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 the polyneuropathy of hATTR. Exploratory analyses included cardiac endpoints.[1]
- In the predefined cardiac subpopulation, the geometric mean level of NT-proBNP decreased at Month 18 for the vutrisiran arm and increased in the external placebo arm.[2]
- In a planned cohort of patients, cardiac uptake of ^{99m}Tc on scintigraphy imaging at Month 18 was reduced from baseline in the majority of evaluable patients following treatment with vutrisiran.[2]
- Cardiac AEs and cardiac SAEs occurred in similar proportions of patients in the vutrisiran and external placebo groups over the 18-month treatment period. The majority of cardiac AEs in the vutrisiran group were mild or moderate in severity.[1,2]

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METHODS

Study Overview and Design

HELIOS-A was a Phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with the polyneuropathy of hATTR. 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 (NCT01960348) as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints.[1,3]

- The primary endpoint was the change from baseline in the mNIS+7 at Month 9.
- Select exploratory endpoints included change from baseline over time in NT-proBNP levels, echocardiographic parameters, and change from baseline in technetium scintigraphy cardiac parameters (in a planned cohort of patients) at Month 18.

A prespecified 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 aortic valve disease or hypertension in medical history).[1]

RESULTS

Baseline Demographics and Disease 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 Demographics and Disease Characteristics in HELIOS-A.

Characteristic	APOLLO mITT[a]	HELIOS-A mITT[a]	APOLLO Cardiac Subpopulation[b]	HELIOS-A Cardiac Subpopulation[b]
	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[c] (ng/L), median (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)
Echocardiographic parameters, mean (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 missing for 2 patients (5.6%) in APOLLO placebo cardiac subpopulation and 2 patients (2.6%) in the mITT population.

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

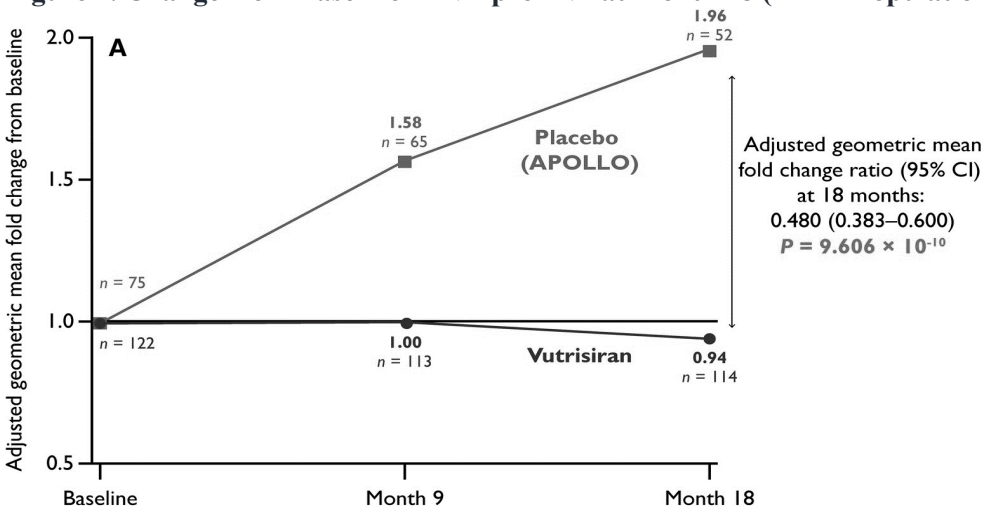
18-Month Results in the mITT Population

Overall, vutrisiran treatment led to improvements in certain exploratory cardiac measures compared with external placebo.[2]

Cardiac Stress

In the mITT population, improvement in NT-proBNP levels at Month 9 with continued improvement to Month 18 was observed in patients receiving vutrisiran compared with the external placebo arm. Geometric mean 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]

