Vutrisiran Reduces Days Lost to Death and/or Hospitalization Versus Placebo in Patients with Transthyretin Amyloidosis with Cardiomyopathy in the HELIOS-B Trial

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HELIOS·B

Conclusions

- In this *post hoc* analysis from HELIOS-B, vutrisiran reduced the number of days lost to death and/or hospitalization (all-cause or CV-related) versus placebo.
- Patients receiving vutrisiran were more likely (64% increased odds) to be completely free from days lost to death or hospitalization compared with patients receiving placebo.
- When days lost to impaired well-being (according to KCCQ and NYHA class) were additionally accounted for, the beneficial effects of vutrisiran were even greater.

Key takeaway

In patients with ATTR-CM, vutrisiran decreased the number of days lost to death and/or hospitalization by more than 1 month versus placebo over a 3-year period.

Introduction

Transthyretin Amyloidosis with Cardiomyopathy

- ATTR-CM is a progressive, debilitating, and ultimately fatal disease caused by the accumulation of misfolded TTR protein (variant or wild-type) as amyloid fibrils in the heart.[1–3]

HELIOS-B Study

- Vutrisiran, an RNAi therapeutic that reduces the production of variant and wild-type TTR, was evaluated in patients with ATTR-CM in the Phase 3 HELIOS-B study (NCT04153149).
- In HELIOS-B, vutrisiran significantly reduced the risk of the composite primary endpoint of all-cause mortality and recurrent CV events versus placebo and met all secondary endpoints in the overall population and the monotherapy population (those not receiving tafamidis, another approved therapy for ATTR-CM, at baseline).[4]

Objective

- To further characterize the benefits of vutrisiran on all-cause mortality and recurrent CV events, in a way that reflects the practical impacts of how early or late deaths occurred during follow-up and/or how long CV events lasted, this *post hoc* analysis from HELIOS-B assessed the effect of vutrisiran versus placebo on days lost to death and/or hospitalization in the overall and monotherapy populations.

Methods

- Patients with ATTR-CM were randomized 1:1 in the Phase 3 HELIOS-B study to receive sc vutrisiran 25 mg or placebo every 3 months for up to 36 months in the DB period.[4]
- Outcomes reflecting days lost to death, hospitalization, and/or impaired well-being were assessed based on mortality and hospitalizations continuously ascertained over the DB period (**Table 1**).

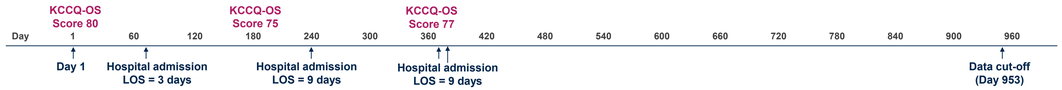
Table 1. Outcomes and Terminology Used in the Analysis

Outcomes	
Days of PFU lost to death and/or hospitalization (DLDH).	
Days of PFU lost to death and/or CV hospitalization (DLDCVH).	
Days of PFU lost to death, hospitalization, or impaired well-being (based on KCCQ-OS or KCCQ-TSS and NYHA FC).	
Days of PFU lost to death, CV hospitalizations, or impaired well-being (based on KCCQ-OS or KCCQ-TSS and NYHA FC).	
Term	**Definition**
PFU	For patients who died during the DB period: Time from date of first study treatment dose to primary analysis cut-off date. For all other patients: Time from date of first study treatment dose to the earliest of primary analysis cut-off date, date of discontinuation from trial, or 83 days after last treatment exposure.
Days in CV hospitalization	Days of PFU on which a patient is hospitalized for CV reasons (inclusive of date of admission and exclusive of discharge date for each CV hospitalization).
Days hospitalized	Days of PFU on which a patient is hospitalized for any cause (inclusive of date of admission and exclusive of discharge date for each hospitalization).
Days dead	Days of PFU on which a patient was not alive (exclusive of date of death).
DLDH	Days of PFU that a patient lost to death or hospitalization (days hospitalized + days dead).
DLDCVH	Days of PFU that a patient lost to death or CV hospitalization (days in CV hospitalization + days dead).
Days of impaired well-being	Days of impaired well-being were calculated as the difference between 1) the total number of days in PFU that were not DLDH or DLDCVH (depending on the outcome of interest) and 2) the sum of these days after they were individually weighted (either through KCCQ-OS or KCCQ-TSS/NYHA FC) by a well-being factor ranging from 0 (worst) to 1 (best). For weighting through KCCQ-OS, the weight used for a given patient on a given day was the patient's most recent KCCQ-OS score divided by 100. For weighting through KCCQ-TSS/NYHA FC, the weight used for a given patient on a given day was the median KCCQ-TSS score (across all patients and all study visits in the HELIOS-B DB period) associated with the patient's most recently measured NYHA FC, divided by 100.

