Vutrisiran: Use in Patients with Wild-type ATTR

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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. Patients with wtATTR were excluded from the study.[1]
- HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR.[2]
  - Among the subgroup of patients with wtATTR (n=578), treatment with vutrisiran resulted in a HR of 0.67 (95% CI 0.51, 0.90) in the primary composite outcome of all-cause mortality and recurrent CV events and a HR of 0.61 (95% CI 0.42, 0.88) in the secondary endpoint of all-cause mortality through 42 months in the overall population.[2]
  - In the overall population of both hATTR and wtATTR patients, the majority of AEs observed were mild or moderate. No AEs were seen ≥3% more frequently with vutrisiran compared with 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 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 mNIS+7 at 9 months.[1]

Select Exclusion Criteria

Patients with wtATTR, other (non-hATTR) forms of amyloidosis, or leptomeningeal amyloidosis were excluded from the study.[4]

HELIOS-B

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed 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. Randomization was stratified according to baseline tafamidis use (yes vs. no), ATTR disease type (hATTR vs. wtATTR), and NYHA class and age at baseline (NYHA class I or II and age < 75 years vs. all others).[2]

At baseline, patients were either receiving tafamidis for ATTR-CM or were not receiving tafamidis, with no active plan to start tafamidis during the first 12 months after randomization. Patients who were not receiving tafamidis at baseline, defined as the monotherapy population, could initiate tafamidis after enrollment if it was considered necessary by the investigator.[2]

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]

Patient Demographics & Baseline Characteristics

Of the 654 patients enrolled in the study, 578 patients had wtATTR (**Table 1**).[2]

Table 1. Select Baseline Characteristics in HELIOS-B.[2]

Baseline Characteristic	Overall Population		Monotherapy Population	
	Vutrisiran (N=326)	Placebo (N=328)[a]	Vutrisiran (N=196)	Placebo (N=199)
Median age at randomization, year (range)	77.0 (45-85)	76.0 (46-85)	77.5 (46-85)	76.0 (53-85)
wtATTR, n (%)	289 (89)	289 (88)	173 (88)	174 (87)
NYHA class, n (%)				
I	49 (15)	35 (11)	15 (8)	12 (6)
II	250 (77)	258 (79)	172 (88)	169 (85)
III	27 (8)	35 (11)	9 (5)	18 (9)
NAC stage, n (%)				
1	208 (64)	229 (70)	113 (58)	138 (69)
2	100 (31)	87 (27)	68 (35)	55 (28)
3	18 (6)	12 (4)	15 (8)	6 (3)

Abbreviations: NAC = National Amyloidosis Centre; NYHA = New York Heart Association; wtATTR = wild-type transthyretin amyloidosis.
[a]329 patients were randomized to receive placebo. One patient withdrew from the study and was not dosed.

Efficacy Results

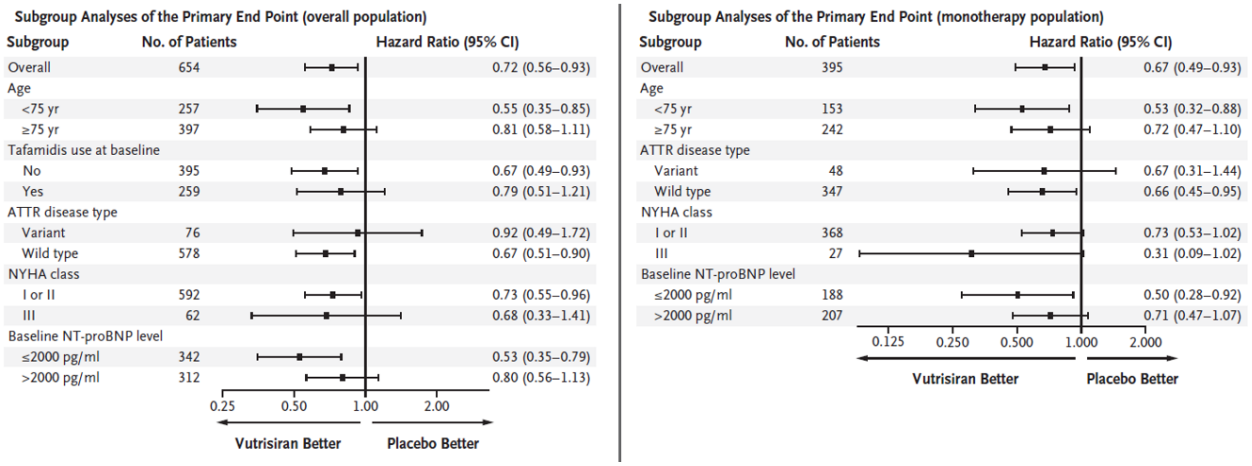
Efficacy endpoints were assessed separately in both the overall population and in the monotherapy population, resulting in 10 prespecified endpoints for analysis. A subgroup analysis of patients with wtATTR (n=578) was conducted in both the overall population and monotherapy population for the primary composite endpoint of all-cause mortality and recurrent CV events and the secondary endpoint of all-cause mortality through 42 months.[2]

