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

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Introduction

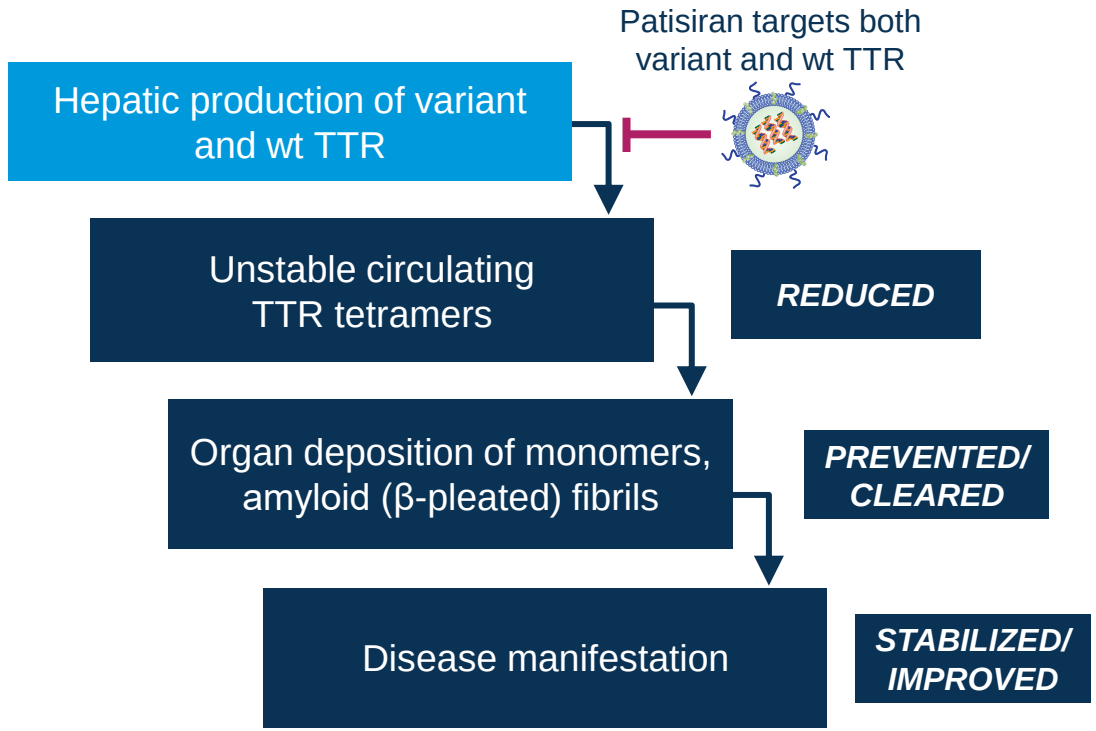
Transthyretin-mediated (ATTR) amyloidosis

- 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, 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 clinical data in patients with hATTR amyloidosis with polyneuropathy suggests the potential for patisiran to improve cardiac manifestations of ATTR amyloidosis[11,12]

