Patisiran: Cardiac Results from the APOLLO Study

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SUMMARY

- APOLLO was a multicenter, international, randomized, double-blind, placebo-controlled, Phase 3 study designed to assess the efficacy and safety of patisiran in patients with the polyneuropathy of hATTR.[1]
- The effect of patisiran on exploratory endpoints reflecting cardiac structure and function was evaluated in a pre-specified subpopulation of APOLLO patients, which included patients with a baseline LV wall thickness of ≥13 mm in the absence of a history of aortic valve disease or hypertension.[2]
  - At 18 months, patients in the patisiran arm demonstrated improvements in change from baseline in specified echocardiographic parameters compared with the patients in the placebo arm in the cardiac subpopulation, including mean LV wall thickness, LV end-diastolic volume, global longitudinal strain, cardiac output, and LV relative wall thickness.[2]
  - Post-hoc analyses were conducted to assess the composite endpoints of any hospitalization and/or all-cause death, and cardiac hospitalization and/or all-cause death in the mITT population. In the patisiran arm, the analyses showed a reduction in the event rate of approximately 50% for all-cause hospitalization and mortality and approximately 45% for cardiac hospitalization and all-cause mortality.[2]
  - In both the APOLLO mITT population and the cardiac subpopulation, the proportion of patients with cardiac AEs and cardiac SAEs was comparable across the patisiran and placebo groups.[2]

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STUDY DESIGN

APOLLO was a multicenter, international, randomized (2:1), double-blind, placebo-controlled, Phase 3 study designed to assess the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=148) versus placebo (n=77) in patients with the polyneuropathy of hATTR. The primary endpoint was the change from baseline in the mNIS+7 at 18 months. Exploratory endpoints included cardiac structure and function measured by echocardiography and NT-proBNP.[1]

The primary population for efficacy and safety analyses was the mITT population. The mITT population is defined as all randomized patients who received ≥1 dose of patisiran or placebo (N=225).[1] Cardiac parameters were analyzed in the pre-specified cardiac subpopulation and included patients with a baseline

LV wall thickness of 13 mm or more without history of aortic valve disease or hypertension (n=126). Within the pre-specified cardiac subpopulation, 90 (71.4%) were in the patisiran treatment group and 36 (28.6%) were in the placebo treatment group. Patients that did not meet the pre-specified criteria for the cardiac subpopulation were referred to as "all other patients" (n=99).[2]

EFFICACY RESULTS

Patient Demographics & Baseline Characteristics

A summary of baseline characteristics of the predefined cardiac subpopulation and all other patients in the APOLLO study are described in **Table 1**.[2]

Table 1. Baseline Demographics, Disease Characteristics, and Echocardiographic Parameters of the Cardiac Subpopulation and All Other Patients.[2]

Characteristics	Cardiac Subpopulation			All Other Patients (n=99)
	Placebo (n=36)	Patisiran (n=90)	Overall (n=126)	
Median age, years (IQR)	62 (57.0–72.0)	60 (54.0–66.0)	61 (54.0–67.0)	65 (51.0–71.0)
Male sex, n (%)	30 (83.3)	68 (75.6)	98 (77.8)	69 (69.7)
TTR genotype, n (%)				
non-Val30Met	24 (66.7)	68 (75.6)	92 (73.0)	37 (37.4)
Val30Met	12 (33.3)	22 (24.4)	34 (27.0)	62 (62.6)
FAP stage, n (%)				
1	13 (36.1)	42 (46.7)	55 (43.7)	49 (49.5)
2	23 (63.9)	48 (53.3)	71 (56.3)	49 (49.5)
3	0	0	0	1 (1.0)
NIS score, n (%)				
<50	12 (33.3)	40 (44.4)	52 (41.3)	45 (45.5)
≥50	24 (66.7)	50 (55.6)	74 (58.7)	54 (54.5)
NYHA Class, n (%)				
Class I	16 (44.4)	34 (37.8)	50 (39.7)	60 (61.9)
Class II	20 (55.6)	56 (62.2)	76 (60.3)	37 (38.1)
NT-proBNP, pg/mL				
Median (IQR)	845.7 (373.2–1581.7)	756.4 (285.4–2432.4)	837.2 (292.4–2354.1)	314.3 (157.6–776.4)
Geometric mean (CV%)	711.1 (190.8)	726.9 (220.3)	722.5 (210.1)	360.7 (230.2)[b]
Echocardiographic Parameters[a]				
LVEF, %, mean (SD)	62.2 (8.6)	60.0 (9.9)	60.6 (9.6)	63.9 (10.1)
LV mass, g, median (IQR)	243.7 (206.2–341.0)	270.9 (216.0–322.8)	264.9 (213.6–322.8)	209.7 (153.3–286.4)
LV wall thickness, mm, median (IQR)	16.2 (14.9–17.9)	16.4 (14.8–18.6)	16.4 (14.8–18.3)	14.6 (11.6–16.7)
Interventricular septum thickness, mm, median (IQR)	16.4 (15.0–18.3)	16.7 (15.5–18.9)	16.5 (15.4–18.7)	14.7 (11.8–16.7)
LV relative wall thickness, mm, median (IQR)	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.7 (0.6–0.8)

