Comparison of Efficacy Outcomes with Vutrisiran vs. Patisiran in hATTR Amyloidosis with Polyneuropathy: Post-hoc Analysis of the HELIOS-A Study

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Author Disclosures for Dr. Michael Polydefkis

Conflict	Disclosures
Akcea, Alnylam Pharmaceuticals, Pfizer	Participation in clinical trials
Akcea, Alnylam Pharmaceuticals, Biogen-Idec, Pfizer, Vertex Pharmaceuticals	Consultancy fees

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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]

RNAi Therapeutics Approved to Treat the Polyneuropathy of hATTR Amyloidosis

- **Patisiran[a]:** First ever approved RNAi, intravenously (IV) administered Q3W, evaluated in the Phase 3, placebo-controlled APOLLO study[7–9]
- **Vutrisiran[b]:** Novel, Q3M subcutaneously (SC) administered RNAi therapeutic evaluated in the Phase 3 HELIOS-A study[10,11]

HELIOS-A and Analysis Rationale

- The HELIOS-A study compared vutrisiran versus external placebo (from APOLLO) for the polyneuropathy of hATTR amyloidosis and met its primary endpoint; a patisiran arm was also included as a reference group[10]
- Although HELIOS-A was not designed to directly compare vutrisiran vs patisiran, there is clinical interest in evaluating their comparative effectiveness for treating polyneuropathy of hATTR amyloidosis

Objective

To compare the efficacy of vutrisiran with that of patisiran for the polyneuropathy of hATTR amyloidosis using post hoc analyses from HELIOS-A

[a]Lipid nanoparticle-encapsulated siRNA. Premedicate with a corticosteroid, acetaminophen, and antihistamines. [b]siRNA–GalNAc conjugate using ESC technology.

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; siRNA, small interfering ribonucleic acid; 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. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf (accessed September 16, 2022); 8. Adams D et al. *N Engl J Med* 2018;379:11–21; 9. APOLLO: NCT01960348; 10. Adams D et al. *Amyloid*. 2023 Mar;30:18-26; 11. Alnylam. US prescribing information: AMVUTTRA™. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215515s000lbl.pdf (accessed September 16, 2022).

Post hoc Analysis of Vutrisiran Phase 3 HELIOS·A Study

Patient Population
N=164

- 18–85 years old
- hATTR amyloidosis with polyneuropathy; any *TTR* variant
- NIS 5–130 and PND ≤IIIB
- KPS ≥60%
- Prior TTR stabilizer use permitted

3:1 RANDOMIZATION

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

n=122

Vutrisiran
25 mg
SC Q3M

or

n=42

Reference group
(patisiran)
0.3 mg/kg
IV Q3W

A Priori Analyses

Vutrisiran vs APOLLO placebo: change from baseline in mNIS+7, Norfolk QOL-DN, 10-MWT at Months 9 and 18; and mBMI and R-ODS at Month 18

Vutrisiran vs patisiran: TTR percent reduction from baseline over 18 months

Post hoc Analyses:

- Vutrisiran vs patisiran: LS mean treatment difference (with 95% CIs and nominal p-values)
- At Months 9 and 18:
  - mNIS+7
  - Norfolk QOL-DN
  - 10-MWT
  - mBMI
  - R-ODS
  - NT-proBNP

10-MWT, 10-meter walk test; CI, confidence interval; hATTR, hereditary transthyretin-mediated amyloidosis; IV, intravenous; KPS, Karnofsky performance status; LS, least squares; 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; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; QOL, quality of life; SC, subcutaneous; TTR, transthyretin.

Baseline Demographic and Disease Characteristics

- As previously reported[1], patients enrolled had a wide range of disease severity and encompassed a variety of TTR variants
- Baseline characteristics were widely overlapping across treatment groups and were clinically comparable

Characteristic	APOLLO	HELIOS-A	
	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
Age, median (IQR), years	63 (15)	60 (20)	60 (12)
Males, n (%)	58 (75.3)	79 (64.8)	27 (64.3)
Median time since hATTR amyloidosis diagnosis, years (IQR)	1.41 (3.04)	1.94 (4.34)	2.39 (3.01)
V30M TTR genotype[a], n (%)	40 (51.9)	54 (44.3)	20 (47.6)
V30M early onset	10 (13.0)	25 (20.5)	8 (19.0)
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)

