Primary Results from APOLLO-B, A Phase 3 Study of Patisiran in Patients with Transthyretin-Mediated 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.

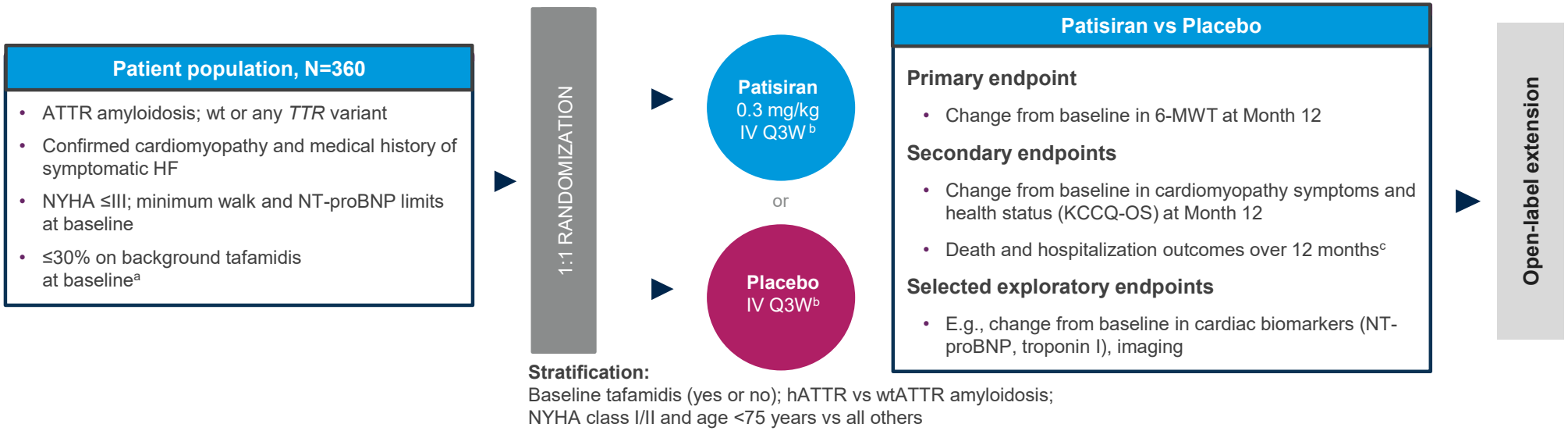
References: Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Maurer et al. J *Am Coll Cardiol* 2016;68:161–7i2; 4. Živković et al. *Amyloid* 2020;27:142–3; 5. Sipe et al. *Amyloid* 2014;21:221–4; 6. Castano et al. *Heart Fail Rev* 2015;20:163–78; 7. Swiecicki 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

Patisiran Phase 3 APOLLO-B Study Design



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

Patient Demographics and Characteristics

- Baseline characteristics were comparable between the patisiran and placebo arms
  - Similarly, characteristics were also consistent between patients receiving tafamidis at baseline and those not receiving tafamidis at baseline (data on file)

Characteristic	Patisiran (n=181)	Placebo (n=178)
Age (years), median (range)	76.0 (47–85)	76.0 (41–85)
Male sex, n (%)	161 (89.0)	160 (89.9)
wtATTR amyloidosis, n (%)	144 (79.6)	144 (80.9)
Gillmore et al 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)
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 (84.3)
Class III	15 (8.3)	13 (7.3)
6-MWT, m, mean (SD)	360.5 (102.3)	374.6 (102.4)
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)

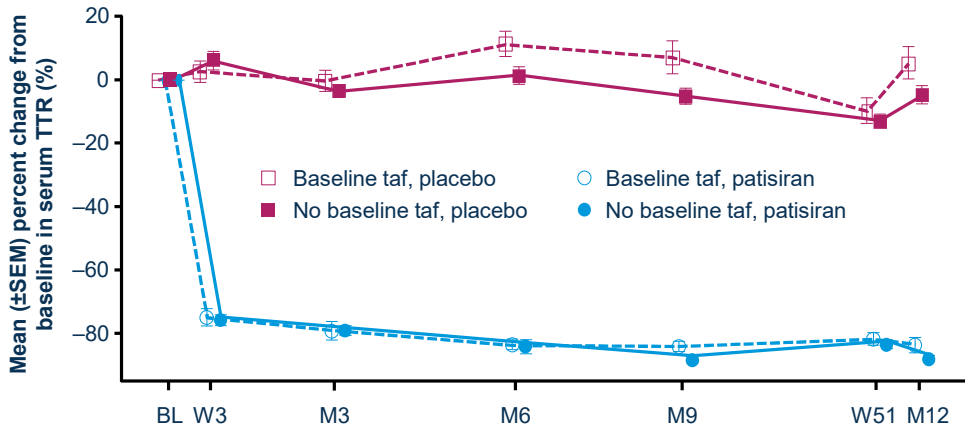
[a]The ATTR amyloidosis disease staging used for this study stratifies patients with ATTR amyloidosis with cardiomyopathy (both hATTR and wtATTR) into prognostic categories using the serum biomarkers NT-proBNP and eGFR. Patients are categorized as follows: Stage 1 (lower risk): NT-proBNP ≤3000 ng/L and 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.[1] **Reference:** Gillmore et al. Eur Heart J 2018;7:2799–806.
Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin-mediated; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; wtATTR, wild-type transthyretin-mediated

