Impact of Baseline Heart Failure Severity on Efficacy of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy in the HELIOS-B Trial: A Subgroup Analysis

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HELIOS·B

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Conclusions

- In these exploratory analyses, vutrisiran demonstrated evidence of benefit versus placebo in all-cause mortality and recurrent CV events, functional capacity, quality of life, and cardiac biomarkers across a range of baseline disease severities in patients enrolled in HELIOS-B
- Greatest benefit was observed in patients with earlier, less severe disease, highlighting the need for timely diagnosis and starting effective therapy as soon as possible

Introduction

Transthyretin Amyloidosis with Cardiomyopathy

- In ATTR-CM, accumulation of wild-type or variant TTR amyloid fibrils in the heart[1–5] causes worsening heart failure, increased hospitalizations, and reduced survival[6–10]

HELIOS-B Study

- The HELIOS-B study (NCT04153149) evaluated vutrisiran, a subcutaneously administered RNA interference therapeutic, in patients with ATTR-CM in a Phase 3, randomized, placebo-controlled trial[11]
- Vutrisiran reduced the risk of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) versus placebo, and also preserved functional capacity and quality of life[11]

Objective

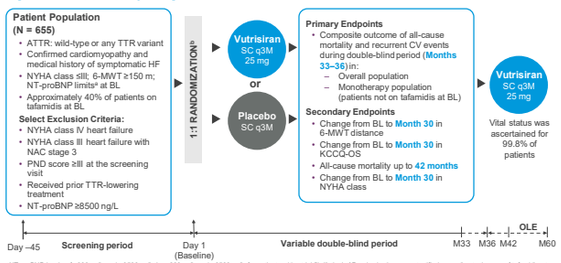
- To assess the consistency of vutrisiran effect versus placebo in patients with different baseline heart failure severities in HELIOS-B

Methods

HELIOS-B Study Design

- The HELIOS-B study is evaluating the efficacy and safety of vutrisiran over a double-blind period of up to 36 months and an open-label extension period of up to 24 months, during which all patients receive vutrisiran[11] (**Figure 1**)

Figure 1. HELIOS-B Study Design



[a]NT-proBNP levels of >300 ng/L and <8500 ng/L (or >600 ng/L and <8500 ng/L for patients with atrial fibrillation). [b]Randomization was stratified according to the use of tafamidis at baseline (yes vs no), ATTR disease type (hATTR or wtATTR), and NYHA class and age at baseline (NYHA class I or II and age <75 years vs all others).

Baseline Disease Severity Group Analyses

- In these exploratory analyses, the effect of vutrisiran versus placebo on selected endpoints was evaluated in the overall and monotherapy populations by different heart failure severities according to:
  - Baseline NYHA class I, II, or III
  - Baseline NT-proBNP levels of ≤2000 ng/L or >2000 ng/L
  - Baseline NAC stage 1 or 2/3
  - Baseline Columbia early stage (score 1–3) or intermediate/late stage (score 4–9)
  - Baseline NT-proBNP tertiles of <1368 ng/L, 1368–2691 ng/L, and >2691 ng/L

Results

Baseline Demographics and Disease Characteristics

- Baseline heart failure severity was generally comparable across the treatment groups, except that among the patients in the monotherapy population, NT-proBNP (**Table 1**) and troponin I (data not shown) levels were higher in the vutrisiran arm than in the placebo arm
- Baseline demographics and characteristics were generally similar across the key baseline heart failure severity groups in the overall (**Table 2**) and monotherapy populations (data not shown)
- Some of the heart failure severity groups included low patient numbers; data in these groups should be interpreted with caution

Table 1. Patient Groups by Baseline Heart Failure Severity

Baseline parameter		Overall Population (N = 654)[a]		Monotherapy Population (N = 395)	
		Vutrisiran (N = 326)	Placebo (N = 328)	Vutrisiran (N = 196)	Placebo (N = 199)
NYHA class, n (%)	I	49 (15.0)	35 (10.7)	15 (7.7)	12 (6.0)
	II	250 (76.7)	258 (78.7)	172 (87.8)	169 (84.9)
	III	27 (8.3)	35 (10.7)	9 (4.6)	18 (9.0)
NT-proBNP level, n (%)	≤2000 ng/L	161 (49.4)	181 (55.2)	81 (41.3)	107 (53.8)
	>2000 ng/L	165 (50.6)	147 (44.8)	115 (58.7)	92 (46.2)

[a]While 655 patients were enrolled in HELIOS-B, 1 patient randomized to placebo did not receive a dose due to withdrawal and is not included in the analysis.

