Exploratory Analyses from APOLLO-B, A Phase 3 Study of Patisiran in Patients with ATTR Amyloidosis with Cardiomyopathy

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Introduction

Transthyretin-Mediated (ATTR) Amyloidosis

- A rapidly progressive and fatal disease caused by accumulation of amyloid fibrils in multiple organs and tissues[1–5]
- Patients with wild-type (wtATTR) or hereditary (hATTR) amyloidosis frequently develop cardiomyopathy[6–10]
- Results in progressive heart failure (HF), arrhythmias, declines in functional status and QOL, increased hospitalizations, and reduced survival[6–10]

Patisiran

- IV administered RNAi therapeutic approved for the treatment of hATTR amyloidosis with polyneuropathy
- Prior exploratory clinical data in patients with hATTR amyloidosis with polyneuropathy suggest the potential for patisiran to improve cardiac manifestations of ATTR amyloidosis[11,12]

Abbreviations: ATTR, transthyretin-mediated; hATTR, hereditary transthyretin-mediated; HF, heart failure; IV, intravenous; QOL, quality of life; RNAi, ribonucleic acid interference; TTR, transthyretin; wt, wild-type; wtATTR, wild-type transthyretin-mediated.

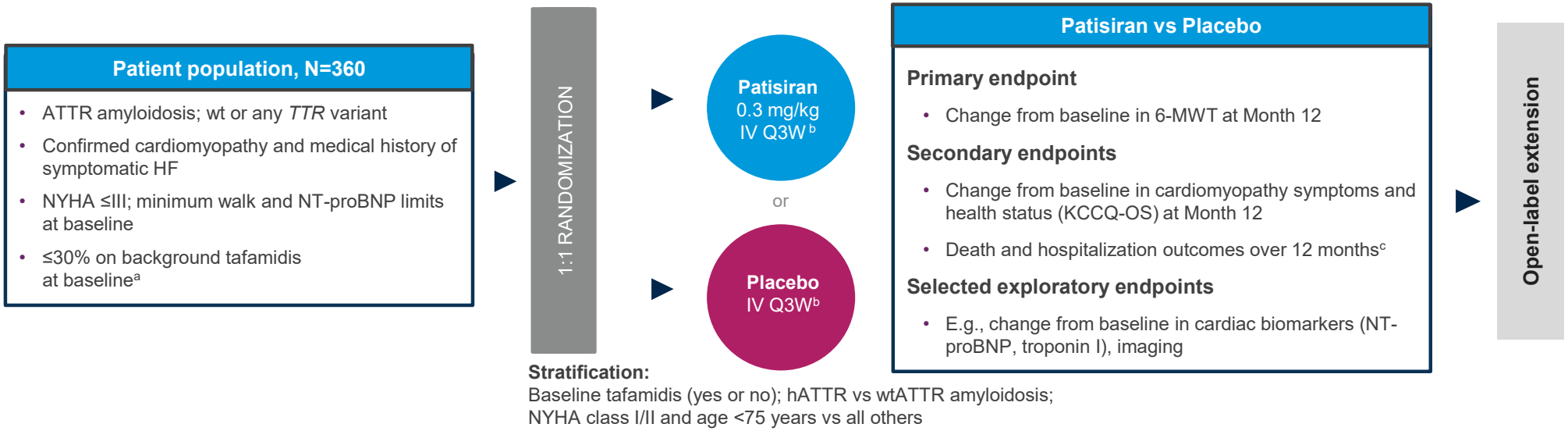
References: Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Maurer et al. J *Am Coll Cardiol* 2016;68:161–7i2; 4. Živković et al. *Amyloid* 2020;27:142–3; 5. Sipe et al. *Amyloid* 2014;21:221–4; 6. Castano et al. *Heart Fail Rev* 2015;20:163–78; 7. Swiecicki et al. *Amyloid* 2015;22:123–31; 8. Ruberg et al. *Am Heart J* 2012;164:222–8.e1; 9. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 10. Gertz et al. *Mayo Clin Proc* 1992;67:428–40; 11. Adams et al. *N Engl J Med* 2018;379:11–21; 12. Solomon et al. *Circulation* 2019;139:431–43.

