2-Year Results From the Open-Label Extension Period of the Phase 3 HELIOS-B Study of Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy

Sarah A.M. Cuddy,[1] Marianna Fontana,[2] Ronald Witteles,[3] Caroline Morbach,[4] Gilbert Habib,[5] Mathew S. Maurer,[6] Juan Pablo Costabel,[7] Michel Khouri,[8] Farooq H. Sheikh,[9] Marcus Urey,[10] Ugochukwu Egolum,[11] W.H. Wilson Tang,[12] Cong Zhu,[13] Cynthia Kwok,[13] Emre Aldinc,[13] Benjamin W. Lee,[13] Pablo Garcia-Pavia[14]

[1]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]National Amyloidosis Centre, University College London, Royal Free Campus, London, UK; [3]Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA; [4]Department of Clinical Research and Epidemiology, Comprehensive Heart Failure Center, and Department of Medicine I, University Hospital Würzburg, Würzburg, Germany; [5]Department of Cardiology, Hospital La Timone of Marseille, Marseille, France; [6]Columbia University Irving Medical Center, New York City, NY, USA; [7]Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina; [8]Duke University School of Medicine, Durham, NC, USA; [9]MedStar Heart & Vascular Institute, Georgetown University School of Medicine, Washington, DC, USA; [10]Department of Medicine, University of California San Diego Health, La Jolla, CA, USA; [11]Georgia Heart Institute, Gainesville, GA, USA; [12]Department of Cardiovascular Medicine, Heart Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH, USA; [13]Alnylam Pharmaceuticals, Cambridge, MA, USA; [14] Hospital Universitario Puerta de Hierro, IDIPHISA, CIBERCV, and Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain.

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Disclosures

- **Sarah A.M. Cuddy** is a researcher for NIH 1K23HL166686-01 and AHA 23CDA857664; and a consultant, advisor, and speaker for Pfizer, BridgeBio, Ionis, AstraZeneca, Alexion, Bayer, Life Molecular Imaging, and Novo Nordisk.
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Introduction and Study Design

ATTR-CM

- ATTR-CM is a progressive, fatal disease caused by deposition of misfolded TTR protein as amyloid fibrils in the heart, leading to progressive congestive heart failure, often accompanied by arrhythmias[1–4]

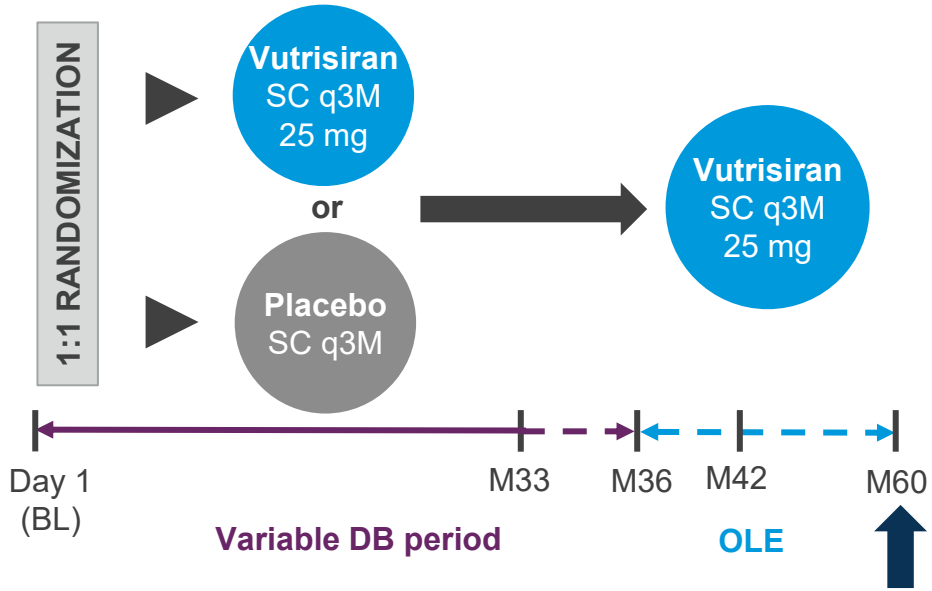
Vutrisiran

- Vutrisiran, an RNAi silencer, inhibits hepatic TTR production through degradation of TTR mRNA (wild-type and variant), leading to **rapid** and **deep knockdown** of the TTR protein in circulation[5–7]
  - Vutrisiran is approved for the treatment of both ATTR-CM and ATTRv-PN
- In HELIOS-B, vutrisiran demonstrated significant benefits vs placebo during the 33–36M DB period, which were sustained through 1 year of the OLE[7,8]

Objective

- To present efficacy and safety data of vutrisiran treatment through 2 years of the OLE period of the HELIOS-B study

HELIOS-B



Current analysis

All patients who entered the OLE and were followed up until the cutoff date of **April 9, 2026**

Endpoints

- **Primary:** Composite of ACM and recurrent CV events
- Time to ACM or first CV event
- ACM
- CV-related mortality
- Change from BL in KCCQ-OS score and cardiac biomarkers
- % of patients with stable or improved NYHA class
- % reduction in circulating TTR
- TEAEs

Abbreviations: ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary (variant) ATTR with polyneuropathy; BL, baseline; CV, cardiovascular; DB, double-blind; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; M, month; NYHA, New York Heart Association; OLE, open-label extension; q3M, every 3 months; RNAi, RNA interference; SC, subcutaneously; TEAE, treatment-emergent adverse event; TTR, transthyretin.