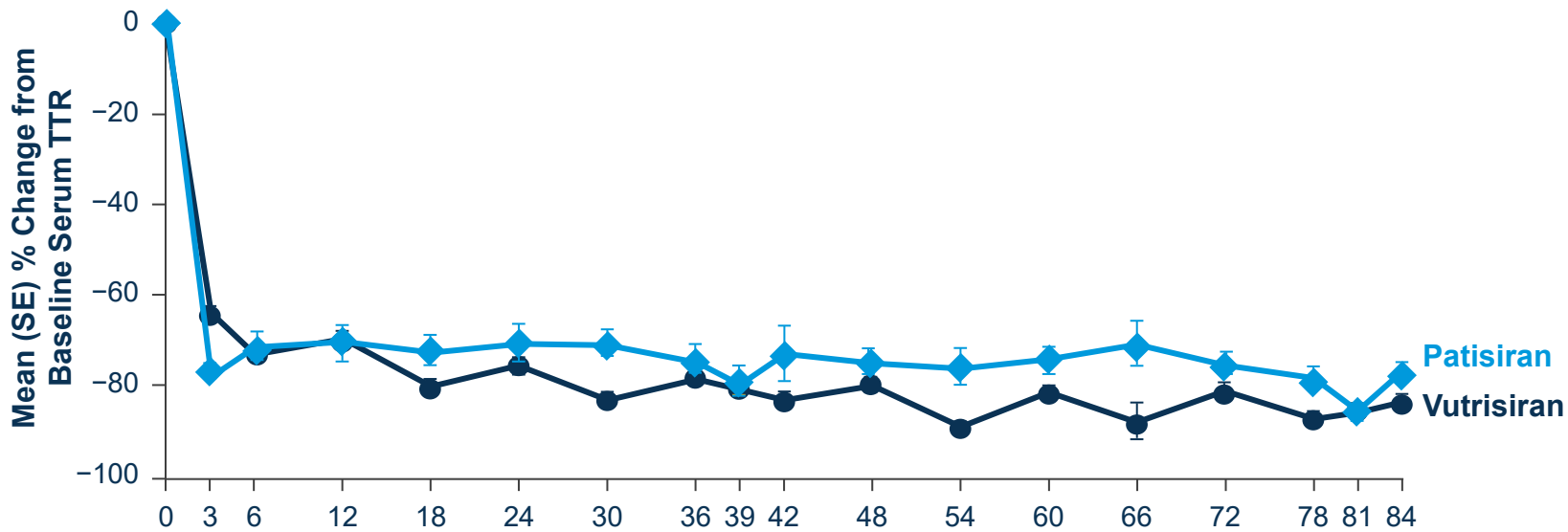
[a]The non-V30M TTR genotype represents 24 different variants in HELIOS-A. [b]One patient (1.3%) in the external placebo group had a PND score of IV defined as confined to wheelchair or bedridden (not shown on the slide). [c]Cardiac subpopulation was defined as patients who had pre-existing evidence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

[1] Adams D et al. *Amyloid*. 2023 Mar;30:18-26.

Non-inferiority of TTR Reduction between Vutrisiran and Patisiran

- Steady-state mean (SD) peak serum TTR percent reduction from baseline over 18 months:
  - Vutrisiran: 88% (SD: 16%)
  - Patisiran: 86% (SD: 10%)
- As previously reported[1], TTR reduction[a] with vutrisiran was non-inferior to that observed with patisiran in the within-study reference group (secondary endpoint) over 18 months
  - Median difference in TTR reduction (vutrisiran–patisiran) [95% CI] was 5.28% [1.17, 9.25][b]

