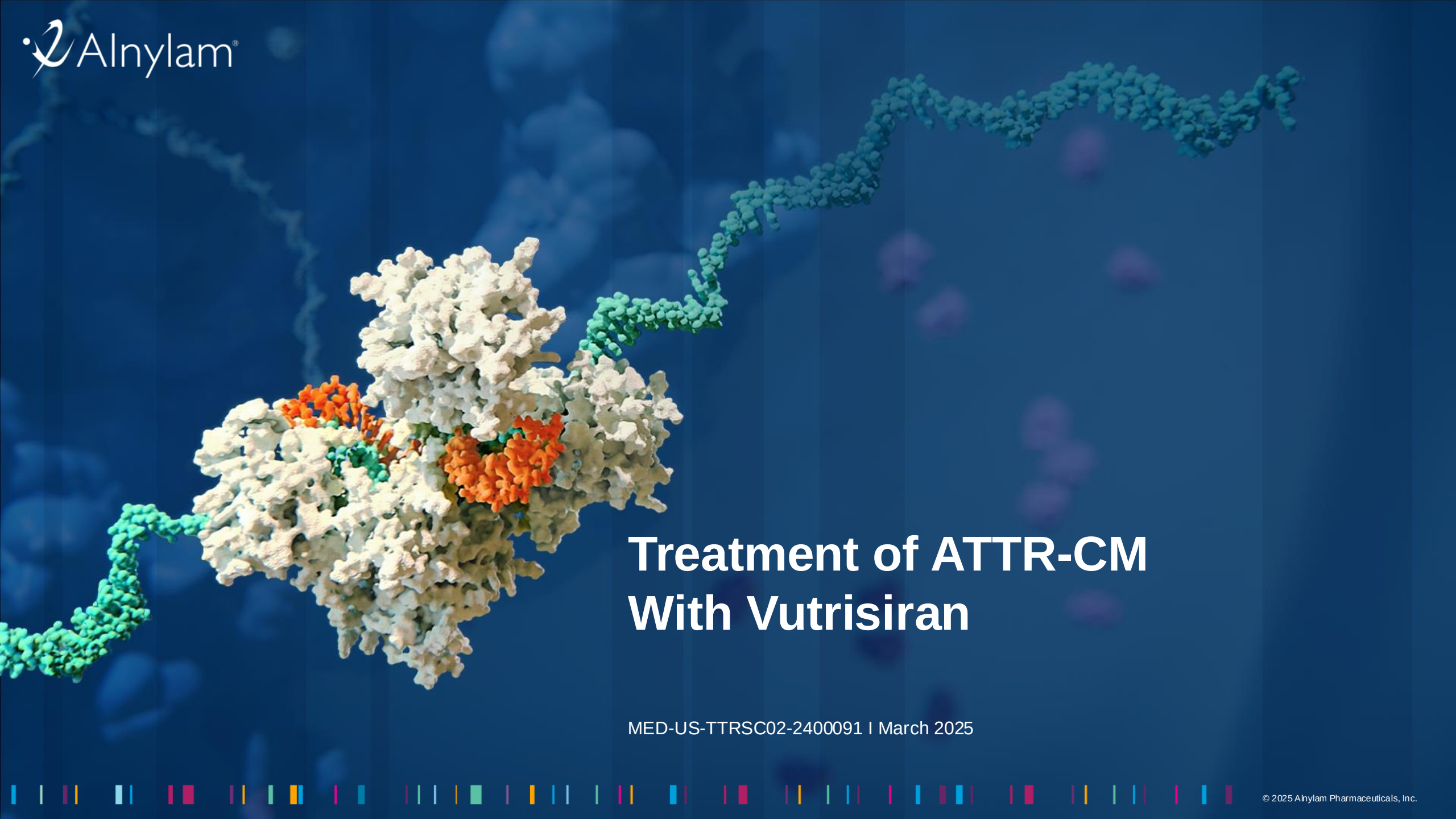

Treatment of ATTR-CM With Vutrisiran

MED-US-TTRSC02-2400091 I March 2025

Treatment of ATTR-CM With Vutrisiran

- This resource is intended to support scientific exchange with HCPs and may contain information that is not in the FDA-approved Prescribing Information for AMVUTTRA® (vutrisiran). The information provided is not intended to serve as recommendations for clinical practice.
- Please see the AMVUTTRA® full Prescribing Information: https://www.alnylam.com/amvuttra-us-prescribing-information
- This resource may contain hyperlinks that are not functional in this format.
- For further information, please see RNAiScience.com to connect with a Medical Science Liaison, submit a medical information request, or access other Alnylam medical and scientific information resources.

Scan for AMVUTTRA full Prescribing Information

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Table of Contents

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; RNAi, ribonucleic acid interference.

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ATTR-CM Disease Background and Unmet Need

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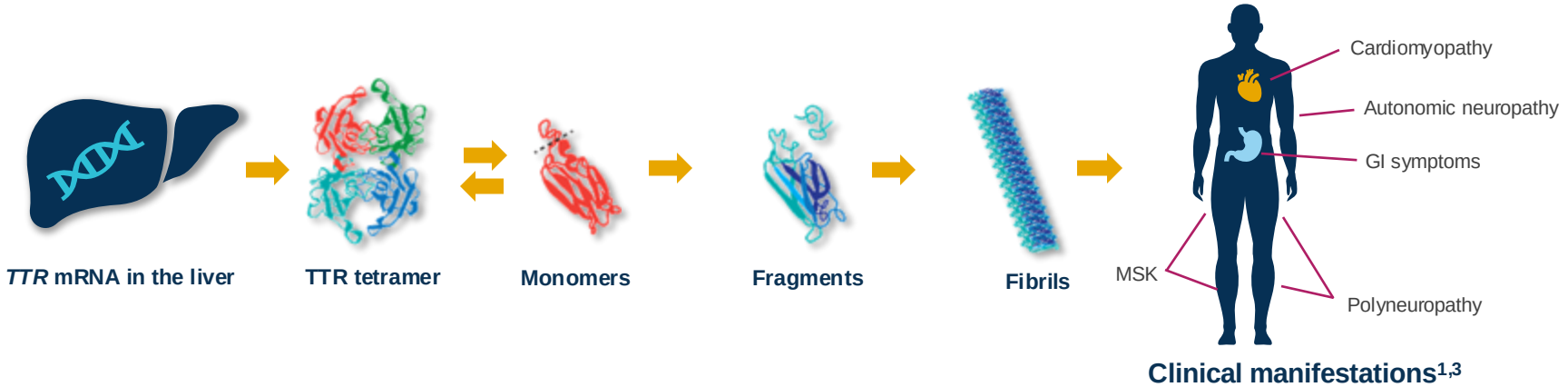
ATTR Amyloidosis Is an Underdiagnosed, Rapidly Progressing, Fatal Disease Caused by Toxic Misfolded TTR Accumulating as Amyloid Deposits in Multiple Organs[1,2]

The TTR protein is primarily **produced in the liver** and transports vitamin A and thyroxine

In ATTR amyloidosis, toxic misfolded TTR accumulates as amyloid deposits…

…in multiple organs and tissues, resulting in **progressive organ damage**[1]



Clinical manifestations[1,3]

Cycle of toxic misfolded TTR deposition[4]

ATTR, transthyretin amyloidosis; GI, gastrointestinal; mRNA, messenger ribonucleic acid; MSK, musculoskeletal; TTR, transthyretin.

1. Adams D, et al. Nat Rev Neurol. 2019;15:387-404; 2. Ghosh S, et al. Amyloid. 2023;30:379-393; 3. Adams D, et al. J Neurol. 2021;268:2109-2122; 4. Ioannou A, et al. Heart Int. 2024;18:30-37.

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There Are 2 Types of ATTR Amyloidosis: Hereditary or Wild-Type

ATTR amyloidosis is classified by the sequence of the *TTR* gene, either wtATTR amyloidosis (no variant) or hATTR amyloidosis (variant present)[1]

Worldwide, there are

~50,000
PATIENTS WITH
hATTR amyloidosis[2]

~200,000-300,000
PATIENTS WITH
wtATTR amyloidosis[3,4,a]

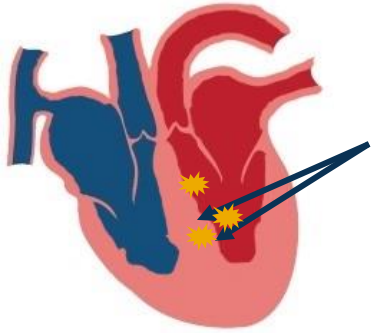
hATTR amyloidosis

- hATTR amyloidosis arises from an inherited variant in the *TTR* gene, resulting in misfolded amyloidogenic monomers.[5,6]
- hATTR amyloidosis is caused by deposition of both variant and wt toxic misfolded TTR amyloid.[5-7]
- Patients with hATTR amyloidosis commonly develop multi-system manifestations, including polyneuropathy and **cardiomyopathy**.[8]

wtATTR amyloidosis

- wtATTR amyloidosis is nonhereditary, but also results in toxic misfolded wt TTR, which accumulates as amyloid deposits.[9,10]
- Patients with wtATTR amyloidosis are typically aged ≥60 years and mostly have **cardiomyopathy**, although polyneuropathy may coexist.[8,11]

Amyloid deposits in the heart can lead to cardiomyopathy



Amyloid deposits form in cardiac tissue

Amyloid heart

Patients' experience[6,10,12-16]

- Progressive HF
- Cardiac arrhythmias
- Restrictive cardiomyopathy
- Intolerance of commonly used CV medications[b]

[a]*Numbers may be underestimated as nonspecific signs/symptoms can lead to misdiagnosis.*[17] *Information based on Alnylam modeling data.* [b]*For example, digoxin, calcium channel blockers, ACEIs, ARBs, and beta-blockers.*

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATTR, transthyretin amyloidosis; CV, cardiovascular; hATTR, hereditary transthyretin amyloidosis; HF, heart failure; TTR, transthyretin; wt, wild-type; wtATTR, wild-type transthyretin amyloidosis.

1. Ruberg FL, et al. J Am Coll Cardiol. 2019;73:2872-2891; 2. Gertz MA. Am J Manag Care. 2017;23(7 supplement):S107-S112; 3. Narotsky DL, et al. Can J Cardiol. 2016;32:1166:e1-10; 4. Karam C, et al. Orphanet J Rare Dis. 2024;19:419; 5. Hawkins PN, et al. Ann Med. 2015;47:625-638; 6. Ruberg FL, et al. Circulation. 2012;126:1286-1300; 7. Ghosh S, et al. Amyloid. 2023;30:379-393; 8. Coelho T, et al. Curr Med Res Opin. 2013;29:63-76; 9. Hanna M. Curr Heart Fail Rep. 2014;11:50-57; 10. Mohty D, et al. Arch Cardiovasc Dis. 2013;106:528-540; 11. González-López E, et al. Eur Heart J. 2015;36:2585-2594; 12. Dungu JN, et al. Heart. 2012;98:1546-1554; 13. Castaño A, et al. Heart Fail Rev. 2015;20:163-178; 14. Dharmarajan K, Maurer MS. J Am Geriatr Soc. 2012;60:765-774; 15. Falk RH. Circulation. 2005;112:2047-2060; 16. Coelho T, et al. A guide to transthyretin amyloidosis. Amyloidosis. Accessed February 21, 2025. https://amyloidosis.org/sites/default/files/pdf-docs/pages/resources/2023-03/2018%20ATTR.pdf 17. Nativi-Nicolau JN, et al. Heart Fail Rev. 2022;27:785-793.

ATTR Amyloidosis Affects Multiple Organs and Results in Progressively Debilitating Symptoms[1-3]

A global online patient survey conducted by the ARC identified the organs most affected by ATTR amyloidosis, and the most common symptoms at diagnosis[1]

hATTR Amyloidosis

Organs most affected in patients

Nervous system **78%**

Heart **71%**

GI system **53%**

Kidneys **10%**

Top 3 initial symptoms

Numbness/tingling in hands or feet **53%**

Carpal tunnel syndrome **33%**

Fatigue **28%**

wtATTR Amyloidosis

Organs most affected in patients

Heart **97%**

Nervous system **24%**

GI system **15%**

Kidneys **10%**

Top 3 initial symptoms

Shortness of breath **51%**

Irregular heart rate or palpitations **45%**

Fatigue **38%**

ATTR amyloidosis is progressive and leads to a decline in physical functioning[2,3]

ARC, Amyloidosis Research Consortium; ATTR, transthyretin amyloidosis; GI, gastrointestinal; hATTR, hereditary transthyretin amyloidosis; wtATTR, wild-type amyloid transthyretin.

1. ARC 2022 community survey results. Amyloidosis Research Consortium. Published 2022. Accessed March 5, 2025. https://arci.org/arc-2022-community-survey/#wild 2. Nativi-Nicolau J, et al. ESC Heart Fail. 2021;8:3875-3388; 3. Lin X, et al. BMC Neurol. 2021;21:70.

