HELIOS-A: 9-month Results from the Phase 3 Study of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

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Disclosures

- David D. Adams has received personal compensation for serving as a Consultant for Alnylam Pharmaceuticals and for serving on a Scientific Advisory or Data Safety Monitoring board for Pfizer

Background and Rationale

hATTR amyloidosis, also known as ATTRv amyloidosis

- Rare, underdiagnosed, inherited, rapidly progressive, debilitating, and fatal disease
- Caused by variants in *TTR* gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs and tissues[1–4]
- Multisystem disease with a heterogeneous clinical presentation (sensory, motor, autonomic, and cardiac symptoms)[4–6]
- The majority of individuals develop a mixed phenotype of both polyneuropathy and cardiomyopathy[7,8]

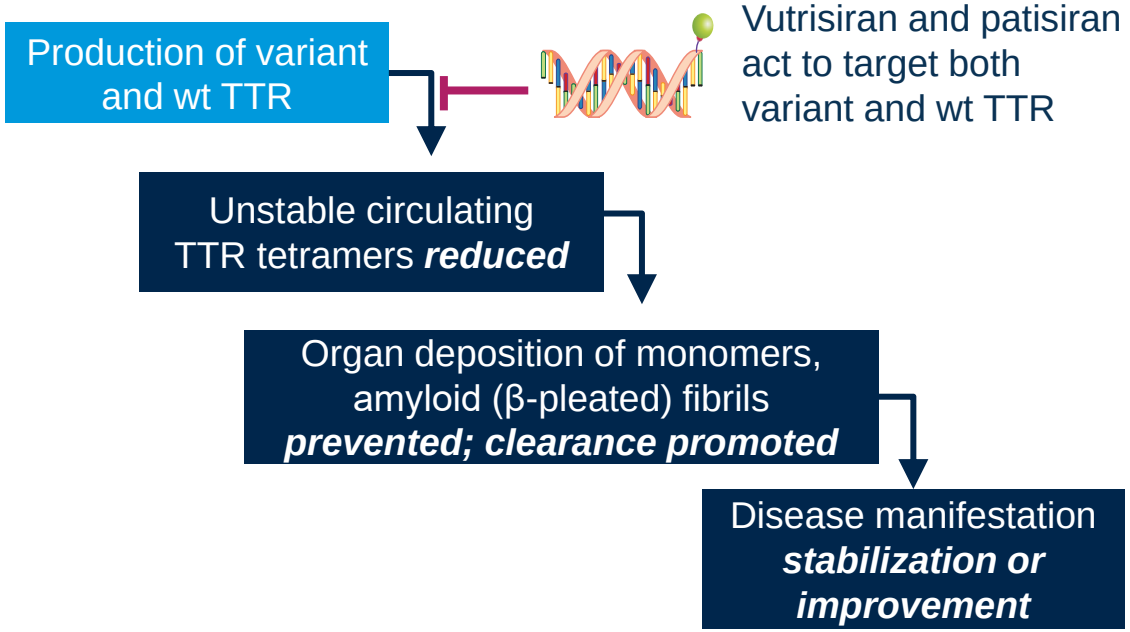
Vutrisiran

- Investigational, subcutaneously administered, RNAi therapeutic targeting hepatic production of variant and wt TTR, in development for the treatment of ATTR amyloidosis[9,10]

Patisiran

- RNAi therapeutic administered via IV infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on phase 3 placebo-controlled APOLLO trial[11–13]

