HELIOS-A: Results From the Phase 3 Study of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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April 2–7, 2022 || American Academy of Neurology (AAN)

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Disclosures for Michael Polydefkis

Conflict	Disclosures
Consultant	Akcea Alnylam Pharmaceuticals Biogen Idec Pfizer Vertex Pharmaceuticals

Background and Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- Rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease
- Caused by variants in the *TTR* gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs and tissues[1–4]
- The majority of individuals develop a mixed phenotype of polyneuropathy and cardiomyopathy[5,6]

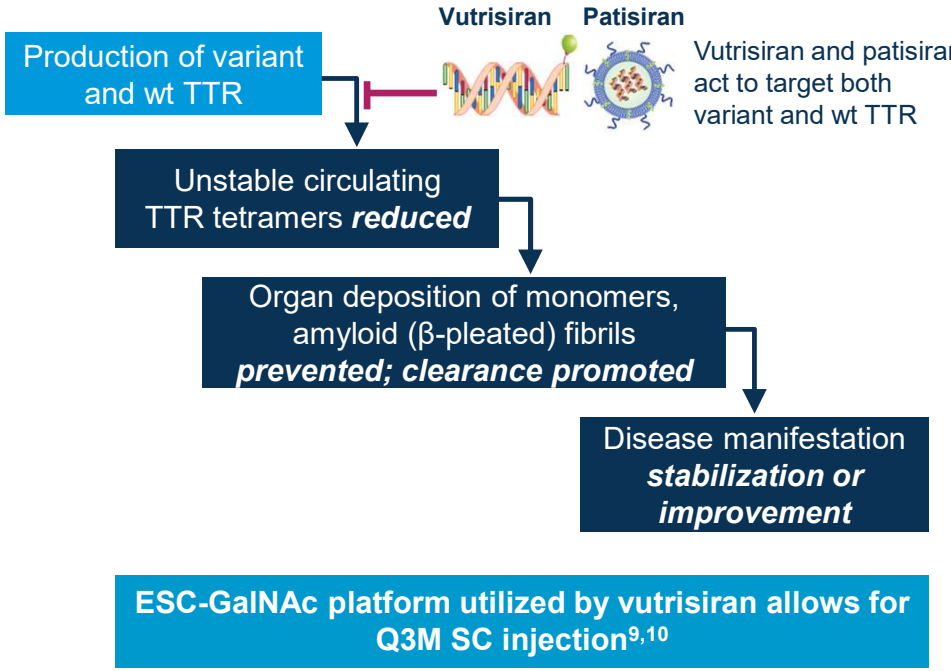
Vutrisiran

- Investigational, subcutaneously administered RNAi therapeutic targeting hepatic production of variant and wt TTR in development for the treatment of ATTR amyloidosis[7,8]

Patisiran

- RNAi therapeutic administered via IV infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on the Phase 3, placebo-controlled APOLLO trial[9–12]

Therapeutic Hypothesis



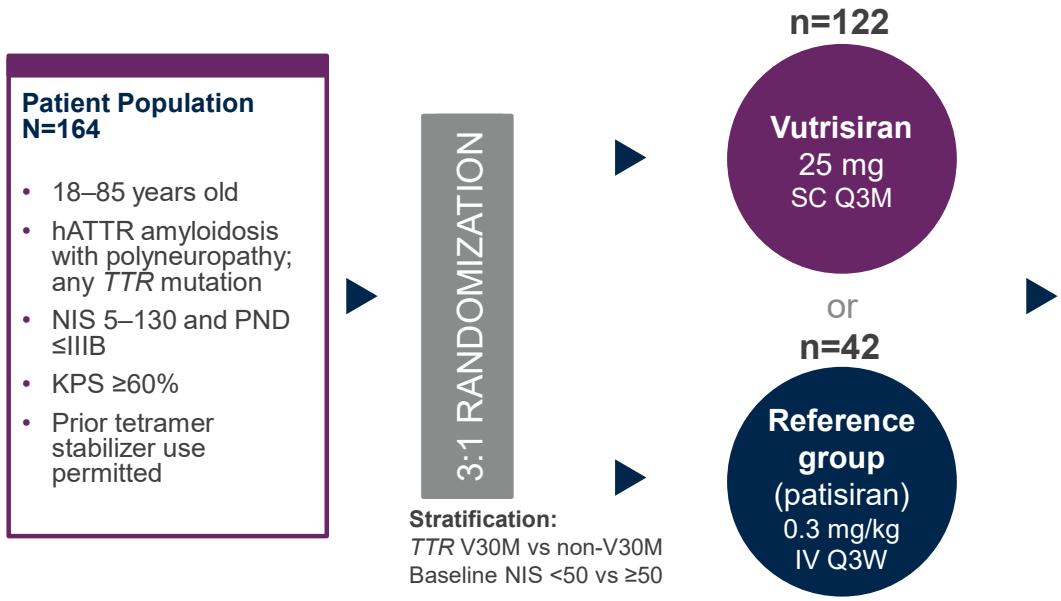
ESC-GalNAc platform utilized by vutrisiran allows for Q3M SC injection[9,10]

ATTRv, hereditary transthyretin (v for variant); ESC, enhanced stabilization chemistry; GalNAc, *N*-acetylgalactosamine; hATTR, hereditary transthyretin-mediated; IV, intravenous; Q3M, every 3 months; RNAi, ribonucleic acid interference; SC, subcutaneous; TTR, transthyretin; wt, wild-type.

