Vutrisiran: Cardiac Results from the HELIOS-A Study

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SUMMARY

- HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. The exploratory analyses of the HELIOS-A study included assessments of cardiac measures in the mITT population and a predefined cardiac subpopulation of study participants.[1]
  - In the mITT population and predefined cardiac subpopulation, the geometric mean level of NT-proBNP decreased from baseline at Month 18 for the vutrisiran arm (273.01 to 227.15 ng/L, and 748.07 to 614.37 ng/L, respectively) and increased in the external placebo arm (531.30 to 844.40 ng/L, and 711.10 to 1116.75 ng/L, respectively).[2]
  - In a planned cohort of patients from the mITT population, cardiac uptake of ^{99m}Tc on scintigraphy imaging at Month 18 was reduced from baseline in the majority of evaluable patients treated with vutrisiran, as demonstrated by normalized LV total uptake (68.1%) and H/CL ratio (64.6%).[2]
- Cardiac AEs and cardiac SAEs occurred in similar proportions of patients in the vutrisiran and external placebo arms over the 18-month treatment period. The majority of cardiac AEs in the vutrisiran arm were mild or moderate in severity.[1,2]

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STUDY DESIGN

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at Month 9.[1]

Select exploratory endpoints were[2]:

- The change from baseline in NT-proBNP levels at Month 18
- Predefined echocardiographic parameters (mean LV wall thickness, LV mass, global longitudinal strain, cardiac output, and LV end-diastolic volume) and LV stroke volume at Month 18

- The change from baseline in ^{99m}Tc scintigraphy cardiac parameters (normalized LV total uptake and H/CL ratio) at Month 18 in a planned cohort of patients

A predefined cardiac subpopulation was included for analysis and defined as patients with pre-existing evidence of cardiac amyloid involvement (baseline LV wall thickness ≥1.3 cm and no medical history of aortic valve disease or hypertension).[1]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

A total of 164 patients were randomized (122 in the vutrisiran arm and 42 in the patisiran arm). Patients in HELIOS-A had characteristics that were widely overlapping with patients in the external placebo arm, and the two populations were clinically comparable.[1] Baseline demographics, disease characteristics, and echocardiographic parameters of the mITT and cardiac subpopulations are described in **Table 1**.[2]

Table 1. Baseline Patient Demographics and Disease Characteristics in HELIOS-A.[2]

Characteristic	mITT Population[a]		Cardiac Subpopulation[b]	
	APOLLO	HELIOS-A	APOLLO	HELIOS-A
	Placebo (N=77)	Vutrisiran (N=122)	Placebo (N=36)	Vutrisiran (N=40)
Median age, years (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)
Mean NIS (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)
Median NT-proBNP[c], ng/L (Q1, Q3)	562.8 (235.5, 580.7)	287.4 (67.8, 965.0)	845.7 (373.2, 1581.7)	824.8 (323.3, 1933.0)
NYHA class[d], n (%)				
No heart failure	N/A	68 (55.7)	N/A	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)
Mean echocardiographic parameters (SD)				
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)

Abbreviations: LV = left ventricular; mITT = modified intent-to-treat; N/A = not available; NIS = Neuropathy Impairment Score; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; Q = quartile; SD = standard deviation; TTR = transthyretin.

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

[d]NYHA class data was missing for 1 patient (1.3%) in the APOLLO placebo mITT population. NYHA class of 'no heart failure' was not captured for the APOLLO placebo arm.

RESULTS

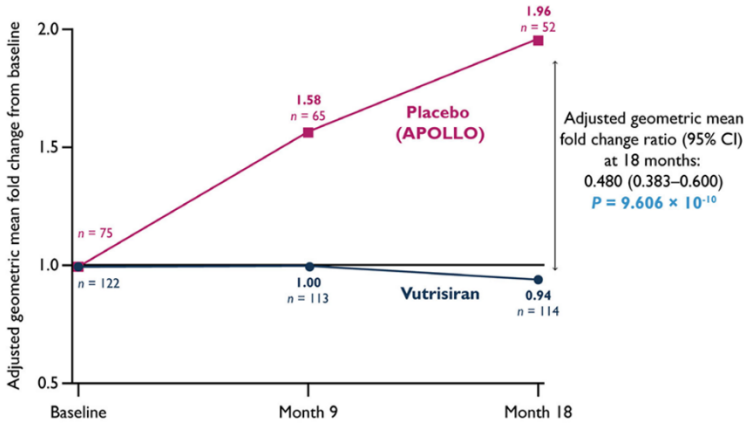
Results at Month 18 in the mITT Population

