Insights from the HELIOS-A study of vutrisiran in patients with hATTR-PN

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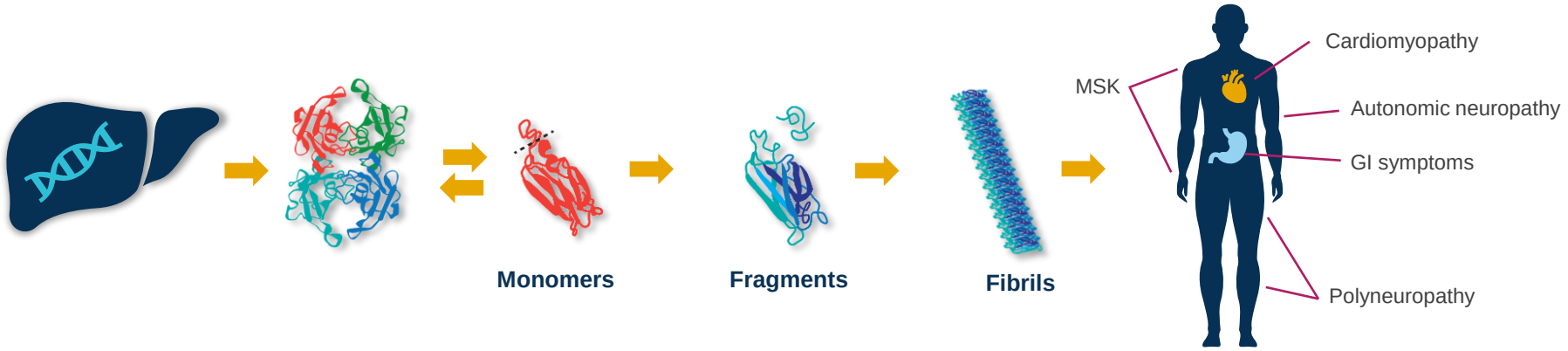
ATTR is a progressive, fatal disease, caused by toxic TTR amyloid deposition, leading to subsequent tissue damage, and multisystem disease burden[1,2]

The TTR protein is primarily **produced in the liver** and transports vitamin A and thyroxine

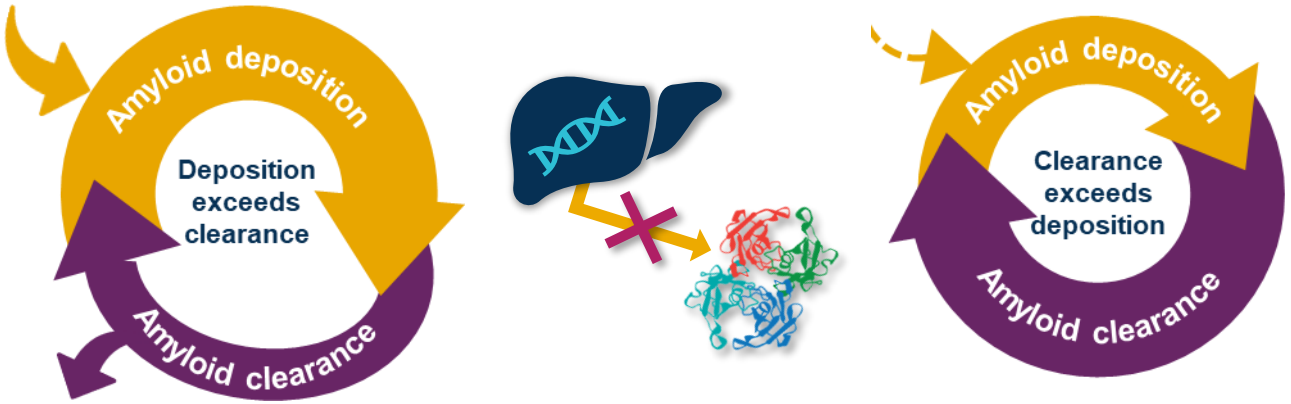
In ATTR, misfolded TTR proteins aggregate and form **toxic amyloid fibrils**…

…which **accumulate** in multiple organs and tissues, resulting in **progressive organ damage**[1]



Clinical manifestations[1,3]

Cycle of toxic TTR deposition[1-3]



GOAL OF TREATMENT IS TO

REDUCE AMYLOID DEPOSITION

ATTR, transthyretin amyloidosis; GI, gastrointestinal; TTR, transthyretin; MSK, musculoskeletal.

1. Adams et al. *Nat Rev Neurol*. 2019;15(7):387-404; 2. Ghosh et al. *Amyloid*. 2023;30(4):379–393; 3. Adams et al. *J Neurol*. 2021:268:2109–2122.

Hereditary ATTR (hATTR) is an inherited, rare, underdiagnosed, and rapidly progressive disease caused by toxic misfolded TTR fibrils that accumulate in multiple tissues[1,2]

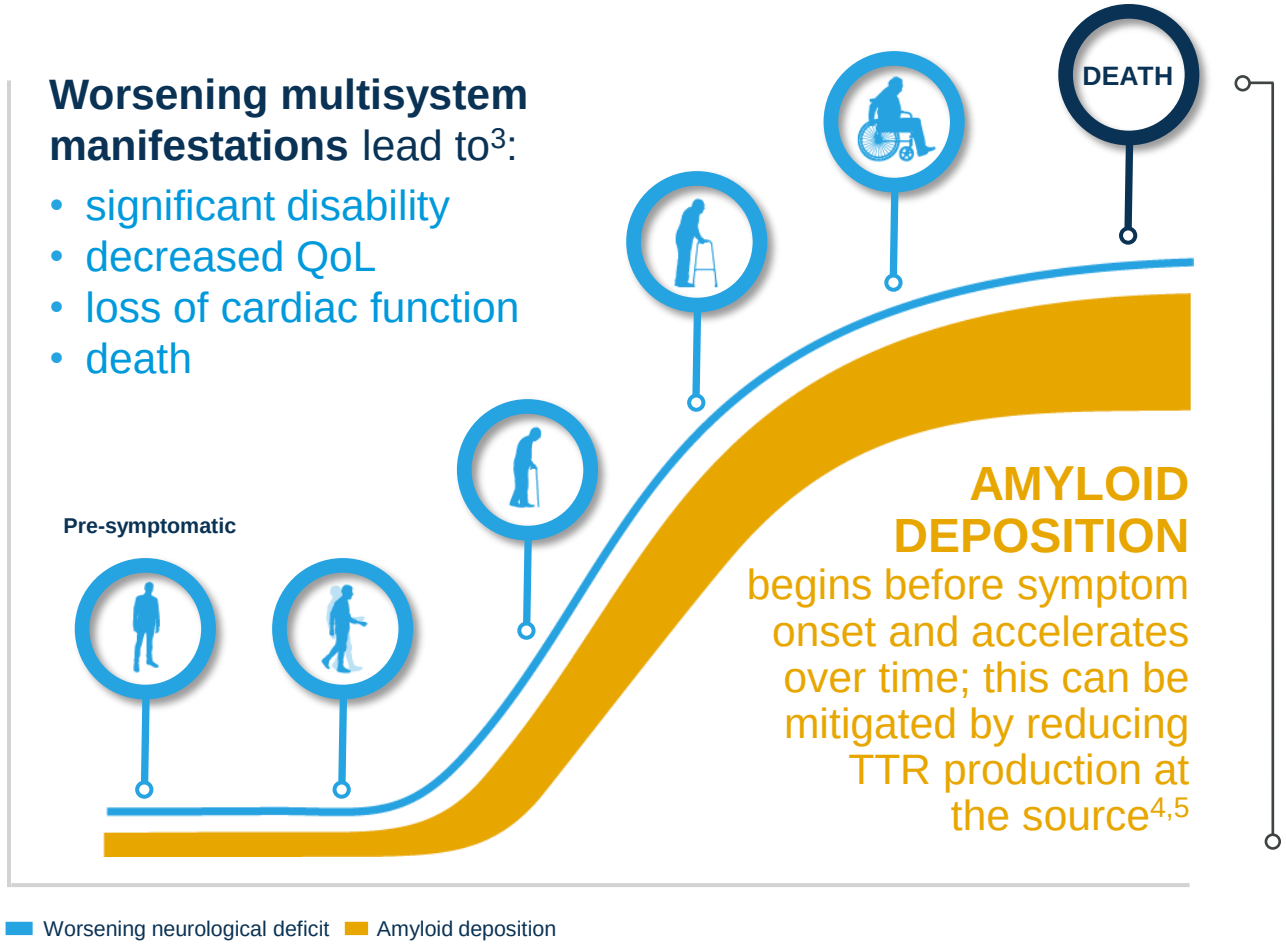
Worldwide, there are

~50,000

PATIENTS WITH **hATTR[3]**

Worsening multisystem manifestations lead to[3]:

- significant disability
- decreased QoL
- loss of cardiac function
- death



Median survival* from diagnosis of hATTR is 4.7 years[6]

*Median survival following diagnosis is reduced (3.4 years) in patients presenting with cardiomyopathy[7]

ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; TTR, transthyretin.

1. Adams et al. *J Neurol*. 2021;268:2109-2122; 2. Adams et al. *Nat Rev Neurol*. 2019;15(7):387–404; 3. Gertz. *Am J Manag Care*. 2017;23:S107-S112; 4. Luigetti et al. *Ther Clin Risk Manag*. 2020;16:109-123; 5. Koike and Katsuno. *Biomedicines*. 2019;5;7(1):11; 6. Swiecicki et al. *Amyloid*. 2015;22(2):123-131; 7. Sattianayagam et al. *Eur Heart J*. 2012;33(9):1120-1127.

hATTR is associated with a profound and rapid worsening of disability and quality of life, even in the early stages of disease[1,2]

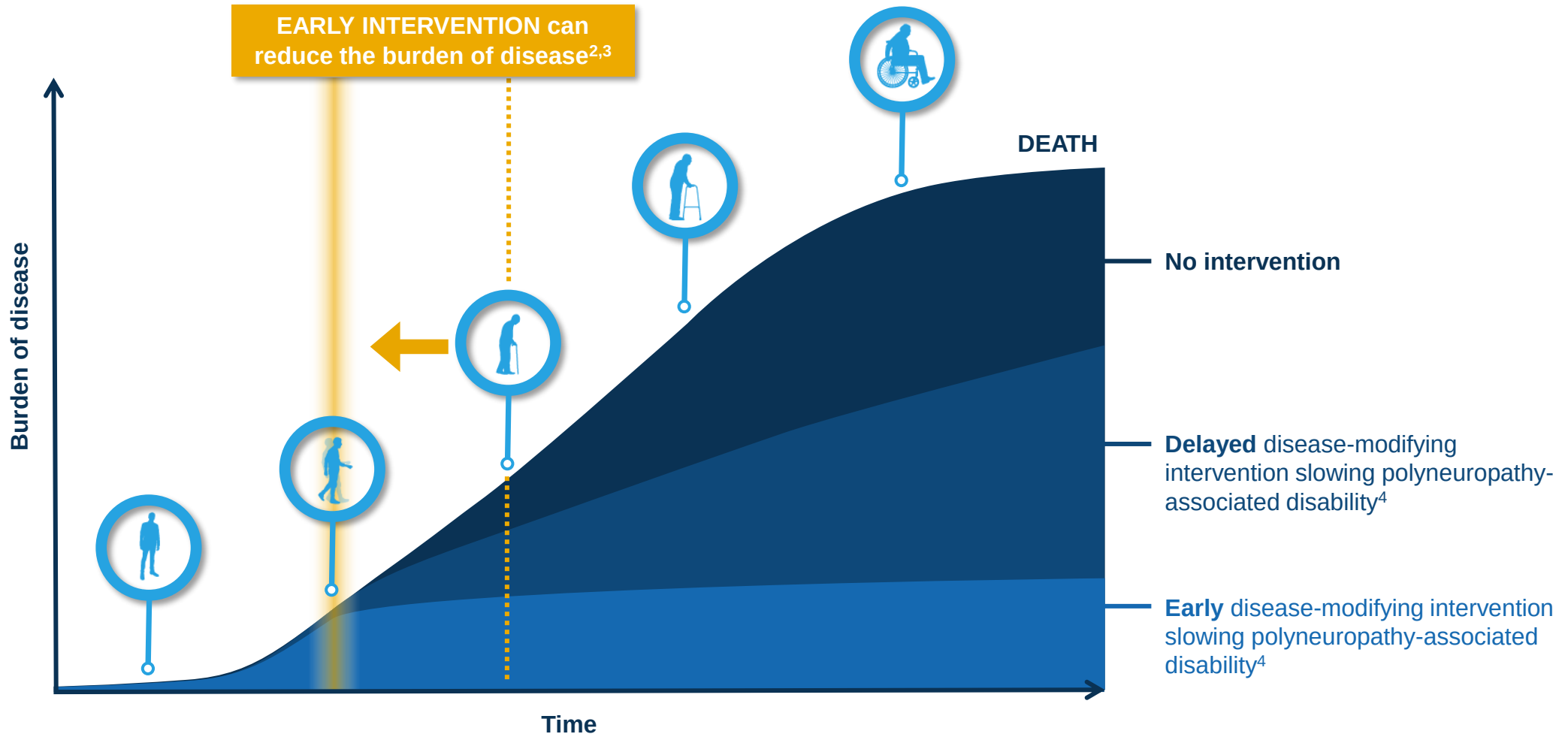


Figure adapted from Giovannoni et al. 2016[5]

hATTR, hereditary ATTR.

1. Adams et al. *Nat Rev Neurol*. 2019;15(7):387-404; 2. Obici et al. *Amyloid*. 2020;27(3):153-162; 3. Adams et al. *Lancet Neurol*. 2021;20(1):49-59; 4. Adams et al. *N Engl J Med*. 2018;379(1):11-21; 5. Giovannoni et al. *Mult Scler Relat Disord*. 2016;9 Suppl 1:S5-S48.

HELIOS-A was a phase 3, global, open-label study comparing the efficacy and safety of vutrisiran in patients with hATTR-PN with an external placebo group (APOLLO study)[1]

Patient population (N=164)

- 18-85 years old
- hATTR; any *TTR* mutation
- NIS 5-130 and PND ≤IIIB
- KPS ≥60%
- Prior TTR stabilizer use permitted
- NYHA Class ≤II

3:1 RANDOMIZATION

Stratification:
TTR V30M vs non-V30M
Baseline NIS <50 vs ≥50

n=122
Vutrisiran
25 mg
SC Q3M

n=42
Reference group
(patisiran)
0.3 mg/kg
IV Q3W

Vutrisiran (n=122) vs APOLLO placebo (n=77)

Primary endpoint[1]:
- Change from baseline in mNIS+7 at Month 9

Secondary endpoints[1]:
Change from baseline in:
- mNIS+7[a] 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

Select exploratory endpoints[2,3]:
Change from baseline in:
- EQ-VAS[f] at Months 9 and 18
- R-ODS and mBMI at Month 9
- Proportion of patients with stable, improved, or worsened KPS[g] from baseline at Month 18
- NT-proBNP levels at Month 18[h]
- Echocardiographic parameters at Month 18[h]
- Technetium scintigraphy at Month 18[i]

Vutrisiran (n=122) vs HELIOS-A patisiran reference group (n=42)

Secondary endpoint[1]:
- % reduction in TTR through Month 18[j]

[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). [f]EQ-VAS (range: 0–100) 0 = best health, 100 = worst health. [g]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. [h]Change from baseline to Month 18 vs. external placebo group. [i]Tc scintigraphy was only performed at select sites in the HELIOS-A study, and no external placebo group comparison was available, comparison to baseline only. [j]Non-inferiority analysis.