Therapeutic Hypothesis



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

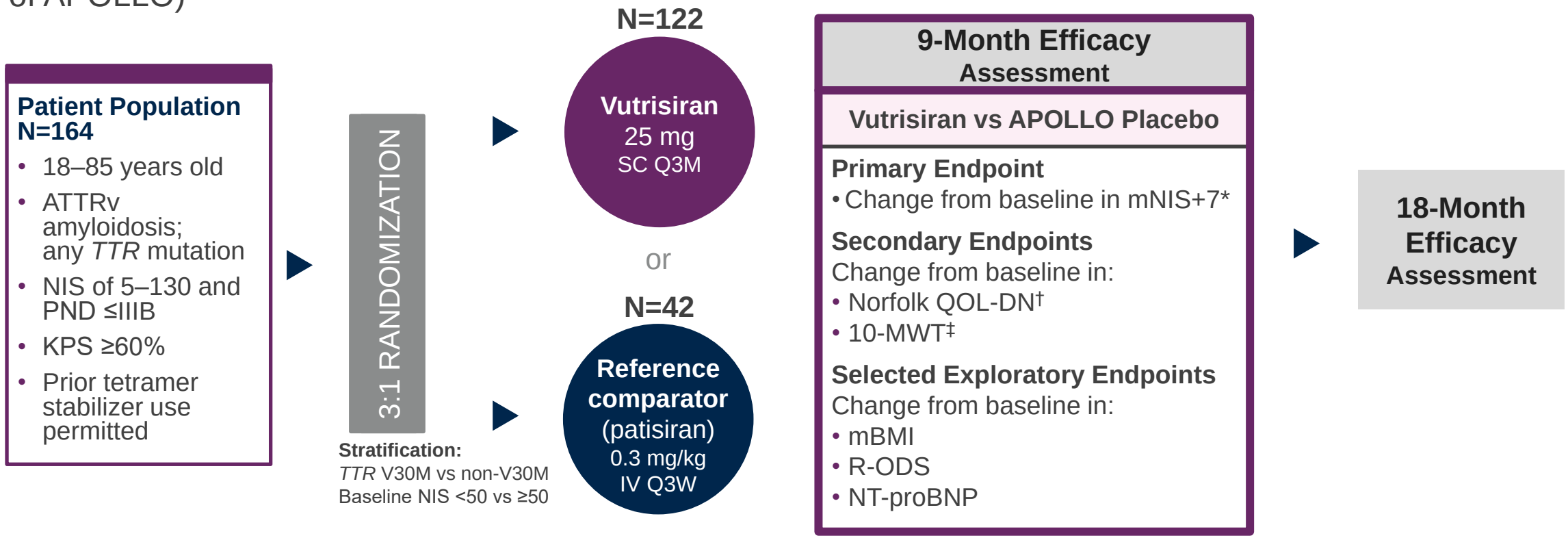
APOLLO: NCT01960348; ATTR, transthyretin-mediated; ESC, enhanced stabilization chemistry; GalNAc, N-acetylgalactosamine; hATTR, hereditary transthyretin-mediated; IV, intravenous; Q3M, every 3 months; RNAi, ribonucleic acid interference; SC, subcutaneous; TTR, transthyretin; wt, wild-type.

1. Hanna M. *Curr Heart Fail Rep* 2014;11:50–57; 2. Hawkins PN et al. *Ann Med* 2015;47:625–638; 3. Damy T et al. *J Cardiovasc Transl Res* 2015;8:117–127; 4. Mohty D et al. *Arch Cardiovasc Dis* 2013;106:528–540; 5. Conceição I et al. *J Peripher Nerv Syst* 2016;21:5–9; 6. Shin SC & Robinson-Papp J. *Mt Sinai J Med* 2012;79:733–748; 7. Rapezzi C et al. *Eur Heart J* 2013;34:520–528; 8. Coelho T et al. *Curr Med Res Opin* 2013;29:63–76; 9. Habtemariam BA et al. *Clin Pharmacol Ther* 2021;109:372–382; 10. Nair JK et al. *J Am Chem Soc* 2014;136:16958–16961; 11. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. February 2020; 12. Adams D et al. *N Engl J Med* 2018;379:11–21; 13. Adams D et al. *Lancet Neurology* 2021;20:49-59