Overall, vutrisiran treatment led to improvements in certain exploratory cardiac measures, including the change in NT-proBNP levels from baseline to Month 18, compared with external placebo.[2]

Cardiac Stress

In the mITT population, NT-proBNP levels improved from baseline to Month 9 with continued improvement to Month 18 in patients receiving vutrisiran compared with the external placebo arm. The geometric mean NT-proBNP level decreased from baseline to Month 18 with vutrisiran (273.01 to 227.15 ng/L) and increased with external placebo (531.30 to 844.40 ng/L) (**Figure 1**).[2]

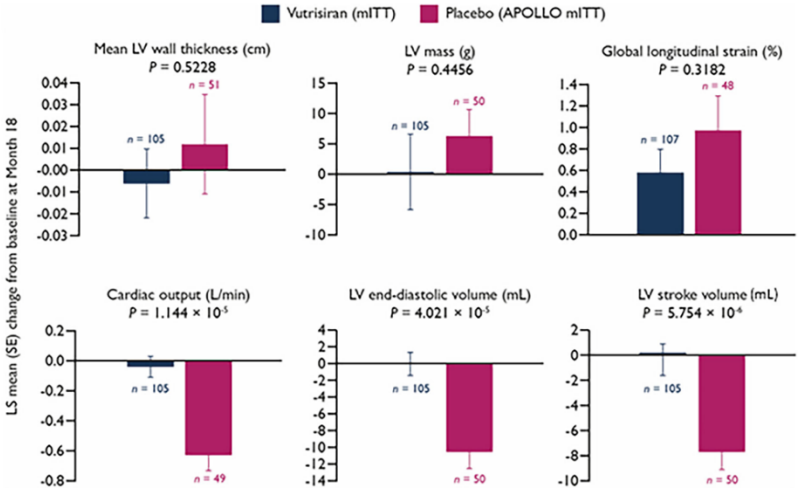
Figure 1. Change from Baseline in NT-proBNP at Month 18 (mITT Population).[2]



Abbreviations: CI = confidence interval; mITT = modified intent-to-treat; NT-proBNP = N-terminal pro-brain natriuretic peptide.
From: Garcia-Pavia et al.[2]

In the mITT population at Month 18, nominally significant benefits in cardiac output, LV end-diastolic volume, and LV stroke volume were observed in the vutrisiran arm compared with external placebo, with LS mean differences (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 ($p = 5.754 \times 10^{-6}$), respectively. A non-significant trend towards benefit was observed in all other predefined echocardiographic parameters as seen in **Figure 2**.[2]

Figure 2. LS Mean Change from Baseline in Predefined Echocardiographic Parameters at Month 18 (mITT Population).[2]

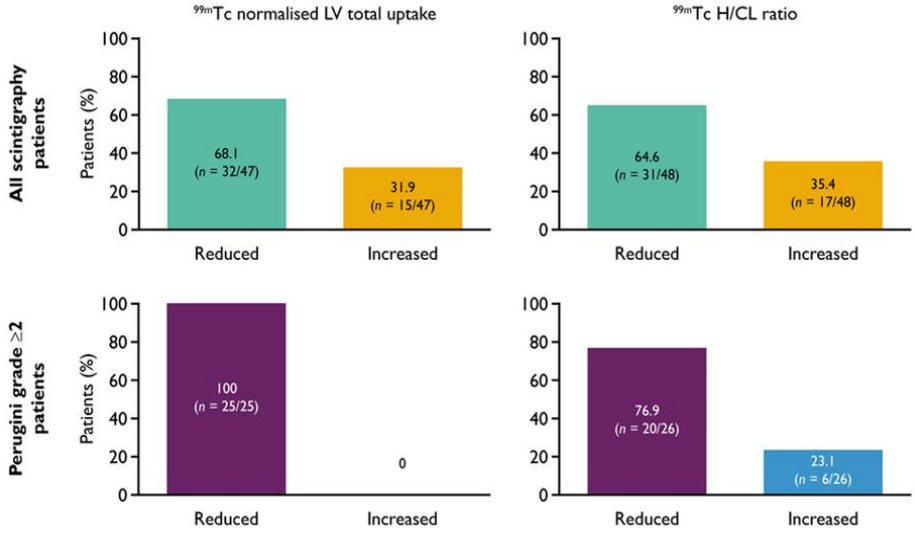


Abbreviations: LS = least squares; LV = left ventricular; mITT = modified intent-to-treat; SE = standard error.
From: Garcia-Pavia et al.[2]