Therapeutic Hypothesis

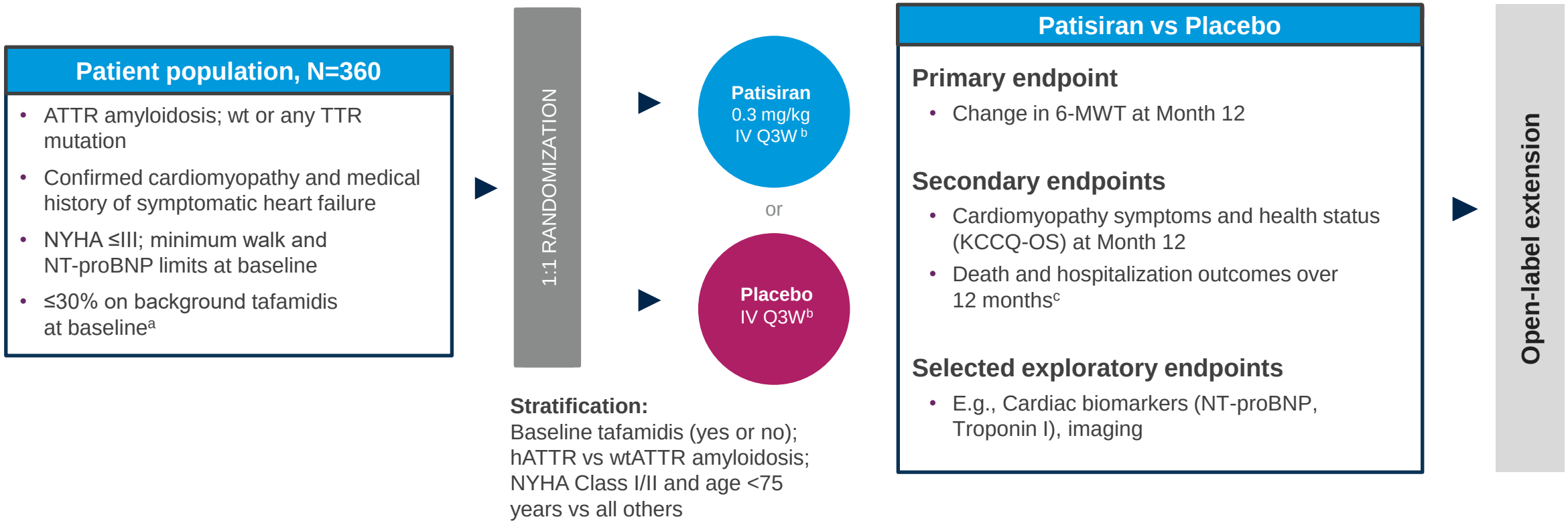


Abbreviations: ATTR, transthyretin-mediated; hATTR, hereditary transthyretin-mediated; IV, intravenous; QOL, quality of life; RNAi, ribonucleic acid interference; TTR, transthyretin; wt, wild-type; wtATTR, wild-type transthyretin-mediated.

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;68:161–7i2; 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.

Study Design: Patisiran Phase 3 APOLLO-B Study

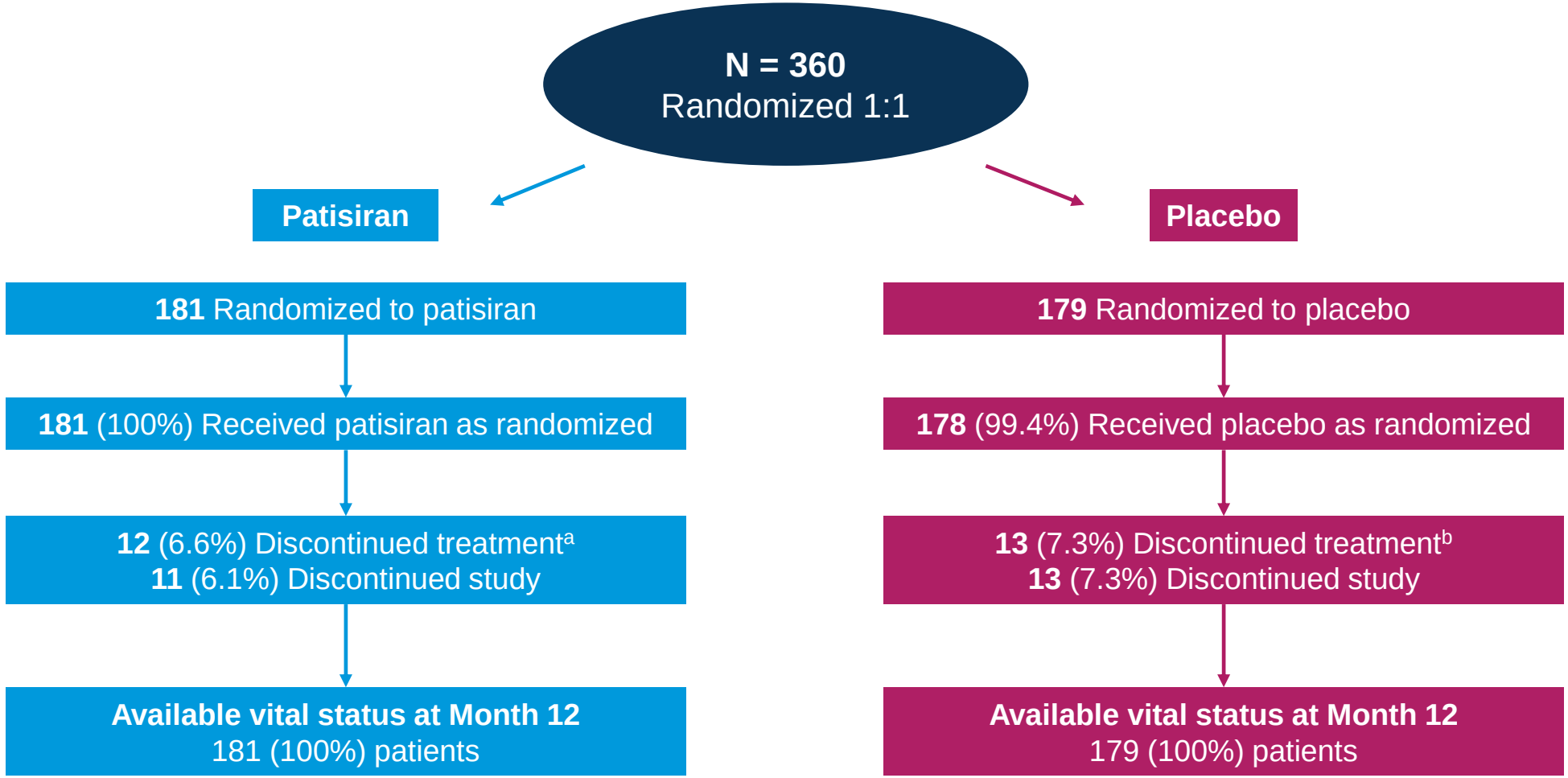
Randomized, Double-Blind, Placebo-Controlled Study in Patients with ATTR Amyloidosis with Cardiomyopathy



[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 min. 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, 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.

