ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3138

RESEARCH ARTICLE

Impact of vutrisiran on exploratory cardiac parameters in hereditary transthyretin-mediated amyloidosis with polyneuropathy

Pablo Garcia-Pavia[1,2,3]*, Martha Grogan[4], Parag Kale[5], John L. Berk[6], Mathew S. Maurer[7], Isabel Conceição[8], Marcelo Di Carli[9], Scott D. Solomon[10], Chongshu Chen[11], Elena Yureneva[11], John Vest[11], and Julian D. Gillmore[12]

[1]Department of Cardiology, Hospital Universitario Puerta de Hierro, Madrid, Spain; [2]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; [3]Universidad Francisco de Vitoria (UFV), Pozuelo de Alarcon, Spain; [4]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA; [5]Center for Advanced Heart and Lung Disease, Baylor University Medical Center, Dallas, TX, USA; [6]Amyloidosis Center, Boston Medical Center, Boston University, Boston, MA, USA; [7]Division of Cardiology, Department of Medicine, Center for Advanced Cardiac Care, Columbia University Irving Medical Center, New York, NY, USA; [8]Centro Hospitalar Universitário Lisboa Norte, Hospital de Santa Maria and Faculdade de Medicina, Lisbon, Portugal; [9]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [10]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA; [11]Alnylam Pharmaceuticals, Cambridge, MA, USA; and [12]National Amyloidosis Centre, University College London, Royal Free Hospital, London, UK

Received 26 July 2023; revised 10 October 2023; accepted 31 December 2023

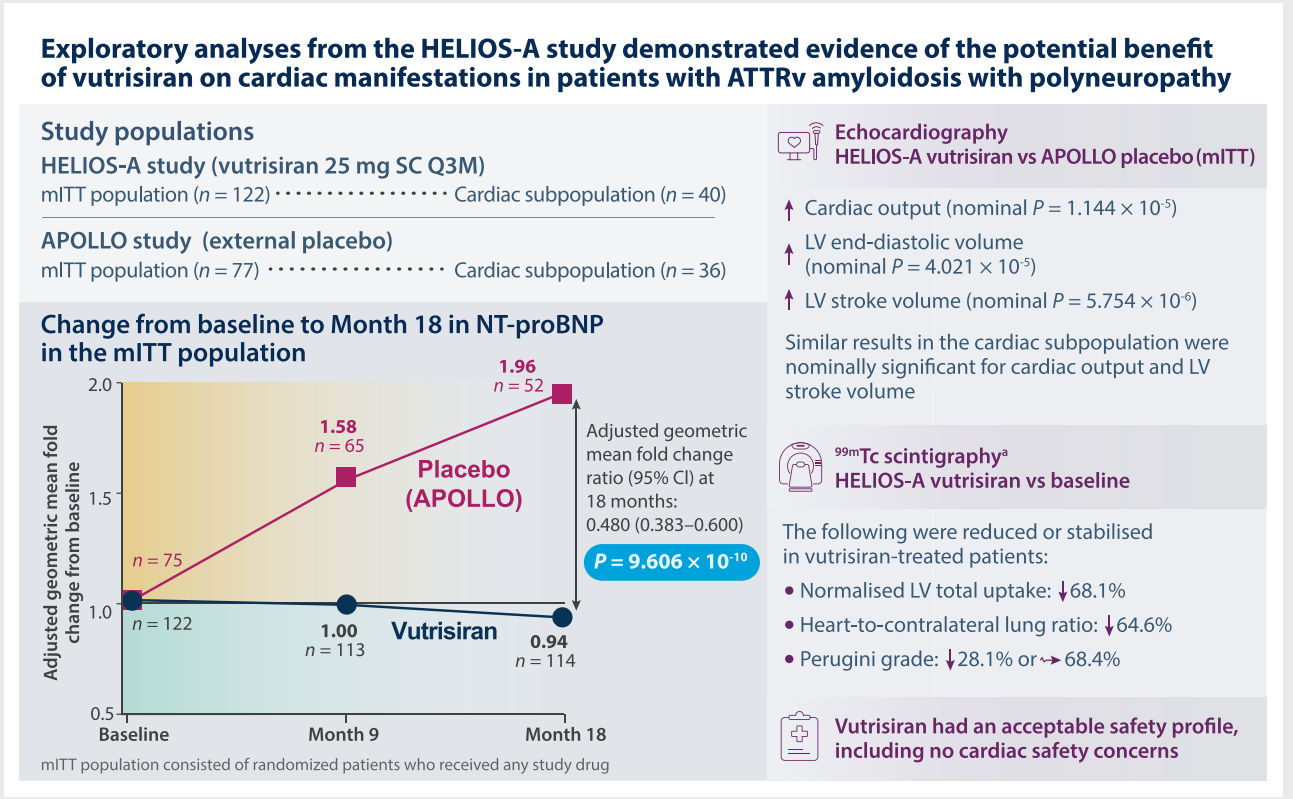
Aims HELIOS-A was a Phase 3, open-label study of vutrisiran, an RNA interference therapeutic, in patients with hereditary transthyretin (ATTRv) amyloidosis with polyneuropathy. This analysis evaluated vutrisiran's impact on exploratory cardiac endpoints in HELIOS-A patients.

Methods and results Patients were randomized 3:1 to subcutaneous vutrisiran 25 mg every 3 months or intravenous patisiran 0.3 mg/kg every 3 weeks (reference group) for 18 months. Exploratory cardiac endpoints included change from baseline in *N*-terminal prohormone of brain-type natriuretic peptide (NT-proBNP) and echocardiographic parameters versus external placebo (APOLLO study). The modified intent-to-treat (mITT) population comprised randomized patients receiving any study drug ($n = 122$). A cardiac subpopulation with evidence of cardiac amyloid involvement ($n = 40$) was prespecified. ^{99m}Tc scintigraphy exploratory assessments in a planned vutrisiran-treated cohort at select sites were compared with baseline. At Month 18, vutrisiran demonstrated beneficial effects on NT-proBNP versus external placebo in the mITT and cardiac subpopulations (adjusted geometric mean fold change ratio [95% confidence interval] 0.480 [0.383–0.600], $p = 9.606 \times 10^{-10}$ and 0.491 [0.337–0.716], $p = 0.0004$, respectively). Benefits or trends towards benefit in echocardiographic parameters versus external placebo were observed for both populations. In ^{99m}Tc scintigraphy assessments, 32/47 (68.1%) and 31/48 (64.6%) patients exhibited reduced normalized left ventricular total uptake and heart-to-contralateral lung ratio, respectively. Perugini grade was reduced or unchanged versus baseline in 55/57 (96.5%) evaluable patients. No increase in cardiac adverse events was observed with vutrisiran versus external placebo.

Conclusions Vutrisiran demonstrated evidence of potential benefit on cardiac manifestations in patients with ATTRv amyloidosis with polyneuropathy, with an acceptable safety profile.

*Corresponding author. Department of Cardiology, Hospital Universitario Puerta de Hierro, Manuel de Falla, 2, 28222 Madrid, Spain. Tel: +34 91 191 7297, Fax: +34 91 191 7718, Email: pablogpavia@yahoo.es

Graphical Abstract



Vutrisiran demonstrated beneficial effects on *N*-terminal prohormone of brain-type natriuretic peptide (NT-proBNP) and other prespecified exploratory echocardiographic parameters versus external placebo in both a modified intent-to-treat (mITT) population and a cardiac subpopulation at Month 18. In a planned cohort undergoing ^{99m}Tc scintigraphy assessments, a majority of vutrisiran-treated patients experienced reduced or stabilized radiotracer uptake versus baseline. Vutrisiran demonstrated evidence of potential benefit on cardiac manifestations in patients with hereditary transthyretin (ATTRv) amyloidosis with polyneuropathy, and an acceptable safety profile, including no cardiac safety concerns. CI, confidence interval; LV, left ventricular; Q3M, every 3 months; SC, subcutaneous. [a]In a planned cohort.

