HELIOS-A: 18-Month Exploratory Cardiac Results from the Phase 3 Study of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis

Pablo Garcia-Pavia[1], Julian D Gillmore[2], Parag Kale[3], John L Berk[4], Mathew S Maurer[5], Isabel Conceição[6], Marcelo DiCarli[7], Scott Solomon[8], Chongshu Chen[9], Seth Arum[9], John Vest[9], Martha Grogan[10]

[1]Hospital Universitario Puerta de Hierro Majadahonda, CIBERCV, Madrid, Spain; [2]National Amyloidosis Centre, University College London, Royal Free Hospital, London, United Kingdom; [3]Center for Advanced Heart and Lung Disease, Baylor University Medical Center, Dallas, Texas, USA; [4]Amyloidosis Center, Boston Medical Center, Boston University, Boston, Massachusetts, USA; [5]Division of Cardiology, Department of Medicine, Center for Advanced Cardiac Care, Columbia University Medical Center, New York, New York, USA; [6]Centro Hospitalar Universitário Lisboa Norte, Hospital de Santa Maria and Faculdade de Medicina, Lisbon, Portugal; [7]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [8]Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts, USA; [9]Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA; [10]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA.

May 21–24, 2022 || European Society of Cardiology: Heart Failure 2022

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]

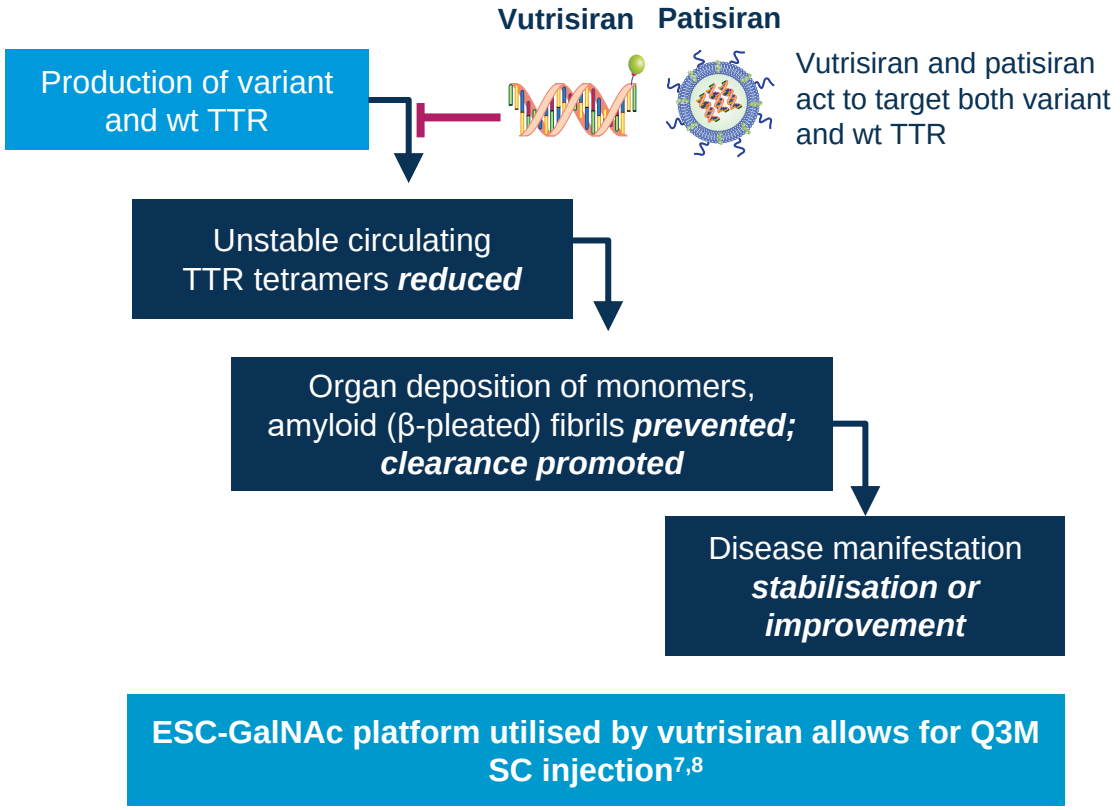
Vutrisiran

- Investigational, subcutaneously administered RNAi therapeutic targeting hepatic production of variant and wild-type TTR in development for the treatment of ATTR amyloidosis[7,8]