Characteristics	Cardiac Subpopulation			All Other Patients (n=99)
	Placebo (n=36)	Patisiran (n=90)	Overall (n=126)	
Global longitudinal strain, %, median (IQR)	-15.5 (-18.0 to -12.8)	-15.1 (-17.2 to -12.6)	-15.1 (-17.5 to -12.6)	-17.3 (-19.5 to -15.6)
Cardiac output, L/min, median (IQR)	3.5 (3.2–4.3)	3.5 (3.0–4.2)	3.5 (3.1–4.2)	4.1 (3.6–5.0)
LV end-diastolic volume, mL, median (IQR)	81.2 (68.7–102.2)	81.4 (69.0–100.7)	81.2 (69.0–101.3)	89.9 (74.6–104.0)

Abbreviations: CV = coefficient of variation; FAP = familial amyloid polyneuropathy; IQR = interquartile range; LV = left ventricular; LVEF = left ventricular ejection fraction; NIS = neuropathy impairment score; NT-proBNP = N-terminal prohormone of brain-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; TTR = transthyretin.
[a]Based on *t* test, all parameters are statistically significantly different when comparing cardiac subpopulation versus all other patients. No significant difference was found between the patisiran and placebo groups in the cardiac population (*P*<0.05).
[b]Statistically significant difference between cardiac subpopulation and all other patients (*P*<0.001).

Echocardiographic Parameters: mITT Population

Overall, the assessments of echocardiographic parameters in the mITT population were comparable with those observed in the cardiac subpopulation (**Table 2**).[2]

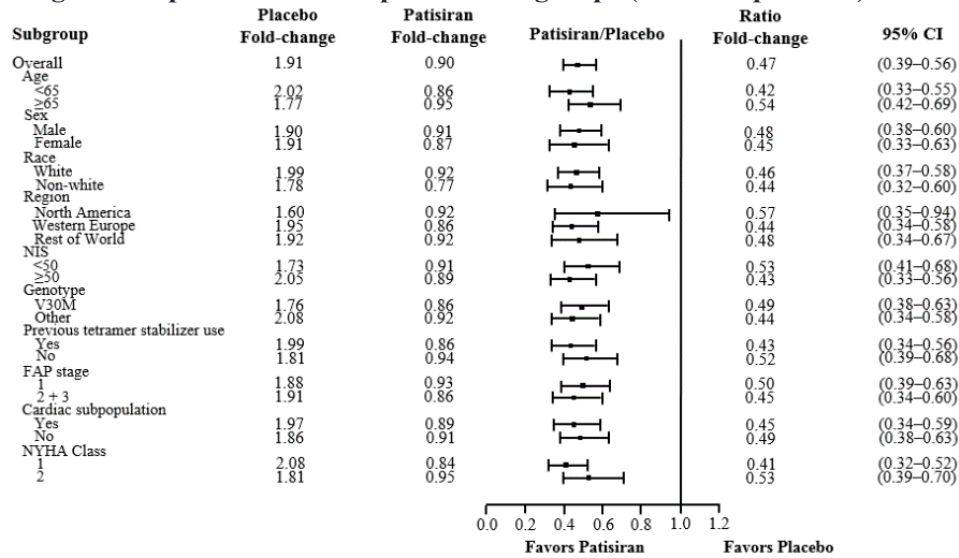**Table 2. Select Echocardiographic Parameters at Baseline and Month 18 in the mITT Population.[2,3]**

