

## 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 hATTR-PN.<sup>1</sup>
- The study used the placebo arm of the APOLLO study as an external control arm for the primary endpoint and most other efficacy endpoints.<sup>1</sup>
- The study met the primary endpoint, with the LS mean change from baseline in mNIS+7 at Month 9 showing a 2.24-point decrease in the vutrisiran arm compared with a 14.76-point increase in the external placebo arm, resulting in a LSMO of -17.00 points (95% CI -21.78, -12.22; p<0.001).<sup>1</sup>
- The study met all efficacy endpoints with vutrisiran at Month 9 and 18 with statistically significant differences in mNIS+7, Norfolk QOL-DN, 10-MWT, mBMI, and R-ODS compared with external placebo at Month 18.<sup>1</sup>
- Steady-state mean (SD) peak and trough percent reductions from baseline in serum TTR level at Month 18 were 87.6% (15.7%) and 81.0% (21.0%), respectively, in the vutrisiran arm.<sup>1</sup>
- In exploratory analyses, improvement in NT-proBNP levels and trend towards improvement in echocardiographic parameters at Month 18 were observed with vutrisiran compared with external placebo.<sup>2</sup>
- In the safety population of HELIOS-A, the majority of AEs were categorized as mild or moderate in severity. There were no treatment-related discontinuations or deaths.<sup>1</sup>

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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.<sup>1</sup>

## Endpoints

The primary endpoint was the change from baseline in mNIS+7 at Month 9.<sup>1</sup>

Secondary endpoints assessed neuropathy impairment, quality of life, functional capacity, nutritional status, disability, and serum TTR levels, including<sup>1</sup>:

- Change from baseline in mNIS+7 at Month 18
- Change from baseline in Norfolk QOL-DN score at Months 9 and 18
- Change from baseline in 10-MWT at Months 9 and 18
- Change from baseline in mBMI at Month 18
- Change from baseline in R-ODS score at Month 18
- Percentage reduction from baseline in serum TTR levels through Month 18

Select exploratory endpoints assessed the cardiac biomarker NT-proBNP, echocardiographic parameters, and technetium-99m scintigraphy imaging.<sup>2</sup>

## Inclusion and Exclusion Criteria

Select inclusion and exclusion criteria for HELIOS-A are presented in **Table 1**.<sup>1,3</sup>

**Table 1. HELIOS-A Inclusion and Exclusion Criteria.**<sup>1,3</sup>

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>• Age 18-85 years</li> <li>• Diagnosis of hATTR with documented TTR variant</li> <li>• NIS of 5-130</li> <li>• PND score of ≤3b</li> <li>• KPS score of ≥60%</li> </ul>	<ul style="list-style-type: none"> <li>• Prior liver transplant or is likely to undergo liver transplantation during the study</li> <li>• Other known (non-hATTR) forms of amyloidosis or leptomeningeal amyloidosis</li> <li>• NYHA heart failure classification &gt;2</li> <li>• Clinically significant LFT abnormalities</li> <li>• Known HIV, HCV, or HBV infection</li> <li>• Received an investigational drug or device within 30 days of dosing</li> <li>• Received prior TTR-lowering treatment</li> <li>• Other known causes of neuropathy</li> </ul>

Abbreviations: hATTR = hereditary transthyretin amyloidosis; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; KPS = Karnofsky performance status; LFT = liver function test; NIS = neurologic impairment score; NYHA = New York Heart Association; PND = polyneuropathy disability; TTR = transthyretin.

## PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline patient demographics and clinical characteristics were comparable among the vutrisiran, patisiran, and APOLLO-placebo arms (**Table 2**).<sup>1</sup>

**Table 2. Baseline Patient Demographics and Clinical Characteristics.**<sup>1</sup>

Characteristic	APOLLO	HELIOS-A		
	Placebo (n=77)	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)

Characteristic	APOLLO	HELIOS-A		
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)	Total (N=164)
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 <sup>a</sup>	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 <sup>b</sup>	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)
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 <sup>c</sup> , 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 <sup>d</sup> , 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 <sup>e</sup> , 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.