Results

Comparable Serum TTR Reduction with Patisiran Irrespective of Baseline Tafamidis Treatment

- At Month 12, patisiran achieved a mean (SD) percent reduction in serum TTR of:
  - 86.8 (13.6) in the full analysis set
  - 83.7 (16.3) for patients receiving tafamidis at baseline and 87.9 (12.3) for those not receiving tafamidis at baseline

Percent Change from Baseline in Serum TTR Levels



N evaluable							
BL taf, placebo	45	43	38	43	42	35	41
BL taf, patisiran	46	44	35	43	44	39	43
No BL taf, placebo	133	127	115	119	120	116	123
No BL taf, patisiran	135	125	117	121	123	105	115

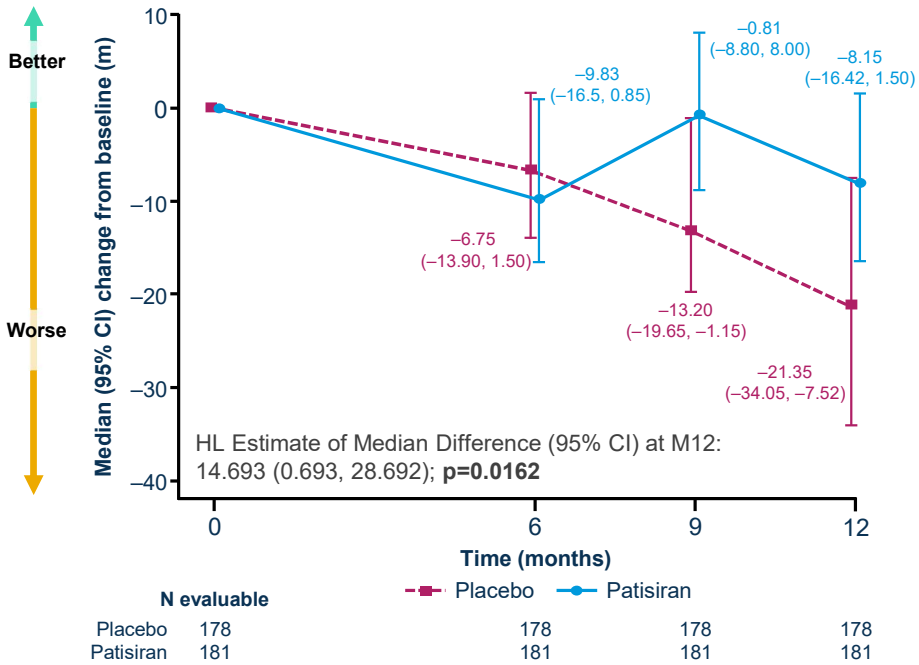
Abbreviations: BL, baseline; M, month; SD, standard deviation; SEM, standard error of the mean; taf, tafamidis; TTR, transthyretin; W, week.

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]
- A 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]



