# Patisiran: Cardiac Results from the Global OLE Study

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## SUMMARY


- The Global OLE study (N=211) was a multicenter, international study designed to evaluate the long-term safety and efficacy of IV patisiran in patients with hATTR-PN. Patients with hATTR-PN who completed the patisiran Phase 2 OLE study or phase 3 APOLLO study and met eligibility criteria were able to start or continue IV patisiran 0.3 mg/kg every 3 weeks for up to 5 years.[1]
  - At enrollment, the median NT-proBNP levels were higher in the APOLLO-placebo group compared to the APOLLO-patisiran and phase 2 OLE-patisiran groups.[1] From Global OLE enrollment to 12 months, NT-proBNP concentrations were stable in both groups previously treated with patisiran. In the APOLLO-placebo group, NT-proBNP levels increased during APOLLO and decreased once patisiran treatment was initiated in the OLE.[2]
  - Risk factors for mortality at the parent study baseline were evaluated. Univariate analyses identified associations between mortality and NT-proBNP, familial amyloid polyneuropathy stage, genotype, LV wall thickness, LV mass, NYHA classification, cardiac subpopulation, parent study treatment, NAC ATTR amyloidosis stage, NIS, and PND score.[1]
  - The rates of AEs and serious AEs were higher in the APOLLO-placebo than the APOLLO-patisiran and phase 2 OLE-patisiran groups. The types of AEs reported were similar to those observed in APOLLO, and the exposure-adjusted event rates were similar or lower than in APOLLO.[1]
- A post-hoc analysis of pooled data from the APOLLO-B OLE and the cardiac subpopulation of the Global OLE evaluated the long-term effects of patisiran on survival, hospitalizations, and cardiac parameters in patients with hATTR-PN and evidence of cardiac involvement or a diagnosis of ATTR-CM.[3]


## INDEX

## GLOBAL OLE

### Study Design

The Global OLE study (N=211) was a multicenter, international study designed to evaluate the long-term safety and efficacy of IV patisiran in patients with hATTR-PN. Patients with hATTR-PN who completed the patisiran Phase 2 OLE study or phase 3 APOLLO study and met eligibility criteria were able to start or continue IV patisiran 0.3 mg/kg every 3 weeks for up to 5 years. The study enrolled 25 patients from the patisiran Phase 2 OLE study (phase 2 OLE-patisiran group), 137 patients from the APOLLO-patisiran arm (APOLLO-patisiran group), and 49 patients from the APOLLO-placebo arm (APOLLO-placebo group).[1]

Efficacy assessments included measures of polyneuropathy, quality of life, nutritional status, disability, and ambulation status.[1]

### Baseline Characteristics

At enrollment, patients in the APOLLO-placebo group had higher levels of NT-proBNP and more severe polyneuropathy compared to patients in the APOLLO-patisiran and phase 2 OLE-patisiran groups. There was a higher proportion of patients in the phase 2 OLE-patisiran group with the V30M genotype compared with the APOLLO-placebo and APOLLO-patisiran groups. Additional baseline characteristics are provided in **Table 1**.[1]