Patient Disposition

12-Month Double-Blind Treatment Period in APOLLO-B



[a]Reasons for discontinuing patisiran treatment: AE (3 [1.7%]), death (3 [1.7%]), other (6 [3.3%]). [b]Reasons for discontinuing placebo treatment: AE (5 [2.8%]), death (3 [1.7%]), physician decision (1 [0.6%]), other (4 [2.2%]). Other excludes AE, death, lost to follow-up, physician decision, pregnancy, protocol deviation, study terminated by sponsor, and non-compliance to study drug. **Abbreviation:** AE, adverse event.

Patient Demographics and Characteristics

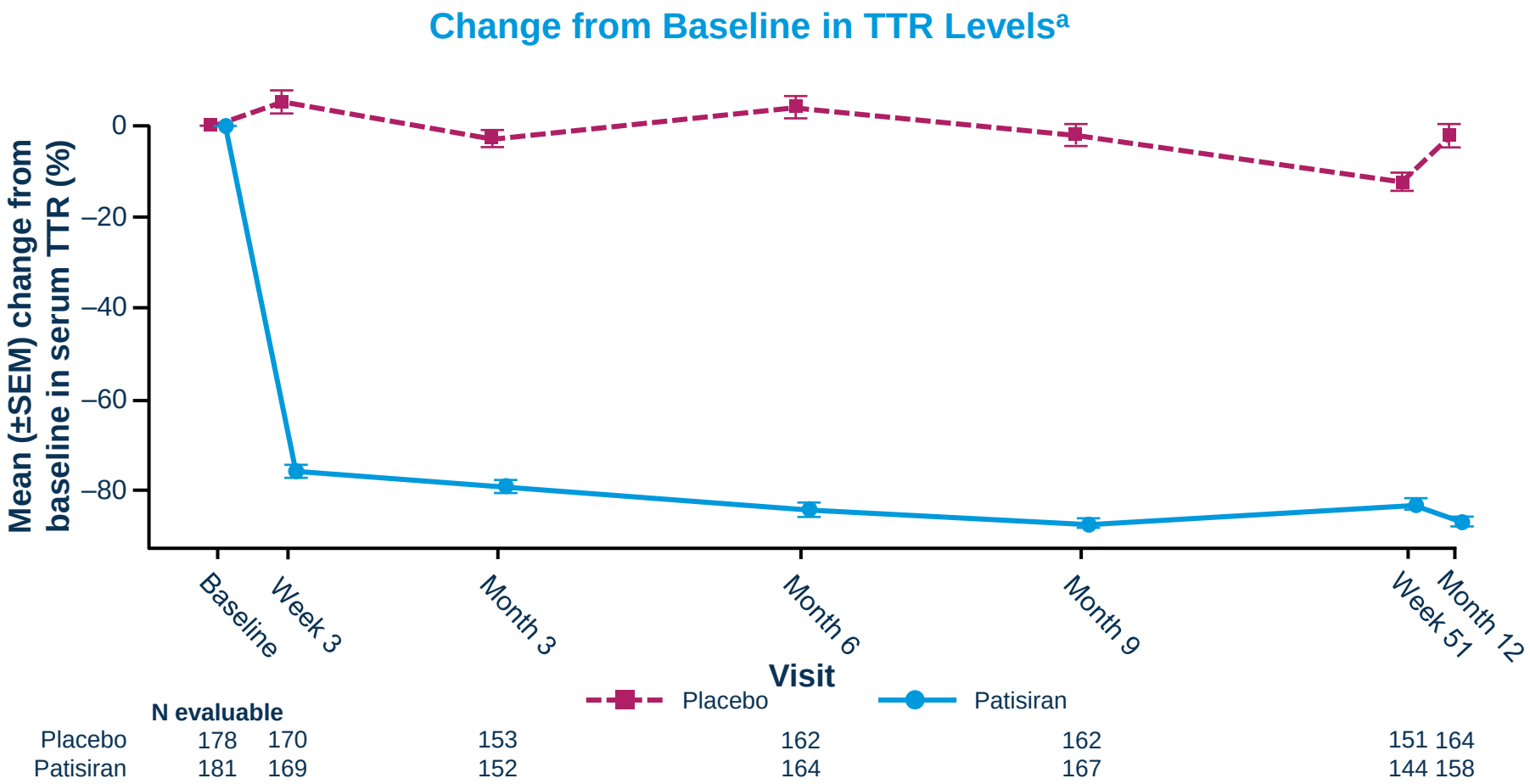
Baseline Characteristics Were Comparable Between the Placebo and Patisiran Arms

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 (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; m, meter; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; wtATTR, wild-type transthyretin-mediated.