Table 2. Baseline Demographics and Disease Characteristics across Disease Severity Groups in the Overall Population

	Baseline NYHA Class						Baseline NT-proBNP Level			
	I		II		III		≤2000 ng/L		>2000 ng/L	
	Vutrisiran (N = 49)	Placebo (N = 35)	Vutrisiran (N = 250)	Placebo (N = 258)	Vutrisiran (N = 27)	Placebo (N = 35)	Vutrisiran (N = 161)	Placebo (N = 181)	Vutrisiran (N = 165)	Placebo (N = 147)
Age, years, median (IQR)	77.0 (72.0, 80.0)	76.0 (70.0, 80.0)	77.0 (72.0, 81.0)	76.0 (72.0, 80.0)	77.0 (71.0, 81.0)	76.0 (71.0, 80.0)	76.0 (70.0, 79.0)	75.0 (70.0, 79.0)	78.0 (74.0, 81.0)	77.0 (73.0, 80.0)
Males, n (%)	49 (100.0)	33 (94.3)	226 (90.4)	241 (93.4)	24 (88.9)	32 (91.4)	148 (91.9)	166 (91.7)	151 (91.5)	140 (95.2)
wtATTR, n (%)	44 (89.8)	30 (85.7)	220 (88.0)	229 (88.8)	25 (92.6)	30 (85.7)	140 (87.0)	159 (87.8)	149 (90.3)	130 (88.4)
Tafamidis use at baseline, n (%)	34 (69.4)	23 (65.7)	78 (31.2)	89 (34.5)	18 (66.7)	17 (48.6)	80 (49.7)	74 (40.9)	50 (30.3)	55 (37.4)
6-MWT, median (IQR), m	422.3 (375.0, 485.4)	421.8 (358.9, 480.0)	360.0 (298.7, 435.3)[a]	383.0 (323.4, 450.0)	318.5 (256.0, 429.4)	295.0 (244.7, 345.0)	406.2 (339.9, 472.0)[b]	405.0 (340.7, 467.5)	332.1 (264.4, 410.5)	360.0 (291.0, 411.6)
KCCQ-OS, mean (SD), points	85.4 (12.7)	83.7 (15.1)	72.0 (19.2)[a]	73.2 (19.3)[c]	58.8 (20.2)	54.2 (17.0)	75.4 (19.1)	74.4 (19.1)	70.6 (19.6)[d]	69.6 (20.6)[e]
NT-proBNP, median (IQR), ng/L	1458 (838, 2703)	1285 (776, 2045)	2159 (1227, 3455)	1814 (1080, 3080)	2468 (1760, 3796)	2563 (1401, 3885)	1126 (807, 1599)	1110 (776, 1479)	3294 (2589, 4579)	3323 (2576, 4424)
Troponin I, median (IQR), ng/L	65.0 (38.0, 99.3)	68.6 (30.3, 130.0)	73.8 (48.4, 117.8)	63.6 (40.4, 104.8)	48.6 (33.6, 140.8)	71.4 (47.7, 121.6)	53.6 (34.5, 81.2)	55.1 (33.6, 81.0)	89.4 (59.6, 143.7)	81.8 (53.0, 121.9)

[a]n = 249; [b]n = 160; [c]n = 257; [d]n = 164; [e]n = 146.

Impact of Vutrisiran on the Composite Endpoint of All-Cause Mortality and Recurrent CV Events and on Standalone All-Cause Mortality by Baseline Heart Failure Severity

- Vutrisiran reduced the risk of the composite endpoint of all-cause mortality and recurrent CV events versus placebo, regardless of baseline heart failure severity, defined by NYHA class and NT-proBNP levels (≤2000 ng/L and >2000 ng/L), in the overall and monotherapy populations enrolled in HELIOS-B **(Figure 2);** similar results were observed for standalone all-cause mortality (data not shown)
- In analyses of other baseline heart failure severity measures (Columbia stage, NAC stage, and NT-proBNP tertiles), similar trends for risk reduction of all-cause mortality and recurrent CV events were observed with vutrisiran versus placebo, with greatest benefit seen in patients with earlier, less severe disease (**Table 3**)

Figure 2. Composite of All-Cause Mortality and Recurrent CV Events during the Double-Blind Period by Baseline Heart Failure Severity, in the Overall and Monotherapy Populations

