Vutrisiran: HELIOS-A Study

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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 the polyneuropathy of hATTR. The study used the placebo arm of the APOLLO study as an external control arm for the primary endpoint and most other efficacy endpoints.[1]
- The study met the primary endpoint of change in the mNIS+7 at 9 months compared with external placebo. The LS mean change from baseline was a 2.24-point decrease in the vutrisiran arm and a 14.76-point increase in the placebo arm, resulting in a LSMD of -17.00 points (95% CI: -21.78, -12.22; p<0.001).[1]
- The study met all secondary efficacy endpoints at 9 and 18 months with significant improvements in neuropathy impairment, quality of life, gait speed, nutritional status, and disability compared with the external placebo group at 18 months.[1]
- Over the 18-month treatment period, patients in the vutrisiran arm demonstrated rapid (≤3 weeks) and sustained reduction in serum TTR.[1]
- At 18 months of the exploratory analysis, vutrisiran treatment demonstrated improvement in NT-proBNP levels and trend towards improvement in echocardiographic parameters compared with external placebo.[2]
- In the study, vutrisiran demonstrated an acceptable safety profile, with the majority of AEs being mild or moderate in severity and no drug-related deaths or treatment discontinuations.[1]
- Serious AEs were reported in 2 (1.6%) patients treated with vutrisiran (1 dyslipidemia and 1 urinary tract infection).[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 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.[1] After the 18-month treatment period was completed, all eligible patients, including those on patisiran, entered the RTE period and received treatment with vutrisiran. The inclusion and exclusion criteria for HELIOS-A are presented in **Table 1**.[1,3]

Table 1. HELIOS-A Inclusion and Exclusion Criteria.[1,3]

Inclusion Criteria	Exclusion Criteria
• Age 18 – 85 years of age • Diagnosis of hATTR with documented TTR variant • NIS of 5 to 130 • PND score of ≤3b • KPS score of ≥60%	• Prior liver transplant or is likely to undergo liver transplantation during the study • Other known (non-hATTR) forms of amyloidosis or leptomeningeal amyloidosis • NYHA heart failure classification >2 • Clinically significant liver function test abnormalities • eGFR ≤30 mL/min/1.73m^2 • Known HIV, HCV or HBV infection • Received an experimental drug within 30 days of dosing • Received prior TTR-lowering treatment • Other known causes of neuropathy

Abbreviations: eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; KPS = Karnofsky performance status; NIS = neurologic impairment score; NYHA = New York Heart Association; PND = polyneuropathy disability; TTR = transthyretin.

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Patient baseline characteristics were comparable between the vutrisiran, patisiran, and APOLLO-placebo arms as shown below in **Table 2**.[1]

Table 2. Baseline Demographics and Disease Characteristics in HELIOS-A.[1]

Characteristic	APOLLO Placebo (N=77)	HELIOS-A		
		Vutrisiran (N=122)	Patisiran (N=42)	Total (N=164)
Age (years), median (IQR)	63 (15)	60 (20)	60 (12)	60 (18)
Males, n (%)	58 (75.3)	79 (64.8)	27 (64.3)	106 (64.6)
Race, n (%)				
White/Caucasian	50 (64.9)	86 (70.5)	29 (69.0)	115 (70.1)
Asian	25 (32.5)	21 (17.2)	8 (19.0)	29 (17.7)
Black or African American	1 (1.3)	4 (3.3)	4 (9.5)	8 (4.9)
Other[a]	1 (1.3)	11 (9.0)	1 (2.4)	12 (7.3)
Time since hATTR diagnosis (years), median (IQR)	1.41 (3.04)	1.94 (4.34)	2.39 (3.01)	2.22 (4.15)
TTR genotype, n (%)				
V30M	40 (51.9)	54 (44.3)	20 (47.6)	74 (45.1)
Early-onset V30M (<50 years)	10 (13.0)	25 (20.5)	8 (19.0)	33 (20.1)
Non-V30M[b]	37 (48.1)	68 (55.7)	22 (52.4)	90 (54.9)
Previous tetramer stabilizer use, n (%)	41 (53.2)	75 (61.5)	33 (78.6)	108 (65.9)
Tafamidis	27 (35.1)	53 (43.4)	25 (59.5)	78 (47.6)