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ATTR Amyloidosis Is Often Underdiagnosed, Leading to a Delay in Treatment and/or Initiation of Potentially Detrimental Treatments[1]

Barriers to Diagnosis Identified in a Global Online Patient Survey Conducted by the ARC[2]

hATTR amyloidosis

Physicians seen on average prior to correct diagnosis

32%
Reported misdiagnosis

26%
Reported trouble getting tested

19%
Reported trouble finding a specialist

wtATTR amyloidosis

Average number of physicians seen prior to correct diagnosis

18%
Reported misdiagnosis

7%
Reported trouble getting tested

14%
Reported trouble finding a specialist

Patients with ATTR amyloidosis can endure a wait of up to 6 years after onset of symptoms before receiving a diagnosis[3]

ARC, Amyloidosis Research Consortium; ATTR, transthyretin amyloidosis; hATTR, hereditary transthyretin amyloidosis; wtATTR, wild-type transthyretin amyloidosis.

1. Nativi-Nicolau JN, et al. Heart Fail Rev. 2022;27:785-793; 2. ARC 2022 community survey results. Amyloidosis Research Consortium. Published 2022. Accessed March 6, 2025. https://arci.org/arc-2022-community-survey/#wild 3. Rozenbaum MH, et al. Cardiol Ther. 2021;10:141-159.

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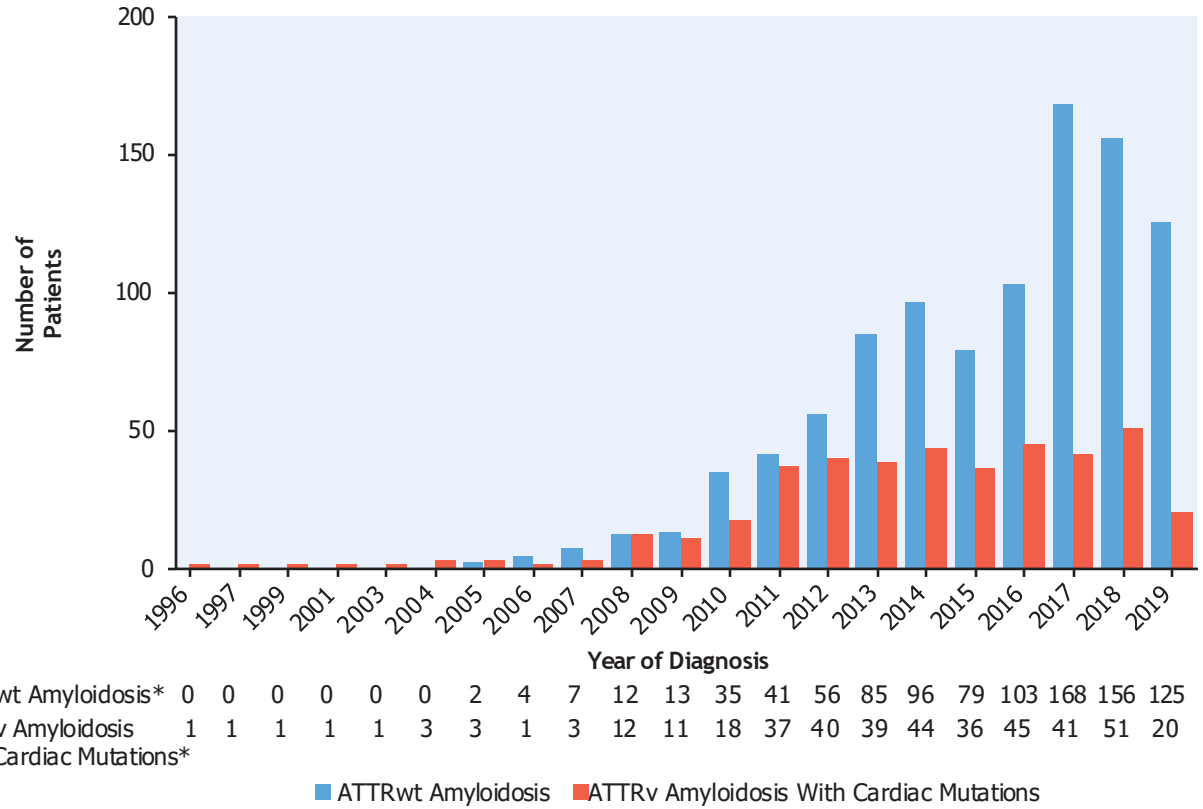
Diagnosis of ATTR Amyloidosis Is Improving; However, Challenges Remain[1-7]

CENTRAL ILLUSTRATION Diagnoses of Wild-Type Transthyretin Amyloidosis Versus Variant Transthyretin Amyloidosis With Cardiac Mutations



Nativi-Nicolau, J. et al. JACC CardioOncol. 2021;3(4):537-546.

Diagnoses in THAOS (the Transthyretin Amyloidosis Outcomes Survey) are shown by year. Wild-type transthyretin amyloidosis (ATTRwt amyloidosis) diagnoses increased from 2 in 2005 to >100 per year starting in 2016. Diagnoses of variant transthyretin amyloidosis (ATTRv amyloidosis) with cardiac mutations increased from 3 in 2005 to 37 in 2011, after which they plateaued.
*Year of diagnosis missing for 87 patients with ATTRwt amyloidosis and 116 patients with ATTRv amyloidosis with cardiac mutations.

Recent advances in the awareness, diagnosis, and treatment of ATTR amyloidosis mean that patients are generally diagnosed earlier and are more intensively treated than ever before[1-3]

Despite improvements in diagnosis and more intensive treatment, many patients still experience progression[5-7]

ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; UK, United Kingdom; wtATTR, wild-type transthyretin amyloidosis.

1. Narotsky DL, et al. Can J Cardiol. 2016;32:1166.e1-1166.e10; 2. Griffin JM, et al. JACC CardioOncol. 2021;3:488-505; 3. Fontana M, et al. N Engl J Med. 2025;392:33-44 (and supplementary appendix); 4. Nativi-Nicolau J, et al. JACC CardioOncol. 2021;3:537-546; 5. Gonzalez-Duarte A, Ulloa-Aguirre A. Int J Mol Sci. 2021;22:13158; 6. Maurer MS, et al. N Engl J Med. 2018;379:1007-1016 (and supplementary appendix); 7. Gillmore JD, et al. N Engl J Med. 2024;390:132-142.

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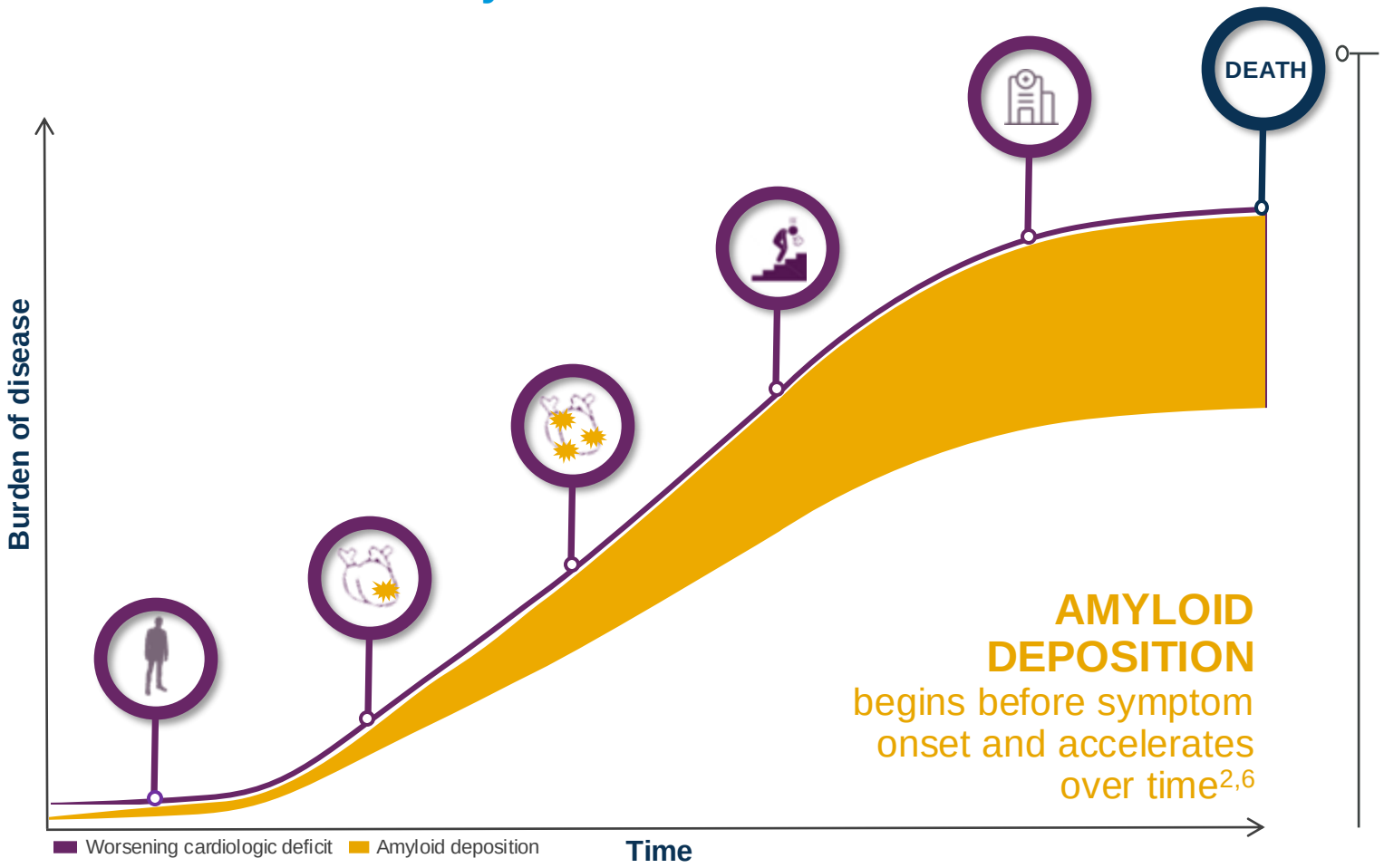
Patients With ATTR Amyloidosis With Cardiomyopathy (ATTR-CM) Experience Substantial Disease Burden Due to Ongoing TTR Amyloid Deposition in the Heart[1,2]

Natural History in Patients With ATTR-CM

Worsening cardiomyopathy manifestations can lead to[2-5]:

- Decline in physical functioning
- Loss of cardiac function
- Decreased QOL
- Increased CV-related hospitalizations
- Death



Median survival from diagnosis of ATTR-CM[a] is 2 to 6 years[7]

[a]*Depending on disease stage.*

ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; QOL, quality of life; TTR, transthyretin.

1. Ruberg FL, et al. J Am Coll Cardiol. 2019;73:2872-2891; 2. Castaño A, et al. Heart Fail Rev. 2015;20:163-178; 3. Ruberg FL, et al. Am Heart J. 2012;64:222-228.e1; 4. Lane T, et al. Circulation. 2019;140:16-26; 5. Maurer MS, et al. Circ Heart Fail. 2019;12:e006075; 6. Koike H, Katsuno K. Biomedicines. 2019;7:11; 7. Gillmore JD, et al. Eur Heart J. 2018;39:2799-2806.