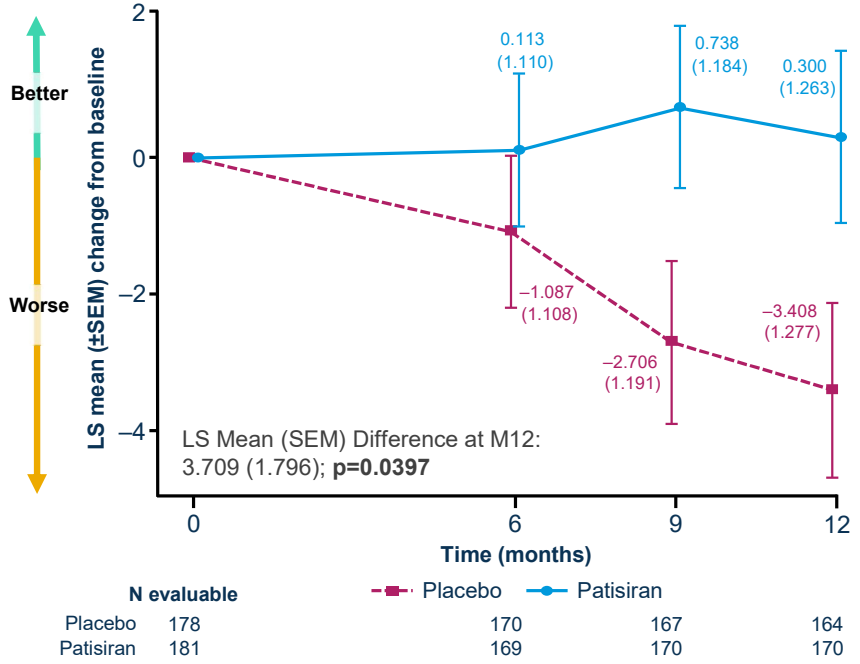
[a]Primary endpoint analysis based on the stratified Wilcoxon Rank Sum test. Median (95% CI) change from baseline values is based on the observed 6-MWT data and the imputed values; for each patient, the change from baseline is averaged across 100 complete datasets. Missing Month 12 values due to non-COVID-19 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; LS, least squared; 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]



[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.

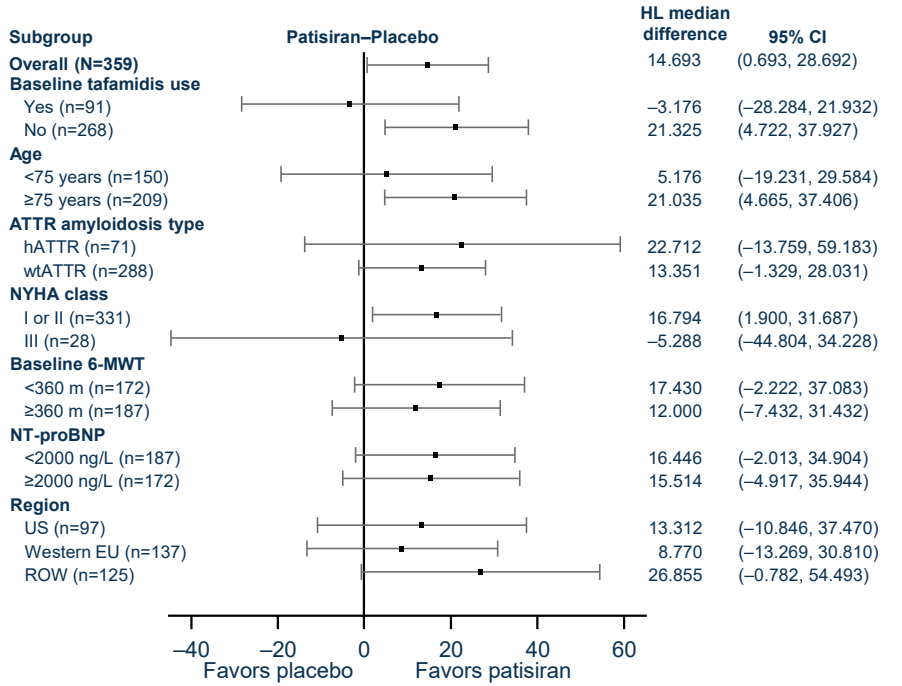
Abbreviations: KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); LS, least squared; M, month; QOL, quality of life; SEM, standard error of the mean.

