Vutrisiran: Concomitant Use with Tafamidis

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SUMMARY

- HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Prohibited medications during the study included tafamidis.[1]
- HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vutrisiran in patients with the cardiomyopathy of ATTR, including both hATTR and wtATTR.[2]
  - Patients who received tafamidis at baseline were eligible to be included in the study. Concomitant tafamidis use at baseline was 40% and 39% in the vutrisiran and placebo arms, respectively.[2]
  - Efficacy endpoints were assessed in both the overall population and monotherapy population, defined as patients who did not receive tafamidis at baseline. During the double-blind period, tafamidis drop-in on the monotherapy population was 22% and 21% for the vutrisiran and placebo arms, respectively.[2]
    - Study participants were not randomized by baseline tafamidis use; therefore, a randomized comparison of vutrisiran monotherapy versus tafamidis monotherapy cannot be made.[2]
  - In a prespecified analysis of patients who received concomitant tafamidis (tafamidis subgroup), treatment with vutrisiran resulted in a HR of 0.79 (95% CI 0.51, 1.21) in the primary composite endpoint of all-cause mortality and recurrent CV events during the double-blind exposure period and a HR of 0.59 (95% CI 0.32, 1.08) for the secondary endpoint of all-cause mortality through 42 months.[2]
  - In the overall population, the proportion of patients with at least one AE was similar between treatment arms, and the majority of AEs were mild or moderate. Cardiac AEs occurred at similar or lower rates with vutrisiran than placebo.[3]

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HELIOS-A

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study

(NCT01960348) as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in the mNIS+7 at 9 months.[1]

Select Exclusion Criteria

Patients were excluded from the study if the following criteria applied[4]:

- Currently taking tafamidis; if previously on tafamidis, the patient must have completed a 14-day wash-out prior to dosing

HELIOS-B

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months.[2]

Select Inclusion Criteria

Patients were eligible to be included in the study if all inclusion criteria applied, including patients meeting one of the following criteria[5]:

- Tafamidis-naïve and not actively planning to commence treatment with tafamidis during the first 12 months following randomization (in addition to patients who have never taken tafamidis, those who have previously been on tafamidis and have not received any tafamidis for at least 30 days before the screening visit will be considered tafamidis-naïve for purposes of this study)
- On tafamidis (must be on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use)

Patients who were on tafamidis at baseline (per the inclusion criteria listed above) were permitted, if medically appropriate in the opinion of the Investigator, to remain on tafamidis for the duration of the study.[5]

Select Exclusion Criteria

Patients were excluded from the study if the following criteria applied[5]:

- Tafamidis-naïve patients for whom the Investigator actively plans or anticipates commencing treatment with tafamidis either during the Screening Period or the first 12 months following randomization, taking into consideration clinical status, patient preference, and/or commercial availability of tafamidis

Randomization was stratified according to tafamidis use at baseline (yes vs. no). The primary endpoint was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind exposure period in the overall population and in the vutrisiran monotherapy population (patients not receiving tafamidis at baseline).[2]

After study enrollment, patients that were not receiving tafamidis at baseline could initiate tafamidis (tafamidis drop-in) if considered to be necessary by the Investigator, per the study protocol.[5]

Concomitant Use with Tafamidis

At baseline, 130 patients of 326 patients (40%) in the vutrisiran arm and 129 of 328 patients (39%) in the placebo arm were on tafamidis.[2]

The monotherapy population comprised 196 patients (60%) in the vutrisiran arm and 199 patients (60%) in the placebo arm who were not on tafamidis at baseline.[2] Tafamidis drop-in on the monotherapy population during the double-blind period is shown in **Table 1**.[6]

Table 1. Concomitant Tafamidis Use During the Double-Blind Period.[6,a]

Tafamidis, n (%)	Vutrisiran (N=326)	Placebo (N=328)[b]
Use at baseline	130 (40)	129 (39)
Drop-in on monotherapy population	44/196 (22)	41/199 (21)
Time from study start to initial drop-in dose, months, median (range)	17.7 (6.6-39.1)	17.0 (1.5-33.8)

[a]Double-blind period consisted of a variable follow-up of 33 to 36 months.
[b]Of the 329 patients randomized to receive placebo, 1 patient withdrew from the study and was not dosed.

