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 the polyneuropathy of hATTR. Patients who completed the patisiran Phase 2 OLE study or phase 3 APOLLO study and met eligibility criteria were able to start or continue patisiran for up to 5 years.[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.[1]
- At 12 months, cardiac AEs were reported in 44/211 (21%) patients and cardiac SAEs were reported in 31/211 (15%) patients. No cardiac AEs were considered related to patisiran.[1]
- In a post-hoc analysis using data from the parent study baseline to the 12-month OLE assessment, the frequency of cardiac death in the APOLLO-placebo group (12%) was higher than in the APOLLO-patisiran group (7%) and Phase 2 OLE-patisiran group (4%).[2]
- A post-hoc analysis conducted at 36 months identified randomization to placebo in the parent study, NT-proBNP >3000 ng/L, and NYHA Class >1 as independent risk factors for mortality.[3]

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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 the polyneuropathy of hATTR. Patients with the polyneuropathy of hATTR 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, autonomic symptoms, nutritional status, disability, ambulation status, motor function, and cardiac stress, as measured by NT-proBNP levels.[1]

BASELINE CHARACTERISTICS

At Global OLE enrollment, patients in the APOLLO-placebo group had higher NT-proBNP levels than patients in the APOLLO-patisiran and Phase 2 OLE-patisiran groups. A summary of baseline characteristics in the Global OLE is described in **Table 1**.[1,3]

Table 1. Baseline Characteristics at Global OLE Enrollment.[1,3]

Characteristic	APOLLO-placebo (N=49)	APOLLO-patisiran (N=137)	Phase 2 OLE-patisiran (N=25)	Global OLE Total (N=211)
Median age, years	66	63	65	64
Sex, n (%)				
Female	12 (24)	35 (26)	8 (32)	55 (26)
Male	37 (76)	102 (74)	17 (68)	156 (74)
Time since diagnosis, years				
To Global OLE enrollment, median (IQR)	2.8 (2.0 - 5.4)	3.0 (2.1 - 4.2)	4.8 (4.0 - 5.6)	3.4 (2.2 – 5.0)
To time of first patisiran dose[a], mean (range)	4.5 (2 – 18)	2.5 (0 – 21)	2.8 (1 – 8)	3.0 (0 – 21)
Genotype, n (%)				
Val30Met	24 (49)	56 (41)	18 (72)	98 (46)
Non-Val30Met	25 (51)	81 (59)	7 (28)	113 (54)
Serum TTR (mg/L), mean (SD)	189 (59)	55 (47)	81 (52)	89 (75)
PND score[b], n (%)				
0	0	1 (1)	0	1 (<1)
I	7 (14)	32 (23)	10 (40)	49 (23)
II	9 (18)	36 (26)	13 (52)	58 (27)
IIIA/B	25 (51)	60 (44)	2 (8)	87 (41)
IV	8 (16)	8 (6)	0	16 (8)
mNIS+7 score[c], mean (min, max)	101 (22, 190)	75 (8, 199)	46 (3, 128)	77 (3, 199)
Norfolk QOL-DN total scored, mean (SD)	73 (28)	55 (31)	N/Ae	59 (31)
NYHA classification, n (%)				
I	22 (45)	67 (49)	19 (76)	108 (51)
II	21 (43)	59 (43)	4 (16)	84 (40)
III	4 (8)	9 (7)	2 (8)	15 (7)
IV	2 (4)	2 (1)	0	4 (2)
NT-proBNP, ng/L, median (range)	868 (56 - 15,101)	375 (21 - 10,282)	166 (5 - 1,897)	376 (5 - 15,101)
LV wall thickness, cm, mean (SD)	1.5 (0.3)	1.5 (0.3)	1.2 (0.3)	1.5 (0.3)

Abbreviations: IQR = interquartile range; LV = left ventricular; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; PND = polyneuropathy disability; SD = standard deviation; TTR = transthyretin.

[a]First dose of patisiran in the parent study (APOLLO-patisiran and Phase 2 OLE groups) or in the Global OLE study (APOLLO-placebo group).

[b]Patients are categorized as follows: 0: no symptoms; I: preserved walking, sensory disturbances; II: impaired walking but can walk without stick or crutch; IIIA/B: walk with 1 or 2 sticks or crutches; IV: confined to wheelchair or bedridden.

[c]Range 0 to 304; higher score reflects greater impairment.

[d]Range -4 to 136; higher score indicates worse QOL.

[e]Norfolk QOL-DN was not collected in the Phase 2 OLE study.

12-MONTH RESULTS

Cardiac Efficacy 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**).[1,2] 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**.[2]

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

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.[2]

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.