Keywords Vutrisiran • Hereditary transthyretin-mediated amyloidosis • Cardiomyopathy • NT-proBNP • Echocardiography • ^{99m}Tc scintigraphy

Introduction

Hereditary transthyretin (ATTRv [v for variant]) amyloidosis, also known as hATTR amyloidosis, is a rapidly progressive, debilitating, and fatal disease caused by variants in the transthyretin (*TTR*) gene, resulting in misfolded TTR accumulating as amyloid deposits in multiple organs, including the nerves and heart.[1–4] Most patients develop a mixed phenotype of polyneuropathy and cardiomyopathy.[5]

Cardiac deposition of TTR amyloid fibrils can lead to progressive biventricular wall thickening, systolic and diastolic dysfunction, atrial and ventricular arrhythmias, conduction disorders, restrictive cardiomyopathy, progressive heart failure, and death.[6,7] Cardiac involvement in ATTRv amyloidosis impacts prognosis, with a median post-diagnosis survival time of 3.4 years without disease-modifying treatment.[8–10] Cardiac manifestations of ATTRv amyloidosis can be assessed through plasma levels of cardiac biomarkers (e.g. *N*-terminal prohormone of brain-type natriuretic peptide [NT-proBNP] and troponins) and imaging techniques, including echocardiography and technetium-99m (^{99m}Tc) scintigraphy. The latter is a well-accepted method for diagnosis of transthyretin-mediated (ATTR) amyloidosis with cardiomyopathy as part of a highly sensitive and specific algorithm,[11] though the utility of scintigraphy as a clinical monitoring tool is uncertain.[12,13]

As ATTRv amyloidosis is rapidly progressive, early, effective treatment targeting underlying amyloidogenesis and addressing the multisystem manifestations is imperative. Current treatment options for the cardiomyopathy of ATTRv amyloidosis are limited. Gene silencing approaches including RNA interference (RNAi) therapeutics and antisense oligonucleotides are being investigated in ongoing clinical trials for this indication.[14–16]

Vutrisiran is a subcutaneously (SC) administered RNAi therapeutic targeting hepatic production of variant and wild-type TTR[17] that utilizes enhanced stabilization chemistry to increase potency and impart high metabolic stability, allowing for infrequent dosing. In the Phase 3, global, randomized, open-label HELIOS-A study (NCT03759379), vutrisiran demonstrated significant benefits in patients with ATTRv amyloidosis with polyneuropathy when compared with an external placebo group from the patisiran APOLLO study,[18] and was subsequently approved for the treatment of the polyneuropathy of ATTRv amyloidosis.[19] Here, we report the impact of vutrisiran on exploratory cardiac endpoints from the HELIOS-A study in the modified intent-to-treat (mITT) population and in a prespecified subpopulation with evidence of cardiac amyloid involvement.

Methods

Study oversight

The HELIOS-A study protocol and amendments were approved by the relevant Institutional Review Board or Independent Ethics Committee. The study was conducted in accordance with all applicable regulatory requirements, the current guidelines of Good Clinical Practice, and the principles that have their origin in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study design and treatment

The HELIOS-A study design has been previously described.[18] Briefly, patients were enrolled between February 2019 and March 2020 and randomized 3:1 to vutrisiran 25 mg SC every 3 months or patisiran 0.3 mg/kg intravenously every 3 weeks (as a reference group), stratified by *TTR* genotype (V30M vs. non-V30M) and baseline Neuropathy Impairment Score (NIS; <50 vs. ≥50). The placebo group of the APOLLO study,[20] which assessed the efficacy and safety of patisiran in patients with ATTRv amyloidosis with polyneuropathy and had similar eligibility criteria and endpoints to HELIOS-A, was used as the external control for the primary and most secondary and exploratory endpoints.

Patients

Eligible patients were aged 18–85 years with a diagnosis of ATTRv amyloidosis (with any documented variant), polyneuropathy demonstrated by a baseline NIS of 5–130, a Polyneuropathy Disability (PND) score of ≤IIIb, a Karnofsky Performance Status score of ≥60%, and adequate liver and renal function. Patients with prior use of TTR stabilizers were permitted to participate following a specified washout period, but use of these agents was not permitted during the study. Patients with New York Heart Association (NYHA) Class III or IV heart failure were excluded. The HELIOS-A mITT population was defined as all randomized patients who received any amount of study drug. 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.[20]

Cardiac efficacy and safety outcomes

Assessments of cardiac measures were included as exploratory endpoints in the HELIOS-A study. These included cmhange from baseline to Month 18 in NT-proBNP and echocardiographic parameters in the mITT population and the cardiac subpopulation. Exploratory assessment of change from baseline to Month 18 for ^{99m}Tc scintigraphy parameters was conducted in a planned cohort of the overall study population at select sites participating in collecting scintigraphy data.

NT-proBNP levels and echocardiographic parameters were assessed at baseline, Month 9, and Month 18. Echocardiographic parameters prespecified in the HELIOS-A statistical analysis plan[21] for the mITT population and cardiac subpopulation at Month 18 (mean LV wall thickness, LV mass, global longitudinal strain, cardiac output, and LV end-diastolic volume) are reported. LV stroke volume, although not prespecified, is also a measure of overall cardiac function and an important prognostic factor in patients with ATTR amyloidosis.[22–24] It was calculated by subtracting LV end-systolic volume from LV end-diastolic volume and is reported here. At select sites, ^{99m}Tc scintigraphy was performed at baseline and Month 18 to assess cardiac amyloid involvement. All patients enrolled at participating ^{99m}Tc scintigraphy sites were invited to participate and were not selected according to any additional criteria. Based on local practice for ^{99m}Tc scintigraphy, either ^{99m}Tc-pyrophosphate, ^{99m}Tc-3,3-diphosphono-1, 2-propanodicarboxylic acid, or ^{99m}Tc-hydroxymethylene diphosphonate was used as the tracer. Changes from baseline to Month 18 in ^{99m}Tc scintigraphy parameters were assessed quantitatively by normalizing counts of radiotracer uptake in the heart to uptake in the contralateral lung to account for background (heart-to-contralateral lung [H/CL] ratio) and to the total amount of radiotracer administered (normalized LV total uptake).[25] Changes were also assessed semi-quantitatively using Perugini grading, an established grading system utilized in the diagnosis of cardiac amyloidosis, assigned based on a visual assessment of radiotracer uptake in the myocardium versus the ribs.[26,27] The ^{99m}Tc scintigraphy results are only reported for vutrisiran-treated patients. NT-proBNP, echocardiography and ^{99m}Tc scintigraphy data were each analysed at a central laboratory blinded to patient treatment group assignment.

Cardiac safety events were reported based on the Medical Dictionary for Regulatory Activities (MedDRA) classifications: cardiac disorders (system organ class), cardiac arrhythmia (high-level group term), and cardiac failure (standardized MedDRA query). The proportion of patients reporting cardiac events was evaluated, including cardiac adverse events (AEs), cardiac serious AEs (SAEs), and events related to heart failure and cardiac arrhythmias.

Statistical analysis

Changes from baseline to Month 18 in NT-proBNP and prespecified echocardiographic parameters were assessed in the mITT population and the cardiac subpopulation. The placebo group of the APOLLO study[28] was used as the external control for NT-proBNP and echocardiographic parameters. Treatment effects on these variables were

estimated using mixed-effects models for repeated measures. The model included baseline value as a continuous covariate, treatment and visit as categorical factors, and an interaction term of treatment by visit. A natural log transformation was applied to NT-proBNP data because of skew detected in the APOLLO study.[29] A post hoc NT-proBNP quartile analysis was also performed, in which patients were divided into four subgroups based on their baseline NT-proBNP levels (ng/L): quartile (Q)1: ≤93.8 (placebo, $n = 10$; vutrisiran, $n = 40$), Q2: >93.8–≤384.2 (placebo, $n = 20$; vutrisiran, $n = 29$), Q3: >384.2–≤1170.5 (placebo, $n = 23$; vutrisiran, $n = 26$), and Q4: >1170.5 (placebo, $n = 22$; vutrisiran, $n = 27$). As all endpoints were exploratory, reported p-values are nominal (alpha level 0.05). Numerical changes of a measure in a favourable direction that did not reach statistical significance were taken to be suggestive of a trend towards benefit. The quartile data are summarized descriptively (geometric mean ± standard error of the mean [SEM]) due to the limitation of sample size within each quartile.

Changes from baseline to Month 18 for ^{99m}Tc scintigraphy parameters were assessed in patients from the HELIOS-A mITT population who underwent ^{99m}Tc scintigraphy, and a post hoc analysis was performed in a subgroup of these patients who had baseline Perugini grade ≥2, the accepted threshold for non-invasive diagnosis of ATTR amyloidosis with cardiomyopathy.[4] ^{99m}Tc scintigraphy parameters were not assessed in the APOLLO study; therefore, the results at Month 18 were compared with baseline only and are summarized descriptively.

Cardiac safety events were assessed in both the mITT population and cardiac subpopulation for patients in the HELIOS-A study and the APOLLO placebo group. Safety data are also summarized descriptively.

Results

Patients

A total of 164 patients were randomized and treated in the HELIOS-A study, 122 (74.4%) of whom received vutrisiran (mITT population). Of these 122, 40 (32.8%) were also included in the cardiac subpopulation according to the predefined criteria. By comparison, the mITT population of the APOLLO placebo group comprised 77 patients, of whom 36 (46.8%) were included in the cardiac subpopulation. The baseline demographics and clinical characteristics in the vutrisiran-treated groups of the mITT population and HELIOS-A cardiac subpopulation were largely overlapping and clinically comparable to the placebo groups of the corresponding populations in APOLLO (*Table 1*).

