Maintenance or Improvement of Functional Capacity, Health Status, and Quality of Life with Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy: Data from the HELIOS-B Study

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HELIOS-B

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Conclusions

- Significantly more patients treated with vutrisiran maintained or improved functional capacity, health status, and quality of life over 30 months compared with placebo, across all cutoff values applied
- The benefits observed with vutrisiran were consistent across the prespecified subgroups, and KCCQ-OS subdomains
- These data provide further evidence of the disease-modifying effect of vutrisiran treatment, and demonstrate benefits beyond reduced risk of all-cause mortality and cardiovascular events

Introduction

ATTR with Cardiomyopathy

- ATTR is a systemic, progressive, and fatal disease affecting multiple tissues and organs, and is caused by the accumulation of misfolded amyloidogenic TTR deposits[1–5]
- Extracellular amyloid deposits frequently accumulate in heart tissue, causing cardiomyopathy (ATTR-CM), which leads to heart failure and arrhythmias that result in progressively debilitating symptoms[6,7]
- Disease progression and heart failure in ATTR-CM have major impacts on the functional capacity, health status, and QOL of patients[7–9]

HELIOS-B Study

- Vutrisiran is an RNAi therapeutic that rapidly decreases circulating levels of the amyloidogenic TTR protein[10]
- Vutrisiran was evaluated in patients with ATTR-CM in the HELIOS-B study (NCT04153149)[11]
  - Vutrisiran reduced the risk of the composite endpoint of all-cause mortality and recurrent cardiovascular events, improved functional capacity and QOL, and prevented worsening of heart failure symptoms versus placebo

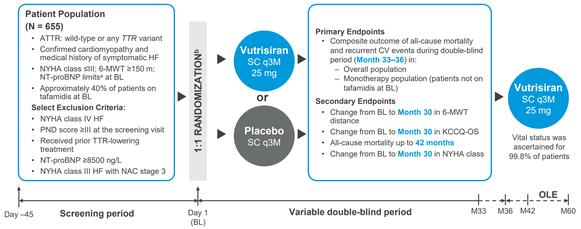
Objectives

- To further determine the impact of vutrisiran on the functional capacity, health status, and QOL of patients with ATTR-CM in the HELIOS-B trial, by presenting LS mean difference in change from baseline in 6-MWT and KCCQ-OS in prespecified subgroups, and KCCQ-OS subdomains
- To analyze the proportion of patients with maintenance or improvement in the 6-MWT and KCCQ-OS according to multiple clinically relevant cutoffs

Methods

Figure 1. HELIOS-B Study Design

Randomized, double-blind study in patients with ATTR-CM[11]



[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).

- 6-MWT and KCCQ-OS were assessed at baseline and every 6 months until Month 30
- Maintenance or improvement was defined as not having a decrease from baseline of >7 m, >15 m, or >35 m[12–14] (6-MWT), and >5 points or >10 points (KCCQ-OS)[15]

Results

Table 1. Baseline Characteristics in the Overall Population Were Similar in the Placebo and Vutrisiran Arms[11]

Parameter		Overall Population	
		Placebo (N = 328)	Vutrisiran (N = 326)
Age, years, median (range)		76 (46, 85)	77 (45, 85)
Men, n (%)		306 (93.3)	299 (91.7)
hATTR amyloidosis, n (%)		39 (11.9)	37 (11.3)
NYHA Class, n (%)	I	35 (10.7)	49 (15.0)
	II	258 (78.7)	250 (76.7)
	III	35 (10.7)	27 (8.3)
ATTR disease stage, n (%)	1	229 (69.8)	208 (63.8)
	2	87 (26.5)	100 (30.7)
	3	12 (3.7)	18 (5.5)
Baseline 6-MWT, meters, mean (SD)		377 (96)	372 (104)[a]
Baseline KCCQ-OS, points, mean (SD)		72.3 (19.9)	73.0 (19.4)[a]
Baseline NT-proBNP, ng/L, median (IQR)		1801 (1042, 3082)	2021 (1138, 3312)
Baseline troponin I, ng/L, median (IQR)		65.2 (41.1, 105.5)	71.9 (44.9, 115.9)

[a]n = 325

Table 2. Baseline Characteristics in the Monotherapy Population Were Generally Similar in the Placebo and Vutrisiran Arms[a,11]

