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]
    - Select exploratory endpoints assessed in the tafamidis subgroup included change from baseline in NT-proBNP and troponin I at 30 months.[3]
  - 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.[4]

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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 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[5]:

- 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[6]:

- 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.[6]

Select Exclusion Criteria

Patients were excluded from the study if the following criteria applied[6]:

- 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 treatment period in the overall population and in the 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.[6]

Concomitant Medications

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**.[7]

Table 1. Concomitant Tafamidis Use During the Double-Blind Period.[7,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.

In the overall population, baseline use of SGLT2 inhibitors was 3% in both treatment arms. Baseline use of diuretics was 80% and 79% in the vutrisiran and placebo arms, respectively.[7]

Efficacy Results

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

All-Cause Mortality and Recurrent CV Events up to 36 Months

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).[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 (**Figure 1**).[2,4]

Figure 1. Time to First CV Event or All-Cause Mortality in the Tafamidis Subgroup.[4,a]
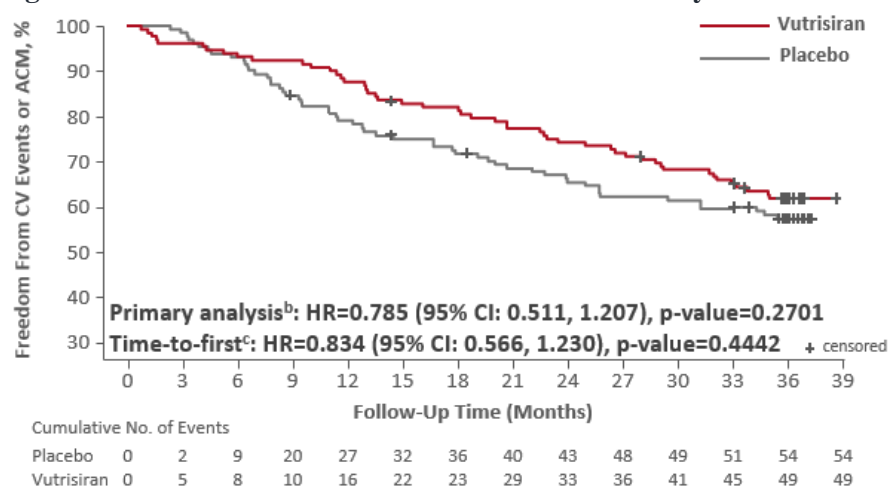
Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; IPTW = inverse probability of treatment weighting; LWYY = Lin, Wei, Yang, and Ying; PH = proportional hazard.
Footnotes: All-cause mortality includes heart transplantation and left ventricular assist device placement.
[a]Based on IPTW-adjusted Kaplan-Meier curves.
[b]Primary analysis based on modified Andersen-Gill model, also known as LWYY.
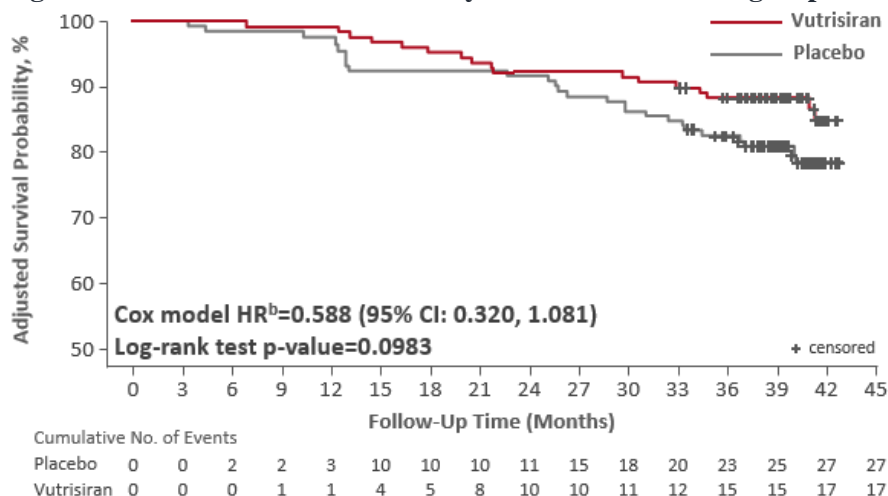[c]Time to first event HR derived from Cox PH model, p-value derived from Log-rank test.
From Fontana et al.[4]

