Vutrisiran Improved Outcomes Versus Placebo in Patients with Transthyretin Amyloidosis with Cardiomyopathy and Severe Chronic Kidney Disease: Post Hoc Analysis of HELIOS-B

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Introduction

Transthyretin Amyloidosis with Cardiomyopathy

- ATTR-CM is a rare, progressive, and fatal systemic disease caused by misfolded amyloidogenic TTR protein accumulating as fibrils in the heart[1]
  - Patients with ATTR-CM can experience complications such as progressive HF and cardiac arrhythmias, leading to a poor QoL[2]

Renal Dysfunction in ATTR-CM

- Decline in renal function is common among patients with ATTR, with 17–46% of patients having CKD at the time of diagnosis,[3–5] increasing to ~60% in patients with confirmed renal amyloid deposition[6,7]
- Renal dysfunction is a risk factor for mortality and CV hospitalization in patients with ATTR, and renal failure is an independent predictor of mortality in patients with HF[8,9]

Vutrisiran and HELIOS-B

- Vutrisiran, an RNAi therapeutic that reduces the hepatic synthesis of variant and wild-type TTR, has been evaluated with over 1500 patient-years of experience in patients with ATTR in the Phase 3 HELIOS-A and HELIOS-B studies[10]
- In the HELIOS-B study (NCT04153149), vutrisiran significantly reduced risk of the composite endpoint of ACM and recurrent CV events in patients with ATTR-CM, whilst preserving functional capacity and quality of life[11]

Objective: To assess the impact of vutrisiran on renal function and the efficacy/safety of vutrisiran in patients who advanced to CKD Stage 4 or greater during the HELIOS-B double-blind period

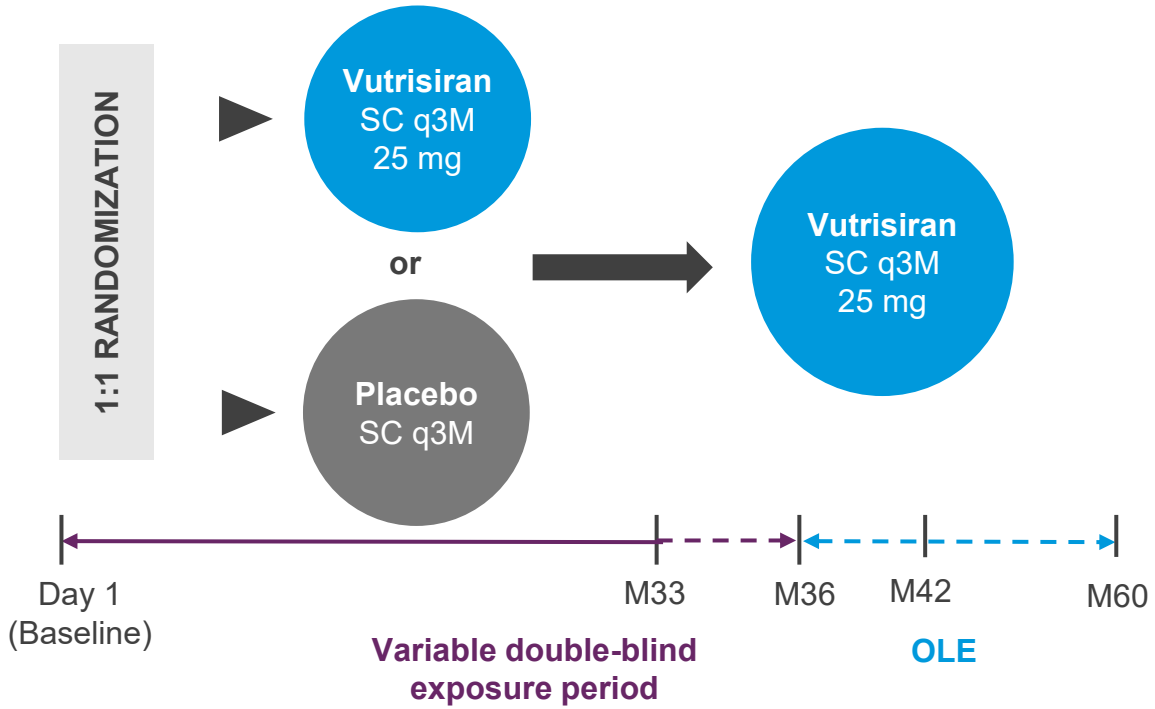
Abbreviations: ACM, all-cause mortality; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; QoL, quality of life; RNAi, RNA interference; TTR, transthyretin.

