Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

Fontana et al. *N Engl J Med*, 2024

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Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

- This presentation was developed by Alnylam Pharmaceuticals to share scientific information about the HELIOS-B clinical study as published in the *New England Journal of Medicine* on August 30th, 2024.
- Vutrisiran is an investigational therapeutic in development for the treatment of [ATTR-CM/transthyretin amyloidosis with cardiomyopathy
- This resource is intended to support scientific exchange and may contain information that is not in the approved Prescribing Information for AMVUTTRA (vutrisiran). The information provided is not intended to serve as recommendations for clinical practice.
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Introduction

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Introduction

Background

Objective: To present efficacy and safety data from the phase 3 HELIOS-B trial, which assessed vutrisiran in patients with variant or wild-type ATTR-CM

- Transthyretin amyloidosis is a progressive, systemic, and fatal disease caused by misfolded TTR protein that accumulates as amyloid fibrils in multiple organs, commonly leading to cardiomyopathy and polyneuropathy[1–4]
- ATTR-CM occurs due to inherited *TTR* gene variants (hereditary or variant ATTR [ATTRv]), often with a mixed phenotype that also includes polyneuropathy, or with aging in the absence of predisposing *TTR* variants (wild-type ATTR [ATTRwt])[2,3,5–8]
- In ATTR-CM, extracellular deposition of TTR amyloid in the heart causes:[3,8–10]
  - Infiltrative cardiomyopathy, leading to heart failure and arrhythmias
  - Progressively debilitating symptoms
  - High morbidity/mortality rates, with a median survival of 2 to 6 years after diagnosis
- The TTR tetramer stabilizer tafamidis is the only approved agent for ATTR-CM
  - In the ATTR-ACT trial, tafamidis was associated with a reduction in all-cause mortality and cardiovascular-related hospitalizations over 30 months, as compared with placebo; however, mortality remained high and quality of life and functional capacity continued to decline.[11]
- Vutrisiran is a subcutaneously administered RNAi therapeutic agent that inhibits hepatic synthesis of both wild-type and variant *TTR* mRNA at their source, resulting in rapid knockdown of the pathogenic protein before amyloid-causing monomers can form[12–14]
- Vutrisiran is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults based on the results from the Phase 3 HELIOS-A trial[13,14]

ATTR (-CM), transthyretin amyloidosis (with cardiomyopathy); ATTRv or ATTRwt, hereditary ATTR (v for variant) or wild-type ATTR; mRNA, messenger ribonucleic acid; RNAi, RNA interference; TTR, transthyretin

1. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 2. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 3. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–91; 4. Gonzalez-Duarte et al. *Int J Mol Sci* 2021;22:13158; 5. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 6. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 7. Gonzalez-Moreno et al. *Cardiol Ther* 2024;13:117–35; 8. Maurer et al. *Circ Heart Fail* 2019;12:e006075; 9. Chacko et al. *Eur J Heart Fail* 2022;24:1700–12; 10. Gillmore et al. *Eur Heart J* 2018;39:2799–806; 11. Maurer et al. *N Engl J Med* 2018;379:1007–16; 12. Habtemariam et al. *Clin Pharmacol Ther* 2021;109:372–82; 13. Adams et al. *Amyloid* 2023;30:18–26; 14. Alnylam Pharmaceuticals Inc. US prescribing information: AMVUTTRA (vutrisiran) injection, for subcutaneous use. 2022. Available from: https://www.alnylam.com/sites/default/files/pdfs/amvuttra-us-prescribing-information.pdf

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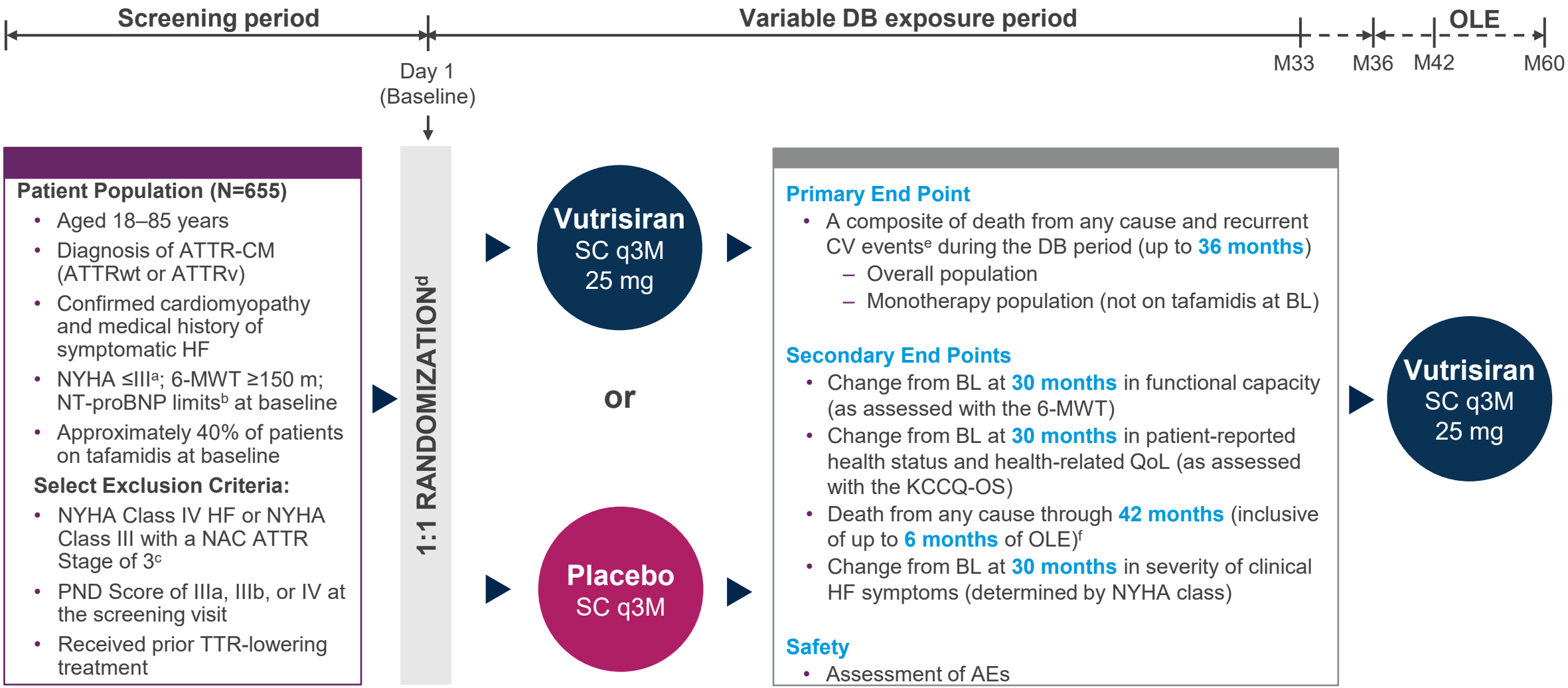
Methods