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RNAi Mechanism of Action

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RNAi Therapeutics Leverage the Natural RNAi Mechanism to Decrease Production of the Target Protein[1-4]

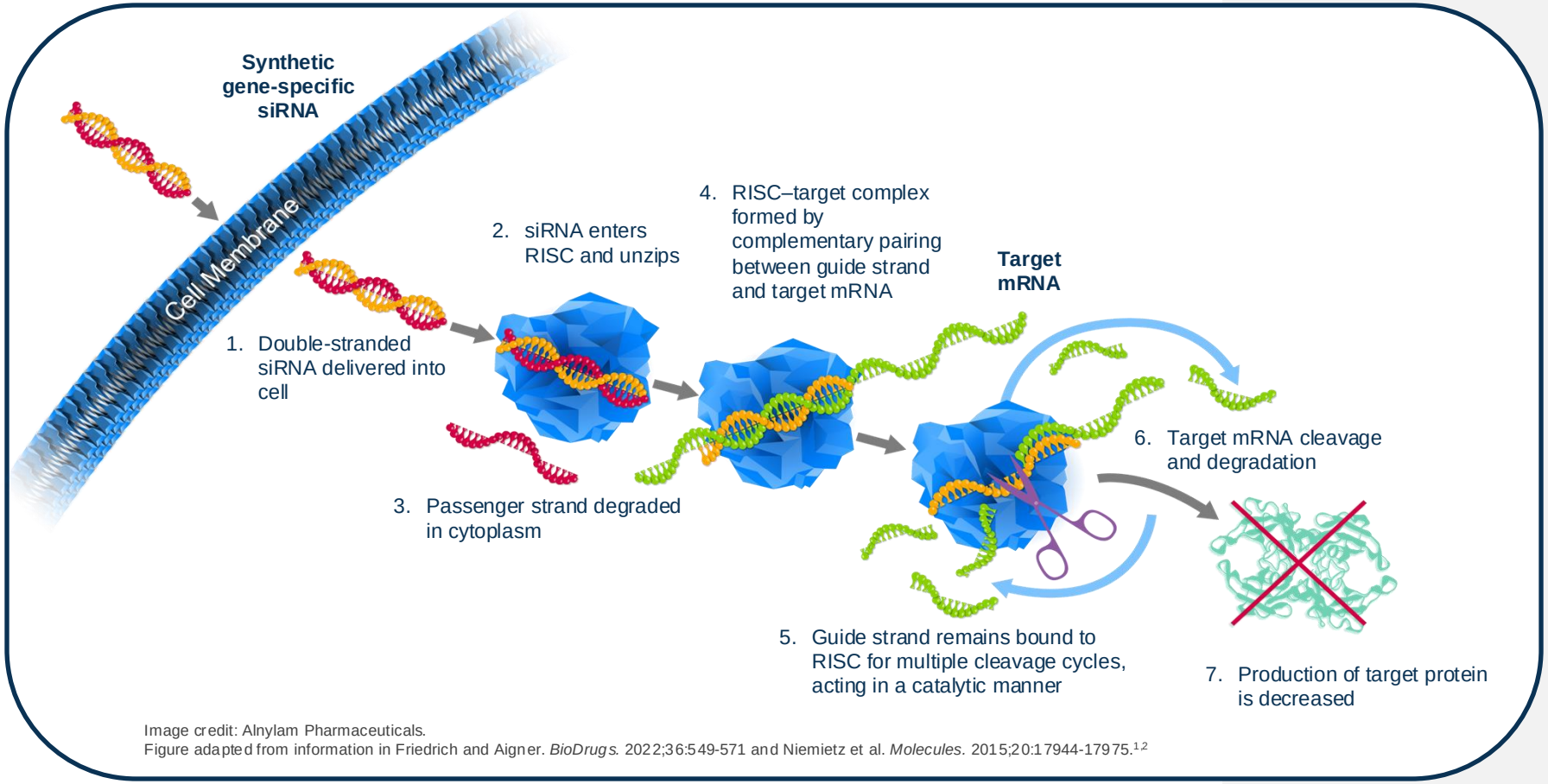

Image credit: Alnylam Pharmaceuticals.
Figure adapted from information in Friedrich and Aigner. *BioDrugs.* 2022;36:549-571 and Niemietz et al. *Molecules.* 2015;20:17944-17975.[1,2]

- Based on Nobel Prize-winning scientific discovery[5]
- Leveraging the naturally occurring mechanism for silencing of gene expression[1-3]
- A single siRNA bound to RISC is recycled and can cleave multiple mRNAs during its lifetime,[1-3,6] and can cause a rapid, targeted, and sustained decrease in the levels of disease-causing protein[1-3,7,8]

Scan QR code for video content: ***RNAi Therapeutics: How Do They Work?***

mRNA, messenger ribonucleic acid; RISC, ribonucleic acid-induced silencing complex; RNAi, ribonucleic acid interference; siRNA, small interfering ribonucleic acid.

1. Friedrich M, Aigner A. BioDrugs. 2022;36:549-571; 2. Niemietz C, et al. Molecules. 2015;20:17944-17975; 3. Jay PY, et al. Int J Cardiovasc Sci. 2021;35:665-667; 4. Coelho T, et al. N Engl J Med. 2013;369:819-829; 5. Montgomery MK. Nat Struct Mol Biol. 2006;13:1039-1041; 6. Hutvágner G, Zamore PD. Science. 2002;297:2056-2060; 7. Raal FJ, et al. N Engl J Med. 2020;382:1520-1530; 8. Keam SJ. Drugs. 2022;82:1419-1425.

GalNAc–siRNA Conjugates Enable Targeted Delivery to the Liver[1-3]

1. The trivalent GalNAc ligand has a high affinity for the ASGPR, expressed on the surface of hepatocytes[1,2]
2. Upon binding, GalNAc–siRNA conjugates are engulfed into hepatocytes by receptor-mediated endocytosis[1,2]
3. GalNAc and the linker are degraded off the siRNA conjugate and free siRNA passes into the hepatocyte cytoplasm[1,2]
4. Once in the cytoplasm, siRNAs are loaded onto RISC, targeting and degrading the corresponding mRNA, and decreasing production of the target protein[1,2]

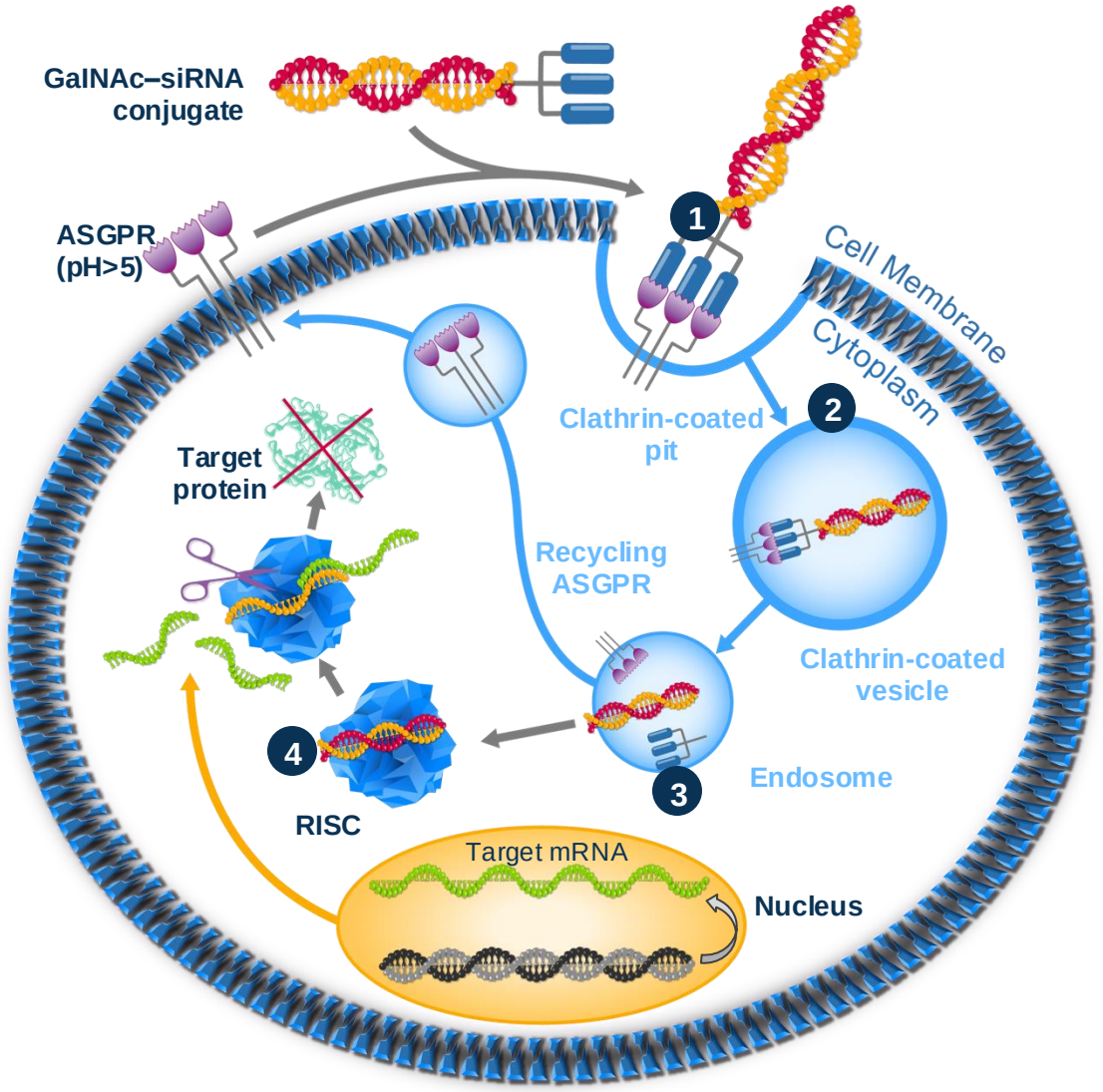

Figure adapted with permission from Benizri et al. *Bioconjug Chem.* 2019;30:366-383. Copyright (2024) American Chemical Society[3]

ASGPR, asialoglycoprotein receptor; GalNAc, N-acetylgalactosamine; mRNA, messenger ribonucleic acid; RISC, ribonucleic acid-induced silencing complex; siRNA, small interfering ribonucleic acid.

1. Springer AD, et al. Nucleic Acid Ther. 2018;28:109-118; 2. Huang Y. Mol Ther Nucleic Acids. 2017;6:116-132; 3. Benizri S, et al. Bioconjug Chem. 2019;30:366-383.

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AMVUTTRA® (vutrisiran) Indications and Important Safety Information

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AMVUTTRA® (vutrisiran) Indications

AMVUTTRA® (vutrisiran) is indicated for the treatment of the:

- cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits.

- polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in adults.

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AMVUTTRA® (vutrisiran) Important Safety Information

Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA treatment leads to a decrease in serum vitamin A levels.

Supplementation at the recommended daily allowance of vitamin A is advised for patients taking AMVUTTRA. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with AMVUTTRA, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

Adverse Reactions

In a study of patients with hATTR-PN, the most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity (15%), arthralgia (11%), dyspnea (7%), and vitamin A decreased (7%).

In a study of patients with ATTR-CM, no new safety issues were identified.

For additional information about AMVUTTRA, please see the full Prescribing Information.

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HELIOS-A Overview

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HELIOS-A Was a Phase 3 Randomized, Open-Label Study to Evaluate Vutrisiran in Patients With hATTR-PN

Patients were randomized 3:1 to vutrisiran 25 mg SC Q3M (n=122) or patisiran 0.3 mg/kg IV Q3W (n=42) as a reference arm, for 18 months. An external placebo group from the APOLLO study (n=77) was used as a control for the primary endpoint and most secondary and exploratory endpoints[1]

- Vutrisiran met the primary and all secondary efficacy endpoints at Months 9 and 18, demonstrating significant improvements in neuropathy impairment, quality of life, gait speed, nutritional status, and disability compared with the external placebo group[1]
  - Vutrisiran treatment resulted in statistically significant improvement in mNIS+7 at Month 9 versus the external placebo group (LS mean change from baseline: -2.24 [vutrisiran] and +14.76 [placebo]; LS mean difference [95% CI]: -17.00 [-21.78, -12.22], p<0.001), meeting the primary endpoint[a]
  - At Month 18, the majority of AEs were mild or moderate in severity. AEs occurring in ≥10% of patients receiving vutrisiran and more frequently than in the external placebo group were pain in extremity and arthralgia. No drug-related discontinuations or deaths were observed[1]

- Results from an analysis of exploratory cardiac endpoints in the HELIOS-A trial indicated a potential benefit of vutrisiran with respect to cardiac manifestations (NT-proBNP level and echocardiographic and ^{99m}Tc-scintigraphy measures) in patients with variant ATTR amyloidosis with polyneuropathy[2,3]
- These findings support the hypothesis that a reduction in the level of amyloidogenic TTR protein could have therapeutic benefit in patients with ATTR-CM[2,3]

[a]*Change in neuropathy impairment from baseline (mNIS+7) compared with the placebo group of the APOLLO study (external placebo group) at Month 9.*[1]

^{99m}Tc, technetium-99m; AE, adverse event; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CI, confidence interval; hATTR, hereditary transthyretin amyloidosis; IV, intravenous; LS, least squares; mNIS+7, modified Neuropathy Impairment Score +7; NT-proBNP; N-terminal prohormone of brain-type natriuretic peptide; PN, polyneuropathy; Q3M, once every 3 months; Q3W, once every 3 weeks; SC, subcutaneous.

1. Adams D, et al. Amyloid. 2023;30:18–26; 2. Garcia-Pavia P, et al. Eur J Heart Fail. 2024;26:397-410; 3. Fontana M, et al. N Engl J Med. 2025;392:33-44.