References: 1. Maurer et al. Circ Heart Fail 2019;12:e006075; 2. Ruberg & Maurer. JAMA 2024;331:778–91; 3. Ruberg et al. J Am Coll Cardiol 2019;73:2872–91; 4. Nativi-Nicolau et al. ESC Heart Fail 2021;8:3875–84; 5. Habtemariam et al. Clin Pharmacol Ther 2021;109:372–82; 6. Adams et al. Amyloid 2023;30:1–9; 7. Fontana et al. N Engl J Med 2025;392:33–44; 8. Garcia-Pavia et al. Circulation 2026; 2026;154:00–00; Available at https://doi.org/10.1161/CIRCULATIONAHA.126.080735.

Patient and Disease Characteristics at OLE Baseline

- Of **654 patients randomized** to vutrisiran (n=326) or placebo (n=328) during the DB period, **466 entered the OLE** (vutrisiran n=243; placebo n=223)
- Placebo patients who started vutrisiran on OLE entry comprised the **placebo/vutrisiran** group; patients initially randomized to vutrisiran comprised the **continuous vutrisiran** group
  - Patients initially randomized to placebo during the DB period entered the OLE with worse disease severity
- 33.6% (87/259) of patients in the monotherapy population started receiving tafamidis during the OLE

	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Placebo/vutrisiran (n=223)	Continuous vutrisiran (n=243)	Placebo/vutrisiran (n=124)	Continuous vutrisiran (n=135)	Placebo/vutrisiran (n=99)	Continuous vutrisiran (n=108)
Age (years), median (range)	79.0 (56.0–88.0)	80.0 (49.0–88.0)	79.0 (56.0–88.0)	79.0 (49.0–88.0)	78.0 (65.0–88.0)	80.0 (61.0–88.0)
Male sex, n (%)	210 (94.2)	221 (90.9)	115 (92.7)	121 (89.6)	95 (96.0)	100 (92.6)
ATTRwt, n (%)	206 (92.4)	219 (90.1)	117 (94.4)	121 (89.6)	89 (89.9)	98 (90.7)
NAC stage, n (%) I II III	 105 (47.1) 67 (30.0) 38 (17.0)	 138 (56.8) 56 (23.0) 32 (13.2)	 48 (38.7) 38 (30.6) 27 (21.8)	 65 (48.1) 35 (25.9) 21 (15.6)	 57 (57.6) 29 (29.3) 11 (11.1)	 73 (67.6) 21 (19.4) 11 (10.2)
NYHA class, n (%) I II III IV	 27 (12.1) 151 (67.7) 44 (19.7) 0	 41 (16.9) 161 (66.3) 37 (15.2) 4 (1.6)	 6 (4.8) 88 (71.0) 29 (23.4) 0	 17 (12.6) 97 (71.9) 19 (14.1) 2 (1.5)	 21 (21.2) 63 (63.6) 15 (15.2) 0	 24 (22.2) 64 (59.3) 18 (16.7) 2 (1.9)
KCCQ-OS, points, mean (SD)	67.3 (23.0)[a]	71.2 (21.3)[b]	62.9 (23.8)[c]	69.3 (21.1)[d]	72.8 (20.7)[e]	73.5 (21.4)[f]
NT-proBNP, ng/L, median (IQR)	2547 (1312, 5149)[g]	1934 (1053, 3419)[h]	3460 (1641, 6266)[i]	2257 (1215, 4014)[j]	1973 (1039, 3863)[k]	1656 (881, 2756)[l]
Troponin I, ng/L, median (IQR)	70.6 (43.0, 108.6)[m]	56.5 (36.6, 92.7)[n]	77.1 (55.3, 134.7)[o]	64.7 (36.8, 94.7)[p]	59.2 (38.8, 87.5)[q]	50.1 (36.3, 89.7)[r]

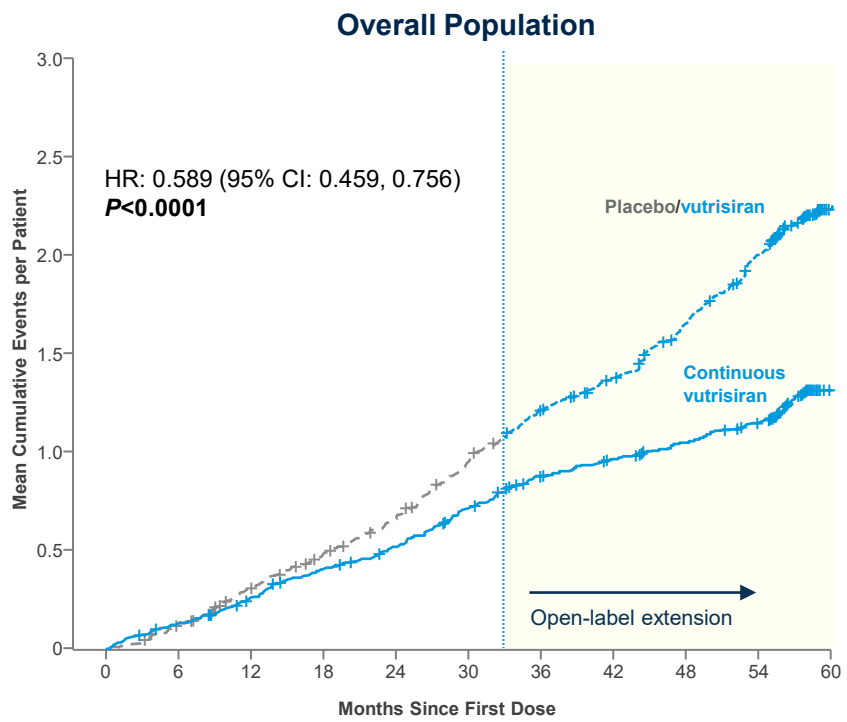
[a]n=221. [b]n=240. [c]n=123. [d]n=134. [e]n=98. [f]n=106. [g]n=213. [h]n=235. [i]n=116. [j]n=130. [k]n=97. [l]n=105. [m]n=204. [n]n=231. [o]n=109. [p]n=128. [q]n=95. [r]n=103.