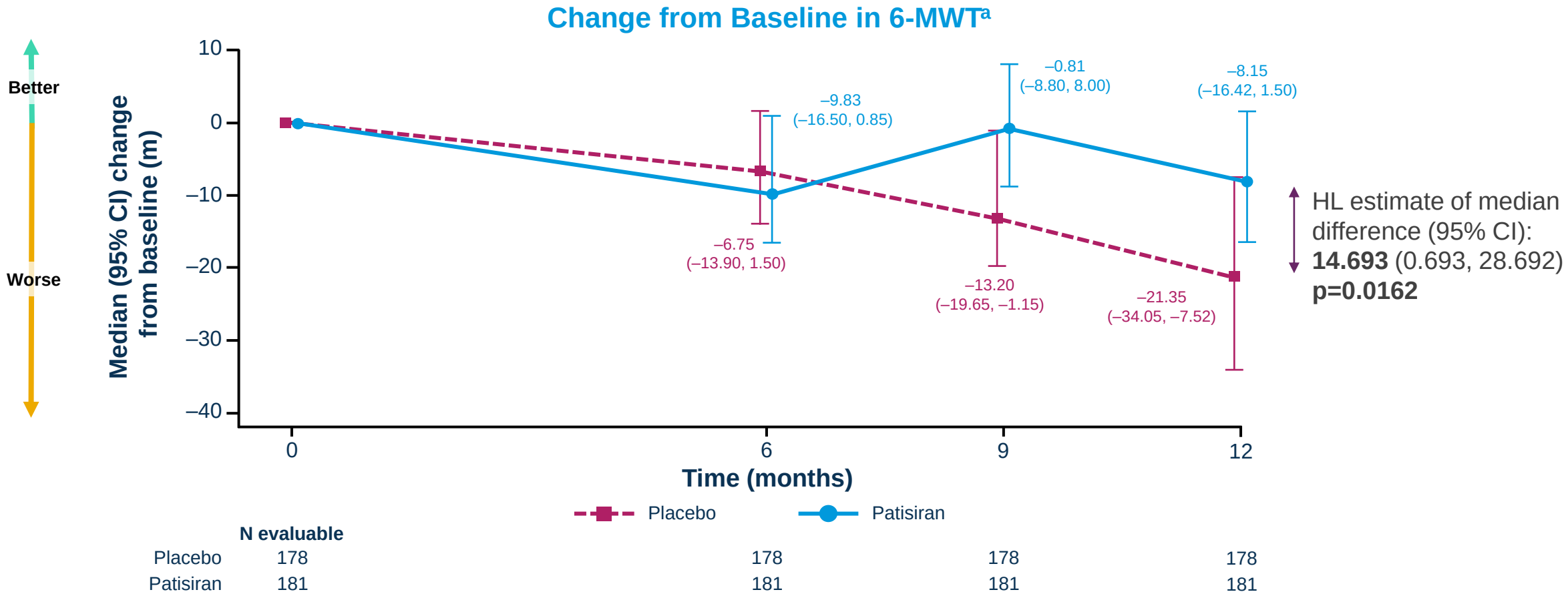
Rapid and Sustained Serum TTR Reduction with Patisiran

- Patisiran achieved a mean (SD) percent reduction in serum TTR of 86.8% (13.6) at Month 12



[a]At baseline mean (SD) serum TTR was 235.32 (68.05) mg/L in the patisiran group and 244.77 (73.17) mg/L in the placebo group. At Month 12 mean (SD) serum TTR was 30.93 (33.60) mg/L in the patisiran group and 229.40 (77.15) mg/L in the placebo group. **Abbreviations:** SD, standard deviation; SEM, standard error of mean; TTR, transthyretin.

Primary Endpoint: Patisiran Demonstrated Significant Clinical Benefit in Functional Capacity (6-MWT) Compared to Placebo at Month 12