In both HELIOS-A and APOLLO, the most common *TTR* variant was V30M (online supplementary *Table S1*). Differences were seen in concomitant treatments in the HELIOS-A and APOLLO groups at baseline; in the mITT population, a greater proportion of patients in the external placebo group were receiving furosemide compared with the vutrisiran group, while in the cardiac subpopulation, a greater proportion of patients were receiving β-blockers, furosemide, or spironolactone in the vutrisiran group compared with the external placebo group. In the cardiac subpopulation, previous use of tafamidis was greater in the vutrisiran group (42.5%) than the external placebo group (25.0%). A higher proportion of patients had pacemakers in the external placebo group than in the vutrisiran group (24.7% vs. 7.4% in the mITT population, and 25.0% vs. 5.0% in the cardiac subpopulation, respectively). Baseline demographics and disease characteristics for the planned cohort of patients in HELIOS-A who underwent ^{99m}Tc scintigraphy ($n = 64$) and the subgroup with Perugini grade ≥2 at baseline ($n = 35$) are shown in online supplementary *Table S2*. Of note, 20 of the 64 (31.3%) patients who underwent ^{99m}Tc scintigraphy met the criteria for the cardiac subpopulation, and of these patients, 17/20 (85.0%) had Perugini grade ≥2 at baseline. A higher proportion of patients in the overall ^{99m}Tc scintigraphy group had previous tafamidis use (43.8%) than in the subgroup of patients with Perugini grade ≥2 (31.4%).

Efficacy

NT-proBNP levels

In the mITT population, baseline NT-proBNP levels were lower in the vutrisiran group compared with the external placebo group (geometric mean ± SEM, 273.0 ± 42.2 ng/L vs. 531.3 ± 86.7 ng/L, respectively) (*Table 1*). Vutrisiran demonstrated a beneficial effect on NT-proBNP levels at Month 9, which was sustained to Month 18, compared with the respective external placebo group (*Figure 4*). In the mITT population at Month 18, the adjusted geometric mean fold change ratio (95% confidence interval [CI]) for NT-proBNP with vutrisiran compared with external placebo was 0.480 (0.383–0.600 [$p = 9.606 \times 10^{-10}$]) (*Figure 1A*) (Graphical Abstract). Geometric mean ± SEM NT-proBNP levels decreased from 273.0 ± 42.2 ng/L at baseline to 227.2 ± 37.0 ng/L in the vutrisiran group but increased from 531.3 ± 86.7 ng/L at baseline to 844.4 ± 167.0 ng/L in the external placebo group at Month 18. Additionally, in the mITT population, the data were consistent with a benefit of vutrisiran compared with external placebo across all quartiles of baseline NT-proBNP levels at Month 18, although statistical testing was not performed to evaluate this treatment effect due to the limited patient numbers in each quartile (online supplementary *Figure S1*).

In the cardiac subpopulation, NT-proBNP levels at baseline were comparable between the vutrisiran and external placebo groups (median: 824.8 ng/L and 845.7 ng/L respectively) (*Table 1*). The adjusted geometric mean fold change ratio (95% CI) at Month 18 for vutrisiran compared with external placebo was 0.491 (0.337–0.716 [$p = 0.0004$]) (*Figure 1B*). In the cardiac subpopulation, geometric mean ± SEM NT-proBNP levels decreased from 748.1 ± 163.2 ng/L at baseline to 614.4 ± 154.7 ng/L in the vutrisiran group but increased from 711.1 ± 151.1 ng/L at baseline to 1116.7 ± 320.8 ng/L in the external placebo group at Month 18.

Echocardiographic parameters

Baseline echocardiographic parameters were generally similar between the vutrisiran and external placebo groups in the mITT population, although LV mass and LV end-diastolic volume were numerically lower in the vutrisiran mITT population compared with the external placebo mITT population (*Table 1*).

In the mITT population at Month 18, vutrisiran demonstrated nominally significant benefits in cardiac output, LV end-diastolic volume, and LV stroke volume compared with external placebo,

Table 1 Baseline patient demographics and clinical characteristics for the modified intent-to-treat population and cardiac subpopulation

	APOLLO mITT population placebo ($n = 77$)	HELIOS-A mITT population vutrisiran ($n = 122$)	APOLLO cardiac subpopulation placebo ($n = 36$)	HELIOS-A cardiac subpopulation vutrisiran ($n = 40$)
Age, years, median (range)	63 (34–80)	60 (26–85)	62.0 (43–80)	63.5 (26–81)
Male sex, *n* (%)	58 (75.3)	79 (64.8)	30 (83.3)	32 (80.0)
Race, *n* (%)				
White/Caucasian	50 (64.9)	86 (70.5)	16 (44.4)	29 (72.5)
Asian	25 (32.5)	21 (17.2)	18 (50.0)	10 (25.0)
Black or African American	1 (1.3)	4 (3.3)	1 (2.8)	0
Other or unknown[a]	1 (1.3)	11 (9.0)	1 (2.8)	1 (2.5)
Region				
North America	10 (13.0)	27 (22.1)	7 (19.4)	5 (12.5)
Western Europe	36 (46.8)	42 (34.4)	12 (33.3)	12 (30.0)
Rest of the world	31 (40.3)	53 (43.4)	17 (47.2)	23 (57.5)
Time since ATTRv amyloidosis diagnosis, years, median (range)	1.41 (0.0–16.5)	1.94 (0.0–15.3)	1.20 (0.1–8.8)	1.13 (0.0–12.5)
TTR genotype, *n* (%)				
V30M	40 (51.9)	54 (44.3)	12 (33.3)	10 (25.0)
Early-onset V30M (<50 years)	10 (13.0)	25 (20.5)	2 (5.6)	1 (2.5)
Non-V30M[b]	37 (48.1)	68 (55.7)	24 (66.7)	30 (75.0)
PND score, *n* (%)				
I	20 (26.0)	44 (36.1)	7 (19.4)	9 (22.5)
II	23 (29.9)	50 (41.0)	12 (33.3)	16 (40.0)
IIIA	22 (28.6)	16 (13.1)	12 (33.3)	7 (17.5)
IIIB	11 (14.3)	12 (9.8)	5 (13.9)	8 (20.0)
IV	1 (1.3)	0	0	0
NIS, *n* (%)				
<50	35 (45.5)	78 (63.9)	12 (33.3)	19 (47.5)
≥50–<100	33 (42.9)	39 (32.0)	18 (50.0)	19 (47.5)
≥100	9 (11.7)	5 (4.1)	6 (16.7)	2 (5.0)
Previous tetramer stabilizer use, *n* (%)				
Tafamidis	27 (35.1)	53 (43.4)	9 (25.0)	17 (42.5)
Diflunisal	14 (18.2)	22 (18.0)	8 (22.2)	8 (20.0)
Cardiac implanted devices, *n* (%)				
Pacemaker	19 (24.7)	9 (7.4)	9 (25.0)	2 (5.0)
Defibrillator	0	2 (1.6)	0	1 (2.5)
Medical history, *n* (%)				
Supraventricular arrhythmias	14 (18.2)	12 (9.8)	6 (16.7)	5 (12.5)
Atrial fibrillation	6 (7.8)	5 (4.1)	3 (8.3)	3 (7.5)
Baseline treatment, *n* (%)				
β-blockers[c]	16 (20.8)	21 (17.2)	2 (5.6)	9 (22.5)
ACE inhibitors[d]	14 (18.2)	14 (11.5)	0	3 (7.5)
Furosemide	29 (37.7)	19 (15.6)	7 (19.4)	14 (35.0)
Spironolactone	5 (6.5)	9 (7.4)	2 (5.6)	4 (10.0)
Hydrochlorothiazide[e]	10 (13.0)	6 (4.9)	1 (2.8)	2 (5.0)
Torasemide	2 (2.6)	1 (0.8)	0	0
NYHA class[f], *n* (%)				
No heart failure	N/A	68 (55.7)	N/A	16 (40.0)
I	40 (51.9)	11 (9.0)	16 (44.4)	4 (10.0)
II	36 (46.8)	43 (35.2)	20 (55.6)	20 (50.0)
NT-proBNP[g], 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)
Geometric mean (SEM)	531.3 (86.7)	273.0 (42.2)	711.1 (151.1)	748.1 (163.2)

Table 1 (Continued)

	APOLLO mITT population placebo ($n = 77$)	HELIOS-A mITT population vutrisiran ($n = 122$)	APOLLO cardiac subpopulation placebo ($n = 36$)	HELIOS-A cardiac subpopulation vutrisiran ($n = 40$)
Echocardiographic parameters[h]				
LV wall thickness, cm	1.568 (0.297)	1.367 (0.385)	1.639 (0.214)	1.649 (0.291)
LV mass, g	248.256 (78.480)	209.907 (91.749)	264.518 (77.709)	269.417 (87.863)
Global longitudinal strain, %	−16.308 (3.722)	−15.788 (4.024)	−15.661 (3.513)	−14.190 (3.925)
Cardiac output, L/min	4.171 (1.345)	3.861 (1.052)	3.918 (1.149)	3.837 (1.080)
LV end-diastolic volume, mL	90.396 (25.691)	83.644 (22.857)	84.899 (23.082)	84.179 (23.296)
LV stroke volume, mL	56.619 (18.386)	51.976 (14.190)	52.269 (14.385)	51.213 (14.033)
LV relative wall thickness	0.790 (0.175)	0.681 (0.247)	0.825 (0.116)	0.842 (0.203)
LV ejection fraction, %	62.660 (9.785)	62.946 (9.024)	62.208 (8.607)	61.951 (10.443)
Interventricular septum thickness, cm	1.599 (0.309)	1.403 (0.386)	1.666 (0.224)	1.678 (0.293)
Posterior wall thickness, cm	1.536 (0.293)	1.331 (0.411)	1.613 (0.212)	1.619 (0.322)

ACE, angiotensin-converting enzyme; ATTRv, hereditary transthyretin (v for variant); eCRF, electronic case report form; LV, left ventricular; mITT, modified intent-to-treat; N/A, not available; NIS, Neuropathy Impairment Score; NT-proBNP, *N*-terminal prohormone of brain-type natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; Q, quartile; SD, standard deviation; SEM, standard error of the mean; *TTR*, transthyretin.