Study Design



[a]Patients with NYHA Class III were excluded if they also had a NAC ATTR Stage of 3. [b]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation). [c]Defined as NT-proBNP level of >3000 pg/mL and an eGFR <45 mL/min/1.73 m^2 of body surface area. [d]Stratified according to baseline tafamidis use (yes vs no), ATTR amyloidosis disease type (ATTRv vs ATTRwt), NYHA Class I or II and age <75 years vs all others. [e]CV events were defined as CV hospitalizations and urgent HF visits. [f]This timepoint was selected as it would allow more events to be included in the analysis and improve the precision of the estimate of treatment effect on mortality. As prior studies in ATTR-CM suggested that there would be a delayed effect on mortality, a mortality benefit within the first 6 months was not expected among patients who had been assigned to receive placebo and switched to vutrisiran in the open-label extension period. 6-MWT, 6-minute walk test; AE, adverse event; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ATTRv, hereditary or variant ATTR; ATTRwt, wild-type ATTR; BL, baseline; CV, cardiovascular; DB, double-blind; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; M, month; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; PND, polyneuropathy disability; q3M, every 3 months; QoL, quality of life; SC, subcutaneous; TTR, transthyretin

Fontana et al. *N Engl J Med* 2024. Epub ahead of print. DOI: 10.1056/NEJMoa2409134. PMID: 39213194

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Key Eligibility Criteria

Inclusion Criteria[1]

- Aged 18–85 years
- Diagnosis of ATTR-CM (either ATTRv or ATTRwt), defined as the presence of TTR amyloid deposits in a tissue biopsy or fulfillment of validated scintigraphy-based diagnostic criteria for ATTR-CM in the absence of monoclonal gammopathy; and evidence of cardiac involvement as assessed with transthoracic echocardiography, with an end-diastolic interventricular septal wall thickness >12 mm
- Clinical history of HF was required with ≥1 previous hospitalization for HF or clinical evidence of HF, with signs and symptoms of volume overload or elevated intracardiac pressures requiring diuretic treatment
- At baseline, patients were either receiving tafamidis for ATTR-CM at the approved dose within their country, or not receiving tafamidis, with no active plan to start tafamidis during the first 12 months after randomization
- NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation) and the ability to complete ≥150 m on the 6-MWT

Exclusion Criteria[1]

- NYHA Class IV HF; or NYHA Class III HF with a NAC ATTR Stage of 3 (defined as NT-proBNP level of >3000 pg/mL and an eGFR <45 mL/min/1.73 m^2 of body surface area)[2]
- Polyneuropathy disability score of IIIa, IIIb, or IV (requiring a cane or stick to walk, or wheelchair bound)
- Cardiomyopathy not associated with ATTR amyloidosis
- eGFR <30 mL/min/1.73 m^2

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ATTRv or ATTRwt, hereditary ATTR (v for variant) or wild-type ATTR; eGFR, estimated glomerular filtration rate; HF, heart failure; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin

1. Fontana et al. *N Engl J Med* 2024. Epub ahead of print. DOI: 10.1056/NEJMoa2409134. PMID: 39213194; 2. Gillmore JD, et al. *Eur Heart J* 2018;39:2799–806

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Statistical Analysis

- A sample size of 654 patients (60% in the monotherapy population) would give the trial approximately 80% power to detect a between-group difference in the composite end point of death from any cause and recurrent cardiovascular events in both the overall and monotherapy populations
- The primary end points were analyzed using a modified Andersen–Gill model with a robust variance estimator (LWYY model), with treatment group, ATTR disease type (ATTRv vs ATTRwt), NYHA Class (I/II vs III), age group (<75 vs ≥75 years old), and log-transformed baseline NT-proBNP as covariates; the model was also stratified by baseline tafamidis use (yes vs no) for the primary end point analysis in the overall population
- Heart transplantation and/or left ventricular assist device placement were treated as deaths in the analyses that included death from any cause
- Sensitivity analyses were also performed for the primary end point and the secondary end point of death from any cause
- The overall Type I error rate for the primary and secondary end points was controlled at a two-sided 0.05 significance level using a truncated Hochberg-based gatekeeping procedure

ATTR, transthyretin amyloidosis; ATTRv or ATTRwt, hereditary ATTR (v for variant) or wild-type ATTR; LWYY, Lin, Wei, Yang, and Ying; NT-proBNP, *N*-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association

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II Results

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Baseline Patient Demographics

Baseline Characteristics	Overall Population		Monotherapy Population[a]	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
Age at randomization, years, median (range)	77.0 (45–85)	76.0 (46–85)	77.5 (46–85)	76.0 (53–85)
Male sex, n (%)	299 (92)	306 (93)	178 (91)	183 (92)
Race, n (%)				
White	277 (85)	275 (84)	169 (86)	169 (85)
Asian	18 (6)	19 (6)	12 (6)	15 (8)
Black	23 (7)	24 (7)	10 (5)	11 (6)
Other/Not reported	8 (2)	10 (3)	5 (3)	4 (2)
ATTRwt, n (%)	289 (89)	289 (88)	173 (88)	174 (87)
Time since diagnosis of ATTR, years, median (range)	0.86 (0–11.1)	1.03 (0–10.8)	0.50 (0–8.3)	0.63 (0–6.2)
Tafamidis use at baseline, n (%)	130 (40)	129 (39)	—	—
Time on tafamidis prior to trial start, months, median (range)	9.2 (1.1–65.3)	11.3 (1.1–65.5)	—	—

[a]Not on tafamidis at baseline, among whom, 44 patients (22%) in the vutrisiran arm and 41 patients (21%) in the placebo arm initiated tafamidis after randomization

ATTR, transthyretin amyloidosis; ATTRwt, wild-type ATTR

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Baseline Disease Characteristics