Cardiac Safety Results

Cardiac AEs at 12 months were reported in 44/211 (21%) patients and cardiac SAEs were reported in 31/211 (15%) patients. No cardiac AEs were considered related to patisiran.[1]

In the APOLLO-placebo group, frequencies of cardiac AEs (16/49, 33%) and cardiac SAEs (11/49, 22%) were higher than in the APOLLO-patisiran (25/137, 18% and 18/137, 13%), and the Phase 2 OLE-patisiran (3/25, 12% and 2/25, 8%) groups. A summary of cardiac SAEs is presented in **Table 4**.[1]

Table 4. Summary of Cardiac SAEs in ≥1% of Patients in the Global OLE Study at 12 Months.[1]

SAE, n (%)	APOLLO-placebo (N=49)	APOLLO-patisiran (N=137)	Phase 2 OLE-patisiran (N=25)	Global OLE Total (N=211)
Cerebrovascular accident	1 (2)	3 (2)	1 (4)	5 (2)
Cardiac arrest	4 (8)	0	0	4 (2)
Acute myocardial infarction	1 (2)	2 (1)	0	3 (1)
Cardiac failure	1 (2)	1 (<1)	1 (4)	3 (1)
Cardiac failure congestive	1 (2)	2 (1)	0	3 (1)
Conduction disorder	0	3 (2)	0	3 (1)

Abbreviations: OLE = open-label extension; SAE = serious adverse event.

Mortality Results

At 12 months, deaths were reported in 23/211 (11%) patients. The frequency of death in the APOLLO-placebo (13/49, 27%) group was higher than in the APOLLO-patisiran (10/137, 7%) and Phase 2 OLE-patisiran (0/25, 0%) groups. Causes of death were consistent with the natural history of hATTR, and most patients who died had known risk factors for poor prognosis (non-Val30Met genotype, advanced age, advanced disease status, long duration of disease, and advanced neuropathic and cardiac involvement) and marked disease burden at Global OLE enrollment. None of the 23 deaths were considered to be related to patisiran treatment by investigators.[1]

In a post-hoc analysis using data from the parent study baseline to the 12-month OLE assessment, the frequency of cardiac deaths in the APOLLO-placebo group (6/49, 12%) was higher than in 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 5**.[2]

Table 5. Integrated Exposure-Adjusted Mortality Rates in Patients with hATTR with Polyneuropathy Enrolled Across the Patisiran Development Program at 12 Months.[2]

	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: ATTRv = hereditary transthyretin-mediated; 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).

36-MONTH RESULTS

Mortality Results

At 36 months, deaths were reported in 35/211 (16.6%) patients. The frequency of death in the APOLLO-placebo (18/49, 36.7%) group was higher than in the APOLLO-patisiran (16/137, 11.7%) and Phase 2 OLE patisiran (1/25, 4%) groups. None of the 35 deaths were considered to be related to patisiran treatment by investigators. Patients in the APOLLO-patisiran and Phase 2 OLE-patisiran groups who received patisiran in their parent studies had a lower disease burden at Global OLE baseline as evidenced by lower mNIS+7 scores and lower NT-proBNP levels. These patients had the lowest mortality rates in the Global OLE at 36 months.[3]

To identify potential risk factors for mortality, a post-hoc multivariate Cox proportional hazards analysis was conducted using factors that were significant in a univariate model as presented in **Table 6**.[3]

Table 6. Risk Factors for Mortality in the Global OLE at 36 Months.[3]

Characteristics at First Dose of Patisiran	All Patisiran-Treated Patients (N=224)[a]	
	Hazard Ratio (95% CI)	P-value
Parent Study Treatmentb, Placebo vs. Patisiran	6.50 (2.82, 14.97)	<0.0001
NT-proBNP, >3000 ng/L vs. ≤3000 ng/L	7.52 (2.93, 19.28)	<0.0001
NYHA Classification, II/III/IV vs. I	2.55 (1.10, 5.89)	0.0286
Genotype, Non-V30M vs. V30M	1.78 (0.83, 3.84)	0.1401
FAP Stage, 3 vs. 1/2	1.97 (0.63, 6.16)	0.2421
Mean LV Wall Thickness, ≥1.3 cm vs. <1.3 cm	1.02 (0.29, 3.61)	0.9728

Abbreviations: CI = confidence interval; FAP = familial amyloid polyneuropathy; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension.
[a]In the multivariate Cox regression model, all 6 terms were included as effects. Survival time was calculated as time from first dose of patisiran to death or last known alive date on or before data cut-off (January 27, 2021).
[b]Patients enrolled from the placebo arm started patisiran treatment 18 months later compared to patients enrolled from the patisiran arms.

Safety Results

The majority of AEs at 36 months were mild or moderate in severity. The most common treatment-related AEs were IRRs. IRRs were mild or moderate in severity and occurred more often in the APOLLO-placebo group (13/49, 26.5%) compared with APOLLO-patisiran (16/137, 11.7%) and Phase 2 OLE-patisiran (4/25, 16%) groups, and the frequency decreased over time.[3]

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ABBREVIATIONS

AE = adverse event; CI = confidence interval; FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; IQR = interquartile range; IRR = infusion-related reaction; IV = intravenous; LV = left ventricular; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; PND = polyneuropathy disability; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; TTR = transthyretin.

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