Vutrisiran Phase 3 HELIOS·A Study

Randomized, Open-label Study in Hereditary Transthyretin-Mediated Amyloidosis Patients with Polyneuropathy

- Presenting 9-month primary efficacy analysis compared with the external placebo group (placebo arm of APOLLO)



*Higher scores of mNIS+7 indicate more neuropathy impairment (range, 0 to 304). †Higher scores of Norfolk QOL-DN indicate worse quality of life (range, -4 to 136). ‡10-meter walk test 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.
10-MWT, 10-meter walk test; ATTRv, transthyretin-mediated amyloidosis (v for variant); 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; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built overall disability scale; SC, subcutaneous; TTR, transthyretin.

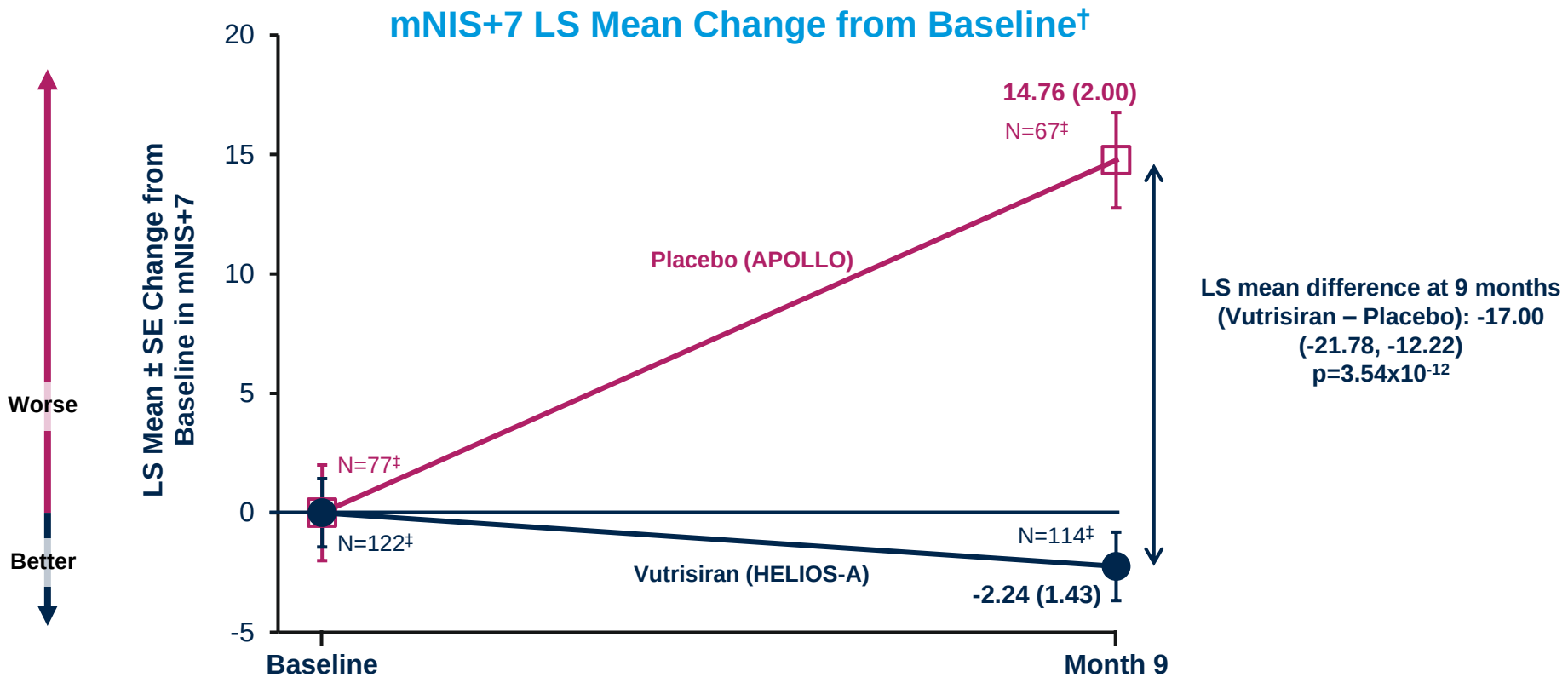
Baseline Demographic and Disease Characteristics

