



HELIOS·A

HELIOS-A: Impact of Vutrisiran on Quality of Life and Functional Status in Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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Disclosures for Senda Ajroud-Driss

Conflict	Disclosures
Advisory board	Anylam Pharmaceuticals Amylyx Pharmaceuticals Biogen Orphazyme
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Background and Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- Rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease¹⁻⁴
- Caused by variants in the *TTR* gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs and tissues¹⁻⁴
 - The majority of individuals develop a mixed phenotype of polyneuropathy and cardiomyopathy^{5,6}
- Progression of hATTR amyloidosis is associated with a deterioration in QOL and physical functioning⁷⁻¹⁰

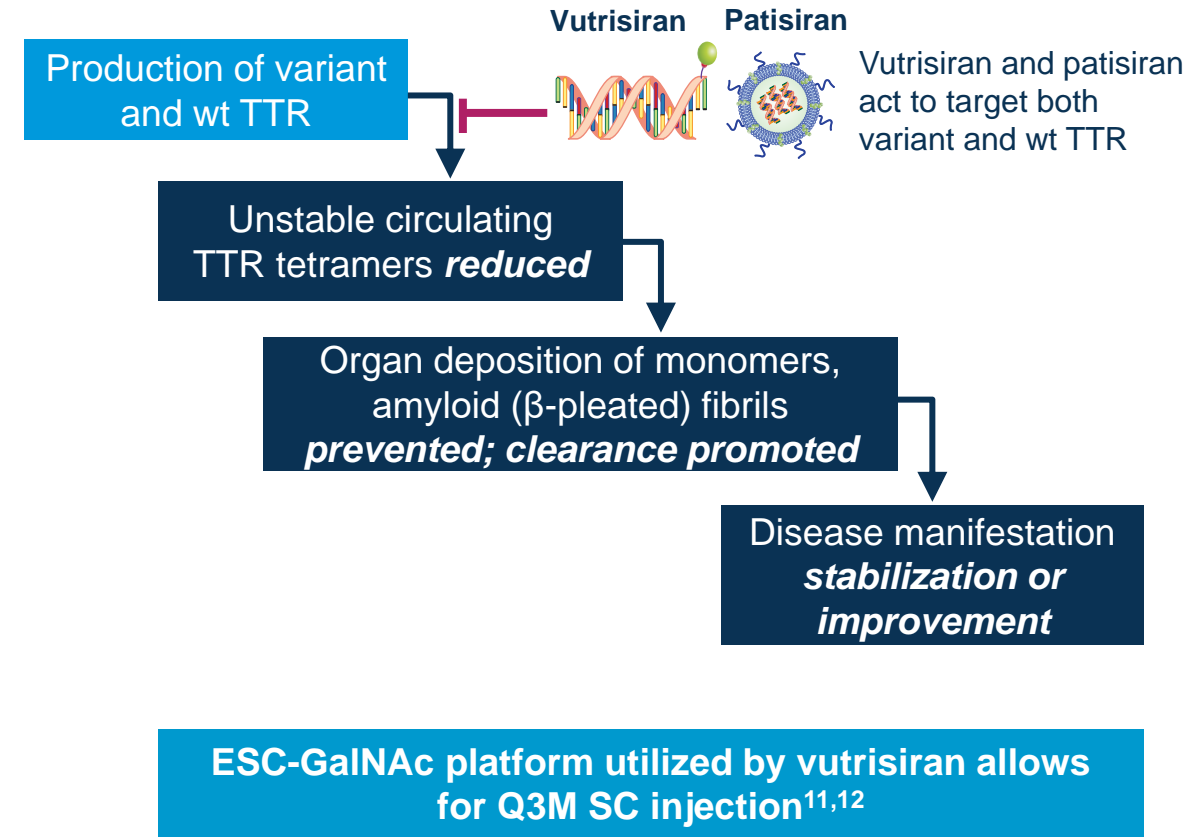
Vutrisiran

- Investigational, subcutaneously administered RNAi therapeutic targeting hepatic production of variant and wt TTR in development for the treatment of ATTR amyloidosis^{11,12}

Patisiran

- RNAi therapeutic administered Q3W via IV infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on the Phase 3, placebo-controlled APOLLO trial^{13,14}

Therapeutic Hypothesis



ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); ESC, enhanced stabilization chemistry; GalNAc, N-acetylgalactosamine; hATTR, hereditary transthyretin-mediated; IV, intravenous; Q3M, every 3 months; Q3W, every 3 weeks; RNAi, ribonucleic acid interference; SC, subcutaneous; TTR, transthyretin; wt, wild-type

