Vutrisiran: Analysis of Quality of Life and Physical Function Outcomes in HELIOS-A

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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. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[1]
  - In an analysis of the study, vutrisiran demonstrated improvement in measures of QOL (Norfolk QOL-DN and EQ-VAS) and benefit in measures of physical function (10-MWT, R-ODS, and KPS) and nutritional status (mBMI) compared with the external placebo arm over the 18-month treatment period.[2]
  - The majority of AEs reported with vutrisiran were mild to moderate or severity.[1]

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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 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]

An analysis of the HELIOS-A study was performed to assess treatment with vutrisiran compared with placebo on QOL and physical function outcomes. Measures of QOL included change from baseline in the following endpoints at Month 9 and 18: Norfolk QOL-DN total score and EQ-VAS. Measures of physical function included change from baseline in the following endpoints at Month 9 and 18: 10-MWT and R-ODS. KPS was assessed at Month 18. Nutritional status was assessed by change from baseline in mBMI at Month 9 and 18.[2]

BASELINE CHARACTERISTICS

Baseline QOL and physical function parameters are presented in **Table 1.**[2]

Table 1. Baseline QOL and Physical Function Parameters.[2]

Assessment	External Placebo (N=77)	Vutrisiran (N=122)
Norfolk QOL-DN, mean (SD)	55.5 (24.3)	47.1 (26.3)
EQ-VAS, mean (SD)	54.6 (18.0)	64.5 (18.5)
R-ODS, mean (SD)	29.8 (10.8)	34.1 (11.0)
10-MWT (m/s), mean (SD)	0.790 (0.319)	1.006 (0.393)
mBMI (kg/m^2 x g/L), mean (SD)	989.9 (214.2)	1057.4 (233.8)
KPS, n (%)		
60%	22 (28.6)	17 (13.9)
70-80%	45 (58.4)	73 (59.8)
90-100%	10 (13.0)	32 (26.2)

Abbreviations: 10-MWT = 10-meter walk test; EQ-VAS = EuroQol-Visual Analog Scale; KPS = Karnofsky Performance Status; mBMI = modified body mass index; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; QOL = quality of life; R-ODS = Rasch-built Overall Disability Scale; SD = standard deviation.

