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

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Introduction

ATTR Amyloidosis

- A progressive and fatal disease caused by accumulation of 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 HF and arrythmias, decline in functional status and QOL, increased hospitalizations, and reduced survival[5–11]

Patisiran

- An IV-administered RNA interference therapeutic approved for the treatment of 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, 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 OLE where all patients received patisiran

Objective

- 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
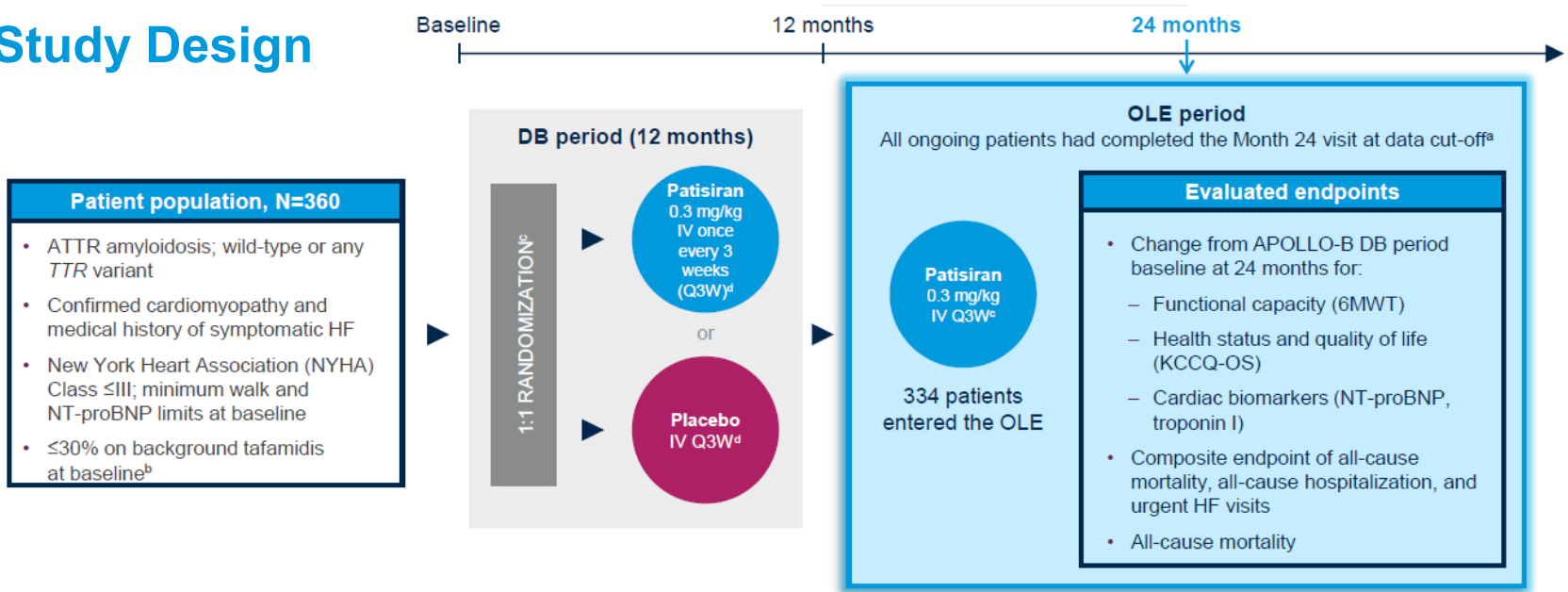
ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); DB, double-blind; HF, heart failure; IV, intravenous; OLE, open-label extension; QOL, quality of life; TTR, transthyretin. 1. Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 4. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 5. Castano et al. *Heart Fail Rev* 2015;20:163–78; 6. Swiecicki et al. *Amyloid* 2015;22:123–31; 7. Ruberg et al. *Am Heart J* 2012;164:222–8.e1; 8. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 9. Gertz et al. *Mayo Clin Proc* 1992;67:428–40; 10. Chacko et al. *Eur J Heart Fail* 2022;24:1700–12; 11. Adams et al. *N Engl J Med* 2018;379:11–21; 12. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. 2020. Available from: https://www.alnylam.com/wp-content/uploads/pdfs/ONPATTRO-Prescribing-Information.pdf (accessed June 23, 2023); 13. Solomon et al. *Circulation* 2019;139:431–43; 14. Maurer et al. *HFSA Congress* 2022. Poster Presentation.