Parameter	Treatment	Baseline Mean (SD)	Change at Month 18 LS Mean (SEM)	LS Mean Patisiran– Placebo (SEM)	*P*-value
Mean LV wall thickness (mm)	Placebo	1.568 (0.2969)	-0.007 (0.0243)	-0.066 (0.0289)	0.0239
	Patisiran	1.576 (0.315)	-0.072 (0.0157)		
LV relative wall thickness	Placebo	0.79 (0.175)	-0.01 (0.017)	-0.05 (0.020)	0.0168
	Patisiran	0.80 (0.190)	-0.05 (0.011)		
Global longitudinal strain (%)	Placebo	-16.31 (3.722)	0.92 (0.343)	-0.59 (0.405)	0.1496
	Patisiran	-15.88 (3.67)	0.33 (0.215)		
Cardiac output (L/min)	Placebo	4.17 (1.345)	-0.64 (0.119)	0.37 (0.141)	0.0097
	Patisiran	3.96 (1.140)	-0.27 (0.076)		
LV end-diastolic volume (mL)	Placebo	90.40 (25.691)	-10.66 (2.428)	5.30 (2.878)	0.0670
	Patisiran	87.80 (24.834)	-5.36 (1.539)		
LV mass (g)	Placebo	248.26 (78.48)	3.09 (6.163)	-11.00 (7.304)	0.1337
	Patisiran	253.54 (88.92)	-7.91 (3.920)		

Abbreviations: LS = least-squares; LV = left ventricular; SD = standard deviation; SEM = standard error of the mean.

NT-proBNP Levels: mITT Population

In the mITT population and all pre-specified subgroups, NT-proBNP was reduced relative to placebo (**Figure 1**). Regardless of treatment group, survival was worse in patients with baseline NT-proBNP levels >3000 pg/mL (n=29) compared with patients with levels ≤3000 pg/mL (n=196) (hazard ratio, 19.3; 95% CI, 5.9–62.8).[2]

Figure 1. Change in NT-proBNP in Pre-Specified Subgroups (mITT Population).[2,3]

Subgroup	Placebo Fold-change	Patisiran Fold-change	Patisiran/Placebo	Ratio Fold-change	95% CI
Overall	1.91	0.90		0.47	(0.39–0.56)
Age					
<65	2.02	0.86		0.42	(0.33–0.55)
≥65	1.77	0.95		0.54	(0.42–0.69)
Sex					
Male	1.90	0.91		0.48	(0.38–0.60)
Female	1.91	0.87		0.45	(0.33–0.63)
Race					
White	1.99	0.92		0.46	(0.37–0.58)
Non-white	1.78	0.77		0.44	(0.32–0.60)
Region					
North America	1.60	0.92		0.57	(0.35–0.94)
Western Europe	1.95	0.86		0.44	(0.34–0.58)
Rest of World	1.92	0.92		0.48	(0.34–0.67)
NIS					
<50	1.73	0.91		0.53	(0.41–0.68)
≥50	2.05	0.89		0.43	(0.33–0.56)
Genotype					
V30M	1.76	0.86		0.49	(0.38–0.63)
Other	2.08	0.92		0.44	(0.34–0.58)
Previous tetramer stabilizer use					
Yes	1.99	0.86		0.43	(0.34–0.56)
No	1.81	0.94		0.52	(0.39–0.68)
FAP stage					
1	1.88	0.93		0.50	(0.39–0.63)
2 + 3	1.91	0.86		0.45	(0.34–0.60)
Cardiac subpopulation					
Yes	1.97	0.89		0.45	(0.34–0.59)
No	1.86	0.91		0.49	(0.38–0.63)
NYHA Class					
1	2.08	0.84		0.41	(0.32–0.52)
2	1.81	0.95		0.53	(0.39–0.70)

