Efficacy and Safety of Vutrisiran and Patisiran

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SUMMARY

- The HELIOS-A study compared vutrisiran with the external placebo arm of the APOLLO study for the primary endpoint (change from baseline in the mNIS+7 at 9 months). The HELIOS-A study was not designed to compare vutrisiran with the patisiran arms in the HELIOS-A study or the APOLLO study.[1]
- The only prespecified endpoint of the HELIOS-A study for which vutrisiran was compared with patisiran was the secondary endpoint of non-inferiority in percentage reduction in serum TTR levels.[1]
- In a post-hoc analysis of the HELIOS-A study, the effects of vutrisiran and patisiran were comparable in patients with hATTR-PN, as demonstrated by the results seen in clinical endpoints including mNIS+7, Norfolk QOL-DN, 10-MWT, mBMI, and R-ODS.[2]
- A cross-trial comparative assessment of the APOLLO and HELIOS-A studies found that the patisiran (APOLLO) and vutrisiran (HELIOS-A) arms had similar results on efficacy endpoints compared to placebo.[3]
- The majority of AEs were mild or moderate in severity in the HELIOS-A and APOLLO studies.[1,4]

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EFFICACY RESULTS

HELIOS-A Study

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.[1]

Baseline Characteristics

Baseline characteristics were similar across treatment groups and clinically comparable (**Table 1**).[2]

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

Characteristic	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
Age, median (IQR), years	63 (15)	60 (20)	60 (12)
Males, n (%)	58 (75.3)	79 (64.8)	27 (64.3)
Median time since hATTR diagnosis, years (IQR)	1.41 (3.04)	1.94 (4.34)	2.39 (3.01)
V30M TTR genotype[a], n (%)	40 (51.9)	54 (44.3)	20 (47.6)
V30M early onset	10 (13.0)	25 (20.5)	8 (19.0)
Previous TTR stabilizer use, n (%)	41 (53.2)	75 (61.5)	33 (78.6)
NIS, mean (range)	57.0 (7.0–125.5)	43.0 (5.0–127.0)	43.1 (5.5–115.6)
PND score[b], n (%)			
I: Preserved walking, sensory disturbances	20 (26.0)	44 (36.1)	15 (35.7)
II: Impaired walking but can walk without stick or crutch	23 (29.9)	50 (41.0)	17 (40.5)
IIIA: Walk with 1 stick or crutch	22 (28.6)	16 (13.1)	7 (16.7)
IIIB: Walk with 2 sticks or crutches	11 (14.3)	12 (9.8)	3 (7.1)
Cardiac subpopulation[c], n (%)	36 (46.8)	40 (32.8)	14 (33.3)

Abbreviations: hATTR = hereditary transthyretin amyloidosis; IQR = interquartile range; LV = left ventricular; NIS = Neuropathy Impairment Score; PND = polyneuropathy disability; TTR = transthyretin.

[a]The non-V30M TTR genotype represents 25 different variants in HELIOS-A.

