Patisiran: APOLLO-B OLE Study

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SUMMARY

- APOLLO-B OLE is an ongoing, multicenter, international study designed to evaluate the long-term safety and efficacy of patisiran in patients with ATTR-CM, including both hATTR and wtATTR.[1] Patients who completed the 12-month treatment period of the APOLLO-B study were eligible to start or continue patisiran for an additional 36 months.[2,3]
  - The mean (±SEM) change from the double-blind baseline in the 6-MWT for patients receiving patisiran during both the double-blind and OLE periods was -9.4 m (6.1) at 18 months and -7.8 m (7.0) at 24 months. In patients receiving placebo during the double-blind period and patisiran in the OLE period, the mean (±SEM) change was -30.6 m (5.5) at 18 months and -26.0 m (6.1) at 24 months.[2,3]
  - The mean (±SEM) change from the double-blind baseline in the KCCQ-OS score in patients receiving patisiran in both the double-blind and OLE periods was 0.2 points (1.5) at 18 months and -1.2 points (1.5) at 24 months. In patients receiving placebo in the double-blind period and patisiran in the OLE period, the mean (±SEM) change was -3.8 points (1.5) at 18 months and -4.3 (1.6) at 24 months.[2,3]
  - Select exploratory endpoints assessed during the APOLLO-B and APOLLO-B OLE studies included changes from baseline in cardiac biomarkers NT-proBNP and troponin I.[1,2]
  - From the double-blind baseline to 24 months of the study, the most common related AE was infusion-related reactions, and the majority of AEs were mild or moderate in severity.[2]
- A post hoc analysis of pooled data from the APOLLO-B OLE and the cardiac subpopulation of the Global OLE evaluated the long-term effects of patisiran on survival, hospitalizations, and cardiac parameters.[4] The Global OLE study included eligible patients with hATTR-PN who completed the patisiran phase 2 OLE study or phase 3 APOLLO study.[5]
  - In patients who were randomized to patisiran in the parent studies, the hazards for mortality and hospitalizations were decreased relative to those who switched from placebo to patisiran at the end of the double-blind periods.[4]

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APOLLO-B

Study Design

APOLLO-B was a multicenter, randomized (1:1), double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=181) versus placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR. The primary endpoint was the change from baseline in the 6-MWT at 12 months.[1]

Patient Demographics & Baseline Characteristics

Baseline demographics and disease characteristics were comparable between the patisiran and placebo arms, as shown below in **Table 1**.[1]

Table 1. Baseline Demographics and Characteristics.[1]

Characteristic	Patisiran (N=181)	Placebo (N=178)
Age, years, median (range)	76 (47–85)	76 (41–85)
Male sex, n (%)	161 (89)	160 (90)
Race, n (%)		
White	138/180 (77)	140/174 (80)
Asian	23/180 (13)	15/174 (9)
Black or African American	16/180 (9)	15/174 (9)
Other	3/180 (2)	4/174 (2)
wtATTR, n (%)	144 (80)	144 (81)
Time since diagnosis of ATTR, years, median (range)	0.8 (0–6)	0.4 (0–10)
Tafamidis use, n (%)		
At baseline	46 (25)	45 (25)
Started during 12-month double-blind period	5 (3)	3 (2)
NYHA class, n (%)		
Class I	10 (6)	15 (8)
Class II	156 (86)	150 (84)
Class III	15 (8)	13 (7)
Gillmore et al. ATTR stage[a], n (%)		
Stage 1	124 (69)	120 (67)
Stage 2	46 (25)	45 (25)
Stage 3	11 (6)	13 (7)
PND score, n (%)		
0: no impairment	96 (53)	109 (61)
I: preserved walking, with sensory disturbances	63 (35)	55 (31)
II: impaired walking without need for a stick or crutches	22 (12)	14 (8)
6-MWT, m, median (IQR)	358.0 (295.0–420.0)	367.7 (300.0–444.3)
Score on the KCCQ-OS[b], mean ± SD	69.8 ± 21.2	70.3 ± 20.7
Laboratory values		
NT-proBNP level, pg/mL, median (IQR)	2008 (1135–2921)	1813 (952–3079)
High-sensitivity troponin I level, pg/mL, median (IQR)[c]	64.0 (38.6–92.0)	60.2 (38.2–103.1)
mBMI, median (IQR)[d]	1147.0 (988.4–1273.8)	1134.0 (1018.7–1259.1)
eGFR, mL/min/1.73 m^2, median (IQR)	71 (58–83)	67 (51–84)
Creatinine, mg/dL, median (IQR)	1.0 (0.9–1.2)	1.0 (0.8–1.4)
Coexisting conditions, n (%)		
Diabetes mellitus	30 (17)	25 (14)
Hypertension	84 (46)	101 (57)
Concomitant medication, n (%)		
Diuretic	168 (93)	164 (92)