Methods

Patisiran Phase 3 APOLLO-B Study

- APOLLO-B is an international, randomized, placebo-controlled study in patients with 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

6MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; DB, double-blind; H, histamine; HF, heart failure; IV, intravenous; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; Q3W, once every 3 weeks; TTR, transthyretin. [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; H1 and H2 blockers.

Baseline Demographic and Disease Characteristics

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

Table 1. Baseline 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)

Characteristic	Patisiran (N=181)	Placebo (N=178)
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 (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]
eGFR, mL/min/1.73 m^2, 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 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]n=174. [c]n=172. 6-MWT, 6MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTRwt, wild-type transthyretin; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

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**)

6MWT, 6-minute walk test; DB, double-blind; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; OLE, open-label extension; QOL, quality of life.

Functional Capacity, and Health Status and QOL (cont'd)

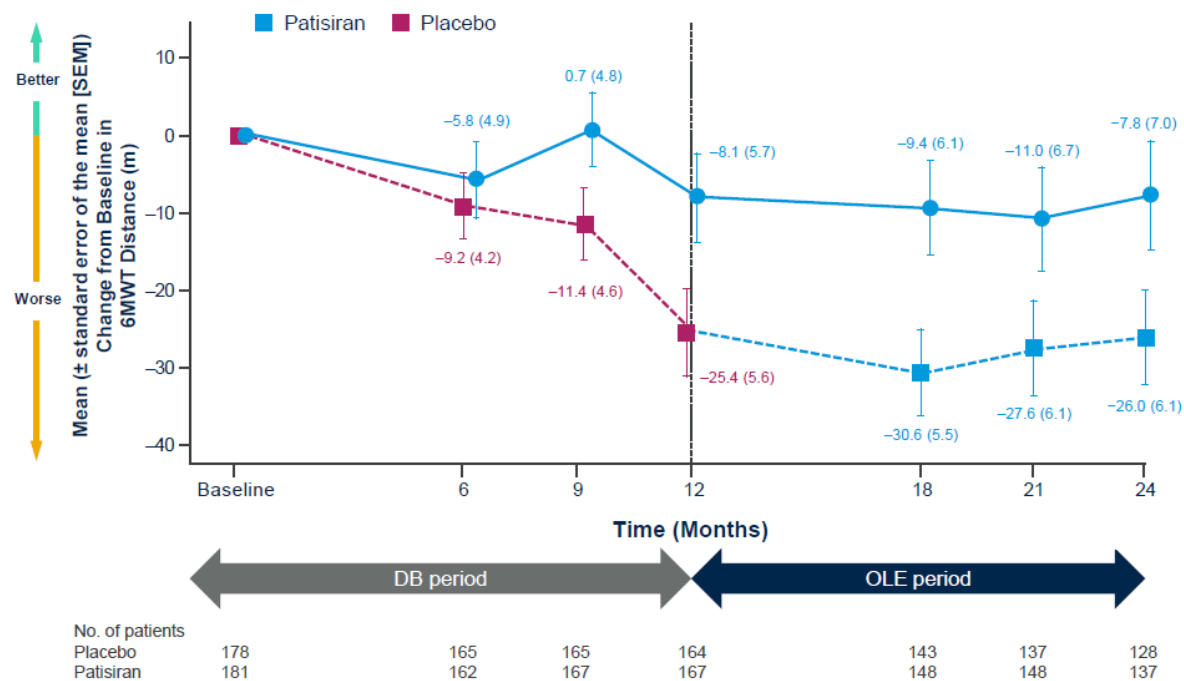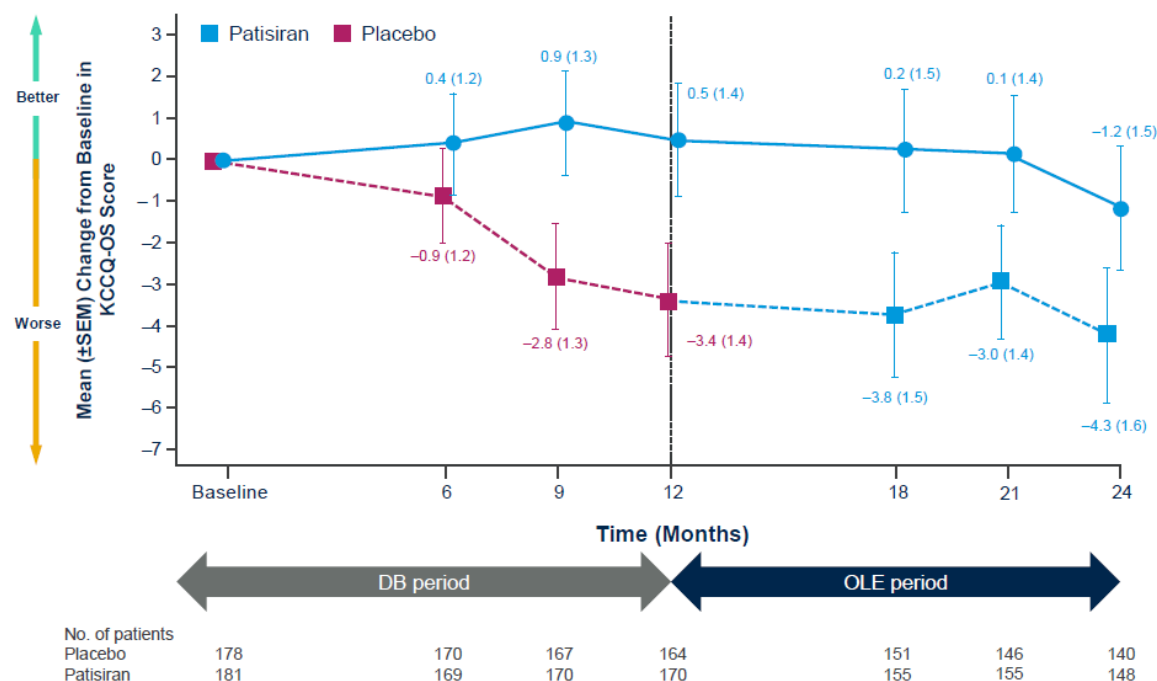## Figure 2. Mean Change from Baseline in 6MWT over 24 Months

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

Assessments where the timer was stopped after ≤4 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. 6MWT, 6-minute walk test; DB, double-blind; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; OLE, open-label extension; QOL, quality of life; SEM, standard error of the mean..

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% 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)

CI, confidence interval; DB, double-blind; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; OLE, open-label extension.

Exploratory Analysis: Cardiac Biomarkers (cont'd)