Patisiran

- RNAi therapeutic administered via IV infusion, approved for the treatment of the polyneuropathy of hATTR amyloidosis based on the Phase 3, placebo-controlled APOLLO trial[9–12]

Therapeutic Hypothesis

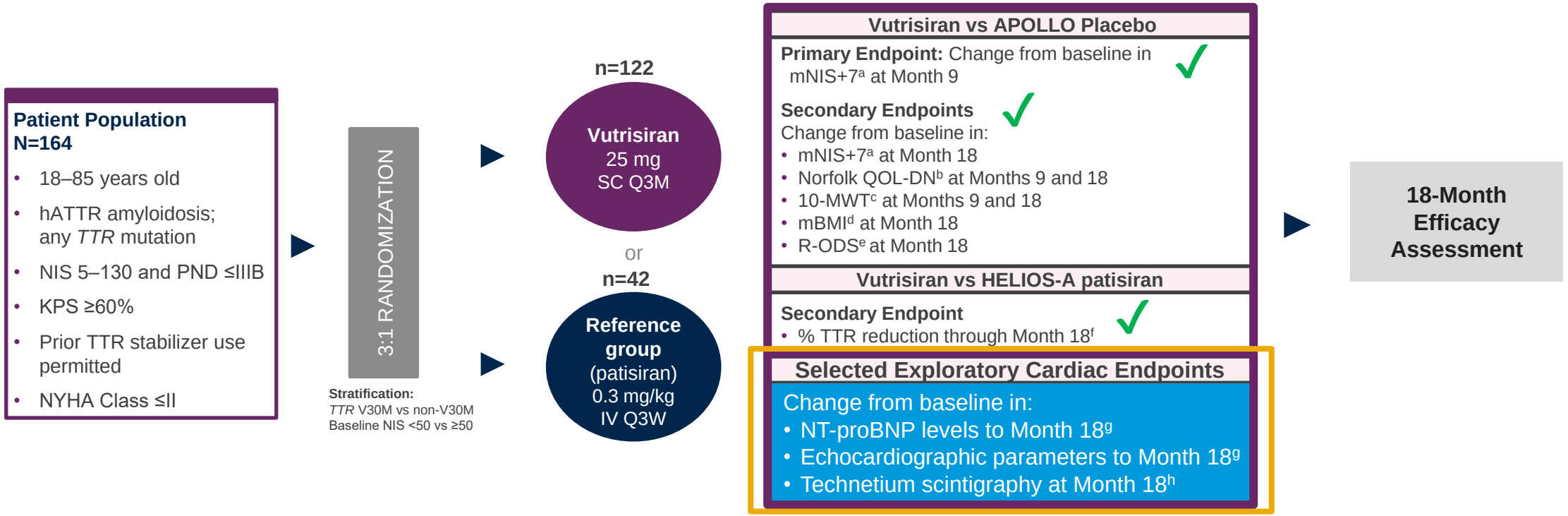


ESC-GalNAc platform utilised by vutrisiran allows for Q3M SC injection[7,8]

ATTRv, hereditary transthyretin (v for variant); ESC, enhanced stabilisation chemistry; GalNAc, *N*-acetylgalactosamine; hATTR, hereditary transthyretin-mediated; IV, intravenous; MRI, magnetic resonance imaging; Q3M, every 3 months; RNAi, ribonucleic acid interference; SC, subcutaneous; Tc, technetium; 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. Habtemariam BA et al. *Clin Pharmacol Ther* 2021;109:372–382; 8. Nair JK et al. *J Am Chem Soc* 2014;136:16958–16961; 9. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. February 2020; 10. Adams D et al. *N Engl J Med* 2018;379:11–21; 11. APOLLO: NCT01960348; 12. Alnylam Netherlands, summary of product characteristics for ONPATTRO® (patisiran).