10-MWT, 10-meter walk test; hATTR, hereditary ATTR; hATTR-PN, hereditary ATTR 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; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; TTR, transthyretin; EQ-VAS, EuroQoL-Visual Analog Scale.

1. Adams et al. *Amyloid.* 2023;30(1):18-26. 2. Obici et al. *Neurol Ther*. 2023;12(5):1759-1775; 3. Garcia-Pavia et al. *Eur J Heart Fail*. 2024;26(2):397-410.

Baseline demographics and disease characteristics

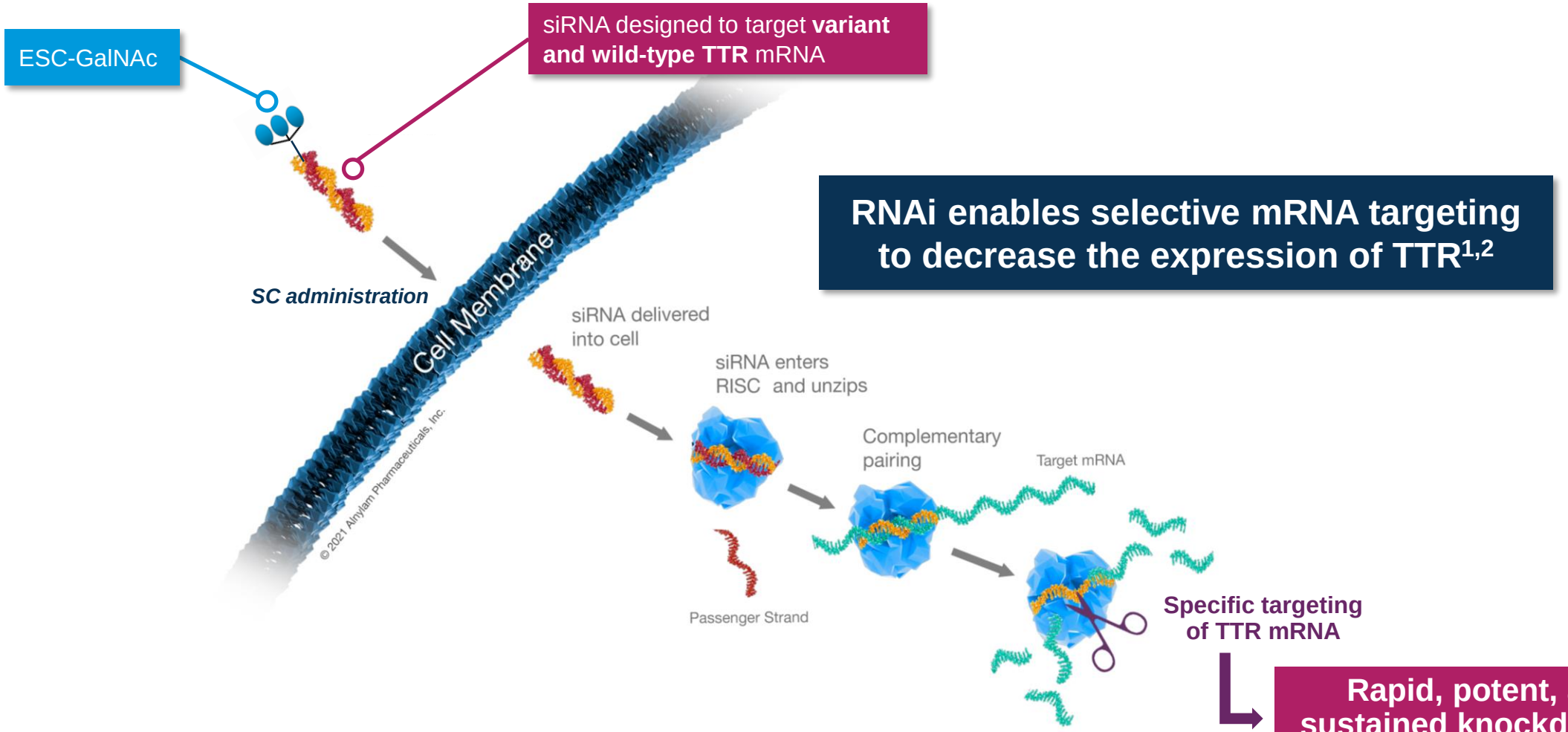
Characteristic	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
Median age, years (IQR)	63 (15)	60 (20)	60 (12)
Males, n (%)	58 (75.3)	79 (64.8)	27 (64.3)
***TTR* genotype, n (%)**			
V30M	40 (51.9)	54 (44.3)	20 (47.6)
Non-V30M	37 (48.1)	68 (55.7)	22 (52.4)
Previous tetramer stabilizer use, n (%)	41 (53.2)	75 (61.5)	33 (78.6)
Tafamidis	27 (35.1)	53 (43.4)	25 (59.5)
NIS, n (%)			
<50	35 (45.5)	78 (63.9)	27 (64.3)
≥50 - <100	33 (42.9)	39 (32.0)	13 (31.0)
≥100	9 (11.7)	5 (4.1)	2 (4.8)
PND score[a], 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 (%)[b,c]	36 (46.8)	40 (32.8)	14 (33.3)

[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.

IQR, interquartile range; LV, left ventricular; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin.

Adams et al. *Amyloid*. 2023;30(1):18-26.

Vutrisiran works by knocking down the underlying pathogenic cause of hATTR[1-3]



RNAi enables selective mRNA targeting to decrease the expression of TTR[1,2]

Rapid, potent, and sustained knockdown of TTR protein production[3]

Figure adapted from Coelho et al. 2013[4]

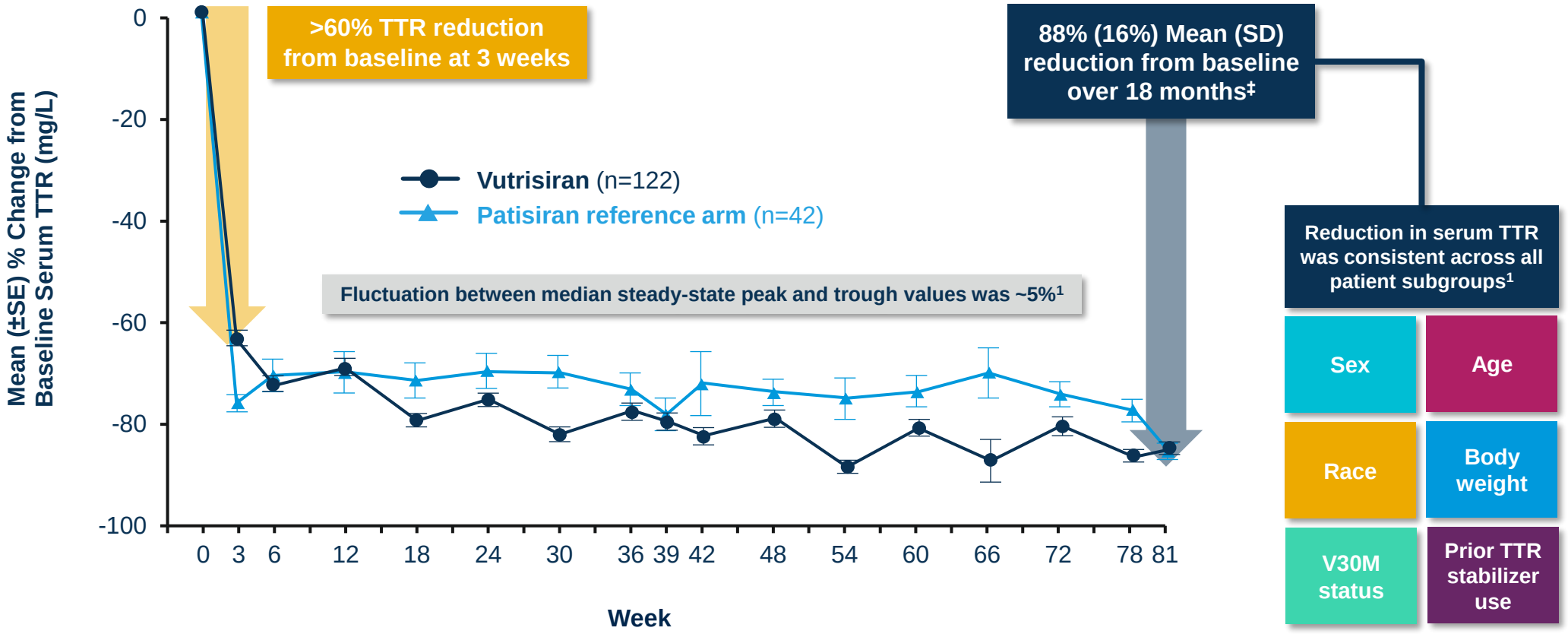
ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; ESC, enhanced stabilization chemistry; GalNAc, N-acetylgalactosamine; mRNA, messenger RNA; RISC, RNA-induced silencing complex; RNA, ribonucleic acid; RNAi, RNA interference; SC, subcutaneous; siRNA, small interfering RNA; TTR, transthyretin.

1. Butler et al. *Amyloid*. 2016;23(2):109-118; 2. Aagaard and Rossi. *Adv Drug Deliv Rev*. 2007;59(2-3):75-86; 3. Adams et al. *Amyloid*. 2023;30(1):18-26; 4. Coelho et al. *N Engl J Med*. 2013;369(9):819-829.

Treatment with vutrisiran provided rapid and durable reduction of serum TTR for all patient subgroups

Secondary endpoint

Rapid and sustained reduction in serum TTR levels with vutrisiran



Reduction in serum TTR was consistent across all patient subgroups[1]

- Sex
- Age
- Race
- Body weight
- V30M status
- Prior TTR stabilizer use

‡Steady state serum TTR reduction, measured using Day 463 samples for vutrisiran.
SD, standard deviation; SE, standard error; TTR, transthyretin.
Adams et al. *Amyloid*. 2023;30(1):18-26.

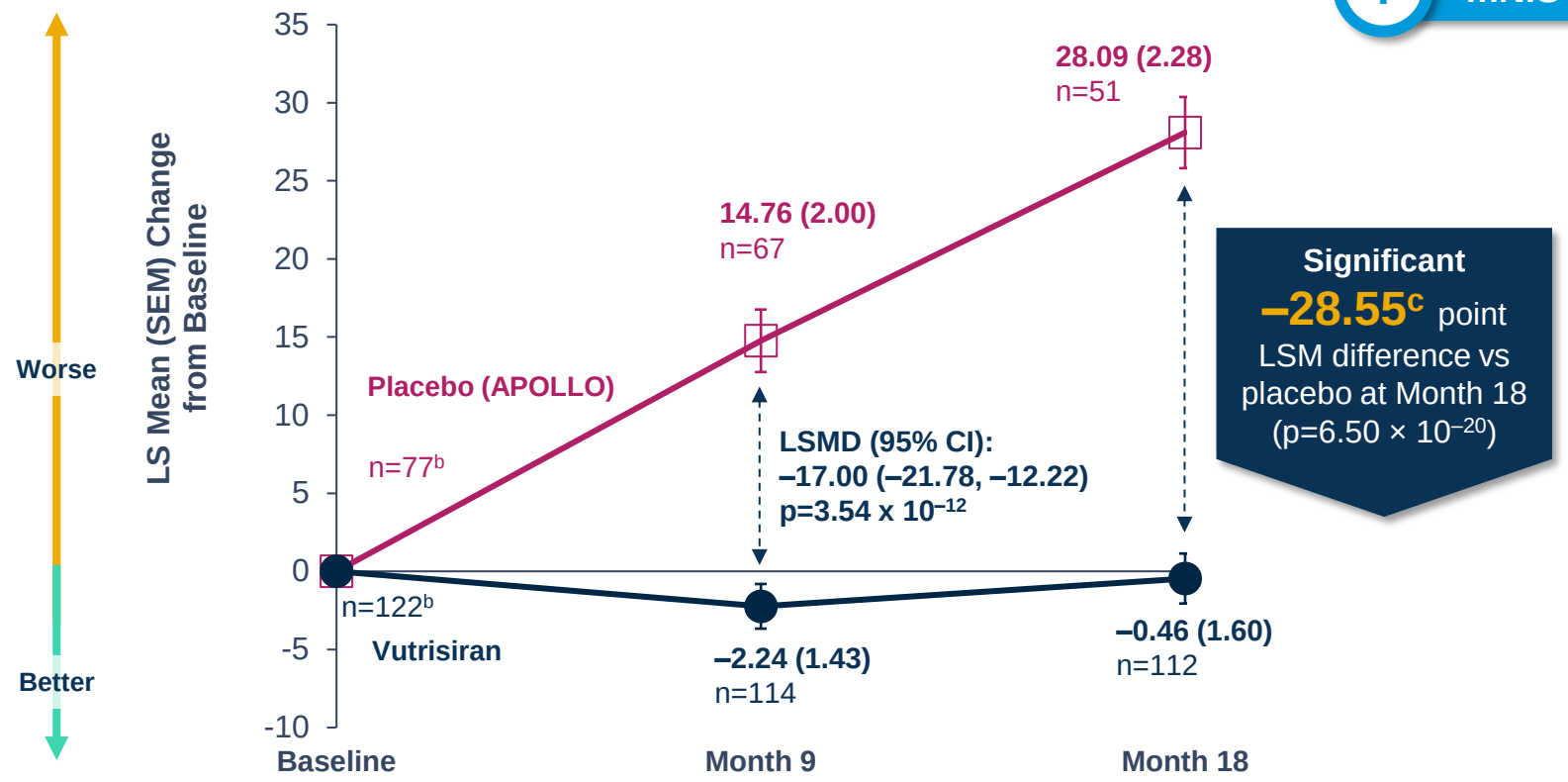
Primary and secondary endpoints

Vutrisiran significantly improved mNIS+7, a measure of neuropathy impairment, compared with external placebo at Months 9 and 18

Primary and secondary endpoint

mNIS+7 LS Mean Change from Baseline[a]

mNIS+7 Scale



Significant
–28.55[c] point
LSM difference vs placebo at Month 18
($p=6.50 \times 10^{-20}$)

This treatment effect was seen at Month 9 (primary endpoint) and persisted through Month 18 (secondary endpoint).