**Table 1. Baseline Characteristics at Global OLE Enrollment.**[4]

| Characteristic | APOLLO-placebo (N=49) | APOLLO-patisiran (N=137) | Phase 2 OLE-patisiran (N=25) | Global OLE Total (N=211) |
|---|---|---|---|---|
| Mean (SD) age, years | 63.5 (11.0) | 61.0 (12.1) | 58.5 (15.1) | 61.3 (12.3) |
| Sex, n (%) | | | | |
| Female | 12 (24.5) | 35 (25.5) | 8 (32.0) | 55 (26.1) |
| Male | 37 (75.5) | 102 (74.5) | 17 (68.0) | 156 (73.9) |
| NYHA classification, n (%) | | | | |
| I | 22 (44.9) | 67 (48.9) | 19 (76.0) | 108 (51.2) |
| II | 21 (42.9) | 59 (43.1) | 4 (16.0) | 84 (39.8) |
| III | 4 (8.2) | 9 (6.6) | 2 (8.0) | 15 (7.1) |
| IV | 2 (4.1) | 2 (1.5) | 0 | 4 (1.9) |
| NAC ATTR amyloidosis stage, n (%) | | | | |
| 1 | 39 (79.6) | 118 (86.1) | 25 (100) | 182 (86.3) |
| 2 | 9 (18.4) | 17 (12.4) | 0 | 26 (12.3) |
| 3 | 1 (2.0) | 2 (1.5) | 0 | 3 (1.4) |
| NT-proBNP, ng/L, mean (SD) | 1957.6 (2731.3) | 1017.2 (1558.8) | 281.9 (422.0) | 1148.5 (1884.8) |
| LV wall thickness, cm, mean (SD) | 1.54 (0.28) | 1.46 (0.32) | 1.25 (0.33) | 1.46 (0.32) |
| LV mass, g, mean (SD) | 238.2 (74.1) | 236.6 (85.8) | 198.6 (89.2) | 232.5 (84.2) |
| Cardiac subpopulation, n (%) | 22 (44.9) | 81 (59.1) | 10 (40.0) | 113 (53.6) |

Abbreviations: ATTR = transthyretin amyloidosis; LV = left ventricular; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; SD = standard deviation.

**12-Month Results**

Cardiac Results

From Global OLE enrollment to 12 months, NT-proBNP concentrations were stable in both groups previously treated with patisiran. In the APOLLO-placebo group, NT-proBNP levels increased (a sign of increased cardiac stress) during APOLLO, but decreased once patisiran treatment was initiated in the OLE (**Table 2**).[2,5] The geometric mean fold change in NT-proBNP at Global OLE 12 months relative to parent study baseline and Global OLE enrollment is presented in **Table 3**.[5]

**Table 2. NT-proBNP at Parent Study Baseline, Global OLE Enrollment, and 12 Months.**[5]

| NT-proBNP, ng/L, geometric mean (SEM) | APOLLO-placebo (N=49)[a] | APOLLO-patisiran (N=137)[a] | Phase 2 OLE-patisiran (N=25)[a] |
|---|---|---|---|
| Parent study baseline | 531.29 (86.66) | 531.04 (59.62) | 508.13 (185.23) |
| Global OLE enrollment | 837.39 (171.19) | 396.84 (47.77) | 113.35 (33.92) |
| Global OLE 12 months[b] | 654.32 (149.75) | 405.44 (51.41) | 120.47 (39.58) |

Abbreviations: NT-proBNP = N-terminal pro-brain natriuretic peptide; OLE = open-label extension; SEM = standard error of the mean.

[a]Patients enrolled in the Global OLE are a subset of the patients in the parent study at baseline. Patients in parent study: APOLLO-placebo, n=77; APOLLO-patisiran, n=148; Phase 2 OLE, n=27.

[b]Patients with data available at 12 months in the Global OLE: APOLLO-placebo, n=38; APOLLO-patisiran, n=119; Phase 2 OLE, n=25.

**Table 3. Geometric Mean Fold Change in NT-ProBNP at 12 Months.**[5]

| NT-proBNP, geometric mean fold change[a] (95% CI) | APOLLO-placebo (N=49)[b] | APOLLO-patisiran (N=137)[b] | Phase 2 OLE-patisiran (N=25)[b] |
|---|---|---|---|
| Fold change relative to Global OLE enrollment | 1.07 (0.86–1.32) | 1.17 (1.06–1.29) | 1.06 (0.85–1.33) |
| Fold change relative to parent baseline | 2.01 (1.61–2.52) | 0.97 (0.87–1.08) | 0.93 (0.61–1.44) |

Abbreviations: CI = confidence interval; NT-proBNP = N-terminal pro-brain natriuretic peptide; OLE = open-label extension.