Vutrisiran Phase 3 HELIOS·A Study in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy

- Vutrisiran was compared with the **external APOLLO placebo group** for the primary and most secondary and exploratory endpoints
- As previously reported, the primary endpoint of change from baseline in mNIS+7 at Month 9[1] and all secondary endpoints[2] were met
- A prespecified cardiac subpopulation (baseline left ventricular wall thickness ≥1.3 cm and no medical history of aortic valve disease or hypertension) was analysed to determine the effect of vutrisiran on exploratory cardiac parameters



[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]Non-inferiority analysis. [g]Change from baseline to Month 18 vs. external placebo group; [h]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.

10-MWT, 10-meter walk test; ATTRv, hereditary transthyretin (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; 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.

1. Adams D et al. *Neurology* 2021;96(15 Supplement):1234. 2. Adams D, et al. *Société Francophone du Nerf Périphérique (SFNP)* 2022.

Baseline Demographics, Disease Characteristics, and Echocardiographic Parameters

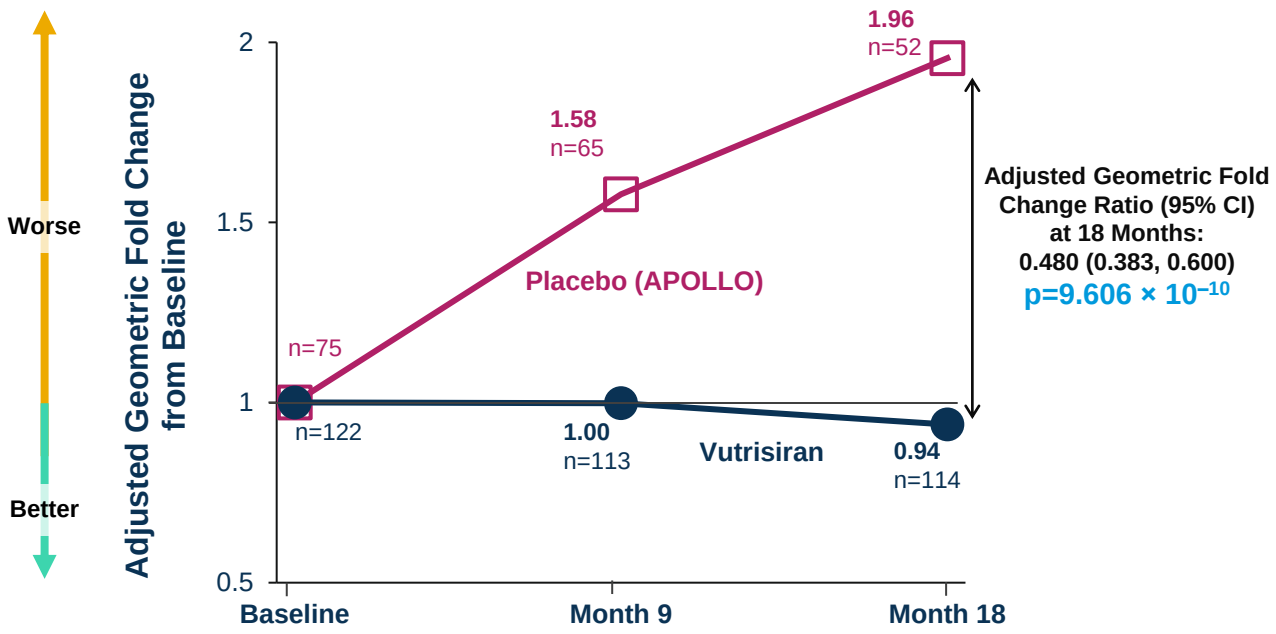
Characteristic	APOLLO mITT[a]	HELIOS-A mITT[a]	APOLLO cardiac subpopulation[b]	HELIOS-A cardiac subpopulation[b,c]
	Placebo (n=77)	Vutrisiran (n=122)	Placebo (n=36)	Vutrisiran (n=40)
Age (years), median (range)	63 (34, 80)	60 (26, 85)	62.0 (43, 80)	63.5 (26, 81)
Males, n (%)	58 (75.3)	79 (64.8)	30 (83.3)	32 (80.0)
Non-V30M *TTR* Genotype, n (%)	37 (48.1)	68 (55.7)	24 (66.7)	30 (75.0)
NIS, mean (range)	57.02 (7.0–125.5)	43.02 (5.0–127.0)	68.72 (23.5–122.6)	55.42 (13.0–127.0)
NT-proBNP[d] (ng/L), median (Q1, Q3)	562.8 (235.5, 1580.7)	287.4 (67.8, 965.0)	845.7 (373.2, 1581.7)	824.8 (323.3, 1933.0)
NYHA Class[e], n (%)				
No Heart Failure	NA	68 (55.7%)	NA	16 (40.0%)
Class I	40 (51.9)	11 (9.0)	16 (44.4)	4 (10.0)
Class II	36 (46.8)	43 (35.2)	20 (55.6)	20 (50.0)
Echocardiographic Parameters, mean (SD)				
LV Wall Thickness (cm)	1.568 (0.297)	1.367 (0.385)	1.639 (0.214)	1.649 (0.291)
Cardiac Output (L/min)	4.171 (1.345)	3.861 (1.052)	3.918 (1.149)	3.837 (1.080)
Global Longitudinal Strain (%)	-16.308 (3.722)	-15.788 (4.024)	-15.661 (3.513)	-14.190 (3.925)
LV End-Diastolic Volume (mL)	90.396 (25.691)	83.644 (22.857)	84.899 (23.082)	84.179 (23.296)
LV Ejection Fraction (%)	62.660 (9.785)	62.946 (9.024)	62.208 (8.607)	61.951 (10.443)