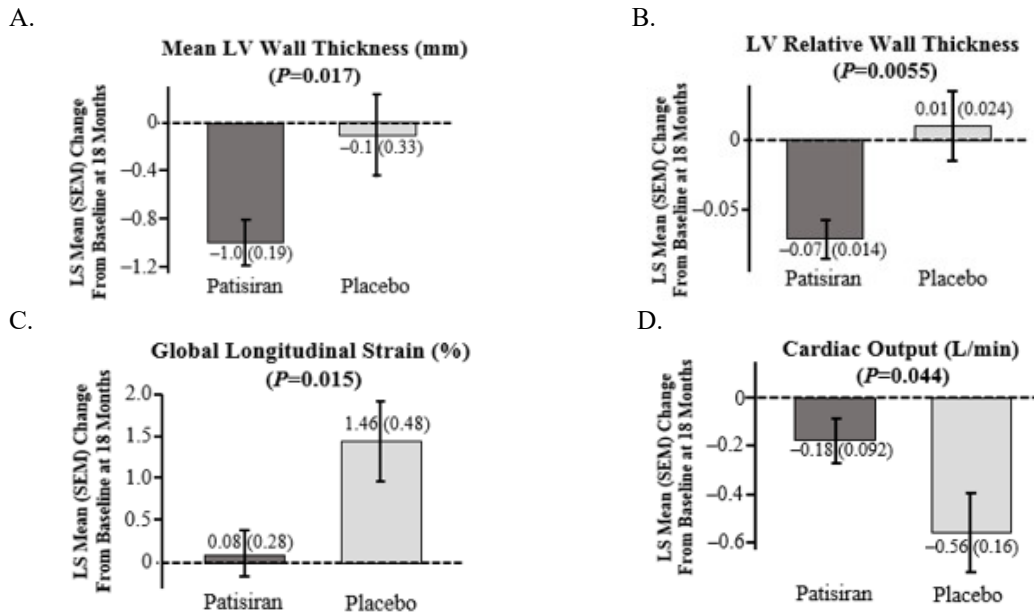Favors Patisiran ← 0.0 0.2 0.4 0.6 0.8 1.0 1.2 → Favors Placebo

Abbreviations: CI = confidence interval; FAP = familial amyloidotic polyneuropathy; NIS = neuropathy impairment score; NT-proBNP = *N*-terminal prohormone of brain-type natriuretic peptide; NYHA = New York Heart Association.
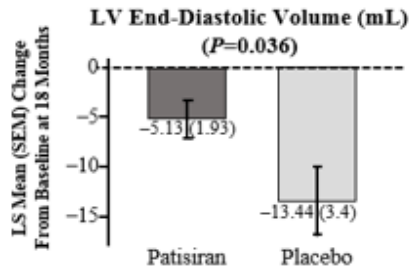
Echocardiographic Parameters: Cardiac Subpopulation

At 18 months, patients in the patisiran arm demonstrated improvements from baseline in specified echocardiographic parameters (**Figure 2**).[2]
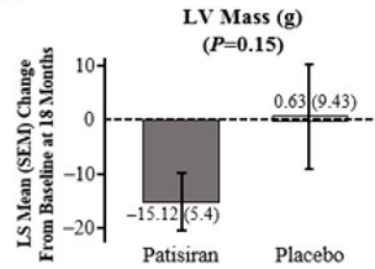
Figure 2. Echocardiographic Parameters in Cardiac Subpopulation.[2]

A. Mean LV Wall Thickness (mm) (*P*=0.017) — Patisiran: −1.0 (0.19); Placebo: −0.1 (0.33)

B. LV Relative Wall Thickness (*P*=0.0055) — Patisiran: −0.07 (0.014); Placebo: 0.01 (0.024)

C. Global Longitudinal Strain (%) (*P*=0.015) — Patisiran: 0.08 (0.28); Placebo: 1.46 (0.48)

D. Cardiac Output (L/min) (*P*=0.044) — Patisiran: −0.18 (0.092); Placebo: −0.56 (0.16)

E.

