Patisiran: APOLLO-B Study

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SUMMARY

- APOLLO-B was a phase 3, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of patisiran in patients with ATTR-CM, including both hATTR and wtATTR.[1]
- The APOLLO-B study met the primary endpoint of change from baseline in the 6-MWT at 12 months compared with placebo (patisiran, -8.15 m vs. placebo, -21.35 m; HL estimate of median difference: 14.69 m [95% CI: 0.69, 28.69]; p=0.02).[1]
- The study also met the first secondary endpoint of change from baseline in health status and quality of life at 12 months compared with placebo, as measured by the KCCQ-OS Score (patisiran, 0.3 points vs. placebo, -3.4 points; LS mean difference, 3.7 points [95% CI: 0.2, 7.2]; p=0.04).[1]
- There was a non-significant result for the secondary composite endpoint of all-cause mortality, frequency of CV events (CV hospitalizations and urgent HF visits), and change from baseline in 6-MWT over 12 months compared with placebo with a win ratio (patisiran vs. placebo) of 1.27 (95% CI: 0.99, 1.61). As a result, no formal statistical testing was performed on two additional composite endpoints.[1]
- 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]

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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) vs. placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR. Randomization was stratified by baseline tafamidis (yes vs. no), genotype (hATTR vs. wtATTR), and NYHA Class I or II and age < 75 years

vs. all other. The primary endpoint was the change from baseline in the 6-MWT at 12 months. After the 12-month double-blind treatment period, all eligible patients received patisiran in an open-label extension period.[1] The inclusion and exclusion criteria for APOLLO-B are presented in **Table 1**.[1,2]

Table 1. APOLLO-B Inclusion and Exclusion Criteria.[1,2]

Inclusion Criteria	Exclusion Criteria
• Age 18 to 85 years • Documented diagnosis of ATTR with cardiomyopathy[a] (either hATTR or wtATTR) • Evidence of cardiac involvement (confirmed by echocardiography), with an end-diastolic interventricular septal wall thickness exceeding 12 mm • Medical history of HF with at least one prior hospitalization for HF, or current clinical evidence (signs and symptoms) of HF • Clinically stable with no CV-related hospitalizations within 6 weeks prior to randomization • Tafamidis naïve[b] or currently on tafamidis for ≥6 months with evidence of disease progression while on tafamidis treatment • Able to complete ≥150 m in the 6-MWT at screening • Screening NT-proBNP >300 pg/mL and <8500 pg/mL; in patients with permanent or persistent atrial fibrillation, screening NT-proBNP >600 pg/mL and <8500 pg/mL	• Known primary amyloidosis or leptomeningeal amyloidosis • NYHA Class III and ATTR stage 3[c] • NYHA Class IV • PND score > II (requiring cane or stick to walk, or is wheelchair bound) • eGFR <30 L/min/1.73 m^2 • Abnormal liver function • Hepatitis B, hepatitis C, or HIV infection • Non-amyloid disease that significantly affects ability to walk (e.g., severe chronic obstructive pulmonary disease, severe arthritis, or peripheral vascular disease affecting ambulation) • Prior or planned heart, liver, or other organ transplant • Received prior TTR lowering treatment • Other cardiomyopathy not related to ATTR (e.g., cardiomyopathy due to ischemic or valvular heart disease)

Abbreviations: 6-MWT = 6-minute walk test; ATTR = transthyretin amyloidosis; CV = cardiovascular; eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; HIV = human immunodeficiency virus; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.
[a]Defined as presence of TTR amyloid deposits on analysis of tissue biopsy specimens or fulfillment of validated nonbiopsy diagnostic criteria.
[b]In addition to patients who have never taken tafamidis, those who have been on tafamidis for 30 days total or fewer and have not received any tafamidis in the 6 months prior to baseline were considered tafamidis naïve.
[c]Defined as NT-proBNP level >3000 pg/mL and eGFR < 45 mL/min/1.73 m^2.