1. Hanna M. *Curr Heart Fail Rep* 2014;11:50–57; 2. Hawkins PN et al. *Ann Med* 2015;47:625–638; 3. Damy T et al. *J Cardiovasc Transl Res* 2015;8:117–127; 4. Mohty D et al. *Arch Cardiovasc Dis* 2013;106:528–540; 5. Rapezzi C et al. *Eur Heart J* 2013;34:520–528; 6. Coelho T et al. *Curr Med Res Opin* 2013;29:63–76; 7. Habtemariam BA et al. *Clin Pharmacol Ther* 2021;109:372–382; 8. Nair JK et al. *J Am Chem Soc* 2014;136:16958–16961; 9. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. February 2020; 10. Adams D et al. *N Engl J Med* 2018;379:11–21; 11. APOLLO: NCT01960348; 12. Alnylam France, Résumé des caractéristiques du produit ONPATTRO® (patisiran).

Vutrisiran Phase 3 HELIOS·A Study in Patients with Hereditary Transthyretin-Mediated Amyloidosis Polyneuropathy

- Efficacy and safety analyses up to Month 18 of vutrisiran compared with the external APOLLO placebo group are presented



Efficacy Assessments

Vutrisiran vs APOLLO Placebo

Primary Endpoint (at Month 9; previously presented[1])
- Change from baseline in mNIS+7[a]

Secondary Endpoints
Change from baseline in:
- mNIS+7 at Month 18
- Norfolk QOL-DN[b] at Months 9 and 18
- 10-MWT[c] at Months 9 and 18
- mBMI[d] at Month 18
- R-ODS[e] at Month 18

Vutrisiran vs HELIOS-A Patisiran

Secondary Endpoint
- % serum TTR reduction to Month 18

[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).

10-MWT, 10-meter walk test; hATTR, hereditary transthyretin-mediated amyloidosis; 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; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; TTR, transthyretin.

1. Adams D et al. *Neurology* 2021;96(15 Supplement):1234.

Baseline Demographic and Disease Characteristics

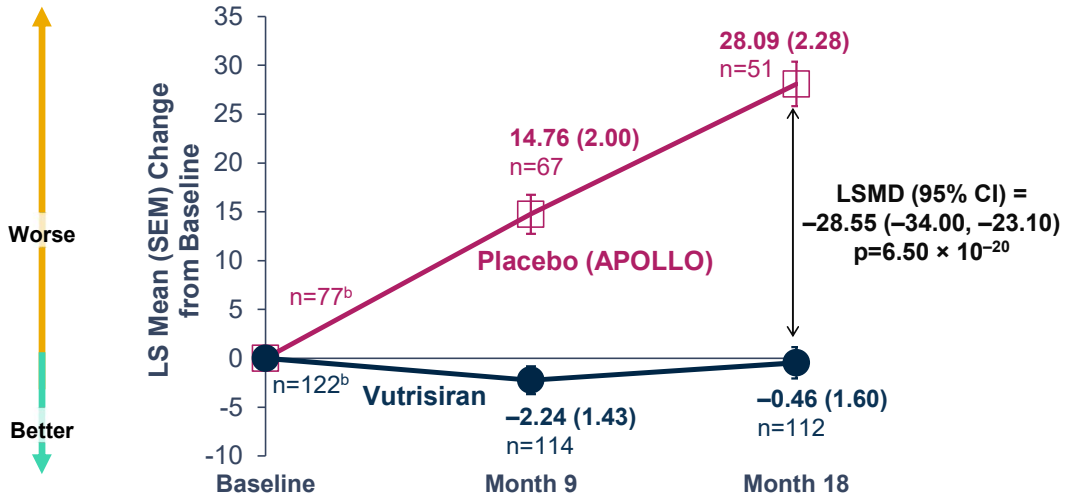
Characteristic	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
Age (years), median (range)	63 (34, 80)	60 (26, 85)	60 (31, 81)
Males, n (%)	58 (75)	79 (65)	27 (64)
TTR genotype, n (%)			
V30M	40 (52)	54 (44)	20 (48)
Non-V30M	37 (48)	68 (56)	22 (52)
NIS, mean (range)	57 (7, 126)	43 (5, 127)	43 (6, 116)
Previous tetramer stabilizer use, n (%)	41 (53)	75 (61)	33 (79)
PND score[a], n (%)			
I: preserved walking, sensory disturbances	20 (26)	44 (36)	15 (36)
II: impaired walking but can walk without stick or crutch	23 (30)	50 (41)	17 (40)
IIIA: walk with 1 stick or crutch	22 (29)	16 (13)	7 (17)
IIIB: walk with 2 sticks or crutches	11 (14)	12 (10)	3 (7)
Cardiac subpopulation, n (%)[b,c]	36 (47)	40 (33)	14 (33)

[a]One patient (1.3%) in the external placebo group had a PND score of IV defined as confined to wheelchair or bedridden (not shown on the slide). [b]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). [c]Select echocardiogram parameters were reread for the Month 18 analysis and the cardiac subpopulation was rederived based on baseline LV wall thickness values after the re-read. As a result, in the Month 18 analysis the cardiac subpopulation status of 9 patients receiving vutrisiran was reclassified and 1 patient receiving patisiran was added to the cardiac subpopulation compared with the cardiac subpopulation defined in the Month 9 analysis.
LV, left ventricular; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin.

