Vutrisiran Reduces the Risk of Developing Advanced Disease and Demonstrates Benefit in Patients Who Do Develop Advanced Disease in ATTR-CM: Analysis From the HELIOS-B Study

HELIOS-B

Scan to View

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Conclusions

- In HELIOS-B, fewer patients receiving vutrisiran developed advanced disease during the double-blind treatment period compared with placebo
- Among patients developing advanced disease, vutrisiran reduced the risk of the primary outcome (composite of ACM and recurrent CV events), as well as ACM (secondary endpoint), compared with placebo in the overall and monotherapy populations
- Vutrisiran had a favorable safety profile in patients with advanced disease, with a similar number of or fewer adverse events in vutrisiran-treated patients versus placebo-treated patients

Key takeaway

Vutrisiran reduces the risk of developing advanced disease in patients with ATTR-CM and has a beneficial impact in those who develop advanced disease

Introduction

ATTR-CM

- ATTR is a progressive and fatal disease caused by accumulation of TTR amyloid fibrils in multiple organs and tissues, predominantly in the heart and peripheral nerves[1–3]
- Patients with ATTR-CM have a median survival of 2.6–5.8 years from diagnosis if untreated,[4–6] and experience significant morbidity including CV-related hospitalizations[4,7,8]
  - Patients with more advanced stages of HF have poorer outcomes[9]

Vutrisiran and HELIOS-B

- Vutrisiran, an RNAi therapeutic that reduces the hepatic synthesis of variant and wild-type TTR, was evaluated in patients with ATTR-CM in the Phase 3, randomized, double-blind, placebo-controlled HELIOS-B study (NCT04153149)[10]
- Vutrisiran significantly reduced the risk of the primary composite endpoint of ACM and recurrent CV events during the 33–36-month double-blind period (HR: 0.72, p=0.01; NNT[a]=4), and the risk of ACM through 42 months (HR 0.65, p=0.01) vs placebo[10,11]
- Limited data are available on treatment outcomes in patients with ATTR-CM and advanced HF

Objectives

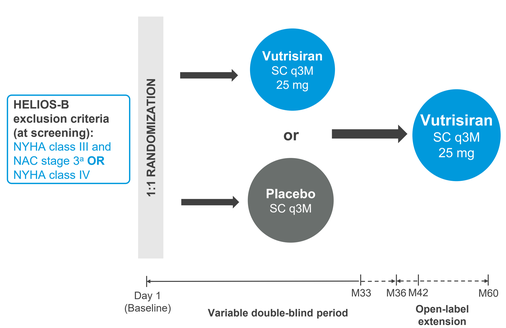
- To compare the risk of developing advanced disease, defined by transitioning to (a) NYHA class III and NAC stage 3 or (b) NYHA class IV, with vutrisiran vs placebo during the double-blind period of HELIOS-B
- To assess the effect of vutrisiran on outcomes in patients with ATTR-CM who developed advanced disease vs placebo

[a]NNT value is derived from event-based NNTs of 10.1 patient-years to prevent 1 primary outcome event during the double-blind period.

Methods

Figure 1. Analysis of Patients Developing Advanced Disease

HELIOS-B: Randomized, double-blind outcomes study in patients with ATTR-CM[10]



[a]Defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min/1.73 m².

Post hoc analyses of patients in the HELIOS-B overall and monotherapy (not on baseline tafamidis) populations:

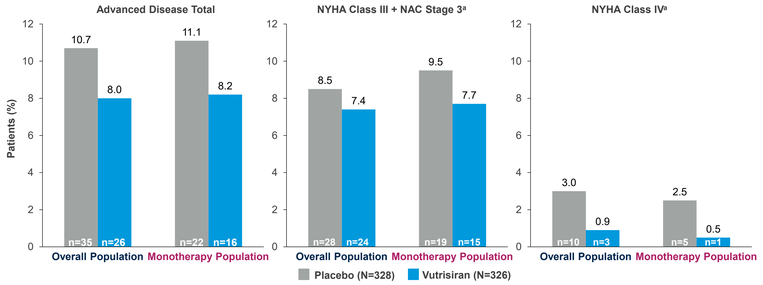
All HELIOS-B patients (N=654)
- Proportion of patients developing advanced disease (NYHA class III and NAC stage 3 or NYHA class IV)

Patients developing advanced disease (defined as NYHA class III and NAC stage 3 or NYHA class IV; n=61)
- ACM and recurrent CV events (M33–M36; primary composite)
- ACM through M42 (double-blind period and M6 of the open-label extension)
- Safety

Only events occurring after developing advanced disease were included in the analysis

Results

Figure 2. Vutrisiran Reduced the Proportion of Patients Who Developed Advanced Disease vs Placebo During the HELIOS-B Double-Blind Period



[a]Number of patients in these categories may add up to more than number of patients with advanced disease in total, as some patients transitioned to NYHA class III + NAC stage 3 and then to NYHA class IV.