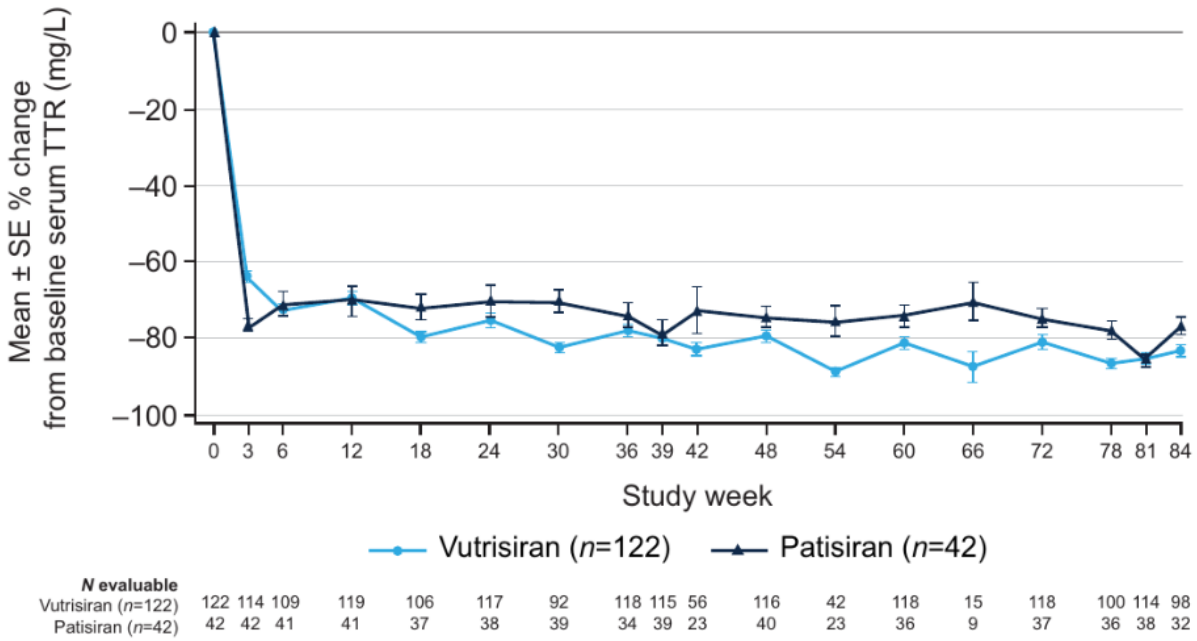
[b]One patient (1.3%) in the external placebo group had a PND score of IV defined as confined to wheelchair or bedridden.

[c]Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline LV wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history).

Pharmacodynamics

In the HELIOS-A study, vutrisiran achieved a mean steady-state serum TTR reduction from baseline of 88%, which was non-inferior to that observed in the within-study patisiran reference arm (86%) over 18 months (**Figure 1**).[1,5]

Figure 1. HELIOS-A: Secondary Endpoint of Percent Change from Baseline in Serum TTR Levels at Month 18 for Vutrisiran and Patisiran.[1]



Abbreviations: SE = standard error; TTR = transthyretin.
From Adams et al.[1]

HELIOS-A Post-Hoc Analysis

A post-hoc analysis evaluated the LS mean change from baseline of the primary and secondary endpoints at months 9 and 18 in the vutrisiran and patisiran groups in the HELIOS-A study. Results from the vutrisiran and patisiran arms were comparable across clinical endpoints (mNIS+7, Norfolk QOL-DN, 10-MWT, mBMI, and R-ODS) (**Table 2**).[2]

Table 2. Post-Hoc Analysis of Primary and Secondary Endpoints from HELIOS-A.[2]

Endpoint	LS Mean Change from Baseline (SE) to Month 9		LS Mean Change from Baseline (SE) to Month 18		
	Patisiran (95% CI)	Vutrisiran (95% CI)	Patisiran (95% CI)	Vutrisiran (95% CI)	LSMD (vutrisiran vs patisiran) (95% CI)
mNIS+7[a]	-0.42 (2.26) n=40	−1.37 (1.32) n=116	1.53 (2.59) n=36	0.06 (1.48) n=112	−1.46 (−7.36, 4.43) p=0.6248[c]
Norfolk QOL-DN[a]	−0.4 (2.7) n=40	−4.0 (1.6) n=115	−0.8 (3.0) n=38	−2.5 (1.8) n=111	−1.6 (−8.6, 5.4) p=0.6472[c]
10-MWT[a] (m/s)	−0.037 (0.029) n=40	0.002 (0.017) n=115	−0.053 (0.043) n=38	−0.019 (0.025) n=112	0.034 (−0.064, 0.132) p=0.4936
mBMI[a,b]	0.5 (13.3) n=38	4.2 (7.7) n=114	7.6 (15.8) n=38	21.8 (9.2) n=113	14.2 (−21.9, 50.3) p=0.4378[c]
R-ODS[a]	−1.8 (0.9) n=40	−0.4 (0.5) n=115	−1.3 (0.9) n=38	−1.2 (0.5) n=113	0.1 (−2.0, 2.2) p=0.9266[c]

Abbreviations: 10-MWT = 10-meter walk test; CI = confidence interval; 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; R-ODS = Rasch-built Overall Disability Scale; SE = standard error.