Percent Change from Baseline in Serum TTR Levels



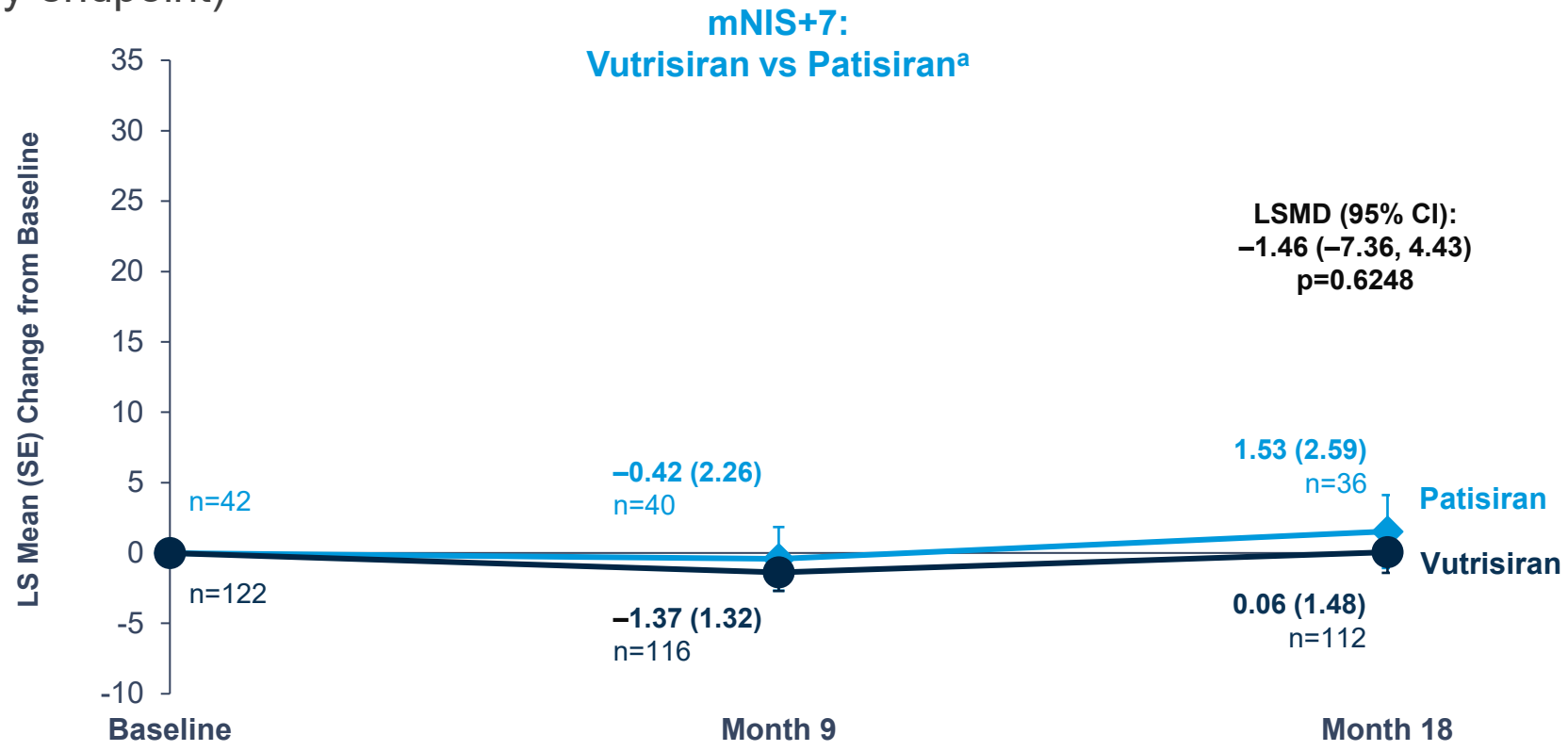
N evaluable																		
Vutrisiran (n=122)	122	114	109	119	106	117	92	118	115	56	116	42	118	15	118	100	114	98
Patisiran (n=42)	42	42	41	41	37	38	39	34	39	23	40	23	36	9	37	36	38	32

[a]Patient percent reduction derived from mean trough (predose) TTR assessments between Months 6 through 18; [b]The lower limit of confidence interval >–10% (pre-specified non-inferiority margin).
SD, standard deviation; SE, standard error; TTR, transthyretin.

1. Adams D et al. *Amyloid*. 2023 Mar;30:18-26.

Vutrisiran and Patisiran Demonstrate Comparable Efficacy on Neuropathy Impairment as Measured by mNIS+7

- Change from baseline in mNIS+7 at Month 18 was comparable between vutrisiran and patisiran (nominal p-value, p=0.6248)
- As previously reported, vutrisiran significantly improved mNIS+7 compared with external placebo at Month 18 (secondary endpoint)[1]



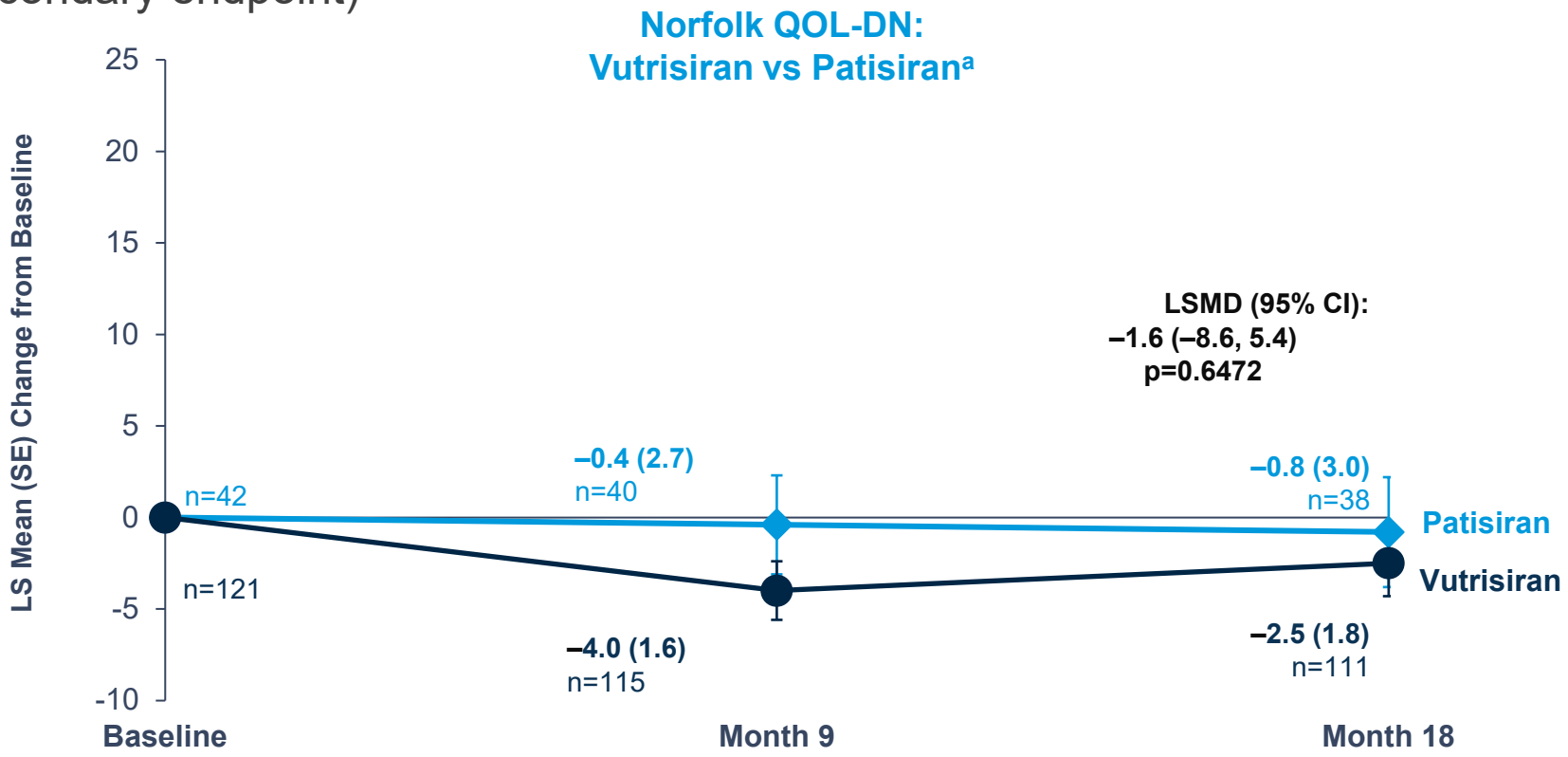
Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304).