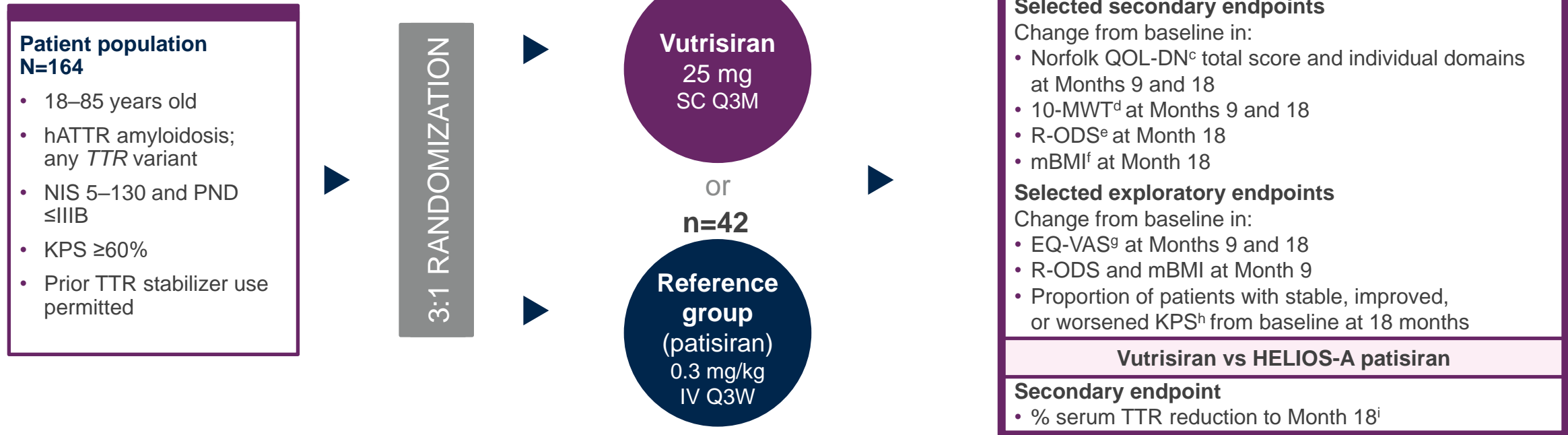
1. Hanna. *Curr Heart Fail Rep* 2014;11:50-7; 2. Hawkins et al. *Ann Med* 2015;47:625-38; 3. Damy et al. *J Cardiovasc Transl Res* 2015;8:117-27; 4. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528-40; 5. Rapezzi et al. *Eur Heart J* 2013;34:520-8; 6. Coelho et al. *Curr Med Res Opin* 2013;29:63-76; 7. Vinik et al. *J Peripher Nerv Syst* 2014;19:104-14; 8. Coelho et al. *Muscle Nerve* 2017;55:323-32; 9. Obici et al. *Amyloid* 2020;27:153-62; 10. Dyck et al. *PNS Congress* 2018. Poster; 11. Habtemariam et al. *Clin Pharmacol Ther* 2021;109:372-82; 12. Nair et al. *J Am Chem Soc* 2014;136:16958-61; 13. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. February 2020; 14. Adams et al. *N Engl J Med* 2018;379:11-21

Vutrisiran Phase 3 HELIOS-A Study



Global, Randomized, Open-Label Study in Patients with hATTR Amyloidosis with Polyneuropathy

- The 18-month QOL analysis is presented^a; for all endpoints, vutrisiran was compared with the external placebo group (placebo arm of APOLLO¹), selected on the basis of similar eligibility criteria and endpoints



^aThe results presented for 9- and 18-month efficacy endpoints (except for KPS) are based on a mixed-effects model for repeated measures analysis. ^bHigher scores of mNIS+7 indicate more neurologic impairment (range: 0–304). ^cHigher scores of Norfolk QOL-DN indicate worse QOL (range: –4 to 136). ^d10-MWT speed (m/s) = 10 meters/mean time (seconds) taken to complete 2 assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function. ^eLower scores of R-ODS indicate more disability (range: 0–48). ^fLower scores of mBMI (weight [in kg/m²] × serum albumin [in g/L]) indicate worse nutritional status. ^gEQ-VAS (range: 0–100) 0 = best health, 100 = worst health. ^hKPS measures functional status on an 11-point scale correlating to % values. 100% (normal; no evidence of disease); 0% (death). Higher scores indicate less functional impairment. ⁱNon-inferiority analysis

10-MWT, 10-meter walk test; EQ-VAS, EuroQoL Visual Analog Scale; 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; QOL, quality of life; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; TTR, transthyretin

1. Adams et al. *N Engl J Med* 2018;379:11–21; 2. Adams et al. *Neurology* 2021;96(15 Suppl.):1234

Baseline Demographic and Disease Characteristics

Characteristic	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
Age, median (range), years	63 (34–80)	60 (26–85)	60 (31–81)
Males, n (%)	58 (75.3)	79 (64.8)	27 (64.3)
Median time since hATTR amyloidosis diagnosis, years (range)	1.41 (0.0–16.5)	1.94 (0.0–15.3)	2.39 (0.1–12.5)
TTR genotype, n (%)			
V30M	40 (51.9)	54 (44.3)	20 (47.6)
Early-onset V30M (<50 years)	10 (13.0)	25 (20.5)	8 (19.0)
Non-V30M ^a	37 (48.1)	68 (55.7)	22 (52.4)
Previous tetramer 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)

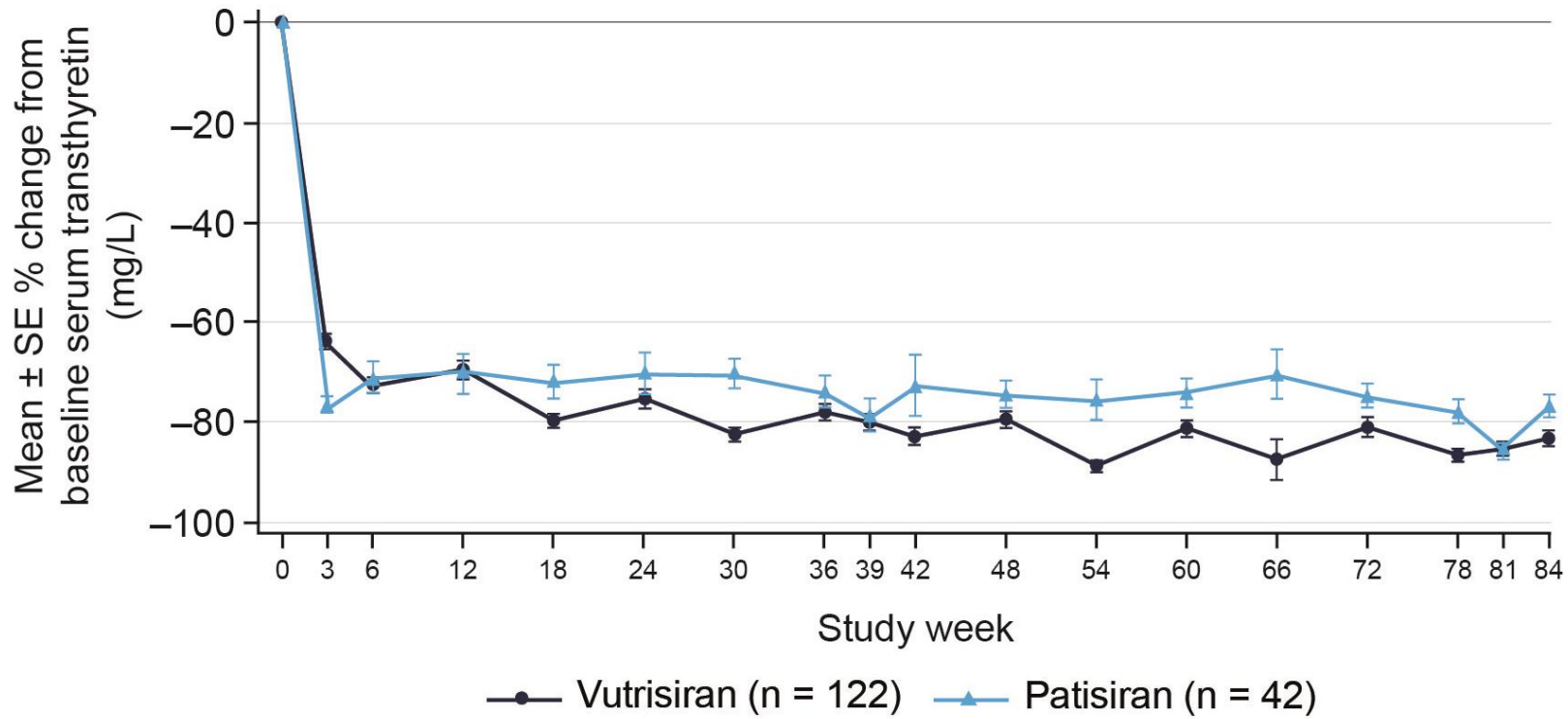
^aThe non-V30M TTR genotype represents 24 different variants in HELIOS-A. ^bOne patient (1.3%) in the external placebo group had a PND score of IV defined as confined to wheelchair or bedridden (not shown on the slide). ^cCardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline LV wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)