Methods

Patisiran Phase 3 APOLLO-B Study

- Randomized, double-blind, placebo-controlled study in patients with ATTR amyloidosis with cardiomyopathy

Study Design: Patisiran Phase 3 APOLLO-B Study



Stratification:
Baseline tafamidis (yes or no); hATTR vs wtATTR amyloidosis;
NYHA class I/II and age <75 years vs all others

[a]Where tafamidis is available as local standard of care; receiving tafamidis treatment ≥6 months with disease progression in opinion of investigator. [b]To reduce likelihood of infusion-related reactions, patients receive following premedications or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen; H1 and H2 blockers. [c]Composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT; composite all-cause mortality, frequency of all-cause hospitalizations, and urgent HF visits in patients not on tafamidis at baseline; composite all-cause mortality, frequency of all-cause hospitalizations, and urgent HF visits in overall population.

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CV, cardiovascular; hATTR, hereditary transthyretin-mediated; HF, heart failure; IV, intravenous; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; Q3W, once every 3 weeks; TTR, transthyretin; wt, wild-type; wtATTR, wild-type transthyretin-mediated

Results

Baseline Biomarker and Echocardiographic Parameters

- Baseline patient demographics and characteristics,[1] including cardiac parameters, were comparable between the patisiran and placebo arms

Baseline Characteristics

Characteristic	Patisiran (n=181)	Placebo (n=178)
NT-proBNP level, ng/L, median (IQR)	2008 (1135–2921)	1813 (952–3079)
Troponin I level, ng/L, median (IQR)	64.00 (38.60–92.00)	60.20 (38.15–103.10)
Echocardiographic parameters, mean (SD)		
Mean LV wall thickness (cm)	1.781 (0.248)	1.786 (0.238)
LV relative wall thickness	0.835 (0.194)	0.855 (0.190)
LV mass (g)	335.485 (91.390)	326.445 (79.385)
LV end-diastolic volume (mL)	89.550 (24.600)	92.903 (26.246)
Global longitudinal strain (%)	–10.89 (3.36)	–11.19 (3.01)
Cardiac output (L/min)	3.442 (0.976)	3.519 (0.971)
LV ejection fraction (%)	55.604 (13.031)	56.219 (13.156)

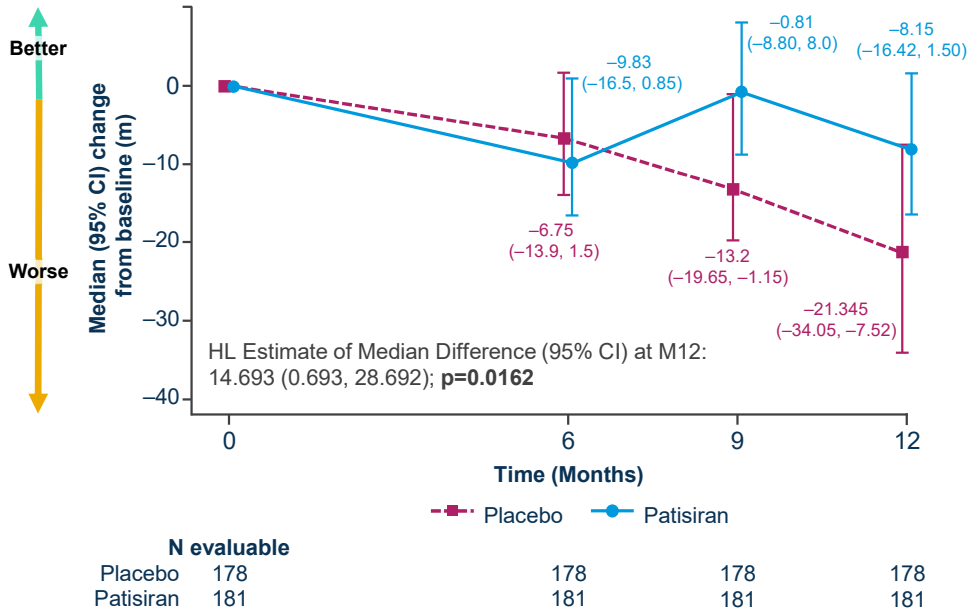
Abbreviations: IQR, interquartile range; LV, left ventricular; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; SD, standard deviation. **Reference:** 1. Maurer et al. *International Symposium on Amyloidosis (ISA)* 2022.