Baseline Characteristics	Overall Population		Monotherapy Population[a]	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
NYHA Class, n (%)				
I	49 (15)	35 (11)	15 (8)	12 (6)
II	250 (77)	258 (79)	172 (88)	169 (85)
III	27 (8)	35 (11)	9 (5)	18 (9)
NAC ATTR stage, n (%)[b]				
1	208 (64)	229 (70)	113 (58)	138 (69)
2	100 (31)	87 (27)	68 (35)	55 (28)
3	18 (6)	12 (4)	15 (8)	6 (3)
6-MWT, m, mean (SD)[c]	372.0 (103.7)	377.1 (96.3)	362.7 (102.7)	372.8 (98.1)
KCCQ-OS, points, mean (SD)[d,e]	73.0 (19.4)	72.3 (19.9)	70.3 (20.2)	69.9 (20.8)
Laboratory parameters, median (IQR)				
NT-proBNP, pg/mL	2021 (1138–3312)	1801 (1042–3082)	2402 (1322–3868)	1865 (1067–3099)
High-sensitivity troponin I level, pg/mL	71.9 (44.9–115.9)	65.2 (41.1–105.5)	76.3 (48.4–138.8)	62.2 (39.2–105.6)
mBMI[f]	1183.8 (1082.7–1306.1)	1210.9 (1098.5–1333.5)	1188.7 (1087.3–1335.2)	1206.1 (1094.9–1324.1)
eGFR, mL/min/1.73 m^2	64 (50–81)	65 (53–81)	64 (50–81)	65 (54–81)
Creatinine, µmol/L	97 (80–124)	97 (80–115)	97 (80–124)	97 (80–106)
Coexisting conditions, n (%)				
Hypertension	185 (57)	187 (57)	107 (55)	111 (56)
Diabetes mellitus[g]	56 (17)	55 (17)	35 (18)	39 (20)
Atrial fibrillation	197 (60)	196 (60)	115 (59)	111 (56)

[a]Not on tafamidis at baseline, among whom, 44 patients (22%) in the vutrisiran arm and 41 patients (21%) in the placebo arm initiated tafamidis after randomization. [b]Risk stratification was based on the levels of the serum biomarkers NT-proBNP and eGFR. Stage 1 (lower risk) was defined by an NT-proBNP level of ≤3000 pg/mL and an eGFR of ≥45 mL/min/1.73 m^2. Stage 2 (intermediate risk) included all patients who did not meet the criteria for Stages 1 or 3. Stage 3 (higher risk) was defined by an NT-proBNP greater than >3000 pg/mL and an eGFR of <45 mL/min/1.73 m^2. [c]6-MWT values were assessed at baseline in 325 patients in the vutrisiran arm of the overall population. [d]KCCQ-OS scores range from 0 to 100, with a score of 0–24 indicating very poor to poor quality of life, 25–49 poor to fair, 50–74 fair to good, and 75–100 good to excellent. [e]KCCQ-OS values were assessed at baseline in 325 patients in the vutrisiran arm and 327 patients in the placebo arm of the overall population, and in 195 patients in the vutrisiran arm and 198 patients in the placebo arm of the monotherapy population; [f]The mBMI was calculated as the conventional BMI (weight in kilograms divided by the square of the height in meters) multiplied by the serum albumin level in grams per liter; [g]Includes categories diabetes mellitus, steroid diabetes and type 2 diabetes mellitus

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; mBMI, modified body mass index; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation

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Summary of Baseline Patient Demographics and Disease Characteristics

- The demographic and clinical characteristics were similar between the placebo and vutrisiran groups, apart from higher NT-proBNP and troponin I levels in the vutrisiran vs placebo group in the monotherapy population
- Baseline data were generally representative of the global population of patients with ATTR-CM
- Among the 76 patients with ATTRv, there were 13 different pathogenic *TTR* variants; V122I (N = 49 [64%]) was the most common variant
- The demographic and clinical characteristics of the patients in the monotherapy population did not differ substantially from the overall population

ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ATTRv, hereditary ATTR; NT-proBNP, *N*-terminal pro–B-type natriuretic peptide; TTR, transthyretin

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Primary End Point: Death From Any Cause and Recurrent Cardiovascular Events

	Overall Population		Monotherapy Population	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
Death from any cause and recurrent cardiovascular events				
Measure of Effect: Vutrisiran vs placebo HR (95% CI), P value	0.72 (0.56, 0.93), P=0.01		0.67 (0.49, 0.93), P=0.02	
Primary end point components				
Death from any cause				
Measure of Effect: Vutrisiran vs placebo HR (95% CI), P value	0.69 (0.49, 0.98), P=0.04		0.71 (0.47, 1.06), P=0.12	
Recurrent cardiovascular events				
Measure of Effect: Vutrisiran vs placebo RRR (95% CI), P value	0.73 (0.61, 0.88), P=0.001		0.68 (0.53, 0.86), P=0.001	
Patients with at least 1 event, n (%)	125 (38)	159 (48)	76 (39)	105 (53)
Death from any cause[a]	51 (16)	69 (21)	36 (18)	46 (23)
Cardiovascular events	112 (34)	133 (41)	66 (34)	87 (44)

- The results of prespecified win-ratio sensitivity analyses in both populations were consistent with those of the primary analyses

In both populations, treatment with vutrisiran led to a lower risk of death from any cause and recurrent cardiovascular events than placebo

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For the analyses that included death from any cause, heart transplantation and implantation of a left ventricular assist device were treated as deaths. The HR for the primary end point was calculated using the LWYY model. Hazard ratios for death from any cause were calculated with the use of the Cox proportional-hazards model. Recurrent cardiovascular events RRR was generated using a Poisson regression model. [a]Three patients in the vutrisiran group and four in the placebo group had a heart transplantation. No patients had implantation of a left ventricular assist device.
CI, confidence interval; HR, hazard ratio, RRR, relative rate ratio
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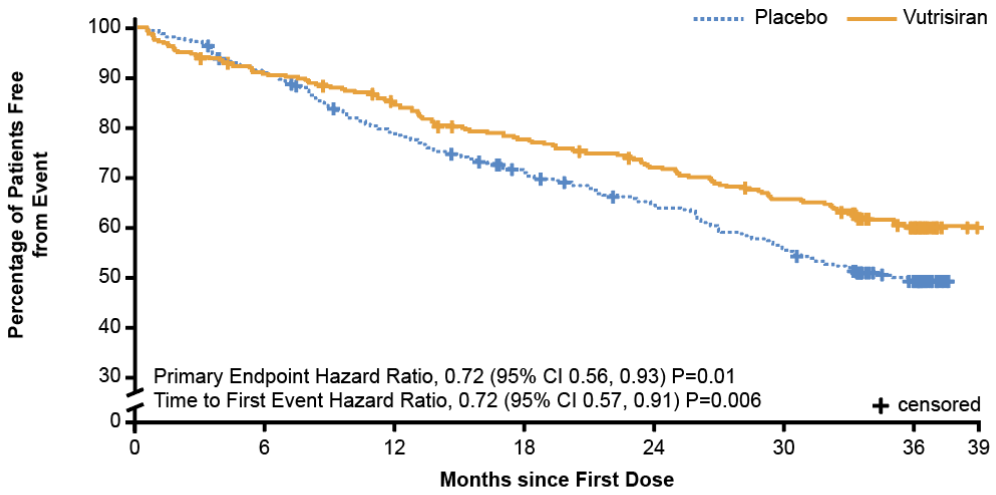
Primary End Point: Time to Death From Any Cause or First Cardiovascular Event

