#AHA23

APOLLO-B, A STUDY OF PATISIRAN IN PATIENTS WITH TRANSTHYRETIN CARDIAC AMYLOIDOSIS: PRIMARY LONG-TERM RESULTS FROM THE OPEN-LABEL EXTENSION PERIOD

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American Heart Association.

DISCLOSURES

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BACKGROUND AND RATIONALE

Transthyretin (ATTR) Amyloidosis

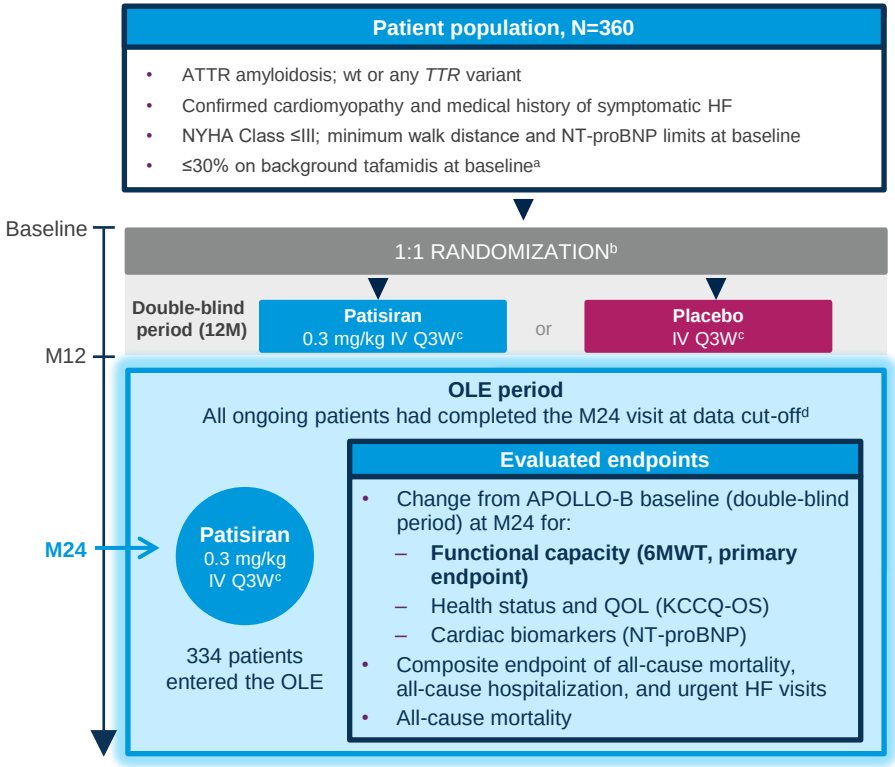
- A progressive and fatal disease caused by accumulation of TTR amyloid fibrils in multiple organs and tissues, including the heart[1–4]
- Ongoing TTR amyloid deposition in the heart drives the progression of cardiomyopathy, leading to worsening HF and arrythmias, decline in functional status and QOL,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

Patisiran & APOLLO-B Phase 3 Study in ATTR Cardiac Amyloidosis

- An IV-administered RNAi therapeutic approved for the treatment of ATTRv amyloidosis with polyneuropathy[12]
- During the 12-month double-blind period of the Phase 3 APOLLO-B study (NCT03997383), patisiran preserved functional capacity (primary endpoint), and health status and QOL in patients with ATTR cardiac amyloidosis[13]
- Patients completing the 12-month double-blind period were eligible to continue treatment in the OLE where all patients received patisiran