Results

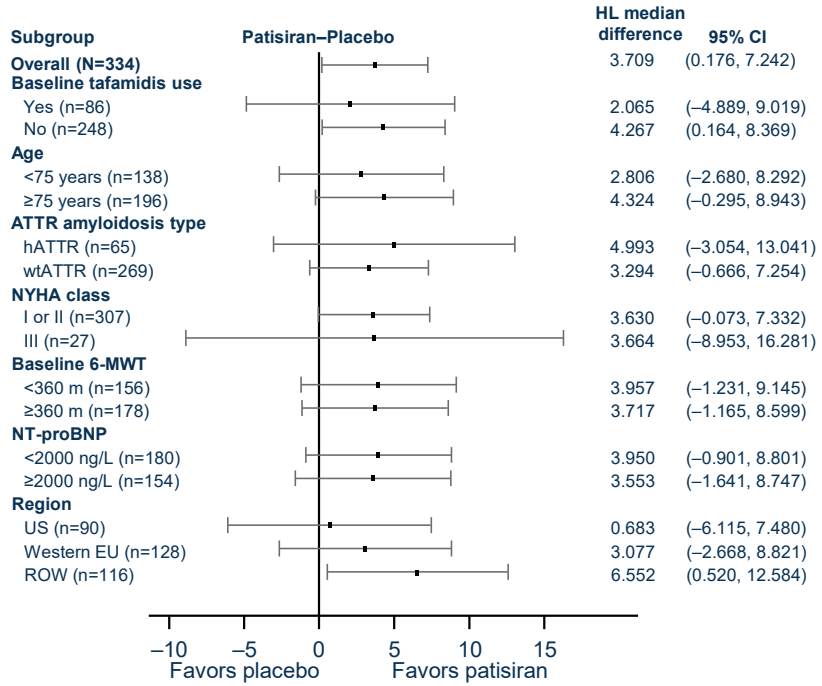
Analyses of Prespecified Subgroups

- Consistent benefit in 6-MWT and KCCQ-OS was observed with patisiran compared with placebo across prespecified patient subgroups at Month 12

Subgroup Analysis of 6-MWT



Subgroup Analysis of KCCQ-OS



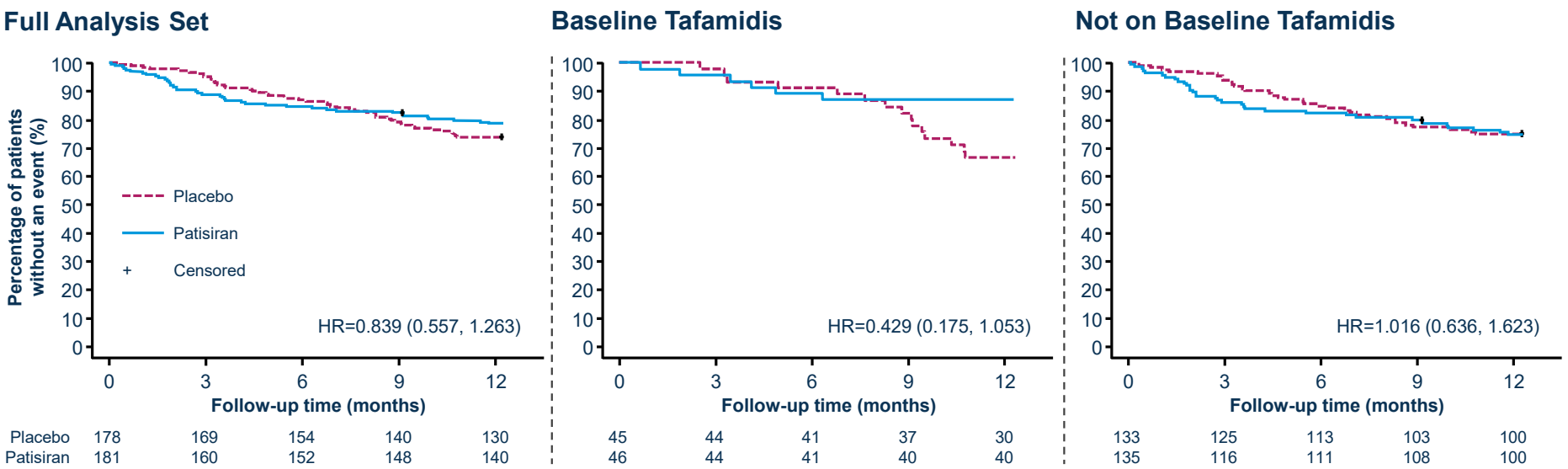
Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; hATTR, hereditary transthyretin-mediated; HL, Hodges–Lehmann; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; ROW, rest of world; wtATTR, wild-type transthyretin-mediated.

Results

Time to First Event over the 12-Month Double-Blind Period

- In the overall population, the HR (95% CI) for time to first event (all-cause hospitalization, urgent HF visit, or a death event) was 0.839 (0.557, 1.263), directionally favoring patisiran over 12 months; subgroup analyses by baseline tafamidis use showed similar trajectories

Kaplan–Meier Plot of Time to First Event over the 12-Month Double-Blind Period



Heart transplantation and left ventricular assist device placement were handled in the same manner as death. Deaths, hospitalizations, and urgent heart failure visits due to COVID-19 were excluded from analysis. Figures are truncated at Day 372 and do not show 2 events on placebo and 3 events on patisiran that occurred after Day 372. However, these events were counted in the 12-month period per SAP definition and are included in the HR estimate.