All-Cause Mortality Through 42 Months

In the overall population, treatment with vutrisiran 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 the tafamidis subgroup, treatment with vutrisiran compared to placebo resulted in a HR of 0.59 (95% CI 0.32, 1.08) in all-cause mortality through 42 months (**Figure 2**).[2,4]

Figure 2. Time to All-Cause Mortality in the Tafamidis Subgroup.[4,a]

Cox model HR[b]=0.588 (95% CI: 0.320, 1.081)
Log-rank test p-value=0.0983   + censored

Cumulative No. of Events	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Placebo	0	0	2	2	3	10	10	10	11	15	18	20	23	25	27	27
Vutrisiran	0	0	0	1	1	4	5	8	10	10	11	12	15	15	17	17

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.[4]

Biomarkers: NT-proBNP and Troponin I at 30 Months

Select exploratory endpoints assessed in the tafamidis subgroup included the adjusted geometric mean fold-change from baseline in NT-proBNP and troponin I at 30 months.[3]

In the overall population, treatment with vutrisiran when compared with placebo resulted in an adjusted geometric mean-fold change ratio of 0.68 (95% CI 0.61, 0.76) for NT-proBNP from baseline to 30 months. In the tafamidis subgroup, treatment with vutrisiran compared to placebo resulted in an adjusted geometric mean fold-change ratio of 0.82 (95% CI 0.71, 0.94) for NT-proBNP from baseline to 30 months (**Figure 3**).[3]

Figure 3. NT-proBNP at 30 Months in the Tafamidis Subgroup.[3]
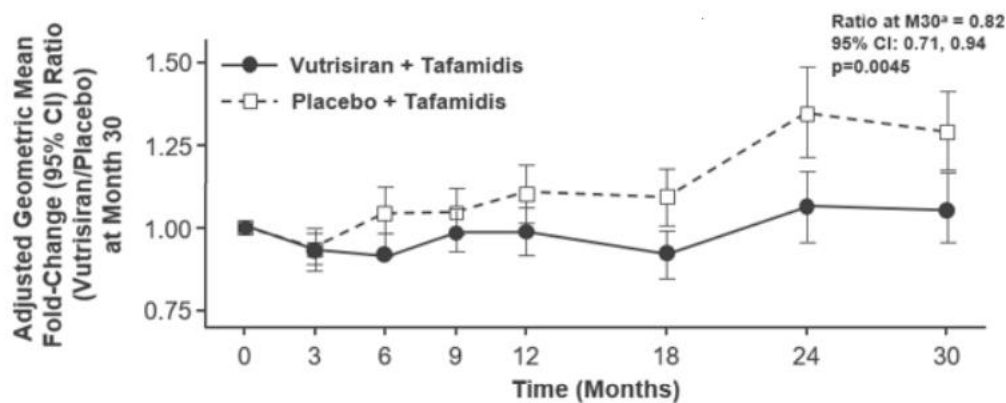

Abbreviations: ATTR = transthyretin amyloidosis; BL = baseline; CI = confidence interval; LS = least squares; MMRM = mixed models for repeated measures; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.
[a]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group.
From Maurer et al.[3]

In the tafamidis subgroup, the median change from baseline in NT-proBNP at 30 months was 15 ng/L in the vutrisiran arm and 278 ng/L in the placebo arm, as shown in **Figure 4**.[3]

Figure 4. Median Change from Baseline in NT-proBNP at 30 Months.[3]
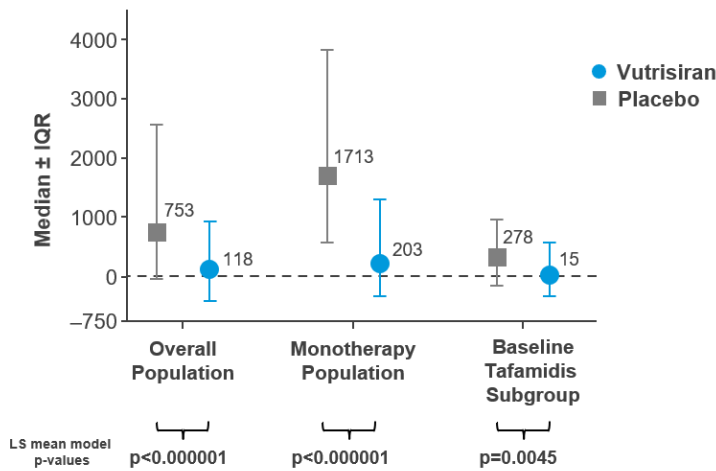
Abbreviations: IQR = interquartile range; LS = least squares.
From Maurer et al.[3]

