Primary Results from APOLLO-B Open-label Extension Study of Patisiran in Patients with Transthyretin Cardiac Amyloidosis

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Conclusions

- Patients with transthyretin-mediated (ATTR) cardiac amyloidosis treated with patisiran for 24 months demonstrated sustained benefit across endpoints (6-minute walk test [6MWT], Kansas City Cardiomyopathy Questionnaire-Overall summary [KCCQ-OS]) and cardiac biomarkers (NT-proBNP and troponin I)
- Placebo-treated patients who initiated patisiran displayed relative stabilization or slowing of progression across multiple endpoints (6MWT, KCCQ-OS, NT-proBNP, troponin I) at Month 24 compared with results at Month 12
- Composite outcome and mortality analyses across the DB and OLE periods did not show significant differences; however, favorable trends were observed
- Patisiran demonstrated an acceptable safety profile
- The overall benefit–risk profile of patisiran in patients with ATTR cardiac amyloidosis continued to be favorable through Month 24

Introduction

ATTR Amyloidosis

- A progressive and fatal disease caused by accumulation of transthyretin (TTR) amyloid fibrils in multiple organs and tissues, including the heart[1–4]
- Ongoing TTR amyloid deposition in the heart drives the progression of cardiomyopathy, leading to worsening heart failure (HF) and arrythmias, decline in functional status and quality of life (QOL), increased hospitalizations, and reduced survival[5–11]

Patisiran

- An intravenously (IV) administered RNA interference therapeutic approved for the treatment of hereditary ATTR (ATTRv) amyloidosis with polyneuropathy[12]
- Prior clinical data in patients with ATTRv amyloidosis with polyneuropathy suggest the potential for patisiran to improve cardiac manifestations of ATTR amyloidosis[11,13]

APOLLO-B Phase 3 Study in ATTR Cardiac Amyloidosis

- During the 12-month, double-blind (DB) period of the Phase 3 APOLLO-B study (NCT03997383), patisiran preserved functional capacity, and health status and QOL in patients with ATTR cardiac amyloidosis whereas placebo was associated with steady worsening[14]
  - Patients completing the 12-month DB period were eligible to continue treatment in the open-label extension (OLE) where all patients received patisiran

Objectives

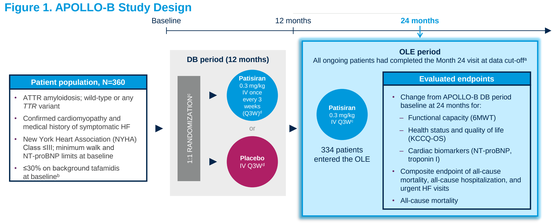
- To evaluate the efficacy and safety of patisiran in patients with ATTR cardiac amyloidosis from an interim analysis after all ongoing patients had completed Month 24 in the APOLLO-B study

Methods

Patisiran Phase 3 APOLLO-B Study

- APOLLO-B is an international, randomized, placebo-controlled study in patients with ATTR (wild-type ATTR [ATTRwt] and ATTRv) cardiac amyloidosis, evaluating the efficacy and safety in a 12-month DB period followed by an OLE period (**Figure 1**)
  - 360 patients enrolled in APOLLO-B at 69 sites in 21 countries
  - 334 patients entered the OLE period; here we present results from an interim analysis performed after all ongoing patients had completed Month 24

Figure 1. APOLLO-B Study Design



[a]All available efficacy and safety data through to cut-off date June 26, 2023; analysis of outcomes endpoints and safety data include all data through the data cut-off, including data beyond the Month 24 timepoint. [b]Where tafamidis is available as local standard of care; receiving tafamidis treatment ≥6 months with disease progression in opinion of investigator. [c]Stratification: Background tafamidis (yes or no); ATTRv versus ATTRwt amyloidosis; NYHA Class I/II and age <75 years versus all others. [d]To reduce likelihood of infusion-related reactions, patients receive the following premedications or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen; histamine (H)-1 and H2 blockers.