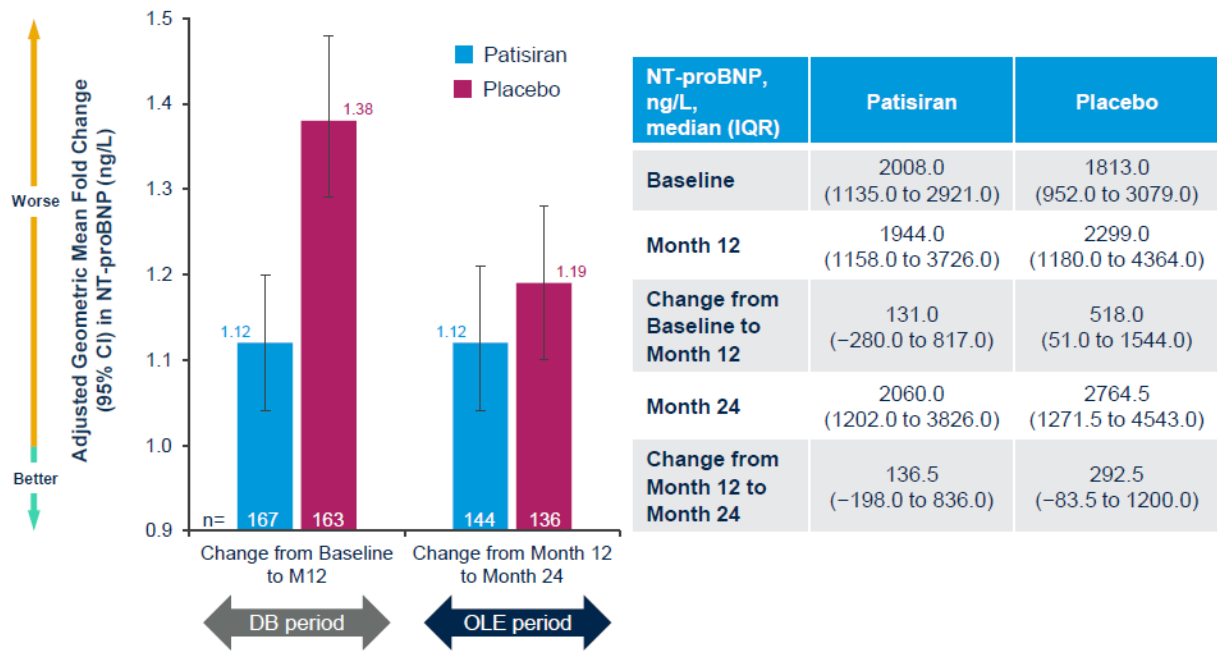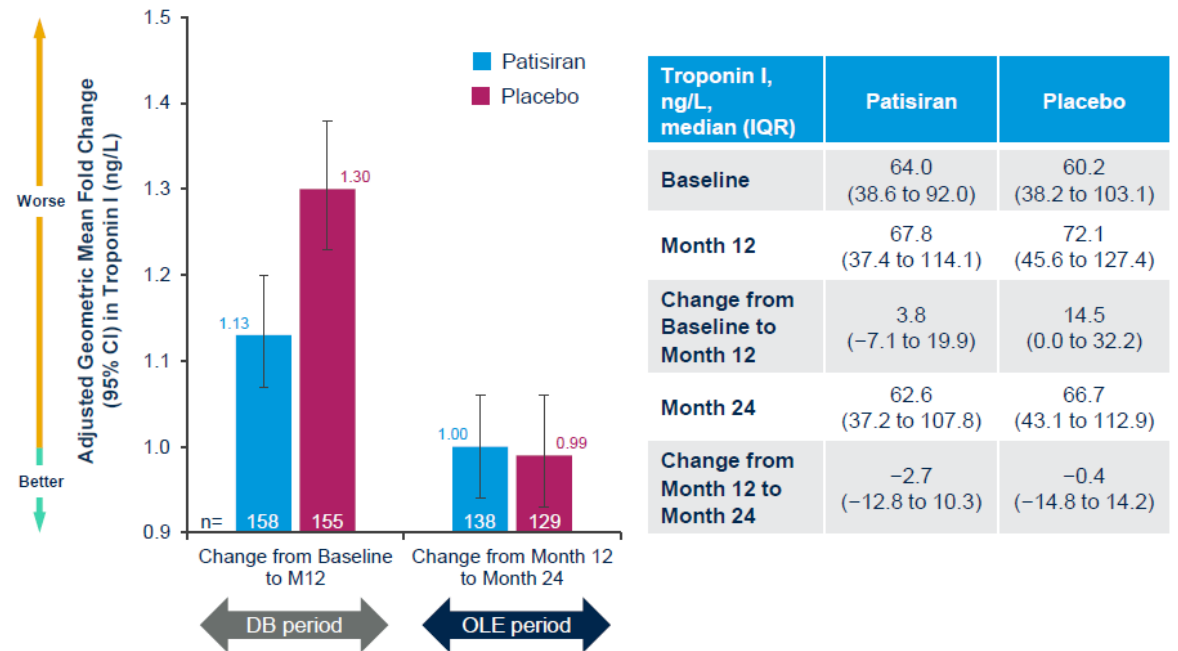## Figure 4. Annual Adjusted Geometric Mean Fold Change in NT-proBNP over 24 Months

