Vutrisiran: Orthostatic Hypotension

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SUMMARY

- In the HELIOS-A study, PBP was measured as a component of mNIS+7 to assess the quantitative effect of vutrisiran on orthostatic hypotension.[1] Orthostatic hypotension was calculated as the mean of two supine readings of SBP taken 15 minutes apart minus the lowest SBP upon standing at 1, 3, and 5 minutes.[2]
  - 85.4% of patients in the vutrisiran arm achieved improvement or stabilization in PBP at 9 months and 80.7% at 18 months compared with 76.1% of patients in the external APOLLO placebo arm at 9 months and 68.6% at 18 months.[2]
  - The LSMD for PBP between vutrisiran and the external APOLLO placebo arm in change from baseline was –0.17 (95% CI: –0.34, –0.01) at 9 months and –0.18 (95% CI: –0.38, 0.03) at 18 months, favoring vutrisiran treatment.[1]
  - During the 18-month treatment period, AEs were reported in 119 (97.5%) patients treated with vutrisiran. The majority of the AEs were mild or moderate in severity.[3]

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HELIOS-A

Study Design

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with the 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. Secondary endpoints included Norfolk QOL-DN total score at 9 and 18 months, 10-MWT at 9 and 18 months, mNIS+7 at 18 months, mBMI at 18 months, and R-ODS score at 18 months.[3]

In the HELIOS-A study, PBP was measured as a component of mNIS+7.[1]

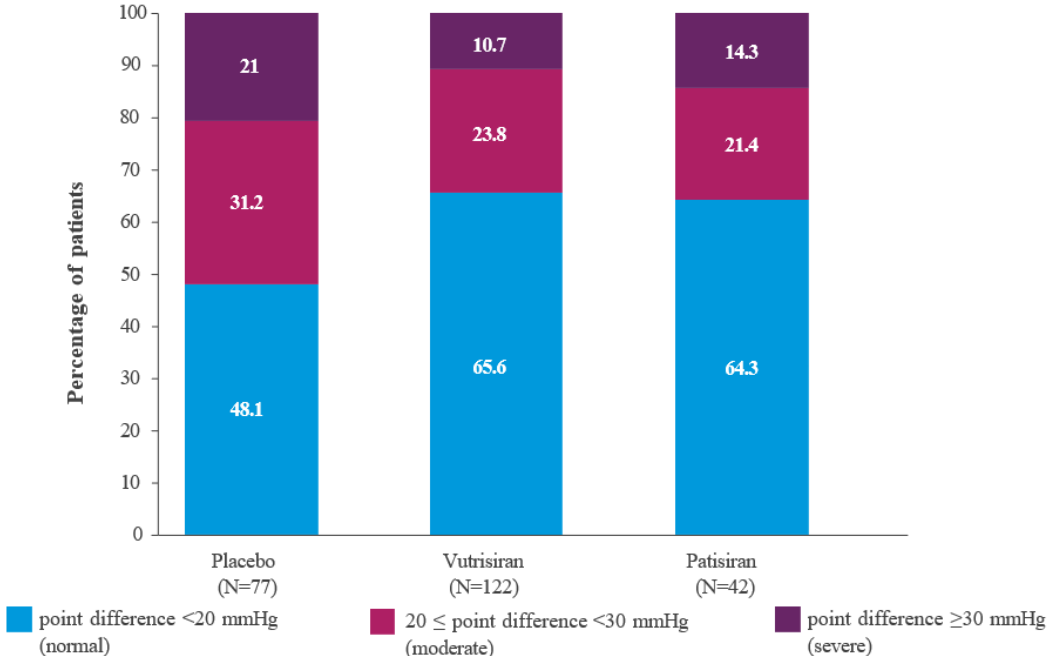
Efficacy Results

mNIS+7: PBP Component

PBP was evaluated to assess the quantitative effect of vutrisiran on orthostatic hypotension. Orthostatic hypotension was calculated as the mean of two supine readings of SBP taken 15 minutes apart minus the lowest SBP upon standing at 1, 3, and 5 minutes. A smaller reduction in SBP between supine and upright positions indicated better PBP. The severity of orthostatic hypotension was categorized as follows: normal (<20 mmHg reduction), moderate (≥20–<30 mmHg reduction), and severe (≥30 mmHg reduction).[2]