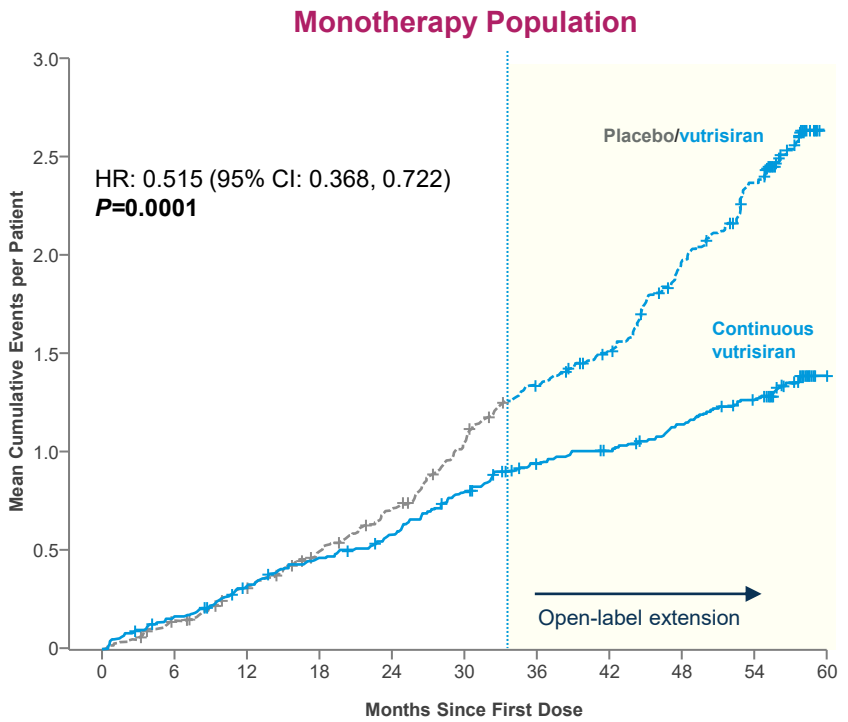
Abbreviations: ATTRwt, wild-type transthyretin amyloidosis; DB, double-blind; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; SD, standard deviation.

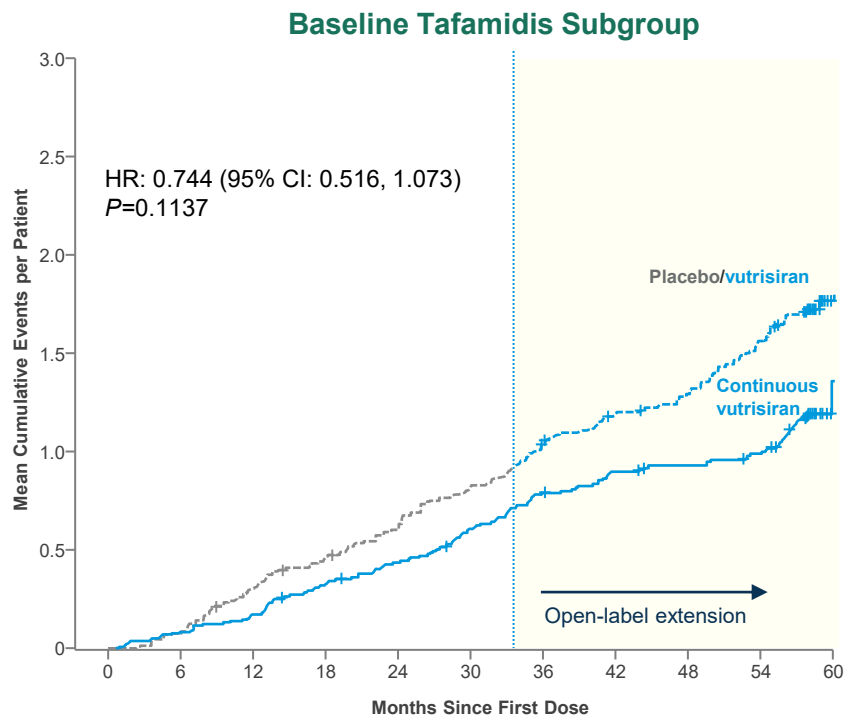
Lower Risk of ACM and Recurrent CV Events With Continuous Vutrisiran Use