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The following HELIOS-B study information is based upon analyses as published in scientific literature and released at scientific meetings. These results include some efficacy and safety analyses that were conducted differently than, or are not contained in, the U.S. Prescribing Information for AMVUTTRA®

HELIOS-B Study

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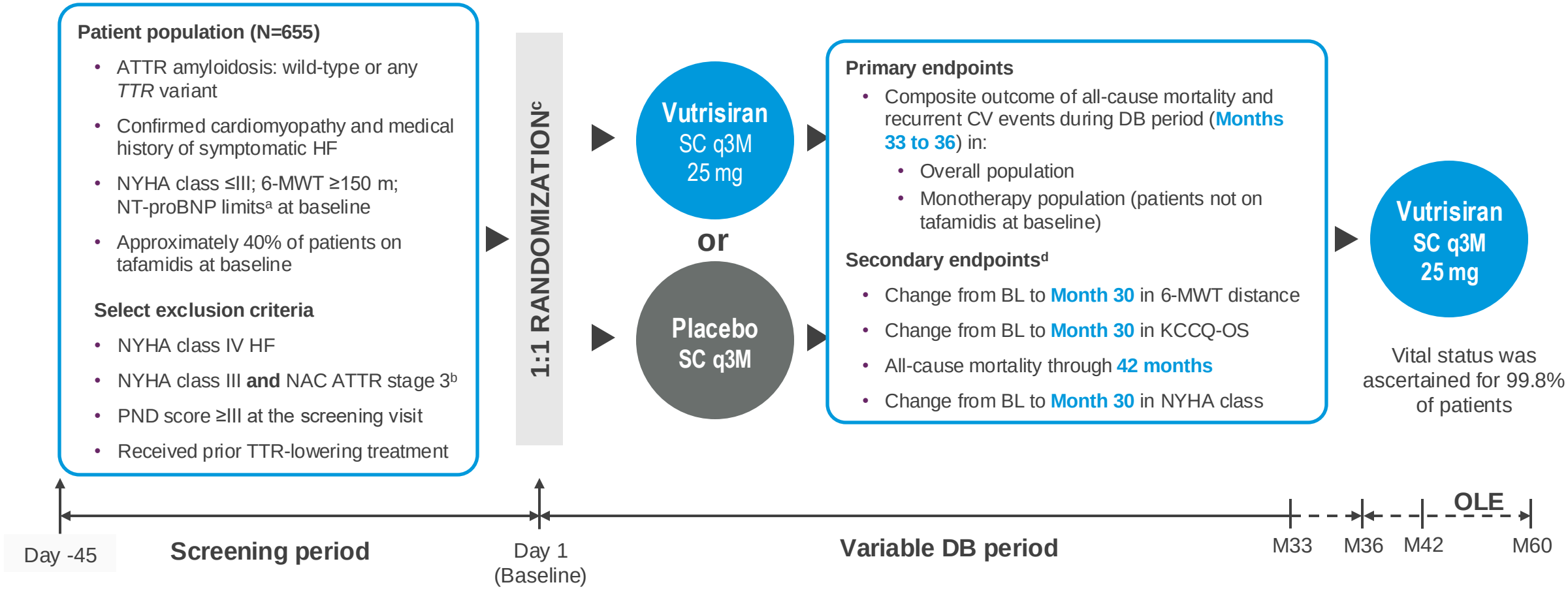
HELIOS-B Was a Phase 3 Randomized, Double-Blind Outcomes Study to Evaluate Vutrisiran in Patients With ATTR-CM

Study Design



[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]*NAC ATTR stage 3 defined as NT-proBNP levels >3000 pg/mL and an eGFR of <45 mL/min/1.73 m² of body surface area.* [c]*Randomization was stratified according to the use of tafamidis at baseline (yes versus no), ATTR disease type (hATTR or wtATTR), and NYHA class and age at baseline (NYHA class I or II and age <75 years versus all others).* [d]*Assessed in the overall population and monotherapy population as separate endpoints.*

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; BL, baseline; CV, cardiovascular; DB, double blind; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin amyloidosis; HF, heart failure; M, month; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; PND, polyneuropathy disability; q3M, every 3 months; SC, subcutaneous; TTR, transthyretin; wtATTR, wild-type amyloid transthyretin.

1. Fontana M, et al. N Engl J Med. 2025;392:33-44; 2. Study protocol, data on file.

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HELIOS-B Recruited a Contemporary Patient Population With Baseline Characteristics Balanced Across Arms

Parameter[1]		Overall population	
		Placebo (n=328)	Vutrisiran (n=326)
Age, median (range), years		76 (46-85)	77 (45-85)
Male sex, n (%)		306 (93)	299 (92)
Race, n (%)	White	275 (84)	277 (85)
	Asian	19 (6)	18 (6)
	Black	24 (7)	23 (7)
	Other/not reported	10 (3)	8 (2)
wtATTR amyloidosis, n (%)		289 (88)	289 (89)
Time since diagnosis of ATTR amyloidosis, median (range), years		1.03 (0-10.8)	0.86 (0-11.1)
NYHA class, n (%)	I	35 (11)	49 (15)
	II	258 (79)	250 (77)
	III	35 (11)	27 (8)
ATTR amyloidosis disease stage, n (%)	1	229 (70)	208 (64)
	2	87 (27)	100 (31)
	3	12 (4)	18 (6)
Baseline 6-MWT, mean (SD), meters		377.1 (96.3)	372.0 (103.7)
Baseline KCCQ-OS, mean (SD), points		72.3 (19.9)	73.0 (19.4)
Baseline NT-proBNP, median (IQR), ng/L		1801 (1042-3082)	2021 (1138-3312)
Baseline troponin I, median (IQR), ng/L		65.2 (41.1-105.5)	71.9 (44.9-115.9)

The HELIOS-B trial was designed to include a contemporary patient population, reflective of patients seen in clinic in the present day

Patients were at an earlier and less severe stage of disease than reported in previous trials, and reported substantial use of background treatment at baseline[1–3]

Substantial use of effective background medications[1]

- **Tafamidis**
  - Baseline ~40% in both treatment arms
  - Drop-in among monotherapy population during DB period ~21% and ~22% for placebo and vutrisiran, respectively
- **SGLT2 inhibitors**
  - Baseline ~3% in both treatment arms
  - Drop-in during DB period ~35% and ~31% for placebo and vutrisiran, respectively

Substantial use of diuretics[1]

- Baseline ~80% in both treatment arms
- Outpatient initiation or intensification of diuretics after first dose was ~56% and ~48% for placebo and vutrisiran, respectively

Patients were not randomized to baseline tafamidis: patients on baseline tafamidis were generally healthier based on NYHA class, NT-proBNP, 6-MWT, and KCCQ-OS score.

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; DB, double blind; hATTR, hereditary transthyretin amyloidosis; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2; wtATTR, wild-type transthyretin amyloidosis.

1. Fontana M, et al. N Engl J Med. 2025;392:33-44; 2. Maurer MS, et al. N Engl J Med 2018;379:1007-1016; 3. Gillmore JD, et al. N Engl J Med 2024;390:132-142.

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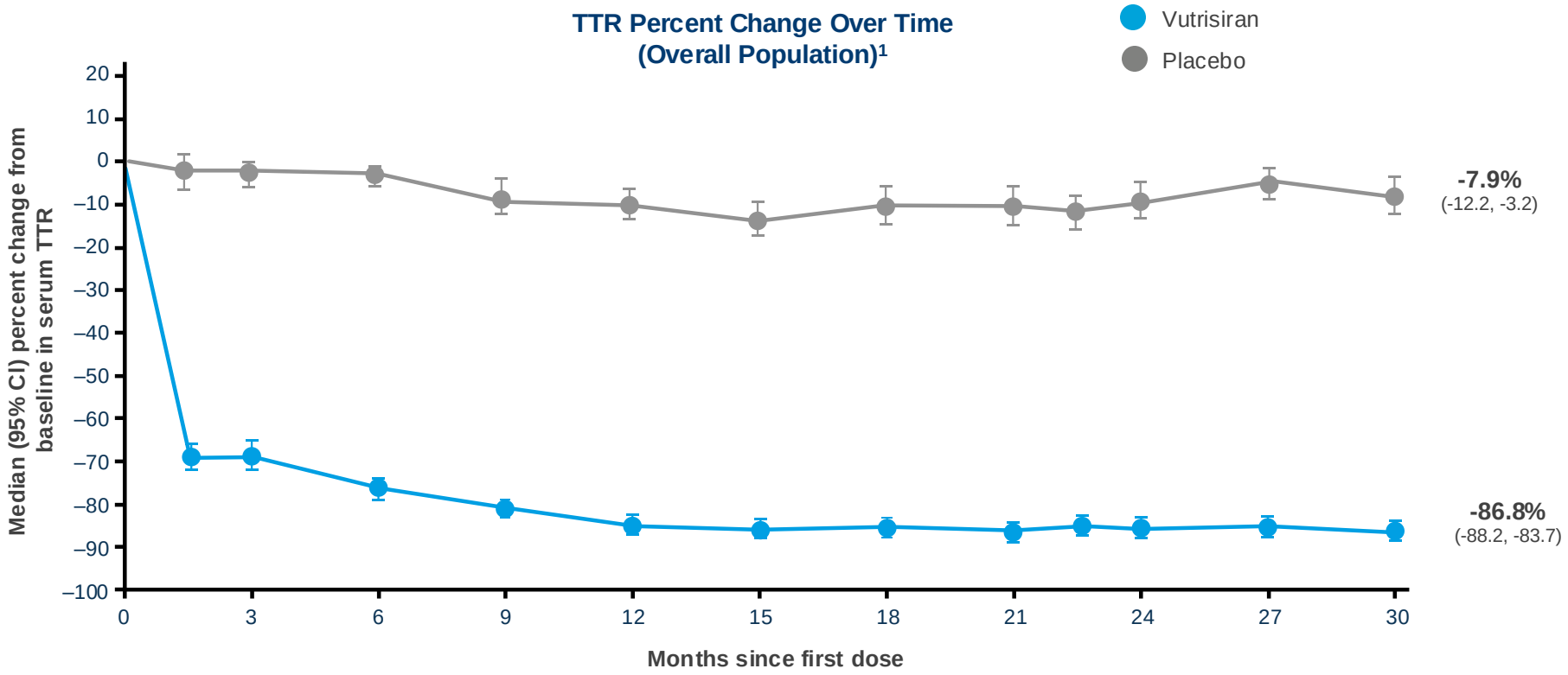
Vutrisiran Demonstrated Durable and Rapid Knockdown of TTR in HELIOS-B



Durable and rapid knockdown of TTR through Month 30 in both the overall and monotherapy populations[2,3]

Knockdown comparable to prior studies with vutrisiran[3]

CI, confidence interval; TTR, transthyretin.

1. Data on File; 2. Jering K, et al. Presented at the Heart Failure Society of America Annual Scientific Meeting 2024; September 27-30, 2024; Virtual; 3. Fontana M, et al. N Engl J Med. 2025;392:33-44.

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HELIOS-B Met All Primary and Secondary Endpoints in the Overall and Monotherapy Populations

Endpoint[1]	Treatment effect estimation	Overall population (N=654)		Monotherapy population (N=395)	
		Treatment effect	*P* value	Treatment effect	*P* value
Primary endpoint Composite outcome of all-cause mortality and recurrent CV events[a,b]	Hazard ratio (95% CI)	**0.72** (0.56-0.93)	**0.01**	**0.67** (0.49-0.93)	**0.02**
Secondary endpoints					
6-MWT change at Month 30[c]	LS mean difference (95% CI)	**26.5** (13.4-39.6)	**<0.001**	**32.1** (14.0-50.2)	**<0.001**
KCCQ-OS change at Month 30[c]	LS mean difference (95% CI)	**5.8** (2.4-9.2)	**<0.001**	**8.7** (4.0-13.4)	**<0.001**
All-cause mortality through Month 42[d]	Hazard ratio (95% CI)	**0.65** (0.46-0.90)	**0.01**	**0.66** (0.44-0.97)	**0.045**
NYHA class: % stable or improved at Month 30[e]	Adjusted % difference	**8.7%** (1.3-16.1)	**0.02**	**12.5%** (2.7-22.2)	**0.01**

[a]Primary analysis based on the modified Andersen-Gill model, also known as LWYY. [b]Assessed at 33 to 36 months. [c]Based on an MMRM model. [d]HR derived from Cox PH model, P value derived from log-rank test. [e]Based on CMH method.

6-MWT, 6-minute walk test; ACM, all-cause mortality; CMH, Cochran-Mantel-Haenszel; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weighting; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS, least squares; LWYY, Lin-Wei-Yang-Ying; MMRM, mixed models for repeated measures; NYHA, New York Heart Association; PH, proportional hazards.

Fontana M, et al. N Engl J Med. 2025;392:33-44.