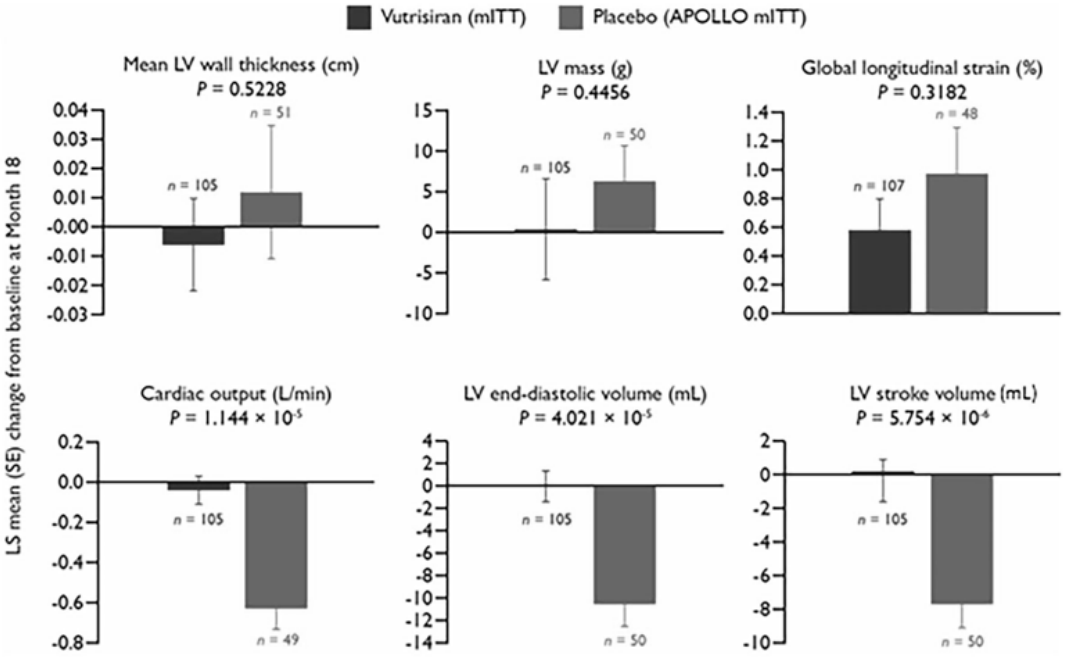
Figure 1. Change from Baseline in NT-proBNP at Month 18 (mITT Population).[2]



Abbreviations: CI=confidence interval; mITT=modified intent-to-treat; NT-proBNP= N-terminal pro-brain natriuretic peptide.

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 difference (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 as seen in **Figure 2**.[2]