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Baseline characteristics were comparable between the patisiran and placebo arms, as shown in **Table 2**.[1]

Table 2. Baseline Patient Demographics and Clinical 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 (77)	140 (80)
Asian	23 (13)	15 (9)
Black	16 (9)	15 (9)
Other	3 (2)	4 (2)

Characteristic	Patisiran (n=181)	Placebo (n=178)
wtATTR, n (%)	144 (80)	144 (81)
Time since diagnosis of ATTR, years, median (range)	0.8 (0.0–6.0)	0.4 (0.0–10.0)
Treatment with tafamidis[a], n (%)		
At baseline	46 (25)	45 (25)
Started during 12-month double-blind period	5 (3)	3 (2)
ATTR Stage[b], 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, sensory disturbances	63 (35)	55 (31)
II: impaired walking without need for a stick or crutches	22 (12)	14 (8)
NYHA class, n (%)		
Class I	10 (6)	15 (8)
Class II	156 (86)	150 (84)
Class III	15 (8)	13 (7)
6-MWT, m, median (IQR)	358.0 (295.0-420.0)	367.7 (300.0-444.3)
KCCQ-OS score[c], mean (SD)	69.8 (21.2)	70.3 (20.7)
Laboratory values		
NT-proBNP level, pg/mL, median (IQR)	2008.0 (1135.0–2921.0)	1813.0 (952.0–3079.0)
Troponin I level[d], pg/mL, median (IQR)	64.0 (38.6–92.0)	60.2 (38.2–103.1)
mBMI[e], median (IQR)	1147.0 (988.4–1273.8)	1134.0 (1018.7–1259.1)
eGFR, mL/min/1.73 m^2, median (IQR)	71.0 (58.0–83.0)	67.0 (51.0–84.0)
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)
Mineralocorticoid receptor antagonist	92 (51)	74 (42)
Beta-blocker	73 (40)	77 (43)
ACEI, ARB, or 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; hATTR = hereditary transthyretin amyloidosis; IQR = interquartile range; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LV = left ventricular; m = meter; 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.

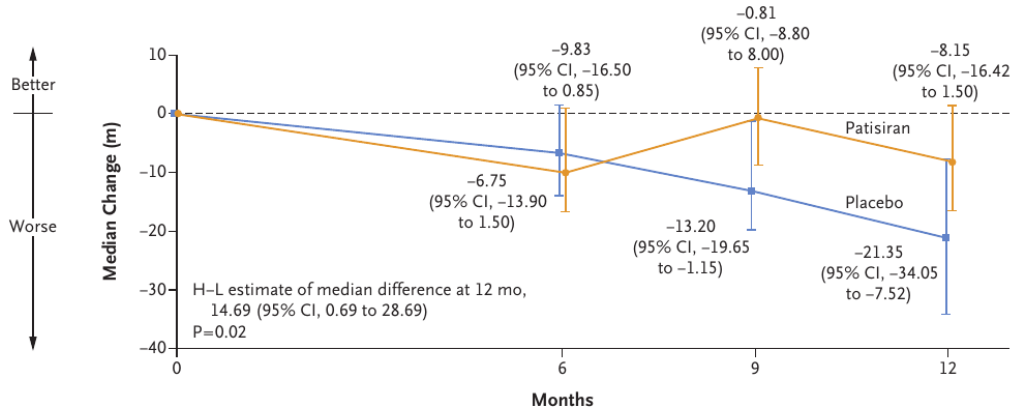
[a]Where tafamidis was available as local standard of care; receiving tafamidis treatment ≥6 months with disease progression in opinion of investigator. Study design allowed for ≤30% enrolled to be on background tafamidis at baseline.

[b]Risk stratification based on the levels of the serum biomarkers NT-proBNP and eGFR. Patients are categorized as follows: Stage 1 (lower risk): NT-proBNP ≤3000 pg/mL 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 pg/mL and eGFR <45 mL/min/1.73 m^2.
[c]KCCQ-OS scores range from 0-100, with a score of 0-24 indicating very poor to poor quality of life, 25-49 poor to fair, 50-74 fair to good, and 75-100 good to excellent.
[d]Troponin I levels were assessed at baseline in 174 patients in the patisiran group and 172 patients in the placebo group.
[e]mBMI was calculated as conventional BMI (weight in kilograms divided by the square of height in meters) x serum albumin level (g/L).

6-MWT

Patisiran demonstrated a statistically significant difference compared with placebo in the primary endpoint of change from baseline in 6-MWT at 12 months, as seen in **Figure 1.** The HL estimate of median difference was 14.69 m (95% CI: 0.69, 28.69; p=0.02).[1] The decline in 6-MWT observed in the patisiran arm was similar to the typical age-related decline seen in healthy adults.[3–6]

Figure 1. Change from Baseline in 6-MWT at 12 Months.[1,a]