Results

Primary Analysis: Functional Capacity

- Patisiran demonstrated significant clinical benefit in functional capacity (6-MWT) compared with placebo at Month 12 (p=0.0162)[a]
  - Decline in 6-MWT with patisiran was similar to typical age-related decline seen in healthy adults[1–7]
- Prespecified sensitivity analysis (MMRM) confirmed robustness of the observed benefit in 6-MWT with patisiran vs placebo; LS mean (SEM) difference: 18.146 m (7.967), nominal p=0.0234[b]

Change from Baseline in 6-MWT at Month 12[a]



N evaluable				
Placebo	178	178	178	178
Patisiran	181	181	181	181

[a]Primary endpoint analysis based on the stratified Wilcoxon Rank Sum test. Median (95% CI) change from baseline values is 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 amyloidosis were imputed as 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 (295.00, 420.00) in the patisiran group and 367.74 (300.00, 444.25) in the placebo group. [b]LS means (SEM), LS mean (SEM) differences, 95% CIs, and Month 12 p-value were estimated from the MMRM model. The LS mean coefficients were computed using the observed proportions of the categorical covariates (baseline tafamidis use, type of ATTR amyloidosis, and age group). At baseline, the mean (SD) 6-MWT was 360.466 (102.268) in the patisiran group and 374.646 (102.392) in the placebo group. 6-MWT data for 2 patisiran patients were updated for this analysis following database lock, as updated by the investigator.

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; HL, Hodges–Lehmann; m, meter; M, month; MMRM, mixed effects model repeated measures; QOL, quality of life; SD, standard deviation; SEM, standard error of the mean.

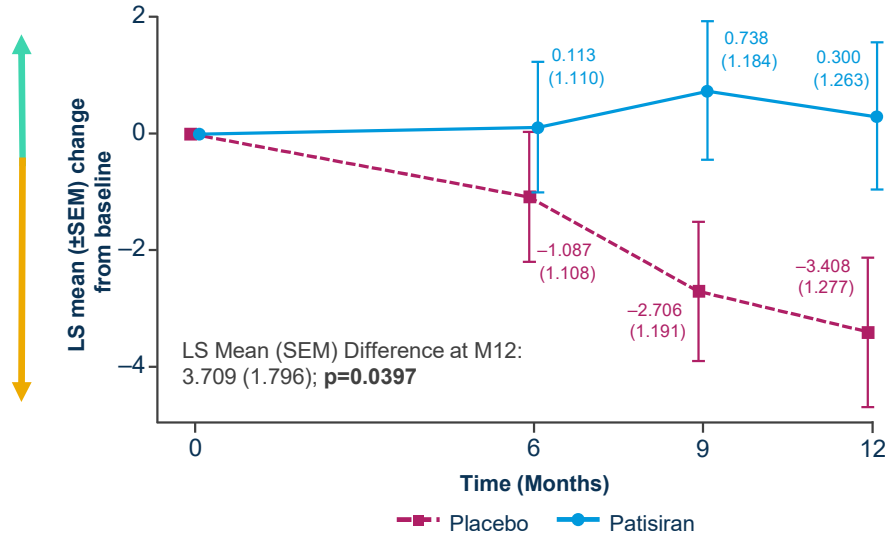
References: 1. Enright et al. *Am J Respir Crit Care Med* 1998;158:1384–7; 2. Troosters et al. *Eur Respir J* 1999;14:270–4; 3. Poh et al. *Respirology* 2006;11:211–6; 4. Camarri et al. *Respir Med* 2006;100:658–65; 5. Jenkins et al. *Physiother Theory Pract* 2009;25:516-22; 6. Casanova et al. *Eur Respir J* 2011;37:150–6; 7. Vaish et al. *Int J Tuberc Lung Dis* 2013;17:698–703.

Results

Secondary Analysis: Health Status/Quality of Life (QOL)

- Patisiran demonstrated significant clinical benefit in health status and QOL (KCCQ-OS) compared with placebo at Month 12 (p=0.0397)[a]

Change from Baseline in KCCQ-OS at Month 12[a]



N evaluable				
Placebo	178	170	167	164
Patisiran	181	169	170	170

[a]Analysis based on MMRM method. Missing data not explicitly imputed and assumed to be missing at random. At baseline, the mean (±SD) KCCQ-OS was 69.836 (21.178) in the patisiran group and 70.330 (20.709) in the placebo group.