[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 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](95% CI = -34.00, -23.10).

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

Adams et al. *Amyloid*. 2023;30(1):18-26.

mNIS+7 Scale

- mNIS+7 is a clinician-reported scale designed to specifically assess polyneuropathy impairment in patients with hATTR
- mNIS+7 uses standardized, quantitative, and referenced assessments to quantify decreased muscle weakness, muscle stretch reflexes, sensory loss, and autonomic impairment

Max score	mNIS+7 components	Assessment
192	Muscle weakness	Assessed in 24 muscle groups (both sides)
20	Reflexes	Assessed in 5 muscle groups (both sides)
80	Sensation	S ST QST; assessed at up to 10 sites (left side)
10	NCS	Five nerve assessments: ulnar motor, tibial motor, peroneal motor, ulnar sensory, sural sensory
2	Autonomic	Postural hypotension

Composition and maximum scores of NIS/NIS-based scales

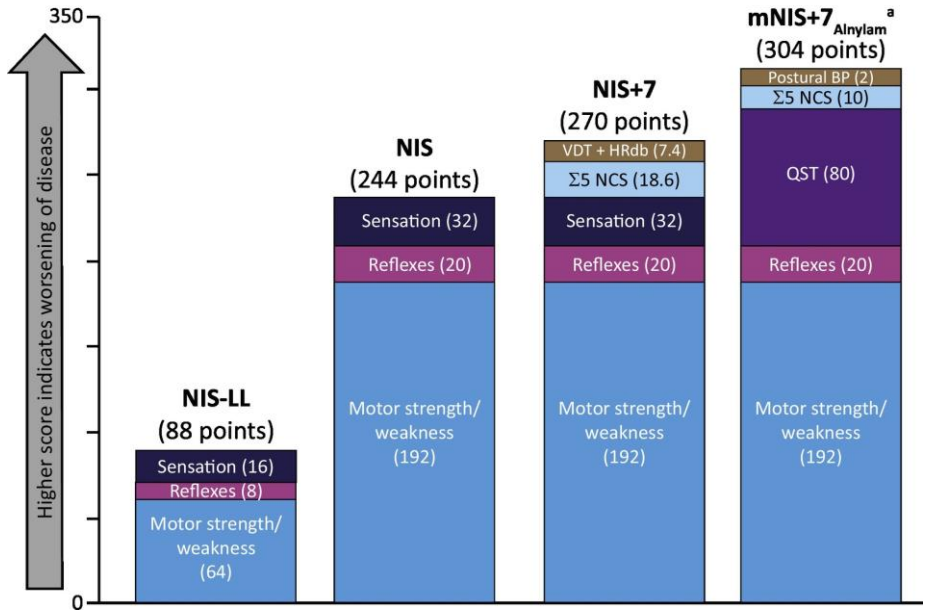


Image taken from Dyck et al. 2019

BP, blood pressure; hATTR, hereditary ATTR; HRdb, heart rate deep breathing; mNIS, modified Neuropathy Impairment Score; NCS, nerve conduction studies; NIS, Neuropathy Impairment Score; NIS-LL, Neuropathy Impairment Score-lower limb; QST, quantitative sensory test; S ST QST, smart somatotopic quantitative sensation testing; VDT vibration detection threshold.

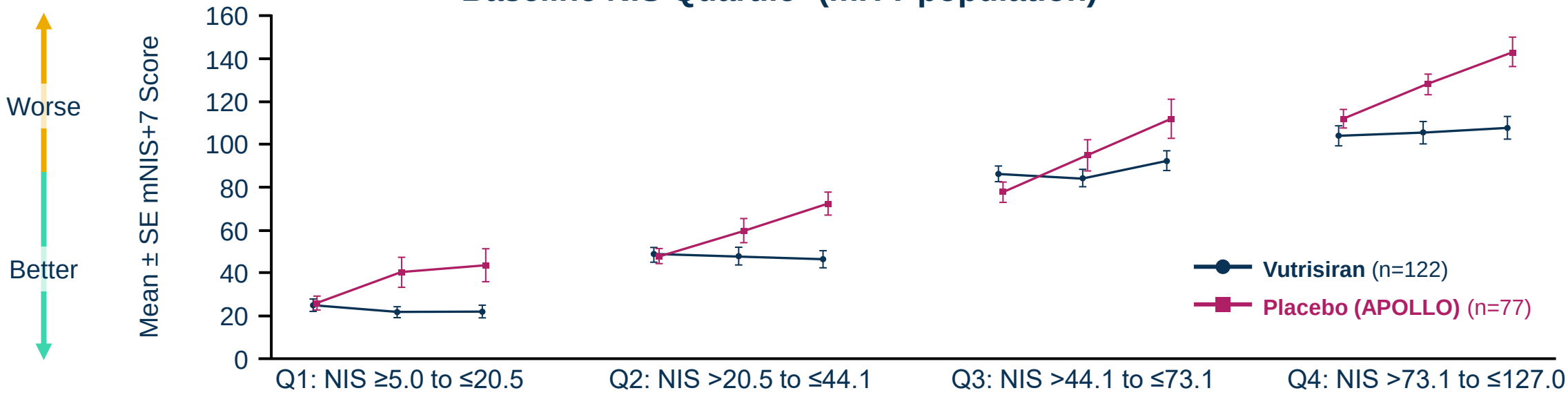
Dyck et al. *J Neurol Sci.* 2019;405:116424.

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

Post hoc analysis

mNIS+7 Scale

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
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)

[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; SEM, standard error of the mean.

Luigetti et al. *Neurol Ther*. 2024;13(3):625-639.

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- mNIS+7 uses standardized, quantitative, and referenced assessments to quantify decreased muscle weakness, muscle stretch reflexes, sensory loss, and autonomic impairment

Max score	mNIS+7 components	Assessment
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2	Autonomic	Postural hypotension

Composition and maximum scores of NIS/NIS-based scales

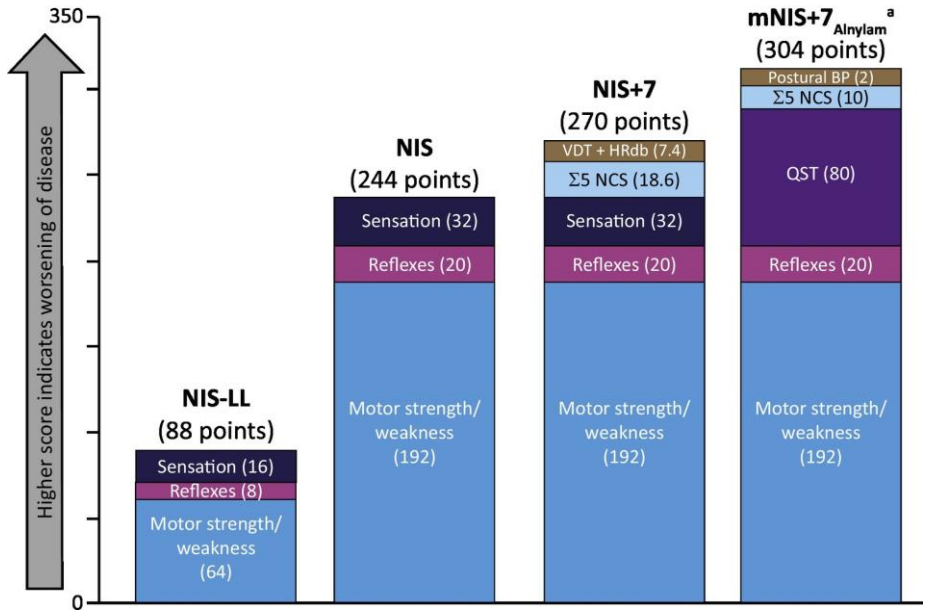


Image taken from Dyck et al. 2019

BP, blood pressure; hATTR, hereditary ATTR; HRdb, heart rate deep breathing; mNIS, modified Neuropathy Impairment Score; NCS, nerve conduction studies; NIS, Neuropathy Impairment Score; NIS-LL, Neuropathy Impairment Score-lower limb; ; QST, quantitative sensory test; S ST QST, smart somatotopic quantitative sensation testing; VDT vibration detection threshold.

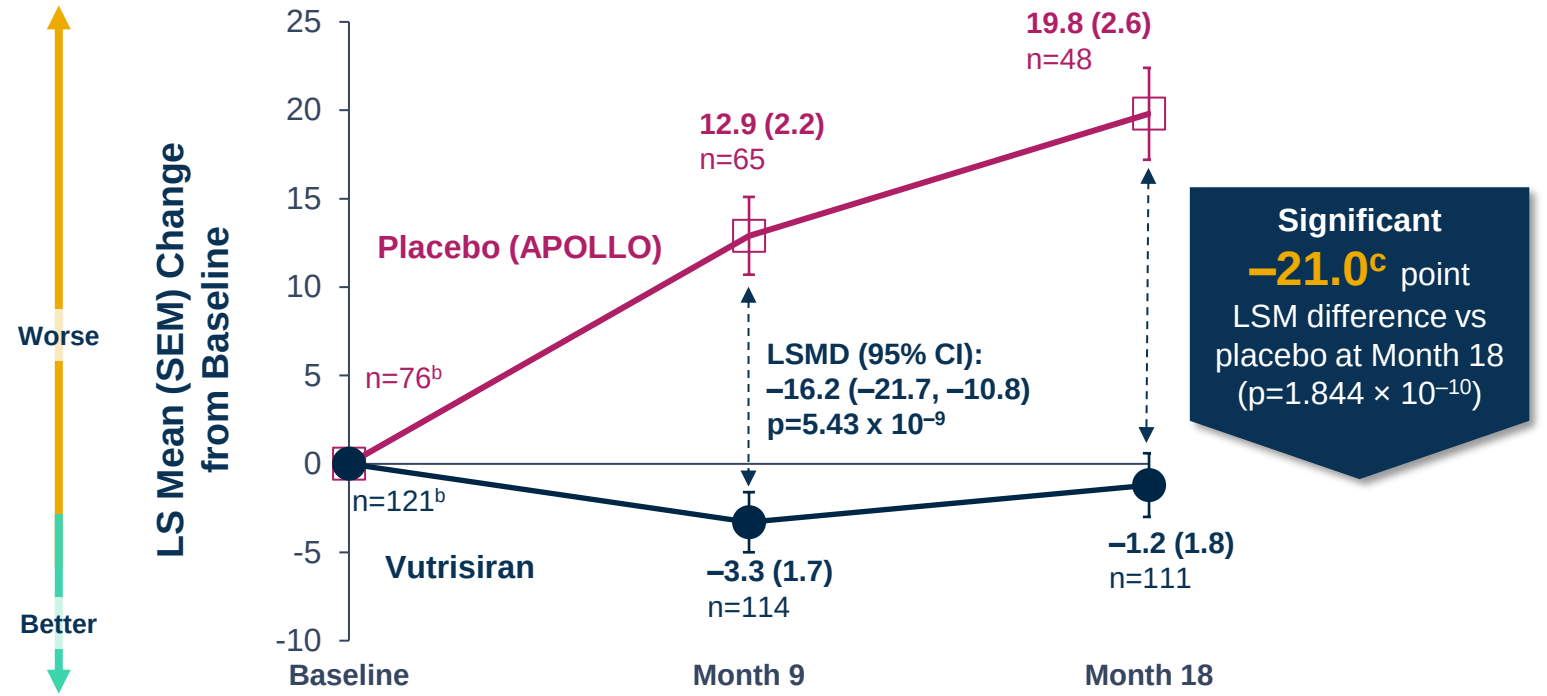
Dyck et al. *J Neurol Sci.* 2019;405:116424.

Vutrisiran significantly improved quality of life compared with external placebo at Months 9 and 18

Secondary endpoint

Norfolk QOL-DN

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



[a]Value of n is the number of evaluable patients at each timepoint. Data plotted for 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) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group. [c](95% CI = -27.1, -14.9).

ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSM, least squares mean; LSMD, LSM difference; MMRM, mixed model for repeated measures; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SD, standard deviation; SEM, standard error of the mean.

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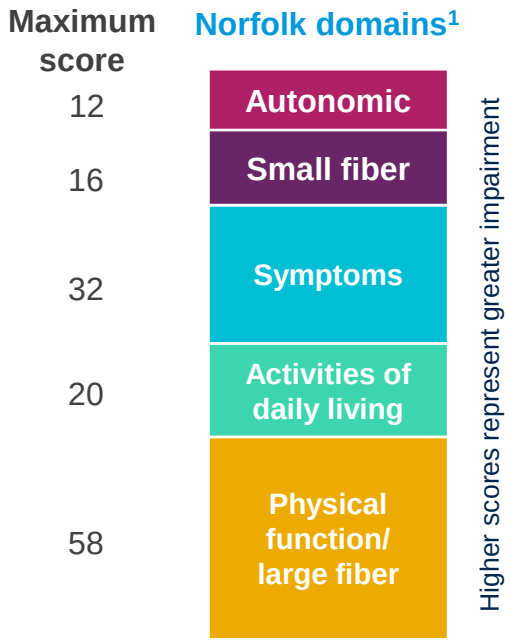
Norfolk QOL-DN autonomic symptoms and QOL score

- Norfolk QoL-DN is 35-question patient-reported questionnaire that assesses patients' subjective perceptions of symptoms associated with specific nerve fiber damage across five domains[1]
  - Maximum impairment: 136 (scale of -4 to 136)



Norfolk QOL-DN requires a license for physician use.

Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; QOL, quality of life.

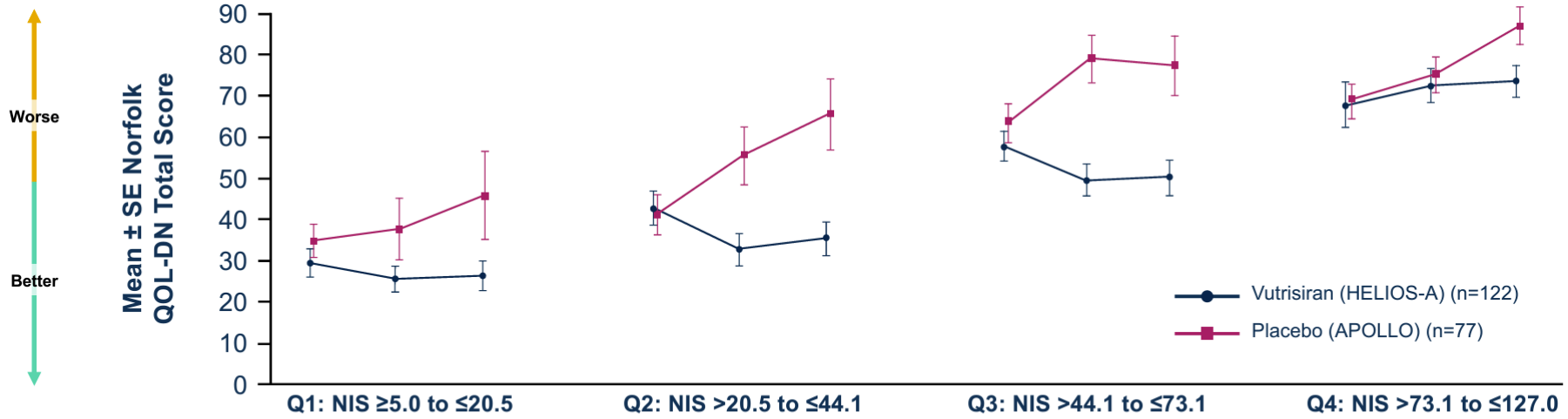
1. Vinik et al. *J Peripher Nerv Syst*. 2014;19:104–14; 2. Vinik and Vinik. In: Farquhar et al, eds. *The Value of Innovation: Impact on Health, Life Quality, Safety, and Regulatory Research*. 2007;16:29-52.