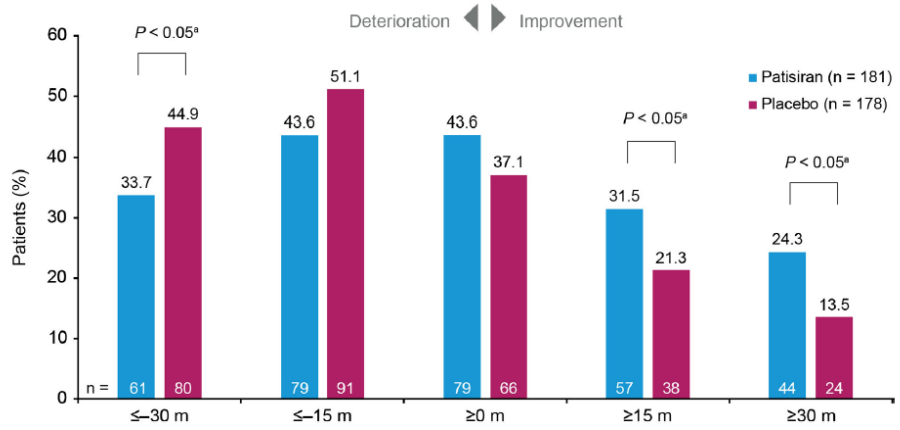


Abbreviations: 6-MWT = 6-minute walk test; ATTR = transthyretin amyloidosis; CI = confidence interval; HL= Hodges-Lehmann; IQR = interquartile range; m = meter.
[a]Primary endpoint analysis based on the stratified Wilcoxon Rank Sum test. Median (95% CI) change from baseline values are based on the observed 6-MWT data and the imputed values; for each patient, the change from baseline is averaged across 100 complete datasets. Missing Month 12 values due to non-COVID-19 death or inability to walk due to progression of ATTR were imputed as -115 meters (the worst 10th percentile change observed across all patients in the double-blind period), capped by the worst possible change for the patient (i.e., 0 minus the patient's baseline 6-MWT). Missing Month 12 data due to other reasons were multiply imputed (assuming data were missing at random) to create 100 complete datasets. At baseline, the median (IQR) 6-MWT was 358.00 m (295.00–420.00) in the patisiran arm and 367.74 m (300.00–444.25) in the placebo arm.
From Maurer et al.[1]

A prespecified sensitivity analysis was conducted using MMRM to confirm the primary endpoint results for change from baseline in 6-MWT at 12 months for patisiran compared with placebo, which resulted in a LS mean difference of 18.15 m (95% CI: 2.48, 33.82).[2]

In a post-hoc analysis, a greater proportion of patients treated with patisiran achieved an improvement in 6-MWT distance at 12 months compared with placebo across specific thresholds assessed (**Figure 2**). At 12 months, 32% of patients in the patisiran arm improved by at least 15 m versus 21% of patients in the placebo arm (p<0.05); and 24% of patients in the patisiran arm improved by at least 30 m compared with 14% of patients in the placebo arm (p<0.01).[7]

Figure 2. Proportion of Patients with Specified Threshold Levels of Change in 6-MWT.[7]

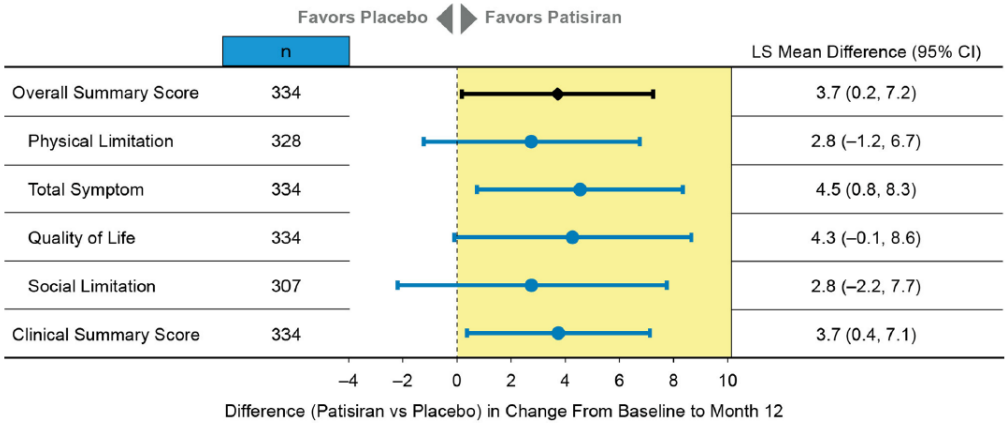


Abbreviations: 6-MWT = 6-minute walk test.
[a]P values were calculated using the Cochran-Mantel-Haenszel test stratified by baseline tafamidis use.
From Berk et al.[7]