LV, left ventricular; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin

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%), which was non-inferior to that observed with the within-study patisiran reference group over 18 months (median difference [vutrisiran–patisiran] [95% CI]: 5.28% [1.17, 9.25], lower limit of CI >−10%)

Percent Change from Baseline in Serum TTR Levels

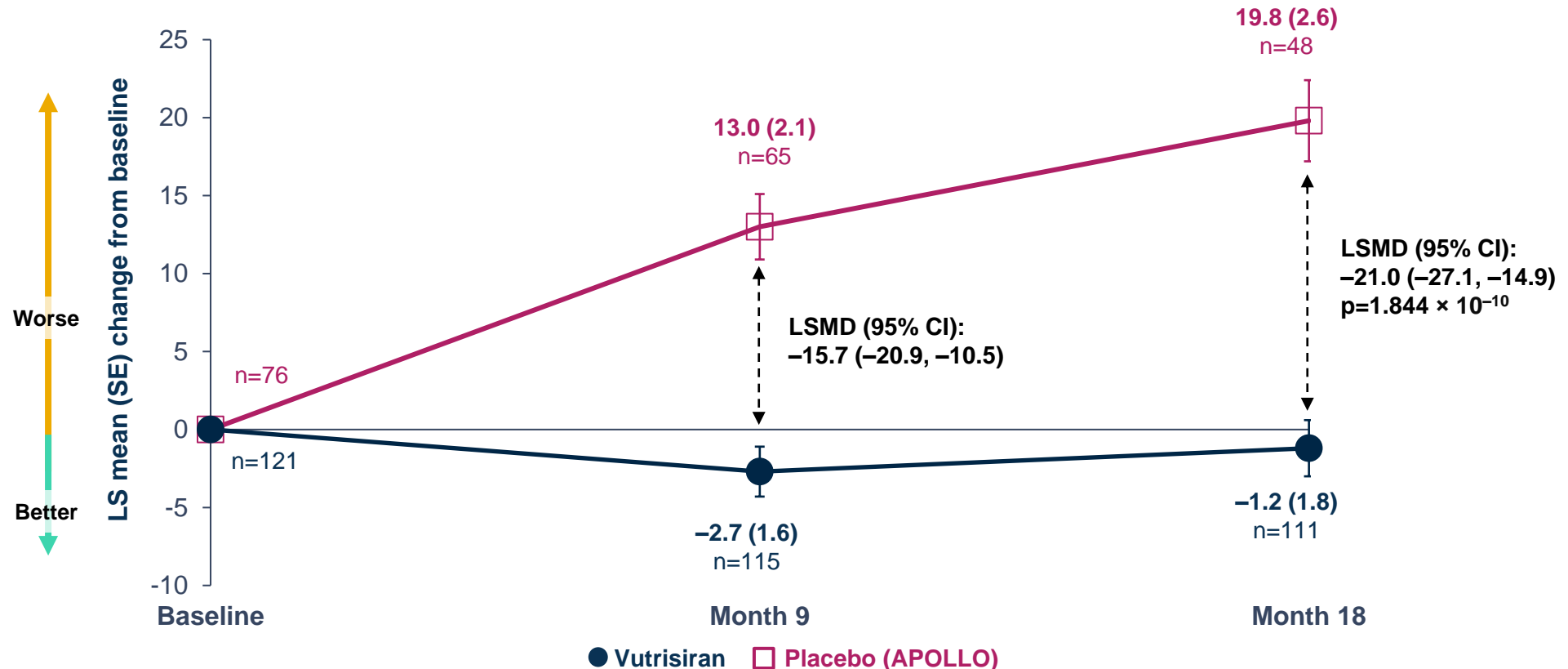


N evaluable	0	3	6	12	18	24	30	36	39	42	48	54	60	66	72	78	81	84
Vutrisiran (n = 122)	122	114	109	119	106	117	92	118	115	56	116	42	118	15	118	100	114	98
Patisiran (n = 42)	42	42	41	41	37	38	39	34	39	23	40	23	36	9	37	36	38	32

Improvement in Quality of Life with Vutrisiran vs External Placebo at Month 9¹ and Month 18