References: 1. Ruberg & Maurer. *JAMA*. 2024;331:778–91; 2. Eldhagen et al. *ESC Heart Fail.* 2023;10:1871–2; 3. Ioannou et al. *JAMA Cardiol.* 2025;10:50–8; 4. Dang et al. *Amyloid.* 2023;30:38–48; 5. Solignac et al. *Clin Kidney J.* 2022;15:1747–54; 6. Dang et al. *Dial Transplant.* 2023;38:2019–30; 7. Dang et al. *Kidney International Reports.* 2025;10:1939–49; 8. Shahi et al. *J Clin Med.* 2024;13:5490; 9. Smith et al. *J Am Coll Cardiol.* 2006;47:1987–96; 10. Witteles et al. *JACC Adv.* 2025;4:102066; 11. Fontana et al. *N Engl J Med.* 2025;392:33–44.

HELIOS-B Analysis of Renal Function and Efficacy/Safety of Vutrisiran in Patients Advancing to CKD Stage 4 or Greater

HELIOS-B: A Randomized, Double-Blind Outcomes Study in Patients with ATTR-CM[1]

HELIOS-B exclusion (at screening):
eGFR <30 mL/min/1.73 m²



Post hoc analyses in the overall and monotherapy (not on baseline tafamidis) populations, and the baseline tafamidis subgroup:

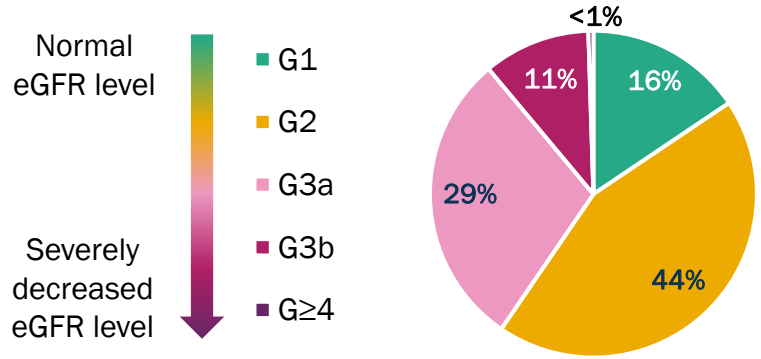
All HELIOS-B patients

- Proportion with eGFR decline ≥40% from baseline
- Change in eGFR from baseline over time

Patients advancing to CKD Stage ≥4 (eGFR<30 mL/min/1.73 m²) during the double-blind period

- ACM and recurrent CV events (M33–36; primary composite)
- ACM through up to M42
- Recurrent CV events (M33–36)
- Safety

