HELIOS·A

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

Senda Ajroud-Driss,[1] John L. Berk,[2] David Adams,[3] Julian Gillmore,[4] Kon-Ping Lin,[5] Parag Kale,[6] Haruki Koike,[7] Emre Aldinc,[8] Chongshu Chen,[8] John Vest,[8] Laura Obici[9]

[1]Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [2]Boston Medical Center, Boston, MA, USA; [3]Neurology Department, Université Paris-Saclay, U1195, INSERM, Neurology Department, AP-HP, CHU Bicêtre, Le Kremlin Bicêtre, France; [4]National Amyloidosis Centre, University College London, Royal Free Hospital, London, UK; [5]Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan; [6]Baylor University Medical Center, Dallas, TX, USA; [7]Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [8]Alnylam Pharmaceuticals, Cambridge, MA, USA; [9]Amyloidosis Research and Treatment Centre; IRCCS Fondazione Policlinico San Matteo, Pavia, Italy

May 14–17, 2022 || Peripheral Nerve Society (PNS)

Disclosures for Senda Ajroud-Driss

Conflict	Disclosures
Advisory board	Alnylam Pharmaceuticals Amylyx Pharmaceuticals Biogen Orphazyme
Research support	Alnylam Pharmaceuticals Amylyx Pharmaceuticals Biogen
Speakers bureau	Alnylam Pharmaceuticals

Background and Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- Rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease[1–4]
- 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]
- Progression of hATTR amyloidosis is associated with a deterioration in QOL and physical functioning[7–10]

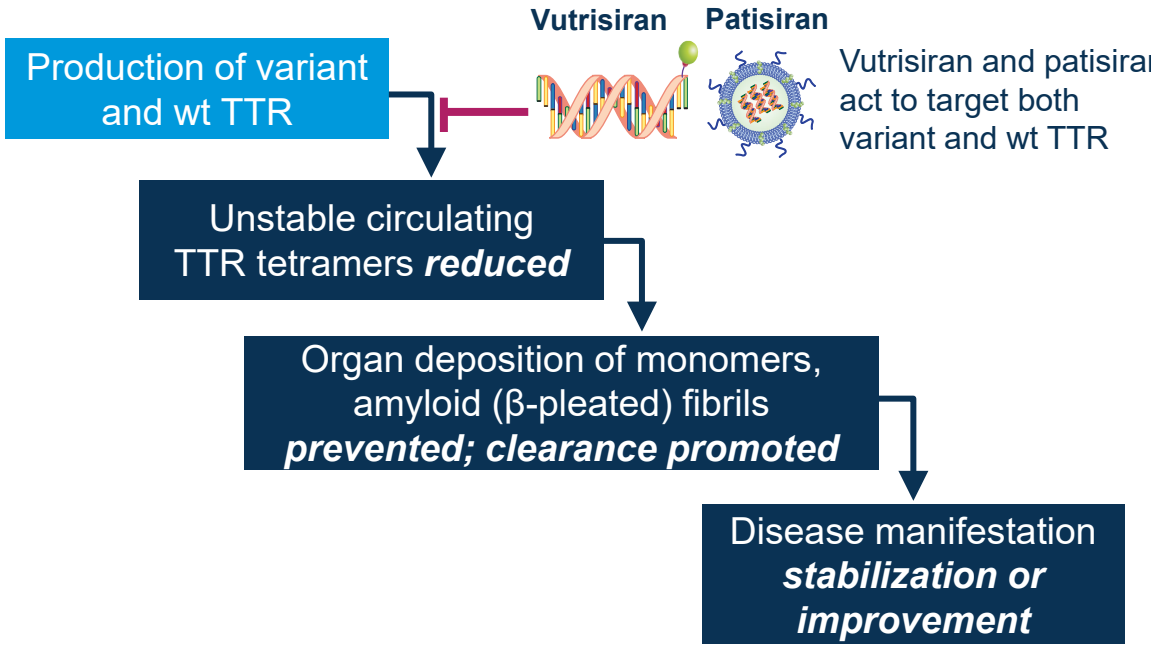
Vutrisiran

- 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



ESC-GalNAc platform utilized by vutrisiran allows for Q3M SC injection[11,12]

