Vutrisiran Reduces All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events in Patients with Transthyretin Amyloid Cardiomyopathy: Analysis from the HELIOS-B Trial

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Introduction

Transthyretin Amyloidosis (ATTR) with Cardiomyopathy (ATTR-CM)

- ATTR is a progressive, fatal and systemic disease, which is caused by misfolded amyloidogenic TTR deposits accumulating in multiple tissues and is associated with high morbidity and mortality; patients with ATTR-CM can experience progressive heart failure, cardiac arrhythmias, and increased hospitalisations[1–5]

HELIOS-B Study

- Vutrisiran, a recently approved[6] RNAi therapeutic that reduces the production of variant and wild-type TTR, was evaluated in patients with ATTR-CM in the HELIOS-B study (NCT04153149)[7]
- In HELIOS-B, vutrisiran reduced risk of a composite endpoint of ACM and CV events in patients with ATTR-CM during the 33–36-month DB period and reduced risk of ACM through 42 months, including up to 6 months of follow-up in the OLE[7]
- At the time of the primary analysis data cut (08 May 2024) vital status was ascertained for >99% of randomised patients, and 42.4% of ongoing patients had data through 42 months

Objectives

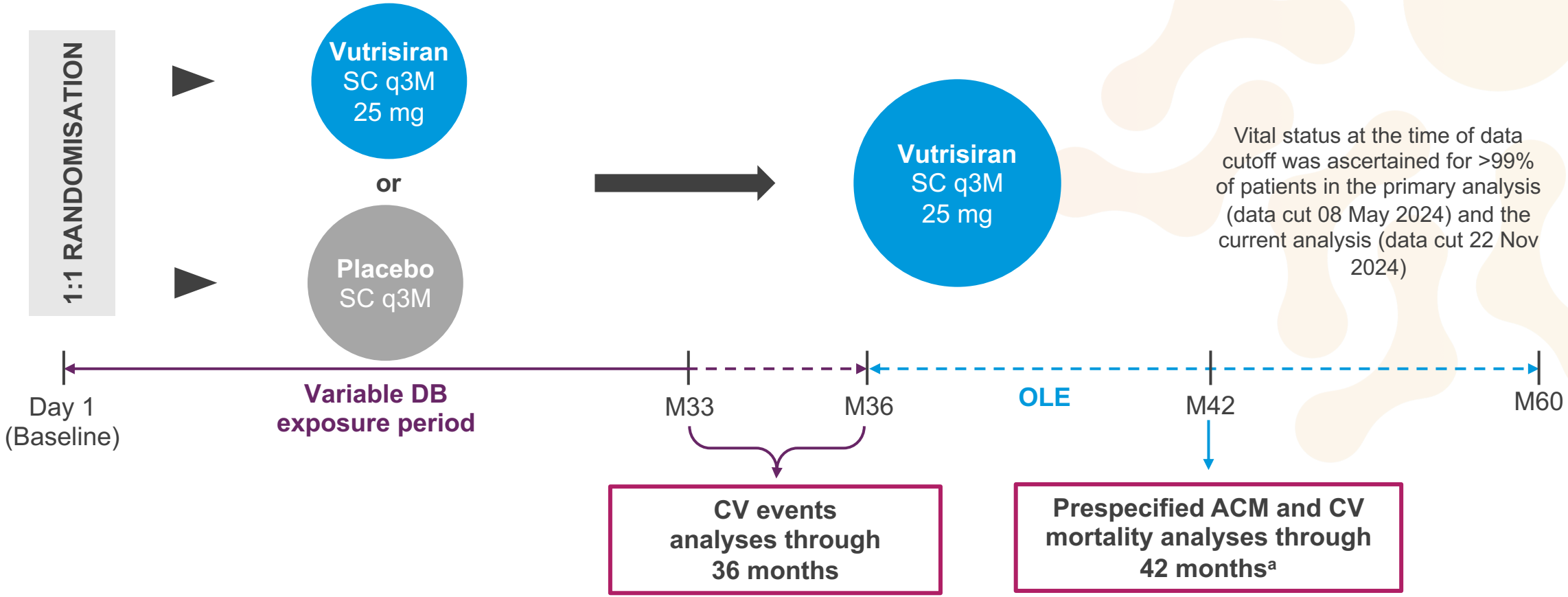
- To report a prespecified analysis of ACM and CV mortality in HELIOS-B based on an updated data cut (22 Nov 2024) with additional patient follow-up through 42 months
- To report analyses of CV events during the 33–36-month DB period using the primary analysis data cut (08 May 2024)

Abbreviations: ACM, all-cause mortality; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; CV, cardiovascular; DB, double-blind; OLE, open-label extension; RNAi, RNA interference; TTR, transthyretin.

References: 1. Maurer MS et al. *Circ Heart Fail* 2019;12:e006075; 2. Ruberg FL et al. *JAMA*. 2024;331:778-791; 3. Nativi-Nicolau JN et al. *Heart Fail Rev*. 2022;27:785–793; 4. Garcia-Pavia et al. *Eur J Heart Fail.* 2021;23:512–526; 5. Brito D et al. *Glob Heart*. 2023;18:59; 6. Alnylam Pharmaceuticals Inc. https://www.alnylam.com/sites/default/files/pdfs/amvuttra-us-prescribing-information.pdf (2025); 7. Fontana M et al. *N Engl J Med*. 2025 Jan 2;392(1):33–44.