[a]The geometric mean fold change was calculated in patients who had data available both at Global OLE enrollment and at 12 months in the Global OLE and in patients who had data available both at parent study baseline and at 12 months in the Global OLE. Therefore, the geometric mean fold change does not directly correlate with the geometric mean values reported in Table 2.

[b]The total number of patients enrolled in the Global OLE.

Mortality Results

In a post-hoc analysis using data from the parent study baseline to the 12-month OLE assessment, a higher frequency of cardiac deaths in the APOLLO-placebo group (6/49, 12%) was observed in comparison to the APOLLO-patisiran group (11/148, 7%) and phase 2 OLE-patisiran group (1/27, 4%). Cardiac deaths were defined as a subset of deaths adjudicated as being cardiovascular related and excluded the subcategory of fatal stroke. A summary of relevant exposure-adjusted mortality rates is presented in **Table 4**.[5]

**Table 4. Integrated Exposure-Adjusted Mortality Rates in Patients with hATTR with Polyneuropathy Enrolled Across the Patisiran Development Program at 12 Months.**[5]

| | APOLLO-placebo (N=49) | APOLLO-patisiran (N=148) | Phase 2 OLE-patisiran (N=27) | All patisiran treated patients[a] (N=224) |
|---|---|---|---|---|
| Total patient-years exposure | 68.6 | 442.2 | 118.6 | 629.4 |
| Deaths[b], n (%) | 13 (27) | 15 (10) | 2 (7) | 30 (13) |
| Overall exposure-adjusted mortality rate, deaths per 100 patient-years (95% CI) | 18.9 (10.4 - 31.2) | 3.4 (2.0 - 5.4) | 1.7 (0.3 - 5.2) | 4.8 (3.3 - 6.7) |
| Cardiac deaths[b], n (%) | 6 (12) | 11 (7) | 1 (4) | 18 (8) |
| Exposure-adjusted cardiac mortality rate, deaths per 100 patient-years (95% CI) | 8.7 (3.5 - 17.7) | 2.5 (1.3 - 4.3) | 0.8 (0.05 - 3.7) | 2.9 (1.7 - 4.4) |

Abbreviations: CI = confidence interval; OLE = open-label extension.

[a]The integrated safety population encompasses all patients exposed to patisiran. Data are recorded from first patisiran dose in either the APOLLO, Phase 2 OLE, or Global OLE studies until Global OLE 12 months.

[b]Includes all deaths reported within 3 months after the last dose of patisiran.

Post hoc analysis of exposure-adjusted mortality rate is calculated as: (total number of deaths/total patient-years of exposure)×100. For each patient, exposure in years is defined as: (last dose date of study drug–first dose date of study drug+91)/365.25. The total patient-years of exposure time is calculated as the sum of each patient's time using the minimum of the exposure time in years or the follow-up time in years (applying the 24 September 2018 data cut-off to data from the Global OLE study).

### 5-Year Results

Mortality

Risk factors for mortality at the parent study baseline were evaluated. Univariate analyses identified associations between mortality and NT-proBNP, familial amyloid polyneuropathy stage, genotype, LV wall thickness, LV mass, NYHA classification, cardiac subpopulation, parent study treatment, NAC ATTR amyloidosis stage, NIS, and PND score. In both full and selection-based multivariate analysis, familial amyloid polyneuropathy stage and parent study treatment were associated with mortality (**Table 5**).[1]