[a]Vutrisiran model estimates are based on the same data as the comparison with the placebo arm. Model estimates for the vutrisiran arm differ per comparison due to the impact of the different comparator data sets (from the patisiran and placebo arms, respectively) on the statistical model. At baseline, the mean (±SD) mNIS+7 was 60.57 (35.99) in the vutrisiran group and 57.68 (33.71) in the patisiran group. CI, confidence interval; LS, least squares; LSMD, least squares mean difference; mNIS+7, modified Neuropathy Impairment Score +7; SD, standard deviation; SE, standard error.

1. Adams D et al. *Amyloid*. 2023 Mar;30:18-26.

Vutrisiran and Patisiran Demonstrate Comparable Efficacy on Quality of Life as Measured by Norfolk QOL-DN

- Change from baseline in Norfolk QOL-DN at Month 18 was comparable between vutrisiran and patisiran (nominal p-value, p=0.6472)
- As previously reported, vutrisiran significantly improved Norfolk QOL-DN compared with external placebo at Month 18 (secondary endpoint)[1]



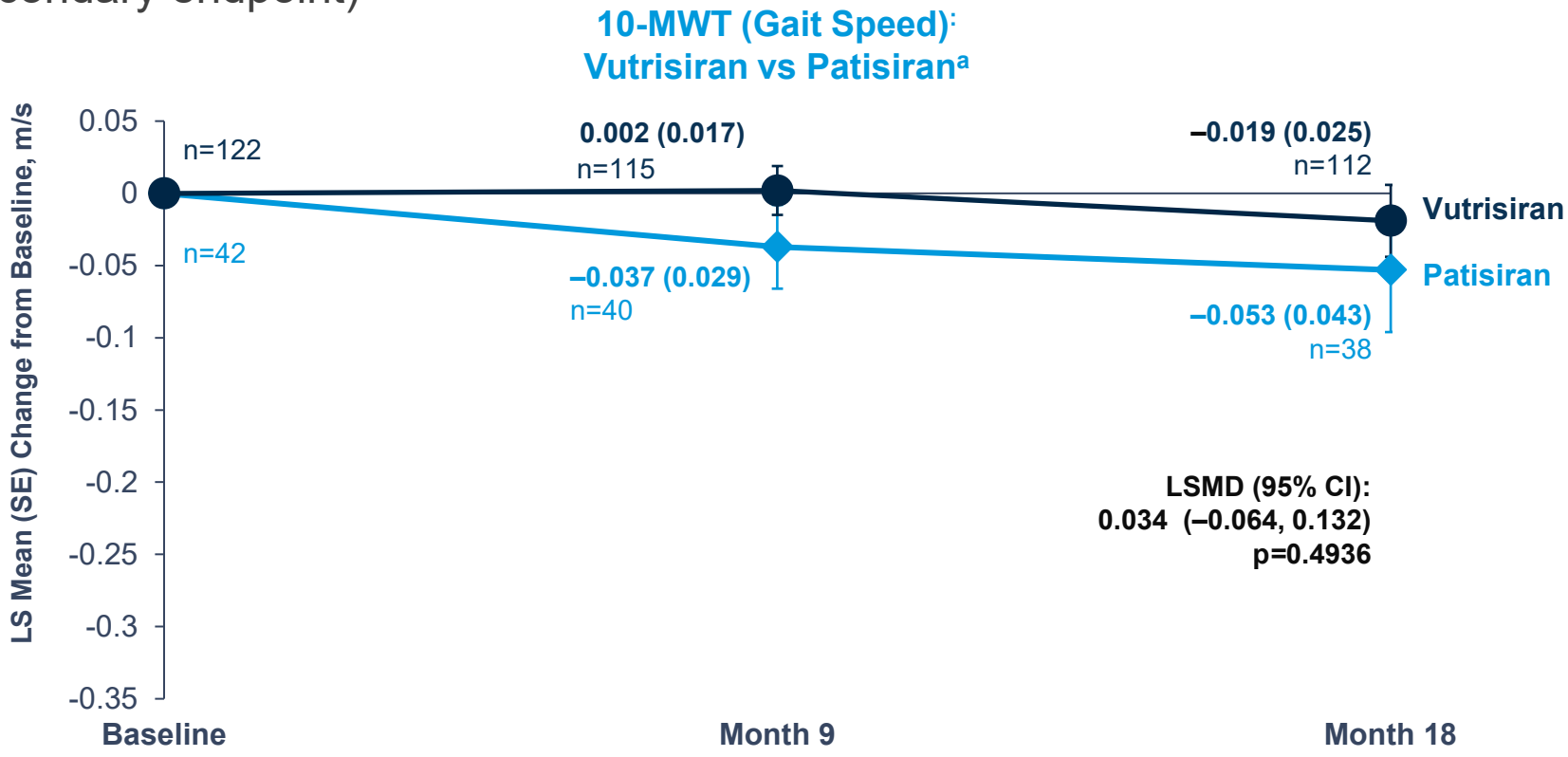
Higher scores of Norfolk QOL-DN indicate worse quality of life (range, −4 to 136).