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

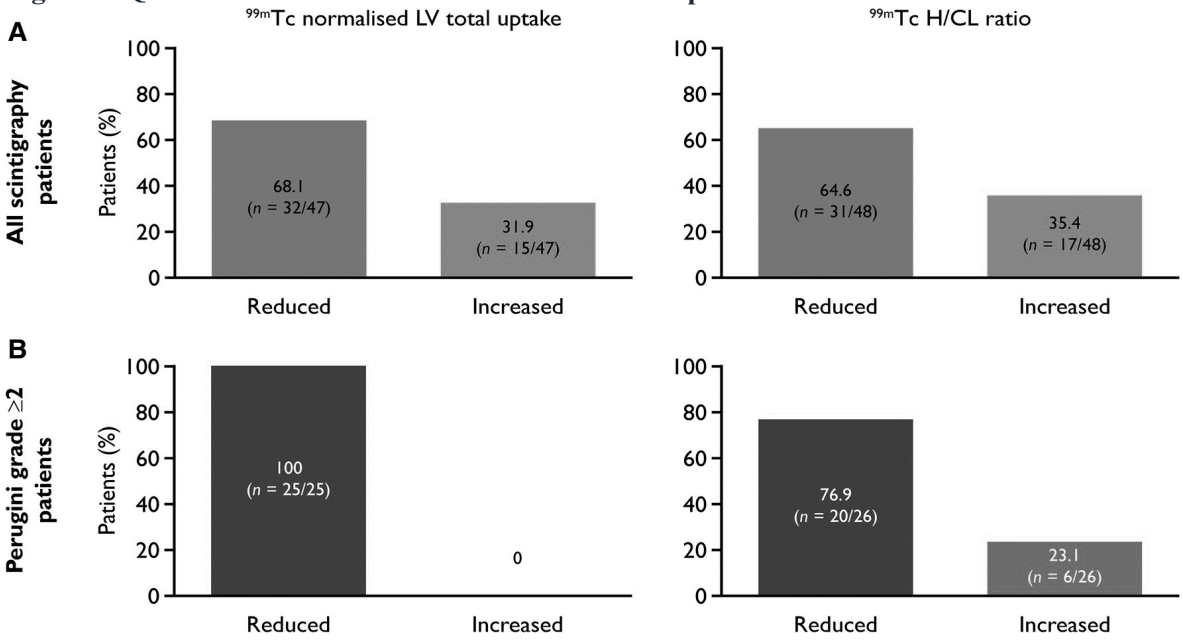


Abbreviations: LS=least squares; LV= left ventricular; mITT=modified intent-to-treat; SE=standard error.

Cardiac Uptake of ^{99m}Technetium on Scintigraphy

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 following treatment with vutrisiran (**Figure 3**), although the clinical significance of this observation is not yet clear.[2]

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



Abbreviations: LV=left ventricular; Tc=technetium; H/CL=heart-to-contralateral lung.
[a]Analysis includes patients from mITT population with evaluable data at baseline and Month 18.

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 had a beneficial effect 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**).[4]

Table 3. Select Endpoints in the V122I/T60A Population.[4,a]

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

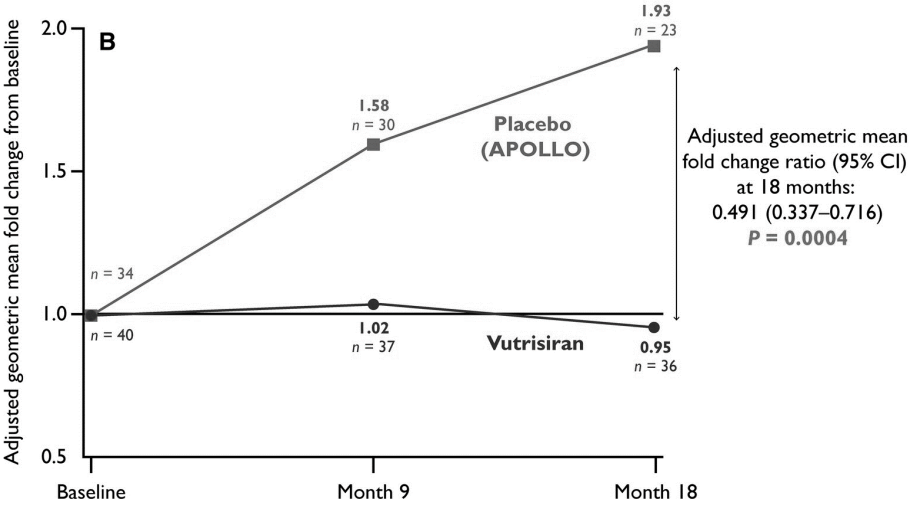
Abbreviations: mITT=modified intent-to-treat; mNIS+7= modified neuropathy impairment score +7; Norfolk QOL-DN= Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP=N-terminal pro-brain natriuretic peptide; SD=standard deviation.
[a]Data are arithmetic mean change from baseline, whereas previously reported 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.