**Table 5. Multivariate Analysis of Risk Factors for Mortality.**[1]

| Characteristics at parent study baseline | Selection-based analysis (n=220)[a] | | Full analysis (n=220)[b] | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Parent study treatment (placebo vs patisiran)[c] | 5.19 (2.79-9.63) | <0.001 | 5.52 (2.91-10.48) | <0.001 |
| FAP stage II/III vs I | 5.74 (2.76-11.92) | <0.001 | 4.89 (1.69-14.12) | 0.003 |
| Genotype | | | | |
| Late-onset V30M vs early-onset V30M | 0.83 (0.16-4.42) | 0.83 | 0.88 (0.16-4.75) | 0.88 |
| Non-V30M vs early-onset V30M | 2.22 (0.44-11.19) | 0.34 | 2.36 (0.47-12.0) | 0.30 |
| NT-proBNP, >3000 ng/L vs ≤3000 ng/L | 3.57 (0.95-13.38) | 0.06 | 3.16 (0.75-13.29) | 0.12 |
| Mean LV wall thickness ≥1.5 cm vs <1.5 cm | 1.96 (0.82-4.71) | 0.13 | 1.60 (0.50-5.11) | 0.43 |
| NAC ATTR amyloidosis stage 2/3 vs 1 | 2.97 (0.86-10.20) | 0.08 | 3.54 (0.91-13.69) | 0.07 |
| LV mass ≥243.67 g vs <243.67 g | n/a | n/a | 1.12 (0.46-2.73) | 0.80 |

| Characteristics at parent study baseline | Selection-based analysis (n=220)[a] | | Full analysis (n=220)[b] | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| NYHA classification II vs I | n/a | n/a | 1.19 (0.61-2.30) | 0.61 |
| Cardiac subpopulation, yes vs no | n/a | n/a | 1.41 (0.72-2.76) | 0.31 |

Abbreviations: ATTR = transthyretin amyloidosis; FAP = familial amyloid polyneuropathy; HR = hazard ratio; LV = left ventricular; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal prohormone of brain-type natriuretic peptide; NYHA = New York Heart Association.
[a]The P value threshold for entry to or removal from the selection-based multivariate Cox proportional hazards analysis was set at 0.15. Forward, backward, and stepwise selection-based models all led to the same variables being selected. Forward: the order of variables added was (1) NT-proBNP, (2) first treatment assignment, (3) FAP stage, (4) genotype, (5) ATTR amyloidosis stage, and (6) LV wall thickness. Backward: the order of variables removed was (1) LV mass, (2) PND score, (3) NYHA classification, (4) cardiac subpopulation, and (5) NIS. Stepwise: the order of variables added or removed was (1) added NT-proBNP, (2) added first treatment assignment, (3) added FAP stage, (4) added genotype, (5) added ATTR amyloidosis stage, and (6) added LV wall thickness.
[b]Full multivariate Cox proportional hazards analysis was conducted using factors that were significant (P<0.05) in a univariate model. Survival time is calculated as time from parent study baseline to death or last known alive date on or before end of study.
[c]This variable shows the effect of delayed patisiran treatment onset of 18 months.

Safety

The rates of AEs and serious AEs were higher in the APOLLO-placebo than the APOLLO-patisiran and phase 2 OLE-patisiran groups. The types of AEs reported were similar to those observed in APOLLO, and the exposure-adjusted event rates were similar or lower than in APOLLO. Cardiac AEs, which were all reported as serious AEs, are summarized in **Table 6**.[1]

**Table 6. Cardiac AEs.**[1]

| Variable | APOLLO-placebo (N=49) | APOLLO-patisiran (N=137) | Phase 2 OLE-patisiran (N=25) | Global total (N=211) |
|---|---|---|---|---|
| Atrial fibrillation | 1 (2.0) | 6 (4.4) | 0 | 7 (3.3) |
| Atrioventricular block complete | 3 (6.1) | 3 (2.2) | 1 (4.0) | 7 (3.3) |
| Cardiac failure | 2 (4.1) | 4 (2.9) | 1 (4.0) | 7 (3.3) |
| Cardiac amyloidosis | 1 (2.0) | 4 (2.9) | 0 | 5 (2.4) |
| Cardiac arrest | 5 (10.2) | 0 | 0 | 5 (2.4) |

