Efficacy of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy by Baseline Health Status and Quality of Life

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HELIOS-B

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Conclusions

- This post hoc analysis of HELIOS-B evaluated the treatment effects of vutrisiran vs placebo by baseline health status/QOL
- Consistent benefits with vutrisiran vs placebo were observed in patients with worse and better health status/QOL at baseline for all efficacy endpoints assessed including ACM and CV events, health status/QOL, NYHA class, and cardiac biomarkers; vutrisiran vs placebo was also associated with a reduction in GI AEs
- These data further support the use of vutrisiran in patients with ATTR-CM, regardless of baseline disease severity

Key takeaway

Regardless of patients' baseline health status/QOL, consistent benefit was observed with vutrisiran treatment versus placebo in the HELIOS-B study

Introduction

ATTR Cardiomyopathy

- ATTR is a progressive, systemic disease caused by misfolded amyloidogenic deposits in multiple tissues and organs; patients with ATTR-CM can experience complications such as progressive heart failure, cardiac arrythmias, and increased hospitalization leading to a decreased QOL[1–5]
- ATTR-CM can also involve extracardiac neuropathic and GI symptoms that negatively impact QOL[6–8]

HELIOS-B Study

- The SC-administered RNAi therapeutic vutrisiran significantly reduced the composite of ACM and recurrent CV events in patients with ATTR-CM, and preserved functional capacity and QOL compared with placebo, in the overall population and the vutrisiran monotherapy population (those not receiving tafamidis at baseline) of the HELIOS-B study[9]

KCCQ-OS

- The KCCQ-OS is a ≤23-item questionnaire used to evaluate health status and QOL; patients are scored between 0 and 100 with higher scores indicating better health status and lower scores representing more severe symptoms, limitations, and poorer QOL[10]
  - In HELIOS-B, treatment with vutrisiran resulted in less of a decline than placebo in the KCCQ-OS score (LS mean difference [95% CI] 5.8 points [2.4, 9.2])[9]

Objective

- This post hoc analysis of HELIOS-B assessed if baseline KCCQ-OS impacted the efficacy of vutrisiran versus placebo across a range of endpoints including the composite of ACM and recurrent CV events

Methods

- Patients with ATTR-CM were randomized 1:1 to receive SC vutrisiran 25 mg or placebo every 12 weeks, for up to 36 months[9]
- In this post hoc analysis, efficacy was assessed in patients with baseline KCCQ-OS of ≤50 (worse health status/QOL) or >50 (better health status/QOL) points
- Prespecified endpoints included:
  - ACM and recurrent CV events[a] observed during the double-blind period (primary composite)
  - ACM observed in the double-blind period and first 6 months of the OLE (secondary)
  - Change from baseline to Month 30 in 6-MWT and KCCQ-OS (both secondary)
  - Percentage of patients with stable or improved NYHA class at Month 30 (secondary)
  - Change from baseline to Month 30 in NT-proBNP and troponin I (both exploratory)
  - Occurrence of AEs classified under the GI disorders system organ class and reported during the double-blind period
- Analyses were performed in the overall and monotherapy populations

[a]Defined as hospitalizations for CV causes or urgent visits for heart failure.

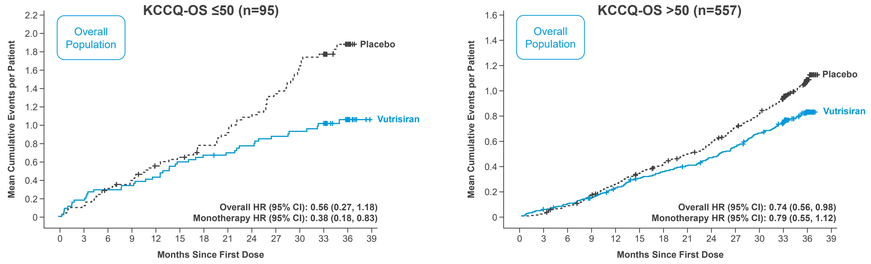
Results

Baseline Characteristics

- Patients with lower baseline KCCQ-OS, and therefore worse QOL, demonstrated worse health status at baseline versus patients with a higher KCCQ-OS, including more patients with NYHA class III, shorter 6-MWT distance, and higher levels of NT-proBNP