Patients with the least severe disease at start of treatment had lower impairment in neuropathy-related QOL at Month 18

Post hoc analysis

Norfolk QOL-DN

Norfolk QOL-DN 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
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)

[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; NIS, neuropathy impairment score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; Q, quartile; QOL, quality of life; SE, standard error; SEM, standard error of the mean.

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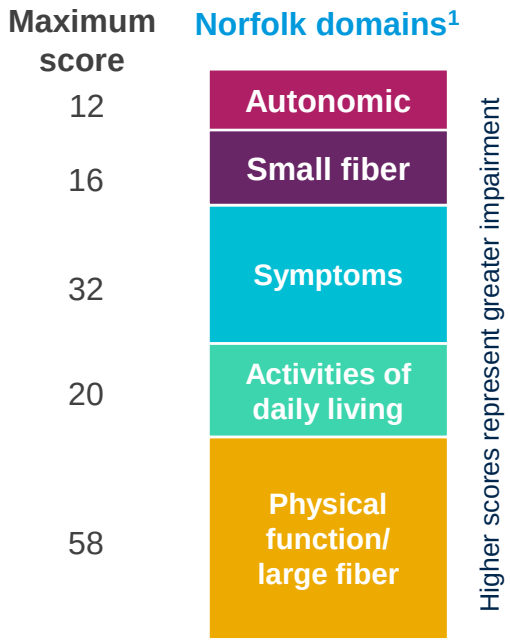
Norfolk QOL-DN autonomic symptoms and QOL score

- Norfolk QoL-DN is 35-question patient-reported questionnaire that assesses patients' subjective perceptions of symptoms associated with specific nerve fiber damage across five domains[1]
  - Maximum impairment: 136 (scale of -4 to 136)



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Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; QOL, quality of life.

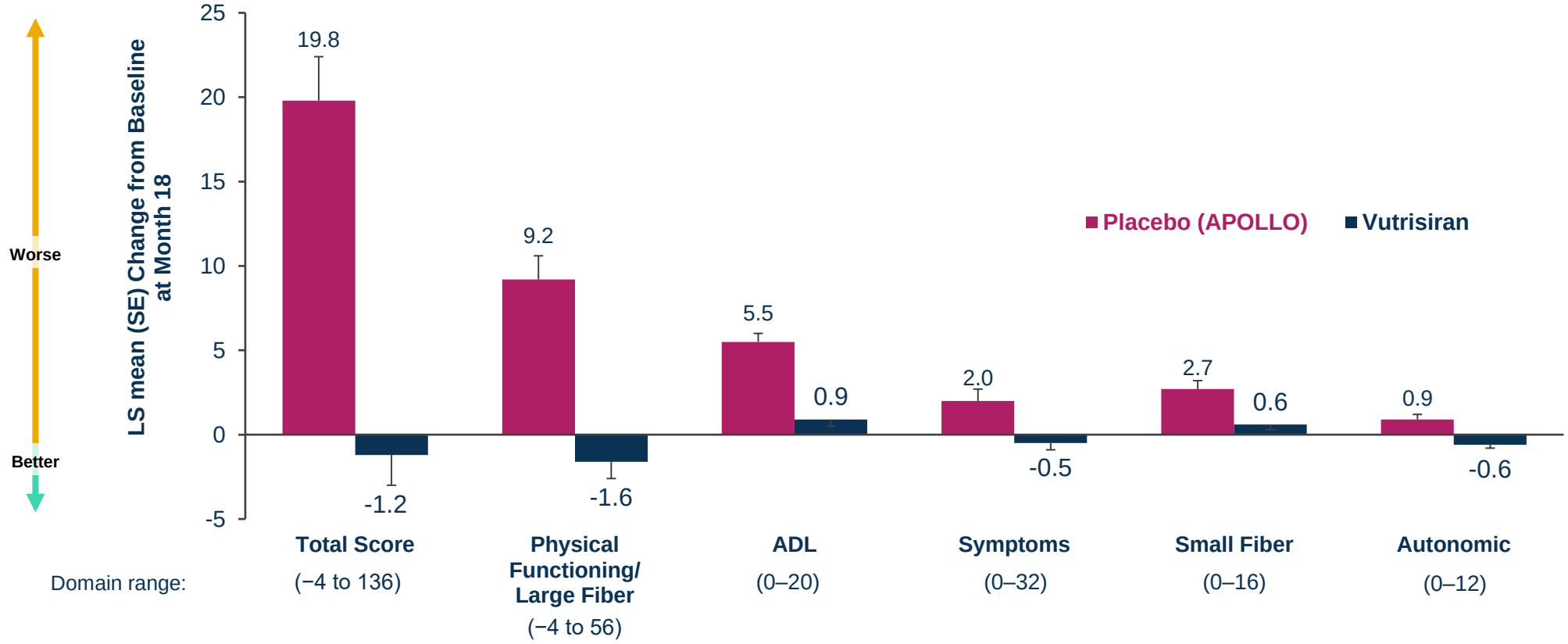
1. Vinik et al. *J Peripher Nerv Syst*. 2014;19:109–14; 2. Vinik and Vinik. In: Farquhar et al, eds. *The Value of Innovation: Impact on Health, Life Quality, Safety, and Regulatory Research*. 2007;16:29-52.

Vutrisiran led to improvement across all Norfolk QOL-DN domains compared with external placebo at Month 18

Post hoc analysis

Norfolk QOL-DN

Norfolk QOL-DN Mean Change from Baseline by Domain[a]



[a]A higher score indicates worse quality of life.

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

Obici et al. *Neurol Ther*. 2023;12(5):1759-1775.

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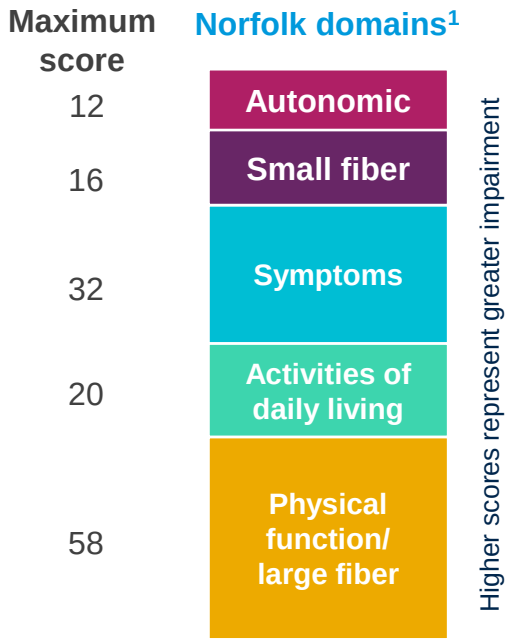
- Norfolk QoL-DN is 35-question patient-reported questionnaire that assesses an individual's subjective perceptions of symptoms associated with specific nerve fiber damage across five domains[1]
  - Maximum impairment: 136 (scale of -4 to 136)



Sample questions[2]

- Have you had a problem with **diarrhea** and/or loss of **bowel control**?
- Have you **burned** or **injured** yourself and been unable to feel it?
- Have you had any **numbness** in your **hands**?
- Have you had a problem with **bathing** or **showering**?
- Have you felt **unsteady on your feet**?
- Have you had a problem with **fainting** or **dizziness** when you stand?
- Have you had any **weakness** in your legs?
- Have you had a problem **walking down stairs**?
- Have you been unable to tell **hot from cold water** with your hands?

Norfolk QOL-DN requires a license for physician use.

DN, diabetic neuropathy; QOL, quality of life.

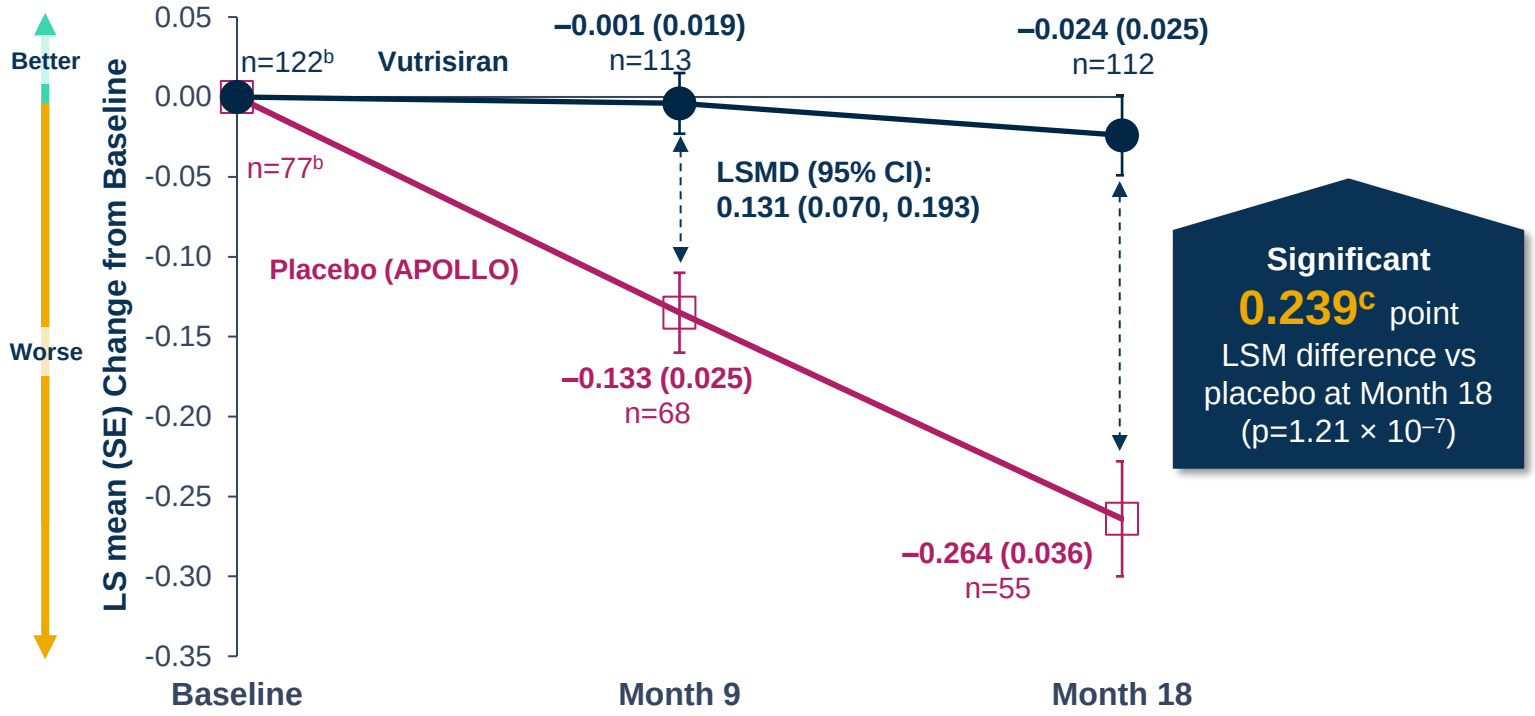
1. Vinik et al. *J Peripher Nerv Syst*. 2014;19:109–14; 2. Vinik and Vinik. In: Farquhar et al, eds. *The Value of Innovation: Impact on Health, Life Quality, Safety, and Regulatory Research*. 2007;16:29-52.

Gait speed, as measured by 10-MWT, favored treatment with vutrisiran compared with external placebo at Months 9 and 18[1]

Secondary endpoint

10-MWT

10-MWT LS Mean Change from Baseline (m/s)[2,a]



Significant
0.239[c] point
LSM difference vs placebo at Month 18
($p=1.21 \times 10^{-7}$)

This treatment effect was seen at Month 9 and persisted through Month 18.

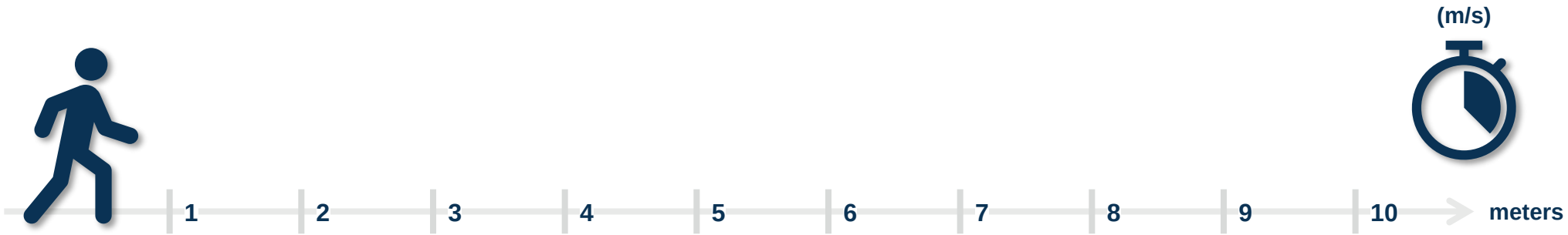
[a]mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted at Month 9 are ANCOVA, analysis of covariance/multiple imputation model data and data plotted at Month 18 are MMRM model data. [b]At baseline, 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](95% CI = 0.154, 0.325).

10-MWT, 10-meter walk test; CI, confidence interval; LS, least squares; LSM, least squares mean; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; SD, standard deviation; SE, standard error.

1. Adams et al. *Amyloid.* 2023;30(1):18-26; 2. Adams et al. Presented at: Société Francophone du Nerf Périphérique (SFNP) Meeting, February 2-3, 2022, Virtual.