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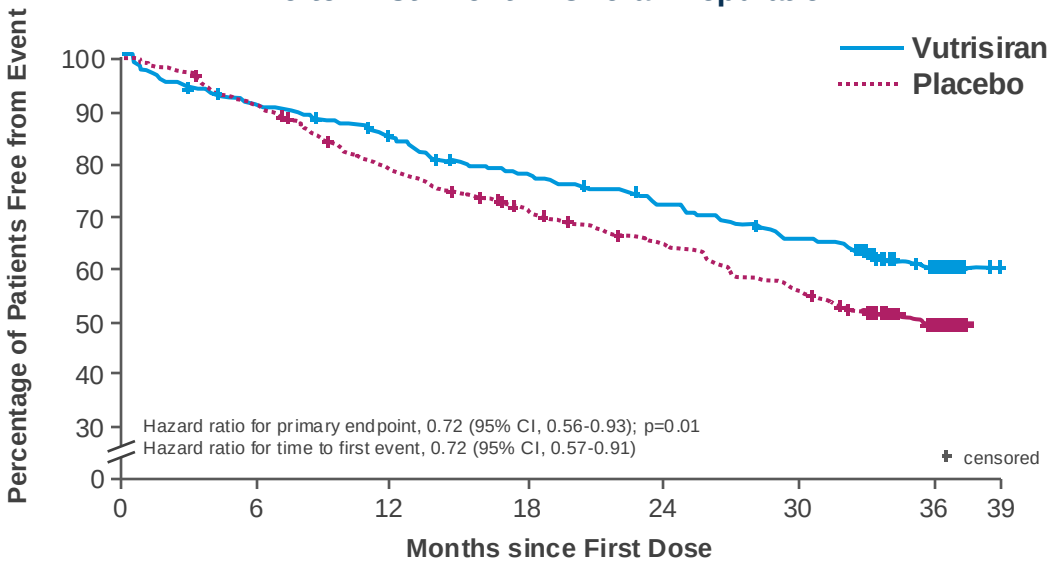
Primary Endpoint: Statistically Significant Reduction Vs. Placebo in Composite of All-Cause Mortality and Recurrent CV Events

Overall population:
Treatment with vutrisiran resulted in a **28% reduction** in the risk of death from any cause and recurrent CV events compared with placebo

Monotherapy population:
Treatment with vutrisiran resulted in a **33% reduction** in the risk of death from any cause and recurrent CV events compared with placebo

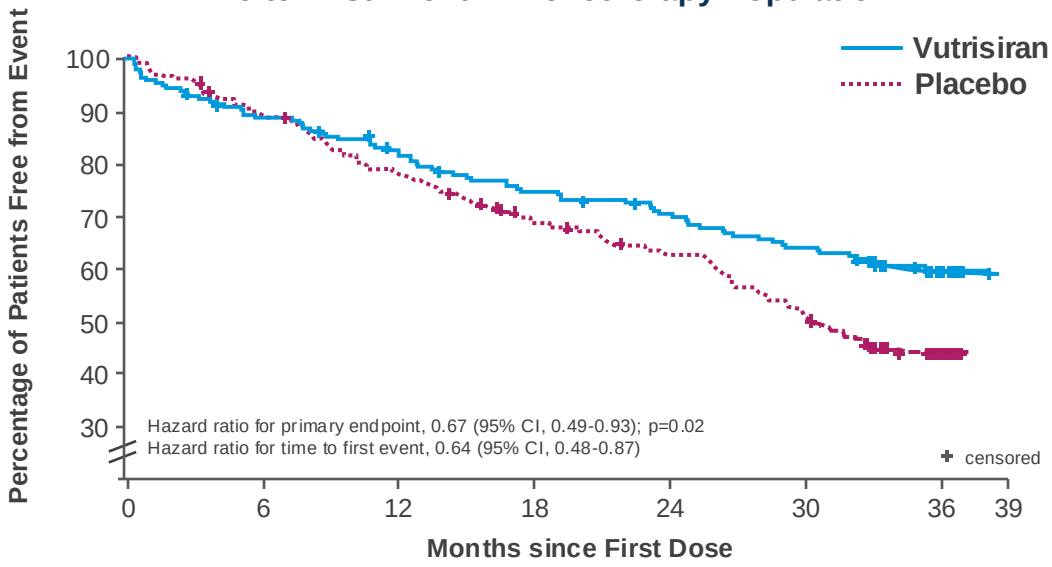
Time to First Event in Overall Population



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 CV event or death from any cause showed 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. The primary endpoint was a composite of death from any cause and recurrent CV events (defined as hospitalizations for CV causes or urgent visits for heart failure). All-cause mortality includes heart transplantation and left ventricular assist device placement. The monotherapy population was defined as the patients who were not receiving tafamidis at baseline. Tick marks indicate censored data.
CV, cardiovascular.
Fontana M, et al. N Engl J Med. 2025;392:33-44.

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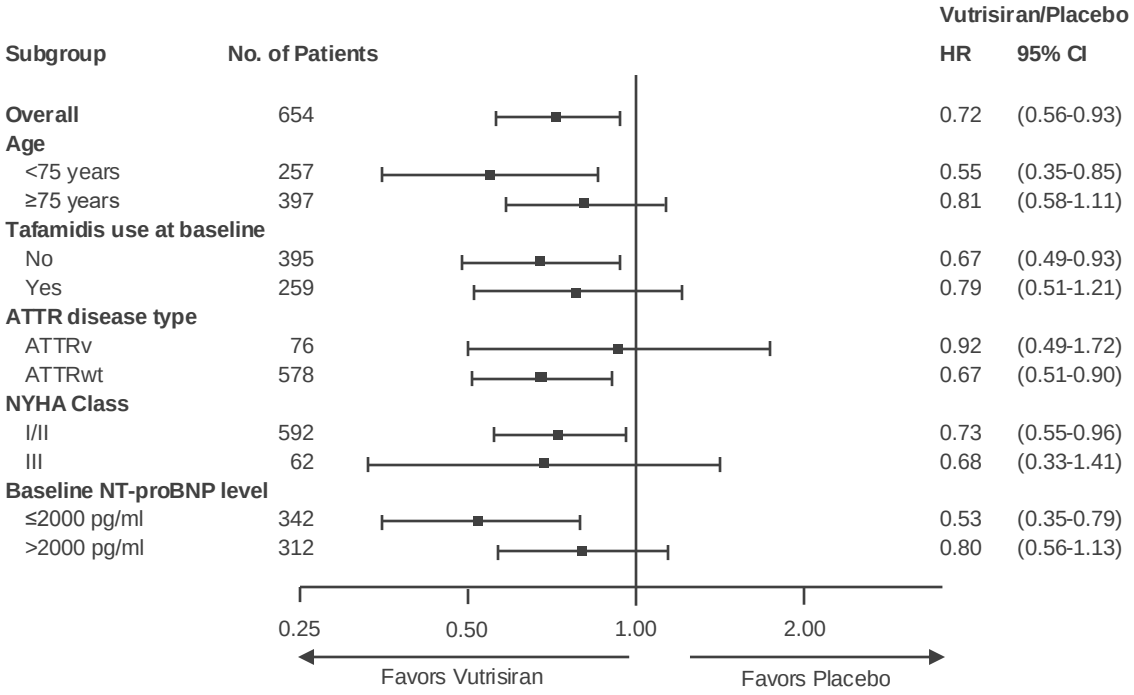
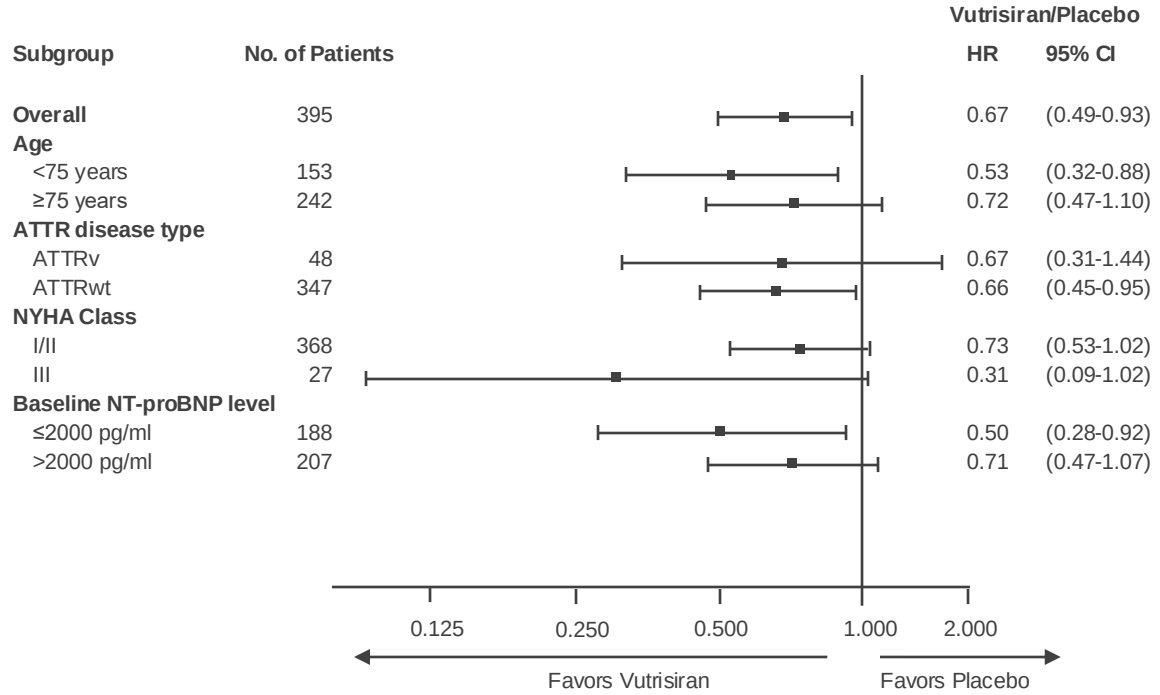
Primary Endpoint: Consistent Benefits Were Observed Across All Prespecified Subgroups

Subgroup Analyses of the Primary Endpoint (Overall Population)



Subgroup Analyses of the Primary Endpoint (Monotherapy Population)



In both populations, consistent effect was observed with respect to all-cause mortality and recurrent CV events across all prespecified subgroups

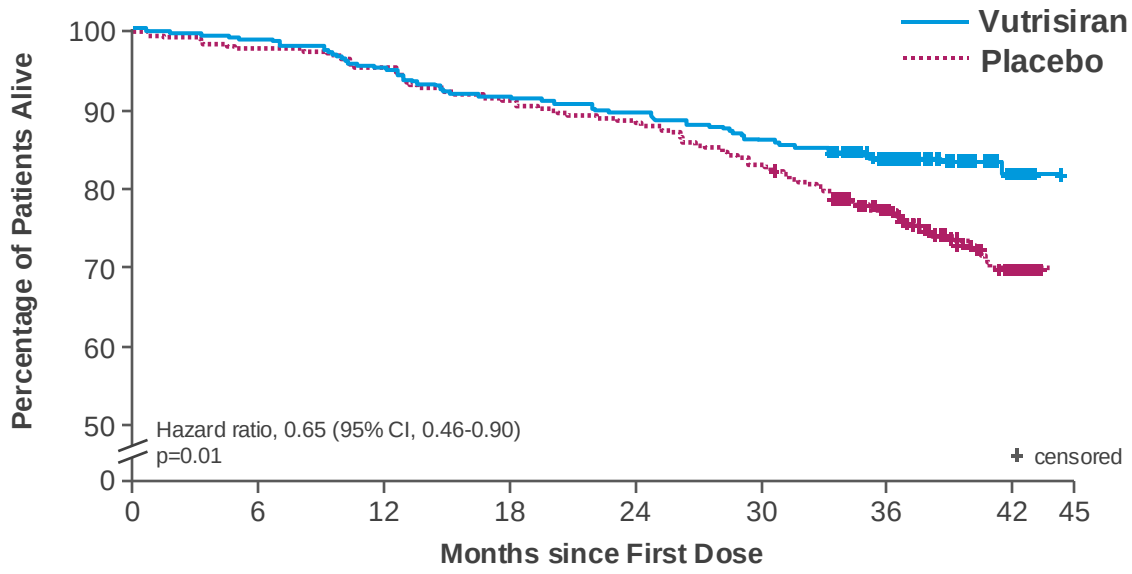
ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CV, cardiovascular; HR, hazard ratio; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association.

Fontana M, et al. N Engl J Med. 2025;392:33-44.