The risk of ACM and recurrent CV events was significantly lower in the overall (41%) and monotherapy (48%) populations with continuous vutrisiran vs placebo/vutrisiran

Mean cumulative function plots for the primary composite endpoint of ACM and recurrent CV events







	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Placebo/vutrisiran (n=328)	Continuous vutrisiran (n=326)	Placebo/vutrisiran (n=199)	Continuous vutrisiran (n=196)	Placebo/vutrisiran (n=129)	Continuous vutrisiran (n=130)
Patients, n (%)	211 (64.3)	156 (47.9)	140 (70.4)	94 (48.0)	71 (55.0)	62 (47.7)
ACM	112 (34.1)	84 (25.8)	72 (36.2)	56 (28.6)	40 (31.0)	28 (21.5)
≥1 CV event	174 (53.0)	131 (40.2)	118 (59.3)	76 (38.8)	56 (43.4)	55 (42.3)

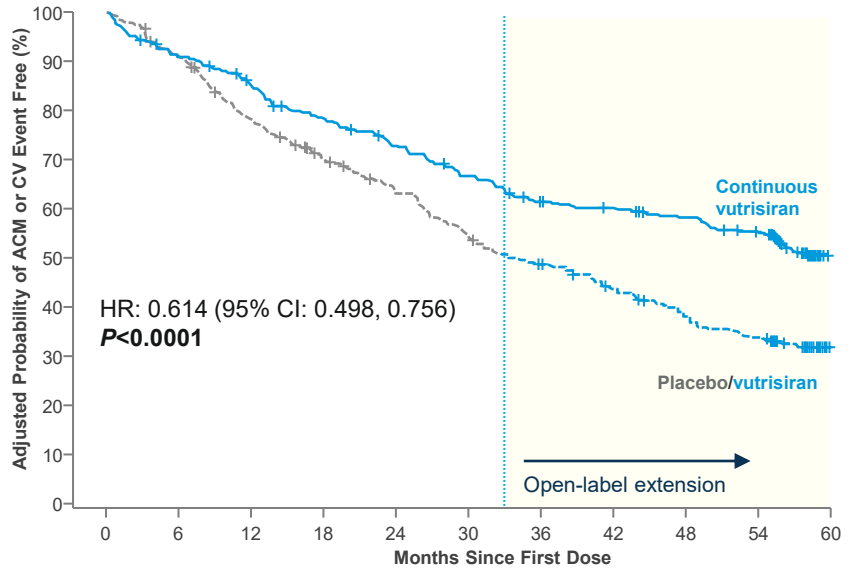
Abbreviations: ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Lower Risk of ACM and First CV Event With Continuous Vutrisiran Use

The risk of ACM and first CV event was significantly lower in the overall (39%) and monotherapy (48%) populations with continuous vutrisiran vs placebo/vutrisiran

Adjusted Kaplan-Meier plots of time to ACM or first CV event

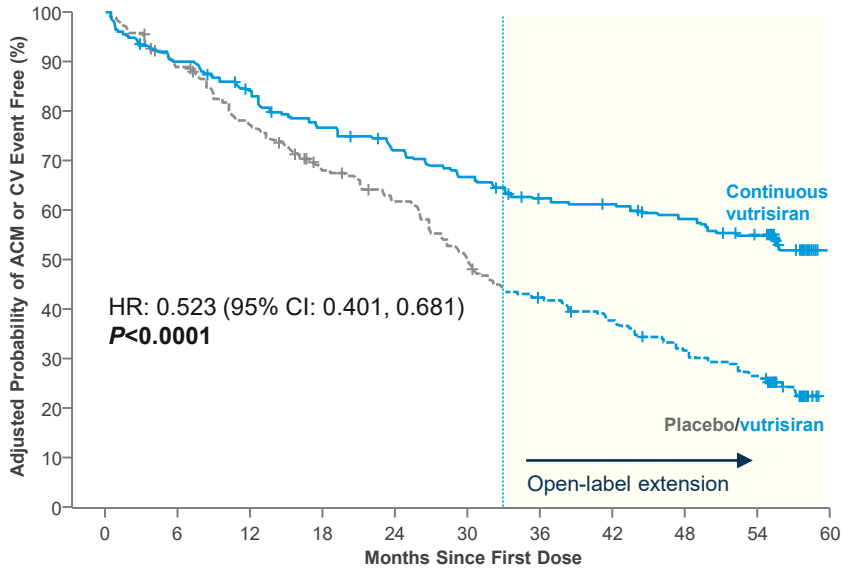
Overall Population



No. at risk (cumulative no. of events)

Placebo/ vutrisiran	328 (0)	295 (31)	253 (70)	221 (96)	199 (115)	171 (143)	150 (161)	132 (176)	114 (192)	101 (205)	6 (210)
Cont. vutrisiran	326 (0)	294 (30)	271 (50)	247 (72)	227 (90)	206 (110)	185 (126)	178 (131)	169 (137)	158 (145)	7 (156)