LV End-Diastolic Volume (mL)
(P=0.036)

F.

LV Mass (g)
(P=0.15)

Abbreviations: LS = least-squares; LV = left ventricular; SEM = standard error of the mean.

Mean LV Wall Thickness: Cardiac Subpopulation

At 18 months, a greater proportion of patients in the patisiran arm had a >2 mm decrease in mean LV wall thickness from baseline compared with patients in the placebo arm (29.1% vs. 4.0%). A lower proportion of patients in the patisiran arm had a >2 mm increase from baseline in mean LV wall thickness compared with patients in the placebo arm (6.3% vs. 8.0%), as shown in **Figure 3A**.[2]

LV Global Longitudinal Strain: Cardiac Subpopulation

At baseline, there were no differences in regional longitudinal strains between the treatment arms. At 18 month of treatment, patients in the patisiran arm showed reduction in the absolute GLS compared with patients in the placebo arm (least-squares mean difference [standard error], 1.4% [0.6%]; 95% CI, 0.3%-2.5%; P=0.02), with the greatest differential increase observed in the basal region (least-squares mean difference [standard error], 2.1% [0.8%]; 95% CI, 0.6%-3.6%; P=0.01). No significant differences in the mid and apical regions were observed between groups. A significant interaction was observed between patisiran treatment and baseline basal LS in which patients with the most preserved basal strain at baseline derived the greatest benefit (P<0.001).[4]

At 18 months, a greater proportion of patients in the patisiran arm had an >2% decrease (indicating improvement in function) in GLS from baseline compared with patients in the placebo arm (21.3% vs 8.0%). A lower proportion of patients in the patisiran arm had >2% increase (indicating worsening in function) from baseline in GLS compared with patients in the placebo arm (25.3% vs. 44.0%), as shown in **Figure 3B**.[2]

Figure 3. Mean LV Wall Thickness and Global Longitudinal Strain at 18 months (Cardiac Subpopulation).[2]

A.

Mean LV Wall Thickness

B.

Global Longitudinal Strain
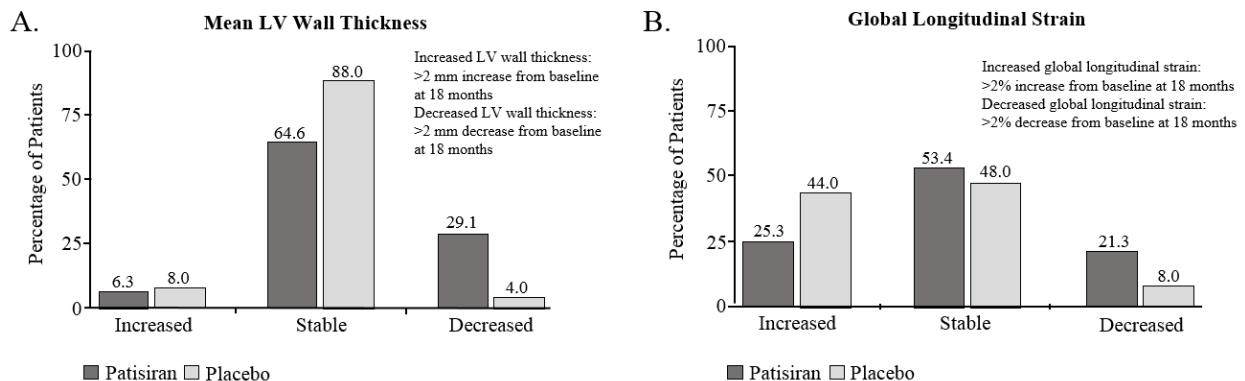


Abbreviations: LV = left ventricular.