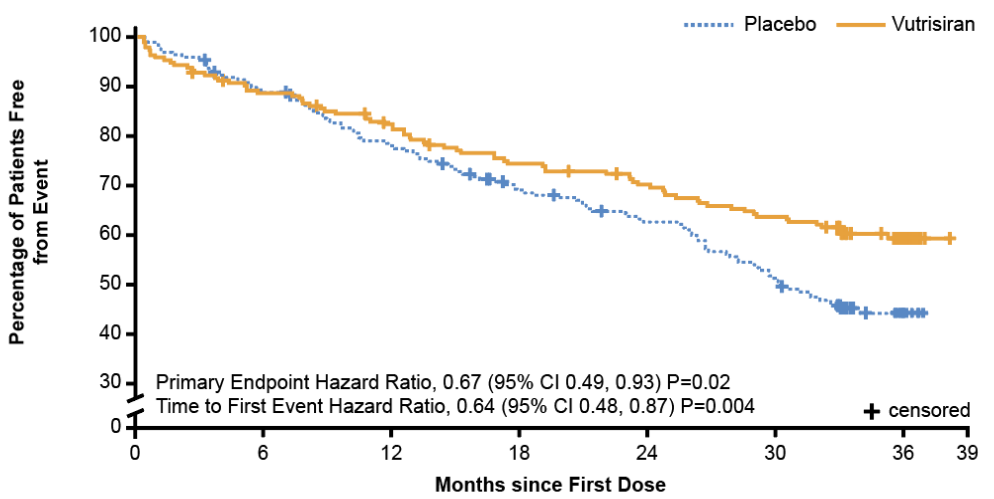
Time to First Event in Overall Population



No. at Risk (cumulative no. of events)

Vutrisiran	326 (0)	294 (30)	271 (50)	247 (72)	227 (90)	206 (110)	62 (125) 0 (125)
Placebo	328 (0)	295 (31)	253 (70)	221 (96)	199 (115)	172 (142)	52 (159) 0 (159)

Time to First Event in Monotherapy Population



No. at Risk (cumulative no. of events)

Vutrisiran	196 (0)	172 (22)	157 (34)	141 (49)	131 (57)	119 (69)	32 (76) 0 (76)
Placebo	199 (0)	175 (22)	152 (43)	130 (60)	116 (72)	95 (93)	26 (105) 0 (105)

- Kaplan–Meier plots illustrating time to first cardiovascular event or death from any cause demonstrated the vutrisiran and placebo curves diverging after approximately 6 months of treatment, although a formal test showed no violation of the proportional-hazards assumption

Results for the individual components of the primary endpoint were consistent with the composite

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The primary end point was a composite of death from any cause and recurrent cardiovascular events (defined as hospitalizations for cardiovascular causes or urgent visits for heart failure). The monotherapy population was defined as the patients who were not receiving tafamidis at baseline. Tick marks indicate censored data.
CI, confidence interval
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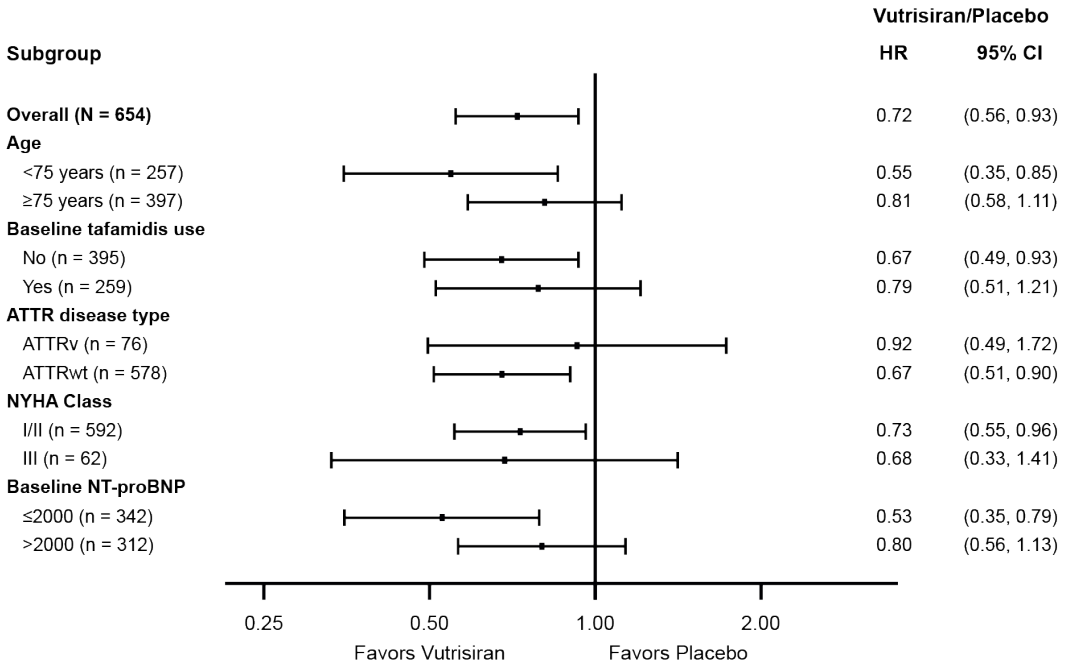
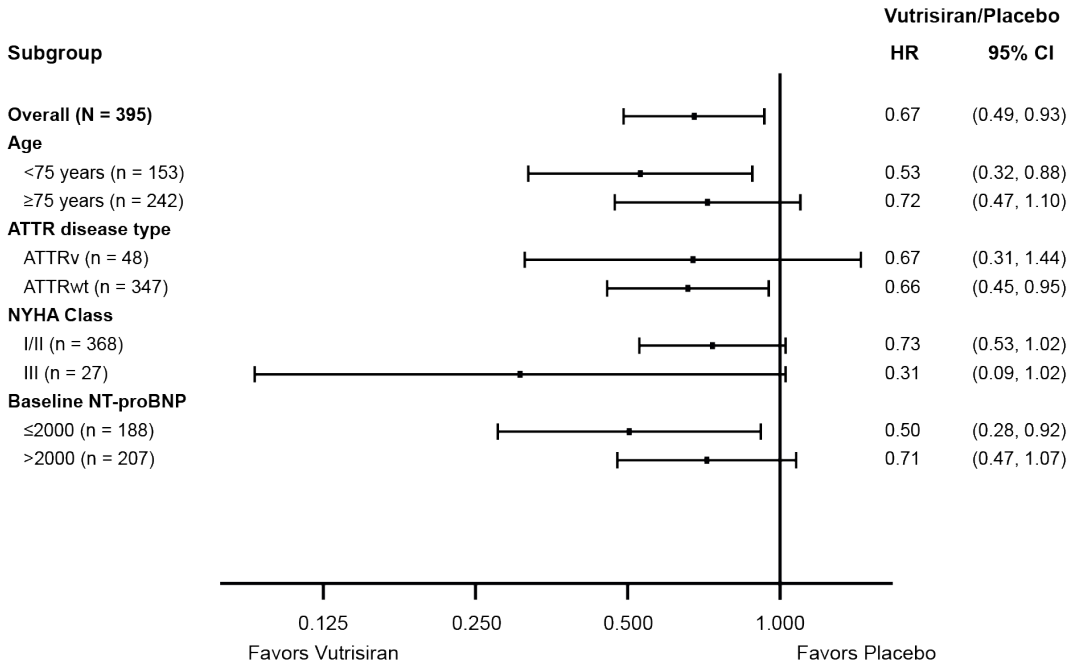
Primary End Point: Death From Any Cause and Cardiovascular Events