[a]mITT refers to all randomized patients who received any amount of study drug. [b]Cardiac subpopulation was defined as patients with 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. [d]NT-proBNP missing for 2 patients (5.6%) in APOLLO placebo cardiac subpopulation and 2 patients (2.6%) in the mITT population. [e]NYHA class data missing for one patient (1.3%) in the APOLLO placebo mITT group. NYHA class of 'no heart failure' not captured for the APOLLO placebo groups. LV, left ventricular; mITT, modified intention-to-treat; NA, not applicable; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin.

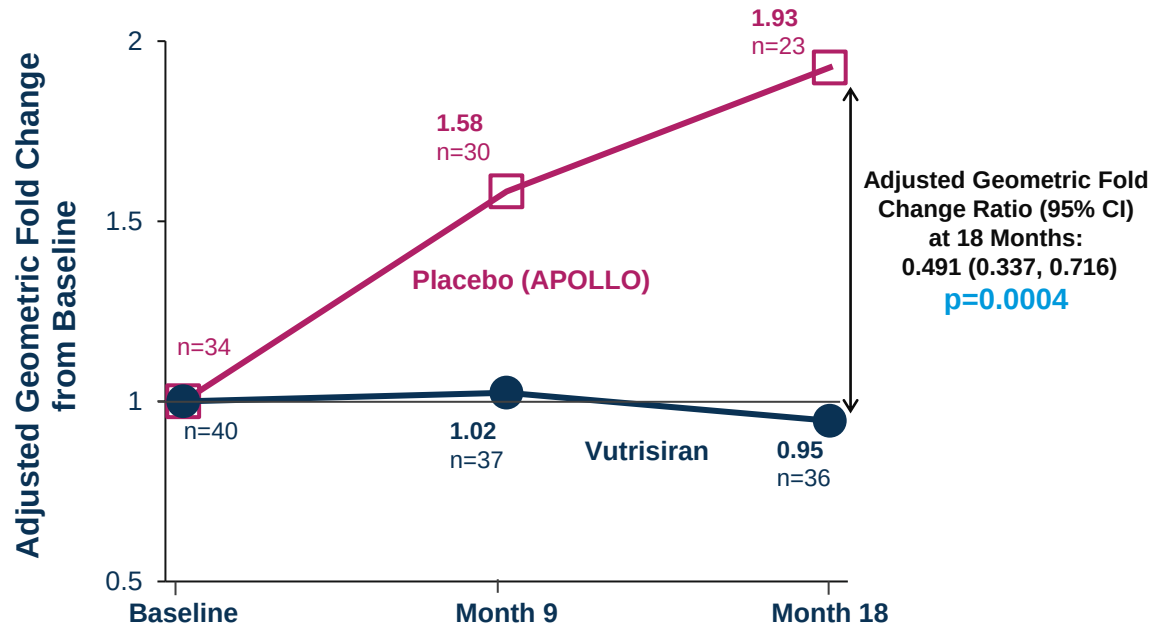
NT-proBNP Levels with Vutrisiran vs External Placebo at Month 18