Baseline KDIGO eGFR category[a] in HELIOS-B patients

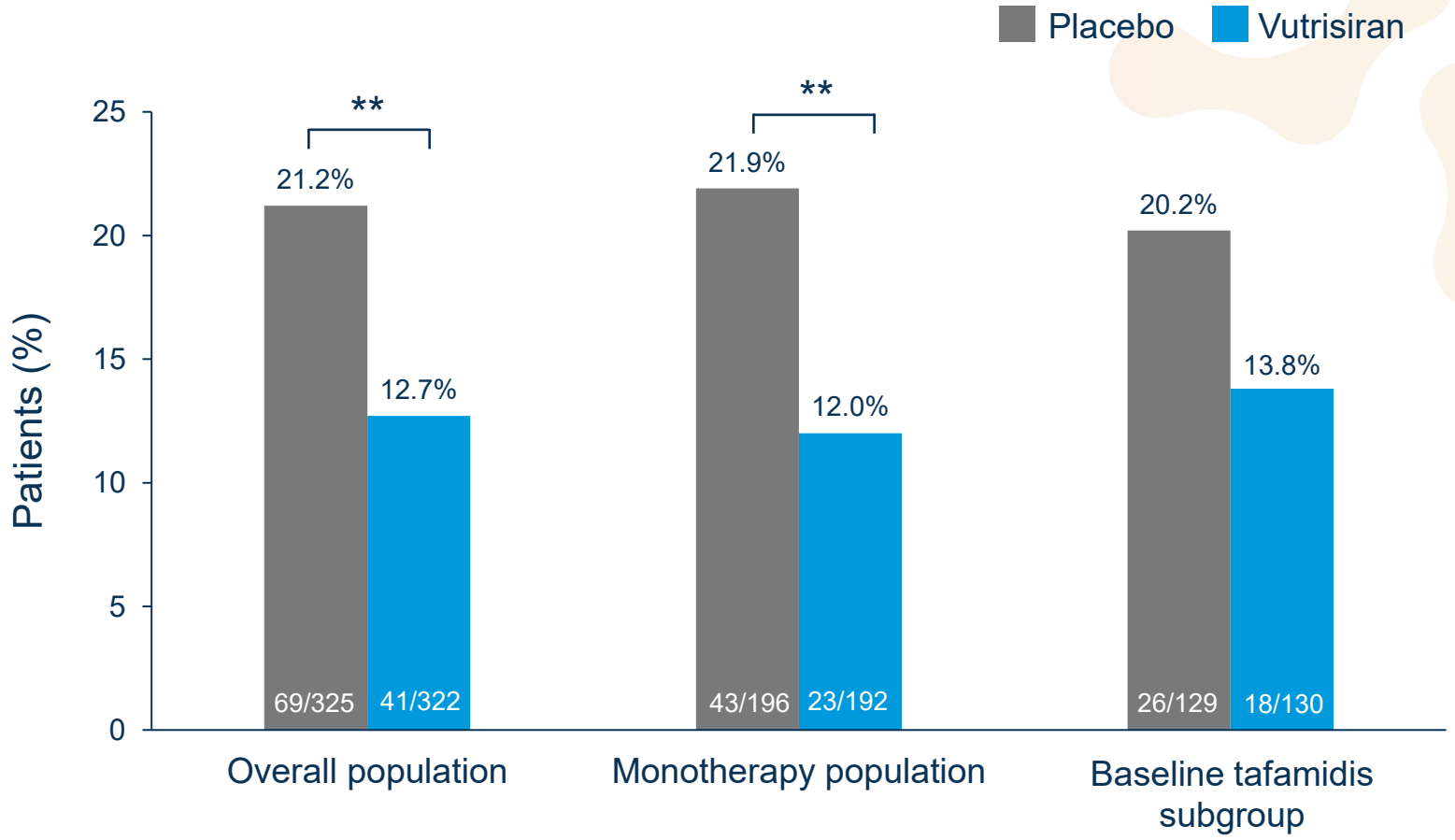


[a]G1, G2, G3a, G3b, and G≥4 based on eGFR ≥ 90, 60–89, 45–59, 30–44, and < 30 mL/min/1.73 m², respectively.

Abbreviations: ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; M, month; OLE, open-label extension; q3M, once every 3 months; SC, subcutaneous. **Reference:** 1. Fontana et al. *N Engl J Med.* 2025;392:33–44.