Characteristic	Patisiran (N=181)	Placebo (N=178)
Mineralocorticoid receptor antagonist	92 (51)	74 (42)
Beta-blocker	73 (40)	77 (43)
ACEI, ARB, ARNI	82 (45)	71 (40)
SGLT2 inhibitor	8 (4)	7 (4)

Abbreviations: 6-MWT = 6-minute walk test; ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor, ATTR = transthyretin amyloidosis; eGFR = estimated glomerular filtration rate; IQR = interquartile range; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; mBMI = modified body mass index; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; SD = standard deviation; SGLT2 = sodium–glucose cotransporter-2; wtATTR = wild-type transthyretin amyloidosis.

[a]Patients are stratified into prognostic categories using the serum biomarker NT-proBNP and eGFR. Patients are categorized as follows: stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min/1.73 m^2; stage 2 (intermediate risk): all other patients not meeting criteria for stages 1 or 3; stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 mL/min/1.73 m^2.

[b]KCCQ-OS scores range from 0 to 100, with a score of 0 to 24 indicating very poor to poor quality of life, 25 to 49 poor to fair, 50 to 74 fair to good, and 75 to 100 good to excellent.

[c]Troponin I levels were assessed at baseline in a total of 174 patients in the patisiran group and in 172 patients in the placebo group.

[d]The mBMI was calculated as the conventional BMI (weight in kilograms divided by the square of the height in meters) multiplied by the serum albumin level in grams per liter.

Efficacy Results

6-MWT

The APOLLO-B study met the primary endpoint of change from baseline in the 6-MWT at 12 months compared with placebo. The median change from baseline in 6-MWT at 12 months was -8.15 m (95% CI, -16.42 to 1.50) in the patisiran arm and -21.35 m (95% CI, -34.05 to -7.52) in the placebo arm, resulting in a HL estimate of median difference of 14.69 m (95% CI, 0.69 to 28.69; p=0.02). The difference in 6-MWT distance between patisiran and placebo were consistent across prespecified subgroups by baseline demographic and disease characteristics, including hATTR and wtATTR.[1]

KCCQ-OS

The APOLLO-B study met the first secondary endpoint of change from baseline in quality of life at 12 months compared with placebo, as measured by the KCCQ-OS score (patisiran, 0.3 points [95% CI, -2.2 to 2.8] vs. placebo, -3.4 [95% CI, -5.9 to -0.9] points; LSMD, 3.7 points [95% CI, 0.2 to 7.2; p=0.04]).[1]

Safety Results

At the end of the double-blind treatment period, the patisiran and placebo arms had similar frequencies of AEs (91% and 94%) and SAEs (34% and 35%). In the safety analysis, there were 5 deaths (3%) in the patisiran arm and 8 deaths (4%) in the placebo arm.[1]

APOLLO-B OLE

Study Design

APOLLO-B OLE (N=334) is an ongoing, multicenter, international study designed to evaluate the long-term safety and efficacy of patisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients who completed the 12-month treatment period of the APOLLO-B study were eligible to start or continue IV patisiran 0.3 mg/kg every 3 weeks for an additional 36 months.[6]