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

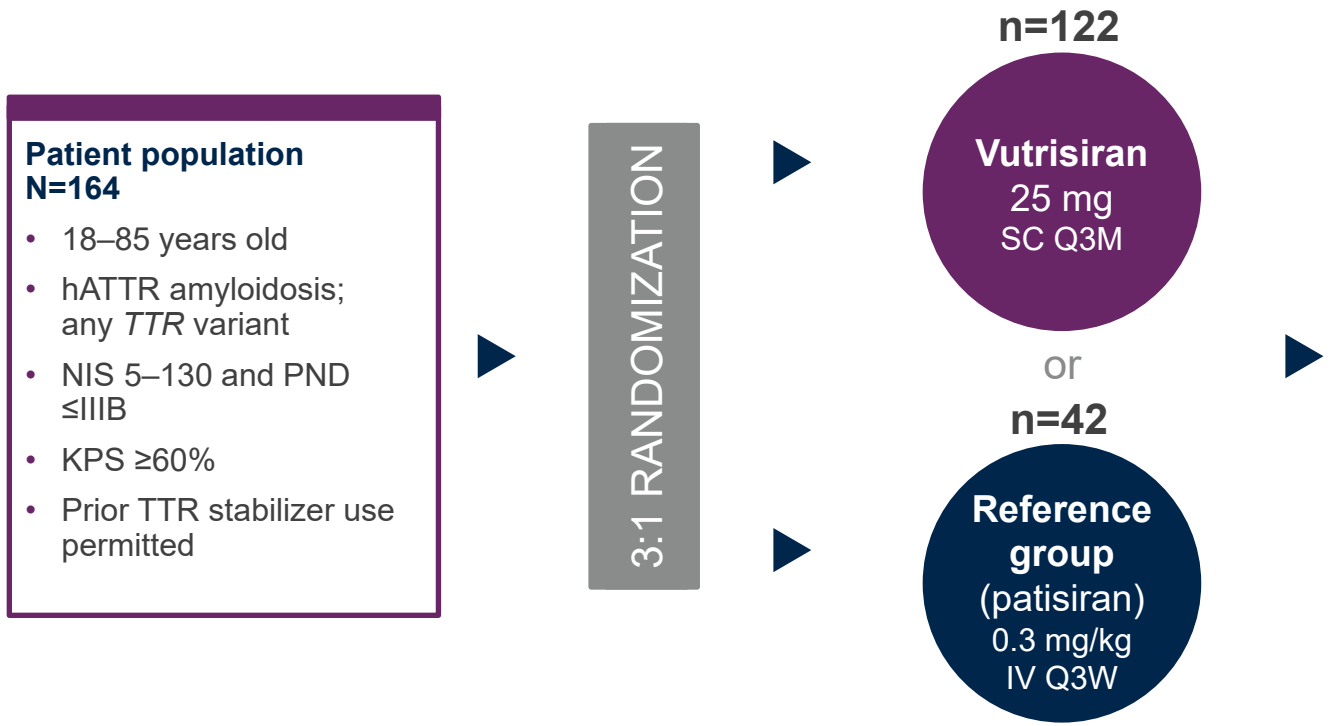
1. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 2. Hawkins et al. *Ann Med* 2015;47:625–38; 3. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 4. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 5. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 6. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 7. 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

HELIOS·A

- The 18-month QOL analysis is presented[a]; for all endpoints, vutrisiran was compared with the external placebo group (placebo arm of APOLLO[1]), selected on the basis of similar eligibility criteria and endpoints



Vutrisiran vs APOLLO placebo

Primary endpoint (previously presented[2])
- Change from baseline in mNIS+7[b] at Month 9

Selected secondary endpoints
Change from baseline in:
- Norfolk QOL-DN[c] total score and individual domains at Months 9 and 18
- 10-MWT[d] at Months 9 and 18
- R-ODS[e] at Month 18
- mBMI[f] at Month 18

Selected exploratory endpoints
Change from baseline in:
- EQ-VAS[g] at Months 9 and 18
- R-ODS and mBMI at Month 9
- Proportion of patients with stable, improved, or worsened KPS[h] from baseline at 18 months

Vutrisiran vs HELIOS-A patisiran

Secondary endpoint
- % serum TTR reduction to Month 18[i]

[a]The results presented for 9- and 18-month efficacy endpoints (except for KPS) are based on a mixed-effects model for repeated measures analysis.[b]Higher scores of mNIS+7 indicate more neurologic impairment (range: 0–304). [c]Higher scores of Norfolk QOL-DN indicate worse QOL (range: −4 to 136). [d]10-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. [e]Lower scores of R-ODS indicate more disability (range: 0–48). [f]Lower scores of mBMI (weight [in kg/m^2] × serum albumin [in g/L]) indicate worse nutritional status. [g]EQ-VAS (range: 0–100) 0 = best health, 100 = worst health. [h]KPS 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. [i]Non-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)