Characteristic	APOLLO Placebo (N=77)	HELIOS-A		
		Vutrisiran (N=122)	Patisiran (N=42)	Total (N=164)
Diflunisal	14 (18.2)	22 (18.0)	8 (19.0)	30 (18.3)
NIS, n (%)				
<50	35 (45.5)	78 (63.9)	27 (64.3)	105 (64.0)
≥50 – <100	33 (42.9)	39 (32.0)	13 (31.0)	52 (31.7)
≥100	9 (11.7)	5 (4.1)	2 (4.8)	7 (4.3)
PND Score[c], n (%)				
I	20 (26.0)	44 (36.1)	15 (35.7)	59 (36.0)
II	23 (29.9)	50 (41.0)	17 (40.5)	67 (40.9)
IIIA	22 (28.6)	16 (13.1)	7 (16.7)	23 (14.0)
IIIB	11 (14.3)	12 (9.8)	3 (7.1)	15 (9.1)
NT-proBNP[d], n (%)				
≤3000 ng/L	66 (85.7)	112 (91.8)	37 (88.1)	149 (90.9)
>3000 ng/L	9 (11.7)	10 (8.2)	5 (11.9)	15 (9.1)
Cardiac subpopulation[e], n (%)	36 (46.8)	40 (32.8)	14 (33.3)	54 (32.9)

Abbreviations: hATTR = hereditary transthyretin amyloidosis; IQR = interquartile range; mITT = modified intent-to-treat; NIS = Neuropathy Impairment Score; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; PND = polyneuropathy disability; TTR = transthyretin.
[a]Includes more than one race, vutrisiran n=1 (0.8%); other, vutrisiran n=10 (8.2%), patisiran n=1 (2.4%); missing, placebo n=1 (1.3%).
[b]The non-V30M TTR genotype represents 25 different TTR mutations in HELIOS-A.
[c]PND score I: preserved walking, sensory disturbances; II: impaired walking but can walk without stick or crutch; IIIA: walk with one stick or crutch; IIIB: walk with two sticks or crutches; 1 patient (1.3%) in APOLLO placebo group had a PND score IV defined as confined to wheelchair or bedridden.
[d]NT-proBNP missing for 2 patients in APOLLO placebo group.
[e]Cardiac subpopulation was defined as mITT population patients who had preexisting evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history).

EFFICACY RESULTS

Primary Endpoint

Neuropathy Impairment (mNIS+7)

At 9 months, vutrisiran treatment achieved statistically significant improvement in mNIS+7 compared with external placebo. The LS mean change from baseline was a 2.24-point decrease in the vutrisiran arm and a 14.76-point increase in the placebo arm, resulting in a LSMD of -17.00 points (95% CI: -21.78, -12.22; p<0.001). Improvement from baseline in mNIS+7 was observed in 50.4% of patients in the vutrisiran arm compared with 18.2% in the external placebo arm.[1]

Secondary Endpoints

Neuropathy Impairment (mNIS+7)

At 18 months, vutrisiran achieved statistically significant improvement in mNIS+7 compared with external placebo, with a LSMD of -28.55 points (95% CI: -34.00, -23.1; p<0.001). Improvement in mNIS+7 from baseline was seen in 48.3% of patients in the vutrisiran arm compared with 3.9% of patients in the external placebo arm.[1]

Quality of Life (Norfolk QOL-DN)

Vutrisiran also achieved statistically significant improvement in quality of life as measured by the Norfolk QOL-DN at 9 and 18 months, compared with external placebo. At 9 months, the LSMD between the two arms was -16.2 points (95% CI: -21.7, -10.8; p<0.001), and improvement from baseline was seen in 53.4% of patients in the vutrisiran arm compared with 23.4% in the external placebo arm. At 18 months, 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.[1]

Table 3. Summary of HELIOS-A Study Efficacy Results at 9 and 18 Months.[1]