Over 96% of Ongoing Patients Had Follow-Up Data Through Month 42

HELIOS-B: A Randomised, Double-Blind Outcomes Study in Patients with ATTR-CM



Percentage of Ongoing Patients Who Had Follow-Up Data Through Month 42:

96.3%

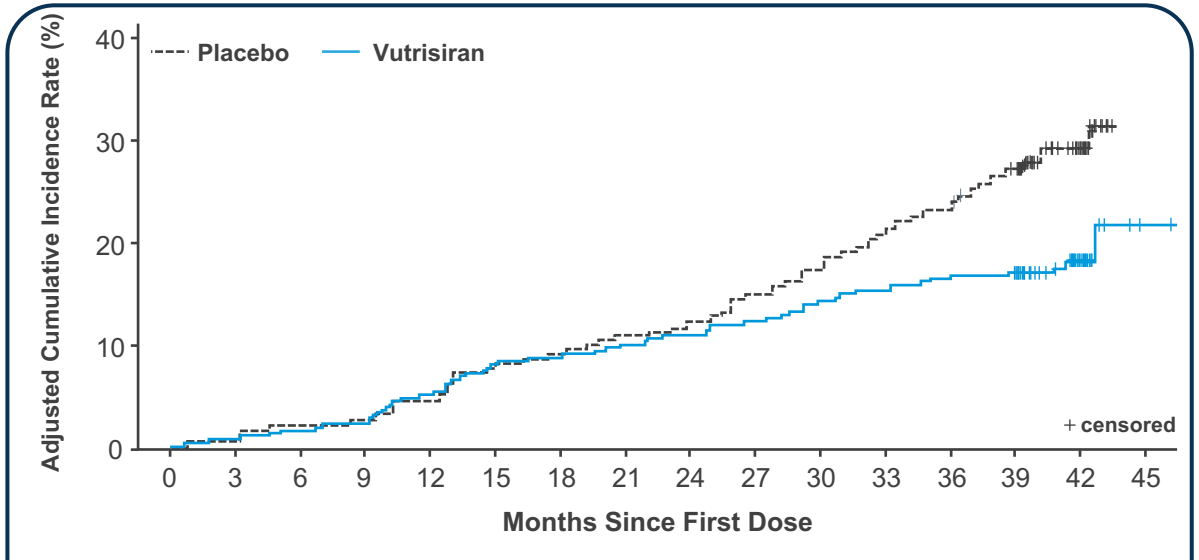
Current analysis data cut **22 Nov 2024**

[a]Placebo patients switching to vutrisiran in the OLE were not expected to have onset of mortality benefit for at least the first 6 months. Accordingly, inclusion of up to 6 months of follow-up data was expected to improve statistical power and precision of estimates owing to accrual of additional events. **Abbreviations:** ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; DB, double-blind; M, month; OLE, open-label extension; q3M, every 3 months; SC, subcutaneous. **References:** Clinicaltrials.gov identifier: NCT04153149; Fontana M et al. *N Engl J Med*. 2025 Jan 2;392(1):33–44.

Vutrisiran Reduced Risk of ACM Through 42 Months vs Placebo

HELIOS-B

Risk Reduction of 36% Through 42 Months in the Overall Population

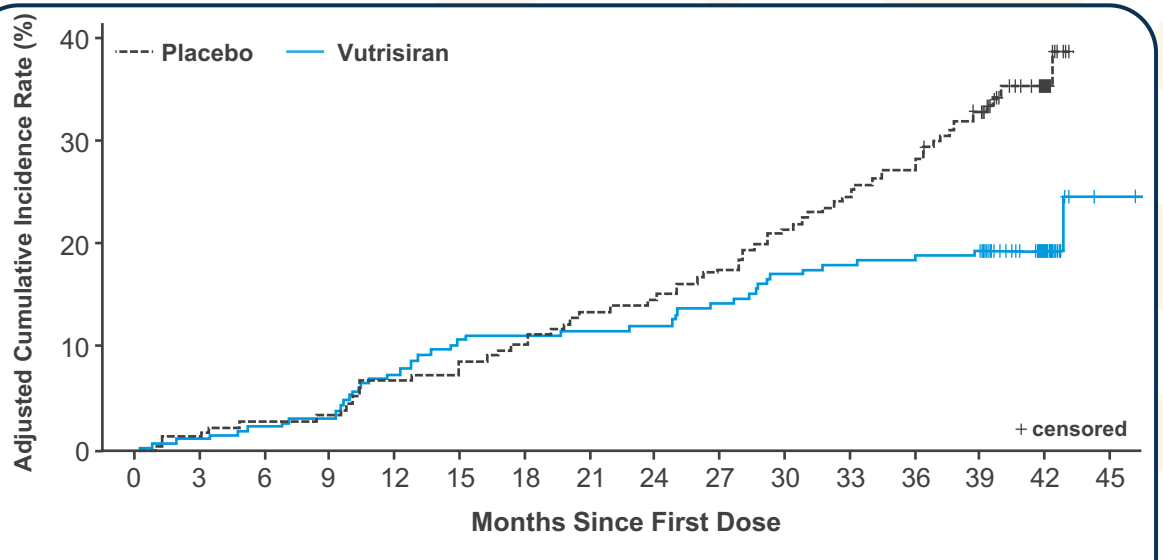


No. at Risk (Cumulative No. of Events)