KCCQ-OS

Patisiran demonstrated a statistically significant difference in the first secondary endpoint of change from baseline in patient-reported health status and quality of life as measured by the KCCQ-OS score at 12 months compared with placebo (patisiran, 0.3 vs. placebo, -3.4) with a LS mean difference of 3.7 (95% CI: 0.2, 7.2; p=0.04). A consistent treatment effect was observed across all KCCQ domains (**Figure 3**).[1,7]

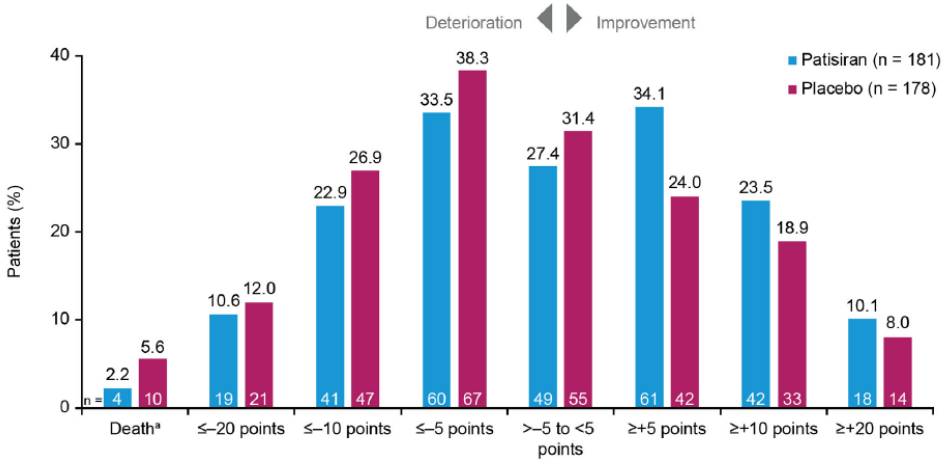
Figure 3. LS Mean Difference in Change from Baseline in KCCQ-OS Domains and Clinical Summary Score at 12 Months.[7]



Abbreviations: CI = confidence interval; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares.
From Berk et al.[7]

In a post-hoc analysis, a greater proportion of patients treated with patisiran had an improvement in the KCCQ-OS score at 12 months compared with placebo across a range of thresholds assessed (**Figure 4**). At 12 months, 34% of patients in the patisiran arm improved from baseline by at least 5 points versus 24% of patients in the placebo arm (p<0.05).[7]

Figure 4. Proportion of Patients by Threshold of Change from Baseline in KCCQ-OS Score at 12 Months.[7]



Abbreviations: KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary.
[a]Deaths include heart transplants – placebo n=2 (1.1%); patisiran n=0 (0%) – and exclude one COVID death in the patisiran arm.
From Berk et al.[7]

SECONDARY COMPOSITE ENDPOINTS

Secondary endpoints were evaluated in a hierarchical manner. There was a non-significant result for the secondary composite endpoint of all-cause mortality, frequency of CV events (CV hospitalizations and urgent HF visits), and change from baseline in 6-MWT over 12 months compared with placebo with a win ratio (patisiran vs. placebo) of 1.27 (95% CI: 0.99, 1.61).[1] Deaths, hospitalizations, and urgent HF visits due to COVID-19 were excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled in the same manner as death in this efficacy analysis.[1]

Because of the non-significant result with the second secondary endpoint, no formal statistical testing was performed on two additional composite endpoints. These secondary endpoints included[2]:

- Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline, which resulted in a HR of 0.997 (95% CI: 0.62, 1.60)
- Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in the overall study population, which resulted in a HR of 0.88 (95% CI: 0.58, 1.34).

PHARMACODYNAMIC ENDPOINT

Serum TTR reduction at 12 months was assessed as a pharmacodynamic endpoint of the APOLLO-B study. Patients treated with patisiran achieved a mean (SD) percent serum TTR reduction of 86.8 (13.6).[1]

The mean (SD) percent reduction in serum TTR in the patisiran arm was 83.7 (16.3) for patients receiving tafamidis at baseline and 87.9 (12.3) for patients not receiving tafamidis at baseline. Patients with hATTR and patients with wtATTR achieved a mean (SD) percent TTR reduction of 85.2 (12.7) and 87.2 (13.9), respectively.[1]