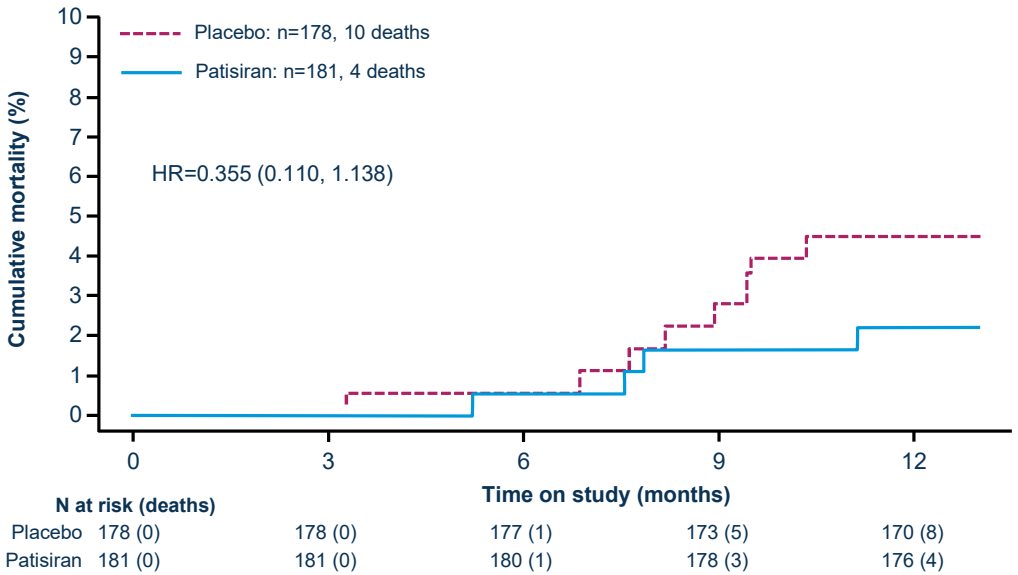
Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; hATTR, hereditary transthyretin-mediated; HL, Hodges–Lehmann; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; ROW, rest of world; wtATTR, wild-type transthyretin-mediated.

Results

All-Cause Mortality over the 12-Month Double-Blind Period

- In the overall population, all-cause deaths[a,b] were observed in 10 (5.6%) placebo vs 4 (2.2%) patisiran patients
  - CV-related deaths: placebo 5 (2.8%); patisiran 2 (1.1%)
    - Heart transplant[a]: placebo 2 (1.1%); patisiran 0 (0.0%)
  - HR estimate (patisiran/placebo): 0.355 (95% CI: 0.110, 1.138)
- For patients on baseline tafamidis, all-cause deaths were observed in 3 (6.7%) placebo vs 1 (2.2%) patisiran patient
  - HR (95% CI): 0.296 (0.031, 2.863)
- For patients not on baseline tafamidis, all-cause deaths were observed in 7 (5.3%) placebo vs 3 (2.2%) patisiran patients
  - HR (95% CI): 0.396 (0.102, 1.538)

All-Cause Mortality over the 12-Month Double-Blind Period[a,b]



[a]Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled the same as death in analyses. [b]Deaths, hospitalizations, and urgent HF visits due to COVID-19 were excluded from event rate calculations. Per SAP definition, for patients who discontinued the study, deaths up to Day 417 were counted in the double-blind period. The figure is truncated at Day 372 (end of Month 12 visit window). 2 placebo deaths that occurred after Month 12 and prior to Day 417 are included in the estimate of HR but not shown on the figure.

Abbreviations: CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; SAP, statistical analysis plan.

Results

APOLLO-B Overall Safety Summary

- The majority of adverse events (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

- Results after 12 months validate the therapeutic hypothesis of RNAi therapeutics targeting TTR as a potential treatment for patients with ATTR amyloidosis with cardiomyopathy
- Patisiran met the primary endpoint of the APOLLO-B study, demonstrating statistically significant and clinically meaningful benefit on functional capacity (6-MWT) compared with placebo at Month 12
- Patisiran also met the first secondary endpoint, demonstrating statistically significant and clinically meaningful benefit on health status and QOL (KCCQ-OS) compared with placebo at Month 12
- Overall, consistent benefits in 6-MWT and KCCQ-OS were observed with patisiran across prespecified patient subgroups
- Time to first event (all-cause hospitalization, urgent HF visit, or a death event) and all-cause mortality directionally favored patisiran vs placebo, but composite outcomes endpoints did not achieve statistical significance over 12 months
- 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: 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); QOL, quality of life; RNAi, ribonucleic acid interference; TTR, transthyretin.