[a]Vutrisiran model estimates are based on the same data as the comparison with the placebo arm. Model estimates for the vutrisiran arm differ per comparison due to the impact of the different comparator data sets (from the patisiran and placebo arms, respectively) on the statistical model.

[b]mBMI = serum albumin (in g/L) x conventional BMI.

[c]p values are nominal.

NT-proBNP

Change in NT-proBNP from baseline was assessed as part of the post-hoc analysis. The change in NT-proBNP was comparable between vutrisiran and patisiran at 18 months. The fold change ratio between vutrisiran and patisiran at 18 months was 0.931 (95% CI: 0.718, 1.207), nominal p=0.5873.[2]

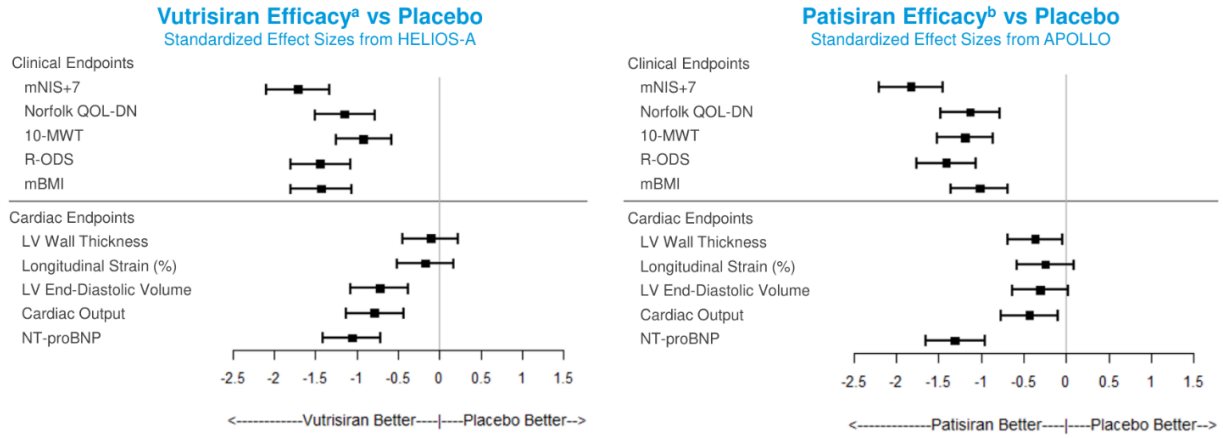
Cross Study Comparative Assessment of the HELIOS-A and APOLLO Study Results

HELIOS-A and APOLLO Comparative Results

APOLLO was a randomized, double-blind, placebo-controlled, phase 3 study to assess the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=148) versus placebo (n=77) in patients with hATTR-PN. The primary endpoint was the change from baseline to Month 18 in the mNIS+7 at 18 months.[4]

In a comparative assessment of the overall results from the HELIOS-A and APOLLO studies, efficacy endpoints in HELIOS-A were similar to those observed in APOLLO (**Figure 2**, **Table 3**).[3,6]

Figure 2. Clinical and Cardiac Endpoints at Month 18 for Vutrisiran (HELIOS-A) and Patisiran (APOLLO) vs. Placebo (APOLLO).[6]



Abbreviations: 10-MWT = 10-meter walk test; LV = left ventricular; mBMI = modified body mass index; mITT = modified intent-to-treat; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; R-ODS = Rasch-built Overall Disability Scale.
[a]HELIOS-A mITT population.
[b]APOLLO mITT population.
From Adams et al.[6]