NT-proBNP Levels: Cardiac Subpopulation

At 18 months, patisiran reduced NT-proBNP by 55% relative to placebo (ratio of fold-change patisiran/placebo 0.45, 95% CI: 0.34–0.59, p=7.7 x 10^{-8}). A greater proportion of patients treated with

patisiran had decreased levels of NT-proBNP ≥30% and ≥300 pg/mL from baseline compared with placebo (31.6% vs. 0.0%). A lower proportion of patients treated with patisiran had increased levels of NT-proBNP ≥30% and ≥300 pg/mL from baseline compared with placebo (21.1% vs. 58.3%), as shown in **Figure 4**.[2]

Figure 4. NT-proBNP Levels over 18 Months (Cardiac Subpopulation).[2]
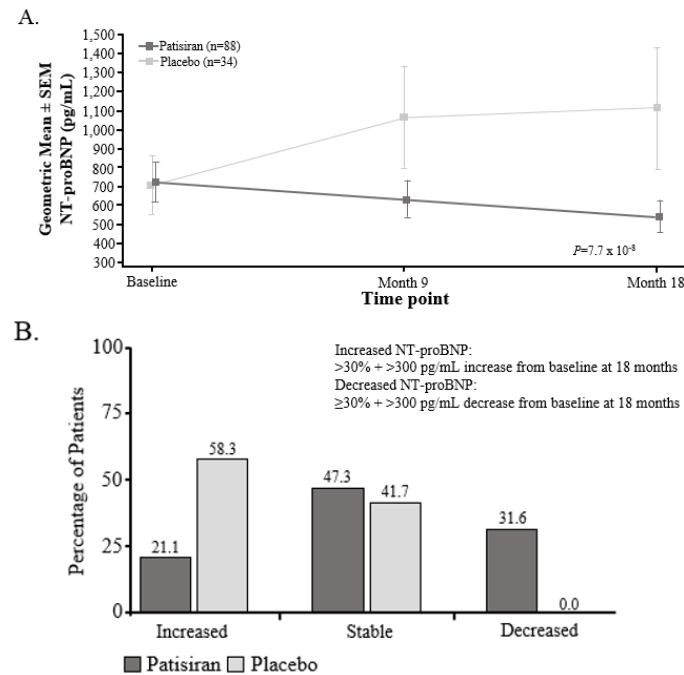
Abbreviations: NT-proBNP = *N*-terminal prohormone of brain-type natriuretic peptide.

10-MWT: Cardiac Subpopulation
Patients in the patisiran arm showed an increase compared with the placebo arm in gait speed of 0.161 m/s (95% CI: 0.076–0.246) at 9 months and 0.354 m/s (95% CI: 0.242–0.466) at 18 months.[2]

LVSV: Cardiac Subpopulation
A post-hoc analysis of the cardiac subpopulation was performed. At baseline, there were no differences in LV stroke volume between the treatment arms. At 18 months, patients in the patisiran arm showed less decline in stroke volume compared with patients in the placebo arm (LS mean change -1.7 ± 1.3 vs. -8.1 ± 2.3 mL, *p*=0.016), with changes demonstrated as early as 9 months (LS mean change -0.3 ± 1.2 vs. -5.4 ± 1.9 mL, *p*=0.021). The decline in LVSV was primarily attributed to the greater reduction of left ventricular capacitance in the patients in the placebo arm compared with patients in the patisiran arm.[5]

Echocardiographic Parameters: All Other Patients Population
In patients who did not fulfil the pre-specified cardiac criteria (all other patients), no significant impact on echocardiographic parameters was observed with patisiran compared with placebo.[2]

NT-proBNP: All Other Patients Population
Over the 18 months treatment period, patisiran reduced NT-proBNP by 51% relative to placebo in all other patients, which was similar to the effect seen in the cardiac subpopulation (**Table 3**).[2]

Table 3. NT-proBNP (pg/mL) at Baseline, Month 9, and Month 18 in all Other Patients.[3]