26

Secondary Endpoint: Death From Any Cause Through 42 Months

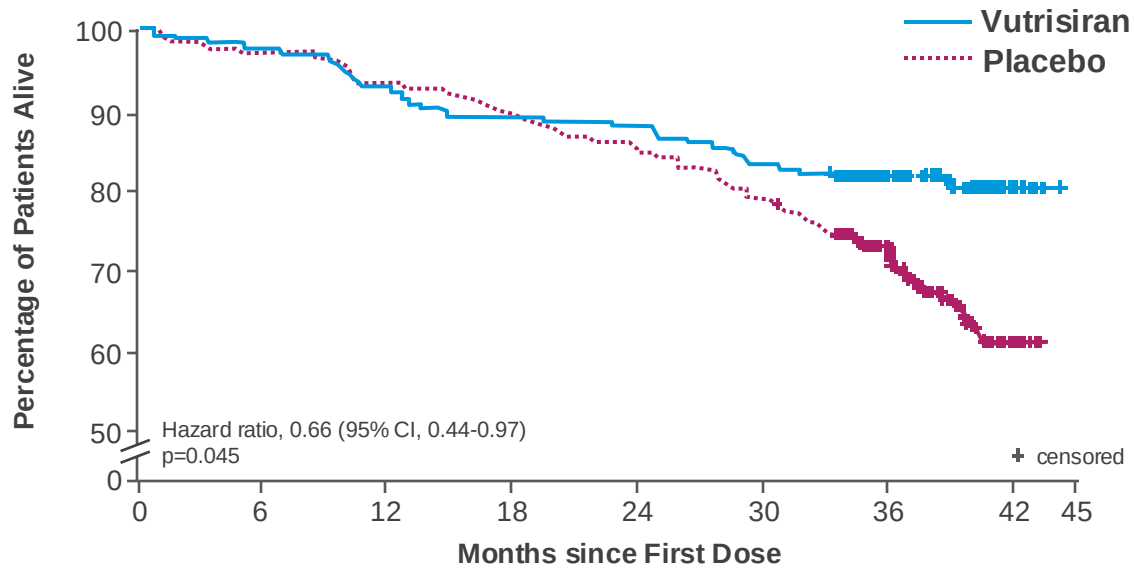
Death From Any Cause in the Overall Population



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)

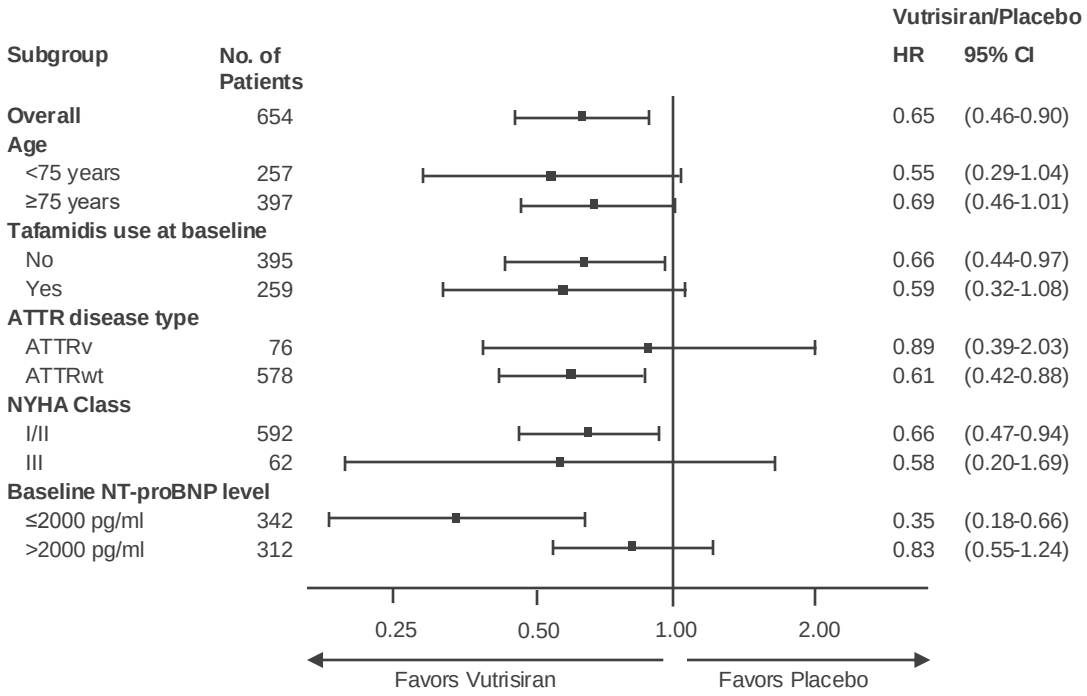
Treatment with vutrisiran resulted in a lower risk of death from any cause through 42 months than placebo in the overall population and monotherapy population, which included up to 6 months of data from the open-label extension period[1]

The Kaplan–Meier curves were adjusted according to disease severity characteristics at baseline with the use of the inverse probability of treatment weighting method. All-cause mortality includes heart transplantation and left ventricular assist device placement.

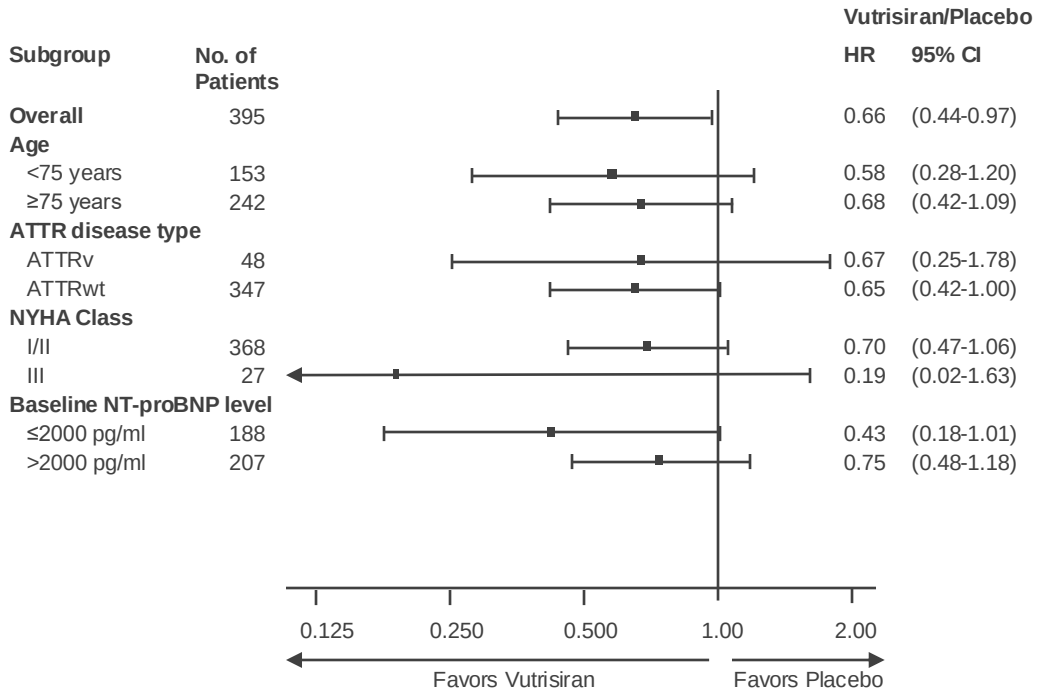
1. Fontana M, et al. N Engl J Med. 2025;392:33-44.

Secondary Endpoint: Consistent Benefits in All-Cause Mortality Were Observed Across All Prespecified Subgroups[a]

Subgroup Analyses of Death From Any Cause Through 42 Months (Overall Population)



Subgroup Analyses of Death From Any Cause Through 42 Months (Monotherapy Population)



In both populations, consistent effect was observed with respect to death from any cause across all prespecified subgroups[b]

[a]*Up to 6 months of follow-up during OLE.* [b]*A sensitivity analysis using a weighted log-rank test (the Fleming–Harrington [1,1] test) showed similar results.*

ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; HR, hazard ratio; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide; OLE, open-label extension.

Fontana M, et al. N Engl J Med. 2025;392:33-44.

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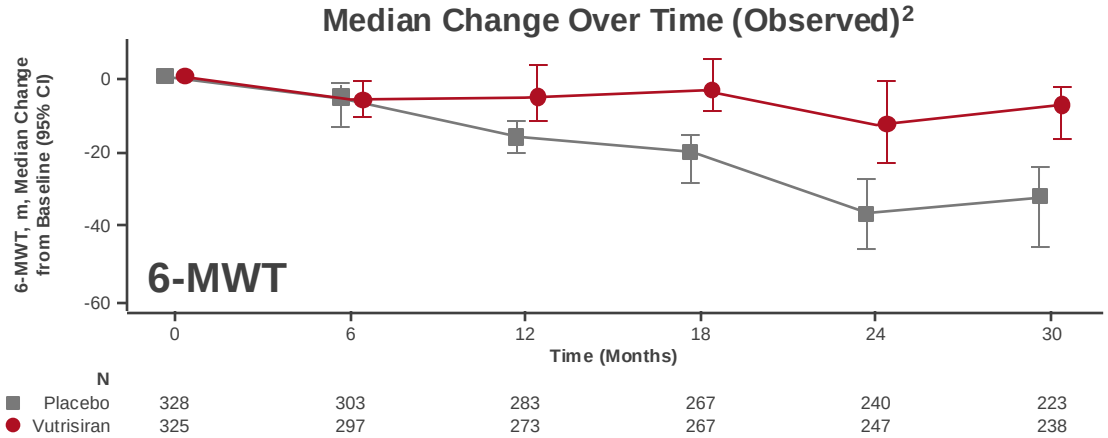
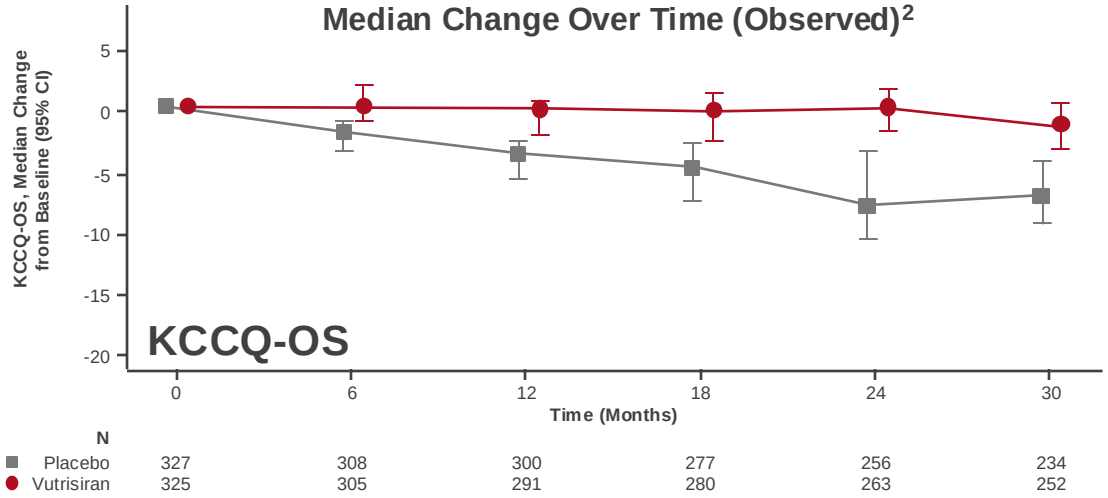
Secondary Endpoints: Vutrisiran Maintained Functional Capacity, Health Status, and Quality of Life Compared With Placebo

Change from baseline at Month 30	Overall population	
	Placebo (n=328)	Vutrisiran (n=326)
6-MWT, n	285	294
Median[1]	-30.65	-7.50
LS mean (95% CI)[2]	-71.9 (-81.3 to -62.4)	-45.4 (-54.5 to -36.3)
LS mean difference (95% CI)[2]	—	26.5 (13.4 to 39.6)
p value[2]	—	<0.001
KCCQ-OS, n	298	306
Median[1]	-6.25	-1.30
LS mean (95% CI)[2]	-15.5 (-18.0 to -13.0)	-9.7 (-12.0 to -7.4)
LS mean difference (95% CI)[2]	—	5.8 (2.4 to 9.2)
p value[2]	—	<0.001
NYHA class, n	328	326
Stable or improved %[2]	61	68
Difference in % patients stable or improved (95% CI)[2]	—	8.7 (1.3 to 16.1)
p value[2]	—	0.02