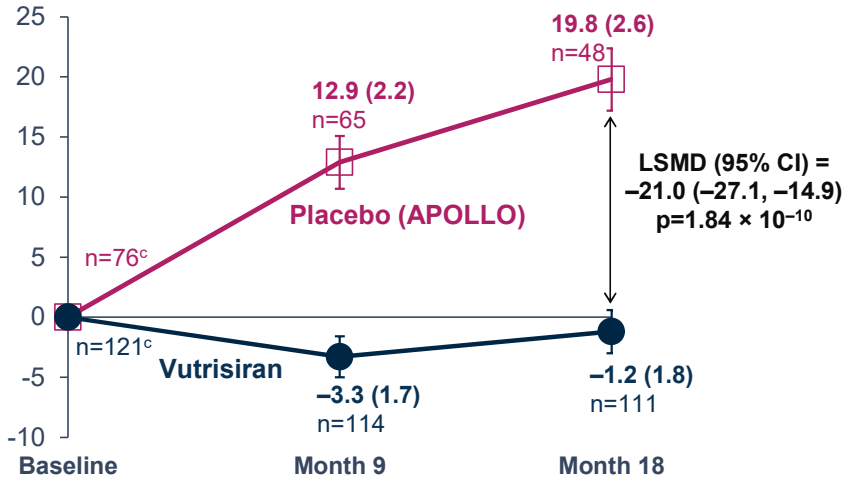
Statistically Significant Improvement in Neuropathy Impairment and Quality of Life with Vutrisiran vs External Placebo at Month 18

- As previously reported, the primary endpoint of change from baseline in mNIS+7 compared with the external placebo group at Month 9 was met[1]
- Improvement in mNIS+7 and Norfolk QOL-DN compared with placebo was consistently observed across all prespecified patient subgroups (data not shown)

mNIS+7 LS Mean Change from Baseline[a]



Norfolk QOL-DN LS Mean Change from Baseline[a]



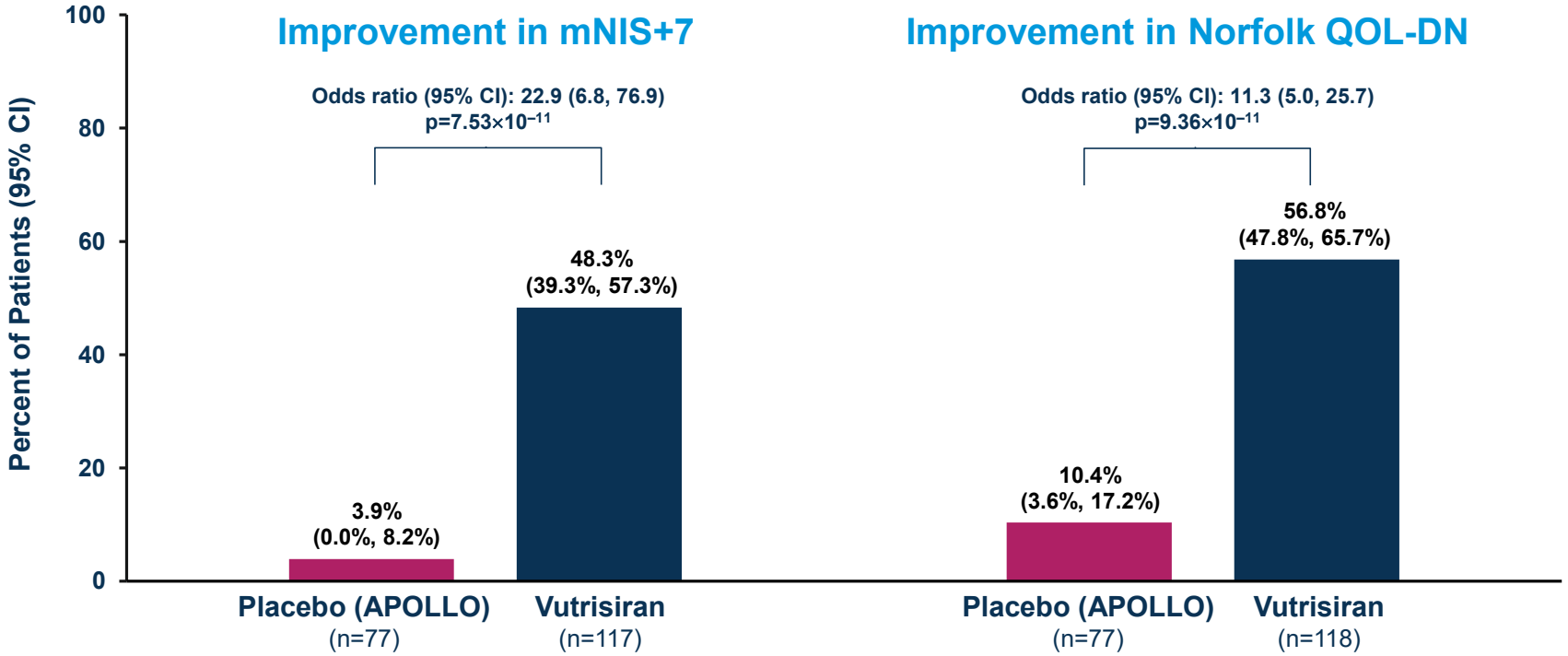
[a]mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted for mNIS+7 and Norfolk QOL-DN at Month 9 are ANCOVA/multiple imputation model data and data plotted at Month 18 are MMRM model data. **[b]At baseline, the mean (±SD) mNIS+7 was 60.6 (36.0) in the vutrisiran group and 74.6 (37.0) in the external placebo group. [c]At baseline, the mean (±SD) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group.**

ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SD, standard deviation; SEM, standard error of the mean.

1. Adams D et al. *Neurology* 2021;96(15 Supplement):1234.

Improvement from Baseline in Neurologic Impairment and Quality of Life at Month 18 in Approximately Half of Patients Receiving Vutrisiran

Percent of Patients Achieving Improvement from Baseline in mNIS+7[a] and Norfolk QOL-DN[a] at Month 18

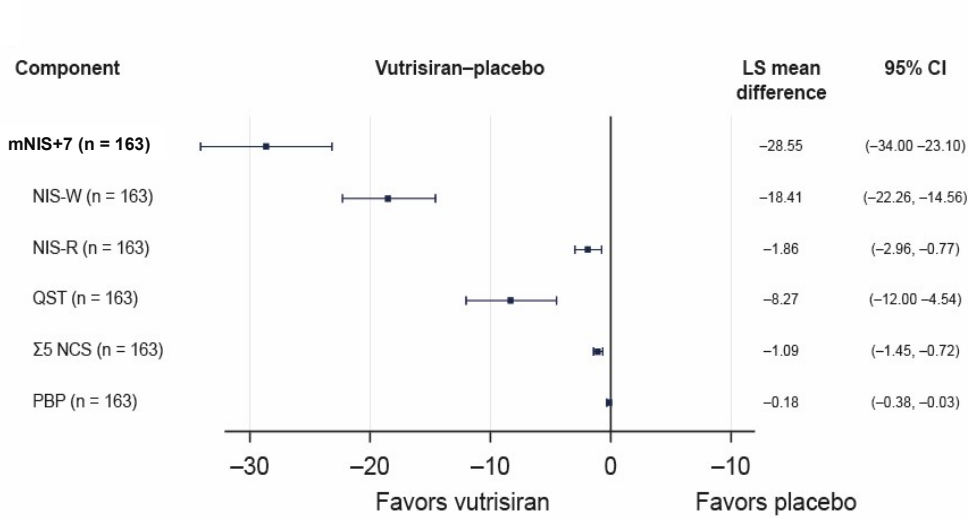


Improvement defined as patients with <0-point increase from baseline to 18 months. [a]Patients with missing postbaseline values due to COVID-19 (including values on or after onset of a serious COVID-19 AE) were excluded from analysis. Assessments after initiation of local standard treatment for hATTR amyloidosis were treated as missing.

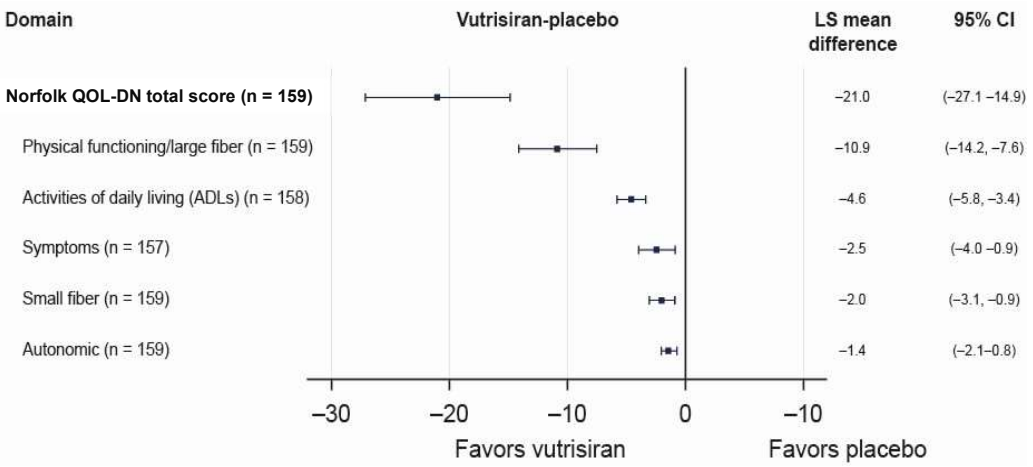
AE, adverse event; CI, confidence interval; hATTR, hereditary transthyretin-mediated; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy.