<sup>a</sup>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%).

<sup>b</sup>The non-V30M TTR genotype represents 25 different TTR mutations in HELIOS-A.

<sup>c</sup>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 arm had a PND score IV defined as confined to wheelchair or bedridden.

<sup>d</sup>NT-proBNP was missing for 2 patients in APOLLO placebo arm.

<sup>e</sup>The 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 Month 9

At Month 9, a statistically significant improvement in mNIS+7 was observed with vutrisiran treatment when compared with external placebo. The LS mean change from baseline showed a 2.24-point decrease in the vutrisiran arm compared with a 14.76-point increase in the external 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 at Month 9 was observed in 50.4% of patients in the vutrisiran arm compared with 18.2% in the external placebo arm.<sup>1</sup>

### Secondary Endpoints

#### Neuropathy Impairment (mNIS+7) at Month 18

At Month 18, a statistically significant improvement in mNIS+7 was observed with vutrisiran treatment compared with external placebo. The LS mean change from baseline showed a 0.46-point decrease in the vutrisiran arm compared with a 28.1-point increase in the external placebo arm, resulting in a LSMD of -28.55 points (95% CI -34.00, -23.10;  $p < 0.001$ ). Improvement in mNIS+7 from baseline was observed in 48.3% of patients in the vutrisiran arm compared with 3.9% of patients in the external placebo arm.<sup>1</sup>

#### Quality of Life (Norfolk QOL-DN)

At Months 9 and 18, a statistically significant improvement in quality of life as measured by the Norfolk QOL-DN was observed with vutrisiran treatment when compared with external placebo. At Month 9, the LSMD between the two arms was -16.2 points (95% CI -21.7, -10.8;  $p < 0.001$ ), and improvement from baseline was observed in 53.4% of patients in the vutrisiran arm compared with 23.4% in the external placebo arm. 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 observed in 56.8% of patients in the vutrisiran arm compared with 10.4% of patients in the external placebo arm.<sup>1</sup>

#### Gait Speed (10-MWT), Nutritional Status (mBMI), and Disability (R-ODS)

Treatment with vutrisiran resulted in improvements for all secondary endpoints, including 10-MWT at Months 9 and 18, mBMI at Month 18, and R-ODS at Month 18, compared with external placebo.<sup>1</sup>

A summary of efficacy results at Months 9 and 18 are shown in **Table 3**.<sup>1</sup>

**Table 3. Summary of Efficacy Results at Months 9 and 18.<sup>1</sup>**

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

<sup>a</sup>Primary endpoint.

<sup>b</sup>Change from baseline.

<sup>c</sup>Decrease (negative change) indicates improvement.

<sup>d</sup>Increase (positive change) indicates improvement.

<sup>e</sup>Data from the analysis of covariance/multiple imputation model.

### Serum TTR Reduction

Steady-state mean (SD) peak and trough percent reductions from baseline in serum TTR level at Month 18 were 87.6% (15.7%) and 81.0% (21.0%), respectively, in the vutrisiran arm. 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%).<sup>1</sup>

### **Select Exploratory Endpoints: Cardiac Endpoints in the mITT Population**

#### NT-proBNP

Improvement in NT-proBNP levels at Month 9 with continued improvement to Month 18 was observed with vutrisiran compared with external placebo. At Month 18, the adjusted geometric fold change ratio was 0.480 (95% CI 0.383, 0.600; nominal p=9.606×10<sup>-10</sup>); geometric mean ± SEM NT-proBNP levels decreased from 273.0 ± 42.2 ng/L at baseline to 227.2 ± 37.0 ng/L in the vutrisiran arm and increased from 531.3 ± 86.7 ng/L at baseline to 844.4 ± 167.0 ng/L in the external placebo arm.<sup>2</sup>