Primary Composite Endpoint

Among the overall and monotherapy populations (including both hATTR and wtATTR patients), treatment with vutrisiran reduced the risk of all-cause mortality and recurrent CV events compared to placebo (HR in the overall population 0.72; 95% CI 0.56, 0.93; p=0.01 and HR in the monotherapy population 0.67; 95% CI 0.49, 0.93; p=0.02).[2]

Among patients with wtATTR, treatment with vutrisiran resulted in a HR of 0.67 (95% CI 0.51, 0.90) and 0.66 (95% CI 0.45, 0.95) compared to placebo in all-cause mortality and recurrent CV events in the overall and monotherapy populations, respectively (**Figure 1**).[2]

Figure 1. Subgroup Analyses of the Risk of All-Cause Mortality and Recurrent CV Events.[2]



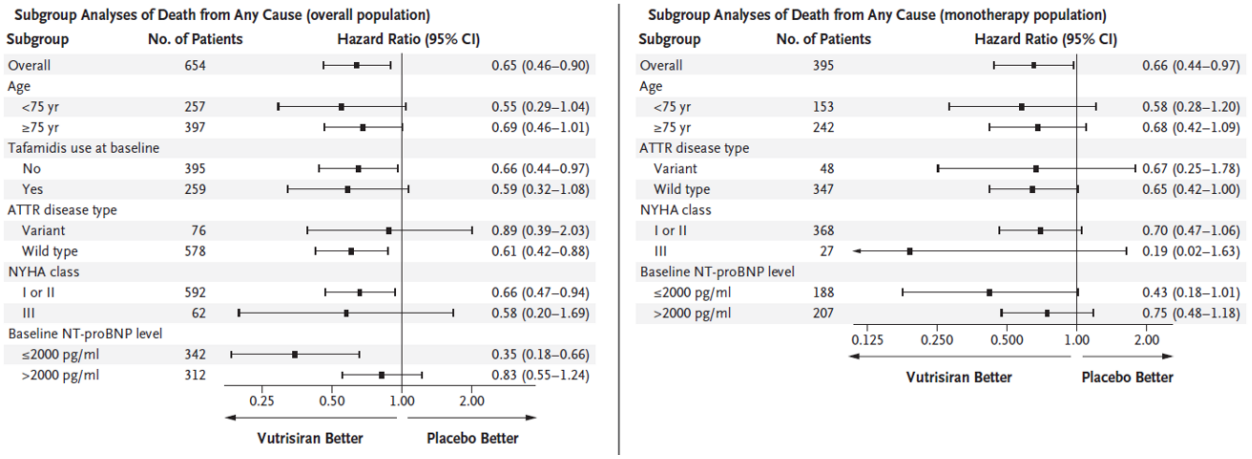
Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association.
From Fontana et al.[2]

Secondary Endpoint

Among the overall and monotherapy populations (including both hATTR and wtATTR patients), treatment with vutrisiran reduced the risk of all-cause mortality through 42 months compared to placebo (HR in the overall population 0.65; 95% CI 0.46, 0.90; p=0.01 and HR in the monotherapy population 0.66; 95% CI 0.44, 0.97; p=0.045).[2]

Among patients with wtATTR, treatment with vutrisiran resulted in a HR of 0.61 (95% CI 0.42, 0.88) and 0.65 (95% CI 0.42, 1.00) compared to placebo in all-cause mortality through 42 months in the overall and monotherapy populations, respectively (**Figure 2**).[2]

Figure 2. Subgroup Analyses of the Risk of All-Cause Mortality Through 42 Months.[2]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association.
From Fontana et al.[2]

Safety Results

In the overall population (including both hATTR and wtATTR patients), 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.**[3,5]

Table 2. HELIOS-B Safety Summary.[5]

Event, n (%)	Overall Population	
	Vutrisiran (N=326)	Placebo (N=328)[a]
At least 1 AE	322 (99)	323 (98)
Any SAE[a]	201 (62)	220 (67)
Any severe AE[b]	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[c]	49 (15)	63 (19)

Abbreviations: AE = adverse event; SAE = serious adverse event.
[a]329 patients were randomized to receive placebo. One 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; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; SAE = serious adverse event; wtATTR = wild-type transthyretin amyloidosis.

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