Consistent Improvement Across All Components of mNIS+7 and All Domains of Norfolk QOL-DN with Vutrisiran vs External Placebo at Month 18

mNIS+7 Total and Component Scores
LS Mean Change From Baseline to Month 18[a]



Norfolk QOL-DN Total and Domain Scores
LS Mean Change From Baseline to Month 18[a]



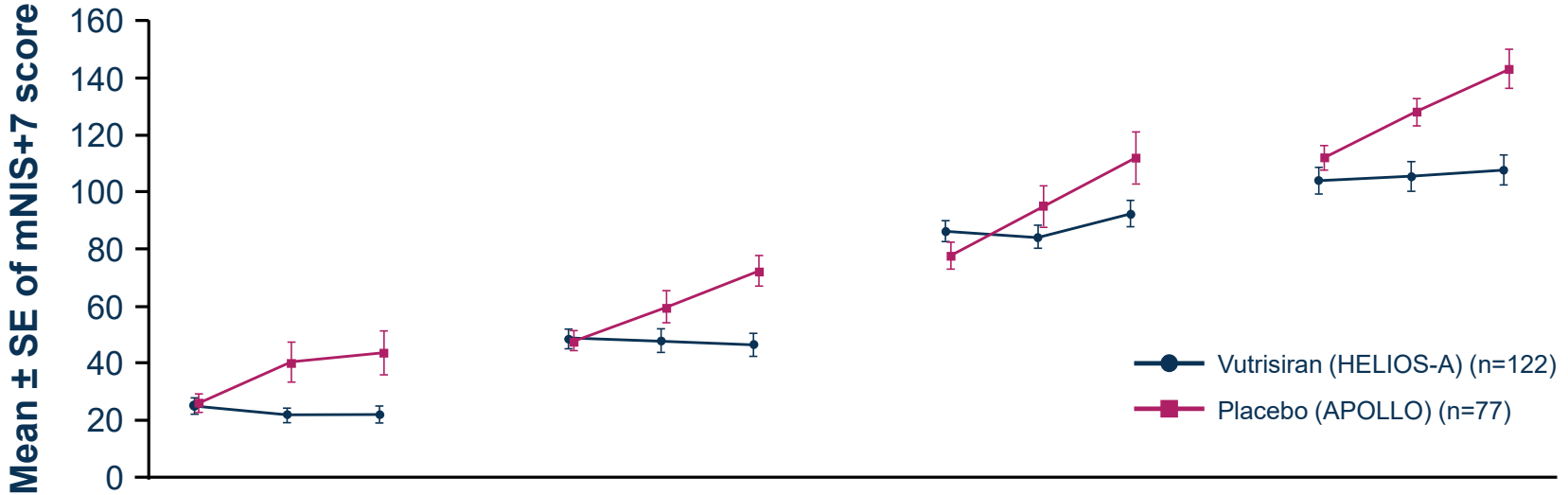
[a]mITT population

Σ5 NCS, Σ5 nerve conduction studies; ADL, activities of daily living; CI, confidence interval; LS, least squares; mITT, modified intent-to-treat; mNIS+7, modified Neuropathy Impairment Score +7; NIS-R, Neuropathy Impairment Score-Muscle Stretch Reflexes; NIS-W, Neuropathy Impairment Score-Weakness; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PBP, postural blood pressure; QST, Quantitative Sensory Testing.

Improvement in Neuropathy with Vutrisiran vs External Placebo Regardless of Baseline Disease Severity

- Patients with the least severe disease at start of treatment retained the greatest level of neurologic function at 18 months

mNIS+7 Score Across 18 Months by Baseline NIS Quartile[a] (mITT population)



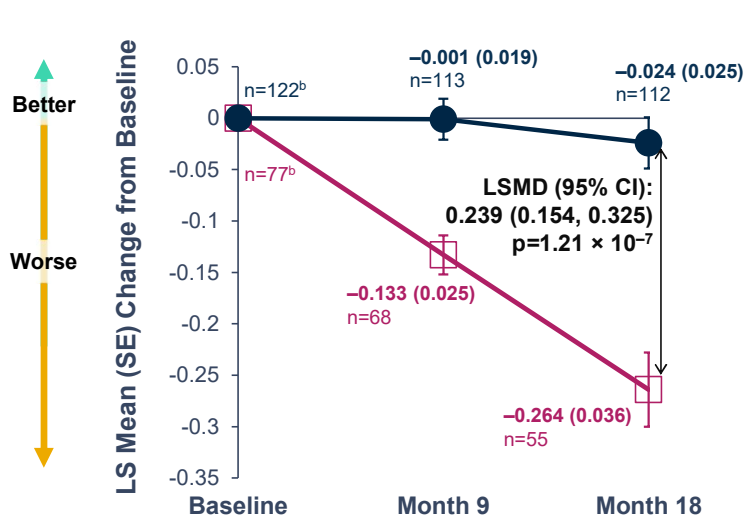
	Q1: NIS ≥5.0 to ≤20.5			Q2: NIS >20.5 to ≤44.1			Q3: NIS >44.1 to ≤73.1			Q4: NIS >73.1 to ≤127.0		
	BL	M9	M18	BL	M9	M18	BL	M9	M18	BL	M9	M18
n evaluable												
Vutrisiran	38	38	37	32	32	29	30	24	25	22	22	21
Placebo	12	11	9	18	13	11	20	19	15	27	24	16