- In both the mITT population and cardiac subpopulation, vutrisiran achieved improvement in NT-proBNP levels at Month 9 with continued improvement to Month 18 compared with the external placebo group (exploratory endpoint)

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



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

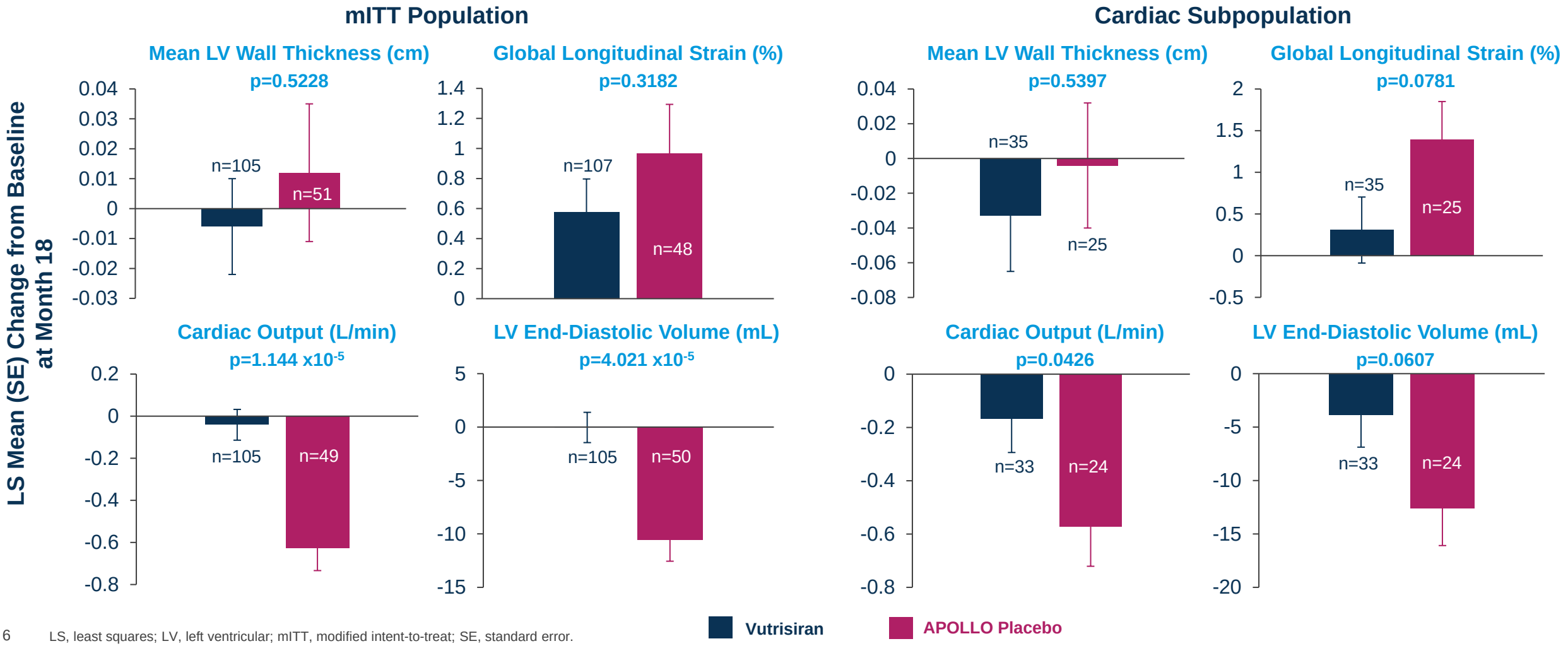


- Geometric mean level decreased from baseline to Month 18 with vutrisiran in the mITT population (273.01 to 227.15 ng/L) and cardiac subpopulation (748.07 to 614.37 ng/L), and increased with external placebo (531.30 to 844.40 ng/L; 711.10 to 1116.75 ng/L, respectively)

[a]NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. NT-proBNP results shown at Month 9 and Month 18 are MMRM model data. Number of evaluable patients at each timepoint are shown.
CI, confidence interval; MMRM, mixed model for repeated measures; NT-proBNP, N-terminal pro–brain natriuretic peptide.