Cardiac Uptake of ^{99m}Technetium on Scintigraphy Imaging

In a planned cohort of patients from the mITT population, cardiac uptake of ^{99m}Tc on scintigraphy imaging (as demonstrated by normalized LV total uptake and H/CL ratio) at Month 18 was reduced from baseline in the majority of evaluable patients following treatment with vutrisiran and particularly in patients with a Perugini grade ≥2 at baseline indicating more substantial cardiac involvement, although the clinical significance of this observation is not yet clear (**Figure 3**).[2]

Figure 3. Quantitative Assessments of Cardiac ^{99m}Tc Uptake at Month 18.[2,a]



Abbreviations: LV = left ventricular; ^{99m}Tc = technetium-99m; H/CL = heart-to-contralateral lung.
[a]Analysis includes patients from mITT population with evaluable data at baseline and Month 18.
From: Garcia-Pavia et al.[2]

Among all evaluable scintigraphy patients (n=57), 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. Five (16%) patients improved by ≥2 Perugini grades (**Table 2**).[2]

Table 2. Change from Baseline in Perugini Grade at Month 18.[2,a]

	Perugini Grade at Month 18, n (%)			
Perugini Grade at Baseline	**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)

[a]Analysis includes patients from mITT population with evaluable data at baseline and Month 18 (n=57).

V122I/T60A Subgroup Analysis

A sub-analysis in patients with the V122I/T60A TTR variants, historically associated with cardiomyopathy, indicated both cardiac and neurologic impairment at baseline. In patients with a V122I or T60A TTR variant, vutrisiran led to improvements on neuropathy (mNIS+7), quality of life (Norfolk QOL-DN), and cardiac stress (NT-proBNP) compared with external placebo at Month 18 similar to that observed in the mITT population (**Table 3**).[3]

Table 3. Select Endpoints in the V122I/T60A Population.[3,a]

Characteristic (Change from baseline at Month 18)	**APOLLO**		**HELIOS-A**	
	Placebo (N=77[b])	**Placebo V122I/T60A (N=5[c])**	**Vutrisiran mITT (N=122[d])**	**Vutrisiran V122I/T60A (N=20[e])**
Mean mNIS+7 change from baseline (SD)	27.9 (22.3)	33.5 (41.2)	0.2 (13.9)	-3.3 (13.6)
Mean Norfolk QOL-DN change from baseline (SD)	20.2 (21.1)	12.3 (18.8)	-2.4 (20.8)	-5.7 (22.3)
Mean NT-proBNP change from baseline (SD)	1310.6 (3318.3)	1419.7 (2135.5)	91.9 (1035.5)	175.0 (943.3)

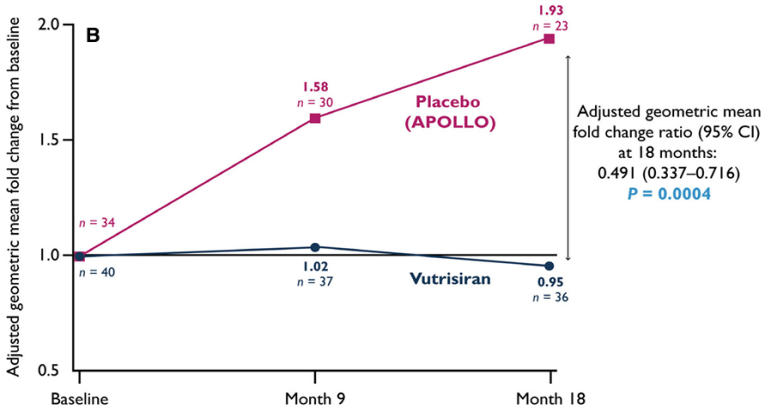
Abbreviations: mITT = modified intent-to-treat; mNIS+7 = modified neuropathy impairment score +7; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP = N-terminal pro-brain natriuretic peptide; SD = standard deviation.
[a]Data are arithmetic mean change from baseline, whereas previously reported data were LS mean changes from baseline for the mITT population. LS mean changes cannot be calculated in this analysis due to small patient numbers.
[b]Number of evaluable patients: mNIS+7, n=51; Norfolk QOL-DN, n=48; NT-proBNP, n=52.
[c]Number of evaluable patients: all measures, n=3.
[d]Number of evaluable patients: mNIS+7, n=112; Norfolk QOL-DN, n=111; NT-proBNP, n=114.
[e]Number of evaluable patients: all measures, n=18.

