Impact of Baseline Polyneuropathy Severity on Vutrisiran Treatment Response in the Phase 3 HELIOS-A Study

P 113

Marco Luigetti[1]✉, Dianna Quan[2], John L. Berk[3], Isabel Conceição[4], Yohei Misumi[5], Chi-Chao Chao[6], Shaun Bender[7], Emre Aldinc[7], John Vest[7], David Adams[8]

[1]Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, Italy; [2]Department of Neurology, University of Colorado Anschutz, Aurora, CO, USA; [3]Boston Medical Center, Boston, MA, USA; [4]Department of Neurology, CHULN, Hospital Santa Maria and Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal; [5]Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; [6]Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan; [7]Alnylam Pharmaceuticals, Cambridge, MA, USA; [8]Neurology Department, CHU Bicêtre, APHP, Université Paris-Saclay, Le Kremlin Bicêtre Cedex, France

Conclusions

- **Vutrisiran treatment demonstrated a beneficial effect on neurologic function and other key disease measures through 18 months, compared with external placebo, over a wide range of polyneuropathy severities, as assessed by baseline Neuropathy Impairment Score (NIS)**
- **These benefits of vutrisiran versus external placebo, observed across all baseline NIS quartiles for polyneuropathy, quality of life, gait speed, disability, and nutritional status measures, highlight the impact of vutrisiran across the spectrum of hereditary transthyretin-mediated (hATTR) amyloidosis disease severity**
  - **Overall, patients who were in lower NIS quartiles (less severe disease) at vutrisiran initiation maintained better scores compared with those in higher NIS quartiles**
  - **The external placebo group progressively worsened in all measures by Month 18**
- **The HELIOS-A randomized treatment extension period is ongoing and may inform the longer-term efficacy and safety of vutrisiran in patients with hATTR amyloidosis with polyneuropathy**

Background & Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- Rare, rapidly progressive, debilitating, and fatal disease caused by variants in the *TTR* gene[1–4]
- Pathogenic *TTR* variants cause the TTR protein to misfold and accumulate as amyloid deposits in multiple organs and tissues[5,6]
- Patients have significant impairment across multiple areas of health and wellbeing, with disease progression leading to poor quality of life, loss of physical function, and death[7–9]

Vutrisiran

- An RNAi therapeutic that targets hepatic production of variant and wild-type TTR
- Approved for the treatment of hATTR amyloidosis with polyneuropathy based on the positive results from the Phase 3 HELIOS-A study[10]
  - Vutrisiran utilizes enhanced stabilization chemistry, designed for increased potency and high metabolic stability, allowing for subcutaneous injection every 3 months

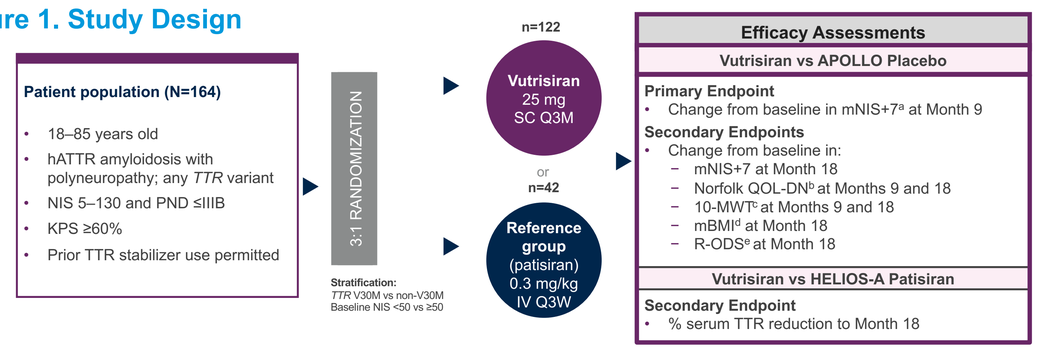
Objective

- To evaluate the impact of baseline polyneuropathy severity on response to vutrisiran treatment in the HELIOS-A study