The baseline assessment of PBP category in HELIOS-A study is presented in **Figure 1**.[2]

Figure 1. Percentage of Patients in Each PBP Category at HELIOS-A Baseline.[2a]



Abbreviation(s): PBP = postural blood pressure.

[a]PBP is the categorized difference between (the average of 2 supine measurements taken 15 minutes apart) and (the lowest of upright measurements taken at 1, 3, and 5 minutes)

From Slama et al[2]

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Safety Results

During the 18-month treatment period, AEs were reported in 119 (97.5%) patients treated with vutrisiran. The majority of the AEs were mild or moderate in severity. A summary of the 18-month safety data is presented in **Table 1**.[3]

Table 1. AEs Reported in the Safety Population in HELIOS-A at 18 Months.[3]

At least one event, n (%)	APOLLO	HELIOS-A	
	Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)
AEs	75 (97.4)	119 (97.5)	41 (97.6)
Serious AEs	31 (40.3)	32 (26.2)	18 (42.9)
Severe AEs	28 (36.4)	19 (15.6)	16 (38.1)
AEs leading to treatment discontinuation	11 (14.3)	3 (2.5)	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	3 (2.5)	2 (4.8)
Deaths	6 (7.8)	2 (1.6)	3 (7.1)
AEs occurring in ≥10% in vutrisiran-treated patients			
Fall	22 (28.6)	22 (18.0)	6 (14.3)
Pain in extremity	8 (10.4)	18 (14.8)	3 (7.1)
Diarrhea	29 (37.7)	17 (13.9)	7 (16.7)
Edema peripheral	17 (22.1)	16 (13.1)	4 (9.5)
Urinary tract infection	14 (18.2)	16 (13.1)	8 (19.0)
Arthralgia	0	13 (10.7)	4 (9.5)
Dizziness	11 (14.3)	13 (10.7)	0

Abbreviation(s): AE = adverse event.

There were 2 (1.6%) patient deaths reported in the vutrisiran arm and 3 (7.1%) patients in the patisiran arm, none of which were considered treatment-related. There was 1 death due to COVID-19 reported in each treatment arm. The other deaths, 1 in the vutrisiran arm and 2 in the patisiran arm, were reported in patients with non-V30M TTR variants with medical histories of cardiac disease. By Month 18, 3 (2.5%) patients in the vutrisiran arm discontinued treatment and stopped study participation due to AEs (two of which were due to death). AEs leading to discontinuation were acute cardiac failure, COVID-19 pneumonia, and iliac artery occlusion (each n=1; 0.8%), none of which were considered related to vutrisiran. There were no cardiac AEs related to vutrisiran reported in the safety population.[3]

Serious AEs considered related to vutrisiran by the investigators were reported in 2 (1.6%) patients (1 dyslipidemia and 1 urinary tract infection).[3]

Injection site reactions were reported in 5 (4.1%) patients receiving vutrisiran and were all mild and transient. There were no safety signals in LFTs, hematology, or renal function related to vutrisiran. A total of 4 (3.3%) vutrisiran-treated patients developed ADAs. ADA titers were low and transient with no evidence of an effect on clinical efficacy, safety, or pharmacodynamic parameters of vutrisiran.[3]

ABBREVIATIONS

10-MWT = 10-meter walk test; ADA = antidrug antibody; AE = adverse event; CI = confidence interval; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; LFT = liver function test; LSMD = least-squares mean difference; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life Diabetic Neuropathy; PBP = postural blood pressure; R-ODS = Rasch-built Overall Disability Scale; SBP = systolic blood pressure; TTR = transthyretin.

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