Abbreviations: AE = adverse event, OLE = open-label extension

## POST-HOC ANALYSIS OF POOLED CARDIAC POPULATION

### Study Design

A post-hoc analysis of pooled data from the APOLLO-B OLE and the cardiac subpopulation of the Global OLE evaluated the long-term effects of patisiran on survival, hospitalizations, and cardiac parameters in patients with hATTR-PN and evidence of cardiac involvement or a diagnosis of ATTR-CM.[3]

### Baseline Characteristics

Baseline demographics and disease characteristics are provided in **Table 7**.[3]

**Table 7. Baseline Characteristics.**[3]

| Characteristic | Patisiran (N=282) | | | | Placebo (N=214) | | |
|---|---|---|---|---|---|---|---|
| | Total (N=282) | APOLLO-B (N=181) | APOLLO (N=90) | Phase 2 (N=11) | Total (N=214) | APOLLO-B (N=178) | APOLLO (N=36) |
| Age at screening, years, median (range) | 72 (24–85) | 76 (47–85) | 60 (24–79) | 69 (58–75) | 74 (41–85) | 76 (41–85) | 62 (43–80) |
| Male sex, n (%) | 237 (84.0) | 161 (89.0) | 68 (75.6) | 8 (72.7) | 190 (88.8) | 160 (89.9) | 30 (83.3) |
| Race, n (%) | | | | | | | |
| White | 212 (75.2) | 138 (76.2) | 63 (70.0) | 11 (100.0) | 156 (72.9) | 140 (78.7) | 16 (44.4) |
| Asian | 46 (16.3) | 23 (12.7) | 23 (25.6) | 0 | 33 (15.4) | 15 (8.4) | 18 (50.0) |
| Black or African American | 18 (6.4) | 16 (8.8) | 2 (2.2) | 0 | 16 (7.5) | 15 (8.4) | 1 (2.8) |
| Age category, years, n (%) | | | | | | | |
| <45 | 11 (3.9) | 0 | 11 (12.2) | 0 | 3 (1.4) | 2 (1.1) | 1 (2.8) |
| 45-<65 | 65 (23.0) | 15 (8.3) | 48 (53.3) | 2 (18.2) | 36 (16.8) | 15 (8.4) | 21 (58.3) |
| 65-<75 | 94 (33.3) | 61 (33.7) | 26 (28.9) | 7 (63.6) | 69 (32.2) | 60 (33.7) | 9 (25.0) |
| ≥75 | 112 (39.7) | 105 (58.0) | 5 (5.6) | 2 (18.2) | 106 (49.5) | 101 (56.7) | 5 (13.9) |
| wtATTR[a], n (%) | 144 (51.1) | 144 (79.6) | 0 | 0 | 144 (67.3) | 144 (80.9) | 0 |
| NYHA class[a], n (%) | | | | | | | |
| Class I | 49 (17.4) | 10 (5.5) | 34 (37.8) | 5 (45.5) | 31 (14.5) | 15 (8.4) | 16 (44.4) |
| Class II | 218 (77.3) | 156 (86.2) | 56 (62.2) | 6 (54.5) | 170 (79.4) | 150 (84.3) | 20 (55.6) |
| Class III | 15 (5.3) | 15 (8.3) | 0 | 0 | 13 (6.1) | 13 (7.3) | 0 |
| NT-proBNP level, ng/L, median (IQR) | 1577 (770–2744) | 2008 (1135–2921) | 756 (285–2432) | 604 (205–1367) | 1607 (837–2893) | 1813 (952–3079) | 846 (373–1582) |
| Average peak longitudinal strain, %, mean (SEM) | −12.44 (0.2) | −10.9 (0.3) | −15.1 (0.4) | −16.6 (1.3) | −11.96 (0.2) | −11.2 (0.2) | −15.7 (0.6) |