Methods

- HELIOS-A is a Phase 3, global, open-label study of vutrisiran 25 mg SC Q3M in patients with hATTR amyloidosis with polyneuropathy **(Figure 1)**
  - In the primary analysis, efficacy and safety of up to 18 months of vutrisiran treatment were compared with the external APOLLO placebo group

Figure 1. Study Design



[a]Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). [b]Higher scores of Norfolk QOL-DN indicate worse quality of life (range, −4 to 136). [c]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. [d]Lower scores of mBMI (weight [in kg/m^2] × serum albumin [in g/L]) indicate worse nutritional status. [e]Lower scores of R-ODS indicate more disability (range, 0 to 48).

Post Hoc Analysis by Baseline Polyneuropathy Severity

- Patients were divided into quartiles based on baseline Neuropathy Impairment Score (NIS):
  - Q1 ≥5.0–≤20.5 (n=50)
  - Q2 >20.5–≤44.1 (n=50)
  - Q3 >44.1–≤73.1 (n=50)
  - Q4 >73.1–≤127.0 (n=49)
- Primary and secondary/exploratory endpoints were analyzed by baseline NIS quartile over 18 months:
  - Polyneuropathy: mNIS+7
  - QOL: Norfolk QOL-DN
  - Disability: R-ODS
  - Gait speed: 10-MWT
  - Nutritional status: mBMI
- Data are descriptively summarized for the mITT population as mean change from baseline for each endpoint in each NIS quartile

Results

Baseline Demographic and Disease Characteristics

- Across baseline NIS quartiles, vutrisiran patients and external placebo patients were generally clinically comparable

Table 1. Baseline Characteristics

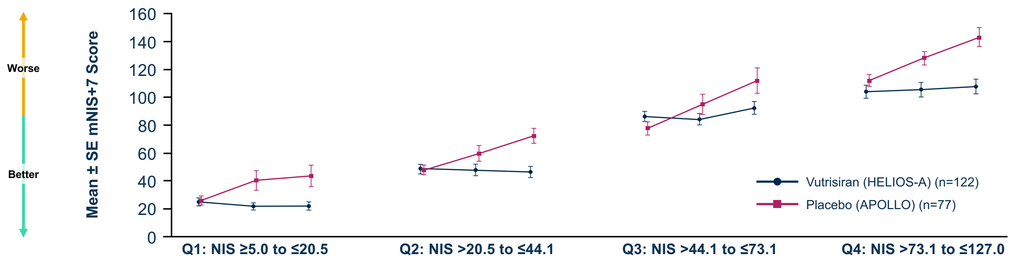
Characteristic	HELIOS-A Vutrisiran (n=122) Q1 ≥5.0 to ≤20.5 (n=38)	Q2 >20.5 to ≤44.1 (n=32)	Q3 >44.1 to ≤73.1 (n=30)	Q4 >73.1 to ≤127.0 (n=22)	APOLLO Placebo (n=77) Q1 ≥5.0 to ≤20.5 (n=12)	Q2 >20.5 to ≤44.1 (n=18)	Q3 >44.1 to ≤73.1 (n=20)	Q4 >73.1 to ≤127.0 (n=27)
Age (years), median (range)	54.5 (31–73)	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, n (%)	18 (47.4)	24 (75.0)	20 (66.7)	17 (77.3)	6 (50.0)	13 (72.2)	16 (80.0)	23 (85.2)
Time since hATTR diagnosis (years), mean (SD)	4.17 (4.12)	2.86 (3.75)	3.38 (3.48)	2.64 (3.00)	3.75 (4.49)	1.92 (2.40)	2.45 (2.58)	2.65 (3.56)
TTR genotype, n (%)								
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, n (%)	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[a]	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, n (%)	24 (63.2)	18 (56.3)	16 (53.3)	17 (77.3)	5 (41.7)	9 (50.0)	16 (80.0)	11 (40.7)
Karnofsky performance status, n (%)								
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[b], n (%)	5 (13.2)	9 (28.1)	12 (40.0)	14 (63.6)	0	8 (44.4)	11 (55.0)	17 (63.0)