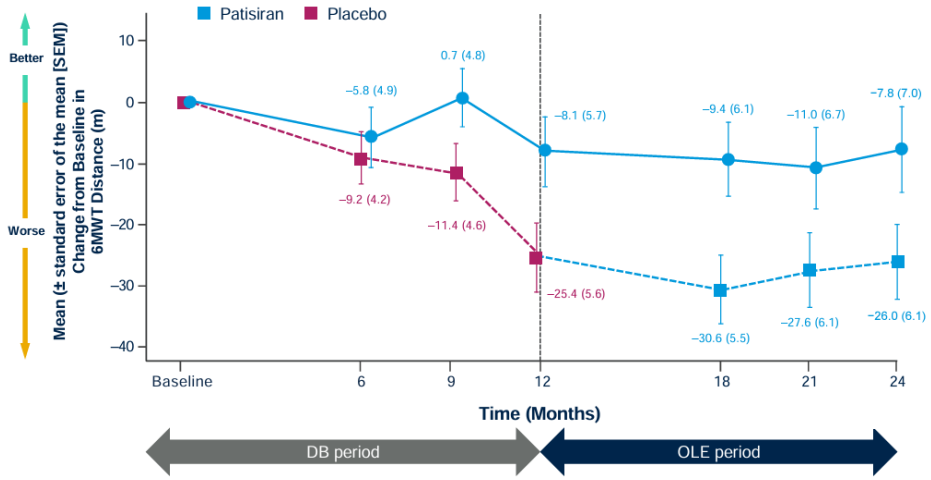
Efficacy Results

6-MWT

The mean (±SEM) change from the double-blind baseline in the 6-MWT for patients receiving patisiran during both the double-blind and OLE periods was -9.4 m (6.1) at 18 months and -7.8 m (7.0) at 24 months.[2] The decline was comparable to the expected age-related decline in healthy adults of approximately 5 m/year.[7] In patients receiving placebo during the double-blind period and patisiran in the OLE period, the

mean (±SEM) change was -30.6 m (5.5) at 18 months and -26.0 m (6.1) at 24 months. **Figure 1** illustrates the mean change of 6-MWT from the double-blind baseline over 24 months.[2]

Figure 1. Mean Change from Baseline in 6-MWT over 24 Months.[2]

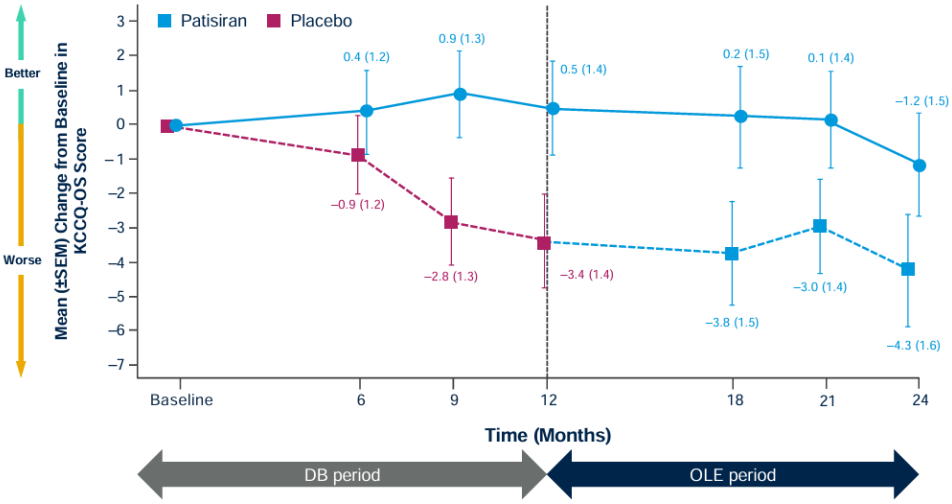


Abbreviations: 6-MWT = 6-minute walk test; DB = double-blind; OLE = open-label extension; SEM = standard error of the mean.
Footnotes: Assessments through 24 months are presented. Baseline is defined as the last non-missing value available prior to first dose of study drug in the DB period. All patients received patisiran after 12 months. Assessments where the timer was stopped after ≤4 minutes or conducted using unapproved walking aid are excluded from the analysis.
From Maurer et al.[2]

KCCQ-OS

The mean (±SEM) change from the double-blind baseline in the KCCQ-OS for patients receiving patisiran during both the double-blind and OLE periods was 0.2 points (1.5) at 18 months and -1.2 points (1.5) at 24 months. In patients receiving placebo during the double-blind period and patisiran in the OLE period, the mean (±SEM) change was -3.8 points (1.5) at 18 months and -4.3 (1.6) at 24 months. **Figure 2** illustrates the mean change of KCCQ-OS from the double-blind baseline over 24 months.[2]

Figure 2. Mean Change from Baseline in KCCQ-OS over 24 Months.[2]



Abbreviations: DB = double-blind; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; OLE = open-label extension; SEM = standard error of the mean.
Footnotes: Assessments through 24 months are presented. Baseline is defined as the last non-missing value available on or before the date of first dose of study drug in the DB period. All patients received patisiran after 12 months.
From Maurer et al.[2]