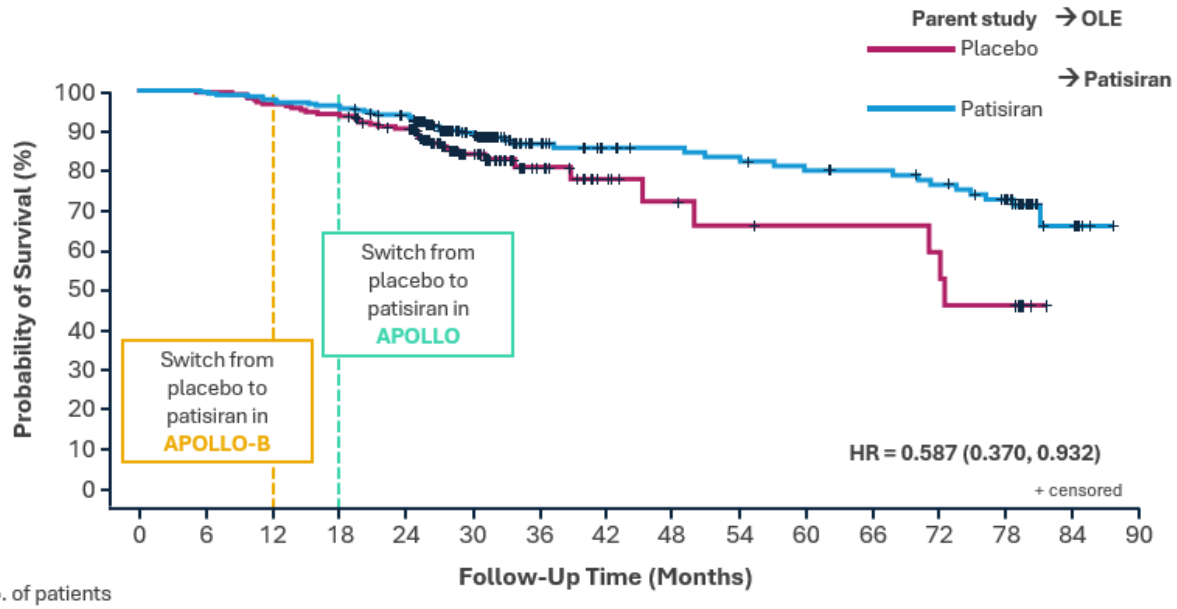
Abbreviations: IQR = interquartile range; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; SEM = standard error of the mean; wtATTR = wild-type transthyretin amyloidosis.
[a]Patients with wtATTR and patients with NYHA class ≥III were excluded from the Global OLE study.

## Results

Survival and Hospitalization

In patients who received patisiran in the parent studies, the hazard for mortality and for hospitalizations decreased by 41.3% and 23.3%, respectively, relative to those who were randomized to placebo (**Figure 1** and **Figure 2**).[3]