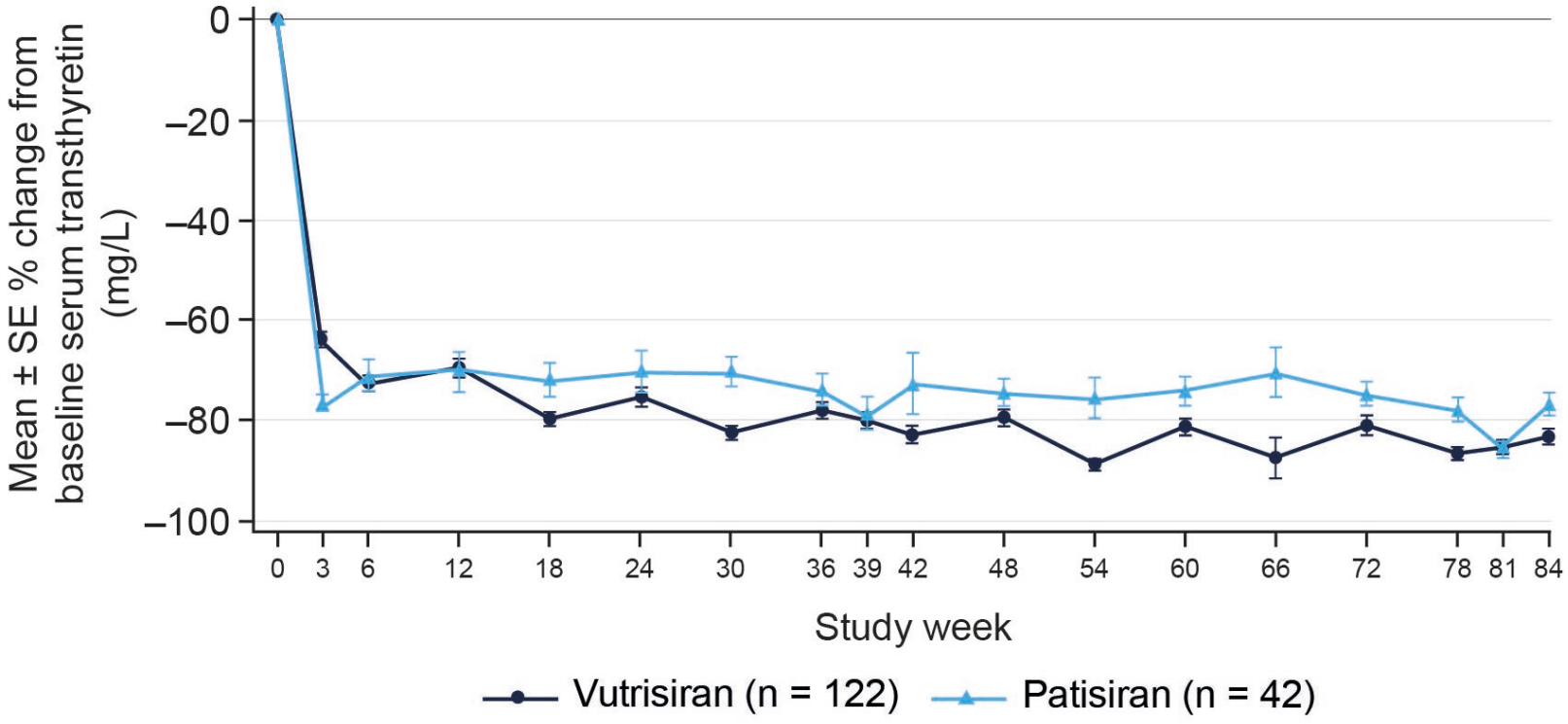
[a]The non-V30M TTR genotype represents 24 different variants in HELIOS-A. [b]One patient (1.3%) in the external placebo group had a PND score of IV defined as confined to wheelchair or bedridden (not shown on the slide). [c]Cardiac subpopulation was defined as patients who had pre-existing evidence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

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



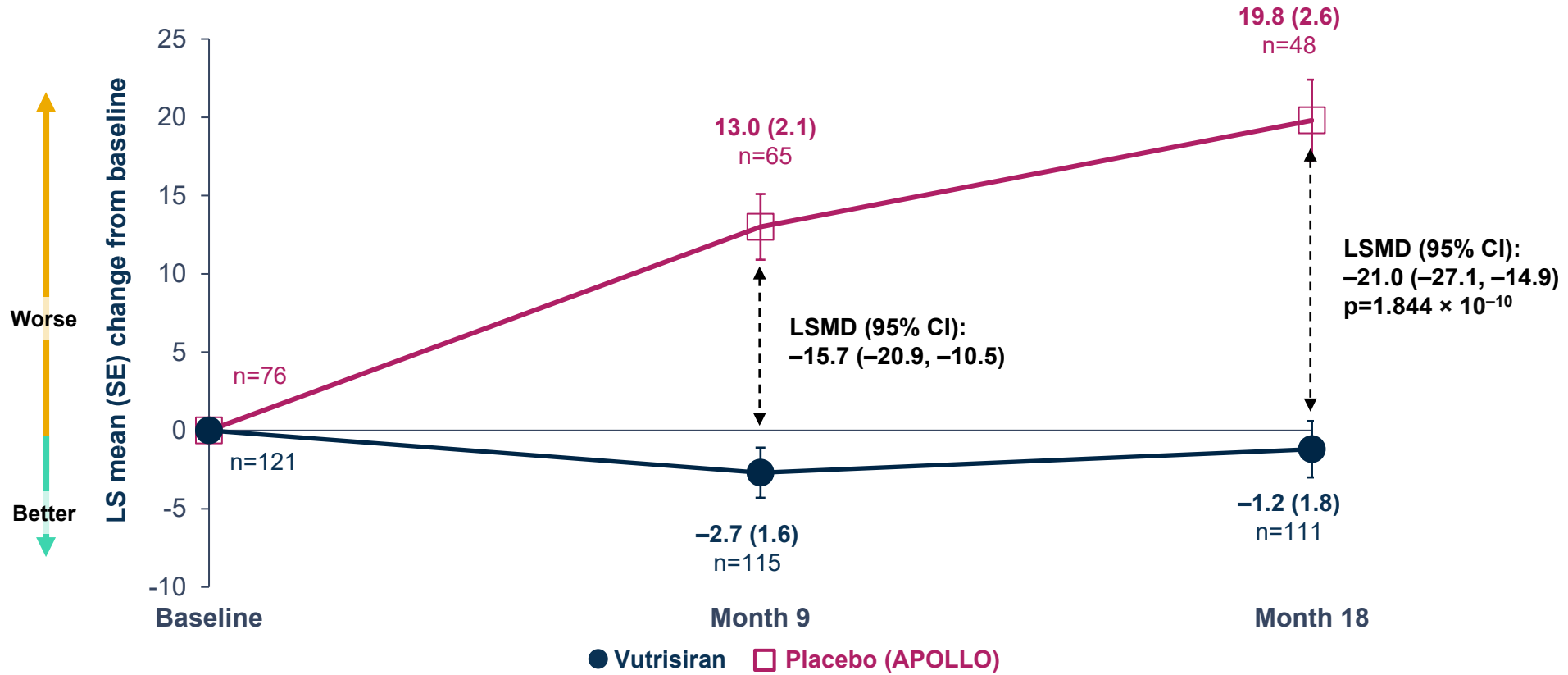
N evaluable																		
Vutrisiran (n = 122)	122	114	109	119	106	117	92	118	115	56	116	42	118	15	118	100	114	98
Patisiran (n = 42)	42	42	41	41	37	38	39	34	39	23	40	23	36	9	37	36	38	32