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)

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. ATTR, transthyretin-mediated; CI, confidence interval; DB, double-blind; IQR, interquartile range; MMRM, mixed-effects model repeated measures; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; OLE, open-label extension.

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**)

CI, confidence interval; DB, double-blind; HF, heart failure; HR, hazard ratio; OLE, open-label extension.

Composite Endpoints of All-Cause Mortality, Hospitalization, and Urgent HF Visits (Cont'd)

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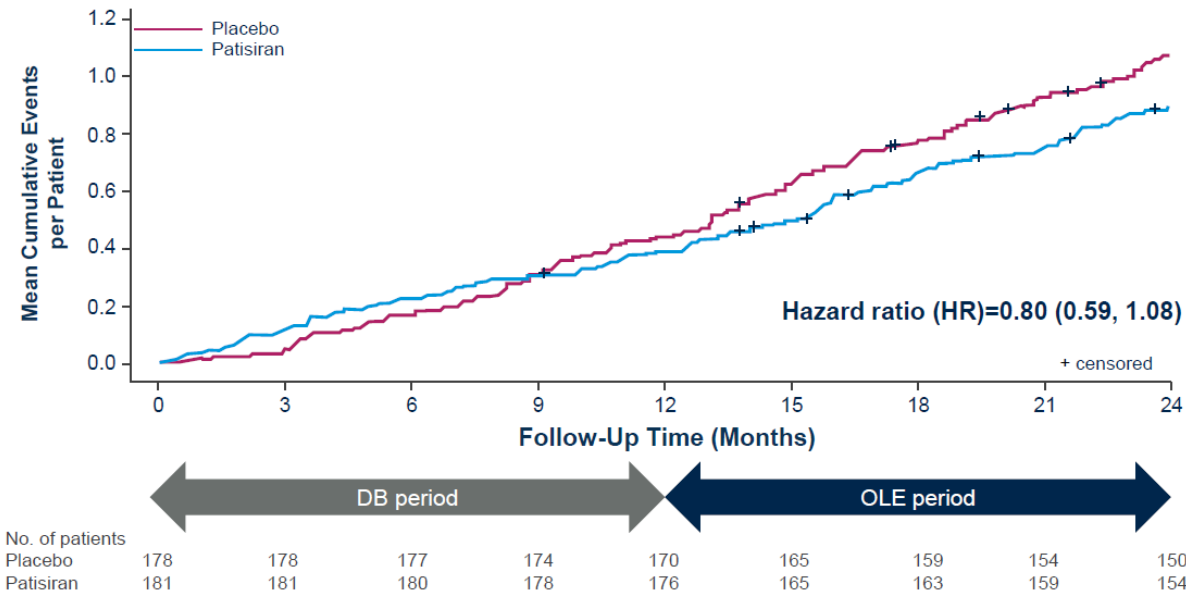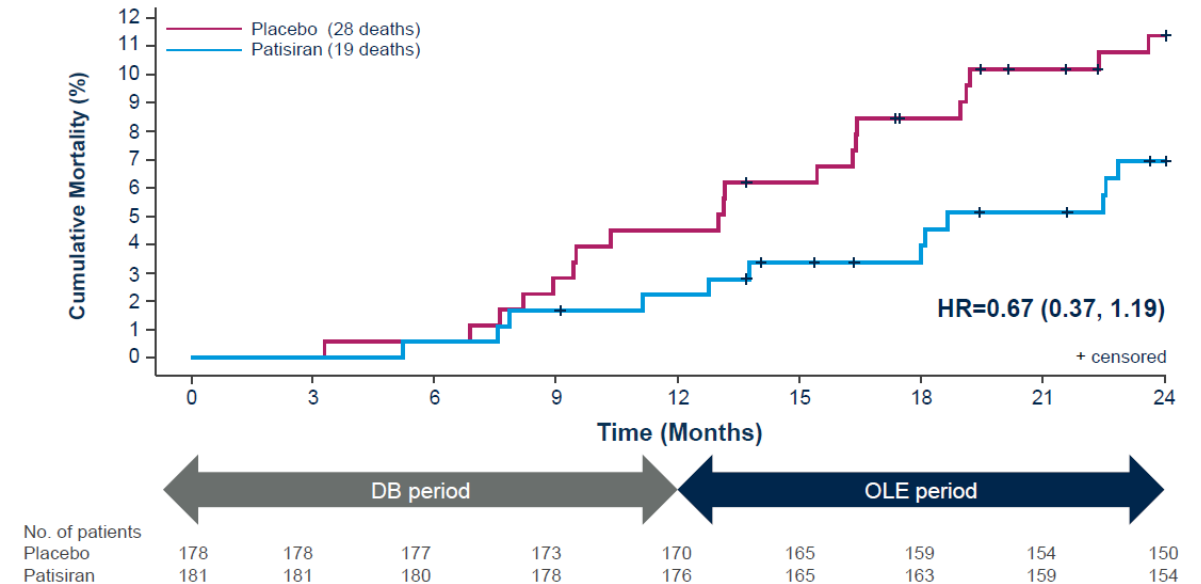
Figure 6B. Cumulative Plot of All-Cause Mortality over 24 Months[a,b,d,e]