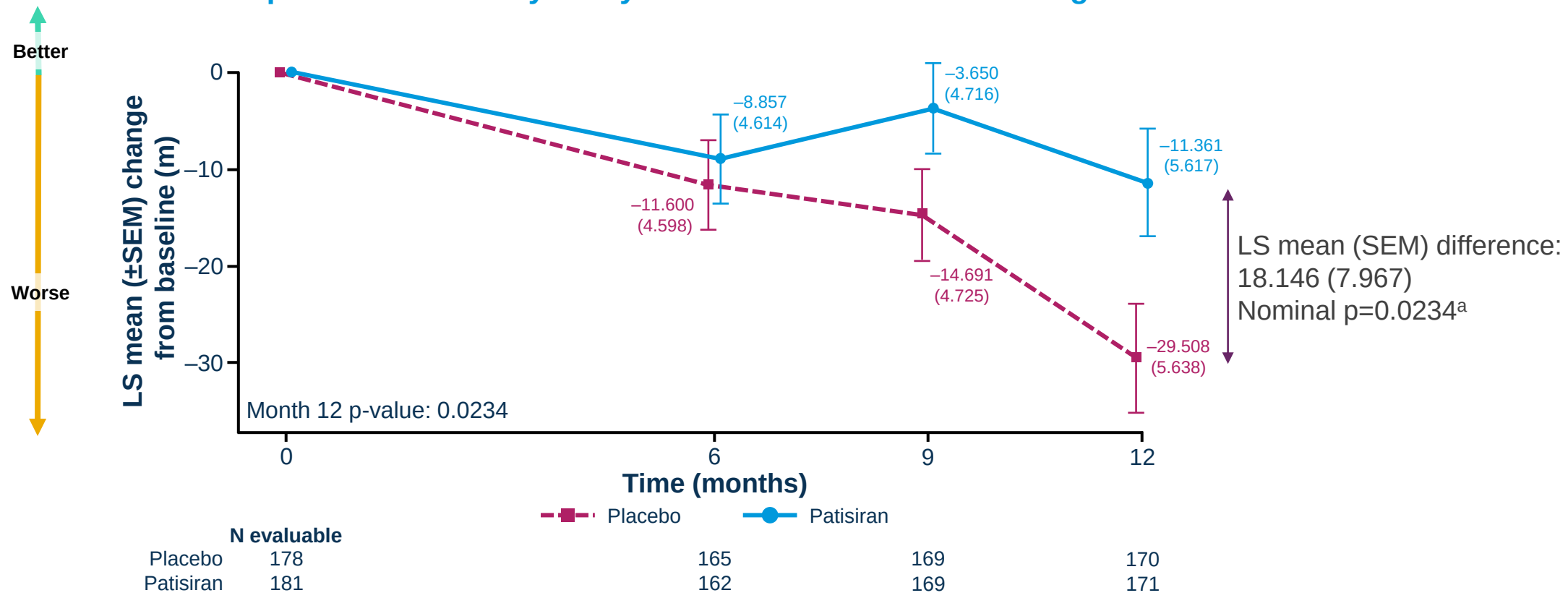


N evaluable				
Placebo	178	178	178	178
Patisiran	181	181	181	181

[a]Primary endpoint analysis based on the stratified Wilcoxon Rank Sum test. Median (95% CI) change from baseline values were based on the observed 6-MWT data and the imputed values; for each patient, the change from baseline was 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 (range) 6-MWT was 358.000 (155.70, 808.00) in the patisiran group and 367.740 (130.00, 740.00) in the placebo group. **Abbreviations:** 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; HL, Hodges–Lehmann; m, meters.

Sensitivity Analysis: Confirms Robustness of the Observed Benefit in 6-MWT with Patisiran Compared to Placebo

Prespecified Sensitivity Analysis of 6-MWT vs Placebo using MMRM[a]

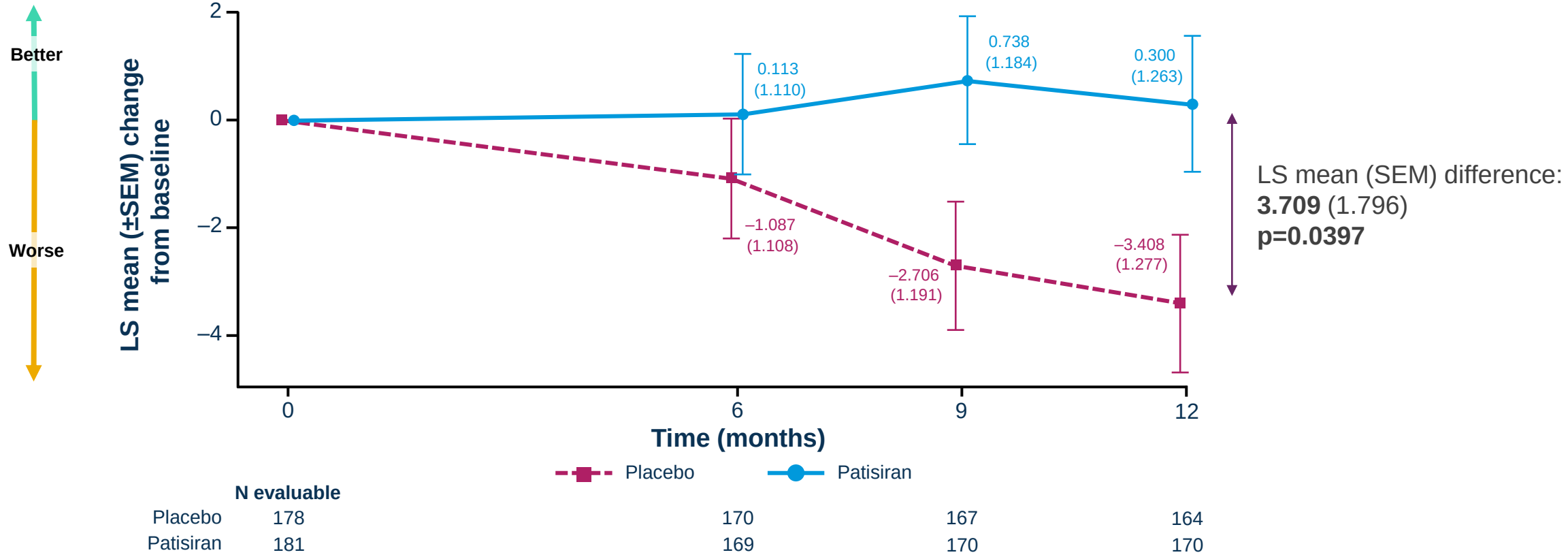


N evaluable				
Placebo	178	165	169	170
Patisiran	181	162	169	171

[a]MMRM model. 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 two 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; LS, least squares; m, meters; MMRM, mixed model repeated measures; SD, standard deviation; SEM, standard error of the mean.