[a]Unknown: mITT placebo $n = 1$ (1.3%); cardiac subpopulation placebo $n = 1$ (2.8%); other: mITT vutrisiran $n = 11$ (9.0%), including 1 patient (0.8%) of more than one race; cardiac subpopulation vutrisiran $n = 1$ (2.5%).

[b]In the HELIOS-A study, the non-V30M *TTR* genotype represents 15 different variants in the cardiac subpopulation and 21 different variants in the total mITT population.

[c]Data include patients receiving selective or non-selective β-blockers.

[d]Data include patients receiving an ACE inhibitor alone or in combination.

[e]Data include patients receiving hydrochlorothiazide alone or in combination.

[f]NYHA class of 'no heart failure' was not included in the APOLLO eCRFs. NYHA class missing for 1 patient (1.3%) in the APOLLO placebo mITT population.

[g]NT-proBNP missing for 2 patients (2.6%) in the APOLLO placebo mITT population and 2 patients (5.6%) in the APOLLO placebo cardiac subpopulation.

[h]All echocardiographic parameter data are mean (SD).

with least squares (LS) mean difference (standard error [SE]) of 0.587 (0.130) L/min ($p = 1.144 \times 10^{-5}$), 10.489 (2.485) mL ($p = 4.021 \times 10^{-5}$), and 7.837 (1.670) mL (5.754×10^{-6}), respectively. A non-significant trend towards benefit was observed in all other prespecified echocardiographic parameters (mean LV wall thickness, LV mass, and global longitudinal strain) (*Figure 2*).

In the cardiac subpopulation, baseline echocardiographic parameters were also generally similar between the vutrisiran and external placebo groups. At Month 18, vutrisiran demonstrated a nominally significant benefit in cardiac output and LV stroke volume compared with external placebo (LS mean difference [SE], 0.407 [0.196] L/min [$p = 0.0426$] and 7.212 [2.906] mL [$p = 0.0160$], respectively). A non-significant trend towards benefit was observed in all other prespecified echocardiographic parameters (*Figure 3*).

^{99m}Tc scintigraphy parameters

Of the 64 vutrisiran-treated patients who underwent ^{99m}Tc scintigraphy at baseline (online supplementary *Figure S2*), 47 had evaluable data for normalized LV total uptake at baseline and Month 18 (*Figure 4A*); of these, 25 were Perugini grade ≥2 at baseline (*Figure 4B*). Evaluable data for H/CL ratio at both time points were available for 48 patients (*Figure 4A*), of whom 26 were Perugini grade ≥2 at baseline (*Figure 4B*). Among these evaluable patients, 32 (68.1%) and 31 (64.6%) demonstrated reduction in cardiac ^{99m}Tc uptake compared with baseline in normalized LV total uptake and H/CL ratio, respectively (*Figure 4*). The mean (SE) normalized LV uptake decreased from 0.027 (0.004) at baseline to 0.015 (0.002) at Month 18, corresponding to a mean (SE) change of −11.4% (8.0). The mean (SE) H/CL ratio decreased from 6.200 (0.875) at baseline to 3.393 (0.424) at Month 18, corresponding to a mean (SE) change of −14.3% (7.8). Among patients with Perugini grade ≥2 at baseline and evaluable data at Month 18, 25 (100.0%) and 20 (76.9%) demonstrated reduction in normalized LV total uptake and H/CL ratio, respectively. In this subset of patients, mean (SE) values for normalized LV uptake decreased from 0.046 (0.005) at baseline to 0.024 (0.002) at Month 18 (mean [SE] change of −41.6% [4.7]), and for H/CL ratio decreased from 10.028 (1.173) at baseline to 5.474 (0.587) at Month 18, (mean [SE] change of −33.8% [8.6]).

In the ^{99m}Tc scintigraphy population at baseline, Perugini grade 0, 1, 2, and 3 was observed in 27 (42.2%), 2 (3.1%), 3 (4.7%), and 32 (50.0%) patients, respectively (online supplementary *Figure S2*). Of these 64 patients, 57 (89.1%) also had evaluable data for Perugini grading at Month 18, of which 55 (96.5%) were unchanged ($n = 39$, 68.4%) or demonstrated a reduction of ≥1 Perugini grade ($n = 16$, 28.1%) at Month 18 compared with baseline (*Figure 5*). Among 30 vutrisiran-treated patients with Perugini grade ≥2 at baseline and evaluable Month 18 ^{99m}Tc scintigraphy data, 15 (50.0%) patients experienced a reduction of ≥1 Perugini grade, and the remaining 15 (50.0%) were unchanged at Month 18. Of note, 28 (93.3%) of these patients had Perugini grade 3 at baseline and were therefore unable to increase in grade by definition (*Figure 5*). Baseline and Month 18 ^{99m}Tc scintigraphy coronal imaging for a vutrisiran-treated patient are shown in *Figure 6* for demonstration.

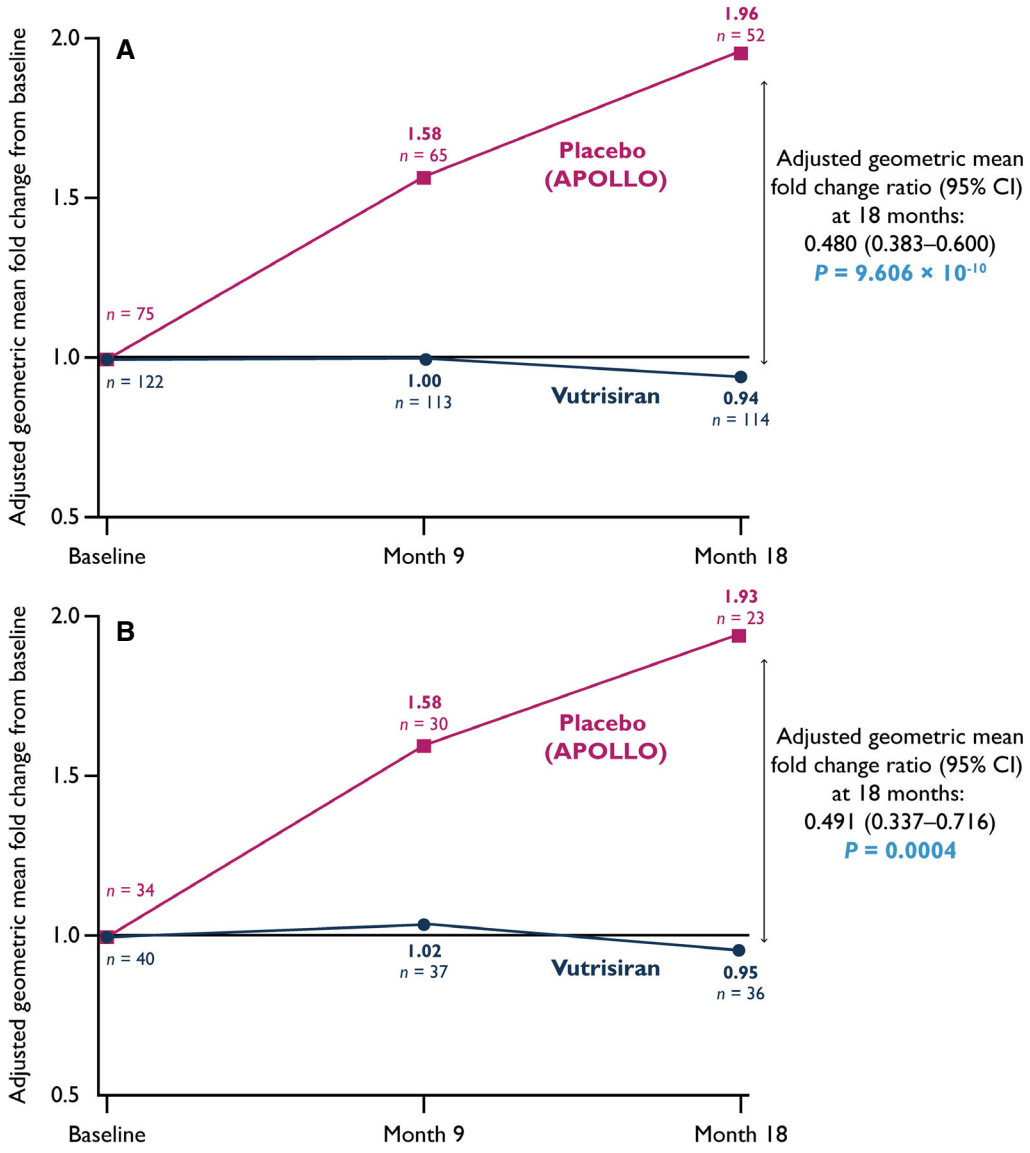


Figure 1 Adjusted geometric mean fold change from baseline in *N*-terminal prohormone of brain-type natriuretic peptide (NT-proBNP) levels over time in the modified intent-to-treat population (*A*) and the cardiac subpopulation (*B*). NT-proBNP results shown at Month 9 and Month 18 are mixed model for repeated measures model data. Number of evaluable patients at each time point are shown. CI, confidence interval.