Placebo	328 (0)	321 (7)	314 (14)	299 (29)	290 (38)	271 (57)	253 (75)	74 (90) 0 (91)
Vutrisiran	326 (0)	321 (5)	308 (18)	296 (30)	289 (37)	277 (49)	269 (57)	89 (63) 1 (64)

	Vutrisiran (n=326)	Placebo (n=328)
Event Rate at Month 42, % (SE)	18.36 (2.21)	28.95 (2.55)
Hazard Ratio (95% CI)	0.64 (0.46, 0.88)	
***P*-value**	0.007	

Risk Reduction of 39% Through 42 Months in the Monotherapy Population



No. at Risk (Cumulative No. of Events)

Placebo	199 (0)	194 (5)	188 (11)	180 (19)	172 (27)	160 (39)	147 (52)	38 (63) 0 (64)
Vutrisiran	196 (0)	191 (5)	179 (17)	171 (25)	169 (27)	158 (38)	154 (42)	43 (44) 1 (45)

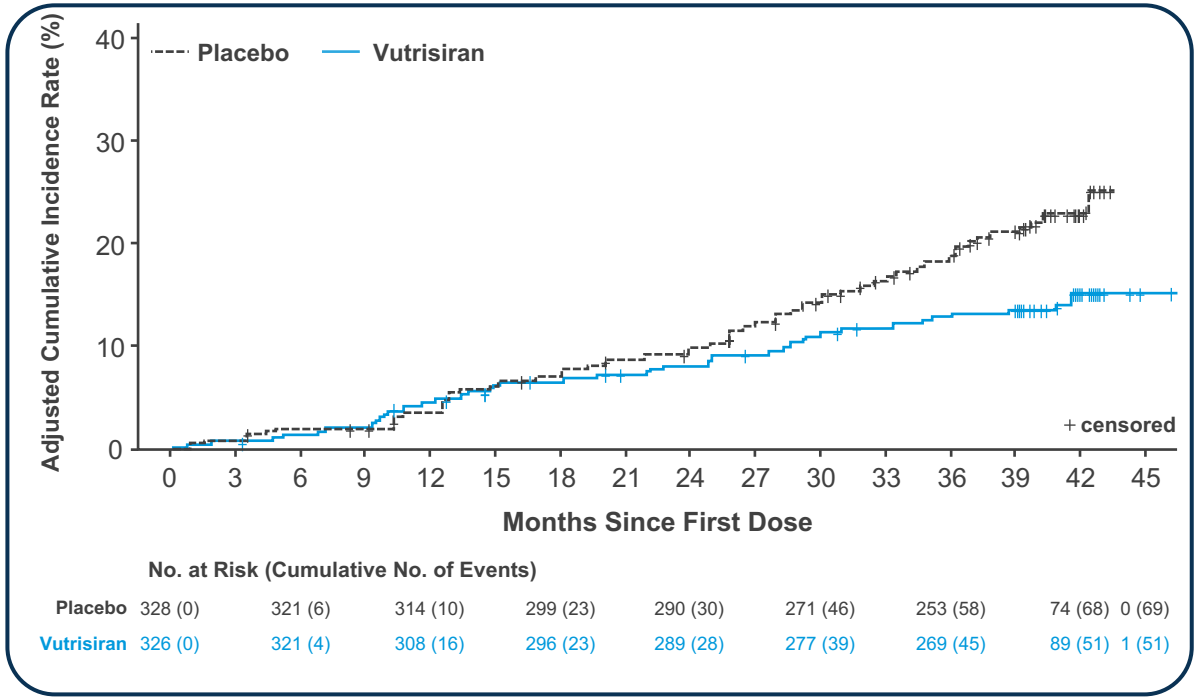
	Vutrisiran (n=196)	Placebo (n=199)
Event Rate at Month 42, % (SE)	19.35 (2.90)	35.06 (3.52)
Hazard Ratio (95% CI)	0.61 (0.42, 0.90)	
***P*-value**	0.016	

Mortality included heart transplantation and left ventricular assist device placement. Deaths after end of study are included in the analysis. Patients were included in the mortality analyses regardless of whether or not they opted for open-label vutrisiran in the OLE. Patients who received placebo during the DB period and entered the OLE continued to be analysed as placebo recipients. **Abbreviations:** ACM, all-cause mortality; DB, double-blind; CI, confidence interval; OLE, open-label extension; SE, standard error.