Secondary Endpoint: Patisiran Demonstrated Significant Clinical Benefit in Health Status and Quality of Life (KCCQ-OS) Compared to Placebo at Month 12

Change From Baseline in KCCQ-OS using MMRM[a]



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

[a]MMRM model. 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; MMRM, mixed model repeated measures; SD, standard deviation; SEM, standard error of mean.

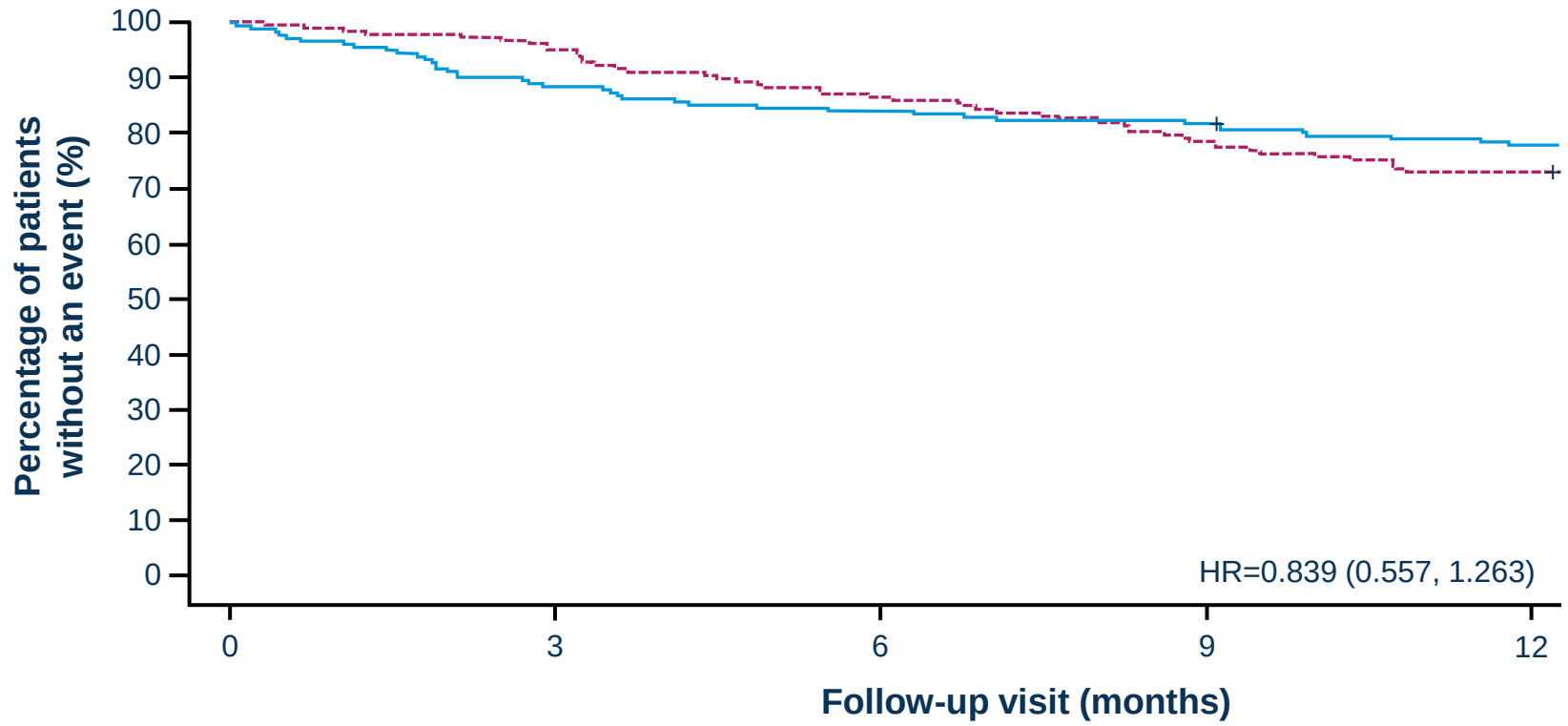
Secondary Composite Outcomes Endpoints over 12 Months[a]

Composite of all-cause mortality, frequency of CV events[b] and change from baseline in 6-MWT over 12 months[a]	
Win ratio (Patisiran vs Placebo)[c]	1.27
95% CI	0.99, 1.61
p-value	0.0574
Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline[a,d]	
HR (Patisiran vs Placebo)	0.997
95% CI	0.620, 1.602
Nominal p-value	0.9888
Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in the overall study population[a,d]	
HR (Patisiran vs Placebo)	0.883
95% CI	0.582, 1.341
Nominal p-value	0.5609