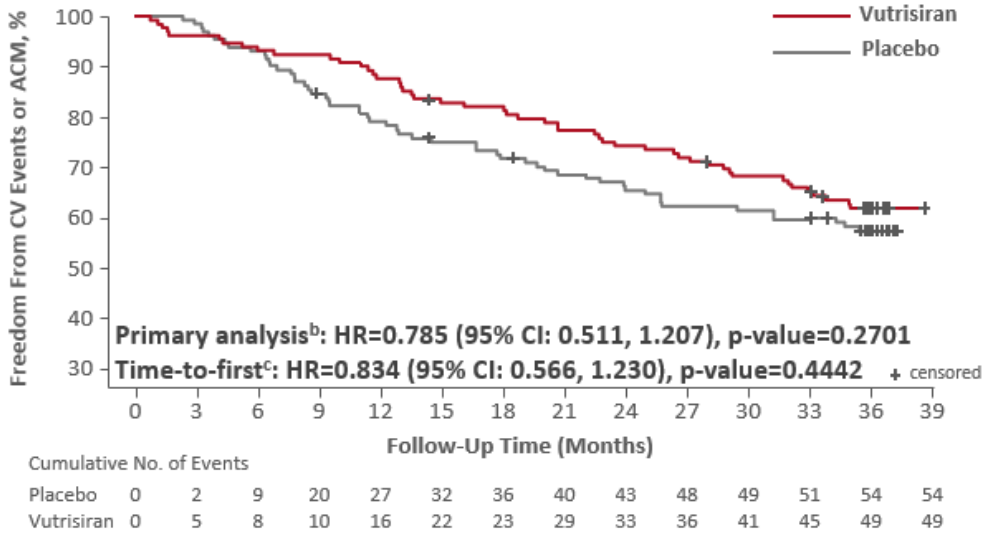
Efficacy Results

In the overall population, treatment with vutrisiran reduced the risk of the primary composite endpoint of all-cause mortality and recurrent CV events when compared to placebo (HR of 0.72; 95% CI 0.56, 0.93; p=0.01). Treatment with vutrisiran also reduced the risk of the secondary endpoint of all-cause mortality through 42 months when compared to placebo (HR of 0.65; 95% CI 0.46, 0.90; p=0.01).[2]

In a prespecified analysis of the baseline tafamidis subgroup, treatment with vutrisiran compared to placebo resulted in a HR of 0.79 (95% CI 0.51, 1.21) in all-cause mortality and recurrent CV events and a HR of 0.59 (95% CI 0.32, 1.08) in all-cause mortality through 42 months (**Figures 1 and 2,** respectively).[2,3]

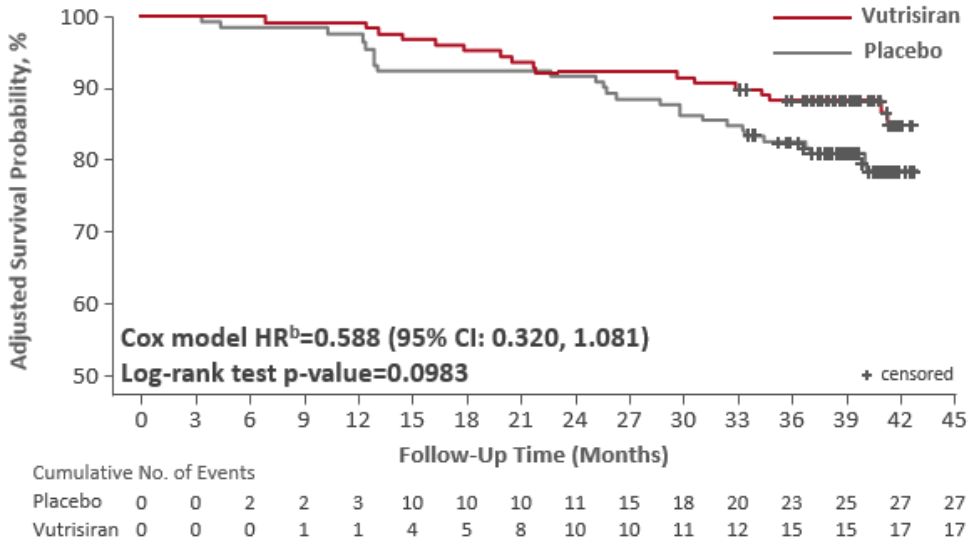
Study participants were not randomized by baseline tafamidis use; therefore, a randomized comparison of vutrisiran monotherapy versus tafamidis monotherapy cannot be made.[2]