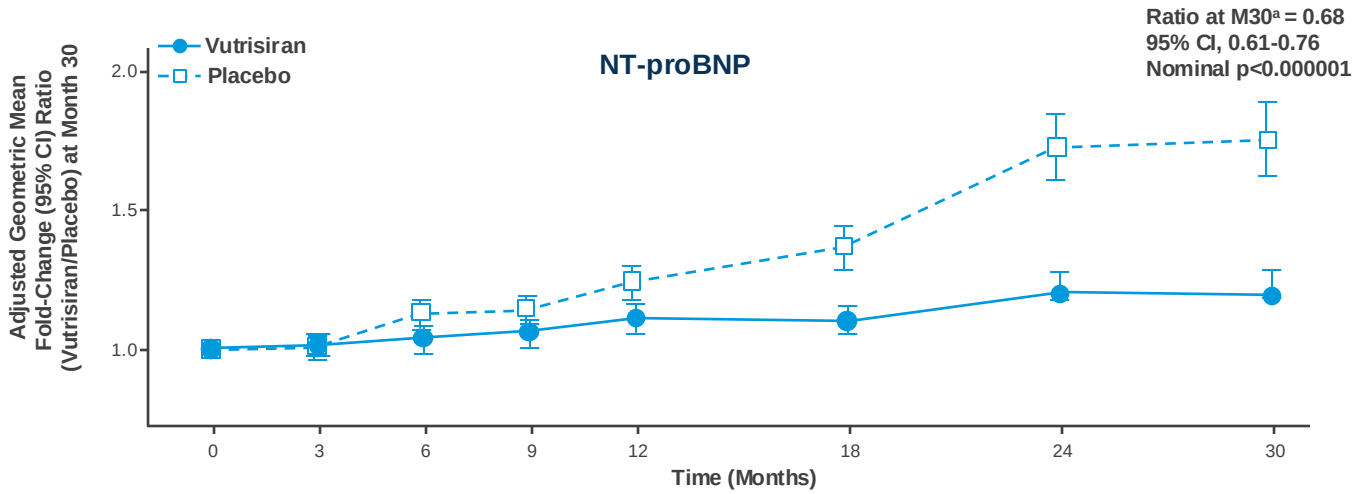


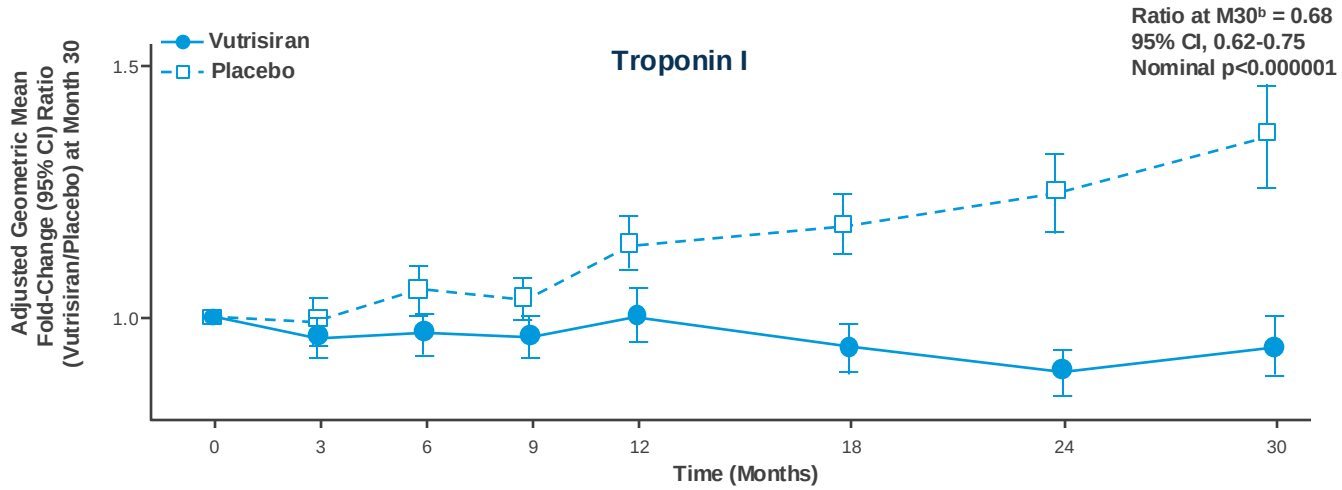
LS mean accounts for missing data due to death or HT/LVAD, or unable to walk due to disease progression (only for 6-MWT) that were imputed from resampling of worst 10%. Median representation is based on observed data only, no imputations due to death/unable to walk due to disease progression.
6-MWT, 6-minute walk test; HT, heart transplant; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS, least squares; LVAD, left ventricular assist device; NYHA, New York Heart Association.

1. Fontana M, et al. presented at European Society of Cardiology Congress, 30 August-2 September 2024, London, UK; 2. Fontana M, et al. N Engl J Med. 2025;392:33-44.

Exploratory Endpoints: NT-proBNP and Troponin I

Impact Observed on NT-proBNP, a Well-Established Cardiac Biomarker Prognostic of Mortality in ATTR-CM; 32% relative reduction of both NT-proBNP and troponin I at Month 30





Exploratory biomarker analyses were conducted as part of HELIOS-B to:

- Evaluate the association of increased cardiac biomarkers NT-proBNP and troponin I on later risk of cardiac outcomes and mortality
- Determine the effect of vutrisiran on cardiac biomarkers over time

[a]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group. [b]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group.

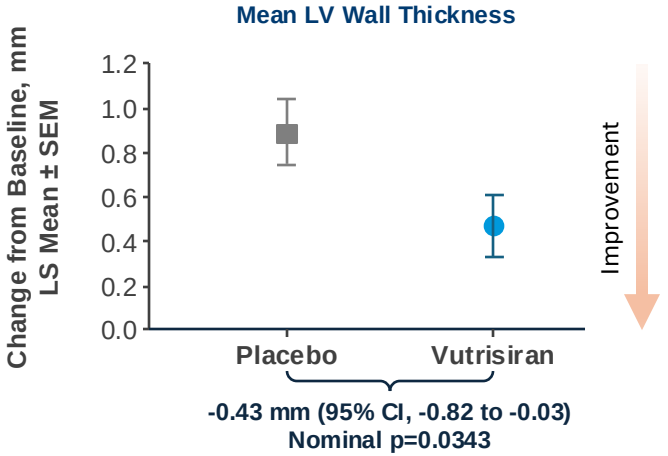
ATTR, transthyretin amyloidosis; LS, least squares; M, month; MMRM, mixed models for repeated measures; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide.

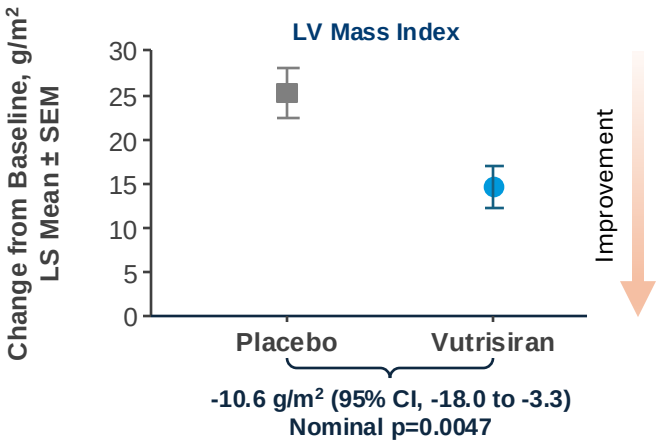
Maurer MS, et al. Presented at the Heart Failure Society of America Annual Scientific Meeting 2024; September 27-30, 2024; Virtual.

Exploratory Endpoints[a]: Cardiac Structure and Function

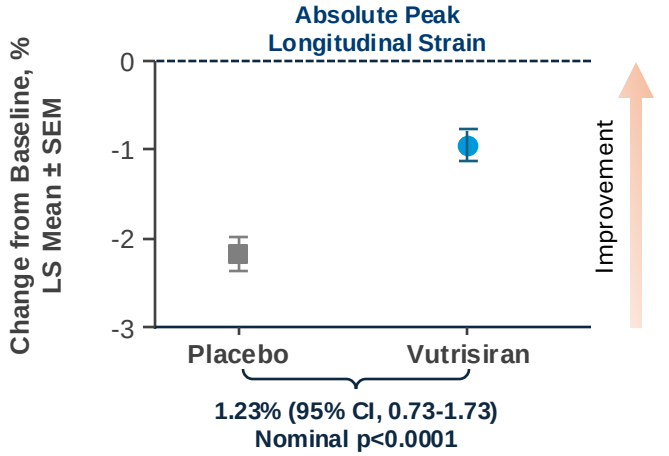
Exploratory echocardiographic assessments at Month 30 (overall population)

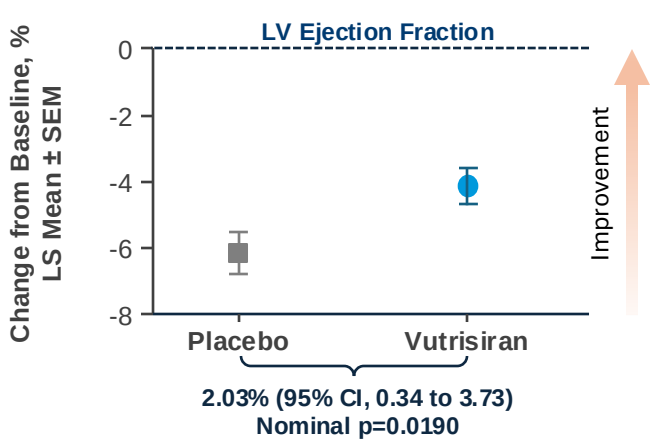
Cardiac Structure[b]



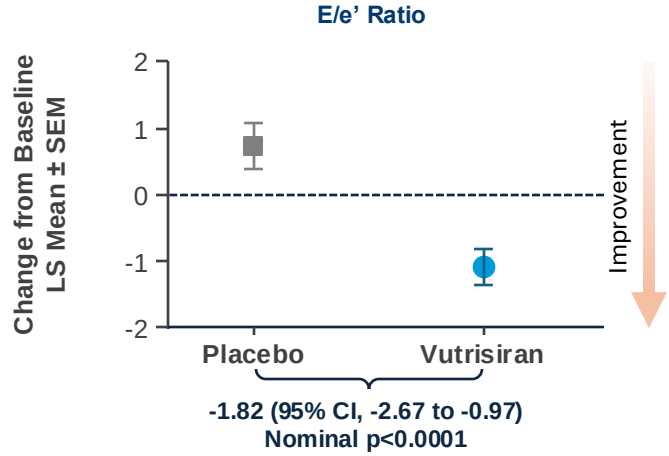


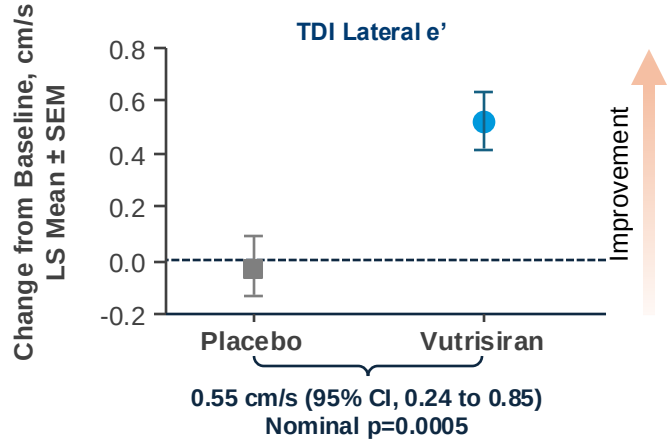
Systolic Function[b]





Diastolic Function[b]





[a]*Exploratory endpoints in the HELIOS-B study included: echocardiographic assessments performed at Months 12, 18, 24, and 30.* [b]*Results are from an MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group.*

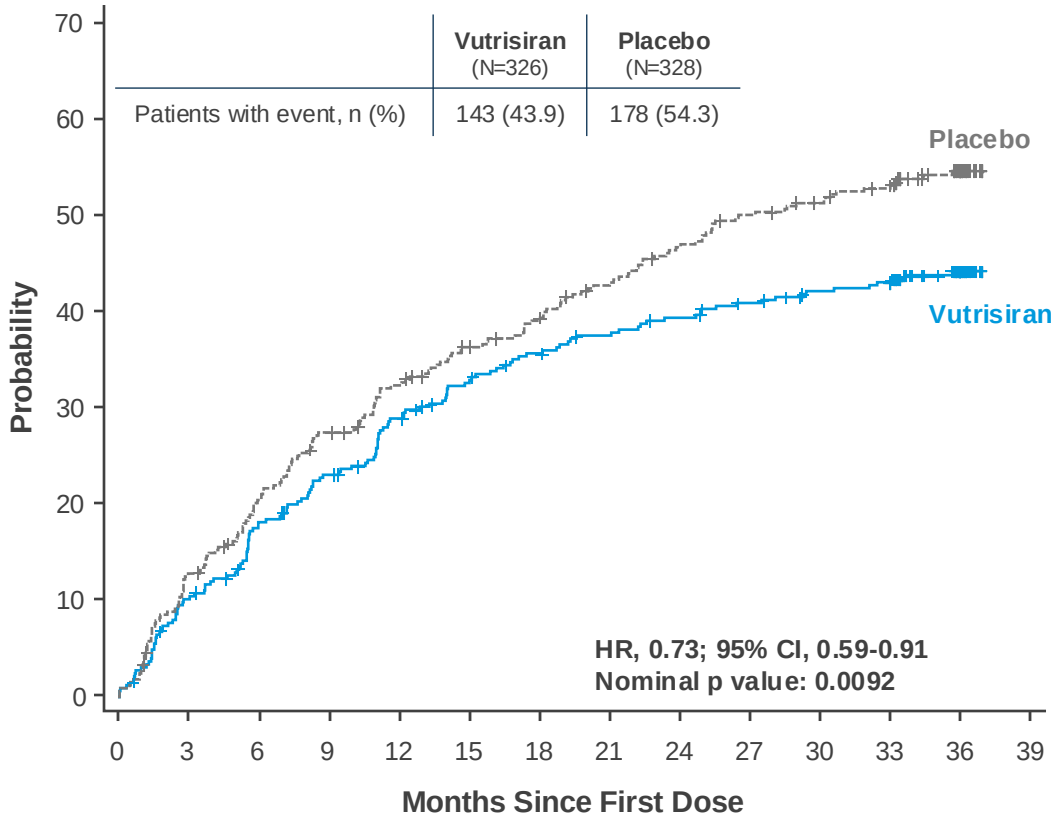
ATTR, transthyretin amyloidosis; E/e', ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; LS, least squares; LV, left ventricular; MMRM, mixed models for repeated measures; SEM, standard error of the mean; TDI lateral e', lateral peak early diastolic mitral annular tissue velocity .

Jering K, et al. Presented at the Heart Failure Society of America Annual Scientific Meeting 2024; September 27-30, 2024; Virtual.