Safety

Overall safety data from HELIOS-A have been previously reported.[18] During the 18 months of the study, vutrisiran demonstrated an acceptable safety profile. Three (2.5%) patients in the vutrisiran group experienced AEs leading to study discontinuation (one event each of acute cardiac failure, COVID-19 pneumonia, and iliac artery occlusion). Two (1.6%) of these events (COVID-19 pneumonia and iliac artery occlusion) were fatal. None were considered related to vutrisiran.

A detailed evaluation of cardiac events was performed in the mITT population. Cardiac AEs (30.3% vs. 36.4%) and cardiac SAEs (9.0% vs. 13.0%) occurred in similar proportions of patients in the vutrisiran and external placebo groups, respectively (*Table* 2). The majority of cardiac AEs in the vutrisiran group were mild or moderate in severity, and no cardiac AEs were considered related to vutrisiran. In the vutrisiran group, cardiac arrhythmia AEs occurred in 24.6% of patients, with supraventricular arrhythmias and cardiac conduction disorder being most common. Cardiac failure AEs were reported in 5.7% of patients. Similar or higher incidences were observed in the external placebo group.

In the cardiac subpopulation, incidences of cardiac AEs (37.5% vs. 36.1%) and cardiac SAEs (15.0% vs. 11.1%) were similar in vutrisiran and external placebo groups, respectively (*Table* 2).

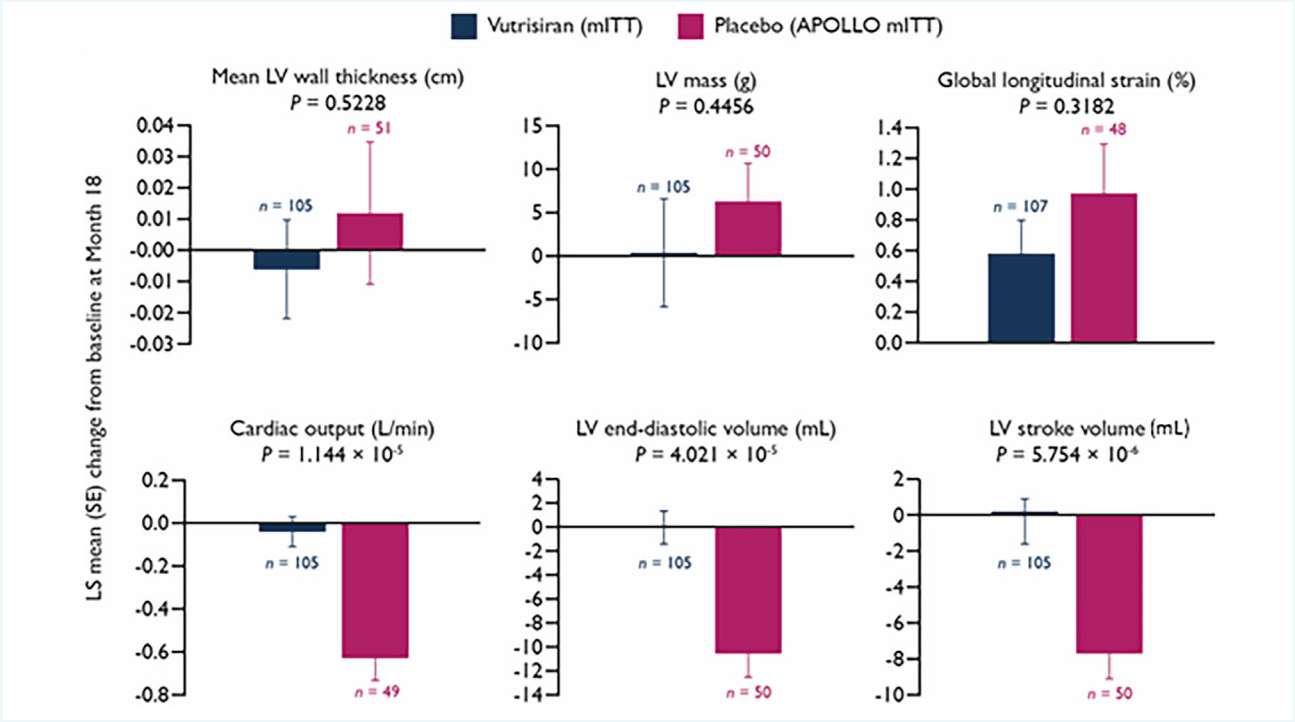


Figure 2 Least squares (LS) mean change from baseline at Month 18 for prespecified echocardiographic parameters and left ventricular (LV) stroke volume in the modified intent-to-treat (mITT) population. SE, standard error.

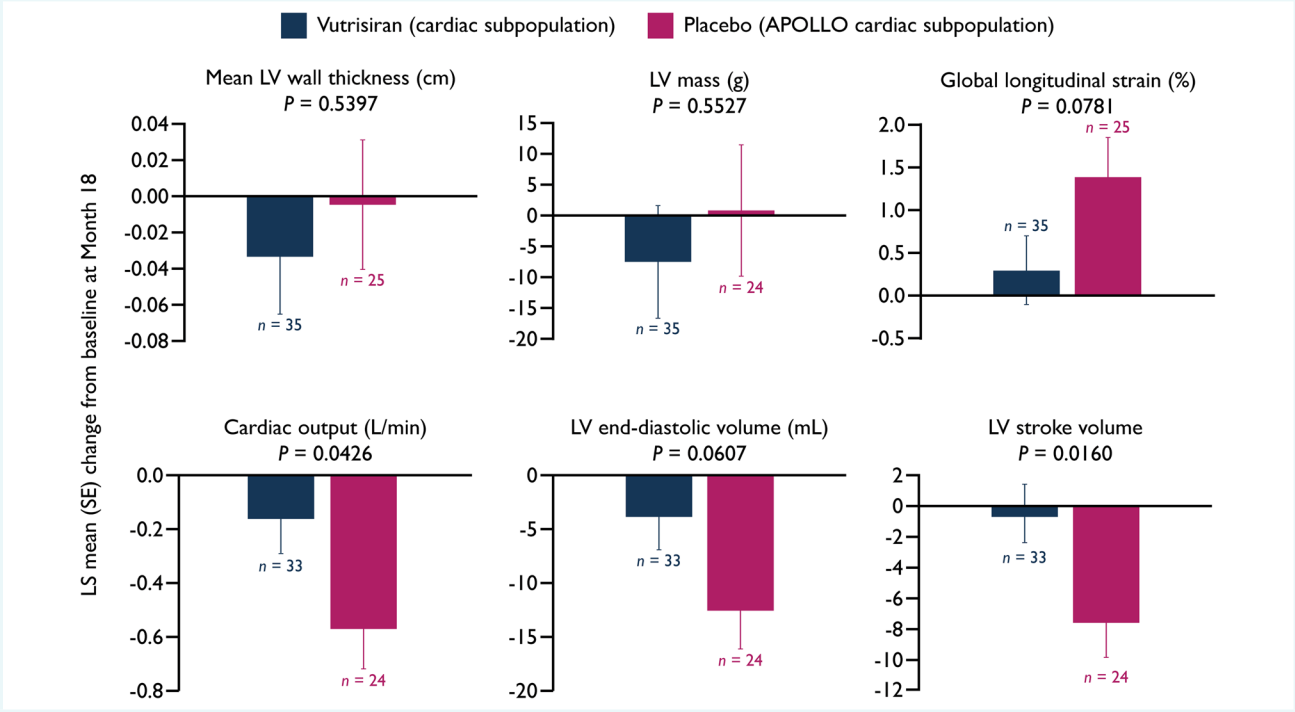


Figure 3 Least squares (LS) mean change from baseline at Month 18 for prespecified echocardiographic parameters and left ventricular (LV) stroke volume in the cardiac subpopulation. SE, standard error.