Patient Population		Baseline	Month 9	Ratio of Fold-Change[a] from Baseline at Month 9 Patisiran/Placebo (95% CI)	Month 18	Ratio of Fold-Change from Baseline at Month 18 Patisiran/Placebo (95% CI)
All other patients (n=99)	Placebo (n=41)	417.2 (298.5)	551.4 (285.4)	0.68 (0.56-0.84)	670 (267.7)	0.49 (0.38-0.63)
	Patisiran (n=58)	324.2 (188.7)	329.0 (224.3)		287.2 (237.8)	

Abbreviations: CI = confidence interval; NT-proBNP = *N*-terminal prohormone of brain-type natriuretic peptide.
Data for NT-proBNP are geometric means (% coefficient of variation).
[a]Ratio of fold-change is equivalent to relative reduction; e.g., 0.63 is equivalent to a 47% reduction in NT-proBNP.

10-MWT: All Other Patients Population

At 18 months, all other patients in the patisiran arm experienced an increase in gait speed by 0.283 m/s (95% CI, 0.156–0.409) compared with patients in the placebo arm.[2]

SAFETY RESULTS

Cardiac Safety Results: mITT Population

In the mITT population, the proportions of patients with cardiac AEs, cardiac SAEs, and cardiac failure AEs were similar in the patisiran and placebo arms. The rate of cardiac arrhythmia high-level group term AEs was lower in the patisiran arm (18.9%) compared with placebo arm (28.6%) (**Table 4**). The median survival follow-up duration on the study was 18.7 months. There were 7 (4.7%) deaths in the patisiran arm (all adjudicated as CV in nature) and 6 (7.8%) deaths in the placebo arm (3 adjudicated as CV in nature, 2 non-CV, and 1 unknown origin), all of which were considered unlikely or unrelated to treatments by the investigators. The exposure adjusted death rate per 100 patient-years was 6.2 (95% CI, 2.5–12.7) in the placebo arm and 3.2 (95% CI, 1.4–6.2) in the patisiran arm. The exposure-adjusted rates of cardiac hospitalizations and/or all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups, respectively.[2]

Table 4. Select Cardiac Events in the mITT Population.[2]

| Adverse Event	Placebo (n=77)	Patisiran (n=148)
Cardiac AEs, n (%)	28 (36.4)	42 (28.4)
Cardiac serious AEs, n (%)	10 (13.0)	20 (13.5)
Cardiac arrhythmia HLGT AEs, n (%)[a]	22 (28.6)	28 (18.9)
Torsades des pointes SMQ AEs, n (%)[b]	14 (18.2)	8 (5.4)
Cardiac failure SMQ AEs, n (%)	8 (10.4)	14 (9.5)
Deaths, n (%)	6 (7.8)	7 (4.7)

Abbreviations: AE = adverse event; HLGT = high-level group term; SMQ = standard MedDRA query.
[a]Cardiac arrhythmia HLGT AEs were AEs that mapped within the cardiac arrhythmias MedDRA high-level group term that included high-level terms of conduction disorders, rate and rhythm disorders, supraventricular and ventricular arrhythmias, and cardiac arrests. [b]The Torsades de pointes SMQ is a search for events that may be associated with Torsades de pointes. It does not mean that these are confirmed events of Torsades de pointes. No events of Torsades de pointes have been reported.

In a post-hoc analysis of the safety data, the rates of any hospitalization and/or all-cause death were 71.8 and 34.7 per 100 patient-years in the placebo and patisiran groups, respectively (Andersen-Gill hazard ratio, 0.48; 95% CI, 0.34–0.69), while the rates of cardiac hospitalizations and/or all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups, respectively. This approximates a reduction

in event rate of 50% for all-cause hospitalization and mortality and 45% for cardiac hospitalization and all-cause mortality (**Figure 5**).[2]

Figure 5. Analysis of Composite Endpoints of Hospitalization and Death Events from Baseline to 18 Months.[2]

A)