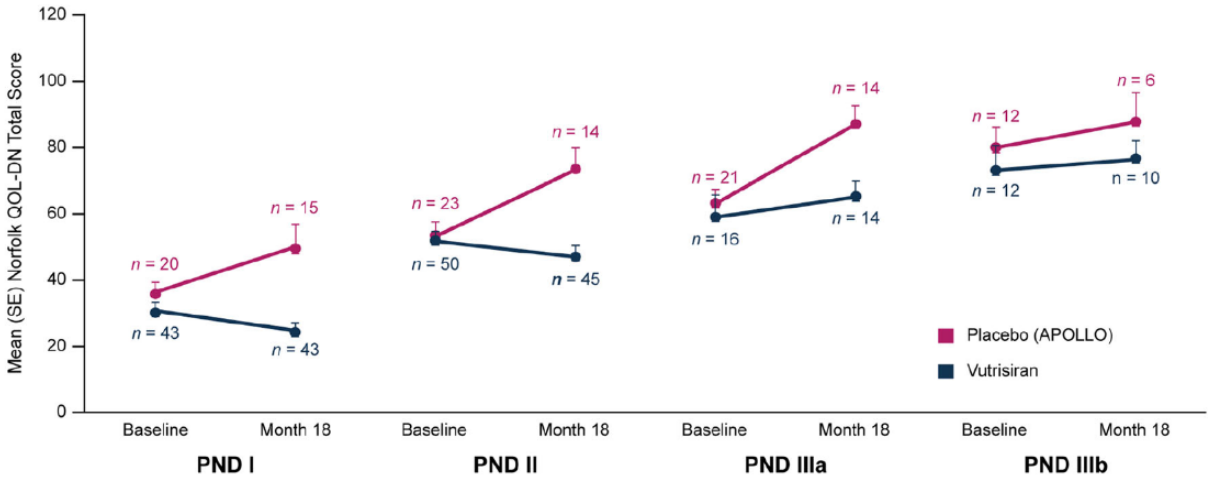
EFFICACY RESULTS

Measures of QOL

Norfolk QOL-DN

At Month 9, the LSMD in the Norfolk QOL-DN between the vutrisiran and external placebo arms was -16.2 points (95% CI: -21.7, -10.8; p<0.001). At Month 18, the LSMD between the two arms was -21.0 points (95% CI: -27.1, -14.9; p<0.001), and improvement from baseline was seen in 56.8% of patients in the vutrisiran arm compared with 10.4% of patients in the external placebo arm. **Figure 1** shows the mean Norfolk QOL-DN total score at baseline and Month 18 by baseline PND score.[2]

Figure 1. Mean Norfolk QOL-DN at Baseline and Month 18 by Baseline PND Score.[2]



Abbreviations: Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; PND = Polyneuropathy Disability; SE = standard error.
From Obici et al[2]

At Month 18, the mean change from baseline in the Norfolk QOL-DN total score was -1.2 points (improvement) in the vutrisiran arm and 19.8 points (worsening) in the placebo arm. Across all individual Norfolk QOL-DN domains, the mean change from baseline at Month 18 was lower in the vutrisiran arm compared with the placebo arm (**Table 2**).[2]

Table 2. Change from Baseline in Norfolk QOL-DN Scores at Month 18.[2]

Domain (Range)	External Placebo (N=77)		Vutrisiran (N=122)	
	Mean Score at Baseline	LS Mean Change at Month 18	Mean Score at Baseline	LS Mean Change at Month 18
Total Score (-4 to 136)	55.5	19.8	47.1	-1.2
Physical Functioning/Large Fiber (-4 to 56)	28.7	9.2	23.2	1.6
ADL (0 to 20)	7.8	5.5	5.7	0.9
Symptoms (0 to 32)	11.2	2.0	11.0	-0.5
Small Fiber (0 to 16)	5.0	2.7	4.6	0.6
Autonomic (0 to 12)	2.9	0.9	2.7	-0.6

Abbreviations: ADL = activities of daily living; LS = least squares; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy.

EQ-VAS

Patient self-rated global health as measured by EQ-VAS at Month 9 and 18 favored treatment with vutrisiran compared with external placebo, as summarized in **Table 3.** At Month 9, the LS mean change from baseline was 2.3 points in the vutrisiran arm and -7.0 points in the placebo arm, resulting in a LSMD of 9.3 points (95% CI: 4.4, 14.2). At Month 18, the LS mean change from baseline was 2.1 points in the vutrisiran arm and -11.6 points in the placebo arm, resulting in a LSMD of 13.7 points (95% CI: 8.7, 18.7; nominal $p<0.001$).[2]

Measures of Physical Function

10-MWT

Gait speed as measured by 10-MWT at Month 9 and 18 favored treatment with vutrisiran compared with external placebo, as summarized in **Table 3**. At Month 9, the LS mean change from baseline was -0.004 m/s in the vutrisiran arm and -0.135 m/s in the placebo arm, resulting in a LSMD of 0.131 m/s (95% CI: 0.071, 0.191; $p<0.001$). At Month 18, the LS mean change from baseline was -0.024 m/s in the vutrisiran arm and -0.264 m/s in the placebo arm, resulting in a LSMD of 0.239 m/s (95% CI: 0.154, 0.325; $p<0.001$).[2]

R-ODS

Disability as measured by R-ODS at Month 9 and 18 favored treatment with vutrisiran compared with external placebo, as summarized in **Table 3**. At Month 9, the LS mean change from baseline was -0.8 points in the vutrisiran arm and -5.0 points in the placebo arm, resulting in a LSMD of 4.2 points (95% CI: 2.6, 5.9). At Month 18, the LS mean change from baseline was -1.5 points in the vutrisiran arm and -9.9 points in the placebo arm, resulting in a LSMD of 8.4 points (95% CI: 6.5, 10.4; $p<0.001$).[2]