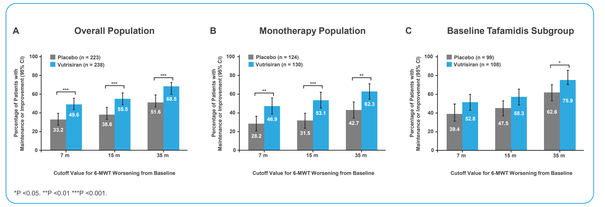
Parameter		Monotherapy Population	
		Placebo (N = 199)	Vutrisiran (N = 196)
Age (years), median (range)		76 (53, 85)	78 (46, 85)
Men, n (%)		183 (92.0)	178 (90.8)
hATTR amyloidosis, n (%)		25 (12.6)	23 (11.7)
NYHA Class, n (%)	I	12 (6.0)	15 (7.7)
	II	169 (84.9)	172 (87.8)
	III	18 (9.0)	9 (4.6)
ATTR disease stage, n (%)	1	138 (69.3)	113 (57.7)
	2	55 (27.6)	68 (34.7)
	3	6 (3.0)	15 (7.7)
Baseline 6-MWT, meters, mean (SD)		373 (98)	363 (103)
Baseline KCCQ-OS, points, mean (SD)		69.9 (20.8)[b]	70.3 (20.2)[c]
Baseline NT-proBNP, ng/L, median (IQR)		1865 (1067, 3099)	2402 (1322, 3868)
Baseline troponin I, ng/L, median (IQR)		62.2 (39.2, 105.6)	76.3 (48.4, 138.8)

[a]NT-proBNP and troponin I levels were higher in the vutrisiran group compared with the placebo group in the monotherapy population. [b]n = 198. [c]n = 195.

Difference of LS-mean Change from Baseline (Vutrisiran–Placebo) in the Overall Population[11]

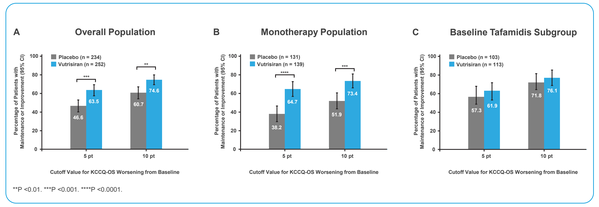
- **6-MWT:** 26.46 m (95% CI 13.38, 39.55; p<0.001)
- **KCCQ-OS:** 5.80 points (95% CI 2.40, 9.20; p<0.001)

Figure 2. Vutrisiran Resulted in Maintenance or Improvement in Functional Capacity in a Higher Percentage of Patients versus Placebo at Month 30 across Multiple Cutoff Values for the 6-MWT



*P <0.05. **P <0.01 ***P <0.001.

Figure 3. Vutrisiran Resulted in Maintenance or Improvement in KCCQ-OS Score in a Higher Percentage of Patients versus Placebo at Month 30 across Both Cutoff Values



**P <0.01. ***P <0.001. ****P <0.0001.

Figure 4. Clinical Benefits with Vutrisiran on Functional Capacity versus Placebo Were Consistent across Prespecified Subgroups

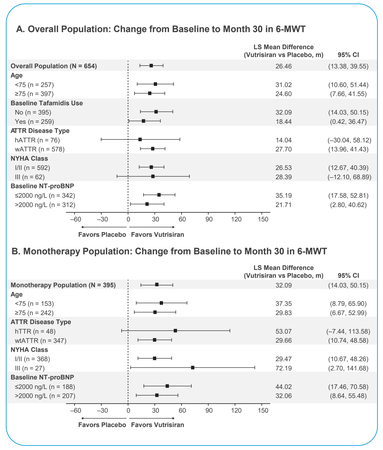


Figure 5. Clinical Benefits with Vutrisiran on Health Status/QOL versus Placebo Were Consistent across Prespecified Subgroups

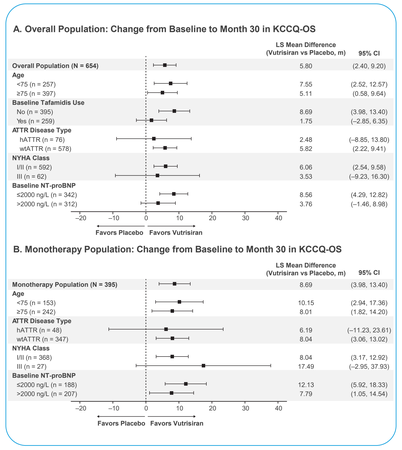
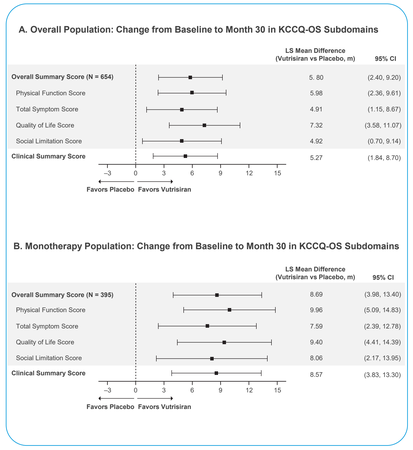


Figure 6. Vutrisiran Improved All Subdomains of the KCCQ-OS Relative to Placebo



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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; HF, heart failure; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Score; LS, least squares; 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; pt, points; q3M, every 3 months; QOL, quality of life; RNAi, RNA interference SC, subcutaneous; SD, standard deviation; TTR, transthyretin; wtATTR, wild-type ATTR.