Vutrisiran: Autonomic Symptom Assessment

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SUMMARY

- In the HELIOS-A study, autonomic symptoms were assessed with the postural BP component of mNIS+7, the autonomic nerve function domain of Norfolk QOL-DN, and mBMI. The HELIOS-A study was not powered to evaluate these assessments individually.[1,2]
- The LS mean change in the postural BP component of mNIS+7, the autonomic nerve function domain of Norfolk QOL-DN, and mBMI from baseline to 9 and 18 months, favored vutrisiran compared to placebo.[1,2]
- During the 18-month treatment period, AEs were reported in 119 (97.5%) patients treated with vutrisiran. The majority of the AEs were mild to moderate in severity.[1]

INDEX

CLINICAL DATA

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with the polyneuropathy of hATTR. 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. Select secondary endpoints included Norfolk QOL-DN total score at 9 and 18 months, mNIS+7 at 18 months, and mBMI at 18 months.[1]

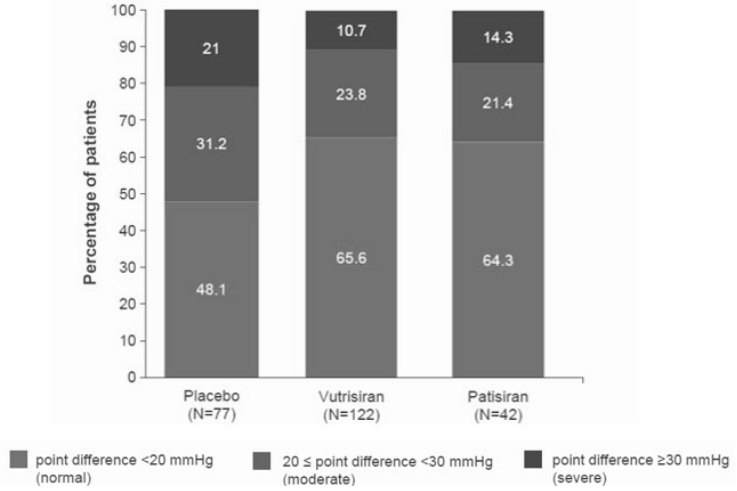
In the HELIOS-A study, autonomic symptoms were assessed with the postural BP component of mNIS+7, the autonomic nerve function domain of Norfolk QOL-DN, and mBMI.[2]

mNIS+7: Postural Blood Pressure Component

Postural BP was evaluated to assess the quantitative effect of vutrisiran on orthostatic hypotension. Orthostatic hypotension was calculated as the mean of 2 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 postural BP. The severity of orthostatic hypotension was categorized as follows: normal (<20 mmHg reduction), moderate (≥20-<30 mmHg reduction), and severe (≥30 mmHg reduction).[3]

The baseline assessment of postural BP category in HELIOS-A study is presented in **Figure 1**.[3]

Figure 1. Percentage of Patients in Each Postural BP Category at HELIOS-A Baseline.[3]



Abbreviations: BP = blood pressure.
Footnotes: Postural BP was the categorized difference between (the average of 2 supine measurement taken 15 minutes apart) and (the lowest of upright measurements taken at 1, 3, and 5 minutes)
From Slama et al.[3]

A greater percentage of patients in the vutrisiran arm achieved improvement or stabilization in postural BP at 9 months (85.4%) and at 18 months (80.7%) compared with patients in the external placebo arm at 9 months (76.1%) and at 18 months (68.6%).[3]

The LS mean difference for postural BP between vutrisiran and the external 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 therapy.[2]

Norfolk QOL-DN: Autonomic Nerve Function Domain

At baseline, the mean score for the autonomic nerve function domain was 2.7 and 2.9 in the vutrisiran and external placebo arms, respectively. At 18 months, the LS mean change from baseline in the autonomic nerve function domain was -0.6 in the vutrisiran arm and 0.9 in the external placebo arm.[4]

The LS mean difference for the autonomic nerve function domain between vutrisiran and the placebo arm in change from baseline was -1.2 (95% CI: -1.8, -0.6) at 9 months and -1.4 (95% CI: -2.1, -0.8) at 18 months, favoring vutrisiran therapy.[2]

mBMI

mBMI is a measure of nutritional status and wasting due in part to GI dysfunction, which can result from autonomic nervous system impairment. mBMI was defined as serum albumin concentration (g/L) multiplied by conventional BMI (weight in kg divided by the square of height in meters). A lower mBMI score indicates worse nutritional status (greater autonomic functional impairment).[5]

At baseline, the mean (SD) mBMI was 1057.4 (234) in the vutrisiran arm and 989.9 (214.2) in the external placebo arm. At 9 months, mBMI was an exploratory endpoint; the LS mean change (SE) was 7.6 (7.9) in the vutrisiran arm and -60.2 (10.1) in the external placebo arm. At 18 months, the LS mean change (SE) was 25 (9.5) in the vutrisiran arm and -115.7 (13.4) in the external placebo arm. There was a statistically significant difference in mBMI favoring vutrisiran therapy with an LS mean difference of 140.7 (95% CI: 108.4, 172.9; $p=4.16 \times 10^{-15}$) at 18 months.[1,4]

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 to moderate in severity. A summary of the 18-month safety data is presented in **Table 1**.[1]

Table 1. HELIOS-A Safety Summary at 18 Months.[1]

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

Abbreviations: AE = adverse event.

ABBREVIATIONS

AE = adverse event; BMI = body mass index; BP = blood pressure; CI = confidence interval; hATTR = hereditary transthyretin amyloidosis; IV = intravenous; LS = least squares; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; SBP = systolic blood pressure; SD = standard deviation; SE = standard error.

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