Efficacy Endpoints	External Placebo (N=77)		Vutrisiran (N=122)		Vutrisiran – Placebo		p value
	LS Mean[b]	(SE)	LS Mean[b]	(SE)	LS Mean Difference[b]	(95% CI)	
Month 9 Efficacy Analyses							
mNIS+7[a,c]	14.76	(2.00)	-2.24	(1.43)	-17.00	(-21.78, -12.22)	p<0.001
Norfolk QOL-DN[c]	12.9	(2.2)	-3.3	(1.7)	-16.2	(-21.7, -10.8)	p<0.001
10-MWT (m/s)[d]	-0.133	(0.025)	-0.001	(0.019)	0.131	(0.070, 0.193)	p<0.001
Month 18 Efficacy Analyses[e]							
mNIS+7[c]	28.1	(2.3)	-0.46	(1.6)	-28.6	(-34.0, -23.1)	p<0.001
Norfolk QOL-DN[c]	19.8	(2.6)	-1.2	(1.8)	-21.0	(-27.1, -14.9)	p<0.001
10-MWT (m/s)[d]	-0.264	(0.036)	-0.024	(0.025)	0.239	(0.154, 0.325)	p<0.001
mBMI[d]	-115.7	(13.4)	25.0	(9.5)	140.7	(108.4, 172.9)	p<0.001
R-ODS[d]	-9.9	(0.8)	-1.5	(0.6)	8.4	(6.5, 10.4)	p<0.001

Abbreviations: 10-MWT = 10-meter walk test; CI = confidence interval; LS = least squares; m/s = meters/second; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score+7; Norfolk QOL-DN = Norfolk Quality of Life–Diabetic Neuropathy; R-ODS = Rasch-built Overall Disability Scale; SE = standard error.
Footnotes: [a]primary endpoint, [b]change from baseline, [c]decrease (negative change) indicates improvement, [d]increase (positive change) indicates improvement. [e]Data from the analysis of covariance/multiple imputation model.

Serum TTR Reduction

Patients in the vutrisiran arm demonstrated rapid (≤3 weeks) and sustained reduction in serum TTR over the 18-month treatment period. Following 18 months of vutrisiran treatment, steady-state mean (SD) peak and trough serum TTR reductions from baseline were 87.6% (15.7%) and 81.0% (21.0%), respectively. TTR reduction with vutrisiran was statistically non-inferior to within-study patisiran in the TTR per-protocol population, assessed by mean trough serum TTR levels over 18 months. 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%).[1]

Select Exploratory Endpoints: Cardiac Endpoints in the mITT Population

NT-proBNP

Vutrisiran showed improvement in NT-proBNP levels at 9 months with continued improvement to 18 months compared with external placebo. At 18 months, the adjusted geometric fold change ratio was 0.480 (95% CI: 0.383, 0.600; nominal $p=9.606\times10^{-10}$).[2]

Echocardiographic Parameters

At 18 months, a nominally significant benefit in cardiac output, LV end-diastolic volume, and LV stroke volume was observed in patients receiving vutrisiran compared with external placebo, with a LSMD (SE) of 0.587 (0.130) L/min ($p=1.144\times10^{-5}$), 10.489 (2.485) mL ($p=4.021\times10^{-5}$), and 7.837 (1.670) mL (5.754×10^{-6}), respectively. Patients treated with vutrisiran showed a nonsignificant trend towards improvement in other echocardiographic parameters relative to external placebo including mean LV wall

thickness (nominal p=0.5228), LV mass (nominal p=0.4456), and global longitudinal strain (nominal p=0.3182).[2]

Technetium (^{99m}Tc) Scintigraphy Imaging

In a planned cohort, vutrisiran reduced cardiac uptake of technetium on scintigraphy imaging, relative to baseline. At 18 months, 32 (68.1%) evaluable patients improved in technetium uptake as assessed by normalized left ventricular total uptake and 31 (64.6%) patients showed improvement in heart to contralateral lung ratio. At 18 months, among all evaluable scintigraphy patients, 55 (96%) were stable or improved by ≥1 Perugini grade(s). Of those patients with a Perugini grade ≥1 at baseline, 16 (50%) improved by ≥1 Perugini grade and 5 (16%) patients improved by ≥2 Perugini grades.[2]

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 4**.[1]

Table 4. AEs Reported in the Safety Population in HELIOS-A 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.

There were 2 (1.6%) patient deaths reported in the vutrisiran arm and 3 (7.1%) patient deaths 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 18 months, 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.[1]

Serious AEs were reported in 2 (1.6%) patients treated with vutrisiran (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; eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquartile range; KPS = Karnofsky performance status; LFT = liver function test; LS = least squares; LSMD = least-squares mean difference; m/s = meters/second; mBMI = modified body mass index; mITT = modified intent-to-treat; mNIS+7 = modified Neuropathy Impairment Score +7; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life–Diabetic Neuropathy; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; R-ODS = Rasch-built Overall Disability Scale; SE = standard error; TTR = transthyretin.

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