Results

Baseline Demographics and Disease Characteristics

- Baseline demographics and disease characteristics were comparable across the treatment groups (**Table 1**)

Results, continued

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Patisiran (N=181)	Placebo (N=178)
Age, median (range), years	76 (47–85)	76 (41–85)
Male sex, n (%)	161 (89.0)	160 (89.9)
Race, n (%)		
White	138 (76.2)	140 (78.7)
Asian	23 (12.7)	15 (8.4)
Black or African American	16 (8.8)	15 (8.4)
ATTRwt amyloidosis, n (%)	144 (79.6)	144 (80.9)
Time since diagnosis of ATTR amyloidosis, median (range), years	0.8 (0–6)	0.4 (0–10)
Baseline tafamidis use, n (%)	46 (25.4)	45 (25.3)
NYHA Class, n (%)		
Class I	10 (5.5)	15 (8.4)
Class II	156 (86.2)	150 (84.2)
Class III	15 (8.3)	13 (7.3)
ATTR amyloidosis stage[a], n (%)		
Stage 1	124 (68.5)	120 (67.4)
Stage 2	46 (25.4)	45 (25.3)
Stage 3	11 (6.1)	13 (7.3)
Polyneuropathy disability score, n (%)		
0: no impairment	96 (53.0)	109 (61.2)
I: preserved walking, with sensory disturbances	63 (34.8)	55 (30.9)
II: impaired walking without need for a stick or crutches	22 (12.2)	14 (7.9)
6MWT, m, median (IQR)	358.0 (295.0–420.0)	367.7 (300.0–444.3)
KCCQ-OS, points, mean (SD)	69.8 (21.2)	70.3 (20.7)
NT-proBNP level, ng/L, median (interquartile range [IQR])	2008 (1135–2921)	1813 (952–3079)
High-sensitivity troponin I level, ng/L, median (IQR)	64.0 (38.6–92.0)[b]	60.2 (38.2–103.1)[c]
Estimated glomerular filtration rate (eGFR), mL/min/1.73 m², median (IQR)	71.0 (58.0–83.0)	67.0 (51.0–84.0)

[a]Patients are stratified into prognostic categories using the serum biomarkers 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 m²; 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 m². [b]n=174. [c]n=172.

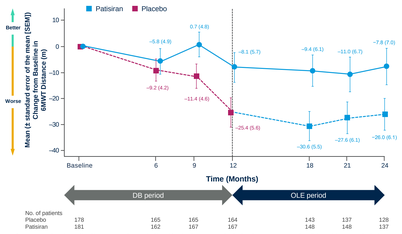
Functional Capacity, and Health Status and QOL

- Patients randomized to patisiran maintained treatment benefit on both functional capacity (6MWT distance) and health status and QOL (KCCQ-OS score) through 24 months of treatment
  - The mean change from baseline in 6MWT distance at Month 24 was −7.8 m, similar to the change from baseline at Month 12 of −8.1 m, suggesting relative stability from Month 12 (**Figure 2**)
    - Decline in 6MWT distance was comparable to the expected age-related decline of ~5 m/year in healthy adults[15]
  - A mean decrease of 1.2 points in KCCQ-OS score at Month 24 compared with baseline was observed (**Figure 3**)
- In patients who received placebo in the DB period, switching to patisiran in the OLE resulted in relative stability in both 6MWT and KCCQ-OS between Month 12 and Month 24 compared with the DB period (**Figures 2 and 3**)

Exploratory Analysis: Cardiac Biomarkers

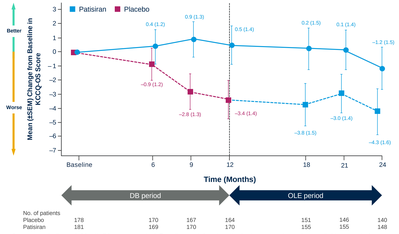
- Patients originally randomized to patisiran demonstrated a similar annual adjusted geometric mean fold change in NT-proBNP (**Figure 4**), and a decreased annual adjusted geometric mean fold change in troponin I (**Figure 5**) between the DB and OLE periods
  - The ratio of adjusted geometric mean fold change between the OLE and DB periods was nominally significant for troponin I (0.88 [95% confidence interval (CI), 0.80, 0.97]; p=0.009)
- Patients randomized to placebo showed higher annual adjusted geometric mean fold changes in cardiac biomarker levels during the DB period compared with the patisiran group, which decreased after initiation of patisiran in the OLE to values comparable to the patisiran group (**Figures 4 and 5**)
  - The ratio of adjusted geometric mean fold change between the OLE and DB periods was nominally 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)

