Vutrisiran: Post-Hoc Analysis of HELIOS-A Results by Baseline NIS Quartile

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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.[1]
- A post-hoc analysis of the HELIOS-A results was conducted to evaluate the impact of baseline polyneuropathy severity, as measured by the NIS, on response to vutrisiran treatment.[2]
- A treatment benefit of vutrisiran versus external placebo was observed across all baseline NIS quartiles in mNIS+7, Norfolk QOL-DN, 10-MWT, R-ODS, and mBMI over the 18-month treatment period. Patients who were in lower NIS quartiles at baseline maintained better scores across all endpoints compared with those in higher NIS quartiles.[2]
- The external placebo group progressively worsened across all endpoints assessed at Month 18.[2]
- During the 18-month treatment period, treatment discontinuations were observed across all NIS quartiles in the external placebo group. In the vutrisiran group, there were no discontinuations in Q1 or Q4, while treatment discontinuations were observed in 2 patients (6.3%) in Q2 and 4 patients (13.3) in Q3.[2]

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METHODS

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 (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]

A post-hoc analysis of the HELIOS-A results was conducted to evaluate the impact of baseline polyneuropathy severity on response to vutrisiran treatment. Patients were divided into quartiles based on baseline NIS: Q1 ≥5.0 to ≤20.5; Q2 >20.5 to ≤44.1; Q3 >44.1 to ≤73.1; Q4 >73.1 to ≤127.0.[2]

The following primary, secondary, and exploratory endpoints were analyzed by baseline NIS quartile at 9 and 18 months: mNIS+7, Norfolk QOL-DN, R-ODS, 10-MWT, and mBMI.[2]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Table 1 below summarizes the baseline characteristics by baseline NIS quartile from HELIOS-A.[2]

Table 1. Baseline Characteristics by Baseline NIS Quartile.[2]

Characteristic[a]	HELIOS-A Vutrisiran (n=122)				APOLLO External Placebo (n=77)			
	Q1 ≥5.0 to ≤20.5 (n=38)	Q2 >20.5 to ≤44.1 (n=32)	Q3 >44.1 to ≤73.1 (n=30)	Q4 >73.1 to ≤127.0 (n=22)	Q1 ≥5.0 to ≤20.5 (n=12)	Q2 >20.5 to ≤44.1 (n=18)	Q3 >44.1 to ≤73.1 (n=20)	Q4 >73.1 to ≤127.0 (n=27)
Age (years), median (range)	54.5 (31–73)	62.5 (31–78)	63.5 (26–85)	64.0 (44–81)	53.0 (36–75)	64.0 (38–80)	62.5 (34–77)	66.0 (43–77)
Male	18 (47.4)	24 (75.0)	20 (66.7)	17 (77.3)	6 (50.0)	13 (72.2)	16 (80.0)	23 (85.2)
Years since diagnosis, mean (SD)	4.2 (4.1)	2.9 (3.8)	3.4 (3.5)	2.6 (3.0)	3.8 (4.5)	1.9 (2.4)	2.5 (2.6)	2.7 (3.6)
TTR genotype								
V30M	18 (47.4)	10 (31.3)	16 (53.3)	10 (45.5)	8 (66.7)	8 (44.4)	10 (50.0)	14 (51.9)
Early onset[b]	10 (26.3)	6 (18.8)	7 (23.3)	2 (9.1)	4 (33.3)	2 (11.1)	1 (5.0)	3 (11.1)
Non-V30M[c]	20 (52.6)	22 (68.8)	14 (46.7)	12 (54.5)	4 (33.3)	10 (55.6)	10 (50.0)	13 (48.1)
Previous TTR stabilizer	24 (63.2)	18 (56.3)	16 (53.3)	17 (77.3)	5 (41.7)	9 (50.0)	16 (80.0)	11 (40.7)
KPS								
60	0	0	6 (20.0)	11 (50.0)	1 (8.3)	1 (5.6)	4 (20.0)	16 (59.3)
70–80	18 (47.4)	23 (71.9)	22 (73.3)	10 (45.5)	10 (83.3)	12 (66.7)	14 (70.0)	9 (33.3)
90–100	20 (52.6)	9 (28.1)	2 (6.7)	1 (4.5)	1 (8.3)	5 (27.8)	2 (10.0)	2 (7.4)
Cardiac subpopulation[d]	5 (13.2)	9 (28.1)	12 (40.0)	14 (63.6)	0	8 (44.4)	11 (55.0)	17 (63.0)
mNIS+7, mean (SE)	25.4 (2.9)	48.5 (3.4)	85.9 (3.6)	104.2 (4.6)	26.3 (3.3)	47.8 (3.4)	77.2 (4.7)	112.1 (4.1)
Norfolk QOL-DN, mean (SE)	29.7 (3.5)[e]	42.7 (4.1)	58.0 (3.6)	68.1 (5.5)	34.9 (4.0)	41.1 (5.0)	63.5 (4.7)	68.9 (4.2)[f]
10-MWT, mean (SE)	1.25 (0.04)	1.24 (0.05)	0.79 (0.05)	0.54 (0.05)	1.05 (0.07)	0.95 (0.06)	0.80 (0.05)	0.56 (0.05)
R-ODS, mean (SE)	41.6 (1.1)	38.5 (1.2)	31.2 (1.4)	18.7 (1.7)	41.3 (2.0)	35.2 (1.7)	31.0 (1.7)	19.7 (1.5)[f]
mBMI, mean (SE)	1171.4 (39.2)	1089.8 (35.8)	927.7 (31.0)	990.2 (51.3)	1098.6 (66.1)	1004.2 (46.4)	899.9 (52.5)	998.8 (35.7)