[a]For this post hoc subgroup analysis, patients were divided into 4 quartiles, with approximately the same number of patients in each quartile, based on increasing baseline NIS

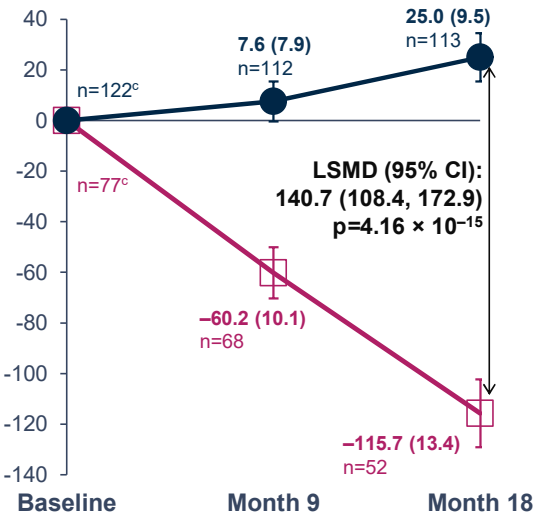
BL, baseline; M, month; mITT, modified intent-to-treat; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Q, quartile; SE, standard error

Statistically Significant Improvement in Secondary Endpoints with Vutrisiran vs External Placebo at Month 18

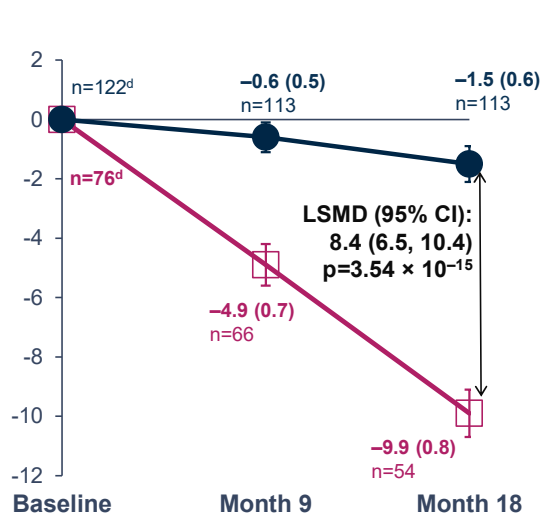
10-MWT (Gait Speed) LS Mean Change from Baseline[a]



mBMI (Nutritional Status) LS Mean Change from Baseline[a]



R-ODS (Disability) LS Mean Change from Baseline[a]



Placebo (APOLLO) — Vutrisiran

[a]mITT population (all randomized patients who received any amount of study drug) for all endpoints. Value of n is the number of evaluable patients at each timepoint. Data plotted for 10-MWT, mBMI and R-ODS at Month 9 are ANCOVA/multiple imputation model data and data plotted at Month 18 are MMRM model data. [b]**At baseline, the mean (±SD) 10-MWT was 1.006 (0.393) in the vutrisiran group and 0.790 (0.319) in the external placebo group.** [c]**At baseline, the mean (±SD) mBMI was 1057.4 (233.8) in the vutrisiran group and 989.9 (214.2) in the external placebo group.** [d]**At baseline, the mean (±SD) R-ODS was 34.1 (11.0) in the vutrisiran group and 29.8 (10.8) in the external placebo group.**

10-MWT, 10-meter walk test; ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSMD, LS mean difference; mBMI, modified body mass index; mITT, modified intent-to-treat; MMRM, mixed model repeated measures; R-ODS, Rasch-built Overall Disability Scale; SD, standard deviation; SE, standard error.

Treatment Effects Observed with Vutrisiran Were Consistent with Patisiran in APOLLO

Post Hoc Cross-Study Assessment of LS Mean Change From Baseline to 18 Months for Various Endpoints for Vutrisiran and APOLLO Patisiran

Endpoint	HELIOS-A		APOLLO	
	Vutrisiran (n=112[a]) LS mean change from baseline (95% CI)	Vutrisiran – Placebo LS mean difference (95% CI)	Patisiran (n=148[e]) LS mean change from baseline (95% CI)	Patisiran – Placebo LS mean difference (95% CI)
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] (m/s)	−0.024 (–0.075, 0.026)	0.239 (0.154, 0.325)	0.077 (0.029, 0.124)	0.311 (0.230, 0.393)