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

Polyneuropathy (mNIS+7)

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on mNIS+7 compared with external placebo, first evident at Month 9 and continued to Month 18 **(Figure 2)**
- In general, patients with less severe disease at baseline had lower impairment in polyneuropathy at Month 18 **(Figure 2)**

Figure 2. Mean Change from Baseline in mNIS+7 Score



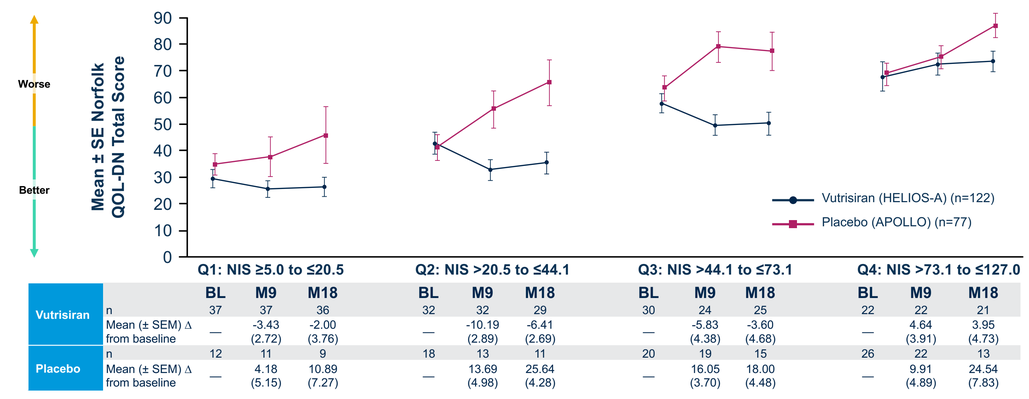
		Q1: NIS ≥5.0 to ≤20.5 BL	M9	M18	Q2: NIS >20.5 to ≤44.1 BL	M9	M18	Q3: NIS >44.1 to ≤73.1 BL	M9	M18	Q4: NIS >73.1 to ≤127.0 BL	M9	M18
Vutrisiran	n	38	38	37	32	32	29	30	24	25	22	22	21
	Mean (± SEM) Δ from baseline	—	-3.34 (2.10)	-2.95 (1.87)	—	-0.64 (2.44)	-3.07 (2.65)	—	-2.14 (3.00)	6.16 (3.13)	—	1.57 (2.31)	3.19 (2.81)
Placebo	n	12	11	9	18	13	11	20	19	15	27	24	16
	Mean (± SEM) Δ from baseline	—	13.82 (6.39)	18.39 (7.87)	—	12.11 (2.95)	24.54 (4.04)	—	16.53 (3.88)	33.10 (6.16)	—	16.51 (3.87)	30.67 (6.15)

Results (cont.)

Quality of Life (Norfolk QOL-DN)

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on Norfolk QOL-DN compared with external placebo, first evident at Month 9 and continued to Month 18 **(Figure 3)**
- In general, patients with less severe disease at baseline had lower impairment in neuropathy-related QOL at Month 18 **(Figure 3)**

Figure 3. Mean Change from Baseline in Norfolk QOL-DN Total Score



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

Gait Speed (10-MWT, m/s)

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on 10-MWT compared with external placebo at Month 18 **(Figure 4)**
- In general, patients with less severe disease at baseline had lower impairment in gait speed at Month 18 **(Figure 4)**