Abbreviations: 10-MWT = 10-meter walk test; KPS = Karnofsky Performance Status; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; Q = quartile; R-ODS = Rasch-built Overall Disability Scale; SD = standard deviation; SE = standard error; TTR = transthyretin; V30M = Val30Met.

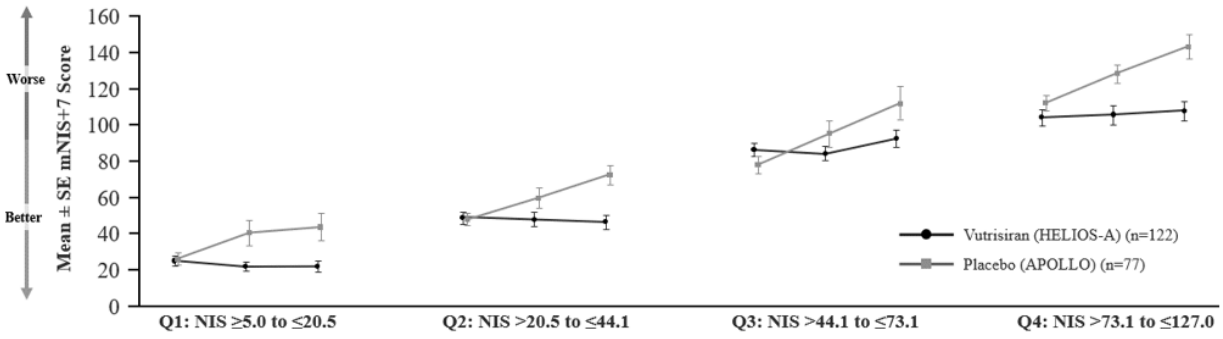
[a]Values are presented as n (%) unless otherwise specified. [b]Defined as <50 years of age at onset. [c]The non-V30M TTR genotype represents 25 different variants in HELIOS-A. [d]Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history). [e]n=37. [f]n=26.