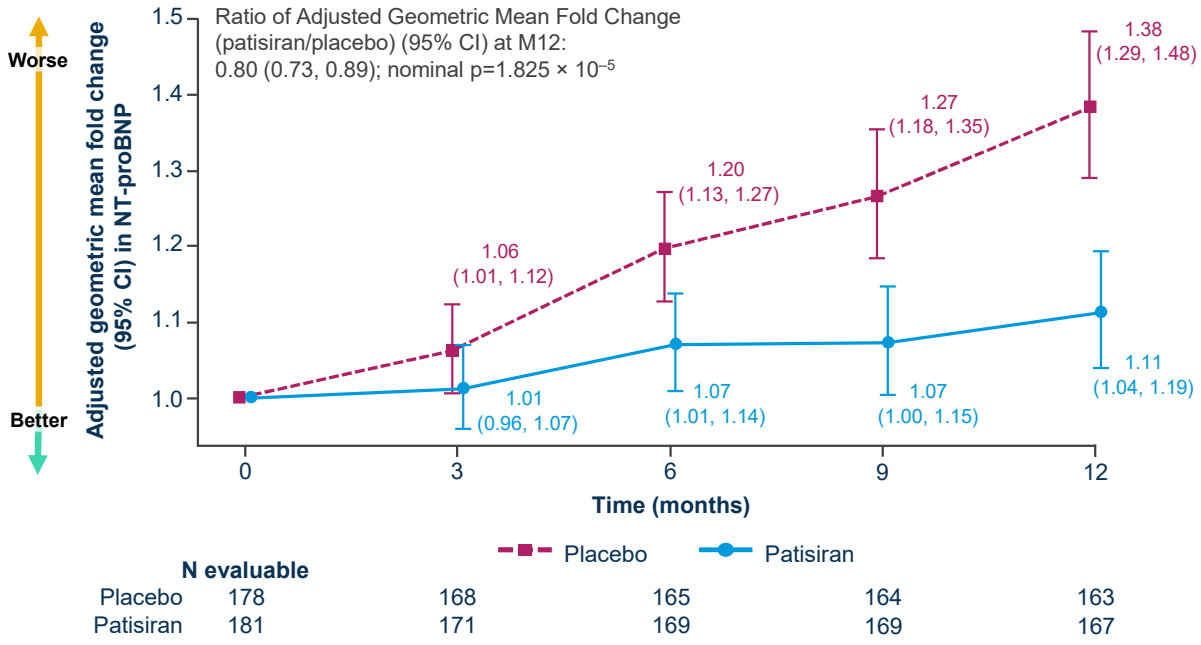
Abbreviations: KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); LS, least squared; M, month; MMRM, mixed effects model repeated measures; QOL, quality of life; SD, standard deviation; SEM, standard error of the mean.

Results

Exploratory Analysis: Change from Baseline in NT-proBNP

- Patisiran demonstrated a beneficial effect on NT-proBNP, a biomarker of cardiac stress, compared with placebo at Month 12 (nominal $p=1.825 \times 10^{-5}$)

Change from Baseline in NT-proBNP at Month 12[a]



NT-proBNP, ng/L, median (IQR)	Patisiran	Placebo
Baseline	2008 (1135 to 2921)	1813 (952 to 3079)
Month 12	1944 (1158 to 3726)	2299 (1180 to 4364)
Change from baseline to Month 12	131 (–280 to 817)	518 (51 to 1544)

[a]NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. Number of evaluable patients at each timepoint are shown.