Vutrisiran Reduced Risk of CV Mortality Through 42 Months vs Placebo

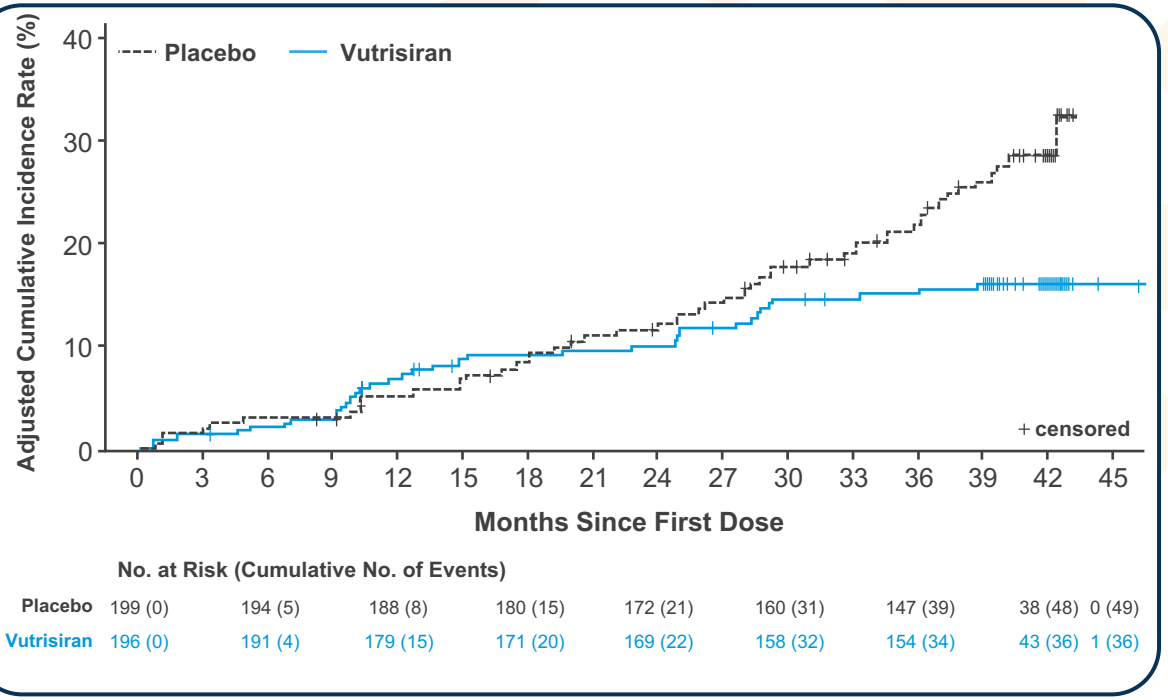
HELIOS-B

Risk Reduction of 33% Through 42 Months in the Overall Population



	Vutrisiran (n=326)	Placebo (n=328)
Event Rate at Month 42, % (SE)	14.96 (2.07)	22.70 (2.40)
Hazard Ratio (95% CI)	0.67 (0.47, 0.96)	
***P*-value**	0.038	

Risk Reduction of 36% Through 42 Months in the Monotherapy Population



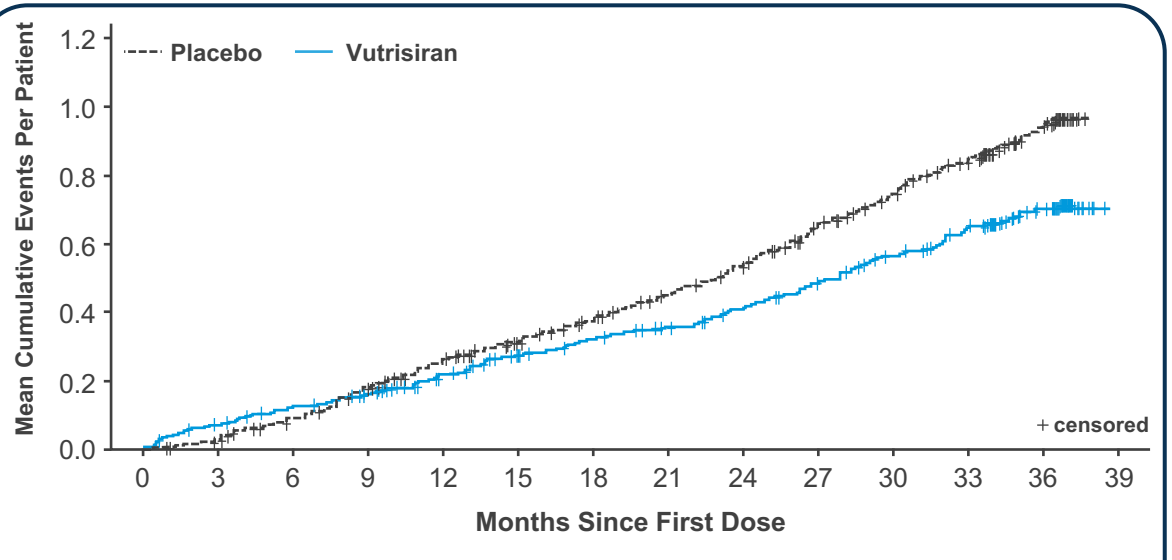
	Vutrisiran (n=196)	Placebo (n=199)
Event Rate at Month 42, % (SE)	15.81 (2.71)	28.34 (3.44)
Hazard Ratio (95% CI)	0.64 (0.41, 0.98)	
***P*-value**	0.052	

Mortality included heart transplantation and left ventricular assist device placement. Deaths after end of study are included in the analysis. Patients were included in the mortality analyses regardless of whether or not they opted for open-label vutrisiran in the OLE. Patients who received placebo during the DB period and entered the OLE continued to be analysed as placebo recipients. **Abbreviations:** CI, confidence interval; CV, cardiovascular; DB, double-blind; OLE, open-label extension; SE, standard error.