**Figure 1. Probability of Survival Over Time.**[3]



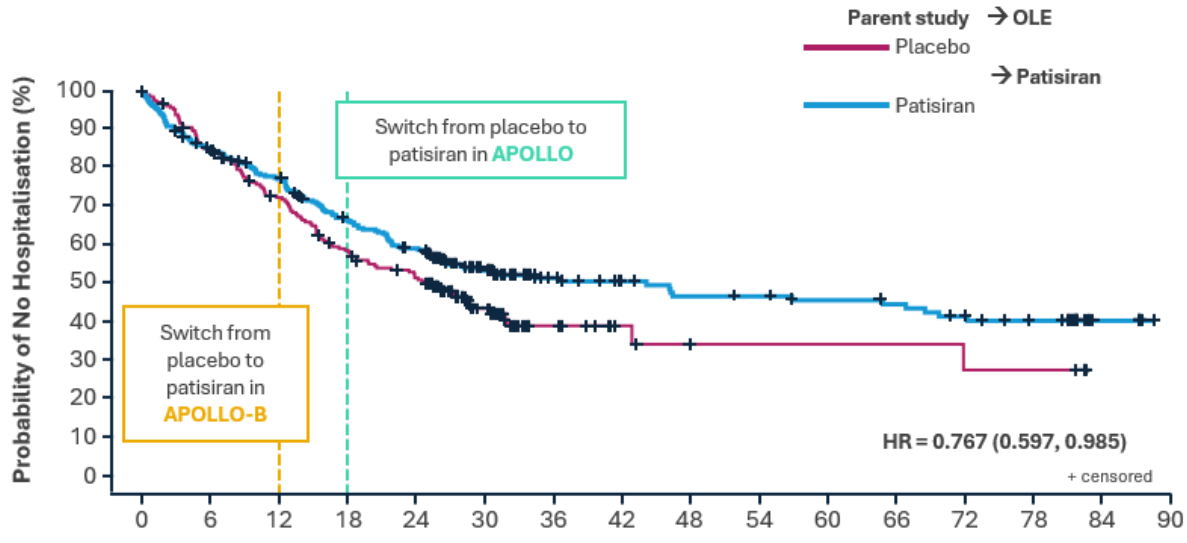

No. of patients

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Parent study → OLE** | | | | | | | | | | | | | | | |
| Placebo | 214 | 209 | 196 | 185 | 171 | 75 | 32 | 19 | 13 | 11 | 10 | 10 | 9 | 7 | 0 |
| **→ Patisiran** | | | | | | | | | | | | | | | |
| Patisiran | 282 | 272 | 264 | 256 | 245 | 151 | 94 | 80 | 77 | 75 | 71 | 69 | 65 | 58 | 12 | 0 |

From Lairez et al[3]

Abbreviations: HR = hazard ratio; OLE = open-label extension.

**Figure 2. Probability of No Hospitalizations Over Time.**[3]




No. of patients

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Parent study → OLE** | | | | | | | | | | | | | | | |
| Placebo | 214 | 178 | 146 | 116 | 99 | 36 | 15 | 8 | 5 | 5 | 5 | 5 | 4 | 4 | 0 |
| **→ Patisiran** | | | | | | | | | | | | | | | |
| Patisiran | 282 | 235 | 210 | 175 | 154 | 96 | 62 | 53 | 48 | 47 | 44 | 42 | 37 | 33 | 9 | 0 |

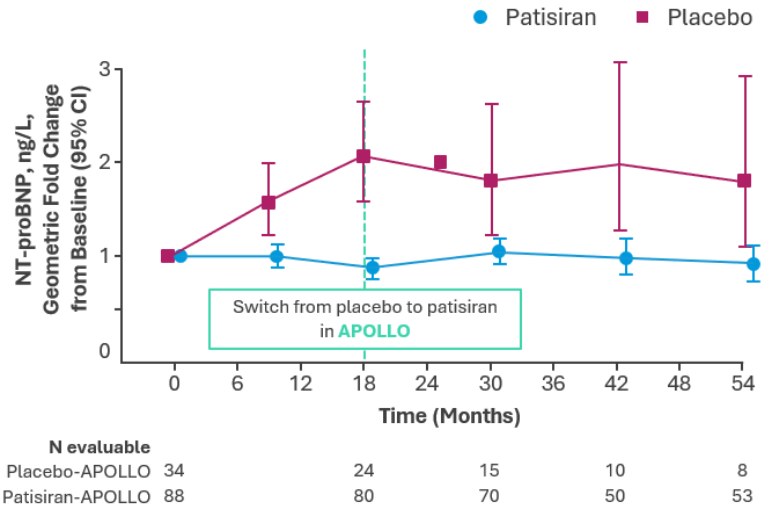
From Lairez et al[3]

Abbreviations: HR = hazard ratio; OLE = open-label extension.