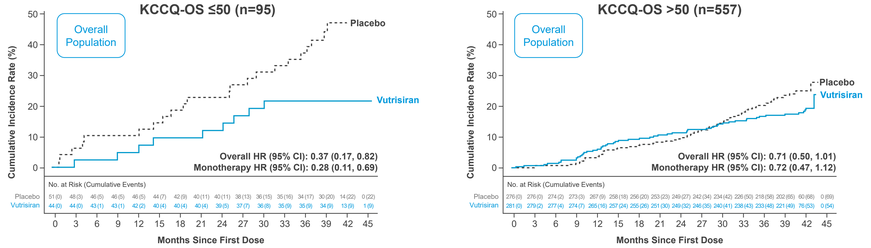
Results

Figure 1. Consistent Benefit of Vutrisiran on the Primary Composite Endpoint of ACM[a] and Recurrent CV Events Through 33–36 Months in Both Baseline KCCQ-OS Subgroups



[a]All-cause mortality includes heart transplantation and left ventricular assist device placement. Analysis based on modified Anderson-Gill model.

Figure 2. Vutrisiran Reduced the Risk of ACM[a] Through Month 42 in Both Baseline KCCQ-OS Subgroups



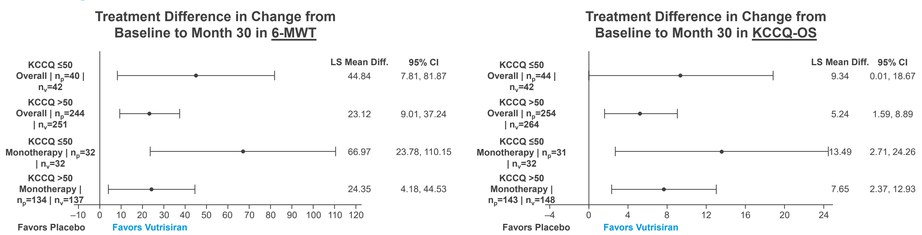
[a]All-cause mortality includes heart transplantation and left ventricular assist device placement. Deaths after the end of the study are included. Analysis based on Cox proportional hazards model.

Table 1. Beneficial Effect of Vutrisiran Versus Placebo Observed Across Multiple Endpoints in Both Baseline KCCQ-OS Subgroups

Overall Population	KCCQ-OS ≤50	KCCQ-OS >50
Change from Baseline at Month 30	Vutrisiran (n=44) vs Placebo (n=51)	Vutrisiran (n=281) vs Placebo (n=276)
6-MWT, m, – LS mean difference (95% CI)[a]	44.84 (7.81, 81.87)	23.12 (9.01, 37.24)
KCCQ-OS, points, – LS mean difference (95% CI)[a]	9.34 (0.01, 18.67)	5.24 (1.59, 8.89)
NT-proBNP, ng/L, – ratio of fold-change (95% CI)[b]	0.55 (0.42, 0.72)	0.70 (0.62, 0.79)
NYHA class, % stable or improved, – adjusted difference in % (95% CI)[c]	13.7 (–6.6, 33.9)	5.7 (–2.4, 13.8)
Troponin I, ng/L, – ratio of fold-change (95% CI)[b]	0.73 (0.55, 0.97)	0.68 (0.62, 0.75)