[a]Vutrisiran model estimates are based on the same data as the comparison with the placebo arm. Model estimates for the vutrisiran arm differ per comparison due to the impact of the different comparator data sets (from the patisiran and placebo arms, respectively) on the statistical model. At baseline, the mean (±SD) Norfolk QOL-DN was 47.1 (26.3) in the vutrisiran group and 47.3 (29.9) in the patisiran group. CI, confidence interval; LS, least squares; LSMD, least squares mean difference; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SD, standard deviation; SE, standard error.

1. Adams D et al. *Amyloid*. 2023 Mar;30:18-26

Vutrisiran and Patisiran Demonstrate Comparable Efficacy on Gait Speed as Measured by 10-MWT

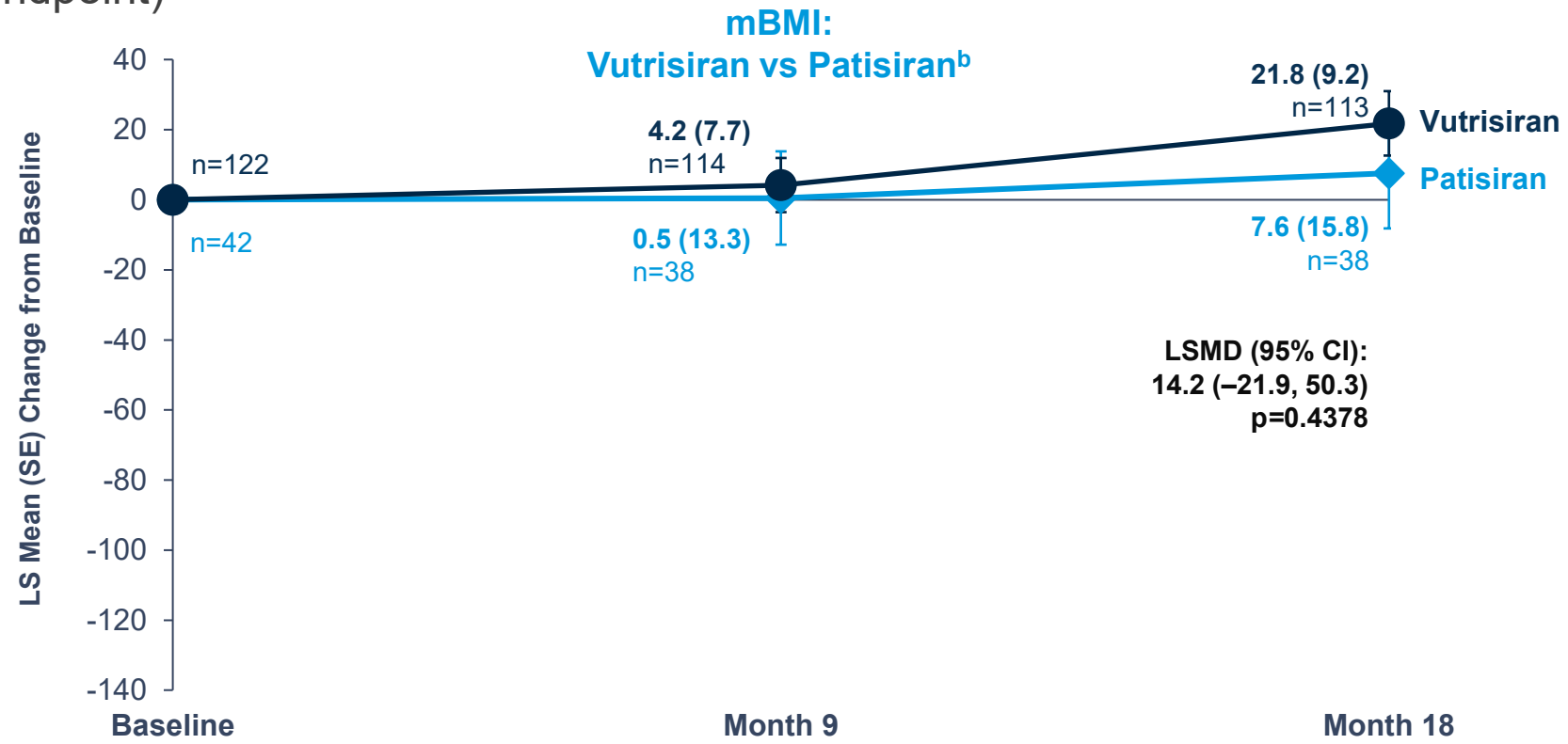
- Change from baseline in 10-MWT at Month 18 was comparable between vutrisiran and patisiran (nominal p-value, p=0.4936)
- As previously reported, vutrisiran significantly improved 10-MWT compared with external placebo at Month 18 (secondary endpoint)[1]