[a]Deaths, hospitalizations, and urgent HF visits due to COVID-19 excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled in the same manner as death in the analysis. [b]CV events were defined as CV hospitalizations and urgent HF visits. [c]The first composite endpoint was analyzed using a generalized rank-based win ratio method stratified by baseline tafamidis use (yes vs. no), which made within-stratum pairwise comparisons for all possible patisiran and placebo patient pairs in a sequential manner (first mortality, then CV events, then 6-MWT). The point estimate, 95% CI and p-value for the stratified win-ratio were based on Dong et al. 2018. [d]The hazard ratio, 95% CI and p-value were derived using an Andersen-Gill model, including treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates. For the analysis in the overall population, the model was also stratified by baseline tafamidis use. A hazard ratio <1 represents a favorable outcome for patisiran. **Abbreviations:** 6-MWT, 6-minute walk test; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association.

Time to First Event for Patisiran vs Placebo over the 12-Month Double-Blind Period

All-Cause Hospitalizations, Urgent HF Visits, or Deaths



N evaluable				
Placebo	178	169	154	140	130
Patisiran	181	160	152	148	140

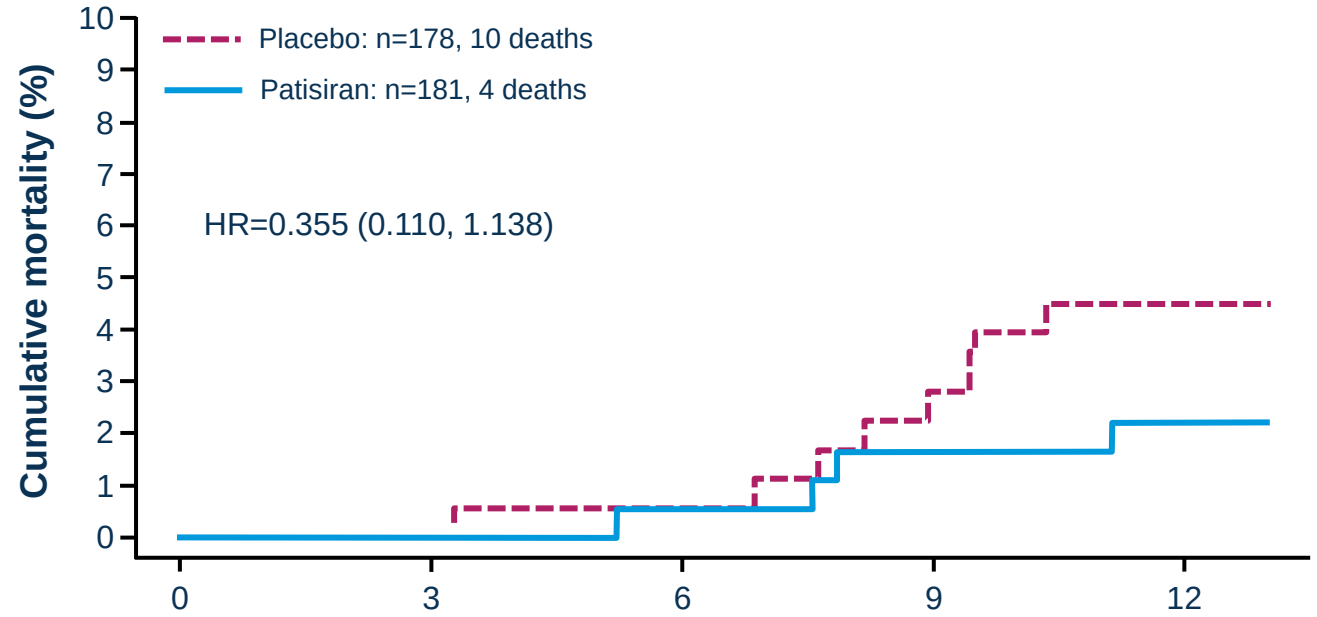
Heart transplantation and left ventricular assist device placement were handled in the same manner as death. Deaths and CV events due to COVID-19 were excluded from the analysis. The figure is truncated at Day 372 and does not show 2 events on placebo and 3 events on patisiran occurred after Day 372. However, these events were counted in the 12-Month period per SAP definition and are included in the hazard ratio estimate. **Abbreviations:** CV, cardiovascular; HF, heart failure; HR, hazard ratio.