EXPLORATORY ENDPOINTS

Cardiac Biomarkers

The change from baseline in NT-proBNP at 12 months was assessed as an exploratory endpoint. At 12 months, the adjusted geometric mean factor change from baseline in NT-proBNP was 1.11 (95% CI: 1.04, 1.19) in the patisiran arm and 1.38 (95% CI: 1.29, 1.48) in the placebo arm. The ratio of adjusted geometric mean factor change (patisiran/placebo) was 0.80 (95% CI: 0.73, 0.89).[1]

The change from baseline in troponin I at 12 months was also assessed as an exploratory endpoint. At 12 months, the adjusted geometric mean factor change from baseline in troponin I was 1.13 (95% CI: 1.07, 1.20) in the patisiran arm and 1.30 (95% CI: 1.22, 1.38) in the placebo arm. The ratio of adjusted geometric mean factor change (patisiran/placebo) was 0.87 (95% CI: 0.80, 0.95).[1]

The changes from baseline in NT-proBNP and troponin I at 12 months are summarized in **Table 3**.[1]

Table 3. Changes from Baseline in NT-proBNP and Troponin I at 12 Months.[1]

	Patisiran	Placebo
NT-proBNP, pg/mL, median (IQR)		
Baseline[a]	2008 (1135–2921)	1813 (952–3079)
Month 12[b]	1944 (1158–3726)	2299 (1180–4364)
Change from baseline to Month 12	131 (-280–817)	518 (51–1544)
Troponin I, pg/mL, median (IQR)		
Baseline[c]	64.00 (38.60–92.00)	60.20 (38.15–103.10)
Month 12[d]	67.75 (37.40–114.10)	72.10 (45.60–127.35)
Change from baseline to Month 12	3.75 (-7.10–19.90)	14.50 (0.00–32.20)

Abbreviations: IQR = interquartile range; NT-proBNP = N-terminal pro-brain natriuretic peptide.
[a]N evaluable=181 (patisiran), 178 (placebo).
[b]N evaluable=167 (patisiran), 163 (placebo).
[c]N evaluable=174 (patisiran), 172 (placebo).
[d]N evaluable=158 (patisiran), 155 (placebo).

Echocardiographic Parameters

Echocardiographic parameters were assessed as exploratory endpoints to evaluate the change from baseline in LV structure and function at 12 months. The change from baseline in LV mass at 12 months was -1.00 g (95% CI: -7.31, 5.32) in the patisiran arm and 8.45 g (95% CI: 2.02, 14.89) in the placebo arm, resulting in a between-group LS mean difference of -9.45 g (95% CI: -18.48, -0.42).[1]

The change from baseline in LV global longitudinal strain at 12 months was 0.36 percentage points (95% CI: 0.01, 0.71) in the patisiran arm and 0.90 percentage points (95% CI: 0.55, 1.26) in the placebo arm, resulting in a between-group LS mean difference of -0.54 percentage points (95% CI: -1.04, -0.05).[1]

The change in LV stroke volume was 0.48 mL (95% CI, -1.19, 2.15) in the patisiran arm and -2.52 mL (95% CI, -4.21, -0.82) in the placebo arm, with a between-group LS mean difference of 3.00 mL (95% CI: 0.61, 5.38).[1]

Technetium Scintigraphy

Overall, 40 patients in the patisiran arm and 37 patients in the placebo arm were evaluated with scintigraphy at baseline, and 37 patients in the patisiran arm and 28 patients in the placebo arm were evaluated at 12 months.[8]

Of the 37 evaluable patients in the patisiran arm, all had either reduced or stable Perugini grade compared to baseline at 12 months; 14 patients (37.8%) showed a reduction of ≥1 Perugini grade, including 3 patients (8.1%) who showed a reduction of ≥2 Perugini grades from baseline at 12 months. Of the 28 evaluable patients in the placebo arm, none had a reduced Perugini grade compared to baseline at 12 months; 1 patient (3.6%) showed an increase in Perugini grade.[8]

SAFETY RESULTS

During the 12-month treatment period, AEs were reported in 91% of patients in the patisiran arm and 94% of patients in the placebo arm (**Table 4**). The majority of AEs were mild or moderate in severity, and the frequency of serious and severe AEs was similar between the two arms. AEs that were reported in ≥5% of patients in the patisiran arm and seen ≥3% more frequently with patisiran than with placebo were IRRs, arthralgia, and muscle spasms. Serious AEs reported in ≥2% of patients in either arm were cardiac failure, atrial fibrillation, complete atrioventricular block, amyloidosis, and syncope. In the safety analysis, 5 deaths (3%) occurred in the patisiran arm and 8 deaths (4%) occurred in the placebo arm. No clinically relevant changes in laboratory measures, vital signs, or electrocardiograms were observed in either treatment arm during the study.[1]