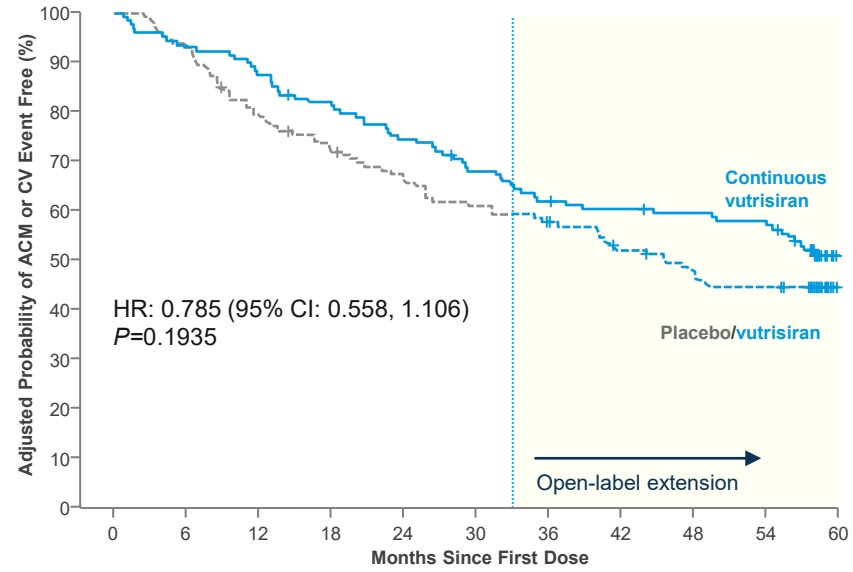
Monotherapy Population



No. at risk (cumulative no. of events)

Placebo/ vutrisiran	199 (0)	175 (22)	152 (43)	130 (60)	116 (72)	95 (93)	79 (107)	70 (115)	58 (126)	49 (135)	0 (140)
Cont. vutrisiran	196 (0)	172 (22)	157 (34)	141 (49)	131 (57)	119 (69)	106 (77)	102 (80)	95 (85)	86 (91)	3 (94)

Baseline Tafamidis Subgroup



No. at risk (cumulative no. of events)

Placebo/ vutrisiran	129 (0)	120 (9)	101 (27)	91 (36)	83 (43)	76 (50)	71 (54)	62 (61)	56 (66)	52 (70)	6 (70)
Cont. vutrisiran	130 (0)	122 (8)	114 (16)	106 (23)	96 (33)	87 (41)	79 (49)	76 (51)	74 (52)	72 (54)	4 (62)

[a]Estimate at month 57 (non-estimable at month 60, as no placebo patients remained at risk).

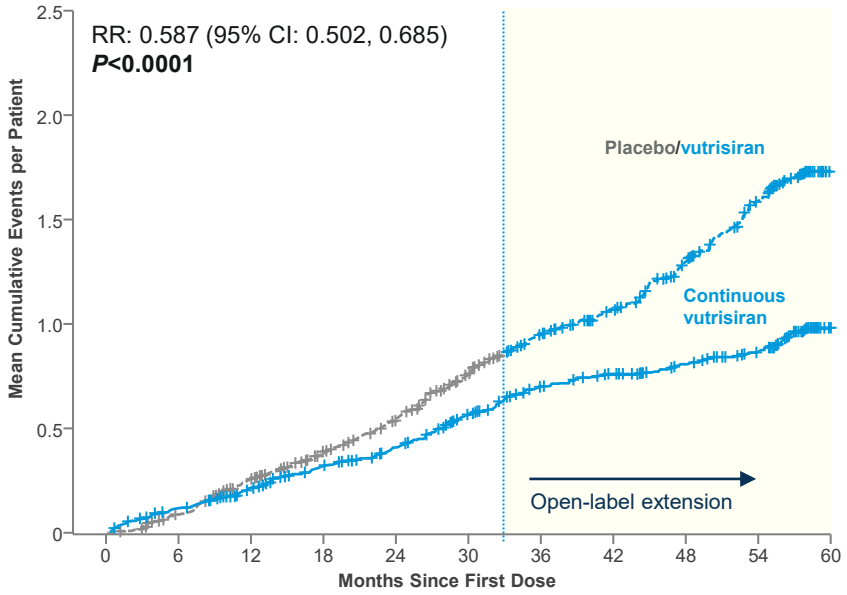
Abbreviations: ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Lower Risk of Recurrent CV Events With Continuous Vutrisiran Use

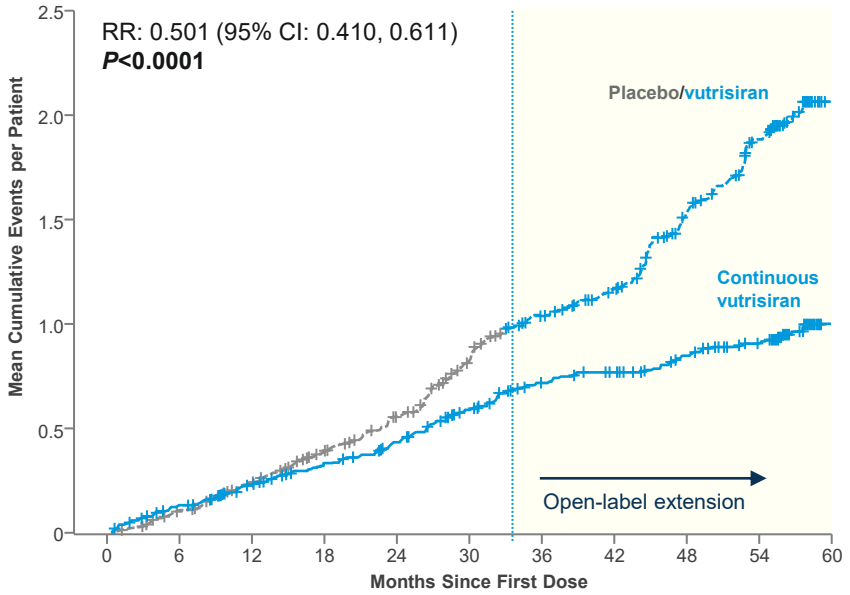
The risk of recurrent CV events was significantly lower in the overall population (41%), monotherapy population (50%), and baseline tafamidis subgroup (23%) with continuous vutrisiran vs placebo/vutrisiran