Characteristic	APOLLO	HELIOS-A	
	Placebo N=77	Vutrisiran N=122	Patisiran (N=42)
Age (years), median (range)	63 (34, 80)	60 (26, 85)	60 (31, 81)
Males, n (%)	58 (75)	79 (65)	27 (64)
TTR genotype, n (%)			
V30M	40 (52)	54 (44)	20 (48)
Non-V30M	37 (48)	68 (56)	22 (52)
NIS, mean (range)	57 (7, 126)	43 (5, 127)	43 (6, 116)
PND score*, n (%)			
I: preserved walking, sensory disturbances	20 (26)	44 (36)	15 (36)
II: impaired walking but can walk without stick or crutch	23 (30)	50 (41)	17 (40)
IIIA: walk with 1 stick or crutch	22 (29)	16 (13)	7 (17)
IIIB: walk with 2 sticks or crutches	11 (14)	12 (10)	3 (7)
Cardiac subpopulation, n (%)†	36 (47)	35 (29)	13 (31)

*One patient (1.3%) in external placebo group had a PND score IV defined as confined to wheelchair or bedridden (not shown on the slide). †Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history).
NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin.

Significant Improvement in Neuropathy Impairment with Vutrisiran

- Vutrisiran achieved statistically significant improvement in mNIS+7 at 9 months, compared with the external placebo group
  - Improvements across all pre-specified patient subgroups* and components of mNIS+7 (data not shown)
  - Consistent treatment effects in vutrisiran and patisiran groups in HELIOS-A (data not shown)



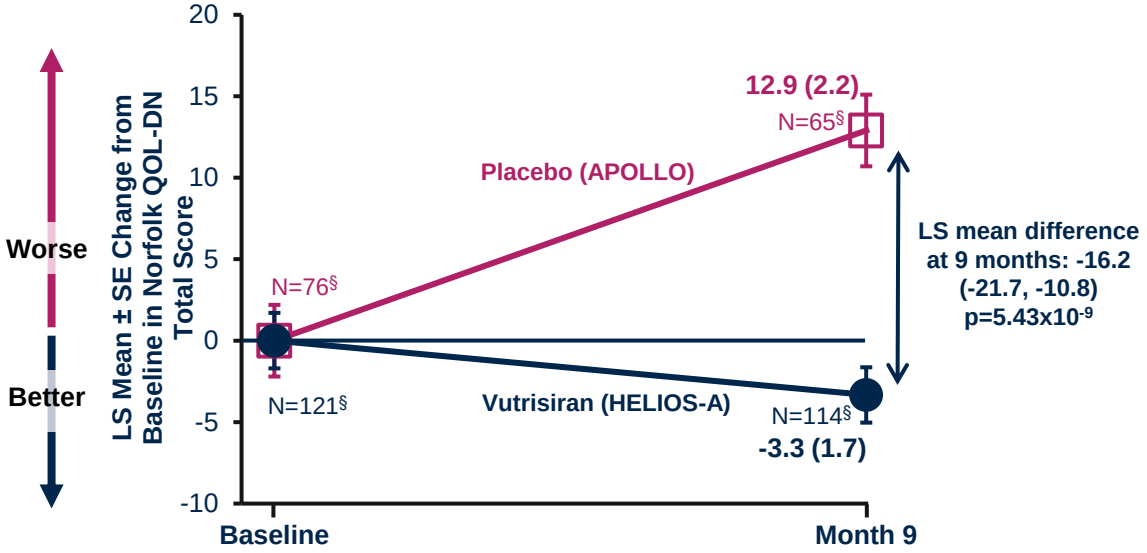
*Pre-specified patient subgroups included age (<65 or ≥65), sex, race, region, baseline NIS (<50 or ≥50), previous tetramer stabilizer use, genotype (V30M or non-V30M), FAP stage (I or II and III), cardiac subpopulation (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history), †mITT population. **At baseline, the mean (±SD) mNIS+7 was 60.6 (36.0) in the vutrisiran group and 74.6 (37.0) in external placebo group.** ‡Number of evaluable patients.