Table 4. Adverse Events in APOLLO-B at 12 Months.[1]

Event, n (%)	Patisiran (n=181)	Placebo (n=178)
Any AE	165 (91)	168 (94)
AEs occurring in ≥10% of patients in either group		
Cardiac failure	54 (30)	68 (38)
Infusion-related reaction	22 (12)	16 (9)
Constipation	20 (11)	19 (11)
Atrial fibrillation	16 (9)	26 (15)
Covid-19	16 (9)	25 (14)
AEs occurring in ≥5% of patients treated with patisiran and ≥3% more common in the patisiran arm		
Infusion-related reaction	22 (12)	16 (9)
Arthralgia	14 (8)	8 (4)
Muscle spasm	12 (7)	4 (2)
Any serious AE[a]	61 (34)	63 (35)
Any severe AE[b]	47 (26)	52 (29)
Serious AEs occurring in ≥2% of patients in either group		
Cardiac failure	15 (8)	13 (7)
Atrial fibrillation	5 (3)	4 (2)
Atrioventricular block complete	2 (1)	4 (2)
Amyloidosis[c]	1 (1)	4 (2)
Syncope	2 (1)	4 (2)
Cardiac AEs[d]	82 (45)	100 (56)
Cardiac serious AEs[d]	32 (18)	28 (16)
AEs leading to treatment discontinuation	5 (3)	5 (3)
Deaths (safety analysis)[e]	5 (4)	8 (4)

Abbreviations: AE = adverse event; ATTR = transthyretin amyloidosis; HF = heart failure; MedDRA = Medical Dictionary for Regulatory Activities.

[a]Defined as AEs that resulted in death, were life-threatening, resulting in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators.
[b]All AEs were graded for severity. Severe AEs were defined as AEs for which more than minimal, local, or noninvasive intervention was received which had a severe effect on limiting self-care activities of daily living; or which had the potential for life-threatening consequences or death.
[c]Included AEs that were reported as worsening amyloidosis, ATTR disease progression, worsening of amyloid polyneuropathy, and amyloidosis in the bladder.
[d]Included all events selected according to the MedDRA, version 23.0, system organ class: Cardiac disorders.
[e]Deaths in the patisiran arm included sudden cardiac death (1 patient), death due to Covid-19, HF, pancreatitis (1 patient each), and undetermined death (1 patient). Deaths in the placebo arm included death due to HF (3 patients), undetermined death (2 patients), and death due to cholangitis, infection, pancreatic cancer (1 patient each). Heart transplantation and the implantation of left ventricular assist devices were counted as deaths in the efficacy analysis but were not counted as deaths in the safety analysis.

Cardiac Safety Summary

Table 5 below summarizes the cardiac safety findings from APOLLO-B, providing the number of events identified within Standardized MedDRA Queries.[9]

Table 5. APOLLO-B Cardiac Safety Summary at 12 Months.[9]

At least one event, n (%)	Patisiran (n=181)	Placebo (n=178)
Cardiac disorders (system organ class)[a]	82 (45.3)	100 (56.2)
Cardiac arrhythmia high-level group term	35 (19.3)	48 (27.0)
Supraventricular arrhythmias (including atrial fibrillation)	24 (13.3)	36 (20.2)
Ventricular arrhythmias and cardiac arrest	5 (2.8)	8 (4.5)
Cardiac conduction disorders	8 (4.4)	10 (5.6)
Rate and rhythm disorders not elsewhere classified	5 (2.8)	4 (2.2)
Cardiac failure SMQ (broad)	69 (38.1)	84 (47.2)
QT Prolongation / Torsade de pointes SMQ[b]	12 (6.6)	18 (10.1)

Abbreviations: QT = QT interval; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query.
[a]Based on MedDRA "Cardiac Disorders" System Organ Class.
[b]There were no identified cases of Torsade de pointes

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; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; HIV = human immunodeficiency virus; HL = Hodges-Lehmann; HR = hazard ratio; IQR = interquartile range; IRR = infusion-related reaction; IV = intravenous; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; LV = left ventricular; m = meter; mBMI = modified body mass index; MMRM = mixed model repeated measures; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; QT = QT interval; ROW = rest of world; SAE = serious adverse event; SD = standard deviation; SE = standard error; SEM = standard error of the mean; SGLT2 = sodium-glucose cotransporter-2; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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