Objective

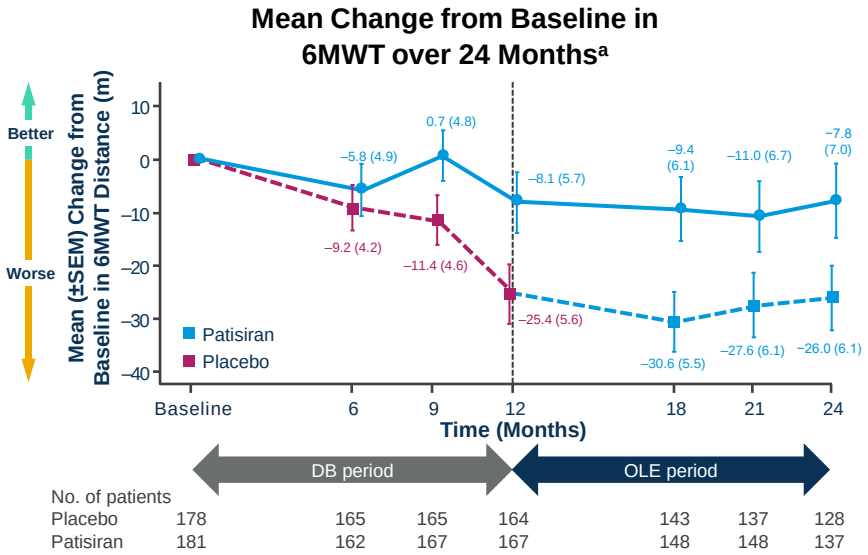
- To evaluate the efficacy and safety of patisiran in patients with ATTR cardiac amyloidosis from an interim analysis after all ongoing patients had completed M24 in the APOLLO-B study

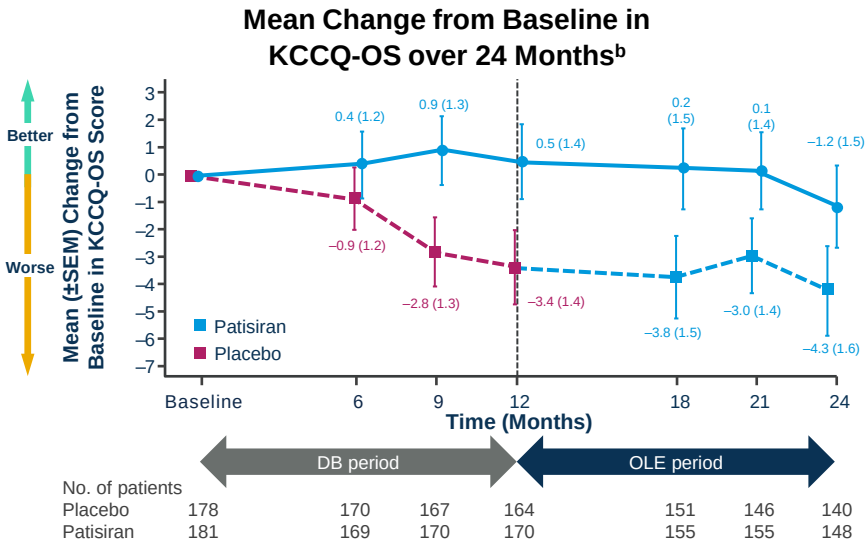


[a]Where tafamidis is available as local standard of care; receiving tafamidis treatment ≥6 months with disease progression in opinion of investigator. [b]Stratification: Background tafamidis (yes or no); ATTRv vs ATTRwt amyloidosis; NYHA Class I/II and age <75 years vs all others. [c]To reduce likelihood 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. [d]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 M24 timepoint. **Abbreviations:** 6MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); HF, heart failure; IV, intravenous; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; M, month; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; Q3W, once every 3 weeks; QOL, quality of life; RNAi, RNA interference; TTR, transthyretin; wt, wild-type.

FUNCTIONAL CAPACITY, 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
- 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



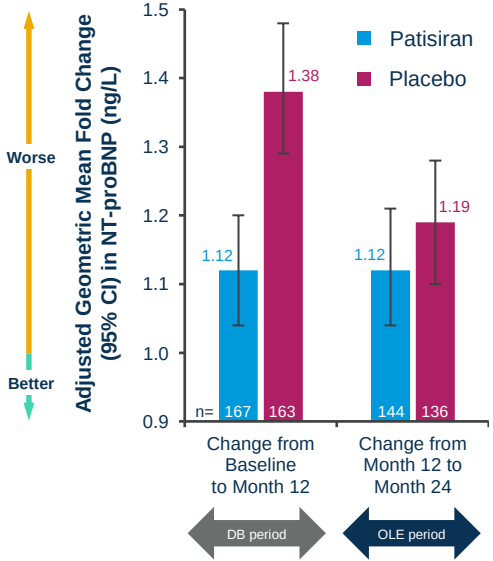


[a]Assessments where the timer was stopped after ≤4 minutes or conducted using unapproved walking aid are excluded from the analysis. Assessments through Month 24 are presented. Baseline is defined as the last non-missing value available prior to first dose of study drug in the DB period. All patients received patisiran after Month 12. [b]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. **Abbreviations:** 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.