LS, least squares; mITT, modified intent-to-treat; mNIS+7, modified Neuropathy Impairment Score +7; SD, standard deviation; SE, standard error.

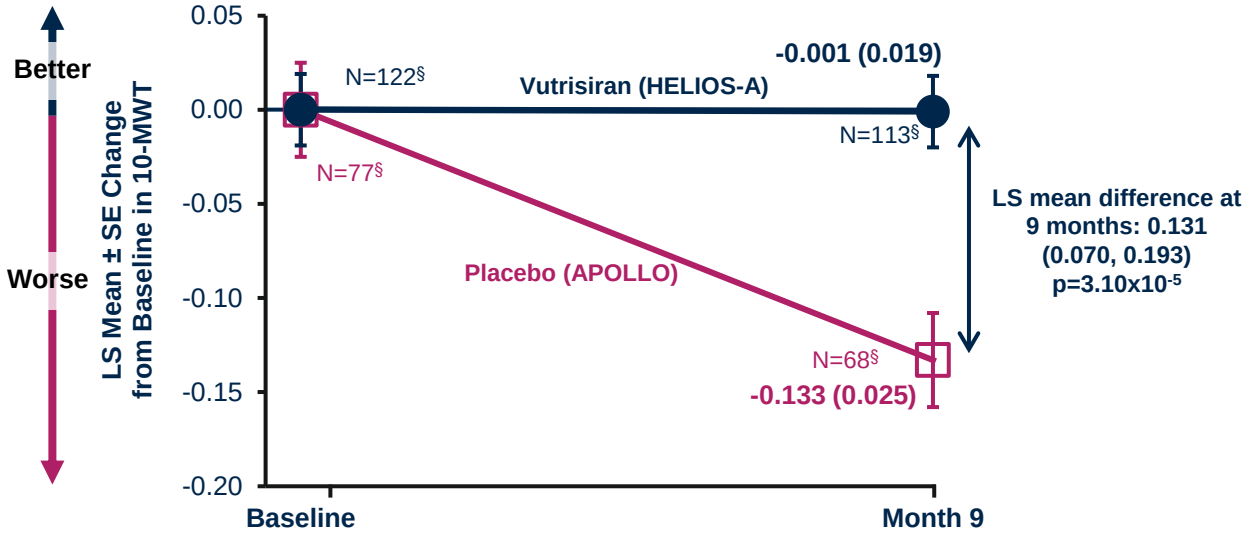
Significant Improvement in Quality of Life and Gait Speed with Vutrisiran

- Vutrisiran achieved statistically significant improvement in Norfolk QOL-DN and gait speed measured by 10-MWT at 9 months, compared with the external placebo group
  - Improvements across all pre-specified patient subgroups* and domains of Norfolk QOL-DN (data not shown)
  - Consistent treatment effects observed in vutrisiran and patisiran groups of HELIOS-A (data not shown)