Figure 6A: Mean Cumulative Events per Patient vs Follow-Up Time (Months). Placebo, Patisiran. Hazard ratio (HR)=0.80 (0.59, 1.08). + censored. DB period, OLE period.

No. of patients									
Placebo	178	178	177	174	170	165	159	154	150
Patisiran	181	181	180	178	176	165	163	159	154

Figure 6B: Cumulative Mortality (%) vs Time (Months). Placebo (28 deaths), Patisiran (19 deaths). HR=0.67 (0.37, 1.19). + censored. DB period, OLE period.

No. of patients									
Placebo	178	178	177	173	170	165	159	154	150
Patisiran	181	181	180	178	176	165	163	159	154

[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 favorable 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. ATTR, transthyretin-mediated; DB, double-blind; HF, heart failure; HR, hazard ratio; OLE, open-label extension.

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 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

AE, adverse event; DB, double-blind; OLE, open-label extension.

APOLLO-B Overall and Cardiac Safety Summary (cont'd)

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

At least 1 event	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]
AEs	175 (96.7)	598.8	160 (96.4)	759.7	335 (96.5)	655.5
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

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 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 (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 MedDRA 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. [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. AE, adverse event; DB, double-blind; ER, exposure-adjusted event rate per 100 patient-years; HLT, high level term; MedDRA, Medical Dictionaries for Regulatory Activities; OLE, open-label extension; PY, patient-years; SAE, serious adverse event; SOC, system organ class.

Conclusions

- Patients with ATTR cardiac amyloidosis treated with patisiran for 24 months demonstrated sustained benefit across endpoints (6MWT, 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

6MWT, 6-minute walk test; ATTR, transthyretin-mediated; DB, double-blind; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; OLE, open-label extension.

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