10-MWT

- 10-MWT is a clinical assessment tool to assess gait speed and mobility in individuals with neurological disorders
- 10-MWT involves measuring the time it takes for an individual to walk a particular distance, with results reported in meters/second (m/s)



10-MWT, 10-meter walk test

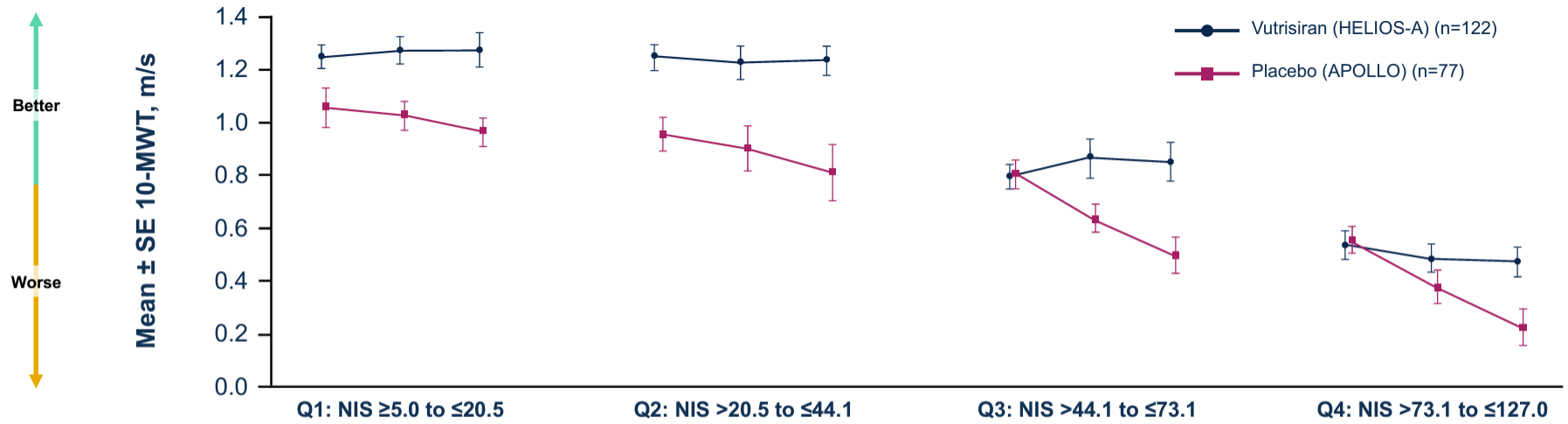
Moore et al. *J Neurol Phys Ther*. 2018;42(3):174-220.

Patients with the least severe disease at start of treatment had lower impairment in gait speed at Month 18

Post hoc analysis

10-MWT

10-MWT (m/s) Across 18 Months by Baseline NIS Quartile[a] (mITT population)[1]

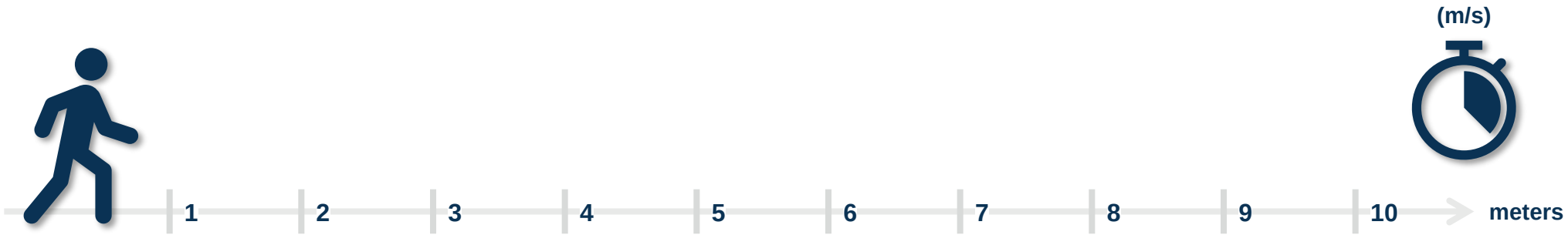


		Q1: NIS ≥5.0 to ≤20.5			Q2: NIS >20.5 to ≤44.1			Q3: NIS >44.1 to ≤73.1			Q4: NIS >73.1 to ≤127.0		
		BL	M9	M18	BL	M9	M18	BL	M9	M18	BL	M9	M18
Vutrisiran	n	38	38	37	32	31	29	30	24	25	22	22	20
	Mean (± SEM) Δ from baseline	—	0.02 (0.03)	0.02 (0.05)	—	-0.01 (0.04)	-0.01 (0.04)	—	0.03 (0.04)	0.02 (0.04)	—	-0.05 (0.03)	-0.10 (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)

[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.
10-MWT, 10-meter walk test; BL, baseline; M, month; NIS, neuropathy impairment score; mITT, modified intent-to-treat; Q, quartile; SE, standard error; SEM, standard error of the mean.
Luigetti et al. *Neurol Ther*. 2024;13(3):625-639.

10-MWT

- 10-MWT is a clinical assessment tool to assess gait speed and mobility in individuals with neurological disorders
- 10-MWT involves measuring the time it takes for an individual to walk a particular distance, with results reported in meters/second (m/s)



10-MWT, 10-meter walk test

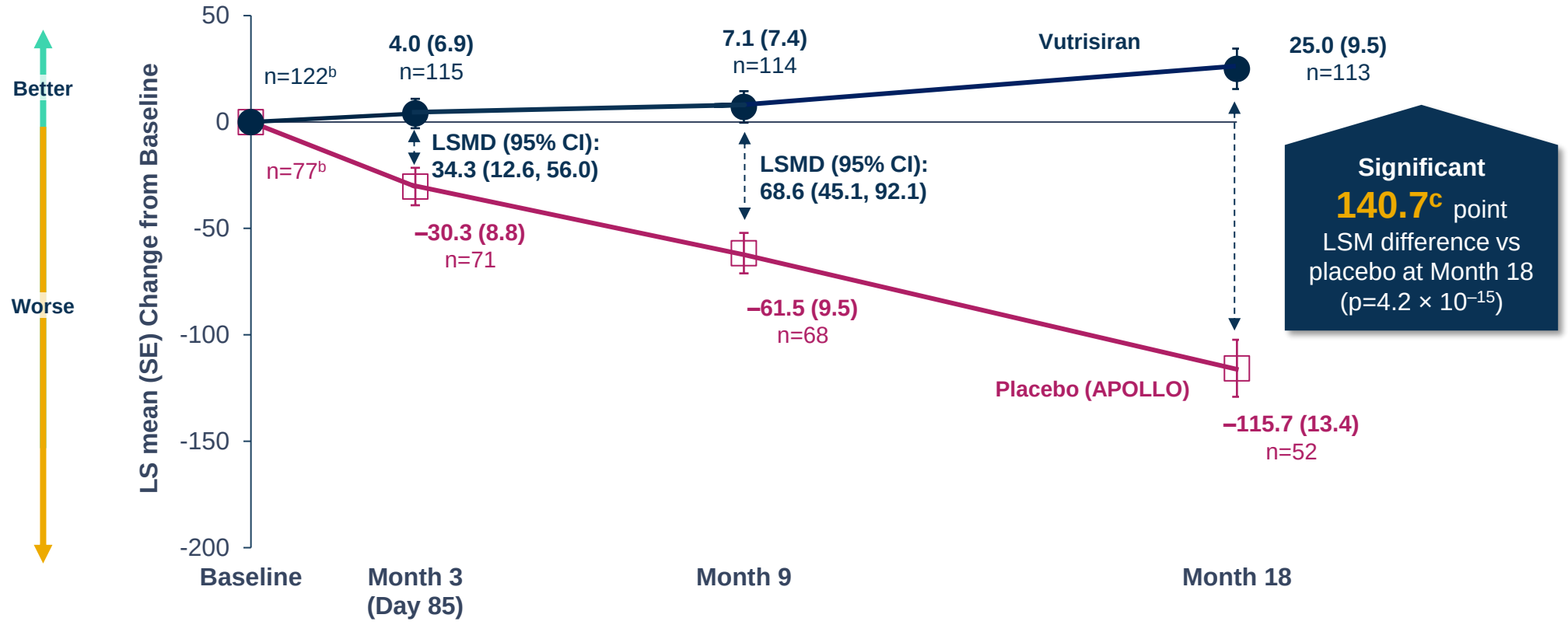
Moore et al. *J Neurol Phys Ther*. 2018;42(3):174-220.

Nutritional status, as measured by mBMI at Months 3, 9, and 18, favored treatment with vutrisiran compared with external placebo[1]

Secondary endpoint

i mBMI

mBMI LS Mean Change from Baseline[2,a]



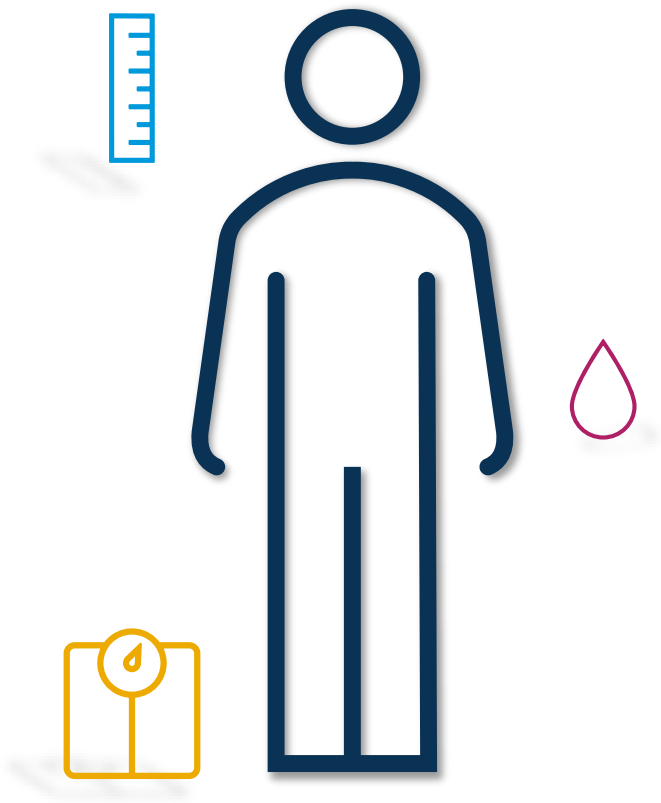
[a]mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted are MMRM model data. [b]At baseline, the mean (± SD) mBMI was 1057.4 (233.8) in the vutrisiran group and 989.9 (214.2) in the external placebo group. [c](95% CI = 108.4, 172.9).

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.

1. Adams et al. *Amyloid.* 2023;30(1):18-26; 2. Ajroud-Driss et al. Presented at: Peripheral Nerve Society (PNS) Annual Meeting, May 14-17, 2022, Miami, FL, USA.

mBMI

- Modified BMI (mBMI) is measured by multiplying BMI (kg/m^2) by serum albumin (g/L)
- mBMI is used as a measurement of nutritional status



mBMI, Modified BMI

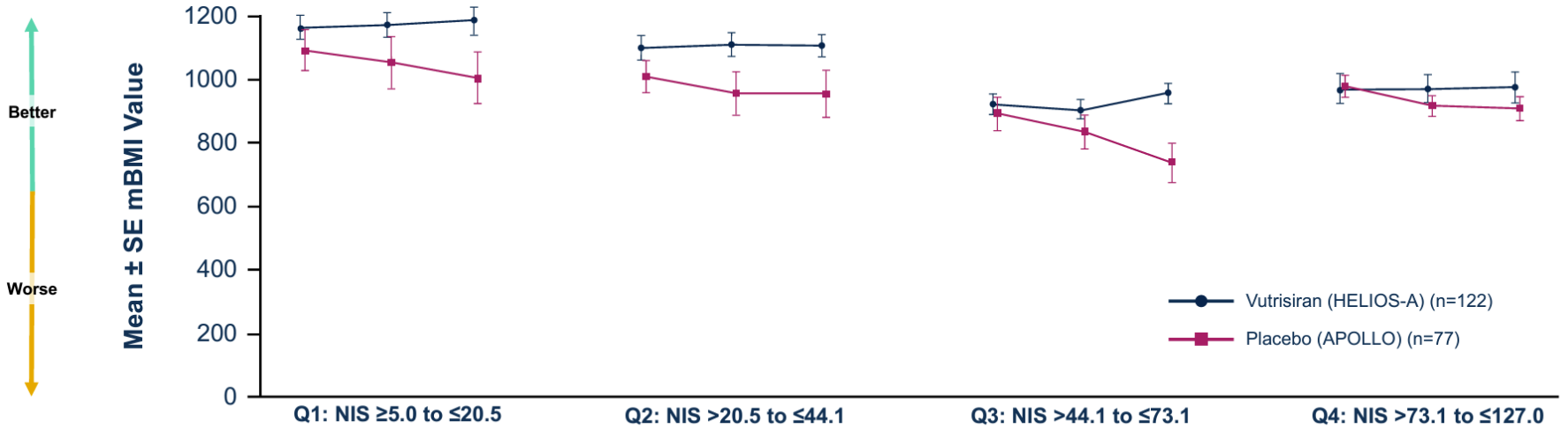
Driggin et al. *Amyloid*. 2020;27(2):73-80.

Patients with the least severe disease at start of treatment had lower impairment in nutritional status at Month 18[1]

Post hoc analysis

mBMI

mBMI Across 18 Months by Baseline NIS Quartile[a] (mITT population)[1]



		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 (± 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)

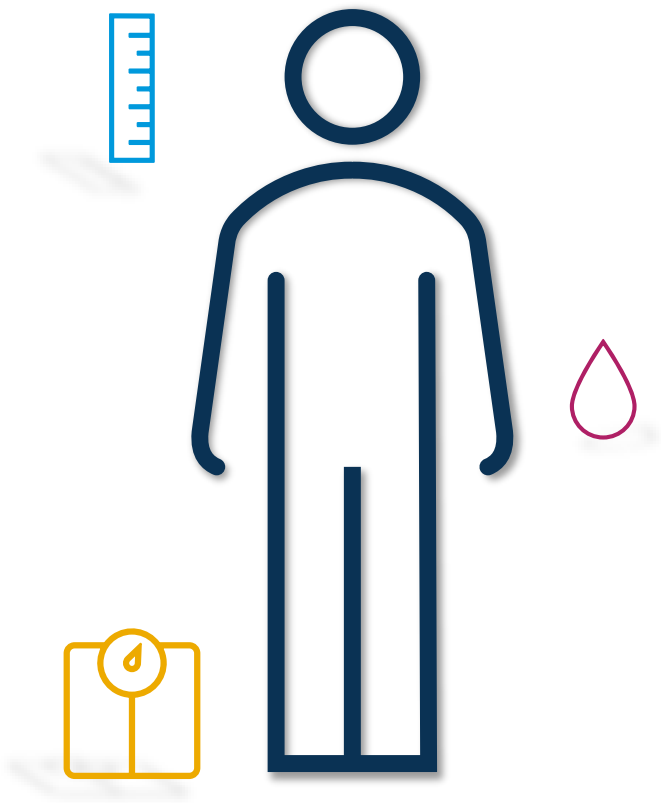
[a]For this post hoc subgroup analysis, patients were divided into 4 quartiles, with approximately the same number of patients in each quartile, based on increasing baseline NIS.