- At Month 18, 56.8% of vutrisiran-treated patients had an improvement in Norfolk QOL-DN total score, relative to baseline, compared with 10.4% of patients in the external placebo group (odds ratio [95% CI]: 11.3 [5.0, 25.7])

Norfolk QOL-DN LS Mean Change from Baseline^a

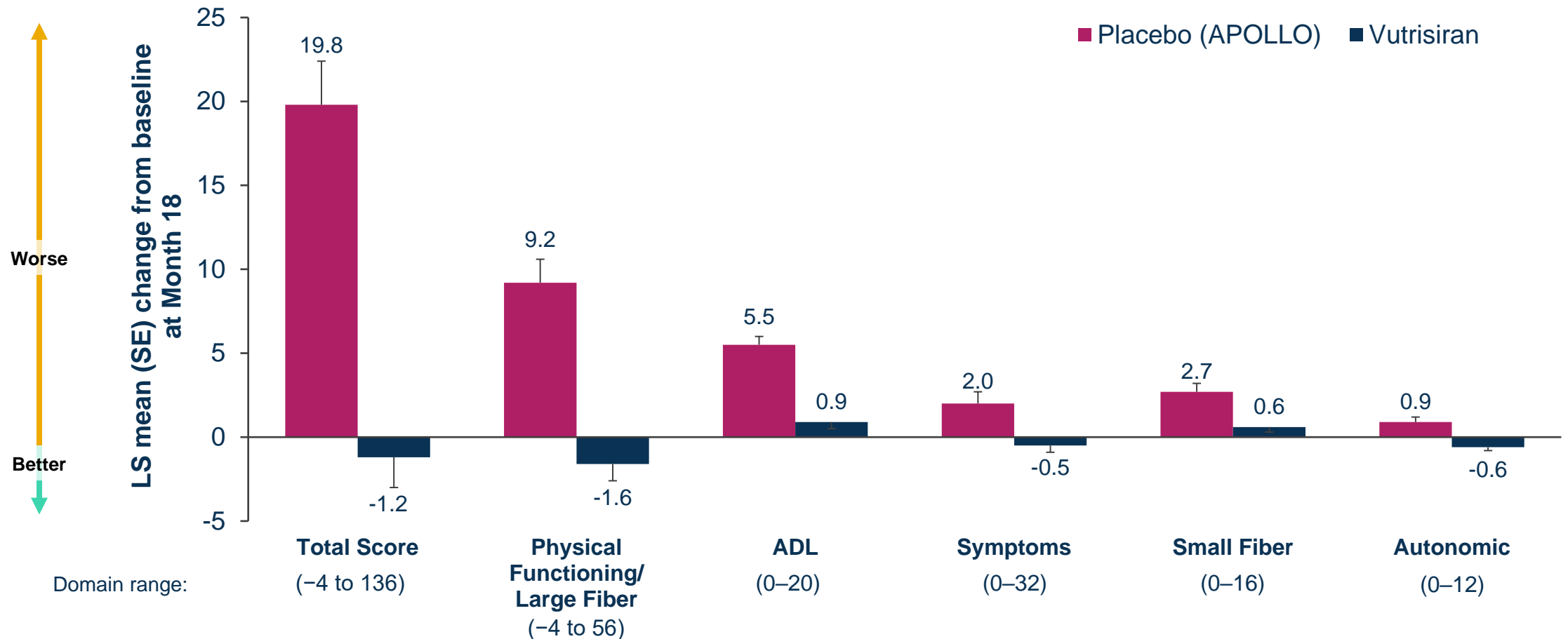


^amITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Higher scores of Norfolk QOL-DN indicate worse quality of life (range: -4 to 136). At baseline, the mean (± SD) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group. Data plotted are MMRM model data

CI, confidence interval; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SD, standard deviation; SE, standard error

Improvement across All Norfolk QOL-DN Domains with Vutrisiran vs External Placebo at Month 18