Echocardiographic Parameters with Vutrisiran vs External Placebo at Month 18

- Vutrisiran demonstrated a trend towards improvement of echocardiographic parameters in the mITT population and cardiac subpopulation at Month 18 compared with the external placebo group (exploratory endpoints)



LS, least squares; LV, left ventricular; mITT, modified intent-to-treat; SE, standard error.

HELIOS-A Technetium (^{99m}Tc) Scintigraphy Imaging in a Planned Cohort

- ^{99m}Tc scintigraphy: non-invasive assessment of cardiac amyloid involvement
  - Conducted at baseline and Month 18, at select sites
  - Assessment of change relative to individual patient's baseline

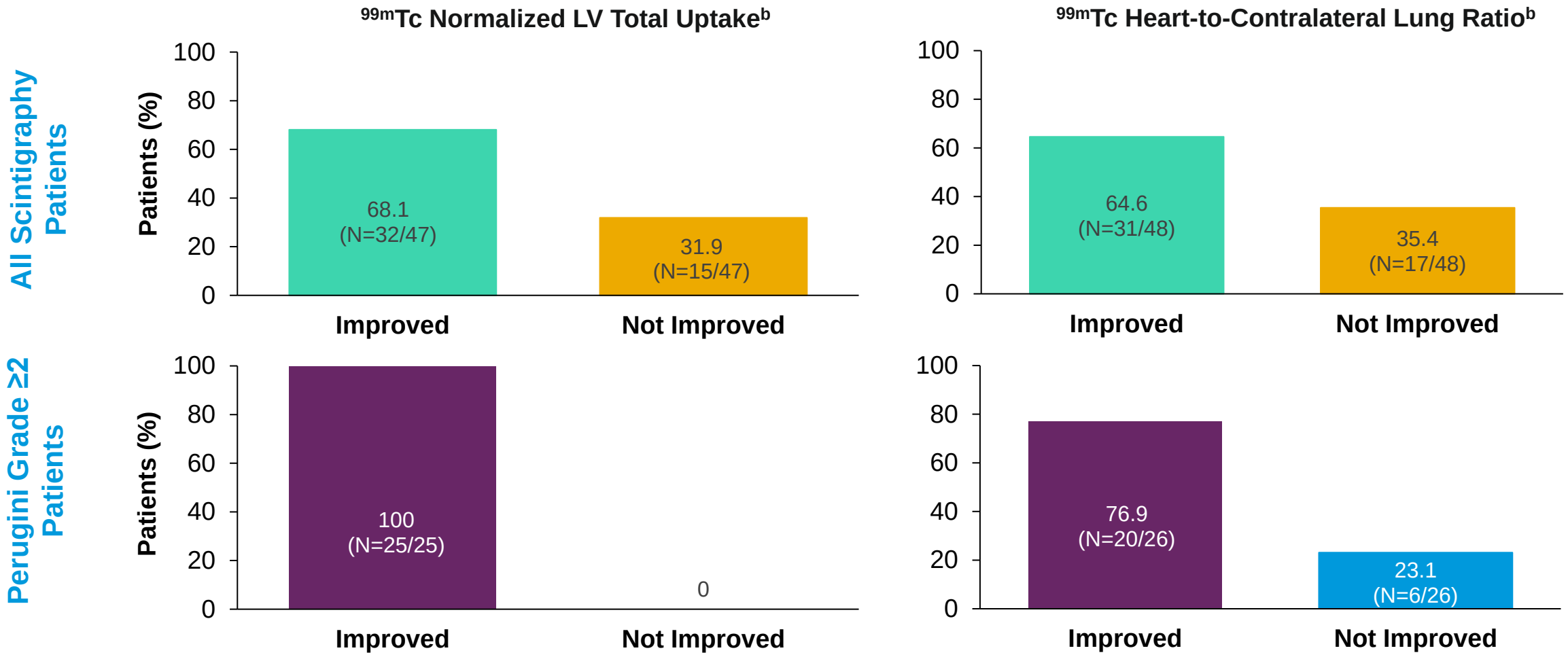
- **Quantitative Assessments:**
  - Uptake in heart normalized to uptake in contralateral lung (heart-to-contralateral lung ratio)
  - Uptake in heart normalized to total amount of radio-tracer administered (normalized LV uptake)

- **Semi-Quantitative Assessment (Perugini Grade):**
  - Visually assesses ^{99m}Tc uptake in myocardium compared to bones
    - Widely used in diagnosis of ATTR amyloidosis

ATTR, transthyretin-mediated; LV, left ventricle; Tc, technetium.