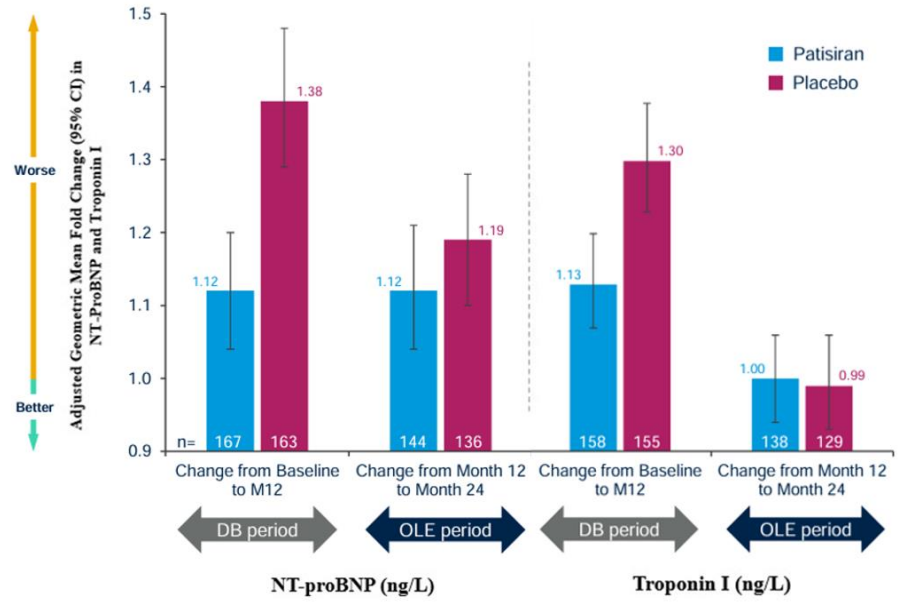
Cardiac Biomarkers

The change in cardiac biomarkers from the double-blind baseline to 24 months of the study is summarized in **Figure 3** and **Table 2**.[2]

At month 18, in patients receiving patisiran during both double-blind and OLE periods, the geometric mean fold change (95% CI) from the double-blind baseline was 1.17 (1.07, 1.27) in NT-proBNP and 1.09 (1.01, 1.17) in troponin I. In patients receiving placebo during the double-blind period and patisiran during the OLE period, the geometric mean fold change (95% CI) was 1.53 (1.38, 1.71) in NT-proBNP and 1.21 (1.13, 1.30) in troponin I.[3]

At month 24, patients receiving patisiran during both double-blind and OLE periods demonstrated a similar annual adjusted geometric mean fold change in NT-proBNP and a decreased annual adjusted geometric mean fold change in troponin I between the double-blind and OLE periods. For troponin I, the ratio of adjusted geometric mean fold change between the OLE and double-blind periods was significant (0.88 [95% CI, 0.80, 0.97]; p=0.009). Patients receiving placebo during the double-blind period and patisiran during the OLE period demonstrated a higher annual adjusted geometric mean fold change in both NT-proBNP and troponin I levels, which decreased after initiation of patisiran in the OLE to values comparable to the patisiran group. The ratio of adjusted geometric mean fold change between the double-blind and OLE period at 24 months was significant for both NT-proBNP (0.86 [95% CI, 0.77, 0.96]; p=0.009) and troponin I (0.76 [95% CI, 0.69, 0.84]; p<0.001).[2]

Figure 3. Annual Adjusted Geometric Mean Fold Change in Cardiac Biomarkers to Month 24.[2]



Abbreviations: CI = confidence interval; DB = double-blind; M12 = 12 months; NT-proBNP = *N*-terminal prohormone of B-type natriuretic peptide; OLE = open-label extension.

Footnotes: Assessments through 24 months are summarized. Baseline is defined as the last non-missing value available on or before the date of first dose of study drug in the DB period. All patients received patisiran after 12 months. The adjusted geometric mean fold-changes and 95% CIs were obtained using MMRM. In the model, the outcome variable was the change from baseline in the log-transformed parameter, and the model included the log-transformed baseline value as a continuous covariate and fixed-effect terms including treatment arm, visit, background tafamidis use, type of ATTR, age group, treatment-by-visit interaction, treatment-by-baseline tafamidis interaction, visit-by-baseline tafamidis interaction, and the treatment-by-visit-by-baseline tafamidis interaction.