Mean cumulative function plots for recurrent CV events

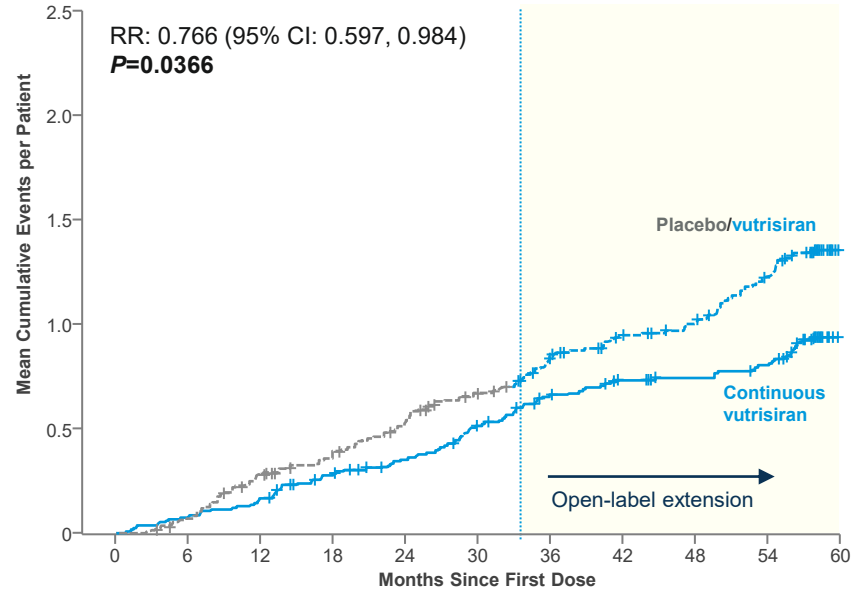
Overall Population



Monotherapy Population



Baseline Tafamidis Subgroup



	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Placebo/vutrisiran (n=328)	Continuous vutrisiran (n=326)	Placebo/vutrisiran (n=199)	Continuous vutrisiran (n=196)	Placebo/vutrisiran (n=129)	Continuous vutrisiran (n=130)
Patients with ≥1 CV event, n (%)	174 (53.0)	131 (40.2)	118 (59.3)	76 (38.8)	56 (43.4)	55 (42.3)
Total CV events, n	417	264	272	153	145	111

Abbreviations: CI, confidence interval; CV, cardiovascular; RR, relative rate ratio (vutrisiran vs placebo) from Poisson regression model.

Lower Risk of ACM and CV-Related Mortality with Continuous Vutrisiran Use

	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Placebo/vutrisiran (n=328)	Continuous vutrisiran (n=326)	Placebo/vutrisiran (n=199)	Continuous vutrisiran (n=196)	Placebo/vutrisiran (n=129)	Continuous vutrisiran (n=130)
ACM						
HR (95% CI)[a]	0.622 (0.476, 0.813)		0.601 (0.435, 0.831)		0.653 (0.403, 1.059)	
Log-rank *P* value	*P*=0.0009		*P*=0.0036		*P*=0.1052	
CV-related mortality						
HR (95% CI)[a]	0.610 (0.448, 0.829)		0.613 (0.423, 0.888)		0.599 (0.342, 1.047)	
Log-rank *P* value	*P*=0.0022		*P*=0.0136		*P*=0.0692	

[a]Cox proportional hazards model.

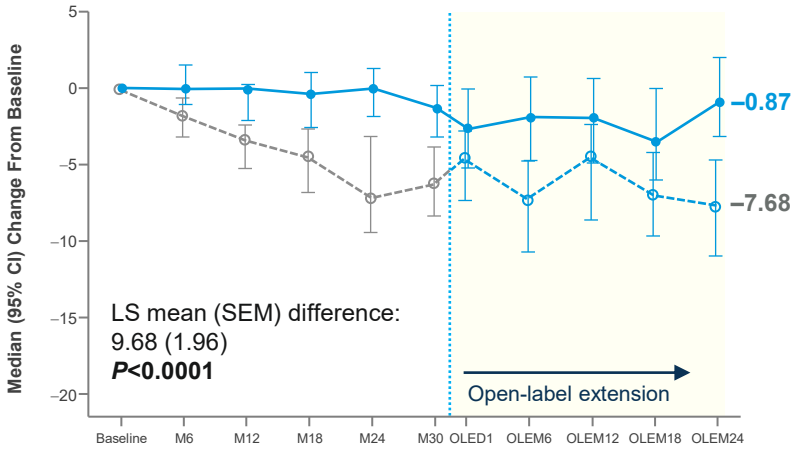
Abbreviations: ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Stable or Improved KCCQ-OS Score With Continuous Vutrisiran Use