- Vutrisiran efficacy in HELIOS-A was similar to that seen with patisiran in APOLLO
- Patisiran efficacy in HELIOS-A was similar to that previously observed in APOLLO
  - Mean change from baseline for the HELIOS-A patisiran arm was 1.59 for mNIS+7, –0.6 for Norfolk, and –0.043 m/s for 10-MWT[f]

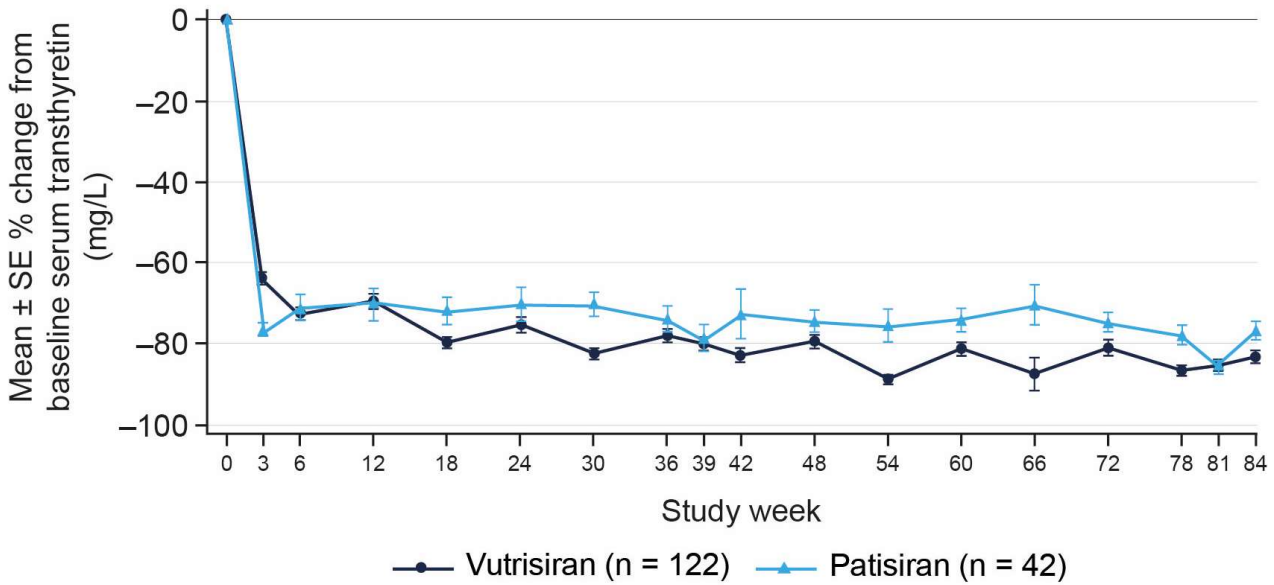
[a]Number of evaluable patients: mNIS+7 and 10-MWT, n=112; Norfolk QOL-DN, n=111. [b]Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). [c]Higher scores of Norfolk QOL-DN indicate worse quality of life (range, -4 to 136). [d]10-meter walk test (10-MWT) speed (m/s) = 10 meters/mean 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. [f]HELIOS-A patisiran arm was not intended for statistical testing vs vutrisiran for mNIS+7, Norfolk QOL-DN, or 10-MWT endpoints, thus the results are presented as arithmetic means per statistical analysis plan.

10-MWT, 10-meter walk test; CI, confidence interval; LS, least squares; mITT, modified intent-to-treat; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy.

Rapid and Sustained Reduction in Serum TTR Levels with Vutrisiran

- Vutrisiran achieved a mean steady-state serum TTR reduction from baseline of 88% (SD: 16%)
- TTR reduction with vutrisiran was non-inferior to that observed with the within-study patisiran reference group (secondary endpoint) over 18 months (median TTR difference (vutrisiran-patisiran) [95% CI], 5.28% [1.17, 9.25], lower limit of confidence interval > –10%)

Percent Change from Baseline in Serum TTR Levels



N evaluable																		
Vutrisiran (n = 122)	122	114	109	119	106	117	92	118	115	56	116	42	118	15	118	100	114	98
Patisiran (n = 42)	42	42	41	41	37	38	39	34	39	23	40	23	36	9	37	36	38	32

SD, standard deviation; SE, standard error; TTR, transthyretin.

HELIOS-A Safety Summary[a]

The majority of AEs were mild or moderate in severity

- No drug-related discontinuations or deaths
- Three study discontinuations (2.5%) due to AEs in the vutrisiran arm (two due to death, as previously reported; one due to a non-fatal heart failure event), none of which were considered related to study drug
  - One death due to COVID-19 pneumonia and the other due to iliac artery occlusion
- As previously reported, two SAEs deemed related to vutrisiran by investigators:
  - Dyslipidemia and urinary tract infection
- AEs ≥10% in the vutrisiran group included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness
  - All except arthralgia and pain in extremity were reported at a similar or lower frequency than external placebo
- Injection-site reactions were reported in 5 patients (4.1%) receiving vutrisiran; all were mild and transient
- No safety signals regarding liver function tests, hematology, or renal function related to vutrisiran

HELIOS-A Safety Summary[a]