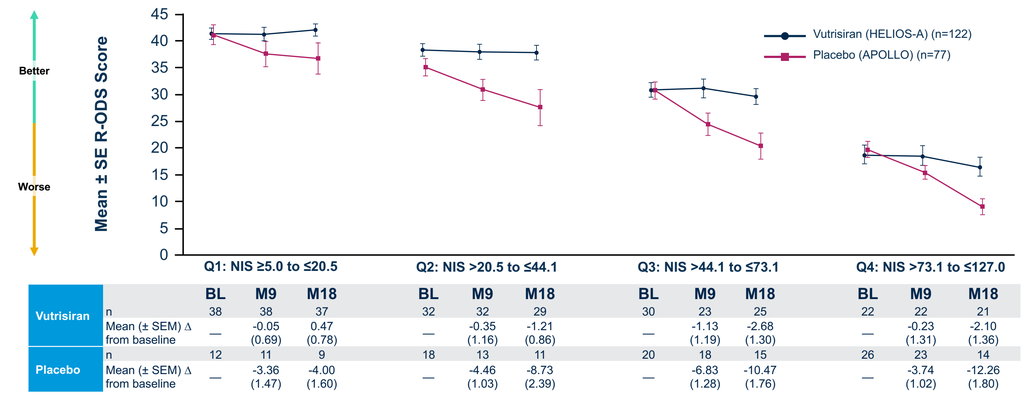
Figure 4. Mean Change from Baseline in 10-MWT (m/s)

		Q1: NIS ≥5.0 to ≤20.5 BL	M9	M18	Q2: NIS >20.5 to ≤44.1 BL	M9	M18	Q3: NIS >44.1 to ≤73.1 BL	M9	M18	Q4: NIS >73.1 to ≤127.0 BL	M9	M18
Vutrisiran	n	38	38	37	32	31	29	30	24	25	22	22	20
	Mean (± SEM) 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	27	24	18
	Mean (± SEM) 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)

Disability (R-ODS)

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on R-ODS compared with external placebo, first evident at Month 9 and continued to Month 18 **(Figure 5)**
- In general, patients with less severe disease at baseline had lower impairment in disability status at Month 18 **(Figure 5)**

Figure 5. Mean Change from Baseline in R-ODS

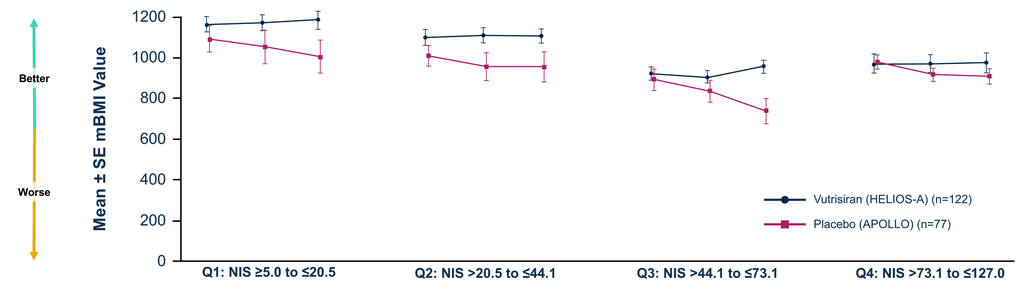


		Q1: NIS ≥5.0 to ≤20.5 BL	M9	M18	Q2: NIS >20.5 to ≤44.1 BL	M9	M18	Q3: NIS >44.1 to ≤73.1 BL	M9	M18	Q4: NIS >73.1 to ≤127.0 BL	M9	M18
Vutrisiran	n	38	38	37	32	32	29	30	23	25	22	22	21
	Mean (± SEM) Δ from baseline	—	-0.05 (0.69)	0.47 (0.78)	—	-0.35 (1.16)	-1.21 (0.86)	—	-1.13 (1.19)	-2.68 (1.30)	—	-0.23 (1.31)	-2.10 (1.36)
Placebo	n	12	11	9	18	13	11	20	18	15	26	23	14
	Mean (± SEM) 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)