B)
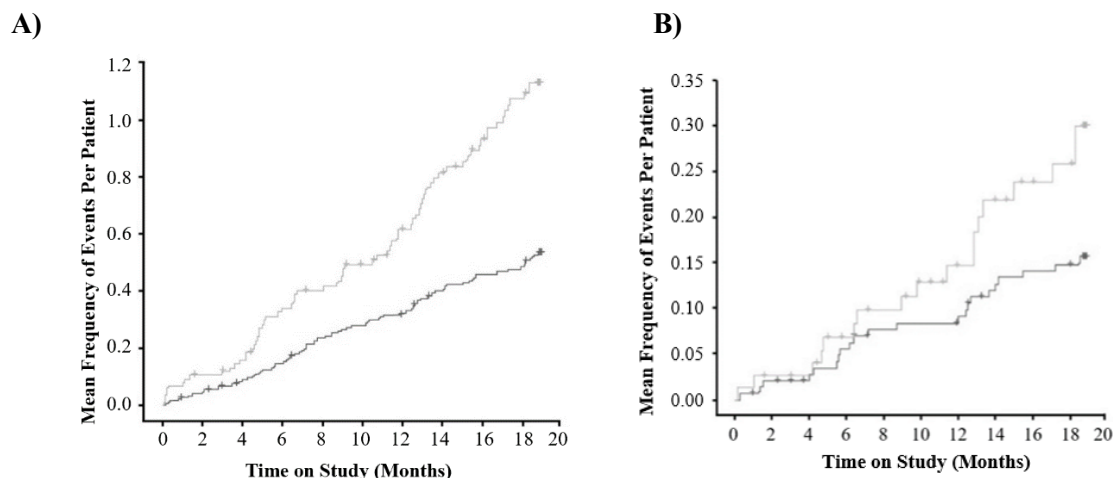
A) Composite rate of all-cause hospitalization and mortality.
B) Composite rate of cardiac hospitalization and all-cause mortality.
For all-cause hospitalization/mortality: negative binomial regression rate ratio, 0.49 (95% CI, 0.30–0.79); Andersen–Gill hazard ratio, 0.48 (95% CI, 0.34–0.69). For cardiac hospitalization/mortality: negative binomial regression rate ratio, 0.54 (95% CI, 0.25–1.16); Andersen–Gill hazard ratio, 0.54 (95% CI, 0.28–1.01).

Cardiac Safety Results: Cardiac Subpopulation

The proportion of patients with cardiac AEs and cardiac SAEs was comparable across the patisiran and placebo groups in the cardiac subpopulation (**Table 5**). A higher proportion of patients in the placebo arm (30.6%) experienced cardiac arrhythmia AEs compared with patients in the patisiran arm (18.9). A higher proportion of patients in the patisiran arm (11.1%) experienced cardiac failure AEs compared with the placebo arm (5.6%). This difference could be attributed to the baseline imbalances in the cardiac subpopulation with respect to cardiac history and NYHA status. There were 5 (5.6%) deaths reported in the patisiran arm (all CV in nature) and 4 (11.1%) deaths in the placebo arm (1 CV, 2 non-CV, and 1 unknown origin).[2]

Table 5. Cardiac Events in the Cardiac Subpopulation.[2]

Adverse Event	Placebo (n=36)	Patisiran (n=90)
Cardiac AEs, %	36.1	32.2
Cardiac SAEs, %	11.1	14.4
Cardiac arrhythmias, %	30.6	18.9
Cardiac failure, %	5.6	11.1
Deaths, %	11.1	5.6

AE = adverse event; SAE = serious adverse event.

ABBREVIATIONS

10-MWT = 10-meter walk test; AE = adverse event; CI, confidence interval; CV, coefficient of variation; FAP = familial amyloid polyneuropathy; GLS = global longitudinal strain; hATTR = hereditary transthyretin amyloidosis; HLGT = high-level group term; IQR, interquartile range; IV = intravenous; LS = least-square; LV = left ventricular; LVSV = LV stroke volume; mITT = modified intention-to-treat; mNIS+7 = modified Neuropathy Impairment Score +7; NIS = neuropathy impairment score; NT-proBNP = N-terminal prohormone of brain-type natriuretic peptide; NYHA = New York Heart Association; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; SMQ = standard MedDRA query; TTR = transthyretin.

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