Vutrisiran Reduced the Rate of CV Events Through 36 Months vs Placebo

HELIOS-B

Rate Reduction of 27% Through 36 Months in the Overall Population

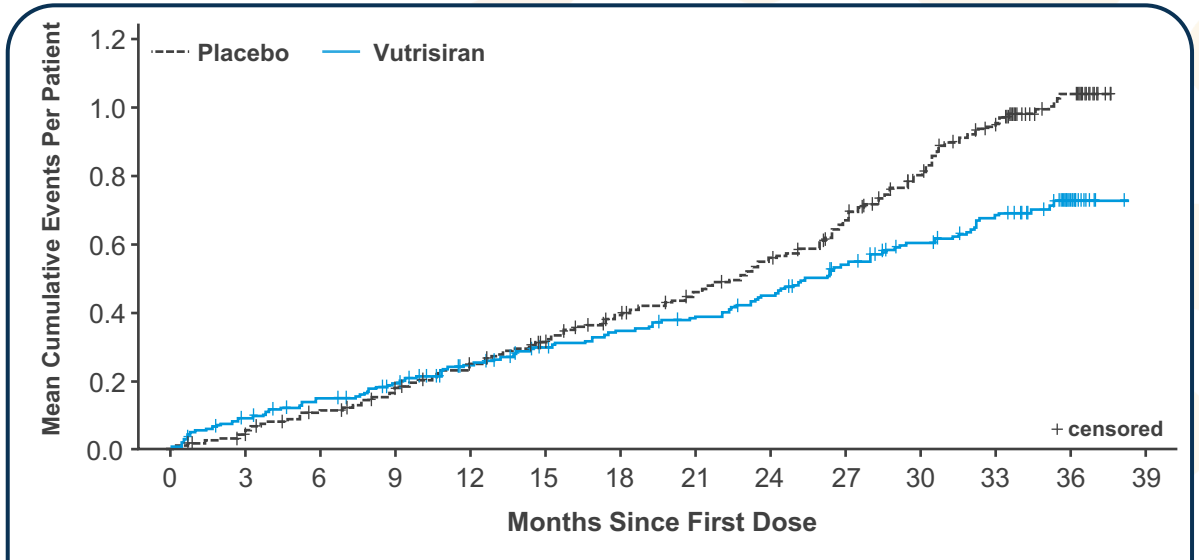


No. at Risk (Cumulative No. of Events)

Placebo	328 (0)	318 (31)	305 (83)	284 (121)	273 (164)	252 (221)	73 (263)	0 (263)
Vutrisiran	326 (0)	320 (37)	305 (67)	291 (99)	281 (124)	268 (167)	87 (200)	0 (200)

	Vutrisiran (n=326)	Placebo (n=328)
Events per 100 Person-Years (SE)	21.09 (7.35)	28.76 (6.49)
Rate Ratio (95% CI)	0.73 (0.61, 0.88)	
***P*-value**	0.001	

Rate Reduction of 32% Through 36 Months in the Monotherapy Population



No. at Risk (Cumulative No. of Events)

Placebo	199 (0)	191 (22)	180 (47)	167 (73)	158 (99)	144 (141)	37 (165)	0 (165)
Vutrisiran	196 (0)	190 (27)	176 (45)	167 (62)	163 (79)	152 (103)	42 (119)	0 (119)

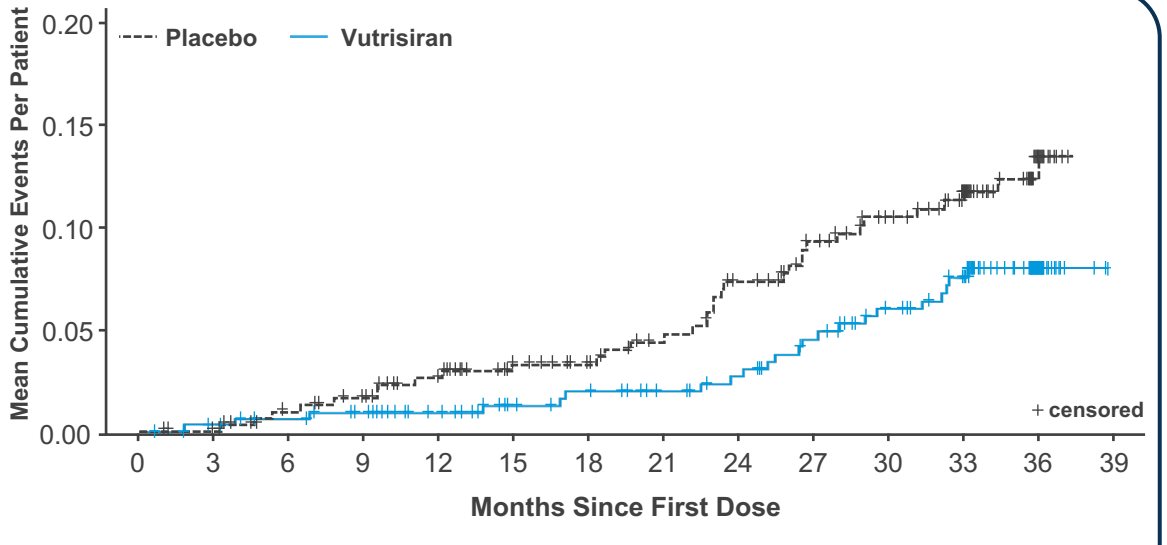
	Vutrisiran (n=196)	Placebo (n=199)
Events per 100 Person-Years (SE)	20.67 (9.75)	30.58 (8.28)
Rate Ratio (95% CI)	0.68 (0.53, 0.86)	
***P*-value**	0.001	

CV events include CV hospitalisations and urgent HF visits. **Abbreviations:** CI, confidence interval; CV, cardiovascular; HF, heart failure; SE, standard error.