NT-proBNP CARDIAC BIOMARKER

- Patients originally randomized to patisiran demonstrated a similar annual adjusted geometric mean fold change in NT-proBNP between the DB and OLE periods
- Patients randomized to placebo showed higher annual adjusted geometric mean fold changes in NT-proBNP 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

Annual Adjusted Geometric Mean Fold Change in NT-proBNP over 24 Months[a]



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)

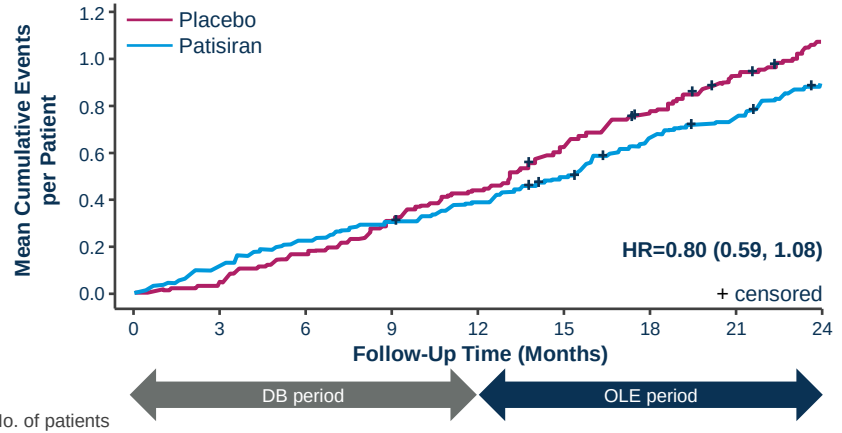
[a]Assessments through Month 24 are summarized. Baseline is defined as the last non-missing value available on or before the date of first dose of study drug in the DB period. All patients received patisiran after Month 12. The adjusted geometric mean fold changes and 95% CIs were obtained using MMRM. In the model, the outcome variable was the change from baseline in log-transformed NT-proBNP, 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-background tafamidis interaction, visit-by-background tafamidis interaction, and the treatment-by-visit-by-background tafamidis interaction.

Abbreviations: ATTR, transthyretin-mediated; CI, confidence interval; DB, double-blind; IQR, interquartile range; M, month; MMRM, mixed-effect 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

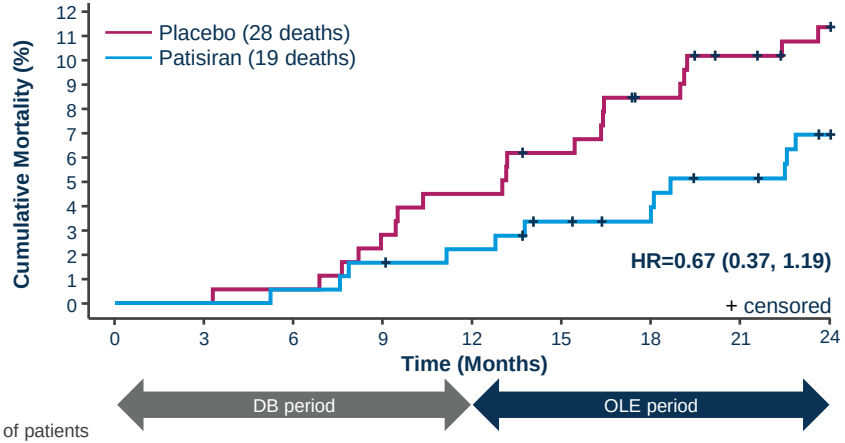
- The study was not powered to detect a treatment difference in death and hospitalization; no statistically significant difference was observed
- During the DB and entire OLE periods, the point estimate of HR for the composite of all-cause mortality and frequency of all-cause hospitalization and urgent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