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.
[a]Vutrisiran model estimates are based on the same data as the comparison with the placebo arm. Model estimates for the vutrisiran arm differ per comparison due to the impact of the different comparator data sets (from the patisiran and placebo arms, respectively) on the statistical model.
At baseline, the mean (±SD) 10-MWT was 1.006 (0.393) in the vutrisiran group and 1.011 (0.400) in the patisiran group. 10-MWT, 10-meter walk test; CI, confidence interval; LS, least squares; LSMD, least squares mean difference; SD, standard deviation; SE, standard error.
1. Adams D et al. *Amyloid*. 2023 Mar;30:18-26.

Vutrisiran and Patisiran Demonstrate Comparable Efficacy on Nutritional Status as Measured by mBMI

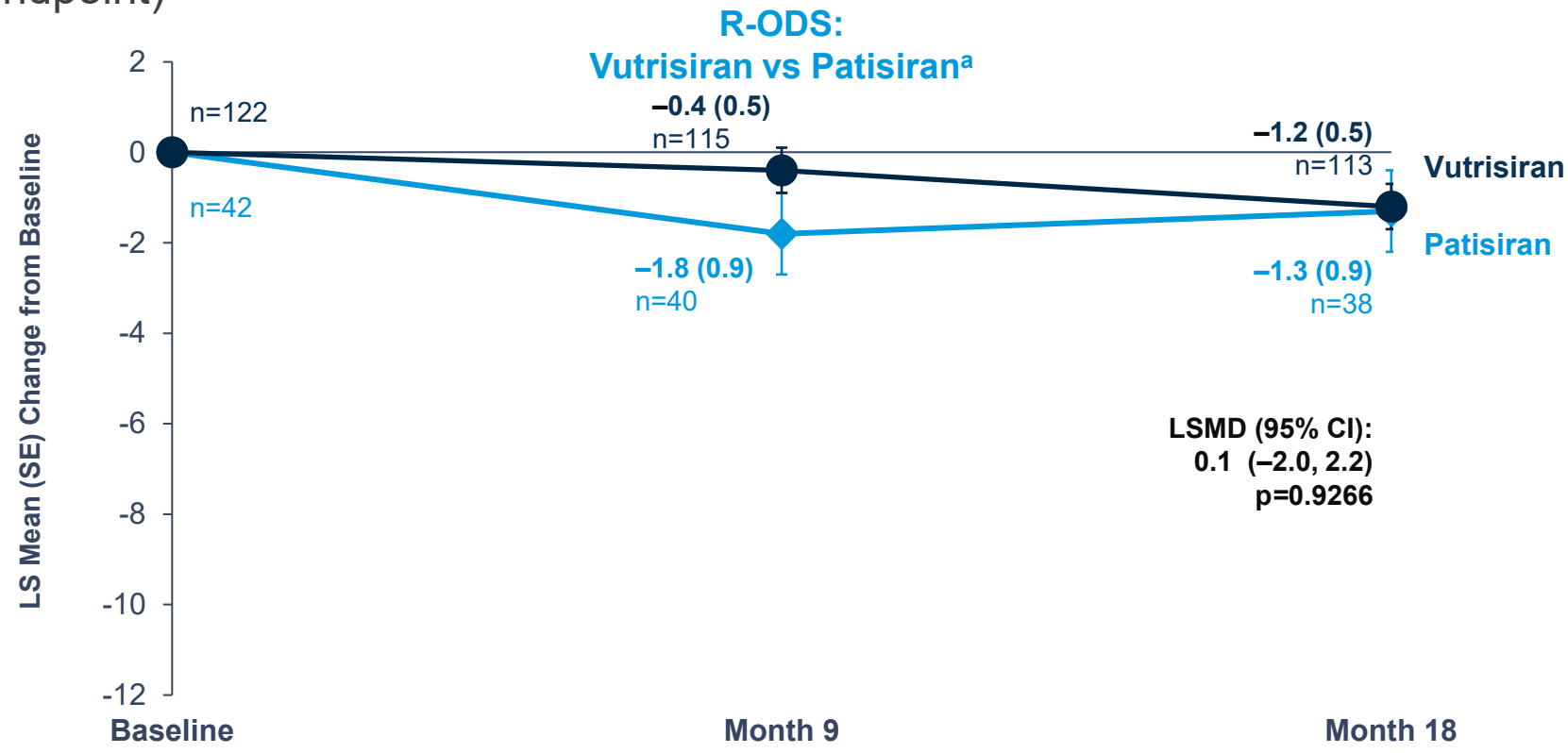
- Change in mBMI[a] from baseline at Month 18 was comparable between vutrisiran and patisiran (nominal p-value, p=0.4378)
- As previously reported, vutrisiran significantly improved mBMI compared with external placebo at Month 18 (secondary endpoint)[1]