CI, confidence interval; SD, standard deviation; SE, standard error; TTR, transthyretin

Improvement in Quality of Life with Vutrisiran vs External Placebo at Month 9[1] 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]



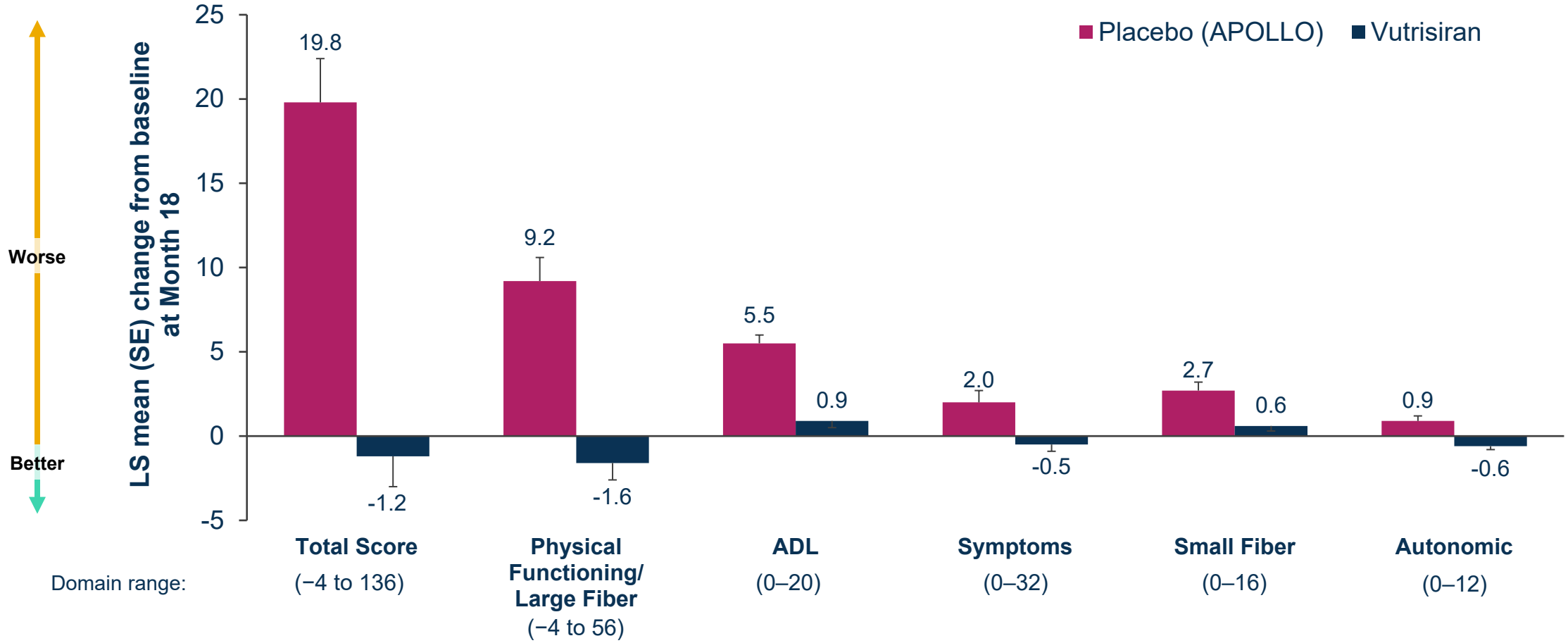
[a]mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Higher scores of Norfolk QOL-DN indicate worse quality of life (range: –4 to 136). At baseline, the mean (± SD) Norfolk QOL-DN score was 47.1 (26.3) in 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