Mean Cumulative Function Plot of All-Cause Mortality, All-Cause Hospitalization, and Urgent HF Visits over 24 Months[a–c]



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

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

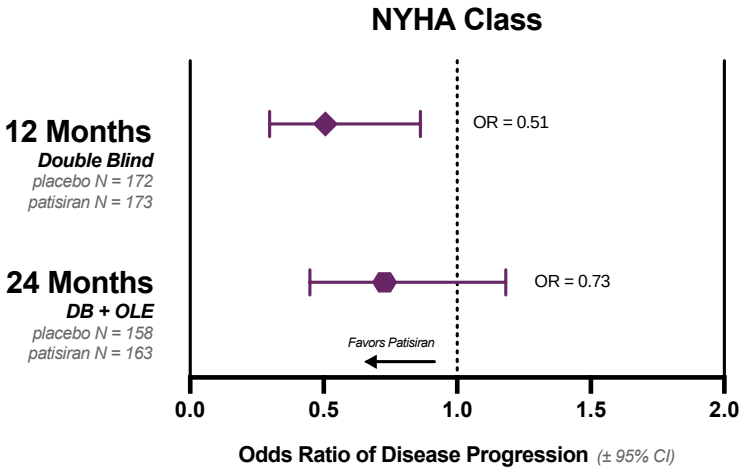


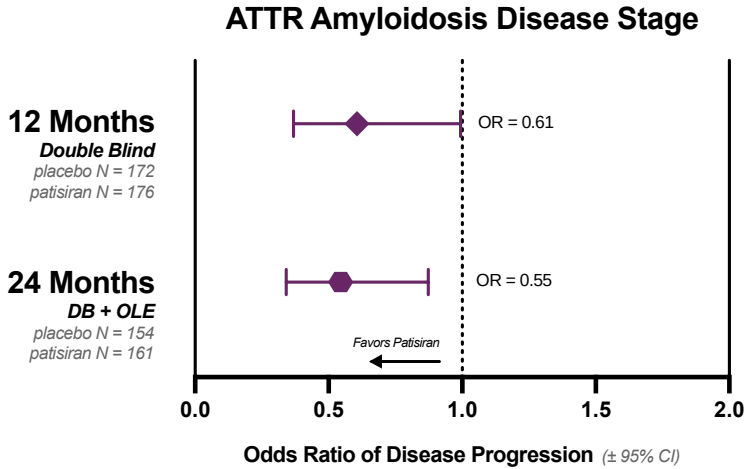
No. of patients									
Placebo	178	178	177	173	170	165	159	154	150
Patisiran	181	181	180	178	176	165	163	159	154

[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.

Abbreviations: ATTR, transthyretin-mediated; CI, confidence interval; DB, double-blind; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association; OLE, open-label extension.

CLINICAL DISEASE PROGRESSION: NYHA CLASS AND ATTR AMYLOIDOSIS DISEASE STAGE





Patisiran decreased the odds of heart failure progression by worsening NYHA class or death:

- 12 month, double blind: OR = 0.51 (95% CI, 0.30 – 0.86)
- 24 month, 1 year OLE: OR = 0.73 (95% CI, 0.45 – 1.18)

Patisiran decreased the odds of general disease progression by worsening ATTR amyloidosis disease stage or death:

- 12 month, double blind: OR = 0.61 (95% CI, 0.37 – 0.99)
- 24 month, 1 year OLE: OR = 0.55 (95% CI, 0.34 – 0.87)

An odds ratio <1 represents a favorable outcome for patisiran.
Abbreviations: ATTR, transthyretin-mediated; CI, confidence interval; DB, double-blind; NYHA, New York Heart Association; OLE, open-label extension; OR, odds ratio.