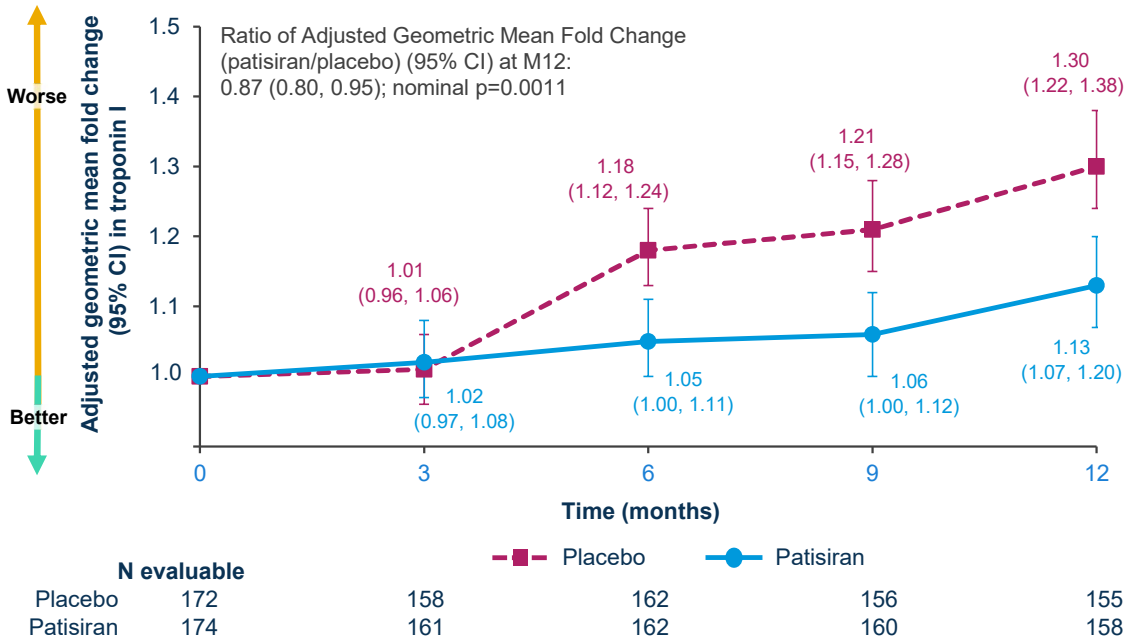
Abbreviations: CI, confidence interval; IQR, interquartile range; M, month; NT-proBNP, *N*-terminal pro-brain natriuretic peptide.

Results

Exploratory Analysis: Change from Baseline in Troponin I

- Patisiran demonstrated a beneficial effect on troponin I, a biomarker of myocardial injury, compared with placebo at Month 12 (nominal p=0.0011)

Change from Baseline in Troponin I at Month 12[a]



N evaluable					
Placebo	172	158	162	156	155
Patisiran	174	161	162	160	158

Troponin I, ng/L, median (IQR)	Patisiran	Placebo
Baseline	64.00 (38.60 to 92.00)	60.20 (38.15 to 103.10)
Month 12	67.75 (37.40 to 114.10)	72.10 (45.60 to 127.35)
Change from baseline to Month 12	3.75 (–7.10 to 19.90)	14.50 (0.00 to 32.20)

[a]Troponin I is a measure of myocardial injury, with higher values indicating a greater level of myocardial injury. Number of evaluable patients at each timepoint are shown.

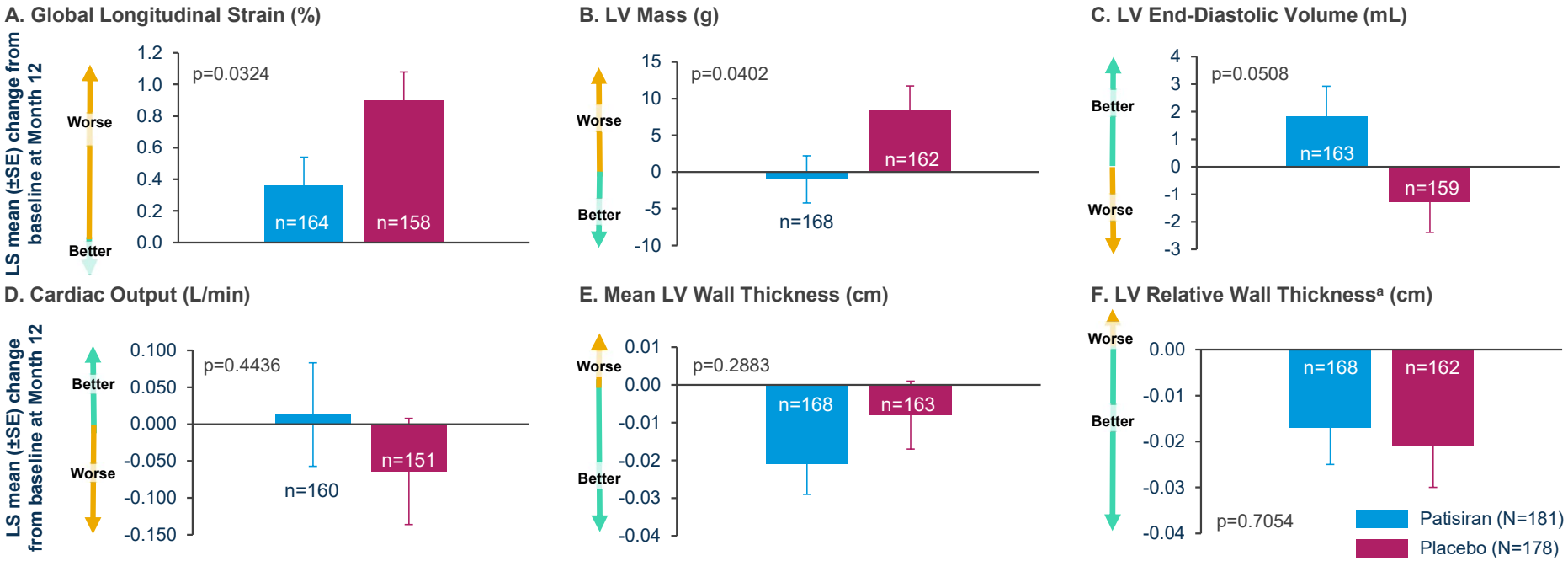
Abbreviations: CI, confidence interval; IQR, interquartile range; M, month.