Fewer Patients Experienced Worsening Renal Function with Vutrisiran versus Placebo in HELIOS-B

Patients Experiencing a ≥40% Decline in eGFR during the Double-Blind Period

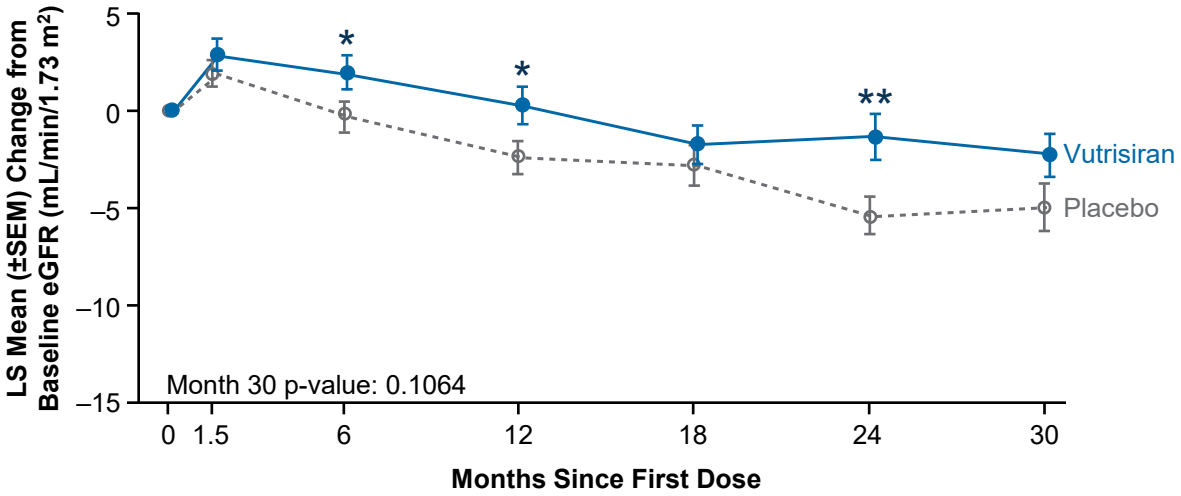


**p≤0.01
Abbreviation: eGFR, estimated glomerular filtration rate.

Vutrisiran Treatment Was Associated with Trends Towards Improvement in eGFR versus Placebo over Time

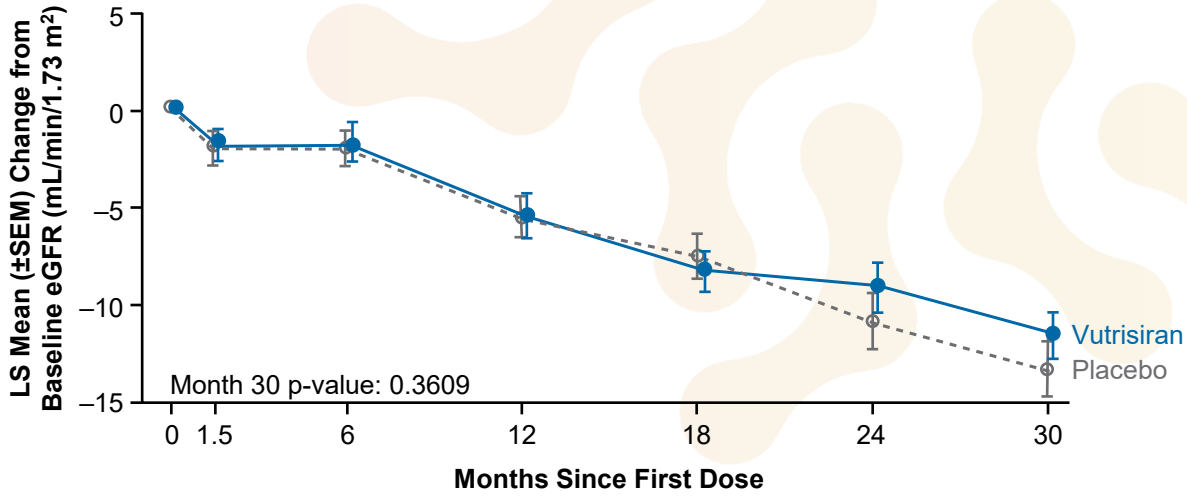
HELIOS-B

Baseline eGFR <60 mL/min/1.73 m²



No. of Patients							
Placebo	129	121	120	116	111	96	90
Vutrisiran	135	125	126	119	113	105	104