BL, baseline; M, month; NIS, neuropathy impairment score; mBMI, modified body mass index; mITT, modified intent-to-treat; Q, quartile; SE, standard error; SEM, standard error of the mean.

Luigetti et al. *Neurol Ther*. 2024;13(3):625-639.

mBMI

- Modified BMI (mBMI) is measured by multiplying BMI (kg/m^2) by serum albumin (g/L)
- mBMI is used as a measurement of nutritional status



mBMI, Modified BMI

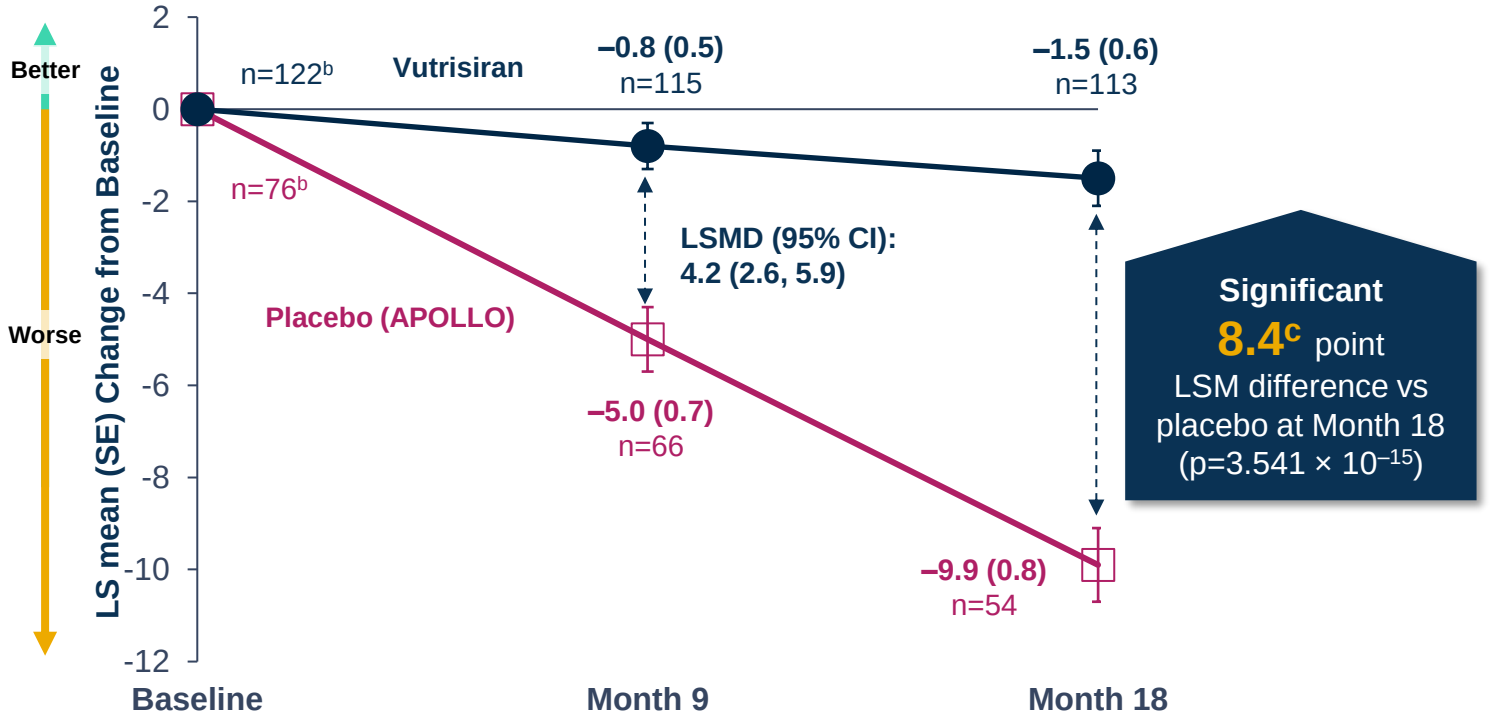
Driggin et al. *Amyloid*. 2020;27(2):73-80.

Disability, as measured by R-ODS at Months 9 and 18, favored treatment with vutrisiran compared with external placebo[1]

Secondary endpoint

R-ODS

R-ODS LS Mean Change from Baseline[2,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. [b]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. [c](95% CI = 6.5, 10.4).

CI, confidence interval; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; QOL, quality of life; R-ODS, Rasch-built Overall Disability Scale; SD, standard deviation; SE, standard error.

1. Adams et al. *Amyloid.* 2023;30(1):18-26; 2. Ajroud-Driss et al. Presented at: Peripheral Nerve Society (PNS) Annual Meeting, May 14-17, 2022, Miami, FL, USA.

R-ODS

- The Rasch-built Overall Disability Scale (R-ODS) is a 24-item questionnaire used to determine the relationship between a patient's polyneuropathy and their ability to carry out daily and social activities

Can you…	It is not possible for me [0]	Possible, but with some difficulty [1]	Possible, without any difficulty [2]
1. read a newspaper or book?	☐	☐	☐
2. eat?	☐	☐	☐
3. brush your teeth?	☐	☐	☐
4. wash the upper part of your body?	☐	☐	☐
5. sit on a toilet?	☐	☐	☐
6. prepare a snack?	☐	☐	☐
7. put clothes on your upper body?	☐	☐	☐
8. wash the lower part of your body?	☐	☐	☐
9. move a chair?	☐	☐	☐
10. turn a key in a lock?	☐	☐	☐

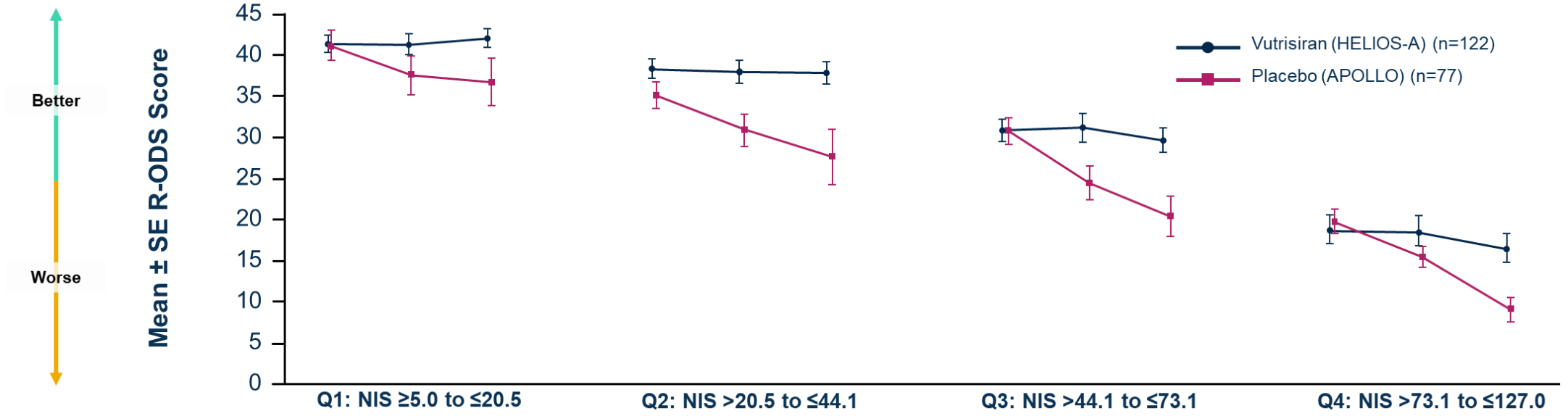
van Nes et al. *Neurology*. 2011;76(4):337-345.

Patients with less severe disease at baseline had lower impairment in disability status at Month 18 compared with external placebo

Post hoc analysis

R-ODS

R-ODS 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
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)

[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; NIS, Neuropathy Impairment Score; Q, quartile; QOL, quality of life; M, month; mITT, modified intent-to-treat; R-ODS, Rasch-built Overall Disability Scale; SE, standard error; SEM, standard error of the mean.

Luigetti et al. *Neurol Ther*. 2024;13(3):625-639.

R-ODS

- The Rasch-built Overall Disability Scale (R-ODS) is a 24-item questionnaire used to determine the relationship between a patient's polyneuropathy and their ability to carry out daily and social activities

Can you…	It is not possible for me [0]	Possible, but with some difficulty [1]	Possible, without any difficulty [2]
1. read a newspaper or book?	☐	☐	☐
2. eat?	☐	☐	☐
3. brush your teeth?	☐	☐	☐
4. wash the upper part of your body?	☐	☐	☐
5. sit on a toilet?	☐	☐	☐
6. prepare a snack?	☐	☐	☐
7. put clothes on your upper body?	☐	☐	☐
8. wash the lower part of your body?	☐	☐	☐
9. move a chair?	☐	☐	☐
10. turn a key in a lock?	☐	☐	☐

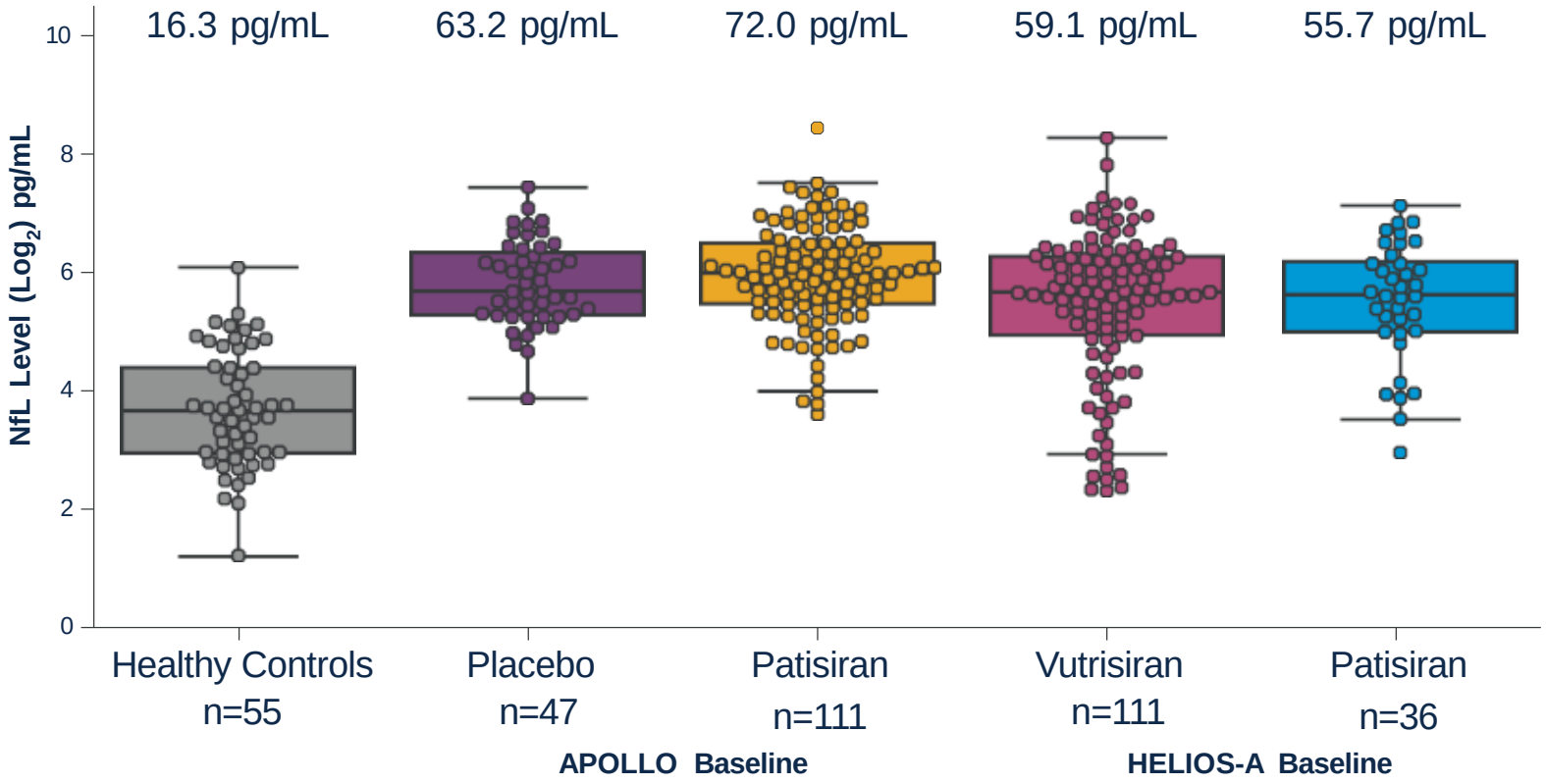
van Nes et al. *Neurology*. 2011;76(4):337-345.

Exploratory endpoints

Neurofilament light chain (NfL), a well-studied biomarker in neurological disorders, is being researched as a potential biomarker in hATTR-PN[1,2]

Post hoc analysis

Baseline NfL Levels in APOLLO and HELIOS-A Studies



HELIOS-A results support that NfL levels are increased in patients with hATTR-PN.