KPS

Compared to baseline at Month 18, 58.2% of patients in the vutrisiran arm and 34.7% of patients in the placebo arm had a stable KPS; 13.1% of patients in the vutrisiran arm and 8.1% of patients in the placebo arm had an improved KPS.[2]

Measure of Nutritional Status

mBMI

Nutritional status as measured by mBMI favored treatment with vutrisiran compared with the external placebo, as summarized in **Table 3**. At Month 9, the LS mean change from baseline was 7.1 kg/m^2 x g/L in the vutrisiran arm and -61.5 kg/m^2 x g/L in the placebo arm, resulting in a LSMD of 68.6 kg/m^2 x g/L (95% CI: 45.1, 92.1). At Month 18, the LS mean change from baseline was 25.0 kg/m^2 x g/L in the vutrisiran arm and -115.7 kg/m^2 x g/L in the placebo arm, resulting in a LSMD of 140.7 kg/m^2 x g/L (95% CI: 108.4, 172.9; $p<0.001$).[2]

Table 3. Change from Baseline in QOL and Physical Function Results at 9 and 18 Months.[1,2]

Endpoints	External Placebo (N=77)		Vutrisiran (N=122)		Vutrisiran – Placebo		p value
	LS Mean	(SE)	LS Mean	(SE)	LSMD	(95% CI)	
Month 9							
Norfolk QOL-DN[a,c]	12.9	(2.2)	-3.3	(1.7)	-16.2	(-21.7, -10.8)	p<0.001
EQ-VAS[b,d]	-7.0	(2.0)	2.3	(1.5)	9.3	(4.4, 14.2)	-
10-MWT (m/s)[a,d]	-0.135	(0.025)	-0.004	(0.019)	0.131	(0.071, 0.191)	p<0.001
R-ODS[b,d]	-5.0	(0.7)	-0.8	(0.5)	4.2	(2.6, 5.9)	-
mBMI[b,d]	-61.5	(9.5)	7.1	(7.4)	68.6	(45.1, 92.1)	-
Month 18							
Norfolk QOL-DN[a,c]	19.8	(2.6)	-1.2	(1.8)	-21.0	(-27.1, -14.9)	p<0.001
EQ-VAS[b,d]	-11.6	(2.1)	2.1	(1.5)	13.7	(8.7, 18.7)	p<0.001[e]
10-MWT (m/s)[a,d]	-0.264	(0.036)	-0.024	(0.025)	0.239	(0.154, 0.325)	p<0.001
R-ODS[a,d]	-9.9	(0.8)	-1.5	(0.6)	8.4	(6.5, 10.4)	p<0.001
mBMI[a,d]	-115.7	(13.4)	25.0	(9.5)	140.7	(108.4, 172.9)	p<0.001

Abbreviations: 10-MWT = 10-meter walk test; CI = confidence interval; EQ-VAS = EuroQol-Visual Analog Scale; LS = least squares; LSMD = least squares mean difference; m/s = meters/second; mBMI = modified body mass index; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; R-ODS = Rasch-built Overall Disability Scale; SE = standard error.
[a]Secondary endpoint
[b]Exploratory endpoint
[c]Decrease (negative change) indicates improvement
[d]Increase (positive change) indicates improvement
[e]Nominal p value

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 from the overall HELIOS-A trial is presented in **Table 4.**[1]

Table 4. Adverse Events in HELIOS-A at Month 18.[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)

At least one event, n (%)	APOLLO	HELIOS-A	
	Placebo (N=77)	Vutrisiran (N=122)	Patisiran (N=42)
AEs occurring in ≥10% in vutrisiran-treated patients[a]			
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.
[a]Safety reported in the safety population during the 18-month treatment period.

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.

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

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.[1]

ABBREVIATIONS

10-MWT = 10-meter walk test; ADA = antidrug antibody; AE = adverse event; CI = confidence interval; EQ-VAS = EuroQol-Visual Analog Scale; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; KPS = Karnofsky Performance Status; LFT = liver function test; LS = least squares; 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; PND = Polyneuropathy Disability Score; QOL = quality of life; R-ODS = Rasch-built Overall Disability Scale; SD = standard deviation; SE = standard error; TTR = transthyretin.

Updated 19 September 2024

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