Table 3. Post-Hoc Cross-Study Assessment of LS Mean Change from Baseline to Month 18 from HELIOS-A and APOLLO.[3]

Endpoint, LS mean change from baseline (95% CI)	HELIOS-A		APOLLO	
	Vutrisiran (n=122[a])	Difference between Vutrisiran – Placebo	Patisiran (n=148[e])	Difference between Patisiran – Placebo
mNIS+7[b]	-0.46 (-3.6, 2.7)	-28.6 (-34.0, -23.1)	-6.0 (-9.5, -2.6)	-34.0 (-39.9, -28.1)
Norfolk QOL-DN[c]	-1.2 (-4.8, 2.4)	-21.0 (-27.1, -14.9)	-6.7 (-10.2, -3.3)	-21.1 (-27.2, -15.0)
10-MWT[d]	-0.024 (-0.075, 0.026)	0.239 (0.154, 0.325)	0.077 (0.029, 0.124)	0.311 (0.230, 0.393)

Abbreviations: 10-MWT = 10-meter walk test; CI = confidence interval; LS = least squares; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy.
[a]Number of evaluable patients: mNIS+7 and 10-MWT, n=112; Norfolk QOL-DN, n=111.
[b]Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304).
[c]Higher scores of Norfolk QOL-DN indicate worse quality of life (range, -4 to 136).
[d]10-MWT speed (m/s) = 10 meters/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function.
[e]Number of evaluable patients: mNIS+7, n=137; Norfolk QOL-DN, n=136; 10-MWT, n=138.

SAFETY RESULTS

The majority of AEs from both the HELIOS-A and APOLLO studies were mild or moderate in severity at month 18 (**Table 4**).[1,4]

Table 4. HELIOS-A and APOLLO Summary of AEs at Month 18.[1,4]

At least one event, n (%)	HELIOS-A		APOLLO	
	Vutrisiran (n=122)	Patisiran (n=42)	Placebo (n=77)	Patisiran (n=148)
AEs	119 (97.5)	41 (97.6)	75 (97.4)	143 (96.6)
SAEs	32 (26.2)	18 (42.9)	31 (40.3)	54 (36.5)
Severe AEs	19 (15.6)	16 (38.1)	28 (36.4)	42 (28.4)
AEs leading to treatment discontinuation	3 (2.5)	3 (7.1)	11 (14.3)	7 (4.7)
AEs leading to stopping study participation	3 (2.5)	2 (4.8)	9 (11.7)	7 (4.7)
Deaths	2 (1.6)	3 (7.1)	6 (7.8)	7 (4.7)

Abbreviations: AE = adverse event; SAE = serious adverse event.

In the vutrisiran arm of HELIOS-A, there were no treatment discontinuations or deaths that were deemed to be related to vutrisiran. 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). 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. AEs occurring in ≥10% of patients in the vutrisiran arm included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness. All AEs, apart from pain in extremity and arthralgia, were reported at a similar or lower frequency than in the external placebo arm. ISRs were reported in 5 patients (4.1%) receiving vutrisiran, all of which were mild and transient. Overall, there were no safety signals regarding liver function tests, hematology, or renal function related to vutrisiran.[1]

In the patisiran arm of HELIOS-A, there were no treatment discontinuations or deaths that were deemed to be related to patisiran. Three patients (7.1%) in the patisiran arm discontinued the study due to death. One death was due to COVID-19 pneumonia, one was due to cardiac arrhythmia, and one was due to triple-vessel coronary artery disease.[1,5]

ABBREVIATIONS

10-MWT = 10-meter walk test; AE = adverse event; CI = confidence interval; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IQR = interquartile range; ISR = injection site reaction; IV = intravenous; LS = least squares; LSMD = least squares mean difference; LV = left ventricular; 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; PND = polyneuropathy disability; R-ODS = Rasch-built Overall Disability Scale; SAE = serious adverse event; SE = standard error; TTR = transthyretin.

Updated 6 April 2026

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