#### Echocardiographic Parameters

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 at Month 18, with a LSMD (SE) of 0.587 (0.130) L/min (p=1.144×10<sup>-5</sup>), 10.489 (2.485) mL (p=4.021×10<sup>-5</sup>), and 7.837 (1.670) mL

( $5.754 \times 10^{-6}$ ), respectively. A nonsignificant trend towards improvement in all other prespecified echocardiographic parameters, including mean LV wall thickness (nominal  $p=0.5228$ ), LV mass (nominal  $p=0.4456$ ), and global longitudinal strain (nominal  $p=0.3182$ ), was observed in patients receiving vutrisiran compared with external placebo at Month 18.<sup>2</sup>

#### Technetium-99m Scintigraphy Imaging

In a planned cohort of patients receiving vutrisiran, reduced cardiac uptake of technetium on scintigraphy imaging relative to baseline was observed. At Month 18, 32 (68.1%) evaluable patients improved in technetium uptake as assessed by normalized LV total uptake and 31 (64.6%) patients showed improvement in heart-to-contralateral lung ratio. At Month 18, among all evaluable scintigraphy patients, 55 (96%) were stable or improved by  $\geq 1$  Perugini grade(s). Of those patients with a Perugini grade  $\geq 1$  at baseline, 16 (50%) improved by  $\geq 1$  Perugini grade and 5 (16%) patients improved by  $\geq 2$  Perugini grades.<sup>2</sup>

## SAFETY RESULTS

During the 18-month treatment period, AEs were reported in 119 patients (97.5%) in the vutrisiran arm. The majority of the AEs were mild or moderate in severity (**Table 4**).<sup>1</sup>

There were no drug-related discontinuations or deaths. Three patients (2.5%) in the vutrisiran arm discontinued the study due to AEs (2 due to death, 1 due to a non-fatal heart failure event), none of which were considered related to vutrisiran. One death was due to COVID-19 pneumonia, and the other was due to iliac artery occlusion. Two SAEs (dyslipidemia and urinary tract infection) were deemed related to vutrisiran by the Investigators.<sup>1</sup>

AEs occurring in  $\geq 10\%$  of patients in the vutrisiran arm included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness; all of these AEs, with the exception of arthralgia and pain in extremity, were reported at a similar or lower frequency than in the external placebo arm. Injection site reactions were reported in 5 patients (4.1%) receiving vutrisiran, all of which were mild and transient. There were no safety concerns regarding liver function tests, hematology, or renal function related to vutrisiran. Four (3.3%) patients in the vutrisiran arm developed ADAs, which were low and transient with no evidence of an effect on clinical efficacy, safety, or pharmacodynamic parameters of vutrisiran.<sup>1</sup>

**Table 4. Safety Summary at Month 18.<sup>1</sup>**

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 <sup>a</sup>	11 (14.3)	3 (2.5) <sup>b</sup>	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	3 (2.5)	2 (4.8)
Deaths <sup>c</sup>	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; COVID-19 = coronavirus-19; TTR = transthyretin.

<sup>a</sup>None were considered related to vutrisiran: acute cardiac failure, COVID-19 pneumonia, and iliac artery occlusion (each n=1; 0.8%).

<sup>b</sup>Three (2.5%) patients in the vutrisiran arm discontinued treatment and stopped study participation due to AEs (two of which were due to death). <sup>c</sup>One death due to COVID-19 was reported in each treatment arm. The other deaths, one in the vutrisiran arm and two in the patisiran arm, were reported in patients with non-V30M TTR variants with medical histories of cardiac disease.

## ABBREVIATIONS

10-MWT = 10-meter walk test; ADA = antidrug antibody; AE = adverse event; CI = confidence interval; COVID-19 = coronavirus disease 2019; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquartile range; IV = intravenous; 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; SAE = serious adverse event; SD = standard deviation; SE = standard error; TTR = transthyretin.

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