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

Overall Population

- In the double-blind period, all-cause deaths[a,b] were observed in 10 (5.6%) placebo vs 4 (2.2%) patisiran patients
  - CV-related: 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)

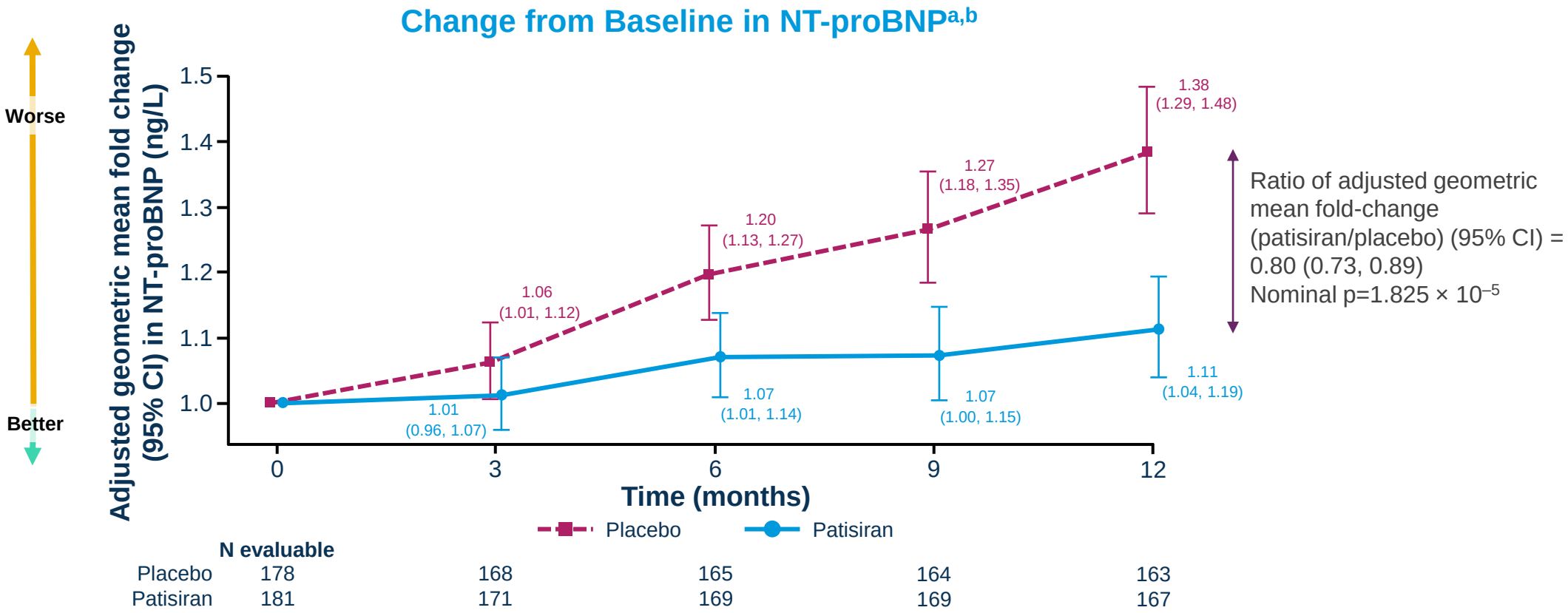
All-Cause Mortality During the 12-Month Double-Blind Period[a,b]



N at risk (deaths)					
Placebo	178 (0)	178 (0)	177 (1)	173 (5)	170 (8)
Patisiran	181 (0)	181 (0)	180 (1)	178 (3)	176 (4)

[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). Two 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; DB, double-blind; HR, hazard ratio; m, months; SAP, statistical analysis plan.

Exploratory Endpoint: Patisiran Demonstrated Benefit in NT-proBNP Change from Baseline Compared to Placebo at Month 12



[a]NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. [b]At baseline, median (IQR) NT-proBNP was 2008 (1135–2921) ng/L in the patisiran group and 1813 (952–3079) ng/L in the placebo group. At Month 12, median (IQR) NT-proBNP was 1944 (1158–3726) ng/L in the patisiran group and 2299 (1180–4364) ng/L in the placebo group. Number of evaluable patients at each timepoint are shown. **Abbreviations:** CI, confidence interval; IQR, interquartile range; NT-proBNP, *N*-terminal pro-brain natriuretic peptide.

APOLLO-B Overall Safety Summary[a]

- 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 reaction (12.2% vs 9.0%), arthralgia (7.7% vs 4.5%), and muscle spasms (6.6% vs 2.2%)

APOLLO-B Safety Summary

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)[a]	5 (2.8)	8 (4.5)
Deaths (efficacy analysis)[b]	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 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.

APOLLO-B Cardiac Safety Summary

Cardiac Events over the 12-Month Double-Blind Treatment Period

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

APOLLO-B Cardiac Safety Summary

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

[a]Based on MedDRA "Cardiac Disorders" System Organ Class. [b]There were no identified cases of Torsade de pointes. **Abbreviations:** QT, QT interval; SMQ, Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query.

Summary

- 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 to placebo at month 12
- Patisiran also met the first secondary endpoint, demonstrating statistically significant and clinically meaningful benefit on health status and quality of life (KCCQ-OS) compared to placebo at Month 12
- Mortality trended favorably for patisiran compared to placebo, but composite outcomes endpoints did not achieve significance over 12 months
- Patisiran demonstrated benefit in NT-proBNP, a biomarker of cardiac stress, compared to placebo at Month 12 (exploratory)
- 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; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; RNAi, ribonucleic acid interference; TTR, transthyretin.

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the APOLLO-B study, especially considering the challenges of continuing the study during the COVID-19 pandemic