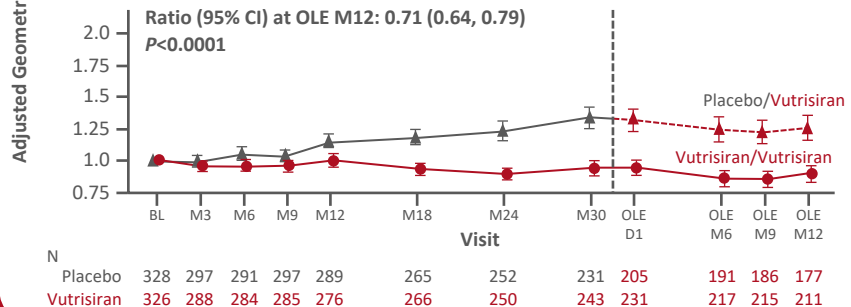
Favourable Impact of Vutrisiran on Established Cardiac Biomarkers

Relative stability maintained with long-term vutrisiran

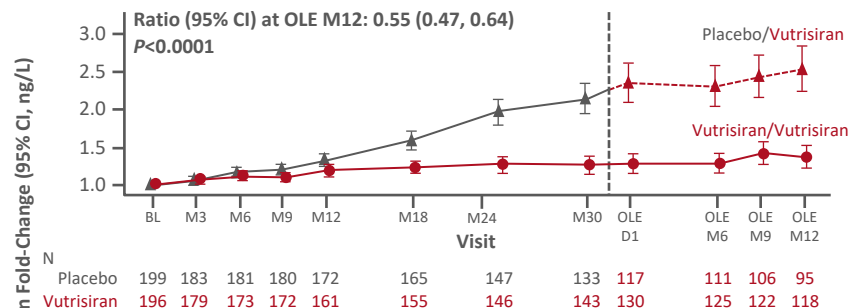
NT-proBNP: Overall Population (n=654)



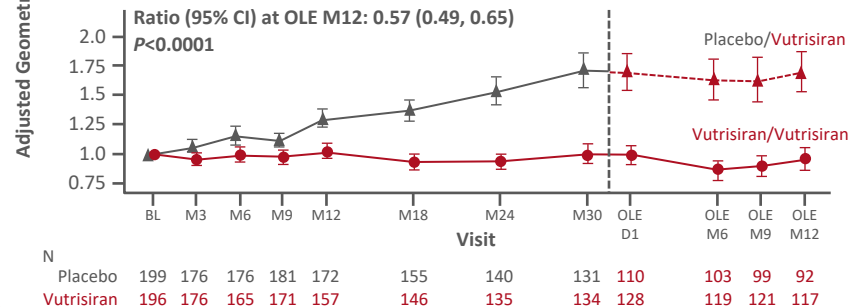
Troponin I: Overall Population (n=654)



NT-proBNP: Monotherapy Population (n=395)



Troponin I: Monotherapy Population (n=395)



Safety Profile During Vutrisiran Exposure Period

Long-term treatment with vutrisiran was well tolerated

	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

Conclusions

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

- 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 reversible 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