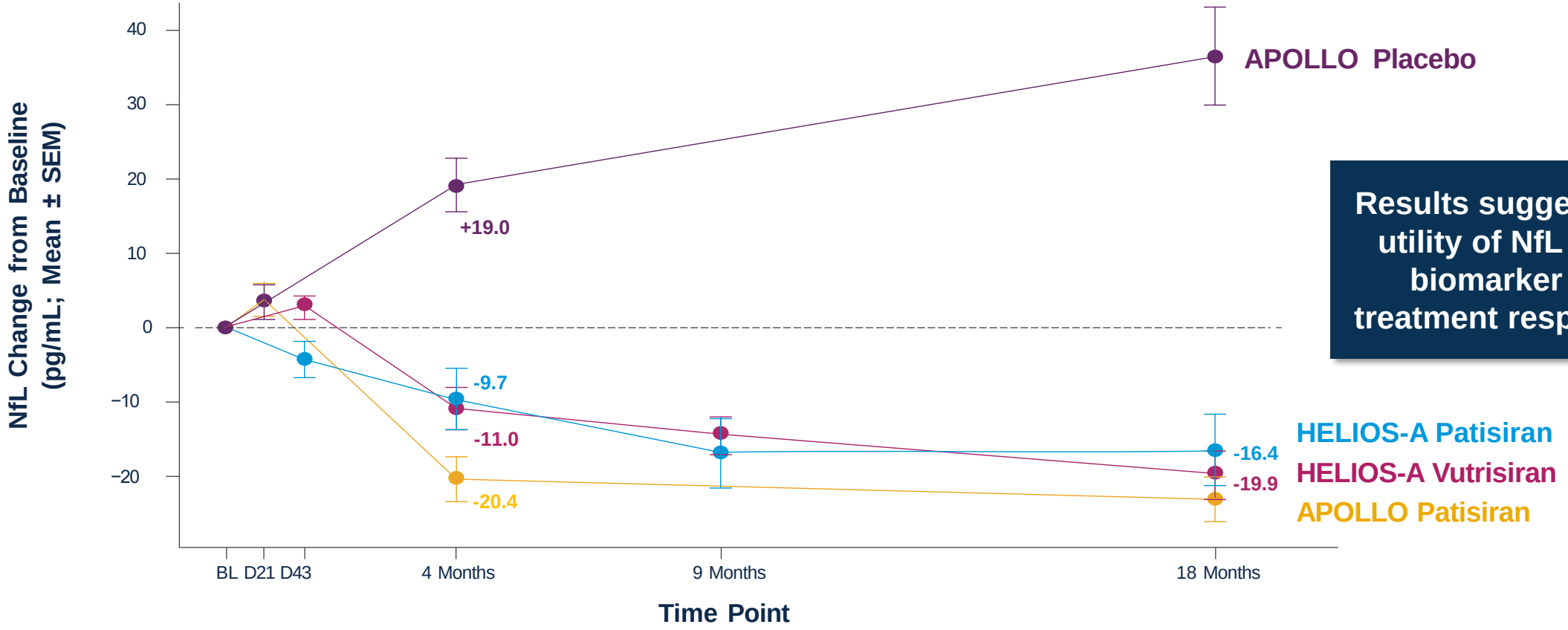
hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; NfL, neurofilament light chain.

1. Aldinc et al. Presented at: American Neurological Association (ANA) Annual Meeting, October 22-25, 2022, Chicago, IL, USA; 2. Ticau et al. *Neurology*. 2021;96(3):e412-22.

In HELIOS-A, NfL levels decreased significantly from baseline as early as Month 4, and were maintained through Month 18

Post hoc analysis

Change in NfL Levels from Baseline in APOLLO and HELIOS-A Studies



Results suggest the utility of NfL as a biomarker of treatment response.

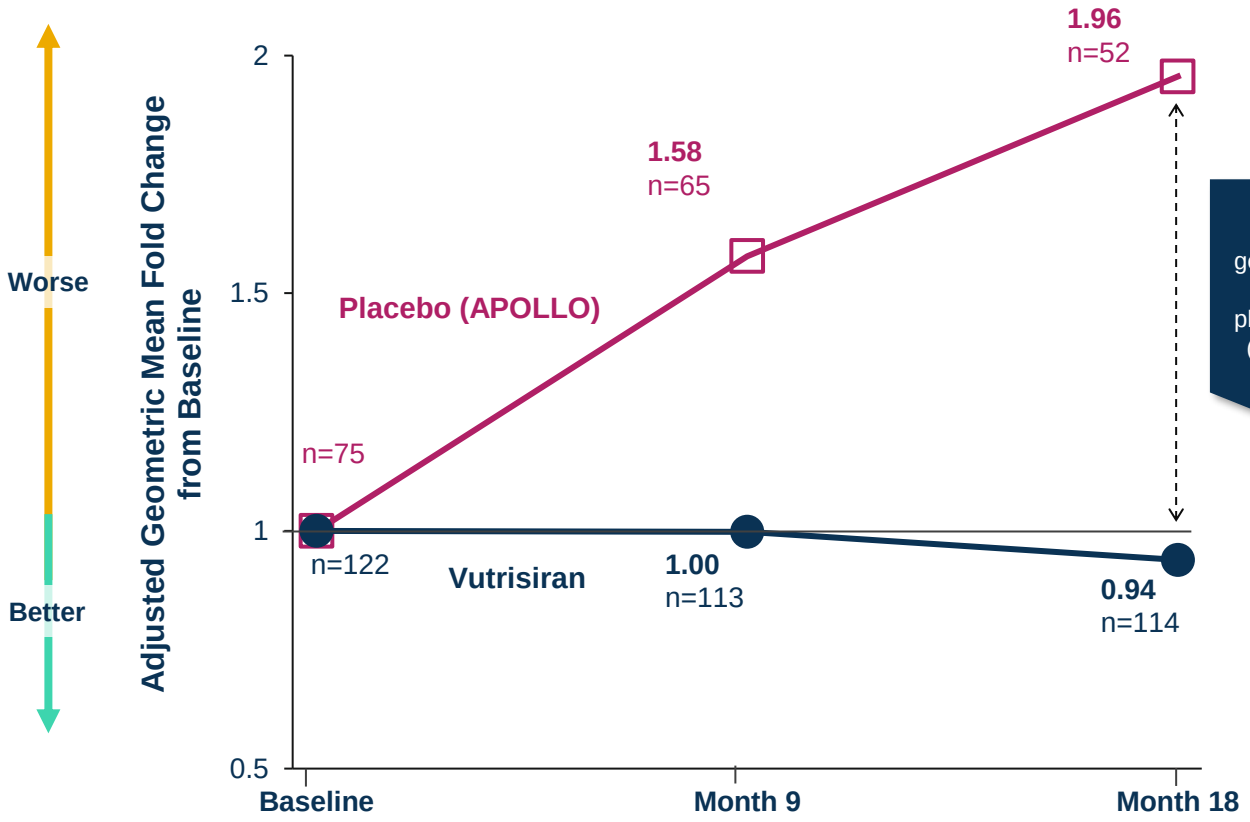
BL, baseline; D, day; NfL, neurofilament light chain; SEM, standard error of the mean;.

Aldinc et al. Presented at: American Neurological Association (ANA) Annual Meeting, October 22-25, 2022, Chicago, IL, USA.

Patients receiving vutrisiran had a decrease in NT-proBNP levels at Months 9 and 18 compared with external placebo

Exploratory cardiac endpoint

Change from Baseline in NT-proBNP (mITT Population)[a]



0.480[b] adjusted geometric mean fold change ratio vs placebo at Month 18 ($p=9.606 \times 10^{-10}$*)

From baseline to Month 18, the geometric mean level ± SEM of **NT-proBNP** in the mITT population…

Decreased with vutrisiran treatment…

273.0 ± 42.2 ng/L to 227.2 ± 37.0 ng/L

And **increased** with external placebo.

531.3 ± 86.7 ng/L to 844.4 ± 167.0 ng/L

[a]mITT population (all randomized patients who received any amount of study drug). [b](95% CI = 0.383-0.600). *nominal p-value.
CI, confidence interval; mITT, modified intent-to-treat; NT-proBNP, *N*-terminal pro–brain natriuretic peptide; SEM, standard error of the mean.
Garcia-Pavia et al. *Eur J Heart Fail*. 2024;26(2):397-410.

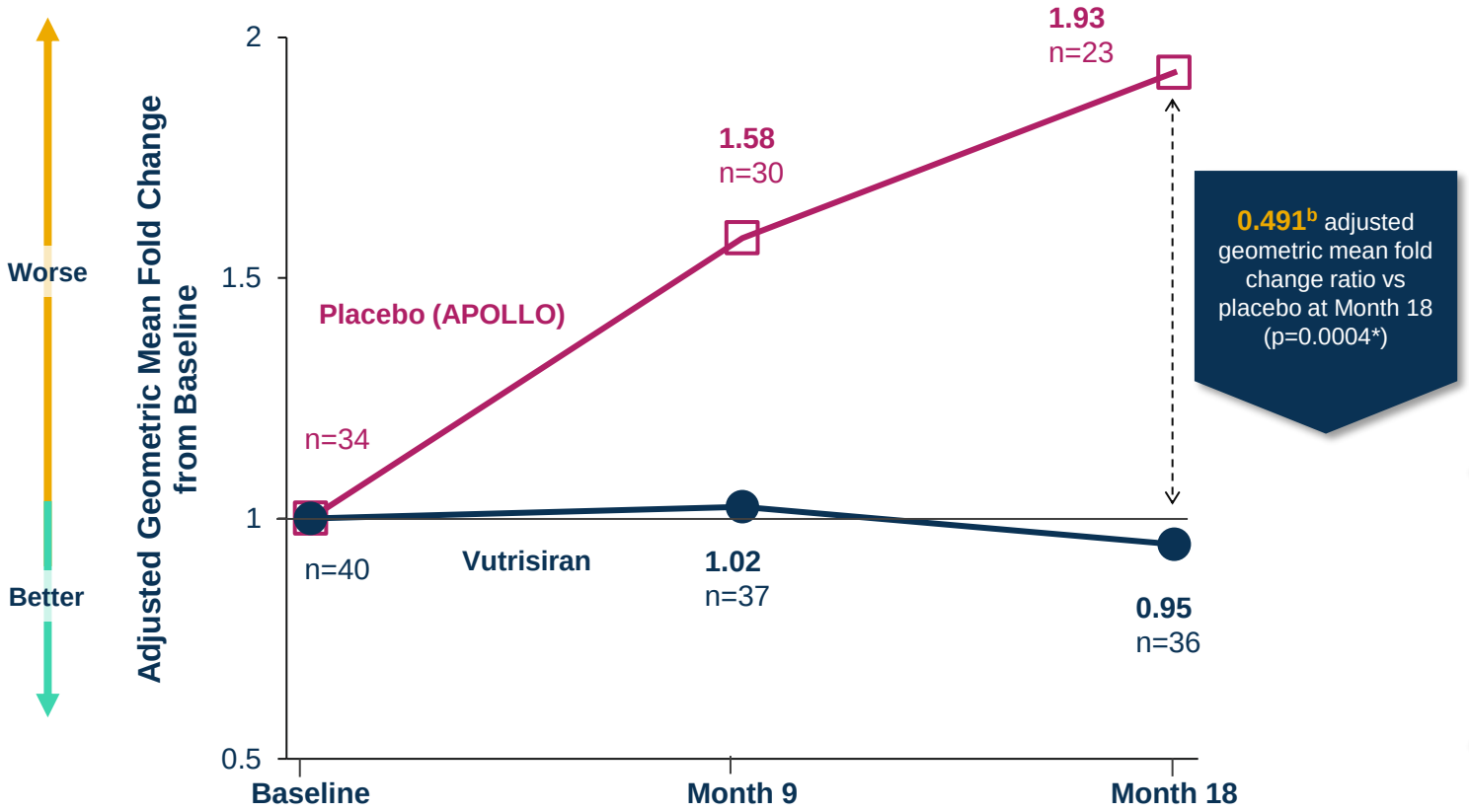
Patients receiving vutrisiran had a decrease in NT-proBNP levels at Months 9 and 18 compared with external placebo

Exploratory cardiac endpoint

Cardiac subpopulation:

- ✓ Baseline LV wall thickness ≥1.3 cm
- ✓ No medical history of aortic valve disease or hypertension

Change from Baseline in NT-proBNP (Cardiac Subpopulation)[a]



From baseline to Month 18, the geometric mean level ± SEM of **NT-proBNP** in the cardiac subpopulation…

Decreased with vutrisiran treatment…

748.1 ± 163.2 ng/L to 614.4 ± 154.7 ng/L

And **increased** with external placebo.

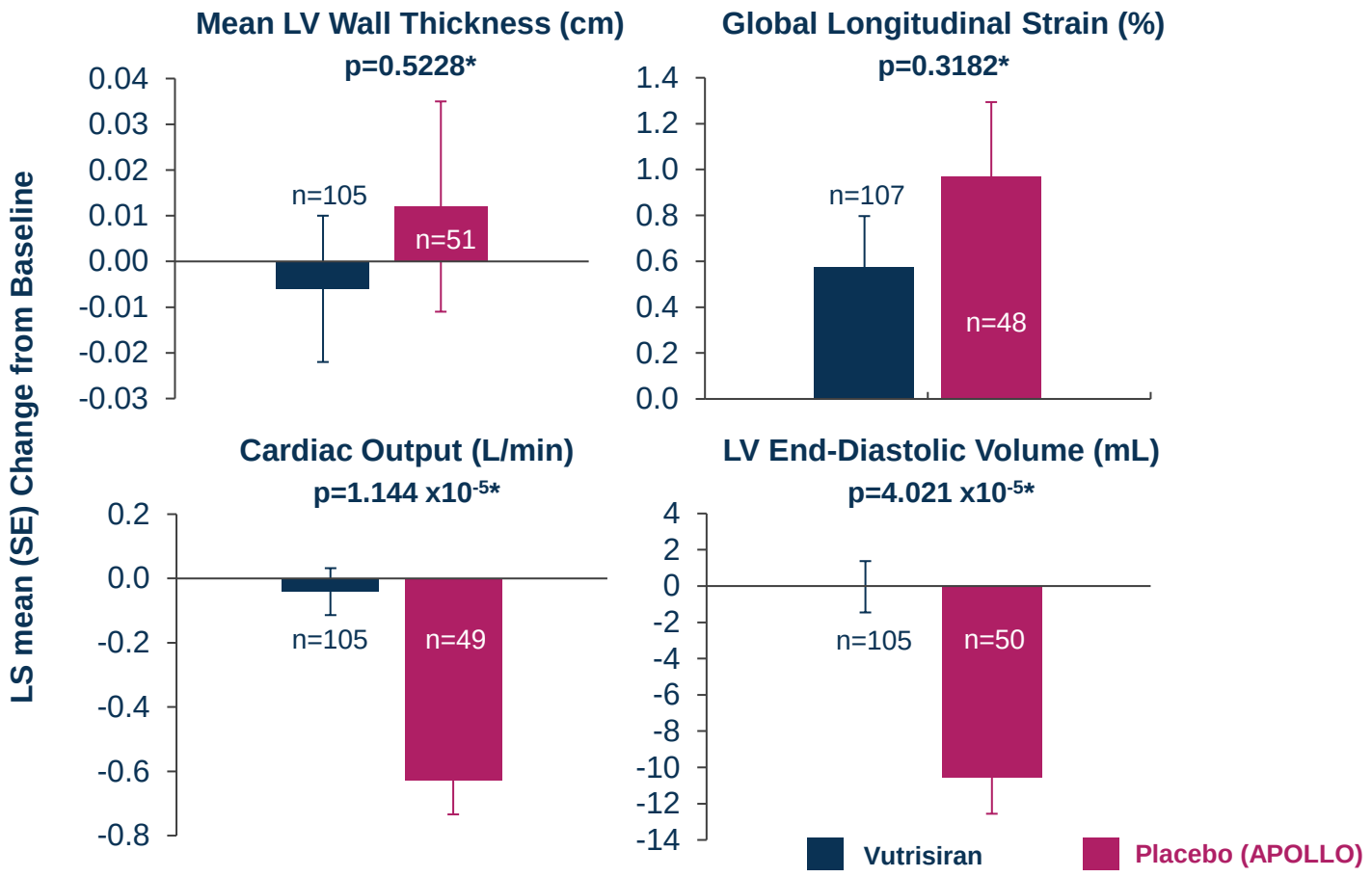
711.1 ± 151.1 ng/L to 1116.7 ± 320.8 ng/L

[a]Cardiac subpopulation of the HELIOS-A study was prespecified, defined as patients with baseline left ventricular (LV) wall thickness ≥1.3 cm and no medical history of aortic valve disease or hypertension, matching the cardiac subpopulation criteria from the APOLLO study.
[b](95% CI = 0.337, 0.716). *nominal p-value.
CI, confidence interval; LV, left ventricular; NT-proBNP, *N*-terminal pro–brain natriuretic peptide; SEM, standard error of the mean.
Garcia-Pavia et al. *Eur J Heart Fail*. 2024;26(2):397-410.