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)
SAEs	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	11 (14.3)	3 (2.5)	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	3 (2.5)	2 (4.8)
Deaths	6 (7.8)	2 (1.6)	3 (7.1)

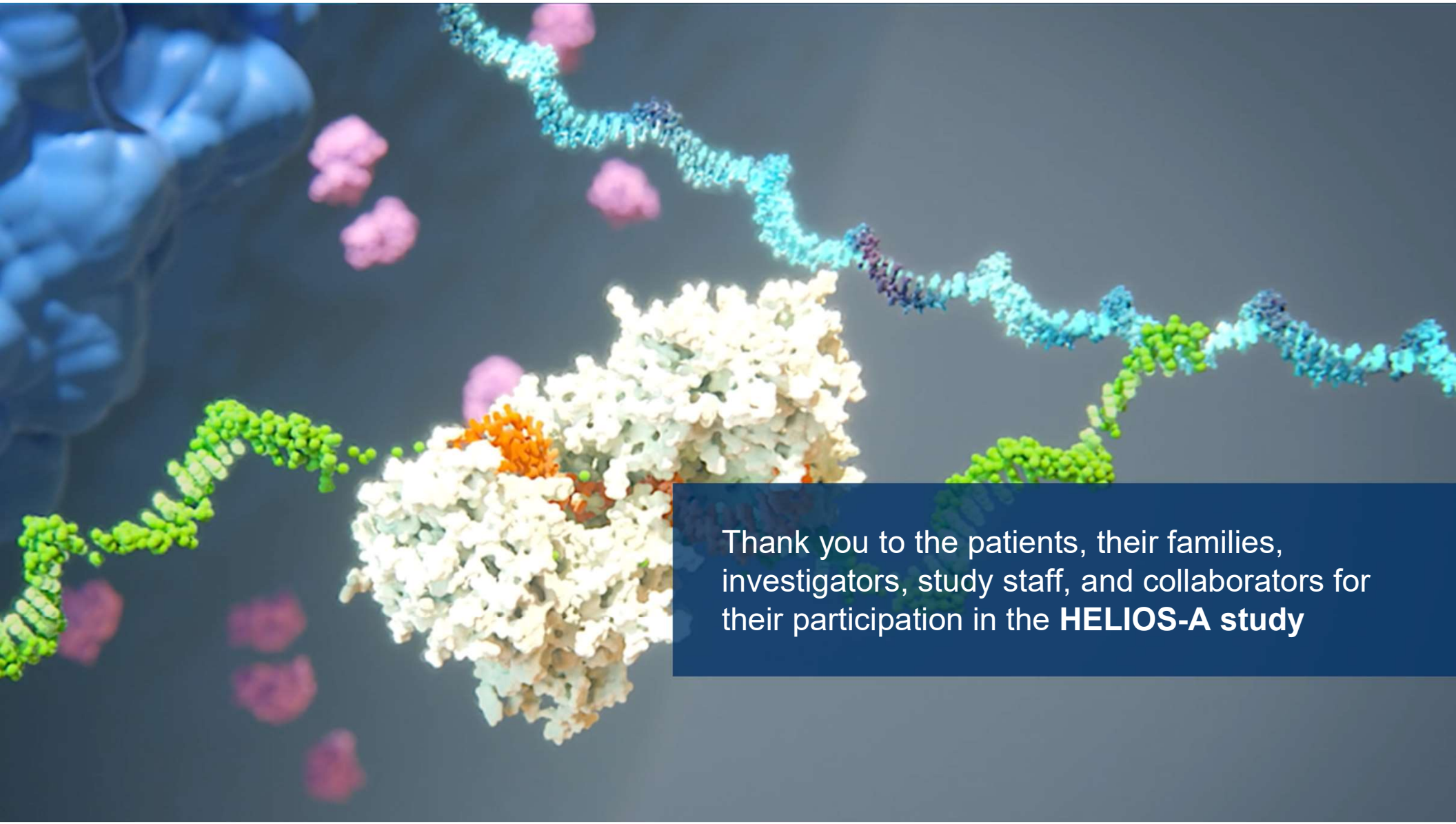
[a]Data reported during 18-month treatment period.
AE, adverse event; SAE, serious AE.

Summary

- As previously reported, vutrisiran met the primary endpoint (mNIS+7) at 9 months in HELIOS-A[1]
- Vutrisiran met all secondary endpoints at 18 months
  - Statistically significant improvement in mNIS+7 compared with external placebo
  - Improvement in QOL (Norfolk QOL-DN), gait speed (10-MWT), nutritional status (mBMI), and disability (R-ODS) compared with external placebo
  - Robust and sustained TTR reduction, non-inferior to within-study patisiran
- Vutrisiran had an acceptable safety profile, with the majority of AEs being mild or moderate in severity during the 18-month treatment period
- The efficacy and safety of vutrisiran will continue to be characterized in the ongoing HELIOS-A randomized extension period

10-MWT, 10-meter walk test; AE, adverse event; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; QOL, quality of life; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin.

1. Adams D et al. *Neurology* 2021;96(15 Supplement):1234.


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