Table 1. In Patients Who Developed Advanced Disease, Certain Baseline Characteristics (Prior HF Hospitalizations and Cardiac Biomarker Levels) Were Worse in Patients Treated with Vutrisiran vs Placebo, Indicating More Advanced Disease

Parameter	Overall Population		Monotherapy Population	
	Placebo (n=35)	Vutrisiran (n=26)	Placebo (n=22)	Vutrisiran (n=16)
Age (years), median (range)	77.0 (64–85)	77.5 (66–85)	77.5 (64–84)	79.0 (70–85)
Male, n (%)	33 (94)	26 (100)	21 (95)	16 (100)
hATTR, n (%)	5 (14)	1 (4)	2 (9)	1 (6)
6-MWT, m, mean (SD)	327.3 (82.4)	363.6 (80.2)	324.3 (87.1)	366.1 (83.7)
KCCQ-OS, mean (SD)	63.4 (19.9)	64.7 (22.9)	63.6 (20.1)	62.0 (24.2)
NYHA class, n (%) I II III	 1 (3) 25 (71) 9 (26)	 0 19 (73) 7 (27)	 1 (5) 17 (77) 4 (18)	 0 14 (88) 2 (13)
Previous HF hospitalization, n (%)	12 (34)	13 (50)	8 (36)	8 (50)
NT-proBNP, ng/L, median (IQR)	3359.0 (2154.0–4548.0)	3650.5 (2425.0–4677.0)	2767.5 (1749.0–4674.0)	4091.5 (2552.0–6992.5)
Troponin I, ng/L, median (IQR)	68.8 (51.0–122.0)	87.7 (52.8–140.7)	64.9 (52.1–123.1)	99.0 (54.0–142.2)

Table 2. At the Time of Advanced Disease Development, Patients Treated with Placebo Appeared Worse Across Multiple Clinical Assessments vs Patients Treated with Vutrisiran

Parameter	Overall Population		Monotherapy Population	
	Placebo (n=35)	Vutrisiran (n=26)	Placebo (n=22)	Vutrisiran (n=16)
6-MWT, m, mean (SD)	235.3 (88.5)	284.5 (67.3)	218.6 (79.5)	287.9 (65.6)
KCCQ-OS, mean (SD)	42.2 (18.4)	48.2 (21.5)	40.5 (18.3)	47.0 (16.6)
NYHA class, n (%) I/II III IV	 0 28 (80) 7 (20)	 0 24 (92) 2 (8)	 0 19 (86) 3 (14)	 0 15 (94) 1 (6)
Average peak longitudinal strain, %, mean (SD)	–10.9 (3.3)	–11.0 (4.1)	–11.4 (3.4)	–11.3 (4.1)
Mean LV wall thickness, cm, mean (SD)	1.9 (0.3)	1.8 (0.3)	1.9 (0.3)	1.7 (0.3)
NT-proBNP, ng/L, median (IQR)	5987 (4698–9010)	5743 (3480–7564)	7240 (4772–11,614)	6857 (4321–12,270)
Troponin I, ng/L, median (IQR)	94.3 (70.1–164.4)	81.0 (47.9–182.6)	152.0 (89.3–193.6)	85.3 (46.4–190.5)

Figure 3. Vutrisiran Reduced the Risk of the Composite of ACM and Recurrent CV Events and the Risk of ACM vs Placebo in Patients Who Developed Advanced Disease

Composite of ACM and Recurrent CV Events During the Double-Blind Period[a]	HR (95% CI)[b]	Placebo Overall, n=35 Monotherapy, n=22		Vutrisiran Overall, n=26 Monotherapy, n=16	
		Total Events, n	Event Rate per PY	Total Events, n	Event Rate per PY
Overall population (n=61)	0.604 (0.287, 1.274)	42	1.19	23	0.75
Monotherapy population (n=38)	0.542 (0.240, 1.223)	25	1.34	15	0.89

0.125 0.25 0.5 1 2

ACM During the Double-Blind Period Plus Up to 6 Months of the Open-Label Extension[a]	HR (95% CI)[c]	Placebo Overall, n=35 Monotherapy, n=22	Vutrisiran Overall, n=26 Monotherapy, n=16
		ACM, n (%)	ACM, n (%)
Overall population (n=61)	0.442 (0.148, 1.323)	12 (34)	6 (23)
Monotherapy population (n=38)	0.226 (0.054, 0.940)	10 (46)	4 (25)

0.03125 0.0625 0.125 0.25 0.5 1 2

← Favors vutrisiran Favors placebo →

[a]ACM includes heart transplantation and LV assist device placement; [b]Analysis based on the modified Andersen–Gill model; [c]Derived from a Cox proportional hazards model.

- Vutrisiran numerically reduced the risk of composite of ACM and recurrent CV events in patients who developed advanced disease by **40% in the overall population** and **46% in the monotherapy population**, vs placebo
- Vutrisiran also reduced the risk of ACM in patients who developed advanced disease by **56% in the overall population** and **77% in the monotherapy population**, vs placebo

Table 3. A Similar Number or Fewer Adverse Events Were Observed with Vutrisiran vs Placebo After Development of Advanced Disease

AE Category	Overall Population, n (%) / Event Rates per 100 PY	
	Placebo (n=35; PY=33.7)	Vutrisiran (n=26; PY=28.3)
≥1 AE	35 (100) / 946.9	24 (92) / 691.9
≥1 Serious AE	21 (60) / 192.9	16 (62) / 165.9
≥1 Severe AE	20 (57) / 160.3	15 (58) / 127.1
≥1 AE leading to treatment interruption	0	0
≥1 AE leading to treatment discontinuation	3 (9) / 17.8	2 (8) / 7.1
≥1 AE leading to study withdrawal	2 (6) / 14.8	0
Deaths, n (%)	9 (26)	4 (15)

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If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.

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Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; AE, adverse event; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CI, confidence interval, CV, cardiovascular; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin amyloidosis; HF, heart failure; HR, hazard ratio; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LV, left ventricular; M, month; NAC, National Amyloidosis Centre; NNT, number needed to treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PY, patient-years; q3M, every 3 months; RNAi, RNA interference; SC, subcutaneous; SD, standard deviation; TTR, transthyretin.