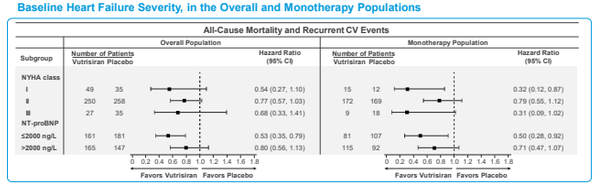


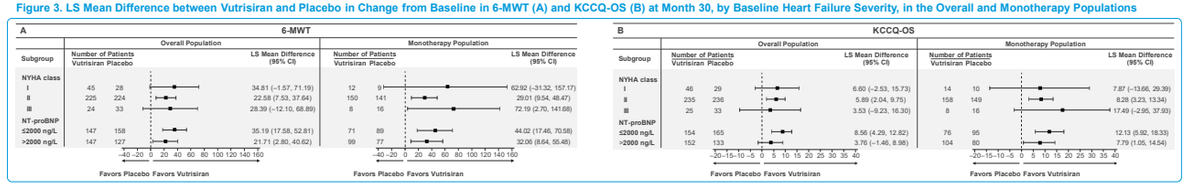
Table 3. Composite of All-Cause Mortality and Recurrent CV Events during the Double-Blind Period by Baseline Heart Failure Severity, in the Overall and Monotherapy Populations

		All-Cause Mortality and Recurrent CV Events			
		Overall Population		Monotherapy Population	
		N	Hazard Ratio (95% CI)	N	Hazard Ratio (95% CI)
Columbia stage	Early (score 1–3)	312	0.69 (0.45, 1.07)	179	0.69 (0.37, 1.28)
	Intermediate/late (score 4–9)	342	0.74 (0.53, 1.02)	216	0.66 (0.45, 0.97)
NAC stage	1	437	0.49 (0.34, 0.72)	251	0.48 (0.29, 0.82)
	2/3	217	1.08 (0.74, 1.56)	144	0.90 (0.58, 1.38)
NT-proBNP tertiles	<1368 ng/L	217	0.52 (0.30, 0.88)	120	0.56 (0.25, 1.26)
	≥1368–<2691 ng/L	218	0.61 (0.37, 1.00)	128	0.56 (0.29, 1.08)
	≥2691 ng/L	219	0.93 (0.64, 1.35)	147	0.82 (0.54, 1.22)

Impact of Vutrisiran on Measures of Functional Capacity and Health Status/Quality of Life by Baseline Heart Failure Severity

- Benefits in 6-MWT distance (**Figure 3A**) and KCCQ-OS score (**Figure 3B**) were observed with vutrisiran versus placebo across baseline heart failure severity subgroups in the overall and monotherapy populations enrolled in HELIOS-B

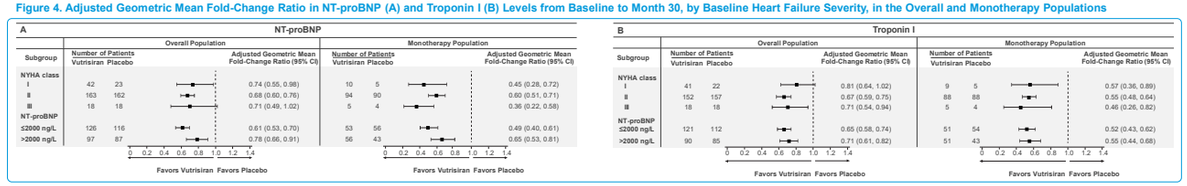
Figure 3. LS Mean Difference between Vutrisiran and Placebo in Change from Baseline in 6-MWT (A) and KCCQ-OS (B) at Month 30, by Baseline Heart Failure Severity, in the Overall and Monotherapy Populations



Impact of Vutrisiran on Cardiac Biomarkers by Baseline Heart Failure Severity

- Benefits in NT-proBNP (**Figure 4A**) and troponin I (**Figure 4B**) levels were observed with vutrisiran versus placebo across baseline heart failure severity subgroups in the overall and monotherapy populations enrolled in HELIOS-B

Figure 4. Adjusted Geometric Mean Fold-Change Ratio in NT-proBNP (A) and Troponin I (B) Levels from Baseline to Month 30, by Baseline Heart Failure Severity, in the Overall and Monotherapy Populations



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References: 1. Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 4. Živković et al. *Amyloid* 2020;27:142–3; 5. Sipe et al. *Amyloid* 2014;21:221–4; 6. Castano et al. *Heart Fail Rev* 2015;20:163–78; 7. Chacko et al. *Eur J Heart Fail* 2022;24:1700–12; 8. Lane et al. *Circulation* 2019;140:16–26; 9. Nativi-Nicolau et al. *ESC Heart Fail* 2021;8:3875–84; 10. Gillmore et al. *Eur Heart J* 2018;39:2799–806; 11. Fontana et al. *N Engl J Med* 2025;392:33–44.
Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; BL, Baseline; CI, confidence interval; CV, cardiovascular; hATTR, hereditary ATTR; HCP, healthcare professional; HF, heart failure; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS, least squares; M, Month; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; PND, polyneuropathy disability; q3M, every 3 months; SC, subcutaneous; SD, standard deviation; TTR, transthyretin; wtATTR, wild-type ATTR.