Vutrisiran: Changes in Serum TTR Levels

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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.[1]
  - Following 18 months of vutrisiran treatment, mean (SD) steady-state peak and trough serum TTR reductions from baseline were 87.6% (15.7%) and 81.0% (21.0%), respectively.[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]
  - In the overall population, the mean trough percent reduction from baseline in serum TTR level was 81.0% (95% CI 79.0, 83.0) at Month 30.[2]
  - The median (95% CI) percent change in TTR level was -86.8 (-88.2, -83.7) in the vutrisiran arm and -7.9 (-12.2, -3.2) in the placebo arm.[3]

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HELIOS-A

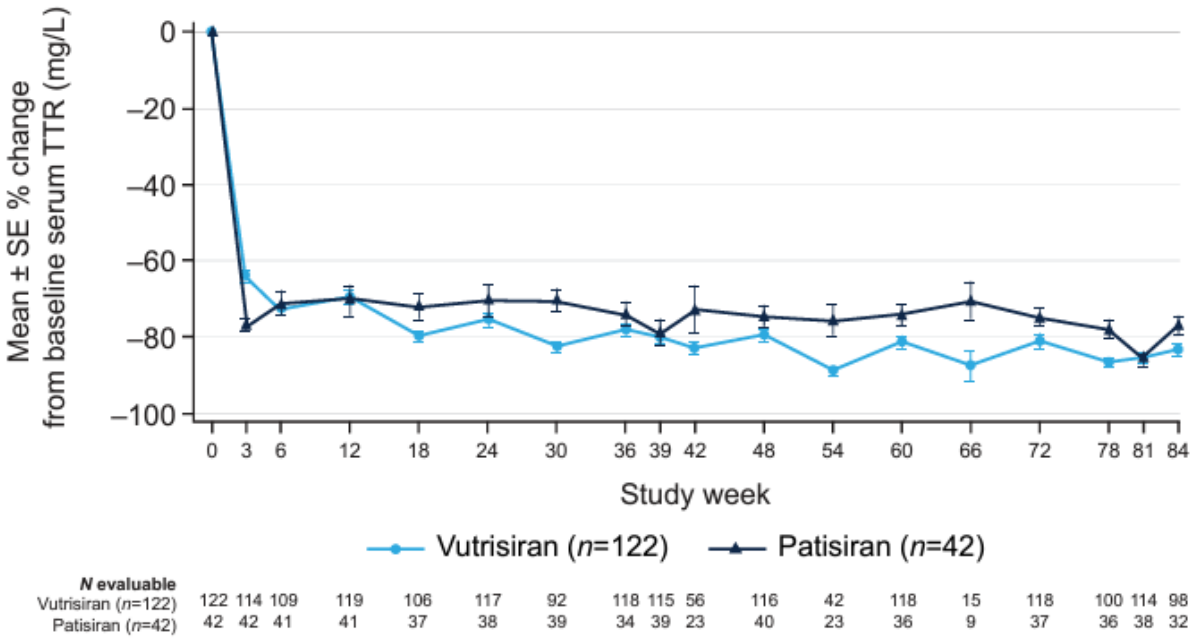
HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by 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]

Pharmacodynamics

A secondary endpoint of the HELIOS-A study was the change in serum TTR levels with vutrisiran as compared with patisiran. Following 18 months of vutrisiran treatment, mean (SD) steady-state peak and trough serum TTR reductions from baseline were 87.6% (15.7%) and 81.0% (21.0%), respectively.

Assessed by mean trough serum TTR levels over 18 months, TTR reduction with vutrisiran was statistically non-inferior to within-study patisiran in the TTR per-protocol population. The fluctuation between median steady-state peak and trough values was lower with vutrisiran (peak-trough=Δ; 91.6%–86.2%=5.4%) compared with patisiran (88.3%–78.2%=10.1%), as seen in **Figure 1** and **Table 1**. Similar serum TTR reduction was observed across all patient subgroups.[1]

Figure 1. HELIOS-A: Mean Percent Change from Baseline in Serum TTR Levels through Month 18 for Vutrisiran and Patisiran.[1]



Abbreviations: SE = standard error; TTR = transthyretin.
From Adams et al.[1]

Table 1. HELIOS-A: Trough and Peak Reductions From Baseline in Serum TTR Levels through Month 18 in the mITT Population.[4]

	Vutrisiran (n=122)	Patisiran (n=42)
Steady-state trough TTR reduction, %[a]	*n*=118	*n*=37
Mean (SD), %	81.0 (21.0)	74.7 (14.7)
Median (IQR), %	86.2 (19.0)	78.2 (14.7)
Steady-state peak TTR reduction, %[b]	*n*=15	*n*=38
Mean (SD), %	87.6 (15.7)	86.0 (10.0)
Median (IQR), %	91.6 (10.0)	88.3 (11.6)

Abbreviations: IQR = interquartile range; mITT = modified intent-to-treat; SD = standard deviation; TTR = transthyretin.
[a]Steady-state trough samples taken at week 72 (day 505) for vutrisiran and patisiran.
[b]Steady-state peak samples taken at week 66 (day 463) for vutrisiran and Month 18 (non-trough) sample for patisiran.