Subgroup Analyses of the Primary End Point (overall population)



Subgroup Analyses of the Primary End Point (monotherapy population)



- Similar effects were observed with respect to death from any cause and recurrent cardiovascular events across all prespecified subgroups

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ATTR, transthyretin amyloidosis; ATTRv, variant ATTR; ATTRwt, wild-type ATTR; CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association; NT-proBNP, *N*-terminal pro–B-type natriuretic peptide

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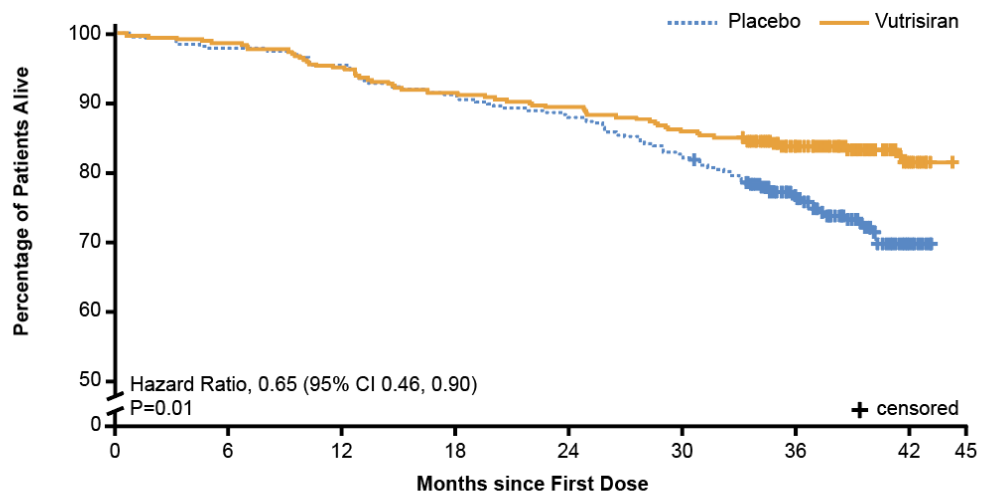
Secondary End Point: Death from Any Cause Through 42 Months

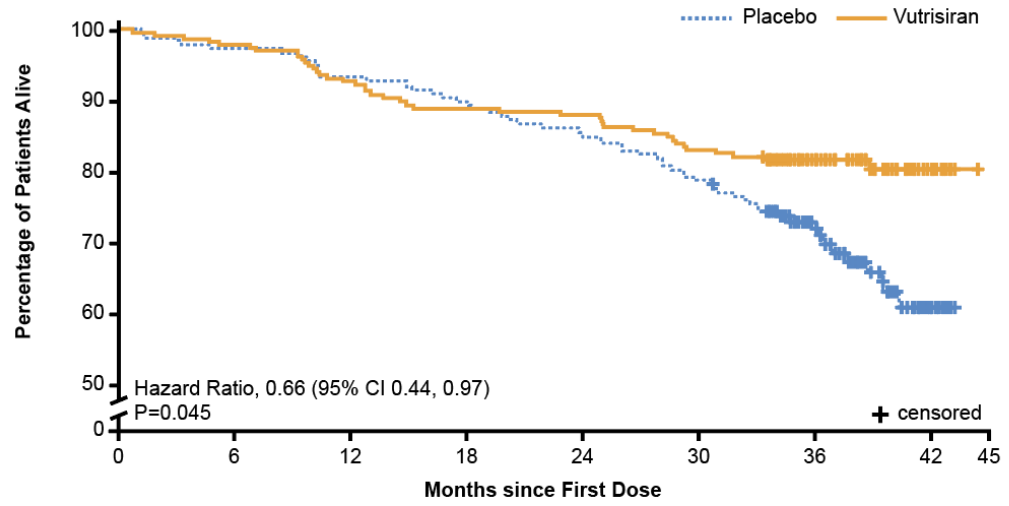
Death from Any Cause in the Overall Population



No. at Risk (cumulative no. of events)

Vutrisiran	326 (0)	321 (5)	308 (18)	296 (30)	289 (37)	277 (49)	198 (56)	33 (60) 0 (60)
Placebo	328 (0)	321 (7)	314 (14)	299 (29)	290 (38)	271 (57)	180 (74)	24 (85) 0 (85)

Death from Any Cause in the Monotherapy Population



No. at Risk (cumulative no. of events)

Vutrisiran	196 (0)	191 (5)	179 (17)	171 (25)	169 (27)	158 (38)	86 (41)	17 (43) 0 (43)
Placebo	199 (0)	194 (5)	188 (11)	180 (19)	172 (27)	160 (39)	79 (51)	16 (58) 0 (58)

- Treatment with vutrisiran resulted in a lower risk of death from any cause through 42 months than placebo in the overall population and monotherapy population