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

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

Norfolk QOL-DN Mean Change from Baseline by Domain

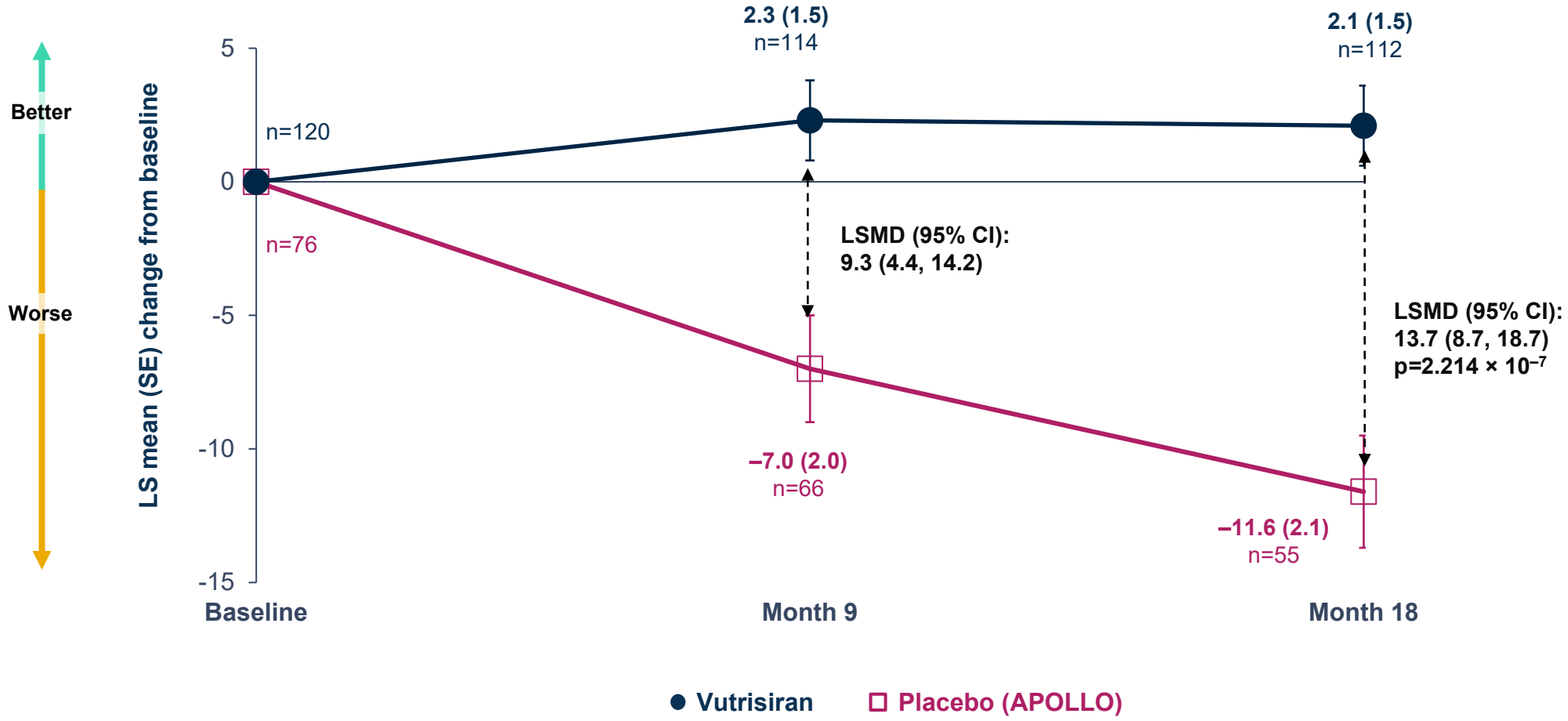


Higher scores of Norfolk QOL-DN indicate worse quality of life (range: –4 to 136). At baseline, the mean (± SD) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group. Mean (± SD) Norfolk QOL-DN scores in individual domains were: 23.2 (13.8) in the 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]

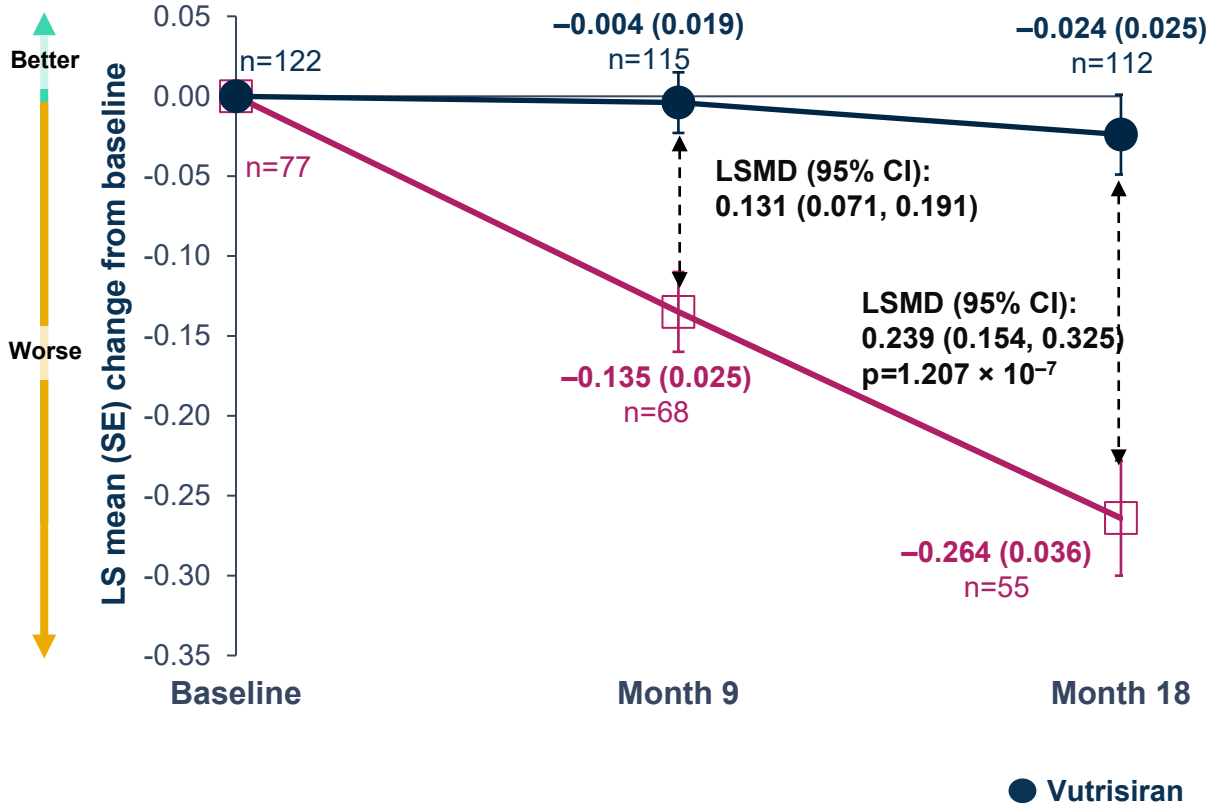


[a]mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted are MMRM model data. At baseline, the mean (± SD) EQ-VAS was 64.5 (18.5) in the vutrisiran group and 54.6 (18.0) in the external placebo group