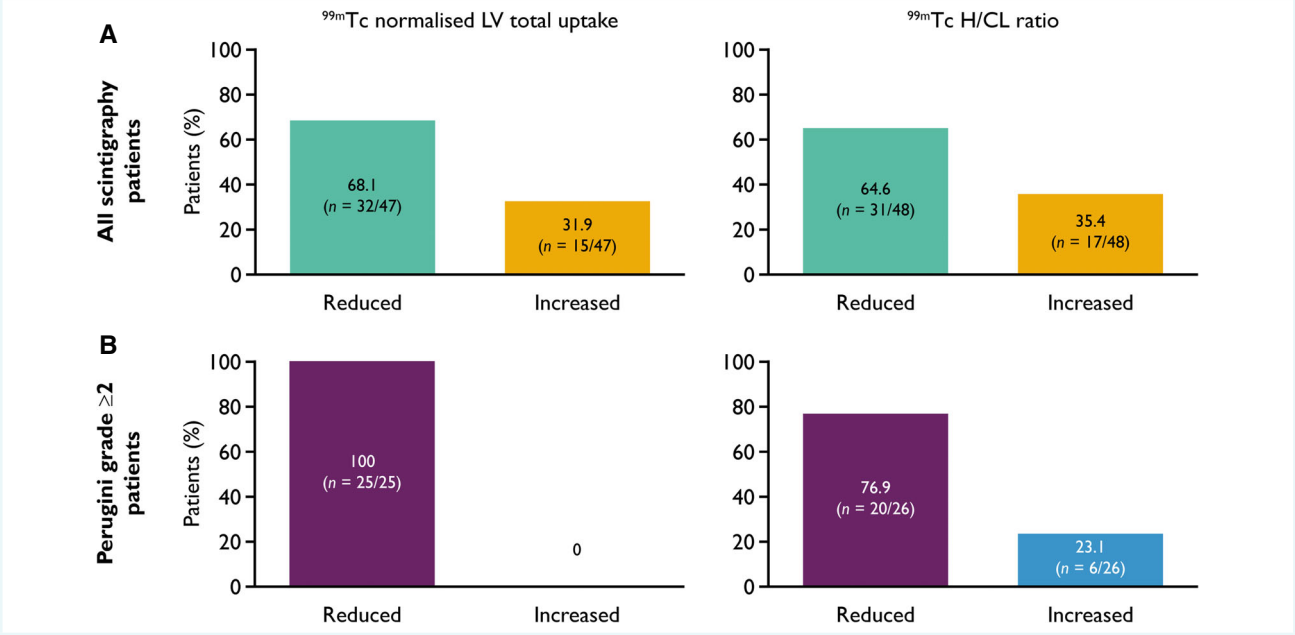


Figure 4 Proportion of vutrisiran-treated patients in a planned ^{99m}Tc scintigraphy cohort with reduction or increase from baseline at Month 18 in normalized left ventricular (LV) total uptake and heart-to-contralateral lung (H/CL) ratio in all vutrisiran-treated patients undergoing ^{99m}Tc scintigraphy (*A*) and those with Perugini grade ≥2 at baseline (*B*). Analysis includes patients from a planned cohort of the modified intent-to-treat population with evaluable data at baseline and Month 18. 'Reduced' refers to a negative change (<0 increase) from baseline to Month 18 in the chosen measure and 'increased' refers to a >0 increase from baseline.

Cardiac arrhythmia AEs and cardiac failure AEs occurred in 32.5% and 12.5% of vutrisiran-treated patients, respectively, compared with incidences of 30.6% and 5.6% in the external placebo group.

Cardiac safety data for patisiran-treated patients in the mITT and cardiac subpopulations of HELIOS-A are shown in online supplementary *Table S3*.

Discussion

In this exploratory analysis from the HELIOS-A study in patients with ATTRv amyloidosis with polyneuropathy, vutrisiran treatment was associated with a beneficial impact on NT-proBNP levels and either a nominally significant benefit or a trend towards benefit on prespecified echocardiographic parameters compared with external placebo in both the mITT population and cardiac subpopulation after 18 months. Furthermore, in a planned subgroup of patients who underwent ^{99m}Tc scintigraphy imaging and had evaluable data, a majority of patients demonstrated reduced cardiac ^{99m}Tc uptake compared with baseline. Vutrisiran was generally well tolerated; no cardiac safety signals were observed, and the majority of cardiac AEs were mild or moderate, with none deemed related to treatment.

The beneficial treatment effect on NT-proBNP with vutrisiran compared with external placebo was observed as early as Month 9 in both the mITT population and the cardiac subpopulation, continuing up to Month 18 and reaching nominal significance in both populations, suggesting that this sensitive biomarker may be an early indicator of the effect of TTR-lowering RNAi therapeutics on cardiac function. Indeed, levels of this biomarker are known to increase progressively over the disease course,[30,31] have been

Perugini grade at baseline, *n* (%)	Perugini grade at Month 18, *n* (%)			
	0	1	2	3
0	24 (42.1)	1 (1.8)	0	0
1	1 (1.8)	0	1 (1.8)	0
2	0	0	2 (3.5)	0
3	2 (3.5)	3 (5.3)	10 (17.5)	13 (22.8)

Reduced (*n* = 16) No change (*n* = 39) Increased (*n* = 2)

Figure 5 Change from baseline in Perugini grade at Month 18 in patients receiving vutrisiran undergoing ^{99m}Tc scintigraphy. Analysis includes patients from the modified intent-to-treat population with evaluable data at baseline and Month 18 ($n = 57$). Perugini grade is a 0–3 scale, where 0 represents no cardiac uptake of the radiotracer and normal bone uptake, 1 represents cardiac uptake that is less than bone uptake, 2 represents cardiac uptake with a similar intensity to bone uptake, and 3 represents cardiac uptake with attenuated or absent bone uptake.

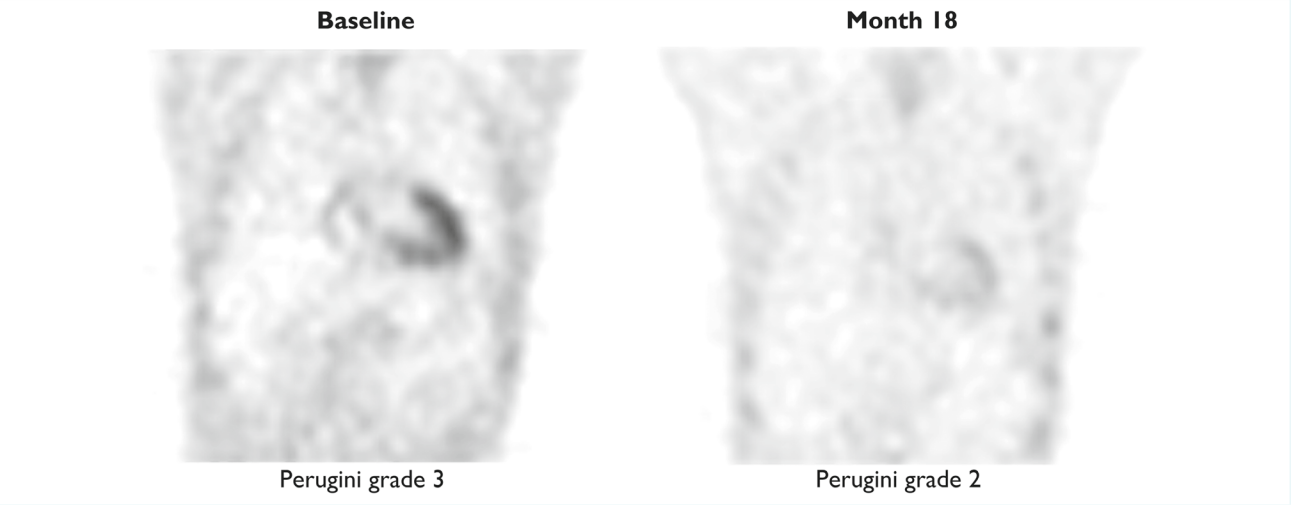


Figure 6 Coronal images of the chest illustrating a reduction of one Perugini grade, from grade 3 at baseline to grade 2 at Month 18 following treatment with vutrisiran.

Table 2 Cardiac safety events with vutrisiran in the modified intent-to-treat population and cardiac subpopulation

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

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; mITT, modified intent-to-treat.
Cardiac AEs included acute myocardial infarction, angina pectoris, arrhythmia, atrial fibrillation, atrial flutter, atrial thrombosis, atrioventricular block, complete atrioventricular block, first-degree atrioventricular block, second-degree atrioventricular block, bradycardia, left bundle branch block, right bundle branch block, cardiac amyloidosis, cardiac failure, acute cardiac failure, chronic cardiac failure, congestive cardiac failure, conduction disorder, intraventricular conduction defect, myocardial ischemia, palpitations, pericarditis, sinus node dysfunction, supraventricular extrasystoles, supraventricular tachycardia, tachyarrhythmia, tachycardia, paroxysmal tachycardia, trifascicular block, ventricular extrasystoles, and ventricular tachycardia. Cardiac serious AEs included acute myocardial infarction, atrial fibrillation, atrioventricular block, complete atrioventricular block, second-degree atrioventricular block, bradycardia, cardiac failure, acute cardiac failure, chronic cardiac failure, congestive cardiac failure, conduction disorder, myocardial ischemia, pericarditis, sinus node dysfunction, and ventricular tachycardia. Supraventricular arrhythmias included atrial fibrillation, atrial flutter, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, and supraventricular tachycardia. Cardiac conduction disorders included atrioventricular block, complete atrioventricular block, first-degree atrioventricular block, second-degree atrioventricular block, left bundle branch block, right bundle branch block, conduction disorder, intraventricular conduction defect, and trifascicular block. Ventricular arrhythmias and cardiac arrest included cardiac arrest, cardiorespiratory arrest, ventricular extrasystoles, and ventricular tachycardia. Rate and rhythm disorders included arrythmia, bradycardia, tachyarrhythmia, tachycardia, and paroxysmal tachycardia. Cardiac failure AEs included cardiac failure, congestive cardiac failure, acute cardiac failure, chronic cardiac failure, acute pulmonary oedema, cardiogenic shock, and pulmonary oedema.
[a]System organ class based on MedDRA.
[b]High-level group term.
[c]Standard MedDRA query, narrow scope term only.