Nutritional Status (mBMI)

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on mBMI compared with external placebo at Month 18 **(Figure 6)**
- In general, patients with less severe disease at baseline had lower impairment in nutritional status at Month 18 **(Figure 6)**

Figure 6. Mean Change from Baseline in mBMI



		Q1: NIS ≥5.0 to ≤20.5 BL	M9	M18	Q2: NIS >20.5 to ≤44.1 BL	M9	M18	Q3: NIS >44.1 to ≤73.1 BL	M9	M18	Q4: NIS >73.1 to ≤127.0 BL	M9	M18
Vutrisiran	n	38	36	37	32	32	29	30	24	25	22	22	21
	Mean (± SEM) 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 (± SEM) 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)

Disclosures: ML reports consulting fees and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Alnylam Pharmaceuticals, Pfizer, and Sobi; DQ reports research funding from Alexion, Alnylam Pharmaceuticals, Cytokinetics, Ionis Pharmaceuticals, Janssen Pharmaceuticals (formerly Momenta Pharmaceuticals), Pfizer, and Viela Bio, and consulting fees from Alnylam Pharmaceuticals and Ionis Pharmaceuticals; JLB reports research funding from Alnylam Pharmaceuticals, AstraZeneca, Eidos Therapeutics, and Ionis Pharmaceuticals, consulting fees from Alnylam Pharmaceuticals, AstraZeneca, Eidos Therapeutics, Ionis Pharmaceuticals, and Intellia Therapeutics, and data safety monitoring and/or advisory board membership for Alnylam Pharmaceuticals, AstraZeneca, Corino Therapeutics, Intellia Therapeutics, and Ionis Pharmaceuticals; IC reports consulting fees from Alnylam Pharmaceuticals and Pfizer, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Akcea Therapeutics, Alnylam Pharmaceuticals, and Pfizer, and data safety monitoring and/or advisory board membership for Alnylam Pharmaceuticals; YM reports research funding and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Alnylam Pharmaceuticals and Pfizer; C-CC has nothing to disclose; SB, EA, and JV are all employees of Alnylam Pharmaceuticals, and EA and JV report ownership of equity in Alnylam Pharmaceuticals; DA reports consulting fees from Alnylam Pharmaceuticals. **Abbreviations:** 10-MWT, 10-meter walk test; ATTRv, hereditary transthyretin (v for variant); BL, baseline; hATTR, hereditary transthyretin-mediated; IV, intravenous; KPS, Karnofsky performance status; M, month; 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; PND, polyneuropathy disability; Q, quartile; Q3M, every 3 months; Q3W, every 3 weeks; QOL, quality of life; RNAi, RNA interference; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; SD, standard deviation; SE, standard error; SEM, standard error of the mean; TTR, transthyretin. **References:** 1. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 2. Hawkins et al. *Ann Med* 2015;47:625–38; 3. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 4. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 5. Kelly. *Structure* 1997;5:595–600; 6. Koike and Katsuno. Biomedicines 2019;7:11; 7. Lane et al. *Orphanet J Rare Dis* 2015;10(Suppl. 1):O26; 8. Adams et al. *Neurology* 2015;85:675–82; 9. Adams et al. *Curr Opin Neurol* 2016;29(Suppl. 1):S14–26; 10. Adams et al. *Amyloid* 2023;30;18–26.
Funding: This study was funded by Alnylam Pharmaceuticals. **Acknowledgments:** Medical writing assistance was provided by Jack Law, PhD, of Adelphi Communications Ltd, UK, and funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice Guidelines.

Thank you to the patients, their families, Investigators, study staff, and collaborators for their participation in the HELIOS-A study.

Presented at: Peripheral Nerve Society (PNS) Annual Meeting, June 17–20, 2023, Copenhagen, Denmark.

✉ **mluigetti@gmail.com**