APOLLO-B OVERALL SAFETY SUMMARY

- Median exposure for patisiran was 27.3 (range 0.0–43.2) months in patients receiving patisiran in both the DB period and OLE (patisiran/patisiran), and 15.2 (range 0.7–30.9) months in patients who previously received placebo and switched to patisiran in the OLE (placebo/patisiran)
- 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

Summary of AEs in Patients Receiving Patisiran[a]

	Placebo/ Patisiran N=166 (PY=221.9)		Patisiran/ Patisiran N=181 (PY=407.8)		All Patisiran N=347 (PY=629.7)	
At Least 1 Event	N (%)	ER[b]	N (%)	ER[b]	N (%)	ER[b]
AEs	160 (96.4)	759.7	175 (96.7)	598.8	335 (96.5)	655.5
Serious AEs	87 (52.4)	107.7	111 (61.3)	71.9	198 (57.1)	84.5
Severe AEs	76 (45.8)	82.0	87 (48.1)	57.1	163 (47.0)	65.9
AEs leading to study drug discontinuation	13 (7.8)	6.3	12 (6.6)	3.7	25 (7.2)	4.6
Deaths[c]	15 (9.0)	6.8	20 (11.0)	4.9	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]Exposure-adjusted ER 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. **Abbreviations:** AE, adverse event; DB, double-blind; ER, event rate; OLE, open-label extension; PY, patient-years.

CONCLUSIONS

- Patients with ATTR cardiac amyloidosis treated with patisiran for 24 months demonstrated sustained benefit across clinical endpoints (6MWT, KCCQ-OS, and NT-proBNP)
- Placebo-treated patients who initiated patisiran displayed relative stabilization or slowing of progression across multiple endpoints (6MWT, KCCQ-OS, and NT-proBNP) at Month 24 compared with results at Month 12
- Odds of disease progression at 12 and 24 months were decreased for patients treated with patisiran, as assessed by NYHA class and ATTR Amyloidosis Disease Stage
- Patisiran demonstrated an acceptable safety profile
  - AEs were mostly mild or moderate and either consistent with the underlying disease or with the known patisiran safety profile; no new safety concerns were identified, including cardiac events, compared with the DB period
- The overall benefit–risk profile of patisiran in patients with ATTR cardiac amyloidosis continued to be favorable through Month 24

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the APOLLO-B study

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References: 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. Maurer et al. HFSA Congress 2022. Poster Presentation.

Abbreviations: 6MWT, 6-minute walk test; AE, adverse event; ATTR, transthyretin-mediated; DB, double-blind; 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.

THANK YOU

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Scientific Sessions

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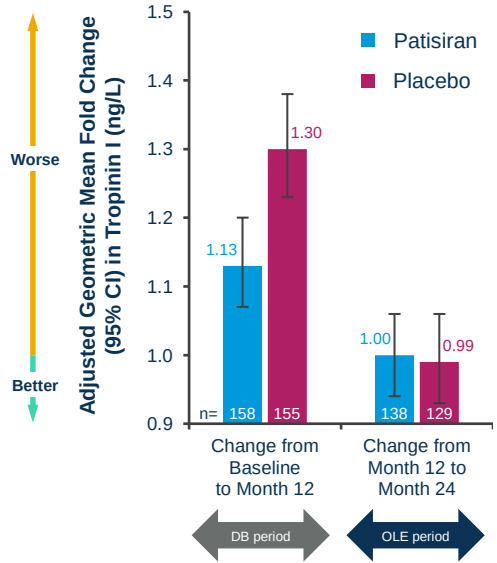
TROPONIN I CARDIAC BIOMARKER

- Patients originally randomized to patisiran demonstrated a decreased annual geometric mean fold change in troponin I, between the DB and OLE periods
- Patients randomized to placebo showed higher annual adjusted geometric mean fold changes in troponin I 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

Annual Adjusted Geometric Mean Fold Change in Troponin I over 24 Months[a]



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)

[a]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 log-transformed troponin I, 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-background tafamidis interaction, visit-by-background tafamidis interaction, and the treatment-by-visit-by-background tafamidis interaction.

Abbreviations: ATTR, transthyretin-mediated; CI, confidence interval; DB, double-blind; IQR, interquartile range; M, month; MMRM, mixed-effect model repeated measures; OLE, open-label extension.