Statistical Analyses

- Outcomes were analyzed as a proportion out of the PFU.
  - Outcomes with ≥10 patients having a value of 0 days lost were fitted to a zero-inflated beta model.
  - Otherwise, the outcome was fitted to a beta model with patients having 0 days lost adjusted to have a value of 1 / PFU.
- Each of the location and shape parameters (and mixture parameter when fitted to the zero-inflated beta model) included treatment, log-transformed PFU, log-transformed NT-proBNP, age group, baseline tafamidis use, and treatment by baseline tafamidis use interaction as covariates.
  - In analyzing the vutrisiran monotherapy population, the models excluded the baseline tafamidis terms.
  - Results are derived from a model-based estimation for a patient with 3 years of PFU.

Figure 1: Example Calculation of Days Lost to Death, Hospitalization, and Days of Impaired Well-Being from a Hypothetical Patient



1–79	79 days × $\left(1-\frac{80}{100}\right)$ = 15.8 days lost to impaired well-being	180–239	60 days × $\left(1-\frac{75}{100}\right)$ = 15 days lost to impaired well-being	360–370	11 days × $\left(1-\frac{77}{100}\right)$ = 2.53 days lost to impaired well-being
80–82	Hospitalized (3 days lost)	240–248	Hospitalized (9 days lost)	371–379	Hospitalized (9 days lost)
83–179	97 days × $\left(1-\frac{80}{100}\right)$ = 19.4 days lost to impaired well-being	249–359	111 days × $\left(1-\frac{75}{100}\right)$ = 27.75 days lost to impaired well-being	380–953	Dead (574 days lost)

Total Days Lost	
Lost to death	**574**
Lost to hospitalisation	**21**
Lost to impaired well-being (KCCQ-OS adjustment)	**80.48**

Results

- The analysis included data from 654 patients (vutrisiran, n=326; placebo, n=328), with 395 patients in the monotherapy subgroup (vutrisiran, n=196; placebo, n=199).
- Baseline demographic and clinical characteristics were generally well balanced between the vutrisiran and placebo groups,[4] except that NT-proBNP and troponin I levels were higher (indicating greater disease severity) in the vutrisiran group than in the placebo group within the monotherapy population.

Figure 2. Vutrisiran Reduced the Mean Days Lost to Death and/or Hospitalization and Mean Days Lost to Death and/or CV Hospitalization Compared with Placebo over a 3-Year Period[a]