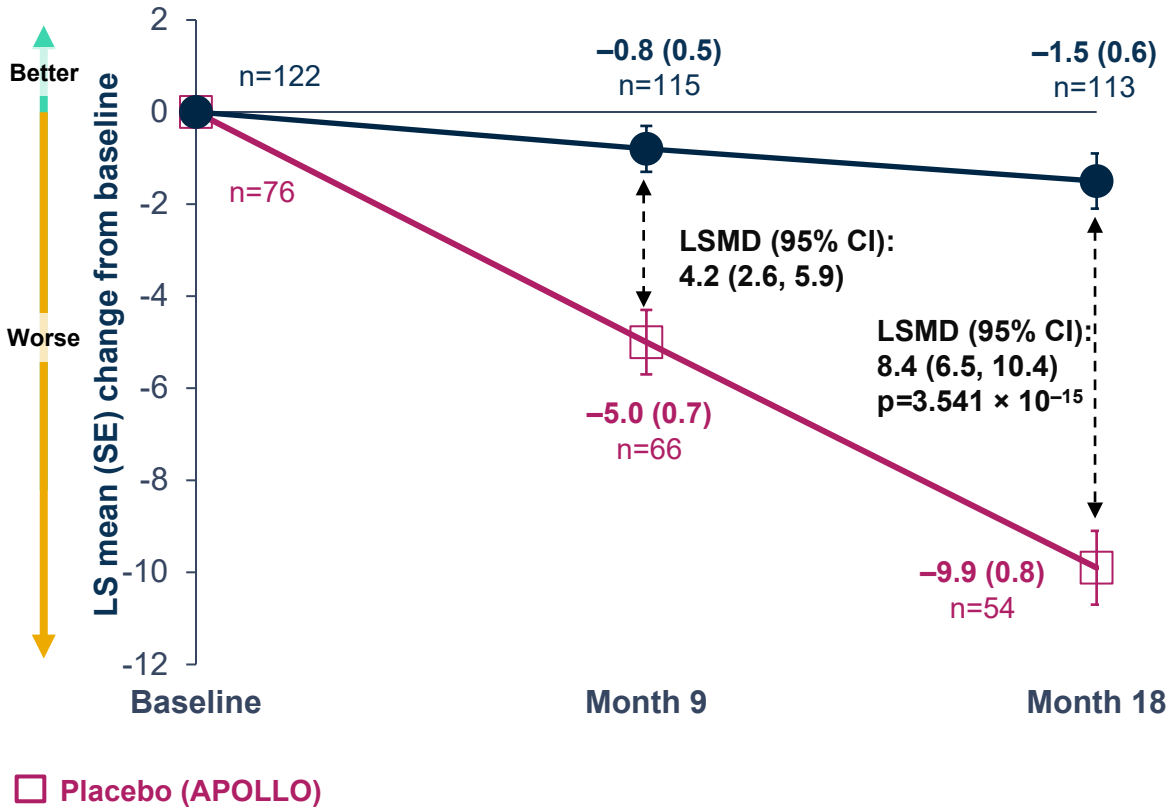
CI, confidence interval; EQ-VAS, EuroQol Visual Analog Scale; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; SD, standard deviation; SE, standard error

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]



● Vutrisiran □ Placebo (APOLLO)

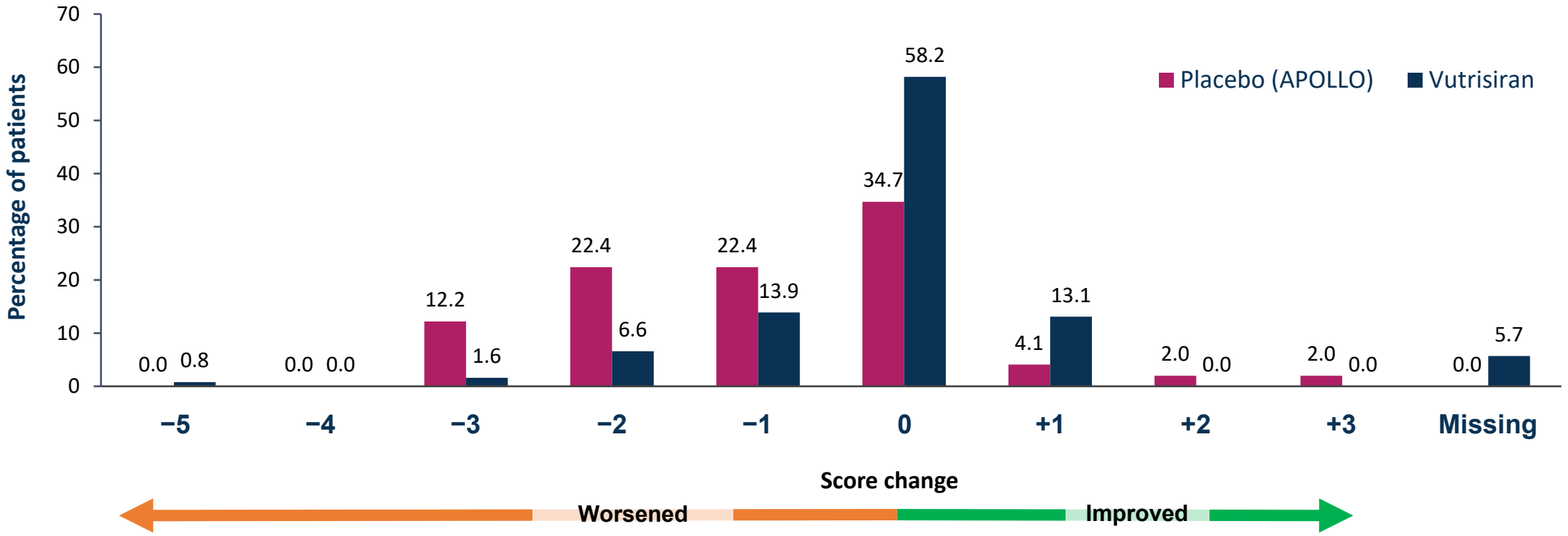
[a]mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted are MMRM model data. At baseline, the mean (± SD) 10-MWT was 1.006 (0.393) in the vutrisiran group and 0.790 (0.319) in the external placebo 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]

