Efficacy and Safety of Vutrisiran and Patisiran

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SUMMARY

- The HELIOS-A study was designed to compare vutrisiran with the external placebo arm of the APOLLO study for the primary endpoint (change from baseline in the mNIS+7 at Month 9). 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 with polyneuropathy, as demonstrated by the results seen in clinical endpoints including mNIS+7, Norfolk QOL-DN, 10-MWT, mBMI, and R-ODS. Full results of the post hoc analysis are presented in **Table 2**.[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 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 mNIS+7 at 9 months.[1]

Patient Demographics and Baseline Characteristics

Baseline characteristics were similar across treatment groups and clinically comparable, as seen below in **Table 1**.[2]

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

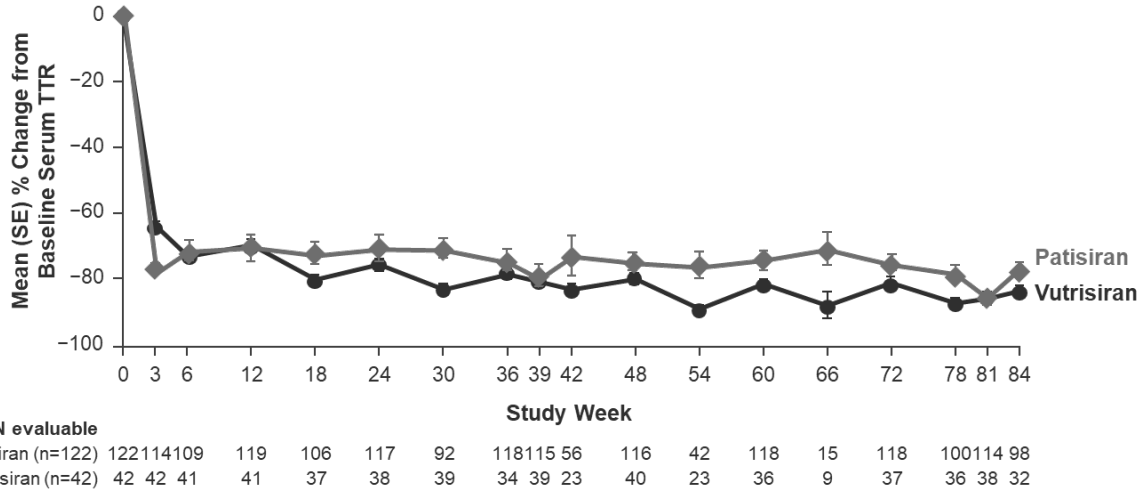
Characteristic	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
Age, median (IQR), years	63 (15)	60 (20)	60 (12)
Males, n (%)	58 (75.3)	79 (64.8)	27 (64.3)
Median time since hATTR diagnosis, years (IQR)	1.41 (3.04)	1.94 (4.34)	2.39 (3.01)
V30M TTR genotype[a], n (%)	40 (51.9)	54 (44.3)	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, n (%)[c]	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]



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

HELIOS-A Post-Hoc Analysis: Vutrisiran vs Patisiran

A post-hoc analysis was conducted on the primary and secondary endpoints of the HELIOS-A study between the vutrisiran and patisiran groups. The LSMD from baseline to Month 18 was assessed, with all

p-values being considered nominal due to the post-hoc nature of the analysis. Change from baseline to Month 9 and Month 18, as well as the results from the post-hoc analysis, are presented below in **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
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
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
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

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) × conventional BMI

NT-proBNP

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

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

A comparative assessment was made between the results of the HELIOS-A (vutrisiran vs. APOLLO placebo) and APOLLO (patisiran vs. placebo) studies.

APOLLO Study

APOLLO was a multicenter, international, randomized (2:1), double-blind, placebo-controlled, Phase 3 study to assess the efficacy and safety of intravenous (IV) patisiran 0.3 mg/kg every 3 weeks (n=148) versus placebo (n=77) in patients with the polyneuropathy of hATTR. The primary endpoint was the change from baseline to Month 18 in the mNIS+7.[4]

HELIOS-A and APOLLO Comparative Results

Overall, findings for the efficacy endpoints in HELIOS-A were similar with the findings for those in APOLLO, as seen in **Figure 2** and **Table 3** below.[3,6]

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

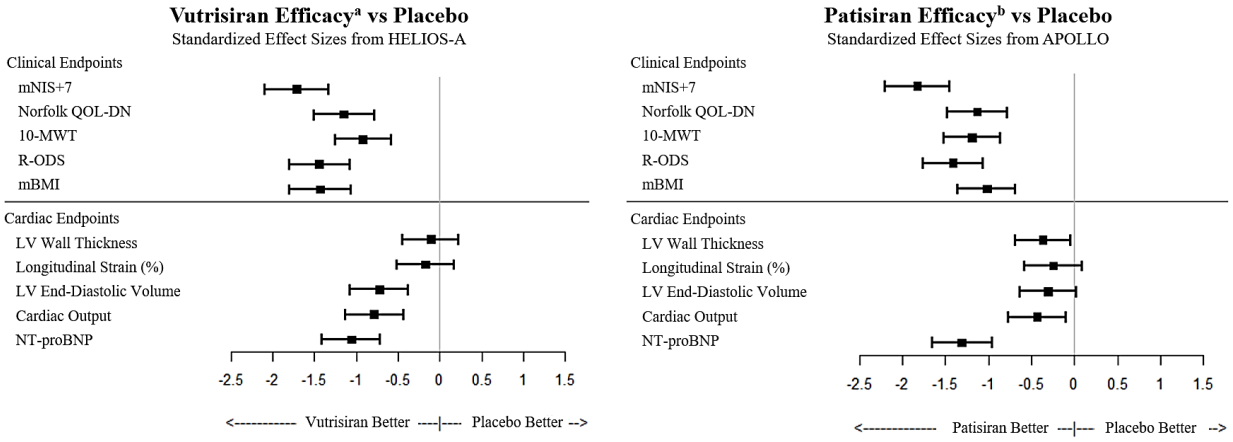


Table 3. Post-Hoc Cross-Study Assessment of LS Mean Change from Baseline to Month 18 from HELIOS-A and APOLLO.[3]

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

A safety summary of HELIOS-A and APOLLO at Month 18 is presented below in **Table 4**. The majority of AEs were mild or moderate in severity in both HELIOS-A and APOLLO.[1,4]

Table 4. HELIOS-A and APOLLO Month 18 Safety Summary.[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)

	Vutrisiran (n=122)	Patisiran (n=42)	Placebo (n=77)	Patisiran (n=148)
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.[1] 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] SAEs that were deemed related to patisiran by the Investigators included IRRs (3 patients), infusion site cellulitis (2 patients), and infusion site phlebitis (1 patient). AEs occurring in ≥10% of patients in the patisiran arm included IRRs, urinary tract infection, diarrhea, fall, constipation, and headache.[7] IRRs were reported in 10 patients (23.8%) receiving patisiran, who had a total of 50 IRRs.[1,7] Of these patients, the maximum severity of IRRs was mild for 5 patients, moderate for 4 patients, and severe for 1 patient. Overall, there were no safety signals regarding liver function tests, hematology, or renal function related to patisiran.[7]

ABBREVIATIONS

10-MWT = 10-meter walk test; AE = adverse event; CI = confidence interval; hATTR = hereditary transthyretin amyloidosis; IRR = infusion related reaction; 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.

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