Vutrisiran Reduced the Rate of Urgent HF Visits and HF Hospitalisations Through 36 Months vs Placebo in the Overall Population

HELIOS-B

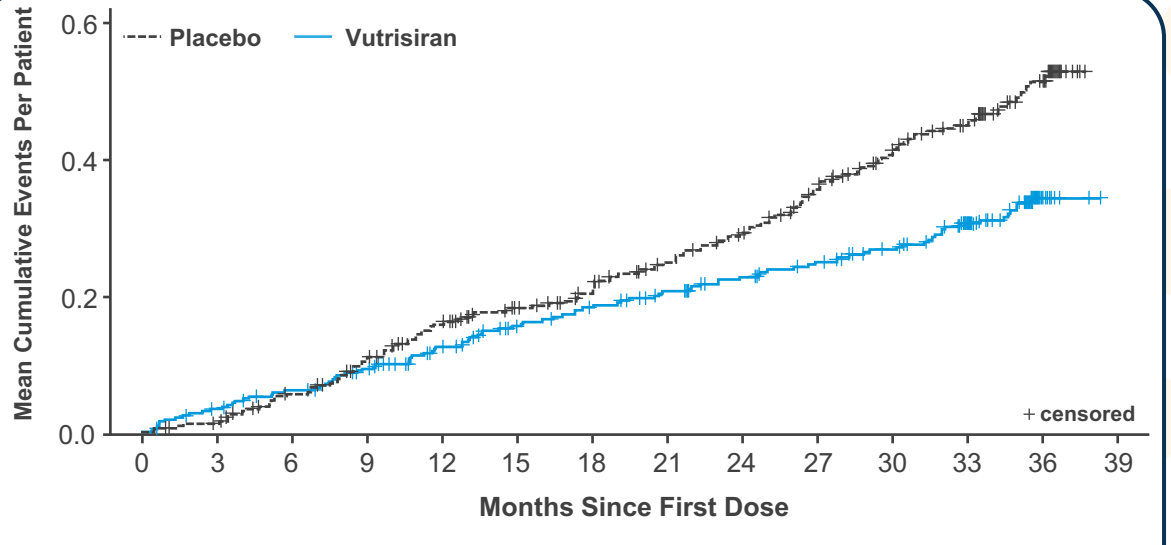
Rate Reduction of 46% Through 36 Months for Urgent HF Visits



No. at Risk (Cumulative No. of Events)

Placebo	328 (0)	318 (3)	305 (8)	284 (10)	273 (21)	252 (29)	73 (34)	0 (34)
Vutrisiran	326 (0)	320 (2)	305 (3)	291 (6)	281 (8)	268 (17)	87 (22)	0 (22)

Rate Reduction of 33% Through 36 Months for HF Hospitalisations



No. at Risk (Cumulative No. of Events)

Placebo	328 (0)	318 (18)	305 (51)	284 (68)	273 (89)	252 (122)	73 (143)	0 (143)
Vutrisiran	326 (0)	320 (20)	305 (40)	291 (57)	281 (69)	268 (81)	87 (98)	0 (98)

	Vutrisiran (n=326)	Placebo (n=328)
Events per 100 Person-Years (SE)	2.01 (25.17)	3.70 (18.16)
Rate Ratio (95% CI)	0.54 (0.30, 0.98)	
***P*-value**	0.041	

	Vutrisiran (n=326)	Placebo (n=328)
Events per 100 Person-Years (SE)	9.41 (10.84)	14.11 (9.33)
Rate Ratio (95% CI)	0.67 (0.52, 0.86)	
***P*-value**	0.002	

HF hospitalisations included all hospitalisations adjudicated as HF admissions. Urgent HF visits included healthcare visits adjudicated as urgent HF visits, and per investigator if conducted at home but not adjudicated. **Abbreviations:** CI, confidence interval; HF, heart failure; SE, standard error.