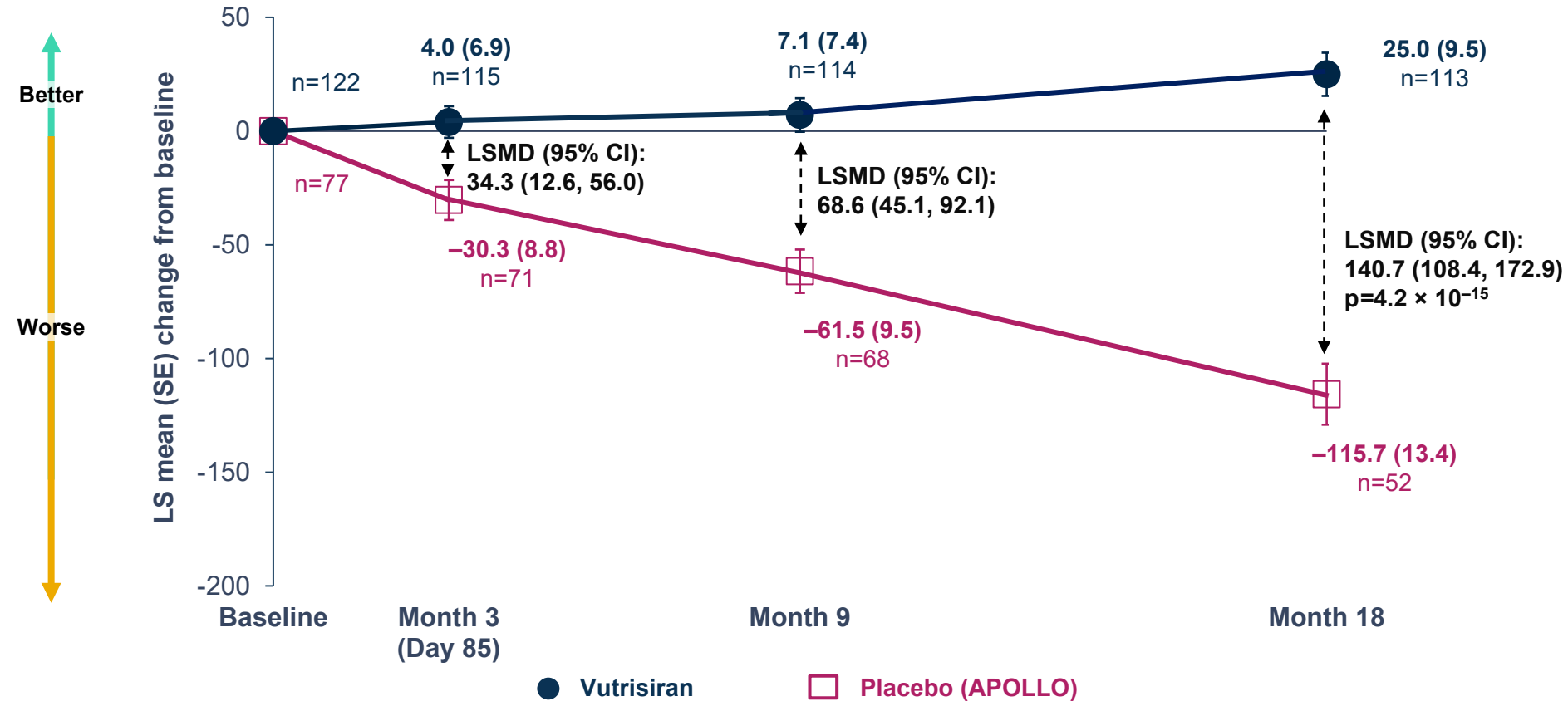


[a]Improvement is defined as an increase in KPS score from baseline. [b]On the KPS scale of 0–100%, 17 (14%), 25 (21%), 48 (39%), 27 (22%), and 5 (4%) of vutrisiran-treated patients had a score of 60, 70, 80, 90, and 100, respectively, at baseline
KPS, Karnofsky performance score

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

mBMI 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 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; LSMD, 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 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 heart failure), 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
- 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)