Norfolk QOL-DN Mean Change from Baseline by Domain

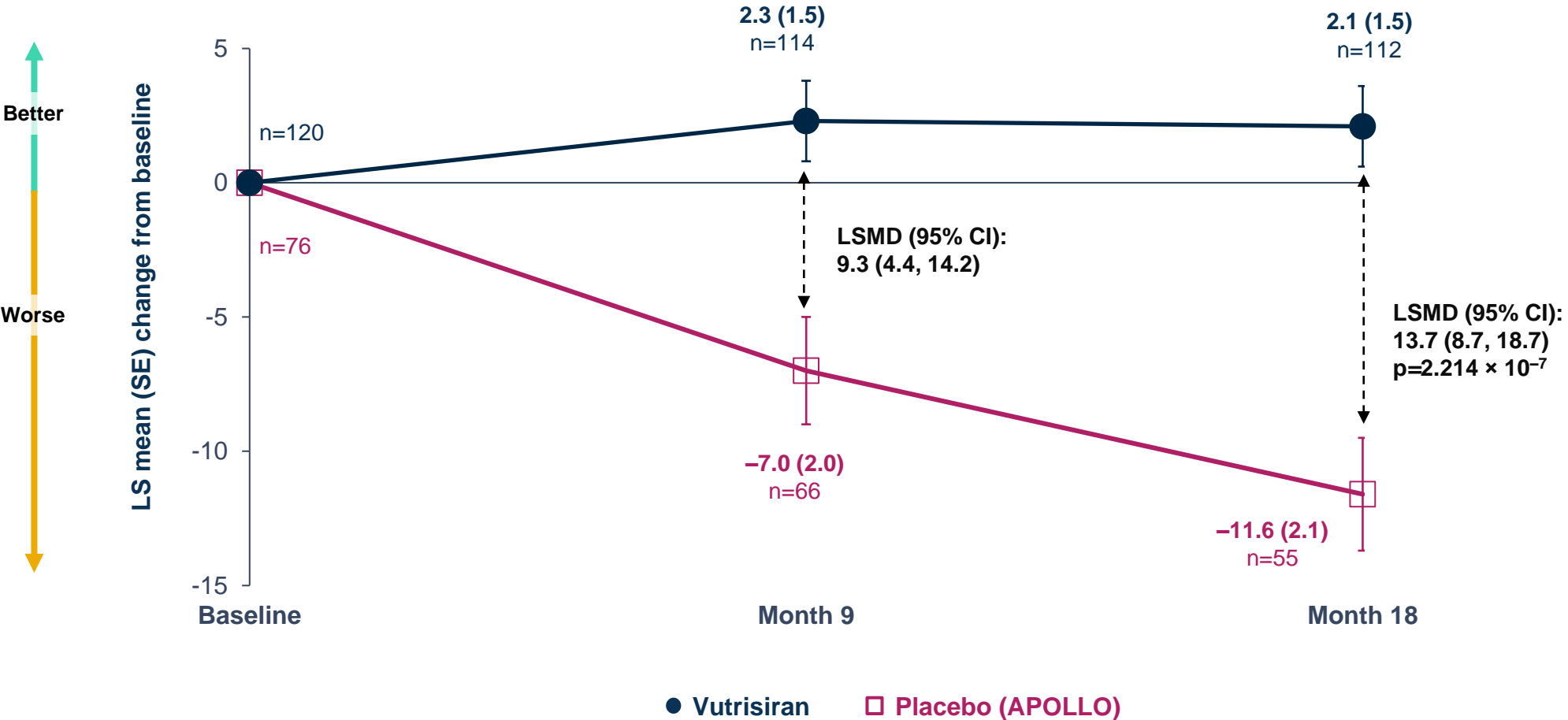


Higher scores of Norfolk QOL-DN indicate worse quality of life (range: -4 to 136). At baseline, the mean (\pm SD) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group. Mean (\pm SD) Norfolk QOL-DN scores in individual domains were: 23.2 (13.8) in the vutrisiran group and 28.7 (13.0) in the external placebo group (physical functioning/large fiber); 5.7 (5.7) in the vutrisiran group and 7.8 (6.0) in the external placebo group (activities of daily living); 11.0 (6.1) in the vutrisiran group and 11.2 (5.8) in the external placebo group (symptoms); 4.6 (4.2) in the vutrisiran group and 5.0 (4.1) in the external placebo group (small fiber); and 2.7 (2.9) and 2.9 (2.9) in the external placebo group (autonomic)

ADL, activities of daily living; LS, least squares; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SD, standard deviation; SE, standard error

Improvement in EQ-VAS with Vutrisiran vs External Placebo at Month 9 and Month 18