18-Month Results in the Cardiac Subpopulation

Cardiac Stress

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

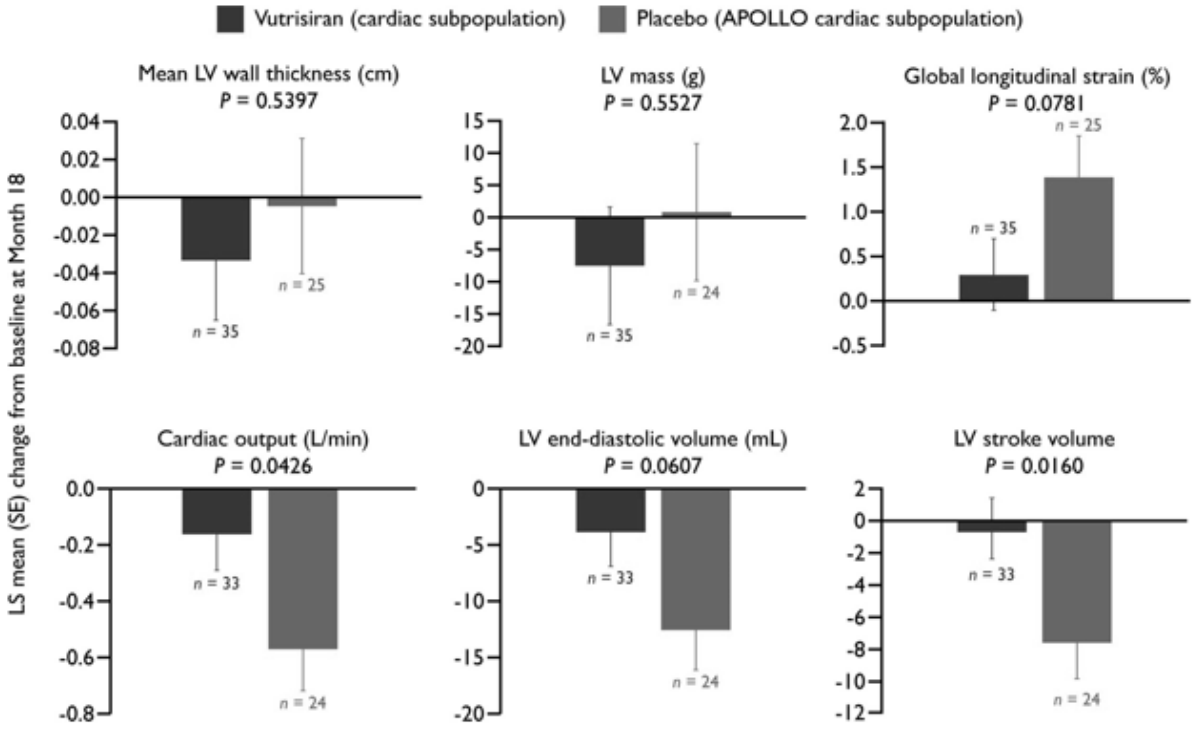
Figure 4. Change from Baseline in NT-proBNP at Month 18 (Cardiac Subpopulation).[2]



Abbreviations: CI=confidence interval; NT-proBNP=N-terminal pro-brain natriuretic peptide.

In the cardiac subpopulation, baseline echocardiographic parameters were also generally similar between the vutrisiran and external placebo groups. 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 prespecified echocardiographic parameters as seen in **Figure 5**.[2]

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



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

SAFETY

18-Month Safety Summary

Vutrisiran demonstrated an acceptable safety profile, 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 serious adverse events (dyslipidemia and urinary tract infection) were deemed related to vutrisiran by the Investigators.[1]

Adverse events 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 cardiac safety summary of HELIOS-A at 18 months is presented in **Table 4**.[2]

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

	APOLLO mITT	HELIOS-A mITT	APOLLO Cardiac Subpopulation	HELIOS-A Cardiac Subpopulation
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

AE = adverse event;; CI = hereditary transthyretin-mediated amyloidosis; hATTR = hereditary transthyretin amyloidosis; 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; 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 ; SD = standard deviation; SE = standard error; Tc = technetium; TTR = tranthyretin.

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