Treatment with vutrisiran showed a trend towards improvement of cardiac parameters at Month 18 compared with external placebo[1]

Exploratory cardiac endpoint

Echocardiographic Parameters with Vutrisiran vs External Placebo at Month 18 (mITT population)[1,a]



[a]mITT population (all randomized patients who received any amount of study drug). *nominal p-value.
hATTR, hereditary ATTR; LS, least squares; LV, left ventricular; SE, standard error.
Garcia-Pavia et al. *Eur J Heart Fail*. 2024;26(2):397-410.

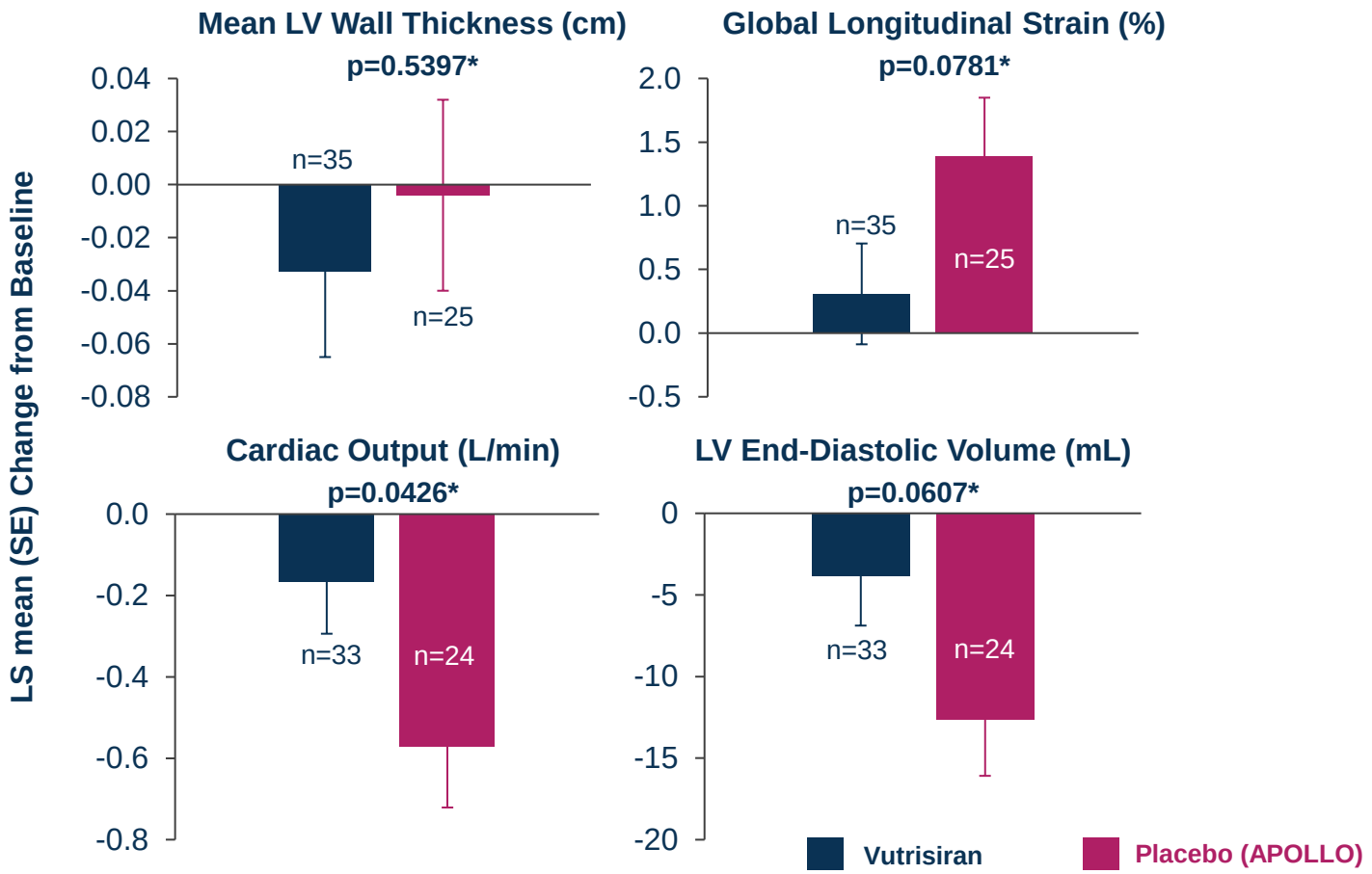
Treatment with vutrisiran showed a trend towards improvement of cardiac parameters at Month 18 compared with external placebo[1]

Exploratory cardiac endpoint

Cardiac subpopulation:

- ✓ Baseline LV wall thickness ≥1.3 cm
- ✓ No medical history of aortic valve disease or hypertension

Echocardiographic Parameters with Vutrisiran vs External Placebo at Month 18 (Cardiac Subpopulation)[1,a]



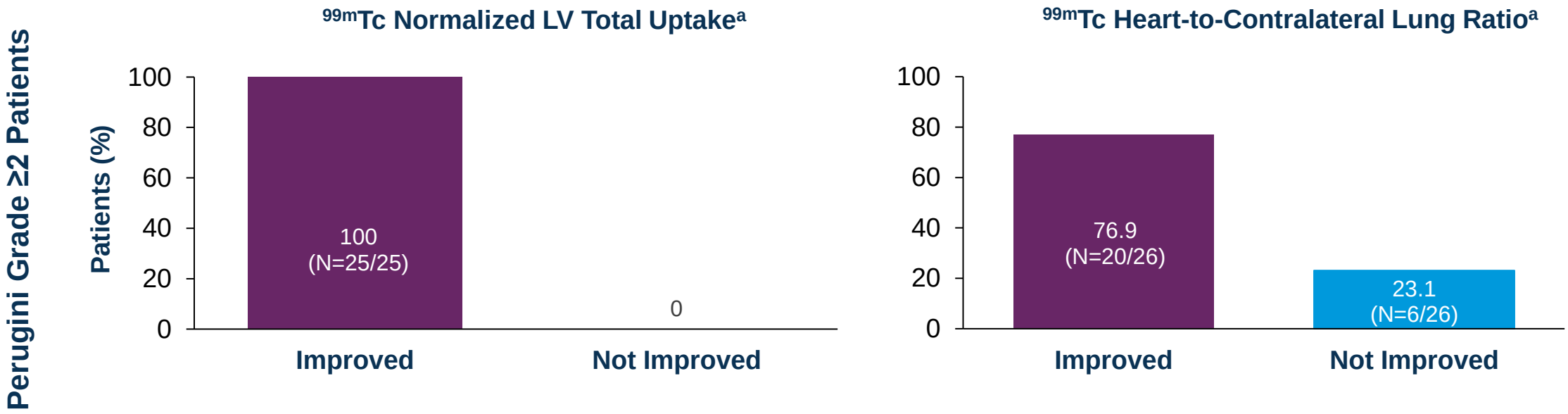
[a]Cardiac subpopulation of the HELIOS-A study was prespecified, defined as patients with baseline left ventricular (LV) wall thickness ≥1.3 cm and no medical history of aortic valve disease or hypertension, matching the cardiac subpopulation criteria from the APOLLO study.
*nominal p-value.
hATTR, hereditary ATTR; LS, least squares; LV, left ventricular; SE, standard error.
Garcia-Pavia et al. *Eur J Heart Fail*. 2024;26(2):397-410.

A reduction in normalized LV total uptake and heart-to-contralateral lung ratio was observed at Month 18 in patients with a baseline Perugini grade ≥2 treated with vutrisiran

Exploratory cardiac endpoint

Quantitative Assessments of Cardiac ^{99m}Tc Uptake at Month 18

*Conducted to assess cardiac amyloid involvement, measured at select sites only**



The decrease in ^{99m}Tc uptake was noted by changes in normalized LV uptake and H/CL ratio, which are indicators of cardiac amyloid burden.

*This analysis was not conducted in the APOLLO study; therefore, there is no placebo comparison available. [a]Improved refers to a negative change (<0 increase) from baseline to Month 18 in the chosen measure and not improved refers to a >0 increase from baseline.
^{99m}Tc, technetium-99m; H/CL, heart-to-contralateral lung; LV, left ventricular.
Garcia-Pavia et al. *Eur J Heart Fail*. 2024;26(2):397-410.

Among patients treated with vutrisiran with evaluable scintigraphy, 96% remained stable or showed an improvement of at least one Perugini grade

Exploratory cardiac endpoint

Change from Baseline in Perugini Grade at Month 18* (Evaluable Patients[a]; n=57)

Perugini Grade at Baseline, n (%)	Perugini Grade at Month 18, n (%)			
	0	I	II	III
0	24 (42.1)	1 (1.8)	0	0
I	1 (1.8)	0	1 (1.8)	0
II	0	0	2 (3.5)	0
III	2 (3.5)	3 (5.3)	10 (17.5)	13 (22.8)

Improved No Change Worsened

*This analysis was not conducted in the APOLLO study; therefore, there is no placebo comparison available. [a]Analysis includes patients from mITT population with evaluable data at baseline and Month 18 (n=57); Improved refers to a reduced Perugini grade and worsened refers to an increased Perugini grade at Month 18 compared with baseline.

mITT, modified intent-to-treat.

Garcia-Pavia et al. *Eur J Heart Fail*. 2024;26(2):397-410.

Safety

HELIOS-A Safety Summary

At least one event, n (%)	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
Summary of AEs*			
Any AE	75 (97.4)	119 (97.5)	41 (97.6)
Serious AEs[a]	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[b]	6 (7.8)	2 (1.6)	3 (7.1)

*Safety reported in the safety population during the 18-month treatment period. [a]Two SAEs in the HELIOS-A study were considered to be related to vutrisiran by investigators: one case of dyslipidemia and one case of UTI. [b]One death was due to COVID-19 (Coronavirus Disease 2019) pneumonia and one due to iliac artery obstruction.

AE, adverse event; SAE, serious adverse event; UTI, urinary tract infection.

Adams et al. *Amyloid*. 2023;30(1):18-26.

HELIOS-A Safety Summary (cont.)

At least one event, n (%)	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
AEs occurring in ≥10% in vutrisiran-treated patients*			
Fall	22 (28.6)	22 (18)	6 (14.3)
Pain in extremity	8 (10.4)	18 (14.8)	3 (7.1)
Diarrhea	29 (37.7)	17 (13.9)	7 (16.7)
Peripheral edema	17 (22.1)	16 (13.1)	4 (9.5)
Urinary tract infection	14 (18.2)	16 (13.1)	8 (19)
Arthralgia	0	13 (10.7)	4 (9.5)
Dizziness	11 (14.3)	13 (10.7)	0

*Safety reported in the safety population during the 18-month treatment period.
AE, adverse event.
Adams et al. *Amyloid*. 2023;30(1):18-26.

HELIOS-A Safety Summary (cont.)

At least one event, n (%)	mITT population[a]		Cardiac subpopulation[b]	
	APOLLO	HELIOS-A	APOLLO	HELIOS-A
	Placebo (n=77)	Vutrisiran (n=122)	Placebo (n=36)	Vutrisiran (n=40)
Cardiac AEs[c]	28 (36.4)	37 (30.3)	13 (36.1)	15 (37.5)
Cardiac serious AEs[c]	10 (13.0)	11 (9.0)	4 (11.1)	6 (15.0)
Cardiac arrhythmia AEs[d]	22 (28.6)	30 (24.6)	11 (30.6)	13 (32.5)
Supraventricular arrhythmias[d]	13 (16.9)	10 (8.2)	9 (25.0)	7 (17.5)
Cardiac conduction disorders[d]	7 (9.1)	10 (8.2)	3 (8.3)	4 (10.0)
Ventricular arrhythmias and cardiac arrest[d]	6 (7.8)	6 (4.9)	3 (8.3)	1 (2.5)
Rate and rhythm disorders[d]	0	8 (6.6)	0	3 (7.5)
Cardiac failure AEs[e]	8 (10.4)	7 (5.7)	2 (5.6)	5 (12.5)

[a]mITT population (all randomized patients who received any amount of study drug). [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]System organ class based on MedDRA (Medical Dictionary for Regulatory Activities).. [d]High-level group term. [d]Standard MedDRA query, narrow scope term only.

AE, adverse event; mITT, modified intent-to-treat.

Garcia-Pavia et al. *Eur J Heart Fail.* 2024;26(2):397-410.

HELIOS-A Study: Key Takeaways

Vutrisiran met the primary and all secondary efficacy endpoints at Months 9 and 18, demonstrating significant improvements in neuropathy impairment, quality of life, gait speed, nutritional status, and disability compared with the external placebo group.

Primary endpoint

- Treatment with vutrisiran was shown to halt or reverse polyneuropathy progression, evidenced by a statistically significant improvement in neuropathy impairment[a] compared with external placebo

Secondary endpoints

- Treatment with vutrisiran improved neuropathy impairment[b], quality of life[a,b], gait speed[a,b], nutritional status[b], and disability[b] compared with external placebo

Safety

- The majority of adverse events were mild or moderate in severity
- AEs occurring in ≥10% of patients receiving vutrisiran and more frequently than in the external group were pain in extremity and arthralgia
- No drug-related discontinuations or deaths were observed

[a]At Month 9; [b]At Month 18.
AE, adverse event.
Adams et al. *Amyloid*. 2023;30(1):18-26.

AMVUTTRA® (vutrisiran) Indications and Important Safety Information

- **Indications**
  - AMVUTTRA is indicated for the treatment of:
    - the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
    - the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits

- **Reduced Serum Vitamin A Levels and Recommended Supplementation**
  - AMVUTTRA treatment leads to a decrease in serum vitamin A levels.
  - Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking AMVUTTRA. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with AMVUTTRA, as serum vitamin A levels do not reflect the total vitamin A in the body.
  - Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

- **Adverse Reactions**
  - The most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity (15%), arthralgia (11%), dyspnea (7%), and vitamin A decreased (7%).

For additional information about AMVUTTRA, please see the full Prescribing Information.

RDA, recommended daily allowance.