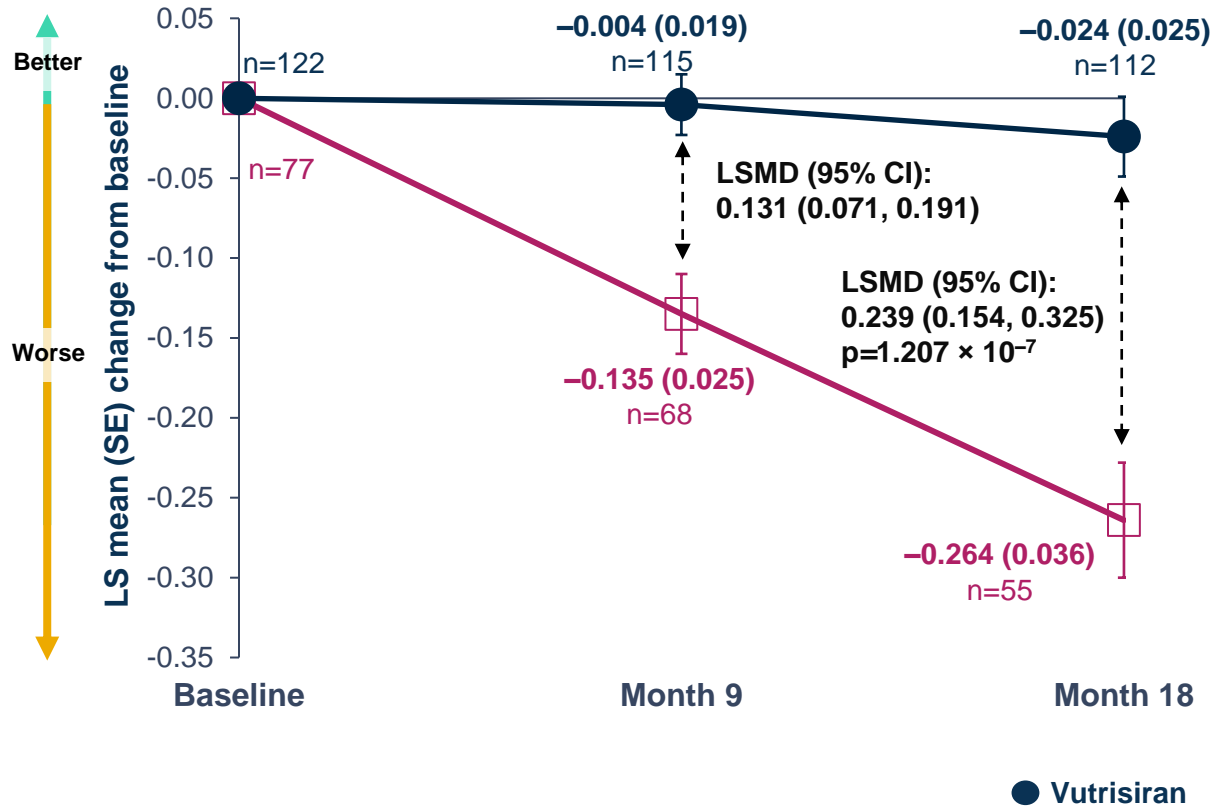
EQ-VAS LS Mean Change from Baseline^a



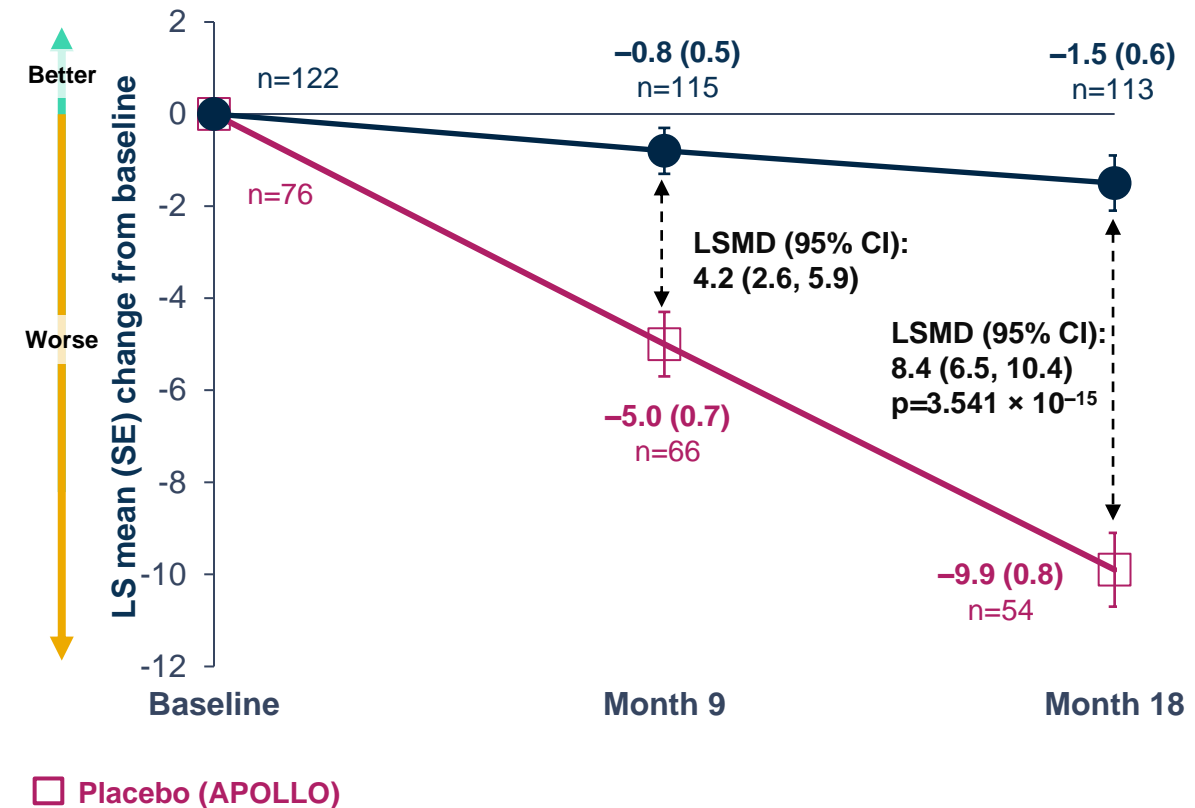
^amITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted are MMRM model data. At baseline, the mean (± SD) EQ-VAS was 64.5 (18.5) in the vutrisiran group and 54.6 (18.0) in the external placebo group
 CI, confidence interval; EQ-VAS, EuroQol Visual Analog Scale; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; SD, standard deviation; SE, standard error

Improvements in R-ODS and 10-MWT with Vutrisiran vs External Placebo at Month 9 and Month 18

10-MWT LS Mean Change from Baseline (m/s)^a



R-ODS LS Mean Change from Baseline^a



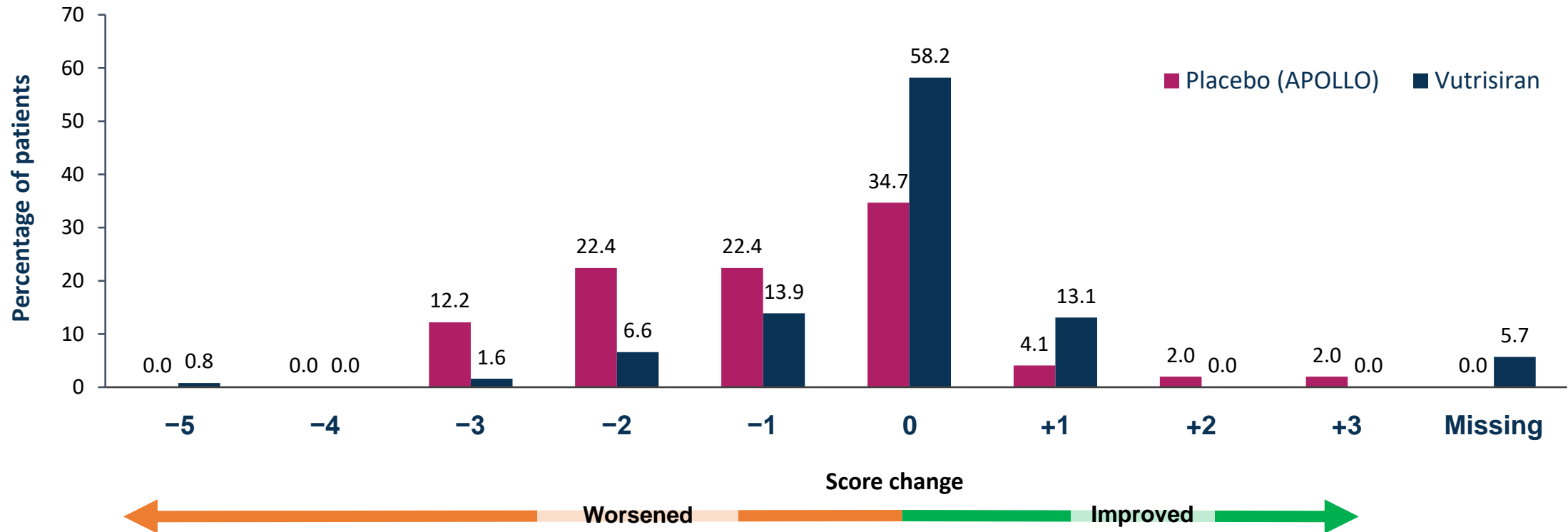
^amITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted are MMRM model data. At baseline, the mean (± SD) 10-MWT was 1.006 (0.393) in the vutrisiran group and 0.790 (0.319) in the external placebo group. 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; CI, confidence interval; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; R-ODS, Rasch-built Overall Disability Scale; SD, standard deviation; SE, standard error