The Kaplan–Meier curves were adjusted according to disease severity characteristics at baseline with the use of the inverse probability of treatment weighting method.
CI, confidence interval
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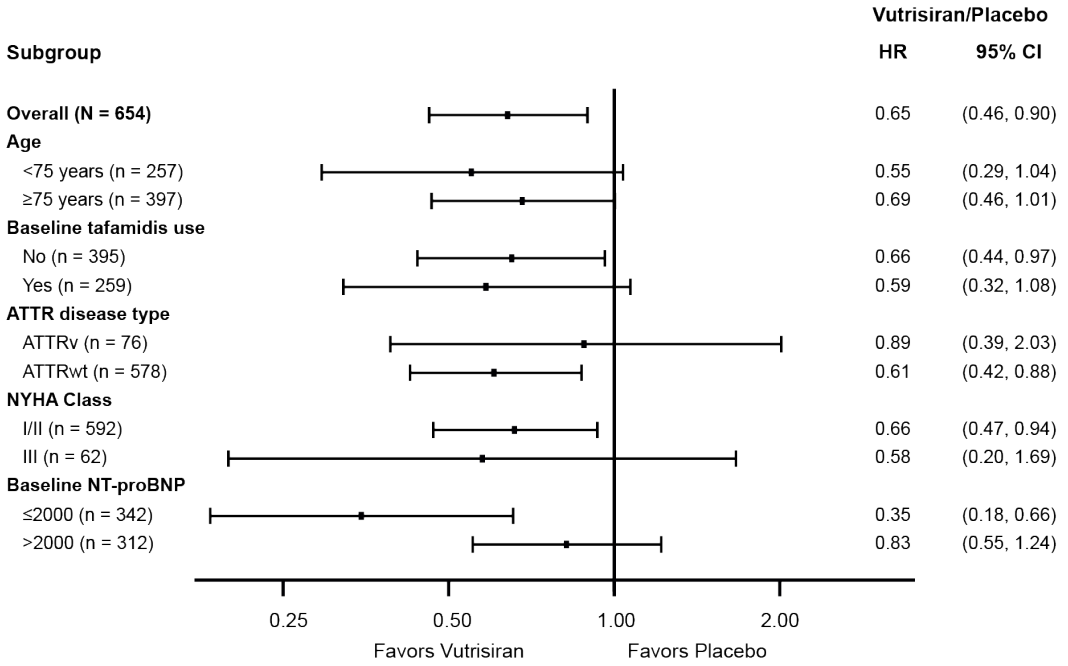
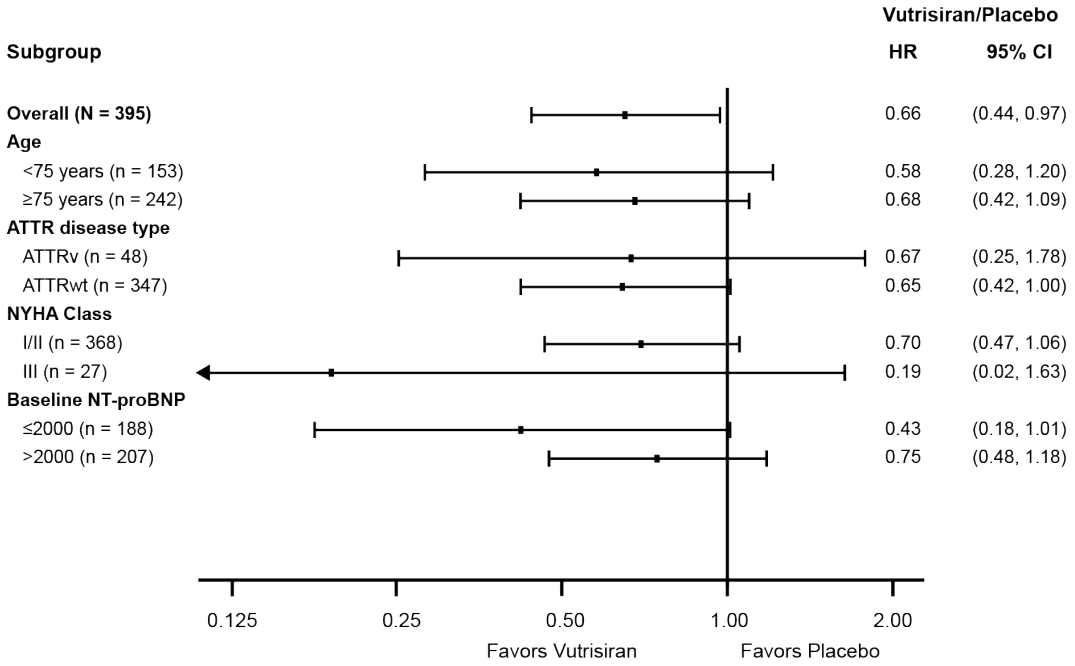
Secondary End Point: Death from Any Cause Through 42 Months[a]

Subgroup Analyses of Death from Any Cause (overall population)



Subgroup Analyses of Death from Any Cause (monotherapy population)



- In both populations, similar effects were observed with respect to death from any cause across all prespecified subgroups
- A sensitivity analysis using a weighted log-rank test (the Fleming–Harrington [1,1] test) showed similar results

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[a]Up to 6 months of follow-up during OLE

ATTR, transthyretin amyloidosis; ATTRv, variant ATTR; ATTRwt, wild-type ATTR; CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association; NT-proBNP, N-terminal pro–B-type natriuretic peptide; OLE, open-label extension

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Secondary End Points: Changes from Baseline at 30 Months for 6-MWT, KCCQ-OS, and NYHA Class

	Overall Population		Monotherapy Population	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
6-MWT change from baseline at 30 months in distance covered, m				
LS mean (95% CI)	−45.4 (−54.5, −36.3)	−71.9 (−81.3, −62.4)	−59.7 (−72.7, −46.7)	−91.8 (−104.4, −79.2)
Measure of Effect: LS mean difference (95% CI), P-value	26.5 (13.4, 39.6), <0.001		32.1 (14.0, 50.2), <0.001	
KCCQ-OS score change from baseline at 30 months, points				
LS mean (95% CI)	−9.7 (−12.0, −7.4)	−15.5 (−18.0, −13.0)	−10.8 (−14.1, −7.5)	−19.5 (−22.9, −16.1)
Measure of Effect: LS mean difference (95% CI), P-value	5.8 (2.4, 9.2), <0.001		8.7 (4.0, 13.4), <0.001	
NYHA Class change from baseline at 30 months				
Stable or improved, %	68	61	66	56
Measure of Effect: Adjusted difference in % of patients with stable or improved (95% CI), P-value	8.7 (1.3, 16.1), 0.02		12.5 (2.7, 22.2), 0.01	

- In both the overall and monotherapy populations, there was less decline from baseline in 6-MWT distance and KCCQ-OS with vutrisiran than with placebo at 30 months
- At 30 months in the overall population, a greater proportion of patients had improvement or no change in NYHA Class with vutrisiran than with placebo
- Similar benefits were observed in the monotherapy population for all secondary endpoints