From Maurer et al.[2]

Table 2. Change in Cardiac Biomarkers over 24 Months.[2]

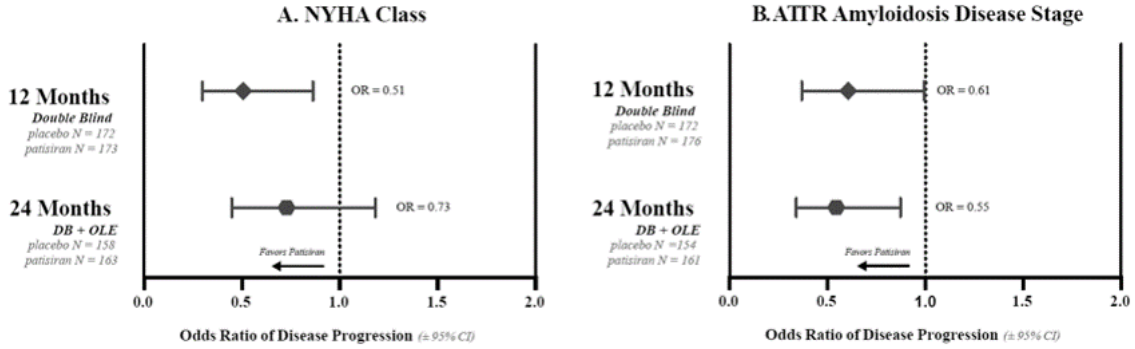
	NT-proBNP, ng/L, median (IQR)		Troponin I, ng/L, median (IQR)	
	Patisiran	**Placebo**	**Patisiran**	**Placebo**
Baseline	2008.0 (1135.0 to 2921.0)	1813.0 (952.0 to 3079.0)	64.0 (38.6 to 92.0)	60.2 (38.2 to 103.1)
Month 12	1944.0 (1158.0 to 3726.0)	2299.0 (1180.0 to 4364.0)	67.8 (37.4 to 114.1)	72.1 (45.6 to 127.4)
Change from Baseline to Month 12	131.0 (-280.0 to 817.0)	518.0 (51.0 to 1544.0)	3.8 (-7.1 to 19.9)	14.5 (0.0 to 32.2)
Month 24	2060.0 (1202.0 to 3826.0)	2764.5 (1271.5 to 4543.0)	62.6 (37.2 to 107.8)	66.7 (43.1 to 112.9)
Change from Month 12 to Month 24	136.5 (-198.0 to 836.0)	292.5 (-83.5 to 1200.0)	-2.7 (-12.8 to 10.3)	-0.4 (-14.8 to 14.2)

Abbreviations: IQR = interquartile range; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.

Clinical Disease Progression Analyses

During the double-blind and OLE periods, the point estimate of the OR for heart failure progression defined by worsening NYHA class or death was 0.51 (95% CI, 0.30, 0.86) at 12 months (double-blind period) and 0.73 (95% CI, 0.45, 1.18) at 24 months (1 year of the OLE period). The point estimate of the OR for general disease progression defined by worsening ATTR disease stage or death was 0.61 (95% CI, 0.37, 0.99) at 12 months (double-blind period) and 0.55 (95% CI, 0.34, 0.87) at 24 months (1 year of the OLE period). The results are summarized in **Figure 4**.[6]

Figure 4. Clinical Disease Progression: NYHA Class and ATTR Disease Stage.[6]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; DB = double-blind; NYHA = New York Heart Association; OLE = open-label extension; OR = odds ratio.
Footnotes: An odds ratio <1 represents a favorable outcome for patisiran.
From Hung et al.[6]

Composite Outcome and Mortality Analyses

The study was not long enough nor powered to show treatment difference in death and hospitalization. In the analysis of composite endpoints during the double-blind and OLE periods, deaths, hospitalizations, and urgent HF visits due to COVID-19 were excluded. Patients who underwent heart transplantation and/or LVAD placement after randomization were included in the same manner as death in this analysis. For patients who discontinued treatment during the double-blind period, events occurring after Day 417 were excluded. For patients who discontinued treatment during the OLE period, events occurring more than 90 days after last patisiran dose were excluded.[2,3]

The point estimate of the HR during the double-blind and OLE periods for the composite of all-cause mortality, frequency of all-cause hospitalization, and urgent HF visits was 0.801 (95% CI, 0.573, 1.118) over 18 months and 0.80 (95% CI, 0.59, 1.08) over 24 months.[2,3]

The HR during the double-blind and OLE periods for all-cause mortality was 0.55 (95% CI, 0.281, 1.094) over 18 months, and 0.67 (95% CI, 0.37, 1.19) over 24 months. There were 13 death events reported in patients randomized to patisiran and 23 death events reported in patients randomized to placebo at 18 months, and there were 19 and 28 death events, respectively, at 24 months.[2,3]

Safety Results

AEs in patients receiving patisiran are summarized below in **Table 3**.