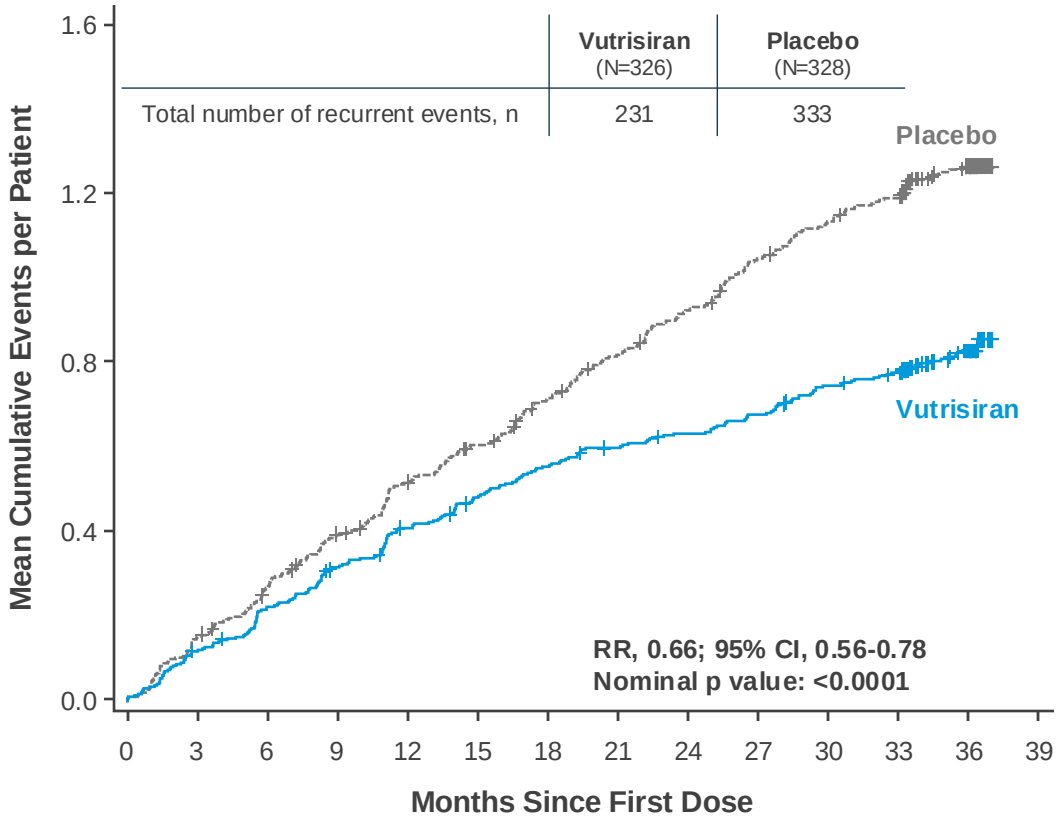
Prespecified Analysis[a]: Risk of Outpatient Worsening HF

Decreased risks of both a first outpatient worsening HF and of recurrent outpatient worsening HF

Impact of Vutrisiran on Time to First Outpatient Worsening HF[b]



Impact of Vutrisiran on Recurrent Outpatient Worsening HF[c]

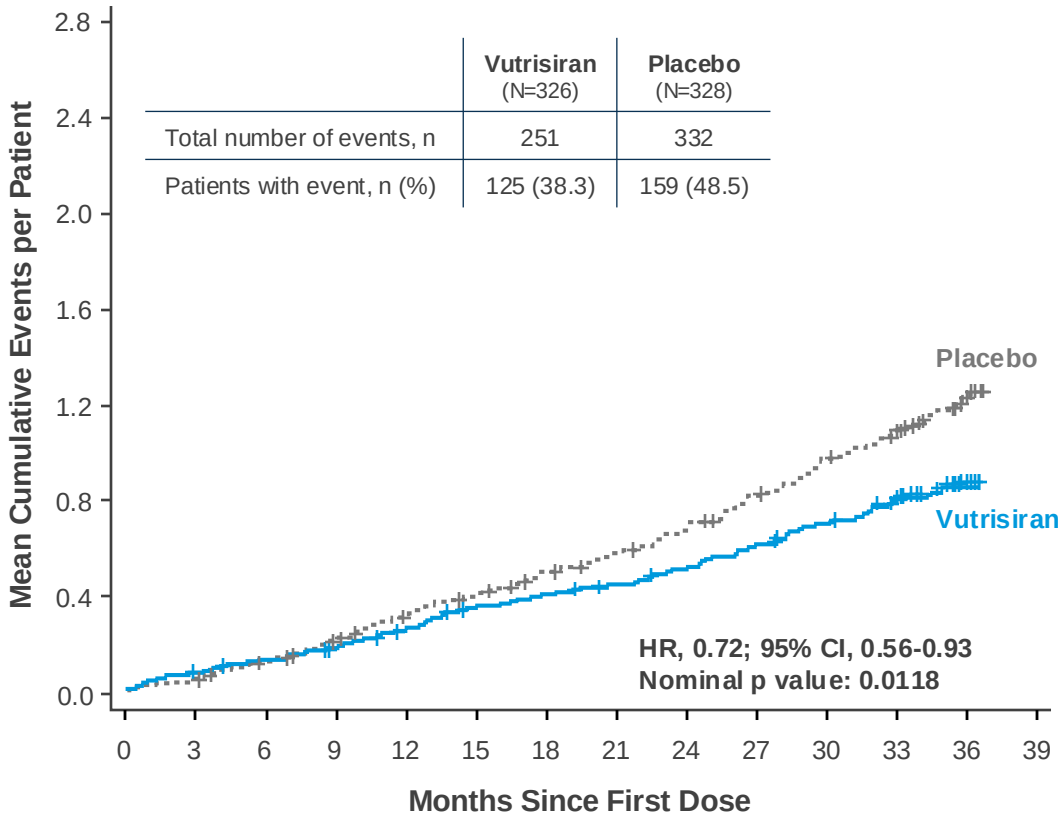


[a]*This prespecified analysis of HELIOS-B was conducted to assess the clinical and prognostic significance of outpatient worsening HF, defined as oral diuretic intensification or initiation, as a marker of disease progression. The associations between outpatient worsening HF and endpoints from HELIOS-B were assessed, in addition to the impact of vutrisiran on outpatient worsening HF, as well as on an expanded composite endpoint including outpatient worsening HF.* [b]*Probabilities are estimated from the cumulative incidence function. HR was derived from a Cox proportional hazards model stratified by baseline tafamidis use, with treatment group, log-transformed baseline NT-proBNP, ATTR amyloidosis type, NYHA functional class, and age group as covariates, and with death treated as a competing risk.* [c]*Mean cumulative events are estimated from the mean cumulative function. RR was derived using the Poisson regression model including treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class, age group, baseline tafamidis use, and treatment-by-baseline tafamidis use interaction as covariates, with the logarithm of the follow-up time as an offset variable. Data are truncated when the at-risk population reaches 5 patients.*
ATTR, transthyretin amyloidosis; HF, heart failure; HR, hazard ratio, NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association; RR, rate ratio.

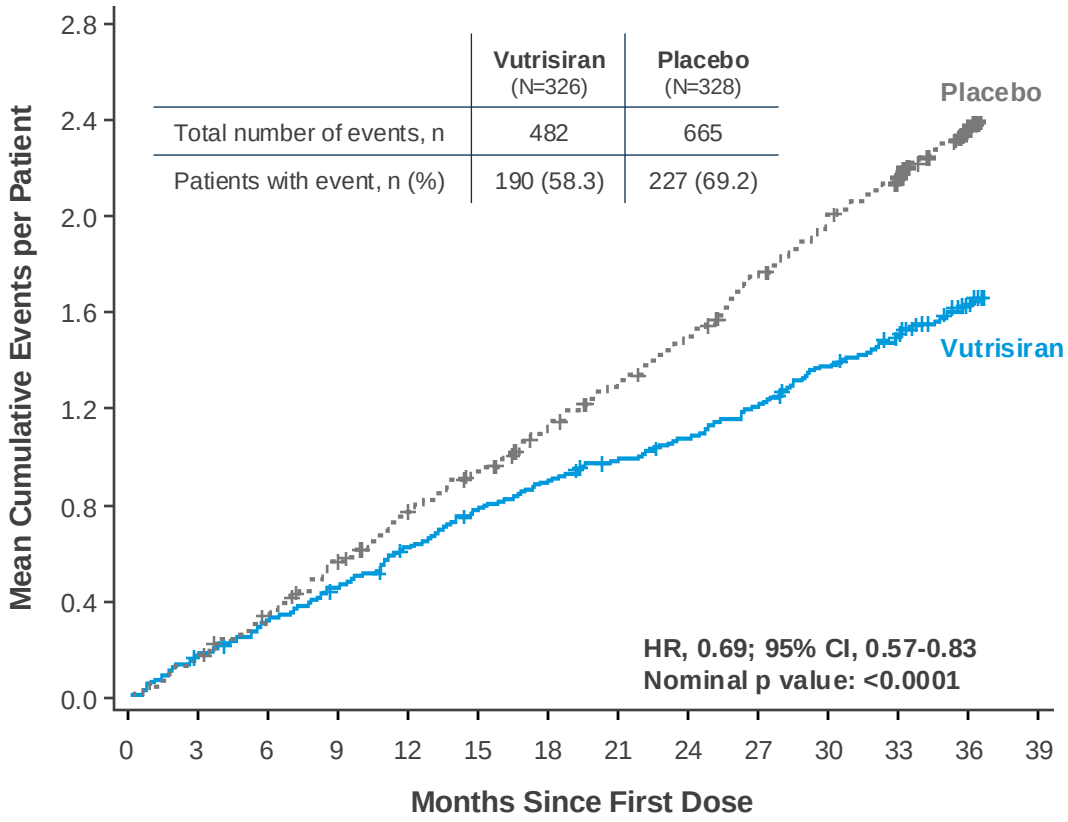
Prespecified Analysis[a]: Vutrisiran Reduced the Risk of Outpatient Worsening HF, Recurrent CV Events, and All-Cause Mortality

Impact on the expanded composite endpoint

Composite of All-Cause Mortality or Recurrent CV Events[b,c]



Composite of All-Cause Mortality, Recurrent CV Events[b], or Recurrent Outpatient Worsening HF Events[c]



[a]*This prespecified analysis of HELIOS-B was conducted to assess the clinical and prognostic significance of outpatient worsening HF, defined as oral diuretic intensification or initiation, as a marker of disease progression. The associations between outpatient worsening HF and endpoints from HELIOS-B were assessed, in addition to the impact of vutrisiran on outpatient worsening HF, as well as on an expanded composite endpoint including outpatient worsening HF.* [b]*CV events defined as CV hospitalizations or urgent HF visits.* [c]*Mean cumulative events are estimated from the mean cumulative function. HRs were derived using the modified Andersen–Gill model with robust variance estimator stratified by baseline tafamidis use, with treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA functional class, and age group as covariates. Data are truncated when the at-risk population reaches 5 patients.*

ATTR, transthyretin amyloidosis; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association.

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

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

- The incidence of AEs in the vutrisiran group was similar or lower than that in the placebo group, and is consistent with the incidence of AEs in the HELIOS-A trial
- No new safety signals were identified in the HELIOS-B trial

[a]Serious adverse events were defined as adverse events 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 adverse events (including serious adverse events) were graded for severity. Severe events were defined as adverse events for which more than minimal, local, or noninvasive 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 serious adverse events are summarized regardless of the treatment emergent classification. Deaths that occurred after the end of study visit or after the data cutoff date are not included.

AE, adverse event; COVID, coronavirus disease 2019.

Fontana M, et al. N Engl J Med. 2025;392:33-44.

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Summary

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Summary

- ATTR amyloidosis is a rapidly progressing, fatal disease caused by toxic misfolded TTR amyloid deposition, leading to tissue damage and multisystem disease burden[1,2]
- Worsening cardiomyopathy manifestations can lead to decline in physical functioning, loss of cardiac function, decreased QOL, increased CV-related hospitalizations, and death[3-6]
- Despite improvements in diagnosis and more intensive treatment, many patients still experience progression[7-9]

The HELIOS-B trial recruited a contemporary patient population to evaluate vutrisiran in patients with ATTR-CM[10]

- Vutrisiran provided durable and rapid knockdown of TTR[10]
- **All primary and secondary endpoints were met in the overall and monotherapy populations[10]**
  - Vutrisian lowered risk of composite of all-cause mortality and CV events, and preserved functional capacity and QOL, compared with placebo
  - Results with vutrisiran were consistent across all prespecified subgroups
- Vutrisiran had an acceptable safety and tolerability profile, with an incidence of AEs that was similar or lower than that of placebo, a finding consistent with the incidence of AEs demonstrated previously[10]

- In exploratory analyses:
  - Impact observed on NT-proBNP and troponin I compared with placebo[11]
  - Impact observed across all measures of cardiac structure and function compared with placebo[12]
- In a prespecified analysis, vutrisiran reduced the risk of outpatient worsening HF and the composite of outpatient worsening HF, all-cause mortality, and recurrent CV events compared with placebo (nominal)[13]

AE, adverse event; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; HF, heart failure; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide; QOL, quality of life; TTR, transthyretin.

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