Norfolk QOL-DN LS Mean Change from Baseline†



10-MWT LS Mean Change from Baseline‡



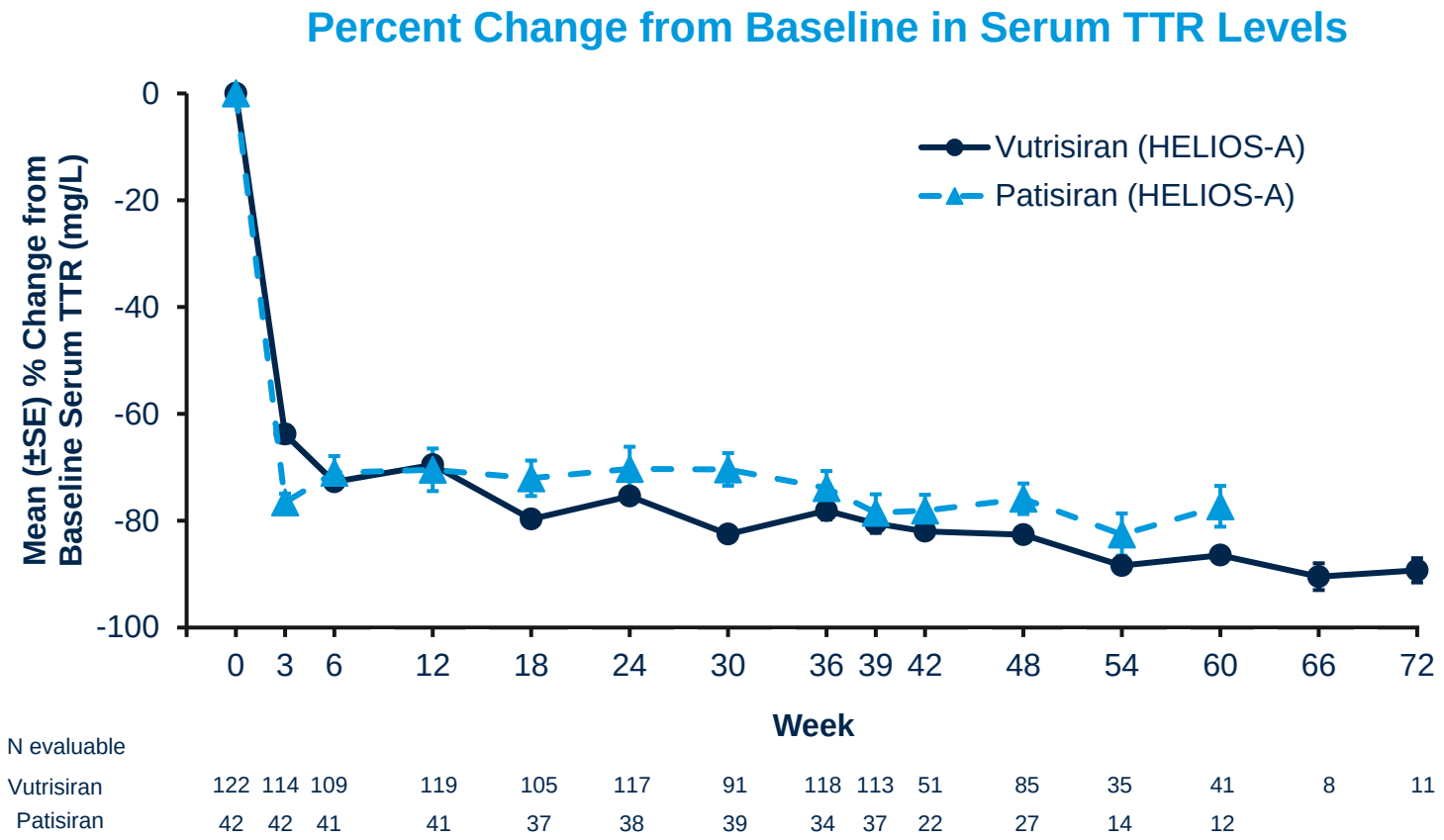
Exploratory endpoints at 9 months, including change from baseline in R-ODS, mBMI and NT-proBNP, demonstrated improvements compared with the external placebo group (data not shown)

*Pre-specified patient subgroups included age (<65 or ≥65), sex, race, region, baseline NIS (<50 or ≥50), previous tetramer stabilizer use, genotype (V30M or non-V30M), FAP stage (I or II and III), cardiac subpopulation (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history), † mITT population. **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.** ‡mITT population. **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.** §Number of evaluable patients.