shown to predict event-free survival and mortality risk in ATTR amyloidosis,[32–34] and are included in staging systems and consensus statements on assessing disease progression,[34–36] thus supporting the clinical significance of the observed treatment effect on NT-proBNP levels. Importantly, a similar beneficial treatment effect was observed across all baseline NT-proBNP quartiles, illustrating the potential impact of vutrisiran across the spectrum of ATTRv amyloidosis cardiac disease severity. In the placebo group, NT-proBNP levels worsened across baseline quartiles, as expected based on the aggressive natural history of this disease, and this suggests substantial cardiac disease progression in the absence of effective therapy.[9]

Nominally significant or trends towards benefit with vutrisiran treatment compared with external placebo were observed for all prespecified echocardiographic parameters in the mITT population and cardiac subpopulation by Month 18, also indicating the possibility that vutrisiran may have a beneficial effect on important measures of cardiac structure and function in patients with ATTRv amyloidosis. The observed trends in echocardiographic parameters are notable, as a worsening in echocardiographic parameters, including wall thickness and global longitudinal strain, are included in criteria for clinically significant ATTRv amyloidosis disease progression.[36,37] Further, parameters such as LV stroke volume and global longitudinal strain are known to be associated with mortality,[22,38] with the latter also being associated with amyloid burden in this patient population.[39]

To further explore a potential effect of TTR-lowering RNAi therapeutics on cardiac disease in patients with ATTRv amyloidosis, scintigraphy imaging was undertaken in a planned cohort of patients from the HELIOS-A mITT population. While a reduction in cardiac uptake of ^{99m}Tc (as demonstrated by normalized LV total uptake and H/CL ratio) compared with baseline was observed at Month 18 in the majority of evaluable scintigraphy patients treated with vutrisiran, the observation was particularly evident in patients with evidence of more substantial cardiac involvement, as indicated by a Perugini grade ≥2 at baseline. Moreover, following 18 months of vutrisiran treatment, just over a quarter of evaluable scintigraphy patients exhibited a reduction in Perugini grade compared with baseline, with some patients demonstrating a reduction of ≥2 Perugini grades and ending below the standard threshold grade for potential diagnosis of ATTR amyloidosis with cardiomyopathy. While these data may indicate regression of cardiac amyloid, the mechanism of ^{99m}Tc uptake in cardiac amyloid is currently unknown, and reduced ^{99m}Tc uptake may not be directly associated with clearance of amyloid deposits. Further placebo-controlled studies are needed to understand the clinical significance of this observation.[40] Nevertheless, it is of interest that these findings have not been observed in the absence of disease-modifying therapy.[12] These results add to previously reported observations in patisiran-treated patients, which include reduction in extracellular volume in patients with ATTRv amyloidosis with cardiomyopathy, beneficial effects on cardiac structure and function compared with placebo in patients with ATTRv amyloidosis with evidence of cardiac involvement (APOLLO),[29,41,42] and positive results on a range of cardiac-relevant endpoints compared with placebo at Month 12 in patients with ATTR amyloidosis with cardiomyopathy (APOLLO-B).[16] Taken together, these data suggest that TTR-lowering RNAi therapeutics could potentially lead to regression of cardiac amyloid and subsequent clinical benefit, and serve as an encouraging basis for future longitudinal studies.

Importantly, vutrisiran also demonstrated an acceptable safety profile, with no drug-related discontinuations, deaths, or cardiac safety signals. The cardiac efficacy and safety of vutrisiran, including its impact on long-term outcomes, is being investigated in the Phase 3 HELIOS-B study (NCT04153149) in patients with ATTR amyloidosis with cardiomyopathy.

Study limitations include the use of an external placebo control. This was chosen to enable an efficient study design in a disease space with multiple approved therapies, ensuring that all patients could receive active treatment, in agreement with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E10 and European Medicines Agency guidance on control groups and small populations in clinical studies.[43,44] While some differences in baseline characteristics were observed between the vutrisiran and external placebo groups in HELIOS-A, they were widely overlapping and were considered clinically comparable.[45] Like APOLLO, HELIOS-A included a wide range of disease severity, but excluded patients with NYHA Class III or IV status at baseline. Consequently, the treatment effect in this subgroup needs further study. It is important to note that the post hoc analysis of patients with different quartiles of baseline NT-proBNP levels demonstrated a consistent benefit of vutrisiran compared with external placebo across patients with different disease severities.

It should also be noted that the cardiac assessments were exploratory endpoints in HELIOS-A, although the beneficial effects of vutrisiran reported here are consistent with those previously reported from the primary and secondary endpoints of the study.[30] A further limitation is the definition of the cardiac subpopulation, as it is likely that some patients who did not qualify for this predefined subpopulation had cardiac involvement. Consequently, the effectiveness of vutrisiran in all patients with cardiac involvement may not have been completely captured by this analysis of the cardiac subpopulation. Importantly however, vutrisiran also demonstrated consistent beneficial effects in the mITT population.

In conclusion, the totality of assessments in this exploratory analysis of the HELIOS-A study provides evidence of potential benefit of vutrisiran on cardiac manifestations in patients with ATTRv amyloidosis with polyneuropathy. In combination with data from the clinical studies of patisiran, the data reported here support the potential utility of TTR-lowering RNAi therapeutics in the treatment of patients with ATTR amyloidosis with cardiomyopathy.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

The authors would like to thank the patients and their families for their participation in the HELIOS-A study. The authors would also like to thank the additional members of the HELIOS-A Collaborators group for their work on the study: Jonas Wixner, Rolf Backlund, Björn Pilebro, Intissar Anan, Fredrik Edbom, Anna Ekman, Sandra Arvidsson, Ulrika Englund, Karin Söderberg, Erik Nordh, Erica Uneus, Kristin Samuelsson, Anna Nilzen, Rayomand Press, Mirjam Bilecen, Teresa Coelho, Marta Novais, Patricia Rodrigues, Ana Martins da Silva, Inês Cardoso, Carla Rodrigues, Joana Ramalho, Helder Martins, Mónica Silva, Nádia Guimaraes, Javier Perez, Antonio Hipólito Reis, Julia Monte, Natalia Ferreira, Cristina Alves, Marcio Cardoso, Ricardo Teixeira, Filipa Lamas, Miguel Oliveira Santos, Catarina Campos, Conceiçao de