EFFICACY RESULTS

mNIS+7

Across all NIS quartiles, a favorable effect of vutrisiran treatment compared with external placebo was observed for mNIS+7 at Month 9 and 18. **Figure 1** shows the mean change from baseline in mNIS+7 across NIS quartiles.[2]

Figure 1. Mean Change from Baseline in mNIS+7 Across NIS Quartiles.[2]



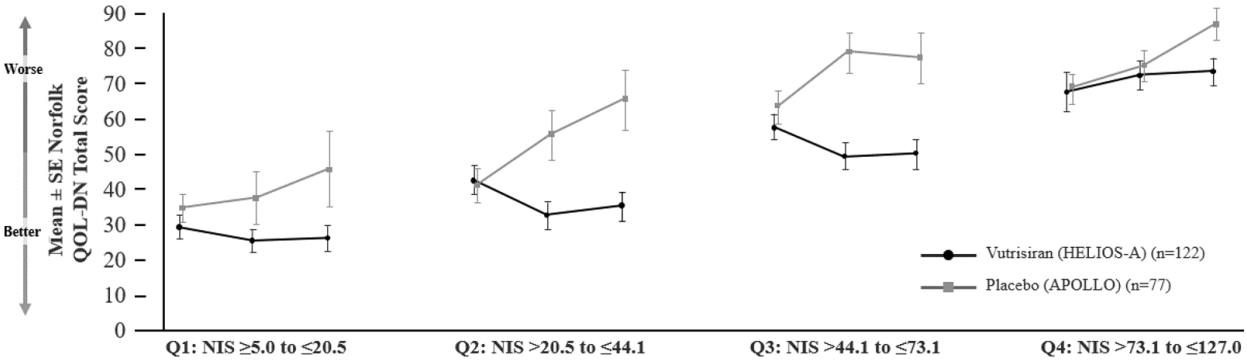
		Q1: NIS ≥5.0 to ≤20.5			Q2: NIS >20.5 to ≤44.1			Q3: NIS >44.1 to ≤73.1			Q4: NIS >73.1 to ≤127.0		
		BL	M9	M18	BL	M9	M18	BL	M9	M18	BL	M9	M18
Vutrisiran	n	38	38	37	32	32	29	30	24	25	22	22	21
	Mean (± SE)	—	-3.34	-2.95	—	-0.64	-3.07	—	-2.14	6.16	—	1.57	3.19
	Δ from baseline		(2.10)	(1.87)		(2.44)	(2.65)		(3.00)	(3.13)		(2.31)	(2.81)
Placebo	n	12	11	9	18	13	11	20	19	15	27	24	16
	Mean (± SE)	—	13.82	18.39	—	12.1	24.54	—	16.53	33.10	—	16.51	30.67
	Δ from baseline		(6.39)	(7.87)		(2.95)	(4.04)		(3.88)	(6.16)		(3.87)	(6.15)

Abbreviations: Δ = change; BL = baseline; M = month; mNIS+7 = modified Neuropathy Impairment Score+7; NIS = Neuropathy Impairment Score; Q = quartile; SE = standard error.
From Luigetti et al[2]

Norfolk QOL-DN

Across all NIS quartiles, a favorable effect of vutrisiran treatment compared with external placebo was observed for Norfolk QOL-DN at Month 9 and 18. **Figure 2** shows the mean change from baseline in Norfolk QOL-DN total score across NIS quartiles.[2]

Figure 2. Mean Change from Baseline in Norfolk QOL-DN Across NIS Quartiles.[2]



		Q1: NIS ≥5.0 to ≤20.5			Q2: NIS >20.5 to ≤44.1			Q3: NIS >44.1 to ≤73.1			Q4: NIS >73.1 to ≤127.0		
		BL	M9	M18	BL	M9	M18	BL	M9	M18	BL	M9	M18
Vutrisiran	n	37	37	36	32	32	29	30	24	25	22	22	21
	Mean (± SE)	—	-3.43	-2.00	—	-10.19	-6.41	—	-5.83	-3.60	—	4.64	3.95
	Δ from baseline		(2.72)	(3.76)		(2.89)	(2.69)		(4.38)	(4.68)		(3.91)	(4.73)
Placebo	n	12	11	9	18	13	11	20	19	15	26	22	13
	Mean (± SE)	—	4.18	10.89	—	13.69	25.64	—	16.05	18.00	—	9.91	24.54
	Δ from baseline		(5.15)	(7.27)		(4.98)	(4.28)		(3.70)	(4.48)		(4.89)	(7.83)