Lower scores of mBMI (weight [in kg/m^2] × serum albumin [in g/L]) indicate worse nutritional status.
[a]mBMI (modified body mass index) = serum albumin × conventional BMI. [b]Vutrisiran model estimates are based on the same data as the comparison with the placebo arm. Model estimates for the vutrisiran arm differ per comparison due to the impact of the different comparator data sets (from the patisiran and placebo arms, respectively) on the statistical model. At baseline, the mean (±SD) mBMI was 1057.4 (233.8) in the vutrisiran group and 1058.1 (228.8) in the patisiran group.
CI, confidence interval; LS, least squares; LSMD, least squares mean difference; mBMI, modified body mass index; SD, standard deviation; SE, standard error.
1. Adams D et al. *Amyloid*. 2023 Mar;30:18-26.

Vutrisiran and Patisiran Demonstrate Comparable Efficacy on Disability as Measured by R-ODS

- Change in R-ODS from baseline at Month 18 was comparable between vutrisiran and patisiran (nominal p-value, p=0.9266)
- As previously reported, vutrisiran significantly improved R-ODS compared with external placebo at Month 18 (secondary endpoint)[1]



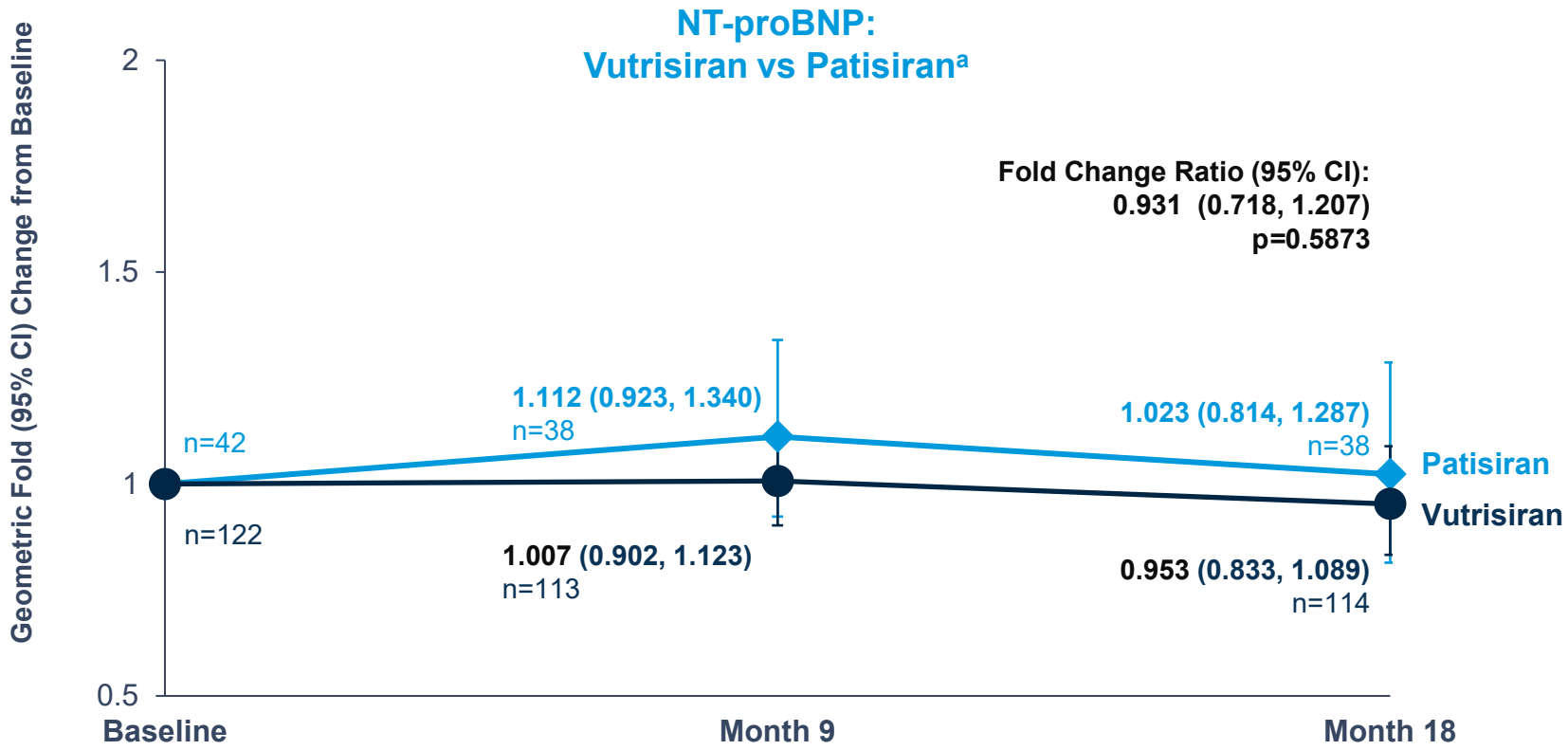
Lower scores of R-ODS indicate more disability (range, 0 to 48).