Vutrisiran Reduced the Rate of CV Events Components Through 36 Months vs Placebo

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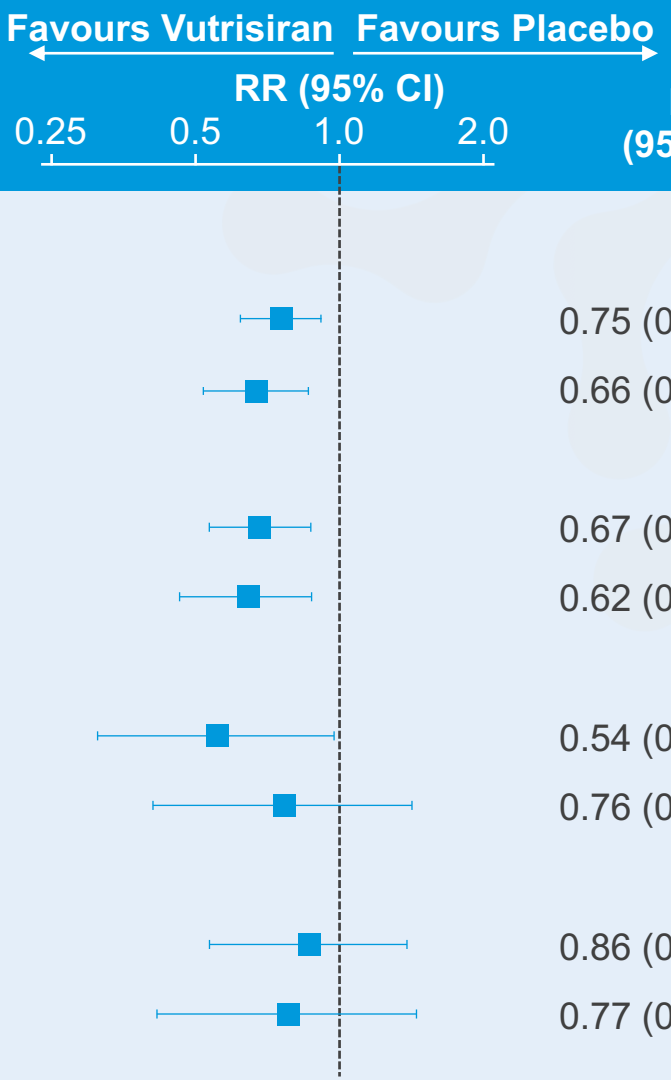
	Events per 100 Person-Years (SE)		RR (95% CI)	*P*-value
	Vutrisiran	Placebo		
CV hospitalisations				
Overall population	18.76 (7.81)	25.05 (6.95)	0.75 (0.62, 0.91)	0.004
Monotherapy population	33.95 (13.59)	51.16 (11.75)	0.66 (0.51, 0.86)	0.002
HF hospitalisations				
Overall population	9.41 (10.84)	14.11 (9.33)	0.67 (0.52, 0.86)	0.002
Monotherapy population	20.77 (17.31)	33.45 (14.58)	0.62 (0.45, 0.86)	0.004
Urgent HF visits				
Overall population	2.01 (25.17)	3.70 (18.16)	0.54 (0.30, 0.98)	0.041
Monotherapy population	2.46 (47.90)	3.25 (45.31)	0.76 (0.40, 1.42)	0.387
Arrhythmia hospitalisations				
Overall population	3.42 (18.46)	3.98 (17.35)	0.86 (0.53, 1.41)	0.546
Monotherapy population	3.80 (43.37)	4.91 (40.87)	0.77 (0.41, 1.47)	0.434



CV events include CV hospitalisations and urgent HF visits. **Abbreviations:** CI, confidence interval; CV, cardiovascular; HF, heart failure; RR, rate ratio; SE, standard error.

Analyses of CV Events in Prespecified Subgroups Consistently Favoured Vutrisiran Over Placebo Through 36 Months