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. 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 period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all remaining eligible patients were allowed to receive vutrisiran in an OLE.[2]

Pharmacodynamics

A pharmacodynamic endpoint of the study was the change in serum TTR levels with vutrisiran in the overall population and in the monotherapy population.[2] Serum TTR levels were measured with the use of an ELISA. All samples for TTR were collected immediately predose (when performed on dosing days) and thus reflect trough TTR reduction at the end of the 3-month dosing interval.[5,6]

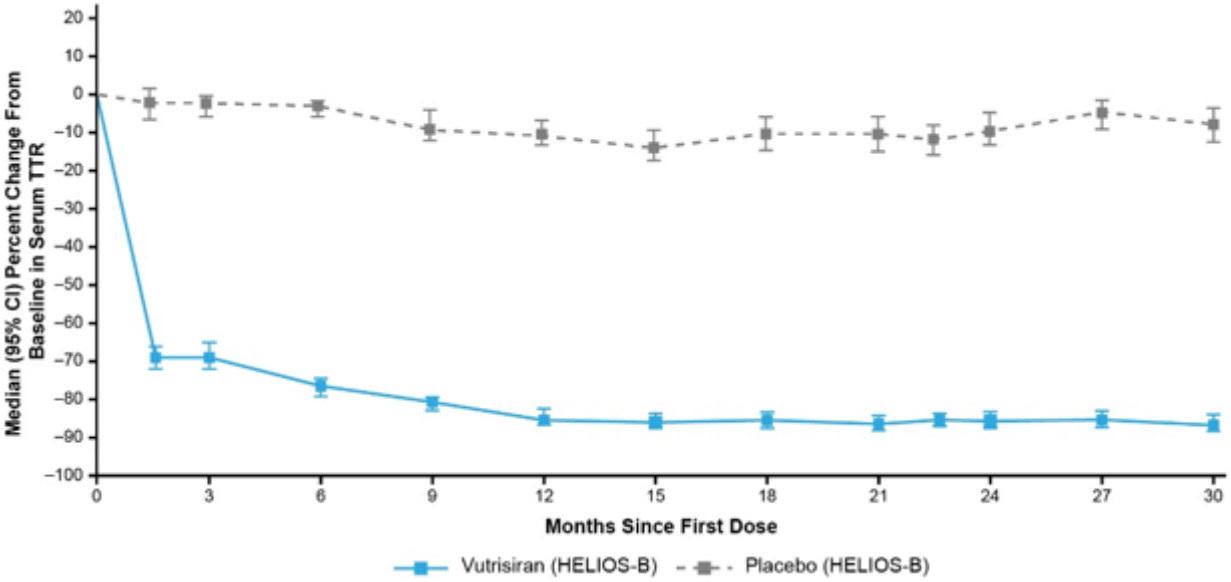
Overall Population

At baseline, the mean (±SD) serum TTR level was 281.4±91.1 mg per liter in the vutrisiran group and 279.3±89.4 mg per liter in the placebo group. At Month 30, the mean serum TTR level was 54.3±51.9 mg per liter in the vutrisiran group and 274.6±90.6 mg per liter in the placebo group.[6] The mean trough percent reduction from baseline in serum TTR level was 81.0% (95% CI 79.0, 83.0) at Month 30.[2] The median (95% CI) percent change in TTR level was -86.8 (-88.2, -83.7) in the vutrisiran arm compared to -7.9 (-12.2, -3.2) in the placebo arm (**Figure 2**).[3]

Monotherapy Population

At baseline, the mean (±SD) serum TTR level was 242.7±71.9 mg per liter in the vutrisiran group and 247.6±86.1 mg per liter in the placebo group. At Month 30, the mean serum TTR level was 49.2±45.8 mg per liter in the vutrisiran group and 240.0±86.0 mg per liter in the placebo group.[6]

Figure 2. Median Percent Change from Baseline in Serum TTR Levels through Month 30 in the Overall Population.[3]



Abbreviations: CI = confidence interval; TTR = transthyretin.
Data on File.[3]

ABBREVIATIONS

ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; ELISA = enzyme-linked immunosorbent assay; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IQR = interquartile range; IV = intravenous; mITT = modified intent-to-treat; mNIS+7 = modified neuropathy impairment score +7; OLE = open-label extension; SD = standard deviation; SE = standard error; TTR = transthyretin; wtATTR = wild-type amyloidosis.

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