Baseline eGFR ≥60 mL/min/1.73 m²



No. of Patients							
Placebo	199	183	187	182	169	161	148
Vutrisiran	191	177	178	170	168	158	154

The trends in eGFR over time in the monotherapy population and the baseline tafamidis subgroup were generally similar to those in the overall population

*p≤0.05; **p≤0.01.

Abbreviations: eGFR, estimated glomerular filtration rate; LS, least squares; SEM, standard error of the mean.

Baseline Characteristics Were Generally Balanced across Treatment Groups among Patients Advancing to CKD Stage 4 or Greater

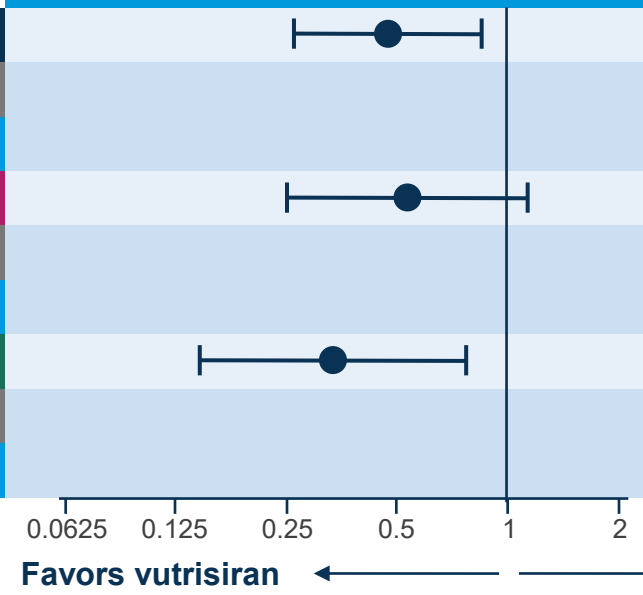
HELIOS-B

	Overall Population		Monotherapy Population		Baseline Tafamidis Population	
	Placebo (n=32)	Vutrisiran (n=31)	Placebo (n=19)	Vutrisiran (n=18)	Placebo (n=13)	Vutrisiran (n=13)
Age in years, mean (SD)	76.4 (6.4)	76.3 (6.4)	76.1 (7.0)	76.7 (6.9)	76.8 (5.6)	75.8 (5.9)
Male, %	96.9	87.1	94.7	83.3	100.0	92.3
BMI at baseline, mean (SD) kg/m^2	28.14 (3.58)	27.66 (3.78)	27.89 (3.66)	26.92 (3.71)	28.52 (3.56)	28.67 (3.79)
eGFR, mL/min/1.73 m^2, mean (SD)	48.4 (10.0)	46.0 (13.3)	47.8 (10.2)	44.6 (13.7)	49.2 (10.2)	48.0 (13.1)
ATTR disease type, n (%)						
Hereditary	2 (6.3)	8 (25.8)	0	6 (33.3)	2 (15.4)	2 (15.4)
Wild-type	30 (93.8)	23 (74.2)	19 (100)	12 (66.7)	11 (84.6)	11 (84.6)

Abbreviations: ATTR, transthyretin amyloidosis; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Vutrisiran Reduced the Risk of Composite ACM and Recurrent CV Events versus Placebo among Patients Who Advanced to CKD Stage 4 or Greater[a]

53% Risk Reduction in Composite ACM and Recurrent CV Events during the Double-Blind Period in the Overall Population