Outcome	Population	Mean Days Lost (SE)		Mean (95% CI) Difference in Days Lost	Proportion of Patients with 0 Days Lost (SE)		OR (95% CI) of 0 Days Lost[b]
		Vutrisiran	Placebo	Placebo–Vutrisiran	Vutrisiran	Placebo	(Vutrisiran/Placebo)
DLDH	Overall	65.1 (9.1)	97.3 (10.7)	32.2 (5.3, 59.3)	51.4 (3.0)	39.2 (2.9)	1.64 (1.19, 2.26)
	Monotherapy	72.8 (12.6)	109.6 (14.7)	36.9 (2.1, 71.8)	55.0 (3.9)	35.4 (3.6)	2.23 (1.46, 3.42)
DLDH adjusted for KCCQ-OS	Overall	351.5 (13.7)	414.3 (14.0)	62.8 (25.6, 99.8)	—	—	
	Monotherapy	380.1 (18.7)	452.5 (19.0)	72.3 (22.2, 122.4)	—	—	
DLDH adjusted for KCCQ-TSS /NYHA FC	Overall	279.3 (9.3)	328.8 (11.0)	49.5 (22.5, 76.6)	—	—	
	Monotherapy	297.1 (12.7)	349.3 (14.1)	52.3 (17.3, 87.2)	—	—	
DLDCVH	Overall	55.3 (9.3)	87.3 (11.2)	32.0 (4.6, 59.5)	68.2 (2.8)	56.7 (3.0)	1.64 (1.18, 2.29)
	Monotherapy	61.0 (12.9)	101.0 (15.8)	40.0 (3.2, 76.8)	71.4 (3.6)	52.1 (3.9)	2.30 (1.48, 3.59)
DLDCVH adjusted for KCCQ-OS	Overall	348.8 (13.6)	413.2 (14.0)	64.4 (27.4, 101.5)	—	—	
	Monotherapy	378.3 (18.7)	450.8 (19.0)	72.5 (22.4, 122.7)	—	—	
DLDCVH adjusted for KCCQ-TSS /NYHA FC	Overall	274.5 (9.1)	327.1 (10.8)	52.6 (26.1, 79.0)	—	—	
	Monotherapy	292.7 (12.5)	348.9 (14.1)	56.2 (21.5, 91.1)	—	—	

[a]Data derived from a model-based estimation for a patient with 3 years of PFU. [b]When adjusting for impaired well-being, no patients had 0 days lost. Therefore, there is no OR listed for outcomes that involve adjustment for impaired well-being.

- In the overall population, vutrisiran treatment resulted in a mean of 32.2 (95% CI 5.3, 59.3) fewer DLDH and 32.0 (95% CI 4.6, 59.5) fewer DLDCVH over 3 years versus placebo (**Figure 2**).
  - Patients treated with vutrisiran had 64% greater odds of being completely free from DLDH or DLDCVH during HELIOS-B follow-up when compared with patients receiving placebo.
- In analyses that assessed days of impaired well-being (for days alive and not hospitalized) as a contributor to days lost, a larger effect of vutrisiran in preventing days lost was observed.
  - In the overall population, the treatment effect of vutrisiran translated to a mean of 62.8 (95% CI 25.6, 99.8) fewer DLDH versus placebo over a 3-year period when weighted by KCCQ-OS, and a mean of 49.5 (95% CI 22.5, 76.6) fewer DLDH versus placebo when weighted by KCCQ-TSS and NYHA FC collectively (**Figure 2**).
  - Similarly, in the overall population, the treatment effect of vutrisiran translated to a mean of 64.4 (95% CI 27.4, 101.5) fewer DLDCVH versus placebo over a 3-year period when weighted by KCCQ-OS, and a mean of 52.6 (95% CI 26.1, 79.0) fewer DLDCVH versus placebo when weighted by KCCQ-TSS and NYHA FC collectively (**Figure 2**).
- Results observed in the monotherapy population were generally similar to those in the overall population (**Figure 2**).

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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. Adams et al. *Nat Rev Neurol* 2019;15:387–404. 4. Fontana et al. *N Engl J Med* 2025;392:33–44.

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CI, confidence interval; CV, cardiovascular; DB, double-blind; DLDCVH, days that a patient is dead or hospitalized with a CV event; DLDH, days that a patient is dead or hospitalized; HCP, healthcare provider; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire; KCCQ-OS, KCCQ-Overall Summary Score; KCCQ-TSS, KCCQ-Total Symptom Score; LOS, length of stay; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA FC, New York Heart Association functional class; OR, odds ratio; PFU, potential follow-up; RNAi, RNA interference; sc, subcutaneous; SE, standard error; TTR, transthyretin.