At 18 months, the median exposure to patisiran during the OLE study was 9.6 months (range 0.7–24.6 months) in the placebo/patisiran group and 21.8 months (range 0.0–37.0 months) in the patisiran/patisiran group. At 24 months, the median exposure to patisiran during the OLE study was 15.2 months (range 0.7–30.9 months) in the placebo/patisiran group and 27.3 months (range 0.0–43.2 months) in the patisiran/patisiran group. The most common related AE was infusion-related reactions (14.1% at 18 months, 15% at 24 months). The majority of AEs were mild or moderate in severity.[2,3]

In the safety analysis, death included all AEs with an outcome of fatal (including COVID-19) regardless of treatment-emergent classification but excluded deaths that occurred after study withdrawal. In the safety analysis population, heart transplant and LVAD were not included or counted as fatal events.[2,3]

Table 3. Safety Summary at 24 Months.[2]

	DB/OLE on Patisiran					
	Patisiran/patisiran N=181, PY=407.8		Placebo/patisiran N=166, PY=221.9		All Patisiran N=347, PY=629.7	
	n (%)	ER	n (%)	ER	n (%)	ER
AEs	175 (96.7)	598.8	160 (96.4)	759.7	335 (96.5)	655.5
Serious AEs	111 (61.3)	71.9	87 (52.4)	107.7	198 (57.1)	84.5
Severe AEs	87 (48.1)	57.1	76 (45.8)	82.0	163 (47.0)	65.9
AEs leading to treatment discontinuation	12 (6.6)	3.7	13 (7.8)	6.3	25 (7.2)	4.6
Deaths	20 (11.0)	4.9	15 (9.0)	6.8	35 (10.1)	5.6

Abbreviations: AE = adverse event; DB = double-blind; ER = exposure-adjusted event rate per 100 patient-years; OLE = open-label extension; PY = patient-year.
Footnotes: Cumulative safety data during patisiran treatment as of a data cut-off date of 26 June 2023. The placebo/patisiran group does not include safety events during treatment with placebo from the double-blind period.

Cardiac Safety Results

The type and nature of cardiac events observed were consistent with the underlying disease and with those reported during the APOLLO-B double-blind period, as summarized in **Table 4**.[2]

Table 4. Cardiac Safety Summary at 24 Months.[2]

	DB/OLE on Patisiran					
	Patisiran/patisiran N=181, PY=407.8		Placebo/patisiran N=166, PY=221.9		All Patisiran N=347, PY=629.7	
	n (%)	ER	n (%)	ER	n (%)	ER
Cardiac AEs (Cardiac disorders SOC)	116 (64.1)	83.4	98 (59.0)	92.8	214 (61.7)	86.7
Cardiac SAEs (Cardiac disorders SOC)	60 (33.1)	25.3	51 (30.7)	36.0	111 (32.0)	29.1
Cardiac arrhythmia (HLGT)	66 (36.5)	32.9	42 (25.3)	32.0	108 (31.1)	32.6
Supraventricular arrhythmias (HLT)	46 (25.4)	22.6	31 (18.7)	19.8	77 (22.2)	21.6
Ventricular arrhythmias and cardiac arrest (HLT)	13 (7.2)	3.9	7 (4.2)	7.7	20 (5.8)	5.2
Cardiac conduction disorders (HLT)	12 (6.6)	3.4	6 (3.6)	2.7	18 (5.2)	3.2
Atrioventricular block complete	2 (1.1)	0.5	3 (1.8)	1.4	5 (1.4)	0.8
Rate and rhythm disorders (HLT)	11 (6.1)	2.9	4 (2.4)	1.8	15 (4.3)	2.5
Cardiac failure SMQ (narrow)	89 (49.2)	46.1	67 (40.4)	54.1	156 (45.0)	48.9

Abbreviations: AE = adverse event; DB = double-blind; ER = exposure-adjusted event rate per 100 patient-years; HLGT = high-level group term; HLT = high-level term; MedDRA = Medical Dictionaries for Regulatory Activities; OLE = open-label extension; PY = patient-year; SAE = serious adverse event; SMQ = standardized MedDRA Query; SOC = system organ class.
Footnotes: Cumulative safety data during patisiran treatment as of a data cut-off date of 26 June 2023. The placebo/patisiran group does not include safety events during treatment with placebo from the double-blind period.