A Higher Proportion of Patients Had Stable or Improved KPS with Vutrisiran vs External Placebo at Month 18

- The majority of patients in the vutrisiran group (71.3%) had stable or improved^a KPS at Month 18 compared with baseline (exploratory endpoint)
 - In the external placebo group, 42.8% of patients had stable or improved KPS at Month 18

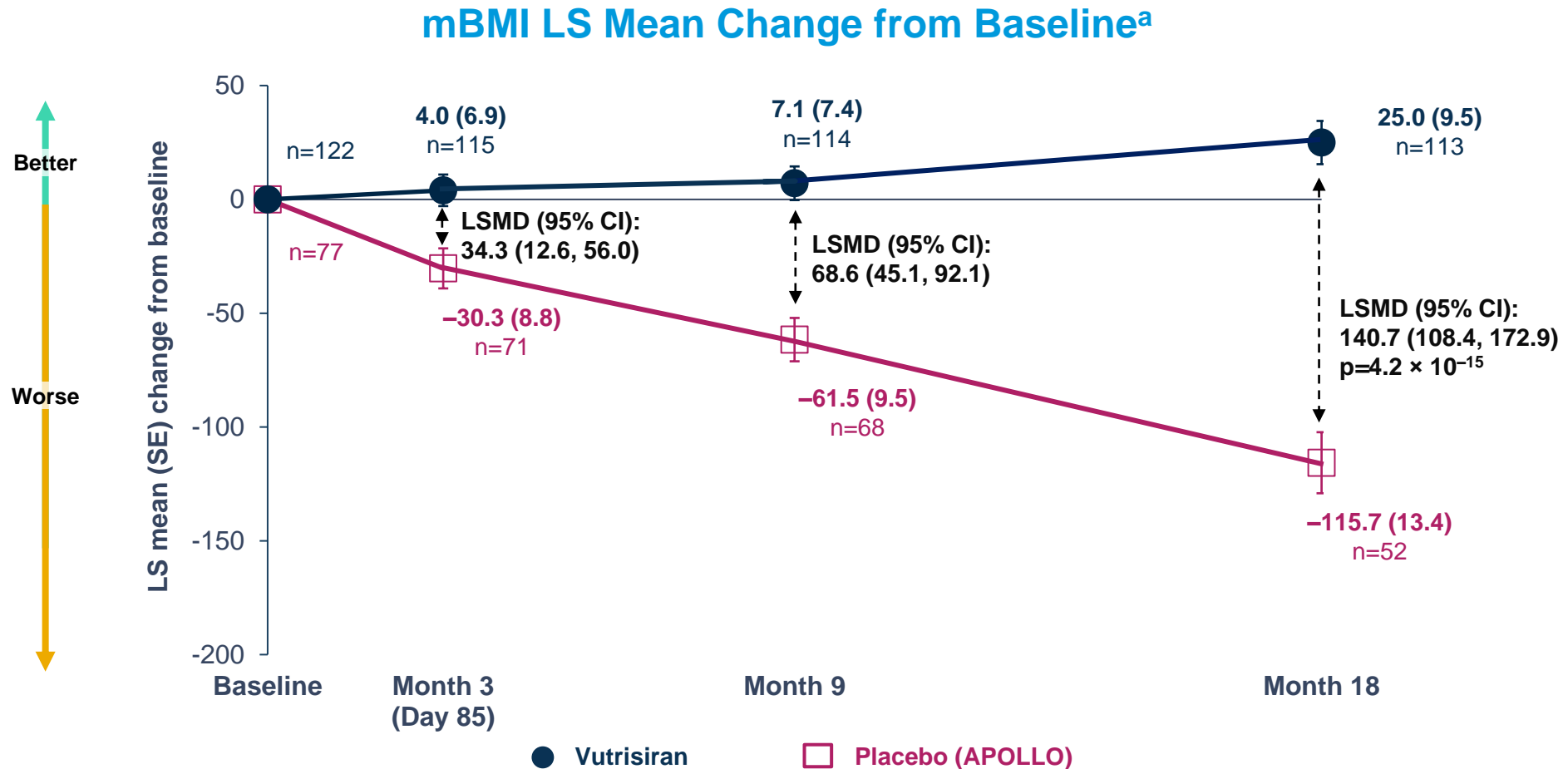
Change from Baseline to Month 18 in KPS^b



^aImprovement is defined as an increase in KPS score from baseline. ^bOn the KPS scale of 0–100%, 17 (14%), 25 (21%), 48 (39%), 27 (22%), and 5 (4%) of vutrisiran-treated patients had a score of 60, 70, 80, 90, and 100, respectively, at baseline KPS, Karnofsky performance score

Improvement in mBMI with Vutrisiran vs External Placebo at Month 9 and Month 18

- The favorable effect of vutrisiran on mBMI compared with the external placebo group was observed at the first post-baseline assessment at Month 3