In the overall population, treatment with vutrisiran compared with placebo resulted in an adjusted geometric mean fold-change ratio of 0.68 (95% CI 0.62, 0.75) for troponin I from baseline at 30 months. In the tafamidis subgroup, treatment with vutrisiran compared with placebo resulted in an adjusted geometric mean fold-change ratio of 0.90 (95% CI 0.80, 1.01) in troponin I from baseline at 30 months (**Figure 5**).[3]

Figure 5. Troponin I at 30 Months in the Tafamidis Subgroup.[3]
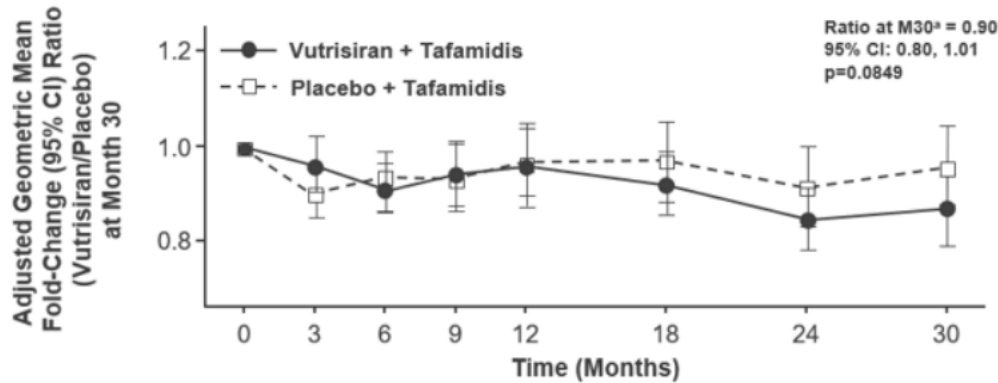

Abbreviations: ATTR = transthyretin amyloidosis; BL = baseline; CI = confidence interval; LS = least squares; MMRM = mixed models for repeated measures.
[a]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group.
From Maurer et al.[3]

In the tafamidis subgroup, the median change from baseline in troponin I at 30 months was -8.4 ng/L in the vutrisiran arm and -3.2 ng/L in the placebo arm, as shown in **Figure 6**.[3]

Figure 6. Median Change from Baseline in Troponin I at 30 Months.[3]
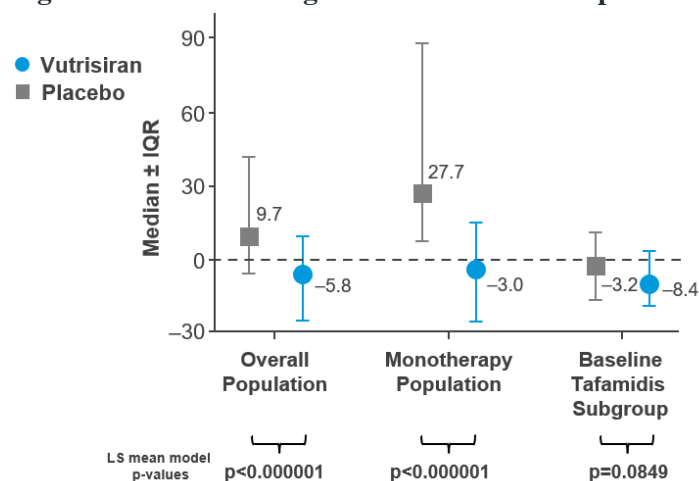
Abbreviations: IQR = interquartile range; LS = least squares.
From Maurer et al.[3]

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.**[4,7]

Table 2. HELIOS-B Safety Summary.[7]

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; BL = baseline; 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; LS = least squares; LWYY = Lin, Wei, Yang, and Ying; mNIS+7 = modified Neuropathy Impairment Score +7; MMRM = mixed models for repeated measures; NT-proBNP = N-terminal prohormone of B-type natriuretic

peptide; OLE = open-label extension; PH = proportional hazard; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2; wtATTR = wild-type transthyretin amyloidosis.

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