For 6-MWT and KCCQ-OS assessments missing due to death, being unable to walk due to ATTR disease progression (for 6-MWT only), heart transplantation, or implantation of a LVAD, data were imputed from resampling of worst 10% of observed changes; for 6-MWT, a further distance walked indicates better function, and for the KCCQ-OS, scores range from 0 to 100, with higher scores indicating better quality of life.
6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS, least squares; LVAD, left ventricular assist device; NYHA, New York Heart Association
Fontana et al. *N Engl J Med* 2024. Epub ahead of print. DOI: 10.1056/NEJMoa2409134. PMID: 39213194

Exploratory End Points: Change from Baseline at 30 Months

	Overall Population		Monotherapy Population	
	Vutrisiran (n=326)	Placebo (n=328)	Vutrisiran (n=196)	Placebo (n=199)
NT-proBNP fold change from baseline at 30 months				
Geometric mean (95% CI)	1.19 (1.11, 1.28)	1.75 (1.62, 1.89)	1.30 (1.17, 1.45)	2.28 (2.04, 2.55)
Geometric fold-change ratio (95% CI)	0.68 (0.61, 0.76)		0.57 (0.49, 0.66)	
Troponin I fold change from baseline at 30 months				
Geometric mean (95% CI)	0.94 (0.88, 1.00)	1.37 (1.28, 1.47)	1.01 (0.92, 1.12)	1.85 (1.68, 2.03)
Geometric fold-change ratio (95% CI)	0.68 (0.62, 0.75)		0.55 (0.48, 0.63)	
Peak longitudinal strain change from baseline at 30 months[a], %				
LS mean (SEM)	0.95 (0.17)	2.18 (0.19)	1.07 (0.26)	2.37 (0.26)
LS mean difference (95% CI)	−1.23 (−1.73, −0.73)		−1.30 (−2.01, −0.59)	
EuroQoL-5D-5L Index change from baseline at 30 months				
LS mean (SEM)	−0.03 (0.008)	−0.06 (0.008)	−0.03 (0.011)	−0.08 (0.011)
LS mean difference (95% CI)	0.03 (0.01, 0.05)		0.05 (0.02, 0.08)	

[a]Peak longitudinal strain was assessed by echocardiography and was analyzed by a blinded reader at a central cardiac imaging core laboratory

CI, confidence interval, EuroQoL-5D-5L, EuroQoL 5-dimensions-5 levels; LS, least squares; NT-proBNP, *N*-terminal pro–B-type natriuretic peptide; SEM, standard error of the mean

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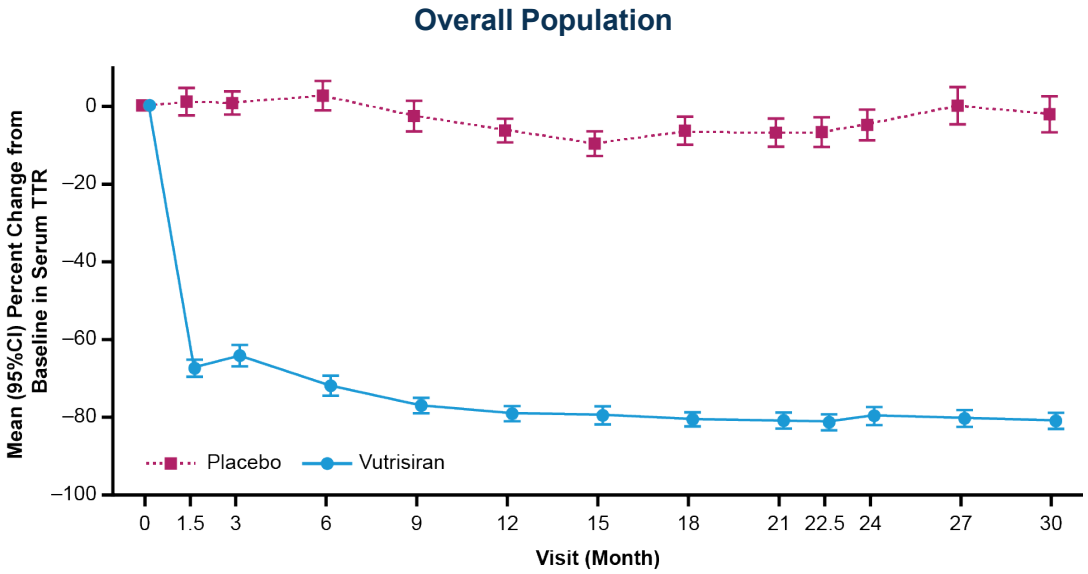
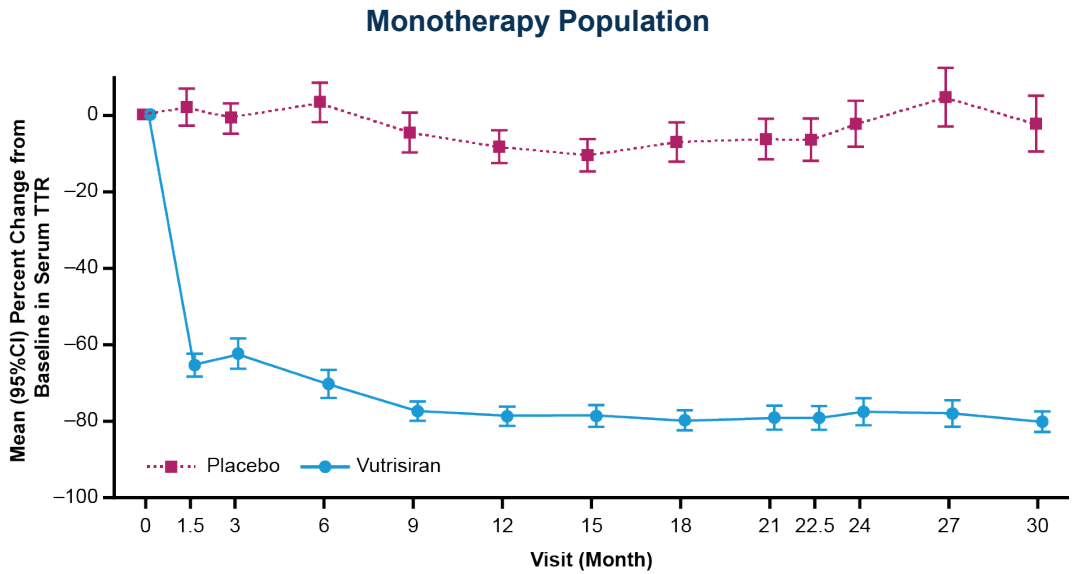
Pharmacodynamics: Percent Change from Baseline in Serum TTR Levels over Time



No. Evaluable

Placebo	324	304	314	306	302	296	286	274	268	263	257	239	230
Vutrisiran	317	294	304	299	295	285	278	272	263	258	254	250	246