Results

Exploratory Analysis: Echocardiographic Parameters

- Patisiran demonstrated a benefit or trend toward benefit in change from baseline of most echocardiographic parameters compared with placebo at Month 12

Change from Baseline in Echocardiographic Parameters at Month 12



ANCOVA model. Nominal p-value of LS mean difference of patisiran–placebo. [a]Defined as 2 times posterior wall thickness divided by LV diastolic diameter.

Abbreviations: ANCOVA, analysis of covariance; LS, least squared; LV, left ventricular; SE, standard error.

Results

Exploratory Analysis in a Planned Technetium Scintigraphy Cohort

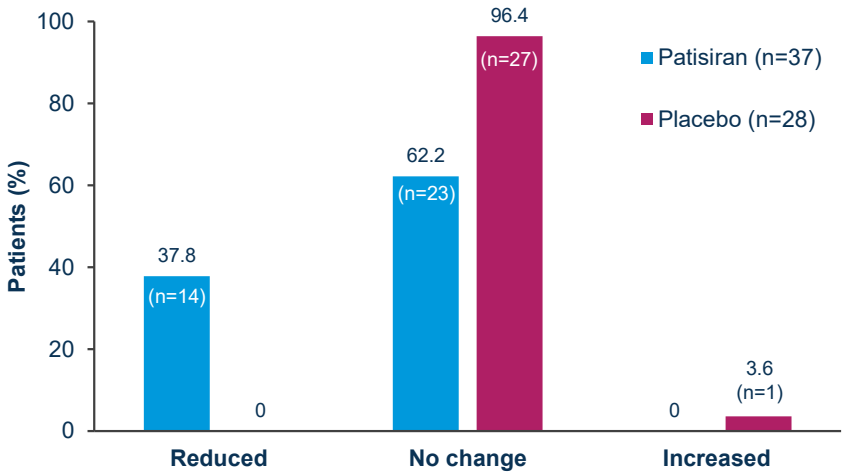
- In 100% of evaluable scintigraphy patients in the patisiran arm (n=37), Perugini grade was reduced or demonstrated no change from baseline at Month 12
  - 14 (37.8%) patients in the patisiran arm demonstrated a reduction from baseline of ≥1 Perugini grade, including 3 (8.1%) patients who reduced by ≥2 Perugini grades at Month 12
  - No patients in the patisiran arm increased from baseline in Perugini grade at Month 12

- Among evaluable patients in the placebo arm (n=28), no patients had a Perugini grade that was reduced from baseline at Month 12