Figure 2. Mean Change from Baseline in 6MWT over 24 Months



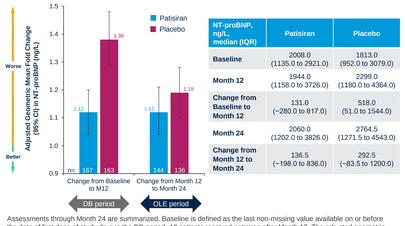
Assessments where the timer was stopped after 64 minutes or conducted using unapproved walking aid are excluded from the analysis. Assessments through Month 24 are presented. Baseline is defined as the last non-missing value available prior to first dose of study drug in the DB period. All patients received patisiran after Month 12.

Figure 3. Mean Change from Baseline in KCCQ-OS over 24 Months



Assessments through Month 24 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 Month 12.

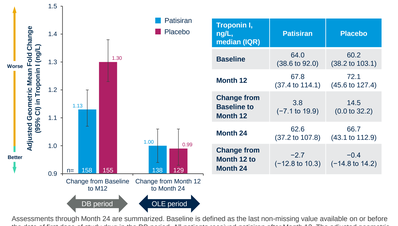
Figure 4. Annual Adjusted Geometric Mean Fold Change in NT-proBNP over 24 Months



NT-proBNP, ng/L, median (IQR)	Patisiran	Placebo
Baseline	2008.0 (1135.0 to 2921.0)	1813.0 (952.0 to 3079.0)
Month 12	1944.0 (1158.0 to 3726.0)	2299.0 (1180.0 to 4364.0)
Change from Baseline to Month 12	131.0 (−280.0 to 817.0)	518.0 (51.0 to 1544.0)
Month 24	2060.0 (1202.0 to 3826.0)	2764.5 (1271.5 to 4543.0)
Change from Month 12 to Month 24	136.5 (−198.0 to 836.0)	292.5 (−83.5 to 1200.0)

Assessments through Month 24 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 Month 12. The adjusted geometric mean fold-changes and 95% CIs were obtained using mixed-effects model repeated measures (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 amyloidosis, 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.

Figure 5. Annual Adjusted Geometric Mean Fold Change in Troponin I over 24 Months



Troponin I, ng/L, median (IQR)	Patisiran	Placebo
Baseline	64.0 (38.6 to 92.0)	60.2 (38.2 to 103.1)
Month 12	67.8 (37.4 to 114.1)	72.1 (45.6 to 127.4)
Change from Baseline to Month 12	3.8 (−7.1 to 19.9)	14.5 (0.0 to 32.2)
Month 24	62.6 (37.2 to 107.8)	66.7 (43.1 to 112.9)
Change from Month 12 to Month 24	−2.7 (−12.8 to 10.3)	−0.4 (−14.8 to 14.2)

Assessments through Month 24 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 Month 12. 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 amyloidosis, 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.

Figure 6A. Mean Cumulative Function Plot of All-Cause Mortality, All-Cause Hospitalization, and Urgent HF Visits over 24 Months[a,b,c]

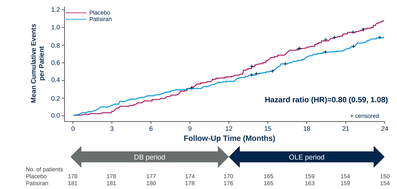
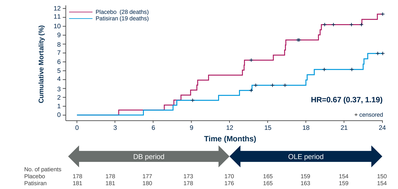


Figure 6B. Cumulative Plot of All-Cause Mortality over 24 Months[a,b,d,e]