10-MWT, 10-meter walk test; LS, least squares; mBMI, modified body mass index; mITT, modified intent-to-treat; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro–brain natriuretic peptide; R-ODS, Rasch-built overall disability scale; SD, standard deviation; SE, standard error.

Rapid and Sustained Reduction in Serum TTR Levels with Vutrisiran Similar to Patisiran in HELIOS-A

- Vutrisiran achieved a mean steady-state* serum TTR reduction from baseline of 83% (SD: 14%)



*Steady state was measured using Day 211 samples for vutrisiran.

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

HELIOS-A Safety Summary*

Acceptable Safety Profile of Vutrisiran

The majority of AEs were mild or moderate in severity

- No drug-related discontinuations or deaths
- Two study discontinuations (1.6%) due to AEs in the vutrisiran arm by Month 9, both due to deaths, neither of which was considered related to study drug
  - One death due to COVID-19 pneumonia and the other due to iliac artery occlusion
- Two SAEs deemed related to vutrisiran by investigators:
  - Dyslipidemia and urinary tract infection
- AEs ≥10% in vutrisiran group included diarrhea, pain in extremity, fall, and urinary tract infections
  - Each of these events occurred at a similar or lower rate compared with the external placebo group
- Injection site reactions were reported in five patients (4.1%) receiving vutrisiran
  - All were mild and transient
- No safety signals regarding liver function tests, hematology or renal function related to vutrisiran

At Least One Event, n (%)	APOLLO†	HELIOS-A	
	Placebo (N=77) PY=96.1	Vutrisiran (N=122) PY=131.3	Patisiran (N=42) PY=43.2
AEs	75 (97.4)	114 (93.4)	40 (95.2)
SAEs	31 (40.3)	21 (17.2)	17 (40.5)
Severe AEs	28 (36.4)	15 (12.3)	12 (28.6)
AEs leading to treatment discontinuation	11 (14.3)	2 (1.6)	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	2 (1.6)	2 (4.8)
Deaths	6 (7.8)	2 (1.6)	3 (7.1)

*Cumulative safety data from first dose of study drug to data cut-off date (November 10, 2020). †External reference to reflect the type of disease-related events commonly reported in this population.

AE, adverse event; PY, patient-years; SAE, serious AE.

Summary

- HELIOS-A is a phase 3, global, open-label study of vutrisiran 25 mg SC Q3M in patients with ATTRv amyloidosis with polyneuropathy
- Vutrisiran met the primary and both secondary endpoints at 9 months, with statistically significant improvements in neuropathy impairment (mNIS+7), quality of life (Norfolk QOL-DN), and gait speed (10-MWT), compared with the external placebo group
  - The effect on neuropathy impairment (mNIS+7) and QOL (Norfolk QOL-DN) was seen across all patient subgroups (data not shown)
  - The majority of patients showed improvements in neuropathy impairment (mNIS+7) and QOL (Norfolk QOL-DN) compared with baseline (data not shown)
  - Exploratory endpoints at 9 months, including change from baseline in R-ODS, mBMI and NT-proBNP, demonstrated improvements compared with the external placebo group (data not shown)
- Treatment with vutrisiran led to rapid and sustained reduction in serum TTR levels
- Vutrisiran has an acceptable safety profile and favorable benefit:risk profile
- HELIOS-A will continue to investigate the efficacy and safety of vutrisiran through an 18-month treatment period and an extension period

Medical writing and editorial assistance were provided by OPEN Health and funded by Alnylam Pharmaceuticals.

10-MWT, 10-meter walk test; AE, adverse event; ATTRv, transthyretin-mediated amyloidosis (v for variant); mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; Q3M, every 3 months; QOL, quality of life; SC, subcutaneous; TTR, transthyretin.

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