Reduced Cardiac ^{99m}Tc Uptake on Scintigraphy Imaging in Majority of Evaluable Vutrisiran-Treated Patients[a] at Month 18

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



[a]Analysis includes patients from mITT population with evaluable data at baseline and Month 18; [b]**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.** LV, left ventricle; Tc, technetium.

Improvement vs Baseline in Perugini Grade with Vutrisiran at Month 18

- Among all evaluable scintigraphy patients[a], 55 (96%) were stable or improved by ≥1 Perugini grade at Month 18
- Among evaluable patients with Perugini grade ≥1 at baseline, 16 (50%) improved by ≥1 Perugini grade
  - 5 (16%) patients improved by ≥2 Perugini grades

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

[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.**

Cardiac Safety Events During the 18-Month Treatment Period

- As previously reported, the majority of AEs reported in the vutrisiran arm of HELIOS-A were mild or moderate in severity[1]
  - Three study discontinuations in the vutrisiran arm (one due to a non-fatal heart failure event), none of which were considered related to the study drug
  - Two deaths in the vutrisiran arm (one due to COVID-19 pneumonia, one due to iliac artery occlusion), neither of which were considered related to the study drug

Variable	APOLLO mITT	HELIOS-A mITT	APOLLO cardiac subpopulation	HELIOS-A cardiac subpopulation
	Placebo n=77	Vutrisiran n=122	Placebo n=36	Vutrisiran n=40
Cardiac AEs (system organ class)[a], n (%)	28 (36.4)	37 (30.3)	13 (36.1)	15 (37.5)
Cardiac serious AEs (system organ class)[a], n (%)	10 (13.0)	11 (9.0)	4 (11.1)	6 (15.0)
Cardiac arrhythmia (high-level group term) adverse events, n (%)	22 (28.6)	30 (24.6)	11 (30.6)	13 (32.5)
Supraventricular arrhythmias (high level term), n (%)	13 (16.9)	10 (8.2)	9 (25.0)	7 (17.5)
Cardiac conduction disorders (high level term), n (%)	7 (9.1)	10 (8.2)	3 (8.3)	4 (10.0)
Ventricular arrhythmias and cardiac arrest (high level term), n (%)	6 (7.8)	6 (4.9)	3 (8.3)	1 (2.5)
Rate and rhythm disorders (high level term), n (%)	0	8 (6.6)	0	3 (7.5)
Torsade des pointes (standard MedDRA query adverse events), n (%)	14 (18.2)	14 (11.5)	5 (13.9)	7 (17.5)
Cardiac failure (standard MedDRA query narrow term adverse events), n (%)	8 (10.4)	7 (5.7)	2 (5.6)	5 (12.5)

[a]Based on MedDRA 'Cardiac Disorders' System Organ Class. AE, adverse event; MedDRA, medical dictionary for regulatory activities; mITT, modified intention-to-treat. 1. Adams et al. *American Academy of Neurology (AAN)* 2022.

Summary

- In this exploratory analysis, vutrisiran treatment was associated with an improvement in NT-proBNP levels and a trend towards improvement in echocardiographic parameters compared with external placebo in patients with prespecified evidence of cardiac amyloid involvement at baseline
  - Consistent beneficial effects on cardiac measures were also observed in the mITT population
- In a planned cohort of patients from the mITT population, cardiac uptake of ^{99m}Tc on scintigraphy imaging was reduced compared with baseline in the majority of evaluable patients following treatment with vutrisiran, potentially suggesting regression of cardiac amyloid, although the clinical significance of this observation is not yet clear
- Vutrisiran demonstrated an acceptable cardiac safety profile
- The ongoing HELIOS-B study (NCT04153149) will investigate the cardiac efficacy and safety of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy

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