[a]Heart transplantation and left ventricular assist device placement are handled in the same manner as death. Deaths, hospitalizations, and urgent HF visits due to COVID-19 are excluded from analysis. For patients who discontinued treatment during the DB period, events occurring after Day 417 are excluded. For patients who discontinued treatment during the OLE period, events occurring more than 90 days after last patisiran dose are excluded. The figure is truncated at Day 731; events that occurred after Day 731 are included in the estimate of the HR but not shown in the figure. [b]The analysis was based on the intention-to-treat principle and analyzed each treatment arm from initial randomization through the cut-off date, ignoring entry into the OLE. [c]The HR is derived using the modified Andersen–Gill model stratified by background tafamidis use, including randomized treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates. An HR <1 represents a favourable outcome for patisiran. [d]The HR is derived using the Cox proportional hazards model including randomized treatment as a covariate. [e]8 and 7 deaths in patients initially randomized to placebo and patisiran, respectively, that occurred after Day 731 are included in the estimate of HR but not shown in the figure.

Composite Endpoints of All-Cause Mortality, Hospitalization, and Urgent HF Visits

- The study was not powered to detect a treatment difference in death and hospitalization; no statistically significant difference was observed
- During the DB and entire OLE periods, the point estimate of HR for the composite of all-cause mortality and frequency of all-cause hospitalization and urgent HF visits was 0.80 (95% CI, 0.59, 1.08) (**Figure 6A**)
- All-cause mortality trended lower with patisiran (19 deaths) compared with placebo (28 deaths) (HR 0.67 [95% CI, 0.37, 1.19]) (**Figure 6B**)

APOLLO-B Overall and Cardiac Safety Summary

- Median exposure to patisiran was 27.3 (range 0.0–43.2) months across the DB and OLE periods in patients randomized to patisiran (patisiran/patisiran) and was 15.2 (range 0.7–30.9) months in patients randomized to placebo who received patisiran in the OLE period (placebo/patisiran)
- The majority of adverse events (AEs) were mild or moderate in severity (**Table 2**)
- The most common related AE was infusion-related reactions (15.0% of patients)
- The rate of AEs, including cardiac events, did not increase with longer treatment
- The type and nature of cardiac events observed were consistent with the underlying disease (**Table 3**)
- The safety profile of patisiran in APOLLO-B was consistent with that previously established in a polyneuropathy population, with no new safety concerns identified

Table 2. Summary of AEs in Patients Receiving Patisiran[a]

At least 1 event	Patisiran/patisiran N=181 (patient-years [PY]=407.8)		Placebo/patisiran N=166 (PY=221.9)		All patisiran N=347 (PY=629.7)	
	N (%)	Exposure-adjusted event per 100 PY (ER)[b]	N (%)	ER[b]	N (%)	ER[b]
AEs	175 (96.7)	598.8	160 (96.4)	759.7	335 (96.5)	655.5
Serious AEs (SAEs)	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 study drug discontinuation	12 (6.6)	3.7	13 (7.8)	6.3	25 (7.2)	4.6
Deaths[c]	20 (11.0)	4.9	15 (9.0)	6.8	35 (10.1)	5.6

[a]Cumulative safety data during patisiran treatment as of a data cut-off date of June 26, 2023. Note: The placebo/patisiran group does not include safety events during treatment with placebo from the DB period. [b]ER rate per 100 PY. [c]Includes all AEs with an outcome of fatal (including COVID-19) regardless of treatment-emergent classification but does not include deaths that occurred after study withdrawal.

Table 3. Summary of Cardiac Safety[a]

Category	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[b]	N (%)	ER[b]	N (%)	ER[b]
Cardiac AEs (Cardiac disorders system organ class [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 arrhythmias (high-level group term)	66 (36.5)	32.9	42 (25.3)	32.0	108 (31.1)	32.6
Supraventricular arrhythmias (high-level term [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 standardized MeDRA query (narrow)	89 (49.2)	46.1	67 (40.4)	54.1	156 (45.0)	48.9

[a]Cumulative safety data during patisiran treatment as of a data cut-off date of June 26, 2023. Note: The placebo/patisiran group does not include safety events during treatment with placebo from the DB period. [b]ER rate per 100 PY.

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