Abbreviations: Δ = change; BL = baseline; M = month; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life Diabetic Neuropathy; Q = quartile; SE = standard error.
From Luigetti et al[2]

10-MWT

Across all NIS quartiles, a favorable effect of vutrisiran treatment compared with external placebo was observed for 10-MWT at Month 18. **Table 2** shows the mean change from baseline in 10-MWT across NIS quartiles.[2]

Table 2. Mean Change from Baseline in 10-MWT (m/s) Across NIS Quartiles.[2]

	Q1 NIS ≥5.0 to ≤20.5			Q2 NIS >20.5 to ≤44.1			Q3 NIS >44.1 to ≤73.1			Q4 NIS >73.1 to ≤127.0		
	BL	M9	M18	BL	M9	M18	BL	M9	M18	BL	M9	M18
Vutrisiran												
n	38	38	37	32	31	29	30	24	25	22	22	20
Mean (± SE) Δ from baseline	—	0.02 (0.03)	0.02 (0.05)	—	-0.01 (0.04)	-0.01 (0.04)	—	0.03 (0.04)	0.02 (0.04)	—	-0.05 (0.03)	-0.1 (0.04)
Placebo												
n	12	11	10	18	14	11	20	19	16	26	24	18
Mean (± SE) Δ from baseline	—	0.01 (0.05)	-0.08 (0.07)	—	-0.13 (0.06)	-0.21 (0.09)	—	-0.16 (0.04)	-0.30 (0.06)	—	-0.17 (0.05)	-0.36 (0.08)

Abbreviations: Δ = change; 10-MWT = 10-meter walk test; BL = baseline; NIS = Neuropathy Impairment Score; Q = quartile; SE = standard error.

R-ODS

Across all NIS quartiles, a favorable effect of vutrisiran treatment compared with external placebo was observed for R-ODS at Months 9 and 18. **Table 3** shows the mean change from baseline in R-ODS across NIS quartiles.[2]

Table 3. Mean Change from Baseline in R-ODS Across NIS Quartiles.[2]

	Q1 NIS ≥5.0 to ≤20.5			Q2 NIS >20.5 to ≤44.1			Q3 NIS >44.1 to ≤73.1			Q4 NIS >73.1 to ≤127.0		
	BL	M9	M18	BL	M9	M18	BL	M9	M18	BL	M9	M18
Vutrisiran												
n	38	38	37	32	32	29	30	23	25	22	22	21
Mean (± SE) Δ from baseline	—	-0.05 (0.69)	0.47 (0.78)	—	-0.35 (1.16)	-1.21 (0.86)	—	-1.13 (1.19)	-2.68 (1.30)	—	-0.23 (1.31)	-2.10 (1.36)
Placebo												
n	12	11	9	18	13	11	20	18	15	26	23	14
Mean (± SE) Δ from baseline	—	-3.36 (1.47)	-4.00 (1.60)	—	-4.46 (1.03)	-8.73 (2.39)	—	-6.83 (1.28)	-10.47 (1.76)	—	-3.74 (1.02)	-12.26 (1.80)

Abbreviations: Δ = change; BL = baseline; NIS = Neuropathy Impairment Score; Q = quartile; R-ODS = Rasch-built Overall Disability Scale; SE = standard error.

mBMI

Across all NIS quartiles, a favorable effect of vutrisiran treatment compared with external placebo was observed for mBMI at Month 18. **Table 4** shows the mean change from baseline in mBMI across NIS quartiles.[2]

Table 4. Mean Change from Baseline in mBMI Across NIS Quartiles.[2]