POST HOC ANALYSIS OF POOLED CARDIAC POPULATION

Study Design

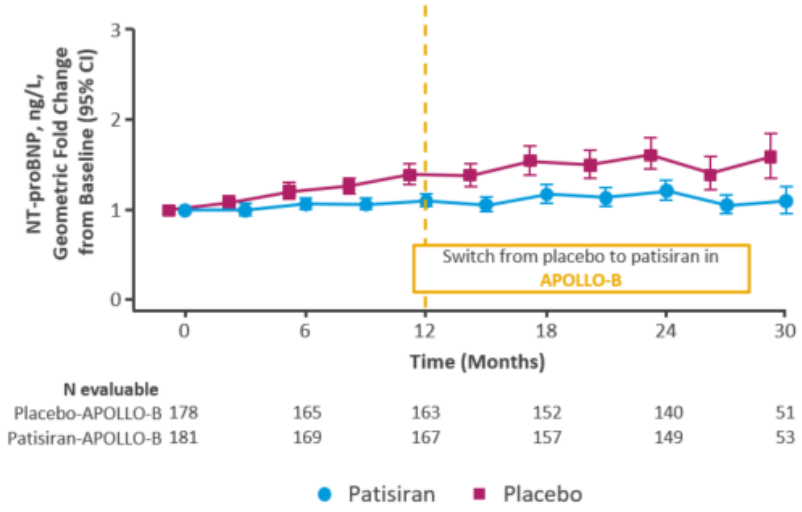
A post hoc analysis of pooled data from the APOLLO-B OLE and the cardiac subpopulation of the Global OLE evaluated the long-term effects of patisiran on survival, hospitalizations, and cardiac parameters in patients with hATTR-PN and evidence of cardiac involvement or a diagnosis of ATTR-CM.[4]

Cardiac Results

Cardiac Biomarkers

During the APOLLO-B study, geometric mean fold change in NT-proBNP remained stable in patients who were receiving patisiran to 30 months. The rate of worsening of geometric mean fold change in NT-proBNP from the double-blind baseline in patients receiving placebo decreased following the switch to patisiran at 12 months, as seen in **Figure 5**.[4]

Figure 5. Geometric Mean Fold Change from Baseline in NT-proBNP over 30 Months.[4]

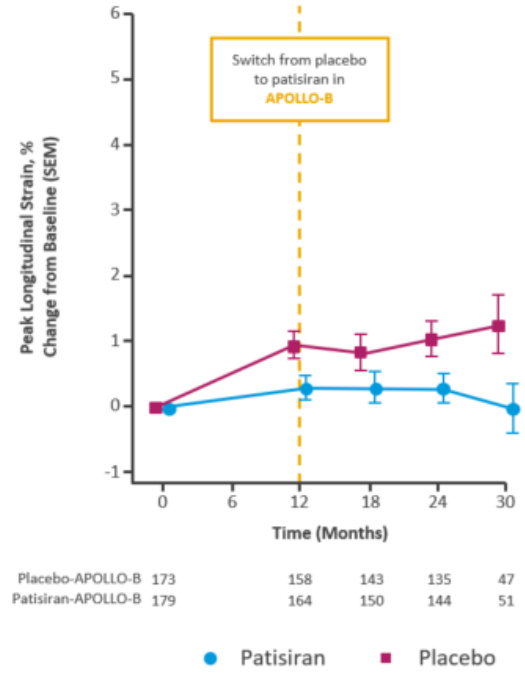


Abbreviations: CI = confidence interval; NT-proBNP = *N*-terminal prohormone of B-type natriuretic peptide.
From Lairez et al.[4]

Left Ventricular Function

During the APOLLO-B study, peak longitudinal strain remained stable in patients who were receiving patisiran from the double-blind baseline over 30 months. The rate of worsening of the peak longitudinal strain in patients who were receiving placebo from the double-blind baseline decreased following the switch to patisiran at 12 months, as seen in **Figure 6**.[4]

Figure 6. Change from Baseline in Peak Longitudinal Strain Through Month 30.[4]