Azevedo Coutinho, José Castro, Isabel Castro, Daniela Silva, Susana Gonçalves, Laura Piera Obici, Eleonora Di Buduo, Claudia Sforzini, Roberta Mussinelli, Vittorio Rosti, Alessandro Lozza, Anna Racchi, Mario Sabatelli, Marco Luigetti, Giulia Bisogni, Angela Romano, Valeria Guglielmino, Andrea Di Paolantonio, Daniela Bernardo, Giuseppe Vita, Anna Mazzeo, Massimo Russo, Davide Pareyson, Daniela Calabrese, Silvia Fenu, Paola Saveri, Hans Nienhuis, Geert Bokhorst, Carlien Roos, Margriet Couperus, Greetje De Jong, Anne Brunger, Gea Drost, Fiete Lange, Adinda Colauto, Márcia Waddington-Cruz, Aline Abreu, Roberto Coury Pedrosa, Renata Gervais de Santa Rosa, Moisés Dias, David Adams, Fetra Rakotondratafika, Andoni Echaniz-Laguna, Cecile Cauquil, Céline Labeyrie, Guillemette Beaudonnet, Yasmine Boubrit, Amina Gaouar, Halima Bourenane, Shahram Attarian, El Khansa Yahia, Annie Verschueren, Aude-Marie Grapperon, Emilien Delmont, Violaine Planté-Bordeneuve, Laetitia Vervoitte, Samar S. Ayache, Philippe Le Corvoisier, Raphaele Arrouasse, Thierry Gendre, Laure Abou Chakra, Cécile Focsénéanu, Caroline Barau, Guilhem Sole, Laurie Belin, Marie Helene Violleau, Fanny Duval-Bontemps, Rami Massie, Xin Dong, Francisco Muñoz-Beamud, Sandra García Garrido, Cristina Borrachero, Alvaro Gragera Martinez, Lucía Galán Dávila, Marta Palacios, Laura M. Vicente, Leopoldo Perez de Isla, Carlos Casasnovas, Carles Díez López, Elena Fabra, José González-Costello, Sonia Guerrero, Sergi Yun Viladomat, Yurema Martinez, Valentina Velez-Santamaria, Velina Nedkova-Hristova, Ariadna Gonzalez Segovia, Fernando De Frutos, Esther Gonzalez-Lopez, Fernando Dominguez, Luis E. Escobar-López, Eva Cabrera-Romero, Paula Sánchez Gismera, María de la Iglesia, Fernando Martinez Valle, Gonzalo Mazuela Aguila, Karen Lorite, Núria Raguer, Pilar Suñé, Pablo Piera, Carlos Ortega, Carla Aguilar, Gisela Gili, Hartmut Schmidt, Christel Langenstroer, Anna Hüsing-Kabar, Iyad Kabar, Matthias Schilling, Frauke Friebel, Phil-Robin Tepasse, Frank Birklein, Monika Firros, Fabiola Escolano-Lozano, Caitlin Brueckner, Vanessa Bahnam, Michelle C. Kaku, K. H. Vincent Lau, Janice Wiesman, Susanna Miller, Janell Frantz, Diane C. Schmidt, Omar AbouEzzeddine, Wayne Miller, Grace Lin, Morie Gertz, Angela Dispenzieri, Thomas Brannagan, Raisy Fayerman, Elizabeth DuVerger, Jorge Cabrera, Christina M. Ulane, Louis H. Weimer, Stephen Tsang, Jeffrey Shije, Nathan Carberry, Sai Si Thu, Dianna Quan, Brianna Blume, J. Scott Overcash, He (Helen) Pu, Kia Lee, Hanh Chu, Karla Zepeda, Michael Waters, Thao Vuong, Derya Coskun, Kimberly Quillin, Allison Davis, Michael Polydefkis, Jing Ye, Xiaoling Li, Mohammad Khoshnoodi, Geno Vista, Tae Hwan Chung, Michele Watt, Dan Tsottles, Ahmad Masri, Dayna Carlson, Brian Drachman, Patricia Divito, Hansie Mathelier, Margaret Shanks, Karen Maslowski, Sami Khella, Janice Pieretti, Senda Ajroud-Driss, Benjamin Joslin, Emma Schmidt, Miriam Freimer, Julie Agriesti, Fabio Barroso, Florencia Picone, Andrea Lautre, Lucas Orellana, Wenqin Du, Joost Felius, Alejandra González-Duarte, Karla Cardenas Soto, Rebecca Traub, Manisha Chopra, Chi-Chao Chao, Chia-Hua Hsu, Li-Kai Tsai, Ming-Jen Lee, Jen-Jen Su, Sung-Tsang Hsieh, Hsueh-Wen Hsueh, Kon-Ping Lin, Hsi-Chieh Chou, Byoung-Joon Kim, Hyesun Kang, Ju-Hong Min, Eun-Seok Jeon, Yeon Hak Chung, Jae Hong Park, Jeeyoung Oh, Hyun Joo Jeong, Ivailo Tournev, Sashka Zhelyazkova, Yohei Misumi, Yumiko Sakamoto, Nami Hashimoto, Yoshimi Misumi, Aya Takahashi, Mitsuharu Ueda, Teruaki Masuda, Akihiko Ueda, Masahisa Katsuno, Kazuki Tajima, Momoko Sumi, Fujiko Hasegawa, Takahiro Okumura, Haruki Koike, Masahiro Iijima, Yuki Fukami, Daisuke Ito, Yoshiyuki Kishimoto, Tomoyuki Kazuta, Katsuhiko Kato, Naohiro Mouri, Soma Furukawa, Ryoji Nishi, Yoshiki Sekijima, Keiko Ito, Nagaaki Kato, Dai Kishida, Hideki Mochizuki, Kaori Okada, Kurumi Ohashi, Kensuke Ikenaka, Masayuki Nakamori, Makoto Kinoshita, Bella Ruth Mapalo, Steven Law, Liza Chacko, Helen Lachmann, Oliver Cohen, Yousuf Siu Kay Razvi, Sindhu Varughese, Ana Martinez-Naharro, Richard Orrell, Marianna Fontana, Lisa Rannigan, Sarah Louth, Eleni Zamba-Papanicolaou, Demetra Charalamnibous, Rana Abu Manneh, Kleopas Kleopa, Theodoros Christodoulides, Savvas Frangos, Michele Galganski-Cleanthous, Eftychia Gaglia, Irene Smoleski, Elena Kkolou, Andry Ploutarchou, Mariana Hanghiuc, Galini Chroidou, Olga Stylianou, Anastasia Krokou, Irene Zannetou, Efstathios Kastritis, Dimitra Papadopoulou, Ilias Spinasas, Panayiotis Bakalis, Nikolaos Kanellias, Despoina Fotiou, Ioanna Dialoupi, Magdalini Migko, Maria Gavriatopoulou, Soon-Chai Low, Mark Taylor, Graeme Stewart, Helen Knight, Steve Vucic, Antonia Carroll, Matthew Silsby, Dan Suan, Simon Gibbs, Carmela Corfield, Suzana Jakicic, Hayden Jina, Stephen Ting, Shi Qin Wong, Peter Mollee, Lynda McKinley, Emad Abro, Dariusz Korczyk, Gauthier Remiche, Nick Alaerts, Fabienne De Veylder, Kristl Claeys, Elisa Debien, Joyce Cremers, Ann D'hondt, and Bram De Wel. In addition, they would like to thank Emre Aldinc, MD, of Alnylam Pharmaceuticals for his contribution to the manuscript content. Medical writing assistance was provided by Olympia Gianfrancesco, PhD, of Adelphi Communications Ltd (Macclesfield, UK), and funded by Alnylam Pharmaceuticals.

Funding

Alnylam Pharmaceuticals sponsored the study, which was designed by the sponsor in collaboration with the principal investigators. Study investigators collected data, which were analysed by the sponsor and interpreted jointly between the sponsor and the authors. All authors participated in the interpretation of the data. The authors who had access to the data vouch for the accuracy and completeness of the data, and all authors vouch for the fidelity of the trial to the protocol. All authors contributed to the critical revision of the manuscript, and all authors confirm that they approve of the data presented in the manuscript.

Conflict of interest: P.G.P. reports speaking fees from Alnylam Pharmaceuticals, Bridgebio, Ionis Pharmaceuticals, and Pfizer; consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, ATTRalus, Bridgebio, Intellia, Neuroimmune, NovoNordisk, and Pfizer; and research/educational support to their institution from Alnylam Pharmaceuticals, Bridgebio, and Pfizer. M.G. reports clinical trials research with Alnylam Pharmaceuticals, Eidos, NovoNordisk, and Pfizer; research grants from Janssen; advisory board and steering committee membership, and consulting fees from Janssen and NovoNordisk (all funds were paid to the Mayo Clinic). P.K. reports consultancy for Alnylam Pharmaceuticals. J.L.B. reports consultancy for AstraZeneca, Corino Therapeutics, Intellia, and Ionis Pharmaceuticals; and research funding from Alnylam Pharmaceuticals, Eidos/BridgeBio, and Ionis Pharmaceuticals. M.S.M. reports grant support from NIH R01HL139671; consulting income from Alnylam Pharmaceuticals, BridgeBio, Intellia, Ionis Pharmaceuticals, NovoNordisk, and Prothena;

and institutional support in the form of clinical trial funding from Alnylam Pharmaceuticals, Attralus, Eidos, Ionis Pharmaceuticals, and Pfizer. I.C. reports speaking fees from Alnylam Pharmaceuticals, Ionis Pharmaceuticals, Pfizer, and Sobi; consulting fees from Alnylam Pharmaceuticals and Pfizer; and research/educational support to their institution from Alnylam Pharmaceuticals and Pfizer. M.D.C. reports consulting fees from MedTrace Pharma and Sanofi; an investigator-initiated institutional research grant from Gilead Sciences; in-kind research support from Amgen; and research funding from Alnylam Pharmaceuticals. S.D.S. reports research funding from Alnylam Pharmaceuticals, AstraZeneca, Bayer, Bellerophon, BMS, Cytokinetics, Eidos, GSK, Ionis Pharmaceuticals, Lilly, MyoKardia, NIH/NHLBI, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI; and consulting fees from Abbott, Action, Akros, Alnylam Pharmaceuticals, American Regent, Amgen, Anacardio, Arena, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cardiac Dimensions, Cardior, Cardurion, CellProThera, Corvia, Cytokinetics, Daiichi-Sankyo, Dinaqor, GSK, Janssen, Lexicon, Lilly, Merck, Moderna, Myokardia, Novartis, Quantum Genomics, Roche, Sanofi Pasteur, Sarepta, Tenaya, Theracos, Tremeau, and Valo. C.C., E.Y., and J.V. are employed by Alnylam Pharmaceuticals and report ownership of Alnylam Pharmaceuticals shares. J.D.G. reports speaking fees from Alnylam Pharmaceuticals, AstraZeneca, Bridgebio, and Pfizer; consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, ATTRalus, Bridgebio, NovoNordisk, and Pfizer; and research/educational support to his institution from Alnylam Pharmaceuticals.

DATA AVAILABILITY STATEMENT

Anonymised individual participant data that support these results would be made available in a secureaccess environment 12 months after study completion and when the product and indication have been approved for no less than 12 months in the USA and the European Union. Access will be provided contingent upon the approval of a research proposal and the execution of a data sharing agreement. Requests for access to data can be submitted via the website www.vivli.org.

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