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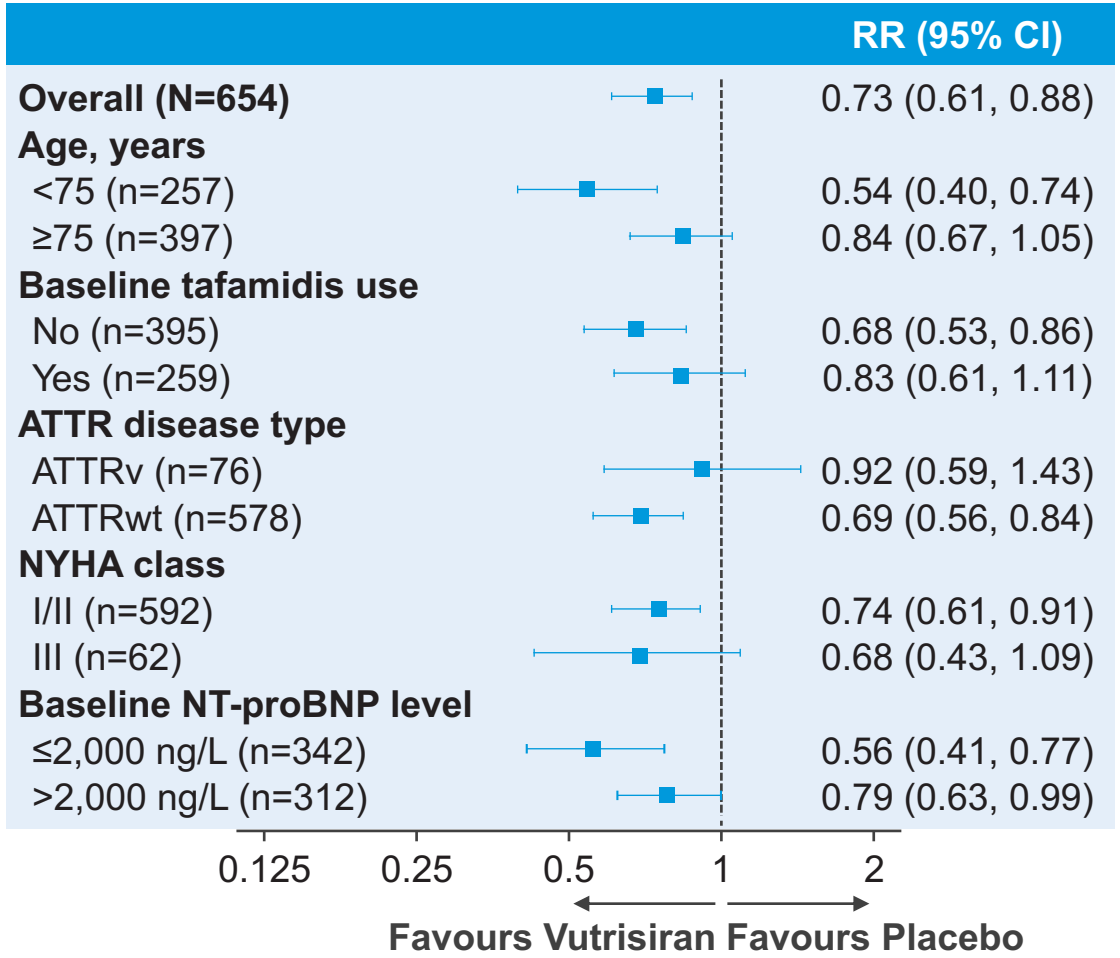
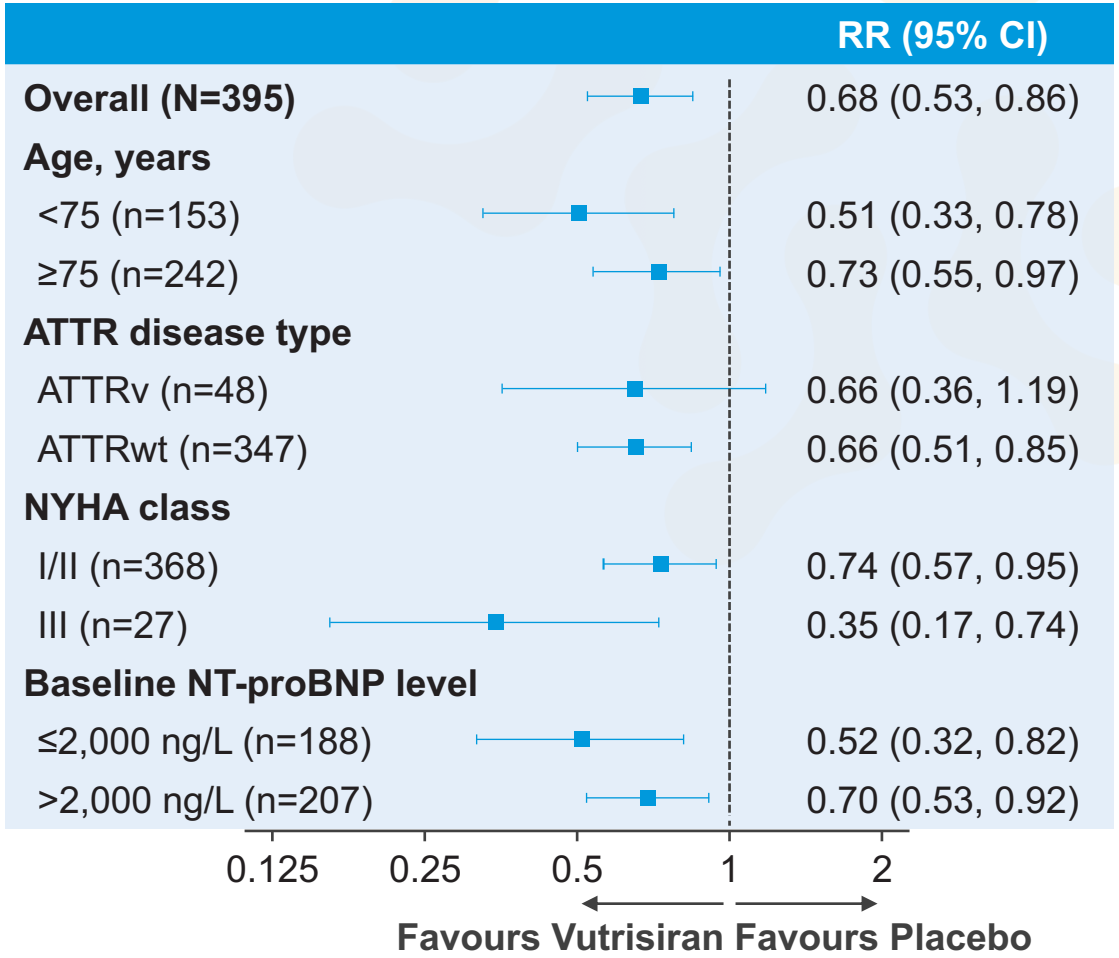
Overall Population (n=654)



Monotherapy Population (n=395)



Analysed using Poisson regression model including treatment group, baseline tafamidis use and log-transformed NT-proBNP as covariates, and the logarithm of the follow-up time as an offset variable. Analysis is based on subgroup data only. For subgroup analysis of baseline tafamidis use, the model includes treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class and age group as covariates. **Abbreviations:** ATTR, transthyretin amyloidosis; ATTRv/wt, variant/wild-type transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; RR, rate ratio.

Summary

- Vutrisiran reduced the risk of the prespecified all-cause and CV mortality outcomes through 42 months using a more recent data cut
  - These results demonstrate that the favourable impact of vutrisiran on mortality appears to increase over time
  - Results were consistent in both the overall and monotherapy populations
  - Vital status ascertainment at the time of data cutoff in both this analysis and the primary analysis was >99%, ensuring highly robust results
- Rates of CV events (including CV hospitalisations, HF hospitalisations, and urgent HF visits) were consistently reduced with vutrisiran vs placebo through 36 months in the overall population
  - These results demonstrate the robust and consistent effect of vutrisiran across a spectrum of CV and HF outcomes, with a notably large impact on urgent HF visits
- These data reinforce the positive results from the HELIOS-B primary analysis, and further demonstrate the beneficial effect of vutrisiran on mortality risk and CV health for patients with ATTR-CM

We thank the patients, their families, investigators, staff, and collaborators for their participation in HELIOS-B

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Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; HF, heart failure.

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Vutrisiran Improves Survival and Reduces Cardiovascular Events in ATTR Amyloid Cardiomyopathy

HELIOS-B

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