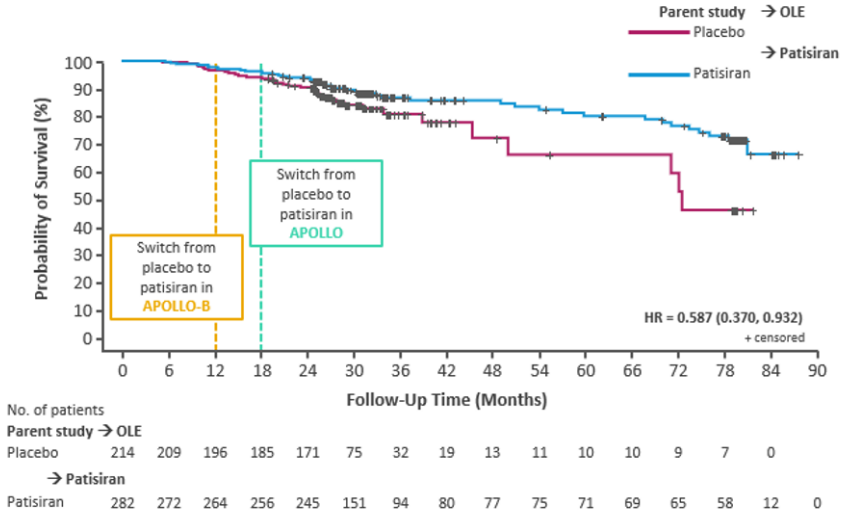


From Lairez et al.[4]

Mortality

In patients who were randomized to patisiran in the parent studies, the hazard for mortality was decreased by 41.3% (HR = 0.587 [0.370, 0.932]) relative to those who switched from placebo to patisiran at the end of the double-blind periods (**Figure 7**).[4]

Figure 7. Probability of Survival by Initial Treatment Arm.[4]

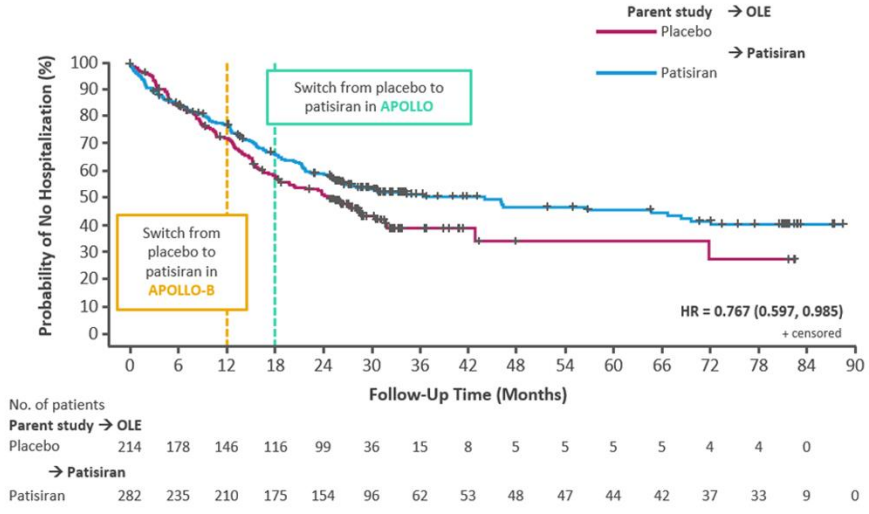


Abbreviations: HR = hazard ratio; OLE = open-label extension.
Footnotes: HR is calculated from a Cox regression model with initial treatment as a covariate.
From Lairez et al.[4]

Hospitalizations

In patients who were randomized to patisiran in the parent studies, the hazard for hospitalizations was decreased by 23.3% (HR = 0.767 [0.597, 0.985]) relative to those who switched from placebo to patisiran at the end of the double-blind periods (**Figure 8**).

Figure 8. Probability of No Hospitalization by Initial Treatment Arm.[4]



Abbreviations: HR = hazard ratio; OLE = open-label extension.
Footnotes: HR is calculated from a Cox regression model with initial treatment as a covariate.
From Lairez et al.[4]

ABBREVIATIONS

6-MWT = 6-minute walk test; ACEI = angiotensin-converting-enzyme inhibitor; AE = adverse event; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; ATTR = transthyretin amyloidosis; CI = confidence interval; DB = double-blind; eGFR = estimated glomerular filtration rate; ER = exposure-adjusted event rate per 100 patient-years; HF = heart failure; HL = Hodges-Lehmann; HLGT = high-level group term; HLT = high-level term; HZ = hazard ratio; IQR = interquartile range; IV = intravenous; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LSMD = least squares mean difference; LVAD = left ventricular assist device; M12 = Month 12; mBMI = modified body mass index; MedDRA = Medical Dictionaries for Regulatory Activities; MMRM = mixed effects model repeated measures; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; OR = odds ratio; PND = polyneuropathy disability; PY = patient-year; SAE = serious adverse event; SD = standard deviation; SEM = standard error of mean; SGLT2 = sodium–glucose cotransporter-2; SMQ = standardized MedDRA Query; SOC = system organ class; wtATTR = wild-type transthyretin amyloidosis.

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