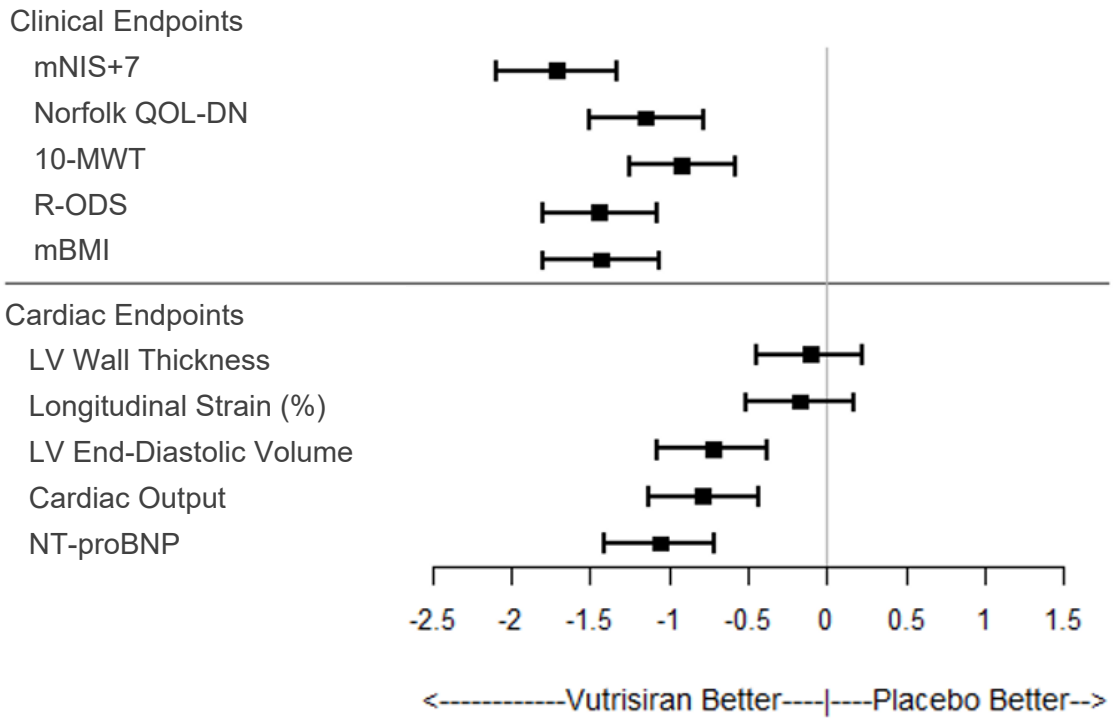
[a]Data reported during 18-month treatment period.

AE, adverse event; SAE, serious AE.

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

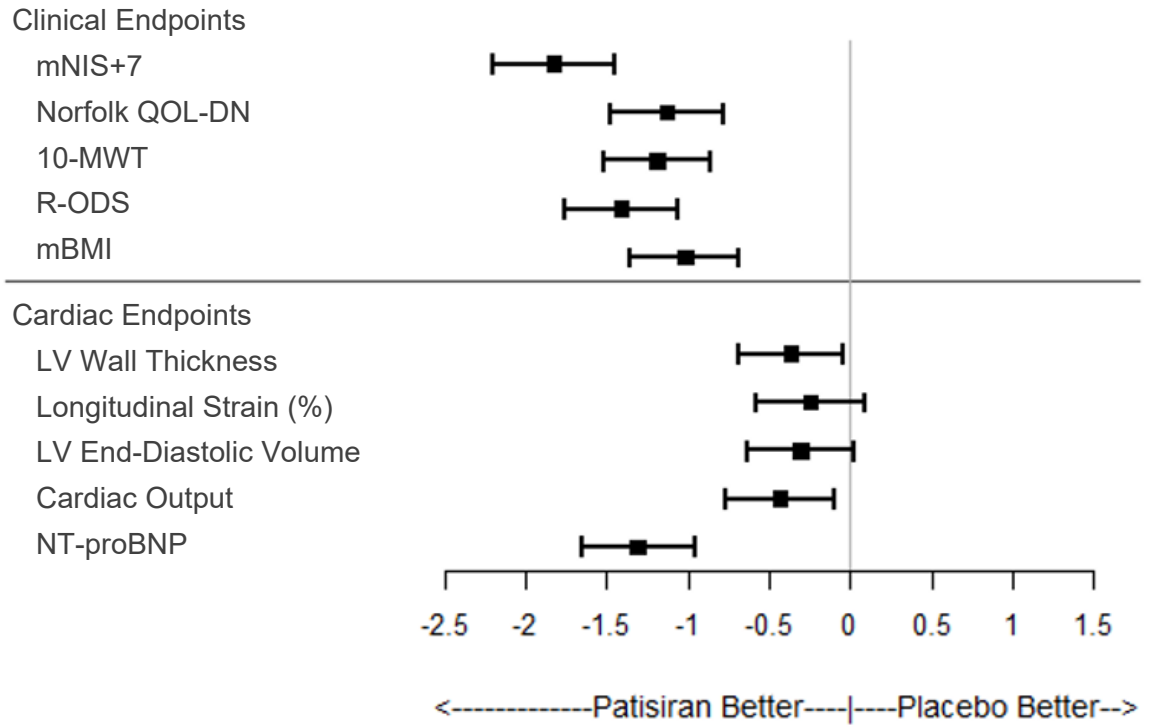
Vutrisiran Efficacy[a] vs External Placebo

Standardized Effect Sizes from HELIOS-A



Patisiran Efficacy[b] vs Placebo

Standardized Effect Sizes from APOLLO



[a]HELIOS-A mITT population. [b]APOLLO 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

10-MWT, 10-meter walk test; EQ-VAS, EuroQOL-Visual-Analog Scale; hATTR, hereditary transthyretin-mediated; KPS, Karnofsky performance scale; mBMI, modified body mass index; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Scale

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