Results at Month 18 in the Cardiac Subpopulation

Cardiac Stress

In the cardiac subpopulation, NT-proBNP levels improved from baseline to Month 9 with continued improvement to Month 18 in the vutrisiran arm compared with the external placebo arm. The geometric mean NT-proBNP level decreased from baseline to Month 18 with vutrisiran (748.07 to 614.37 ng/L) and increased with external placebo (711.10 to 1116.75 ng/L) (**Figure 4**).[2]

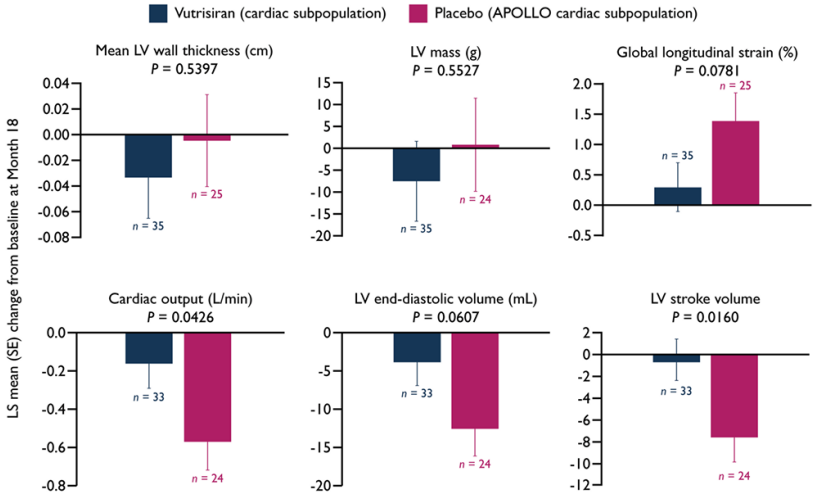
Figure 4. Change from Baseline in NT-proBNP at Month 18 (Cardiac Subpopulation).[2]



Abbreviations: CI = confidence interval; NT-proBNP = N-terminal pro-brain natriuretic peptide.
From: Garcia-Pavia et al.[2]

In the cardiac subpopulation, baseline echocardiographic parameters were also generally similar between the vutrisiran and external placebo arms. At Month 8, a nominally significant benefit in cardiac output and LV stroke volume was observed in patients receiving vutrisiran 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 predefined echocardiographic parameters as seen in **Figure 5**.[2]

Figure 5. LS Mean Change from Baseline in Predefined Echocardiographic Parameters at Month 18 (Cardiac Subpopulation).[2]



Abbreviations: LS = least squares; LV = left ventricular; mITT = modified intent-to-treat; SE = standard error.
From: Garcia-Pavia et al.[2]

SAFETY

Safety Summary at Month 18

AEs were reported in 119 patients (97.5%) in the vutrisiran arm, with the majority of AEs, including cardiac AEs, being mild or moderate in severity during the 18-month treatment period.[1,2]

There were no drug-related discontinuations or deaths. Three patients (2.5%) in the vutrisiran arm discontinued the study due to AEs (2 due to death, 1 due to a non-fatal heart failure event), none of which were considered related to vutrisiran. One death was due to COVID-19 pneumonia, and the other was due

to iliac artery occlusion. Two SAEs (dyslipidemia and urinary tract infection) were deemed related to vutrisiran by the Investigators.[1]

AEs occurring in ≥10% of patients in the vutrisiran arm included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness; all of these AEs, with the exception of arthralgia and pain in extremity, were reported at a similar or lower frequency than in the external placebo arm. Injection-site reactions were reported in 5 patients (4.1%) receiving vutrisiran, all of which were mild and transient. Overall, there were no safety signals regarding liver function tests, hematology, or renal function related to vutrisiran.[1] A summary of cardiac AEs at Month 18 in HELIOS-A is presented in **Table 4**.[2]

Table 4. Cardiac Safety Summary at Month 18 in HELIOS-A.[2]

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

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; mITT = modified intention-to-treat; SAE = serious adverse event.
[a]Based on MedDRA 'Cardiac Disorders' System Organ Class.
[b]High-level group term
[c]Standard MedDRA query, narrow scope term only.

ABBREVIATIONS

^{99m}Tc = technetium-99m; AE = adverse event; CI = confidence interval; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; H/CL = heart-to-contralateral lung; IV = intravenous; LS = least squares; LV= left ventricular; MedDRA = Medical Dictionary for Regulatory Activities; mITT = modified intent to treat; mNIS+7 = modified neuropathy impairment score +7; N/A = not available; 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; Q = quartile; SAE = serious adverse event; SD = standard deviation; SE = standard error; TTR = transthyretin.

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