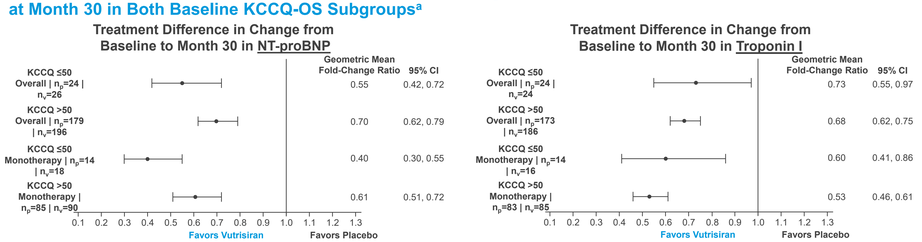
[a]Analysis based on MMRM with baseline 6-MWT/KCCQ-OS as continuous covariates and fixed-effect terms including treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use. [b]Analysis based on MMRM with change from baseline in log-transformed NT-proBNP/troponin I as the outcome, log-transformed baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use. [c]Difference and 95% CI are derived from multiple imputation procedure by combining estimates per Rubin's rules based on 100 datasets where missing NYHA class values due to death, heart transplantation, and left ventricular assist device placement are imputed as class IV, and the other missing NYHA class values are imputed using an MCMC procedure including select baseline variables and postbaseline NYHA class assessments.

Figure 3. Consistent Benefit of Vutrisiran Observed in Both Baseline KCCQ-OS Subgroups for Change from Baseline in 6-MWT and KCCQ-OS at Month 30[a]



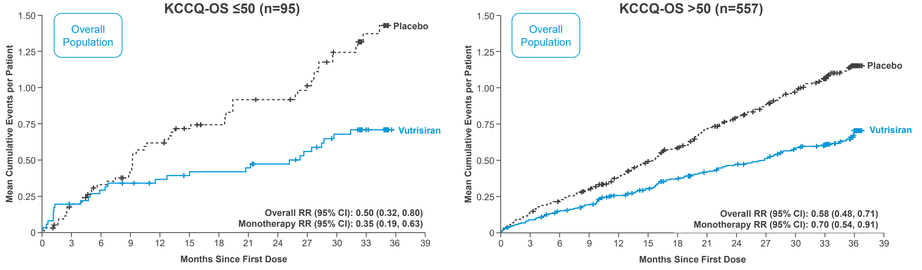
[a]Analysis based on MMRM with baseline 6-MWT/KCCQ-OS as continuous covariates, and fixed-effect terms including treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use.

Figure 4. Consistent Benefit of Vutrisiran Observed for Change from Baseline in Cardiac Biomarkers at Month 30 in Both Baseline KCCQ-OS Subgroups[a]



[a]Analysis based on MMRM with change from baseline in log-transformed NT-proBNP/troponin I as the outcome, log-transformed baseline as a covariate, and fixed-effect terms including treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use.

Figure 5. Vutrisiran Treatment Was Associated with Lower Rates of GI AEs Through 33–36 Months in Both Baseline KCCQ-OS Subgroups



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References: 1. Maurer et al. *Circ Heart Fail.* 2019;12:e006075; 2. Ruberg et al. *JAMA.* 2024;331:778–91; 3. Nativi-Nicolau et al. *Heart Fail Rev.* 2022;27:785–93; 4. Garcia-Pavia et al. *Eur J Heart Fail.* 2021;23:512–26; 5. Brito et al. *Glob Heart.* 2023;18:59; 6. Urey et al. HFSA. 2025; Abstract 2662; 7. Wixner et al. *Orphanet J Rare Dis.* 2014;9:61; 8. Obici et al. *Clin Auton Res.* 2019;29(Suppl 1):55–63; 9. Fontana et al. *N Engl J Med.* 2025;392:33–44; 10. Spertus et al. *J Am Coll Cardiol.* 2020;76:2379–90.

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; Diff., difference; GI, gastrointestinal; HCP, healthcare professional; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS, least squares; MCMC, Markov chain Monte Carlo; MMRM, mixed model repeated measures; n_P, placebo n; NT-proBNP, N-terminal pro-B-type natriuretic peptide; n_V, vutrisiran n; NYHA, New York Heart Association; OLE, open-label extension; QOL, quality of life; RNAi, RNA interference; RR, relative rate ratio; SC, subcutaneous.

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.