Significant benefit with continuous vutrisiran vs placebo/vutrisiran in health status and QoL

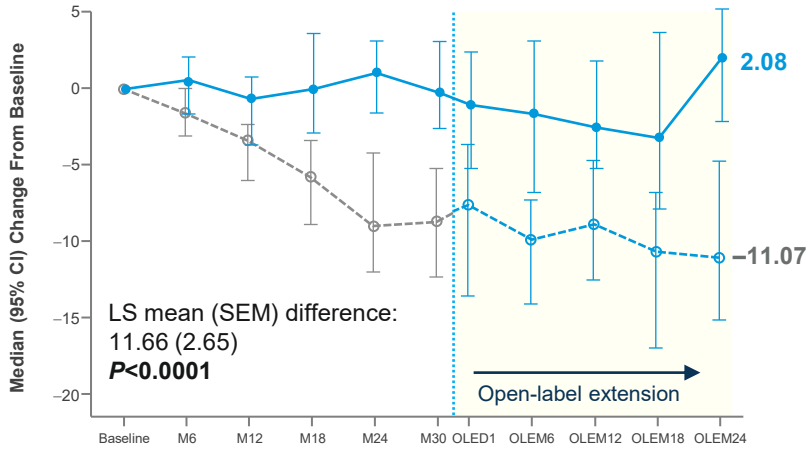
Median change from study baseline in KCCQ-OS score

Overall Population



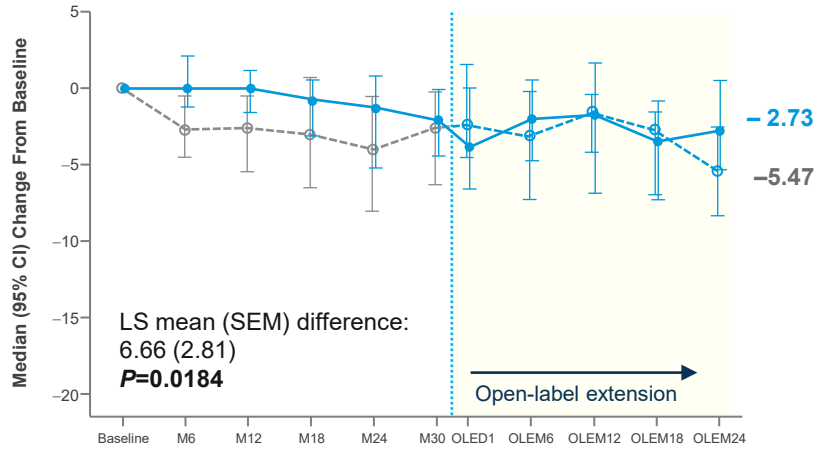
N											
Placebo/ vutrisiran	327	308	300	277	256	234	221	203	190	176	164
Cont. vutrisiran	325	305	291	280	263	252	240	231	219	210	196

Monotherapy Population



N											
Placebo/ vutrisiran	198	184	177	163	146	131	123	112	101	92	84
Cont. vutrisiran	195	182	164	158	145	139	134	127	120	115	108

Baseline Tafamidis Subgroup



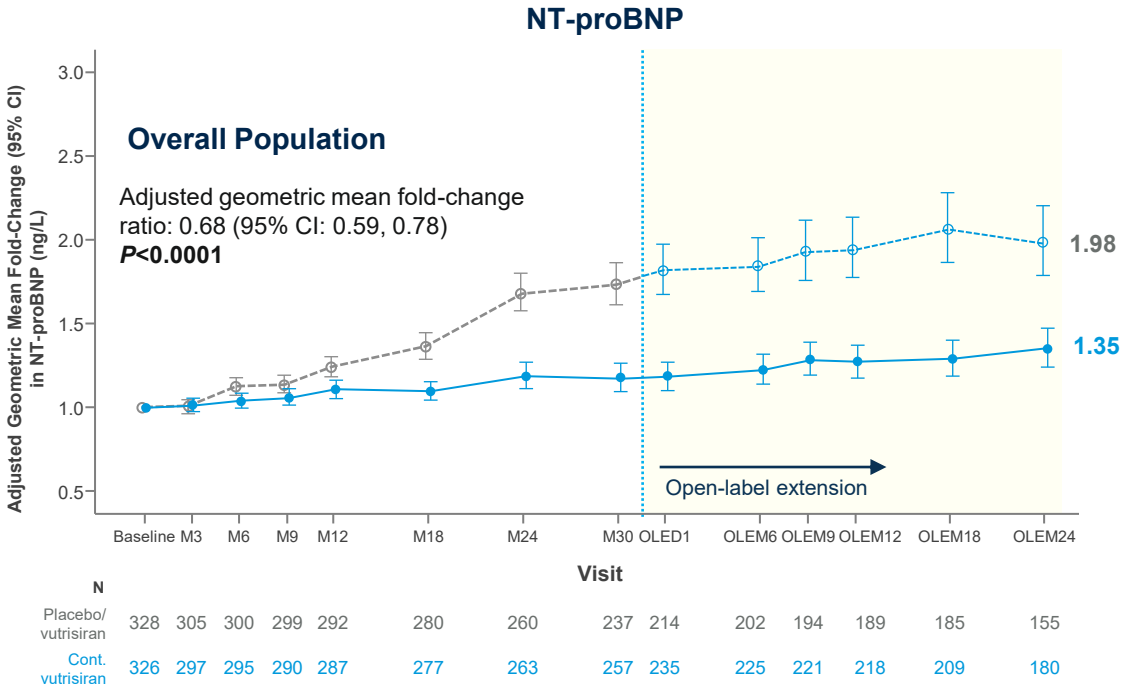
N											
Placebo/ vutrisiran	129	124	123	114	110	103	98	91	89	84	80
Cont. vutrisiran	130	123	127	122	118	113	106	104	99	95	88