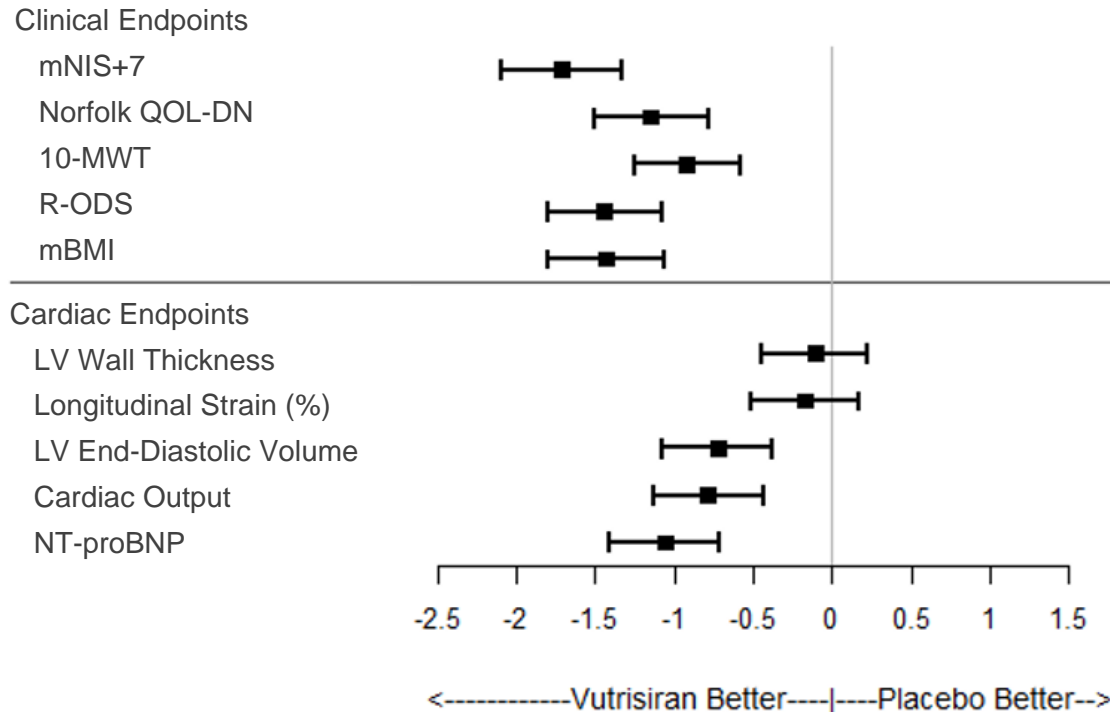


^amITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted are MMRM model data. At baseline, the mean (± SD) mBMI was 1057.4 (233.8) in the vutrisiran group and 989.9 (214.2) in the external placebo group

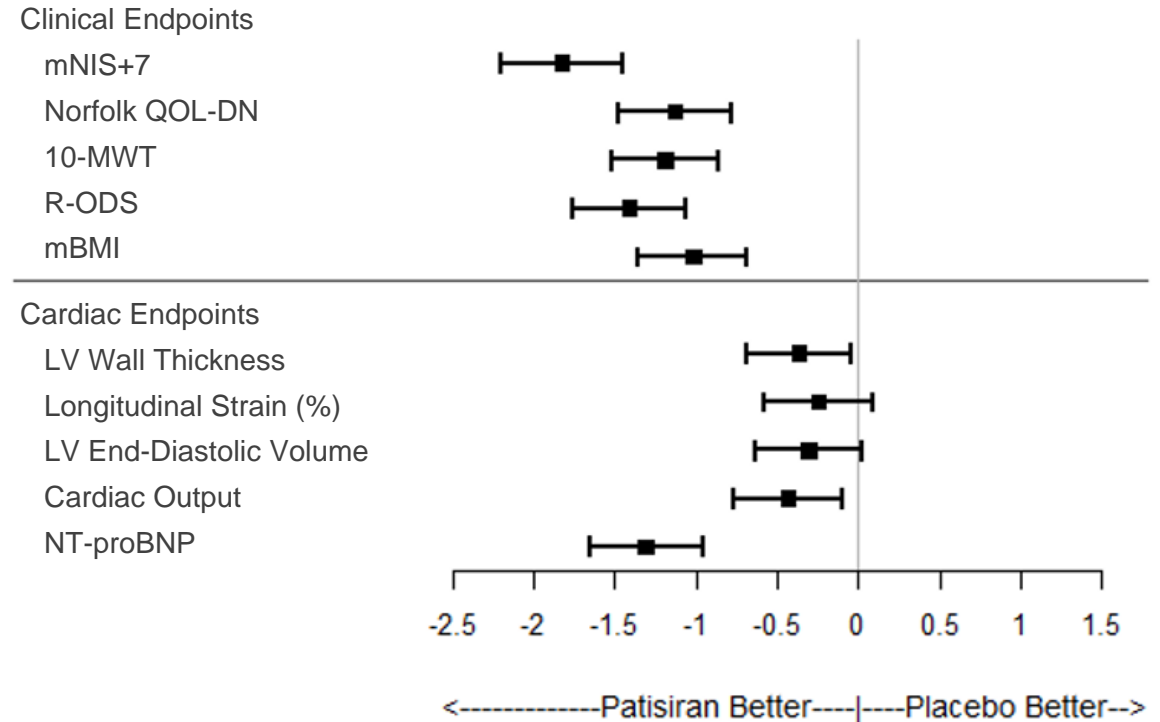
CI, confidence interval; LS, least squares; LSM, LS mean difference; mBMI, modified body mass index; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; SD, standard deviation; SE, standard error

HELIOS-A Vutrisiran Efficacy Results Consistent with APOLLO Patisiran at Month 18

Vutrisiran Efficacy^a vs External Placebo
Standardized Effect Sizes from HELIOS-A



Patisiran Efficacy^b vs Placebo
Standardized Effect Sizes from APOLLO



^aHELIOS-A mITT population. ^bAPOLLO mITT population. The HELIOS-A patisiran arm was not intended for statistical testing vs vutrisiran for the endpoints listed.

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.

Summary

- At Month 18, patients in the vutrisiran group demonstrated significant improvements in measures of
 - **Quality of life** (Norfolk QOL-DN, EQ-VAS) compared with external placebo
 - The treatment effect favoring vutrisiran over external placebo was consistent across all Norfolk QOL-DN domains at Month 18
 - **Functional status** (gait speed [10-MWT], disability [R-ODS], KPS) compared with external placebo
 - The majority (71%) of patients in the vutrisiran group improved or stabilized in the exploratory assessment of KPS score compared with baseline, whereas 43% of patients in the external placebo group improved or stabilized in KPS score compared with baseline
 - **Nutritional status** (mBMI) compared with external placebo
- The efficacy and safety of vutrisiran will continue to be characterized in the ongoing HELIOS-A randomized extension period in patients with hATTR amyloidosis with polyneuropathy



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