No. Evaluable

Placebo	196	185	190	183	183	177	172	162	155	152	147	137	131
Vutrisiran	190	180	182	178	175	160	160	154	149	145	141	138	136

- A rapid and sustained reduction in serum TTR levels was observed with vutrisiran. The mean trough percent reduction was 81.0% (95% CI, 79.0, 83.0) at 30 months in the overall population

CI, confidence interval; TTR, transthyretin

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Safety Summary

Safety Summary in the Overall Population during the Double-Blind Exposure Period

- In the overall population, the proportion of patients with at least one AE was similar between treatment arms (vutrisiran, 99% [n=322]; placebo, 98% [n=323])
- In the vutrisiran and placebo arms, respectively, SAEs occurred in 62% (n=201) and 67% (n=220) of patients, and AEs leading to study drug discontinuation occurred in 3% (n=10) and 4% (n=13) of patients
- No clinically relevant changes in laboratory measures (including hematologic measures, blood chemistry measures, liver-function tests, and renal-function tests), vital signs, or electrocardiograms were observed in either treatment arm

Event, n (%)	Vutrisiran (N=326)	Placebo (N=328)
At least 1 AE	322 (99)	323 (98)
AEs occurring in ≥15% of patients in either arm		
Cardiac failure Covid-19 Atrial fibrillation Gout Dyspnea Fall	101 (31) 87 (27) 69 (21) 48 (15) 43 (13) 42 (13)	128 (39) 99 (30) 68 (21) 51 (16) 51 (16) 69 (21)
Any SAE[a]	201 (62)	220 (67)
Any severe AE[a]	158 (48)	194 (59)
SAEs occurring in ≥5% of patients in either arm		
Cardiac failure Atrial fibrillation Cardiac failure acute	38 (12) 26 (8) 13 (4)	57 (17) 20 (6) 18 (5)
Cardiac AEs	227 (70)	242 (74)
Cardiac SAEs	116 (36)	124 (38)
AEs leading to discontinuation	10 (3)	13 (4)
Any AE leading to death[b]	49 (15)	63 (19)

[a]SAEs defined as AEs that resulted in death, were life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators. All AEs were graded for severity. Severe AEs defined as AEs for which more than minimal, local, or non-invasive intervention was received; which had a severe effect on limiting self-care activities of daily living; or which had the potential for life-threatening consequences or death. [b]All fatal SAEs are summarized regardless of the treatment-emergent classification. Deaths that occurred after the end of study visit or after the data cut-off date are not included

AE, adverse event; SAE, serious adverse event

Fontana et al. *N Engl J Med* 2024. Epub ahead of print. DOI: 10.1056/NEJMoa2409134. PMID: 39213194

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II Discussion

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Discussion

- In this randomized, placebo-controlled trial involving patients with ATTR-CM, treatment with vutrisiran resulted in a lower risk of death from any cause and recurrent cardiovascular events than placebo in the overall population and in the monotherapy population (the patients who were not receiving tafamidis at baseline)[1]
  - Similar effects were seen in all prespecified subgroups
- Preservation of functional capacity and quality of life were better with vutrisiran than with placebo, and vutrisiran prevented the worsening of heart failure symptoms[1]
- HELIOS-B trial results extend the favorable effects of TTR lowering by RNA interference, initially seen in patients with polyneuropathy due to ATTRv, to patients with cardiomyopathy due to either ATTRwt or ATTRv[1]
  - In HELIOS-A, a previous trial of vutrisiran in patients with ATTRv with polyneuropathy, vutrisiran improved change from baseline in modified Neuropathy Impairment Score +7 at 9 months; and outcomes for all secondary efficacy end points assessing multiple disease-relevant outcomes were better among patients who received vutrisiran than those in an external placebo group
- The HELIOS-B trial was designed to include a patient group representative of contemporary ATTR-CM populations. Over the past decade, advances in non-invasive imaging techniques have led to a higher proportion of patients being diagnosed earlier in their disease process, with a less severe clinical phenotype and better prognosis[2]
- Despite a healthier patient population at the outset and substantial concurrent tafamidis and SGLT2 inhibitor use, vutrisiran, as compared with placebo, was associated with a hazard ratio of 0.65 for death from any cause through 42 months in the overall population.[1]
  - These data also suggest that vutrisiran may provide benefit to patients in relatively early stages of disease, when functional capacity and quality of life may be more effectively preserved
- In HELIOS-B, the incidence of AEs among patients in the vutrisiran group was similar or lower than that among the patients in the placebo group, a finding that is consistent with the incidence of adverse events in the HELIOS-A trial[1]

AE, adverse event; ATTR-CM, ATTR with cardiomyopathy; ATTRv or ATTRwt, hereditary ATTR (v for variant) or wild-type ATTR; HF, heart failure; RNA, ribonucleic acid; SGLT2, sodium/glucose cotransporter 2; TTR, transthyretin

1. Fontana et al. *N Engl J Med* 2024. Epub ahead of print. DOI: 10.1056/NEJMoa2409134. PMID: 39213194; 2. Ioannou et al. *Circulation* 2022;146:1657–70

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Study Limitations

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Study Limitations

Several limitations should be considered when interpreting the study results

- Tafamidis was an allowed background therapy at baseline to which patients were not randomly assigned; therefore, this study does not allow for a randomized comparison of vutrisiran alone with tafamidis alone
- In addition, although 40% of the patients were taking tafamidis at baseline, the trial was not powered to show statistical significance within this subgroup
- The main limitation of the primary analysis method (LWYY) is that it treats recurrent cardiovascular events and death equally. However, additional analyses, including analyses of the individual components of the primary end point, win ratio analyses, and time-to-first-event analyses all yielded consistent results
- The majority of patients were men and White, but this was expected based on reported demographics of ATTR-CM patient populations
- The trial also had a low proportion of patients with ATTRv, likely reflecting the global preponderance of ATTRwt-CM relative to ATTRv-CM

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ATTR-CM, ATTR with cardiomyopathy; ATTRv or ATTRwt, hereditary ATTR (v for variant) or wild-type ATTR; LWYY, Lin, Wei, Yang, and Ying

II Conclusions

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Conclusions

- In patients with ATTR-CM, treatment with vutrisiran resulted in a lower risk of death from any cause and recurrent cardiovascular events. Vutrisiran also preserved functional capacity and quality of life and prevented worsening of HF symptoms
- These effects were consistent across all prespecified subgroups, including in patients who were receiving background tafamidis
- Collectively, these data suggest that rapid knockdown of TTR by vutrisiran reduces morbidity and mortality among patients with ATTR-CM

ATTR-CM, ATTR with cardiomyopathy; HF, heart failure; TTR, transthyretin

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