NT-proBNP Levels

Patients randomized to patisiran had a stable geometric mean fold change in NT-proBNP from baseline throughout APOLLO. The rate of worsening of geometric mean fold change in NT-proBNP from baseline decreased in patients randomized to placebo when they were switched to patisiran at month 18 (**Figure 3**).[3]

**Figure 3. Long-Term Stability of NT-proBNP with Patisiran in the APOLLO Trial.**[3]



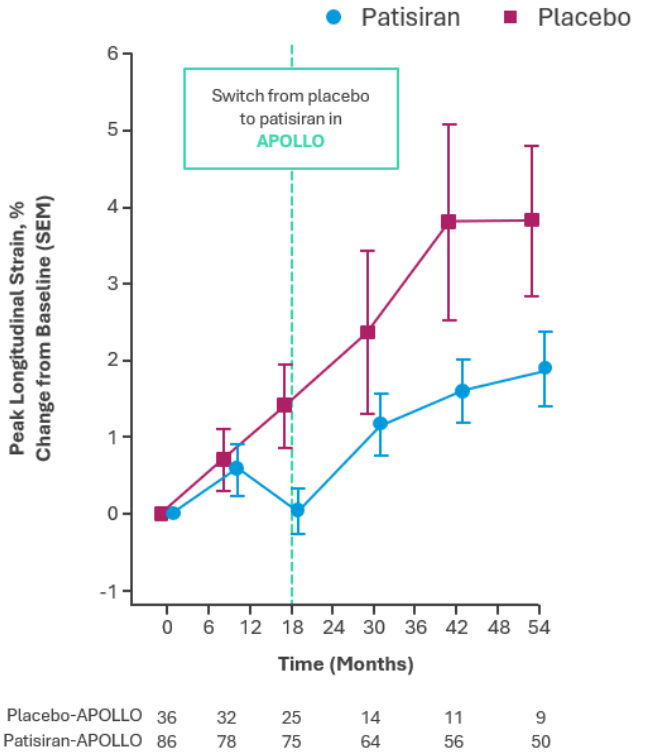

From Lairez et al[3]

Abbreviations: CI = confidence interval; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Left Ventricular Function

Better preservation of peak longitudinal strain was observed with patisiran when compared with placebo in the APOLLO study (**Figure 4**).[3]

**Figure 4. Impact of Patisiran on Left Ventricular Function in the APOLLO Trial.**[3]




From Lairez et al[3]
Abbreviations: SEM = standard error of the mean.

## ABBREVIATIONS

AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; FAP = familial amyloid polyneuropathy; hATTR-PN = hereditary transthyretin amyloidosis; IQR = interquartile range; IV = intravenous; LV = left ventricular; NAC = National Amyloidosis Centre; NIS = Neuropathy Impairment Score; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; PND = polyneuropathy disability; SD = standard deviation; SEM = standard error of the mean; wtATTR = wild-type transthyretin amyloidosis.

*Updated 27 February 2025*

## REFERENCES


1. Adams D, Wixner J, Polydefkis M, et al. Five-year results with patisiran for hereditary transthyretin amyloidosis with polyneuropathy: A randomized clinical trial with open-label extension. *JAMA Neurol*. Published online January 13, 2025. doi:10.1001/jamaneurol.2024.4631
2. Adams, Polydefkis, González-Duarte, et al. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. *Lancet Neurol*. 2021;20(1):49-59. doi:10.1016/S1474-4422(20)30368-9
3. Lairez O, Algalarrondo V, Damy T, et al. Long-term effects of patisiran on survival and cardiac parameters in patients with transthyretin-mediated cardiac amyloidosis: Post hoc analysis of APOLLO-B and cardiac subpopulation of APOLLO OLE. Presented at: European Society of Cardiology (ESC) Congress; August 30 - September 2, 2024; London, UK.

4. Supplement to: Adams D, Wixner J, Polydefkis M, et al. Five-year results with patisiran for hereditary transthyretin amyloidosis with polyneuropathy: A randomized clinical trial with open-label extension. *JAMA Neurol*. Published online January 13, 2025. doi:10.1001/jamaneurol.2024.4631.
5. Supplement to: Adams D, Polydefkis M, González-Duarte A, et al. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. *Lancet Neurol*. 2021;20(1):49-59. doi:10.1016/S1474-4422(20)30368-9