[a]Vutrisiran model estimates are based on the same data as the comparison with the placebo arm. Model estimates for the vutrisiran arm differ per comparison due to the impact of the different comparator data sets (from the patisiran and placebo arms, respectively) on the statistical model. At baseline, the mean (±SD) R-ODS was 34.1 (11.0) in the vutrisiran group and 34.0 (10.4) in the patisiran group. CI, confidence interval; LS, least squares; LSMD, least squares mean difference; R-ODS, Rasch-built Overall Disability Scale; SD, standard deviation; SE, standard error.

1. Adams D et al. *Amyloid*. 2023 Mar;30:18-26.

Vutrisiran and Patisiran Demonstrate Comparable Efficacy on Cardiac Stress as Measured by NT-proBNP

- Change in NT-proBNP from baseline at Month 18 was comparable between vutrisiran and patisiran (nominal p-value, p=0.5873)
- As previously reported, vutrisiran significantly improved levels of NT-proBNP compared with external placebo at Month 18 (exploratory endpoint)[1]



NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress.

[a]Vutrisiran model estimates are based on the same data as the comparison with the placebo arm. Model estimates for the vutrisiran arm differ per comparison due to the impact of the different comparator data sets (from the patisiran and placebo arms, respectively) on the statistical model. At baseline, the mean (±SD) NT-proBNP was 1010 (2148) ng/L in the vutrisiran group and 1197 (2381) ng/L in the patisiran group. CI, confidence interval; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; SD, standard deviation.

1. Garcia-Pavia P et al. *ESC-HF 2022 Congress* Oral.

Vutrisiran and Patisiran Demonstrate Acceptable Safety Profiles Over 18 Months

- Vutrisiran and patisiran both demonstrate acceptable safety profiles over 18 months; the safety profile of patisiran was consistent with that previously observed
- The majority of AEs were mild or moderate in severity
- There were no drug-related discontinuations or deaths

At least one event[a], n (%)	APOLLO Placebo (N=77; PY=96.1)	Vutrisiran (N=122; PY=191.3)	Patisiran (N=42; PY=63.3)
AEs	75 (97.4)	119 (97.5)	41 (97.6)
SAEs	31 (40.3)	32 (26.2)	18 (42.9)
Severe adverse events	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; PY, patient-years exposure; SAE, serious adverse event.

Summary

- Vutrisiran and patisiran demonstrated comparable efficacy for treating hATTR amyloidosis with polyneuropathy at Months 9 and 18 of the HELIOS-A study
  - Patterns of stabilization or improvement across endpoints observed in APOLLO (patisiran) were also observed in HELIOS-A (vutrisiran and patisiran)[1]

- Although vutrisiran and patisiran use different siRNA delivery platforms, serum TTR reduction was comparable, resulting in consistent clinical benefits

- These results further support vutrisiran as a treatment option for hATTR amyloidosis with polyneuropathy, providing patients and physicians an additional RNAi therapeutic option that offers Q3M SC dosing and comparable efficacy to patisiran with an acceptable safety profile

hATTR, hereditary transthyretin-mediated; Q3M, every 3 months; Q3W, every 3 weeks; RNAi, ribonucleic acid interference; SC, subcutaneous; siRNA, small interfering ribonucleic acid; TTR, transthyretin.

1. Adams D et al. *Amyloid*. 2023 Mar;30:18-26.

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the HELIOS-A study, especially considering the challenges of continuing the study during the COVID-19 pandemic