	HR (95% CI)	≥1 event, n Patients (%)	ACM, n Patients (%)	Recurrent CV Events, n Patients (%)
Overall population (N=63)	0.47 (0.26, 0.85)			
Placebo (n=32)		22 (68.8)	16 (50.0)	17 (53.1)
Vutrisiran (n=31)		19 (61.3)	9 (29.0)	14 (45.2)
Monotherapy population (n=37)	0.53 (0.25, 1.13)			
Placebo (n=19)		13 (68.4)	10 (52.6)	9 (47.4)
Vutrisiran (n=18)		12 (66.7)	6 (33.3)	9 (50.0)
Baseline tafamidis subgroup (n=26)	0.33 (0.15, 0.77)			
Placebo (n=13)		9 (69.2)	6 (46.2)	8 (61.5)
Vutrisiran (n=13)		7 (53.8)	3 (23.1)	5 (38.5)

In the overall population, vutrisiran **reduced the risk of ACM by 57%** during the double-blind period plus 6 months of the OLE, and **the risk of recurrent CV events by 51%** during the double-blind period

[a]Includes events occurring on or after advancement to CKD Stage ≥4.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; OLE, open-label extension.

The Safety Profile of Vutrisiran in Patients Who Developed CKD Stage 4 or Greater Was Comparable with Placebo[a]

HELIOS-B

n (%)	Overall Population		Monotherapy Population		Baseline Tafamidis Population	
	Placebo (n=32)	Vutrisiran (n=31)	Placebo (n=19)	Vutrisiran (n=18)	Placebo (n=13)	Vutrisiran (n=13)
≥1 AE	29 (90.6)	28 (90.3)	17 (89.5)	17 (94.4)	12 (92.3)	11 (84.6)
Related to study drug	1 (3.1)	2 (6.5)	0	1 (5.6)	1 (7.7)	1 (7.7)
≥1 serious AE	23 (71.9)	22 (71.0)	13 (68.4)	13 (72.2)	10 (76.9)	9 (69.2)
Related to study drug	0	0	0	0	0	0
≥1 severe AE	20 (62.5)	19 (61.3)	13 (68.4)	12 (66.7)	7 (53.8)	7 (53.8)
Related to study drug	0	0	0	0	0	0
≥1 AE leading to study drug interruption	1 (3.1)	2 (6.5)	0	2 (11.1)	1 (7.7)	0
Related to study drug	0	0	0	0	0	0
≥1 AE leading to study drug discontinuation	1 (3.1)	0	1 (5.3)	0	0	0
Related to study drug	0	0	0	0	0	0
≥1 AE leading to study withdrawal	1 (3.1)	0	1 (5.3)	0	0	0
Related to study drug	0	0	0	0	0	0
Death	14 (43.8)	9 (29.0)	8 (42.1)	6 (33.3)	6 (46.2)	3 (23.1)

The safety profile of vutrisiran in patients who advanced to CKD Stage ≥4 during the double-blind period was comparable with that established in the overall population during the HELIOS-B study[1]

[a]Includes events occurring on or after advancement to CKD Stage ≥4.
Abbreviations: AE, adverse event; CKD, chronic kidney disease.
Reference: 1. Fontana et al. *N Engl J Med.* 2025;392:33–44.

Conclusions

For US HCPs

HELIOS-B

Vutrisiran may slow eGFR decline and improve outcomes versus placebo in patients with ATTR-CM and advanced CKD

- Vutrisiran appeared to preserve renal function in patients with ATTR-CM, with fewer patients experiencing ≥40% decreases in eGFR during the double-blind period of HELIOS-B versus placebo
- Consistent with results from the overall population,[1] treatment with vutrisiran reduced the risk of ACM and CV events versus placebo in patients with ATTR-CM who progressed to CKD Stage 4 or greater during the double-blind period of HELIOS-B
- The safety profile of vutrisiran in patients with impaired renal function was consistent with its established profile[1]
- These data demonstrate vutrisiran is an effective and well-tolerated treatment option for patients with ATTR-CM experiencing impaired renal function

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Abbreviations: ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HCP, healthcare professional.

Reference: 1. Fontana et al. *N Engl J Med.* 2025;392:33–44.