Figure 1. Time to First CV Event or All-Cause Mortality in the Tafamidis Subgroup.[3,a]



Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; IPTW = inverse probability of treatment weighting; LWYY = Lin, Wei, Yang, and Ying; PH = proportional hazard.
Footnotes: All-cause mortality includes heart transplantation and left ventricular assist device placement.
[a]Based on IPTW-adjusted Kaplan-Meier curves.
[b]Primary analysis based on modified Andersen-Gill model, also known as LWYY.
[c]Time to first event HR derived from Cox PH model, p-value derived from Log-rank test.
From Fontana et al.[3]

Figure 2. Time to All-Cause Mortality in the Tafamidis Subgroup.[3,a]



Abbreviations: CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; LWYY = Lin, Wei, Yang, and Ying; OLE = open-label extension; PH = proportional hazard.
[a]Based on IPTW-adjusted Kaplan-Meier curves.
[b]Time to all-cause mortality included data from the double-blind period and up to 6 months in the OLE, deaths after end of the study were included in the analysis, HR derived from Cox PH model.
From Fontana et al.[3]

Safety Results

In the overall population, the proportion of patients with at least one AE was similar between treatment arms, and the majority of AEs were mild or moderate. Cardiac AEs occurred at similar or lower rates with vutrisiran than placebo. A summary of the safety results during the double-blind period are presented in **Table 2.**[3,6]

Table 2. HELIOS-B Safety Summary.[6]

Event, n (%)	Overall Population	
	Vutrisiran (N=326)	Placebo (N=328)[a]
At least 1 AE	322 (99)	323 (98)
Any SAE[b]	201 (62)	220 (67)
Any severe AE[c]	158 (48)	194 (59)
Cardiac AEs	227 (70)	242 (74)
Cardiac SAEs	116 (36)	124 (38)
Any AE leading to treatment discontinuation	10 (3)	13 (4)
Any AE leading to death[d]	49 (15)	63 (19)

Abbreviations: AE = adverse event; SAE = serious adverse event.
[a]Of the 329 patients randomized to receive placebo, 1 patient withdrew from the study and was not dosed.
[b]Serious AEs were defined as AEs that resulted in death, were life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators.
[c]Severe AEs were defined as AEs for which more than minimal, local, or noninvasive intervention was received; which had a severe effect on limiting self-care activities of daily living; or which had the potential for life-threatening consequences or death.
[d]Deaths that occurred after the end of study visit or after the data cut-off date were not included.

There were no clinically relevant changes in laboratory measures (including hematologic measures, blood chemistry measures, liver function tests, and renal function tests), vital signs, or electrocardiograms in either treatment arm.[2]

ABBREVIATIONS

AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; HR = hazard ratio; IPTW = inverse probability of treatment weighting; IV = intravenous; LWYY = Lin, Wei, Yang, and Ying; mNIS+7 = modified Neuropathy Impairment Score +7; NYHA = New York Heart Association; OLE = open-label extension; PH = proportional hazard; SAE = serious adverse event; wtATTR = wild-type transthyretin amyloidosis.

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