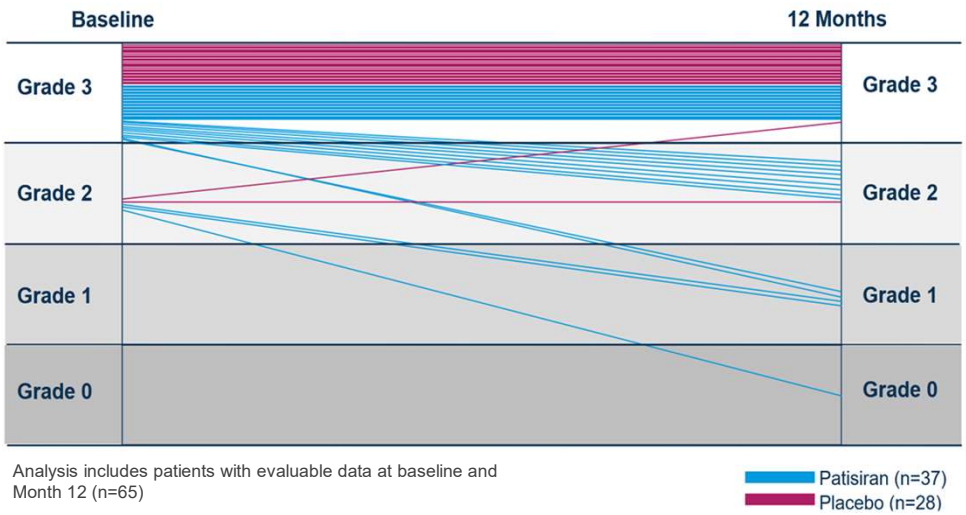
Results

Exploratory Analysis in a Planned Technetium Scintigraphy Cohort

Change from Baseline in Perugini Grade at Month 12 in All Evaluable Patients[a]



Trajectories of All Evaluable Individual Patients in Change from Baseline in Perugini Grade[a]



Analysis includes patients with evaluable data at baseline and Month 12 (n=65)

[a]Analysis includes patients in the patisiran (n=37) and placebo (n=28) arms from the full analysis set with evaluable data at baseline and Month 12. 40 patients in the patisiran group and 37 patients in the placebo group were evaluated at baseline. 37 patients in the patisiran group and 28 patients in the placebo group were evaluated at Month 12.

Results

APOLLO-B Overall Safety Summary

- The majority of AEs were mild or moderate in severity
- AEs ≥5% in the patisiran group observed 3% more commonly than in placebo included infusion-related reactions (12.2% vs 9.0%), arthralgia (7.7% vs 4.5%), and muscle spasms (6.6% vs 2.2%)

Summary of AEs[a]

At least one event, n (%)	Patisiran (n=181)	Placebo (n=178)
AEs	165 (91.2)	168 (94.4)
SAEs	61 (33.7)	63 (35.4)
Severe AEs	47 (26.0)	52 (29.2)
AEs leading to treatment discontinuation	5 (2.8)	5 (2.8)
Deaths (safety analysis)[b]	5 (2.8)	8 (4.5)
Deaths (efficacy analysis)[c]	4 (2.2)	10 (5.6)

[a]Safety is reported for the 12-month double-blind treatment period. [b]Deaths in the patisiran arm included sudden cardiac death, undetermined death, death due to COVID-19, death due to HF, and death due to pancreatitis. [c]Efficacy analysis of deaths presented in accordance with pre-defined statistical analysis plan, which excluded deaths due to COVID-19 (1 patisiran patient) and treated cardiac transplant as death (2 placebo patients).

Abbreviations: AE, adverse event; HF, heart failure; SAE, serious adverse event.

Results

APOLLO-B Cardiac Safety Summary

- Compared with placebo, patisiran demonstrated fewer events within Standardized MedDRA Queries (SMQs) exploring potential cardiac safety issues

Summary of Cardiac Safety[a]

At least one event, n (%)	Patisiran (n=181)	Placebo (n=178)
Cardiac disorders (system organ class)[b]	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[c]	12 (6.6)	18 (10.1)

[a]Safety is reported for the 12-month double-blind treatment period. [b]Based on MedDRA "Cardiac Disorders" System Organ Class. [c]There were no identified cases of Torsade de pointes.
Abbreviations: QT, QT interval; SMQ, Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query.

Conclusions

- Exploratory data of APOLLO-B further support the overall study results, which validate the therapeutic hypothesis of RNAi therapeutics targeting TTR as a potential treatment for patients with ATTR amyloidosis with cardiomyopathy

- Assessments across a comprehensive set of exploratory endpoints support the potential benefit of patisiran the potential benefit of patisiran on cardiac structure and function, and cardiac stress and injury, at Month 12
  - NT-proBNP and troponin I levels demonstrated a trend toward benefit with patisiran compared with placebo
  - Most echocardiographic parameters also demonstrated a trend toward benefit with patisiran compared with placebo
  - Perugini grade in patisiran-treated patients was reduced or stable from baseline; no placebo patients reduced from baseline

- Patisiran demonstrated an acceptable safety profile, including no cardiac safety concerns

- The efficacy and safety of patisiran will continue to be investigated in the APOLLO-B open-label extension period

Abbreviations: ATTR, transthyretin-mediated; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; RNAi, ribonucleic acid interference; TTR, transthyretin.