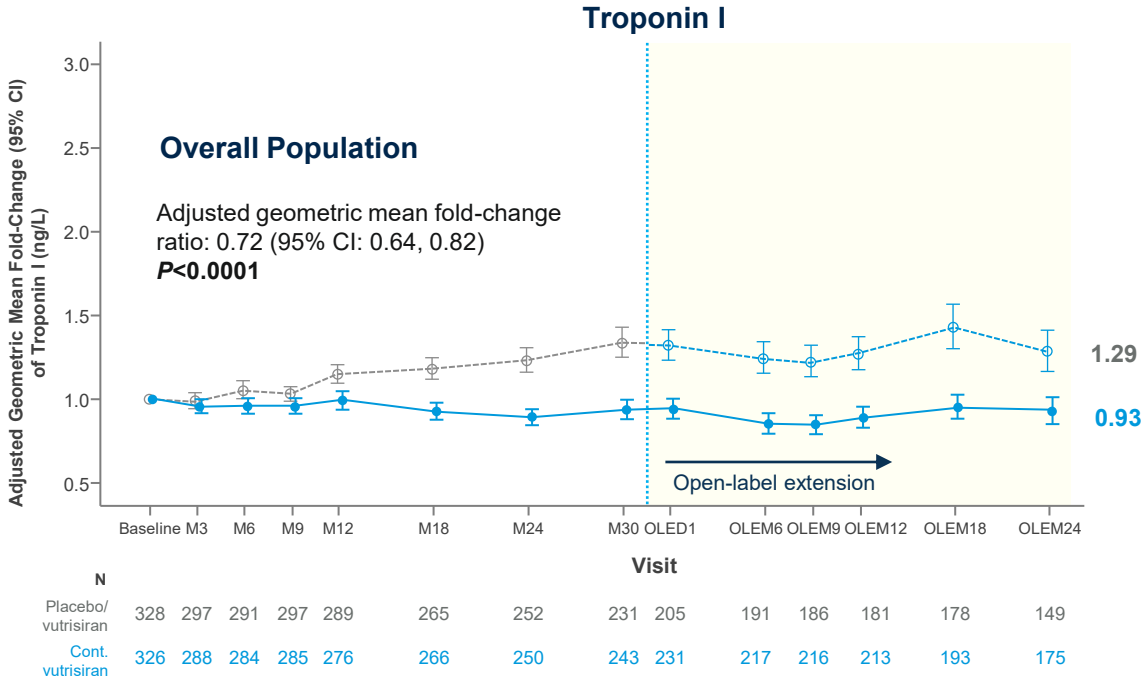
Abbreviations: D, day; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS, least squares; M, month; OLE, open-label extension; QoL, quality of life; SEM, standard error of the mean.

Significant Benefit in Cardiac Biomarker Levels With Vutrisiran Use

Continuous vutrisiran achieved stability or attenuated worsening in cardiac biomarker levels vs placebo/vutrisiran

Adjusted geometric mean fold-change from study baseline in cardiac biomarker levels





Abbreviations: D, day; M, month; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OLE, open-label extension.

Acceptable Safety Profile of Long-term Vutrisiran

The findings were consistent with the known safety profile of vutrisiran

Vutrisiran exposure period (DB + OLE)

Type of event, [EAER (E/100 PY)]	Total (N=549; PY=1614.2)
Any TEAE	7330 [454.1]
Any serious TEAE	1197 [74.2]
Any severe TEAE	833 [51.6]
Any TEAE leading to treatment discontinuation	17 [1.1]
Deaths[a]	120 [7.4]

[a]All fatal serious adverse events are summarized regardless of the treatment-emergent classification; deaths occurring after the end of study visit or after the data cutoff date are not included.

Abbreviations: DB, double-blind; E, number of events; EAER, exposure-adjusted event rate; OLE, open-label extension; PY, patient-years; TEAE, treatment-emergent adverse event.

Conclusions

Scan to View
Country Restrictions Apply

- In the HELIOS-B OLE, **continuous vutrisiran over 60 months demonstrated significant clinical benefit** vs patients initially randomized to placebo:
  - Lower risk of ACM and recurrent CV events (**41%** and **48%** lower in the overall and monotherapy populations)
  - Preservation or attenuated worsening of patient-reported health status and QoL
  - Stability or attenuated worsening of cardiac biomarker levels
  - Acceptable safety profile
- In patients receiving continuous combination of vutrisiran and tafamidis, there was a significant risk reduction in recurrent CV events compared with to tafamidis monotherapy at baseline followed by addition of vutrisiran in the OLE
- These results further underscore the importance of early treatment with vutrisiran

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

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