	Q1 NIS ≥5.0 to ≤20.5			Q2 NIS >20.5 to ≤44.1			Q3 NIS >44.1 to ≤73.1			Q4 NIS >73.1 to ≤127.0		
	BL	M9	M18	BL	M9	M18	BL	M9	M18	BL	M9	M18
Vutrisiran												
n	38	36	37	32	32	29	30	24	25	22	22	21
Mean (± SE) Δ from baseline	—	7.89 (12.80)	30.52 (17.41)	—	7.97 (11.60)	31.13 (18.77)	—	-6.88 (12.67)	29.79 (18.80)	—	-2.34 (20.24)	-8.98 (21.55)
Placebo												
n	12	11	9	18	14	11	20	19	14	27	24	14
Mean (± SE) Δ from baseline	—	-73.59 (28.27)	-151.56 (34.55)	—	-61.46 (18.41)	-99.57 (28.07)	—	-63.30 (14.16)	-111.14 (17.75)	—	-60.44 (20.75)	-128.92 (30.20)

Abbreviations: Δ = change; BL = baseline; NIS = Neuropathy Impairment Score; Q = quartile; R-ODS = Rasch-built Overall Disability Scale; SE = standard error.

SAFETY RESULTS

In the external placebo group, treatment discontinuations were observed in all NIS quartiles, with 3 patients (25.0%) in Q1, 7 patients (38.9%) in Q2, 6 patients (30.0%) in Q3, and 13 patients (48.1%) in Q4 discontinuing treatment. In the vutrisiran group, there were no discontinuations in Q1 and Q4, while 2 patients (6.3%) in Q2 and 4 patients (13.3%) in Q3 discontinued treatment. Reasons for discontinuation across each treatment group and NIS quartile are summarized below in **Table 5**.[2]

Table 5. Treatment Discontinuations Across NIS Quartiles.[2]

	HELIOS-A Vutrisiran (n=122)				APOLLO External Placebo (n=77)			
	Q1 ≥5.0 to ≤20.5 (n=38)	Q2 >20.5 to ≤44.1 (n=32)	Q3 >44.1 to ≤73.1 (n=30)	Q4 >73.1 to ≤127.0 (n=22)	Q1 ≥5.0 to ≤20.5 (n=12)	Q2 >20.5 to ≤44.1 (n=18)	Q3 >44.1 to ≤73.1 (n=20)	Q4 >73.1 to ≤127.0 (n=27)
Discontinuations[a]	0	2 (6.3)	4 (13.3)	0	3 (25.0)	7 (38.9)	6 (30.0)	13 (48.1)
Reason for discontinuation[a]								
AE	0	0	0	0	1 (33.3)	2 (28.6)	1 (16.7)	3 (23.1)
Death	0	0	2 (50.0)	0	0	0	0	4 (30.8)
Other	0	2 (100.0)[b]	1 (25.0)[c]	0	0	0	0	0
Physician decision	0	0	1 (25.0)	0	0	0	0	2 (15.4)
Progressive disease	0	0	0	0	0	0	2 (33.3)	2 (15.4)
Withdrawal by patient	0	0	0	0	2 (66.7)	5 (71.4)	3 (50.0)	2 (15.4)

Abbreviations: AE = adverse event; NIS = Neuropathy Impairment Score; Q = quartile.

[a]Values are presented as n (%).

[b]Other reason for discontinuation reported as: patient withdrew informed consent (n=1); patient withdrew from study due to disease progression and hospice (n=1).

[c]Other reason for discontinuation reported as: withdrawal of consent from treatment. Health data collection still allowed (n=1).

ABBREVIATIONS

10-MWT = 10-meter walk test; AE = adverse event; BL = baseline; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; KPS = Karnofsky Performance Status; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; Q = quartile; R-ODS = Rasch-built Overall Disability Scale; SD = standard deviation; SE = standard error; TTR = transthyretin; V30M = Val30Met.

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