Patisiran: APOLLO Study Results

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SUMMARY

- APOLLO was a multicenter, international, randomized (2:1), double-blind, placebo-controlled, phase 3 study designed to assess the efficacy and safety of patisiran in patients with the polyneuropathy of hATTR.[1]
- The study met the primary endpoint of change in mNIS+7 at 18 months compared with placebo. The LS mean (±SE) change in mNIS+7 from baseline was -6.0±1.7 for patisiran and 28.0±2.6 for placebo, which resulted in a LS mean difference (95% CI) of -34.0 points between groups (-39.9, -28.1; $P<0.001$).[1]
- The study met all secondary efficacy endpoints, which included change from baseline at 18 months in Norfolk QOL-DN, NIS-W, R-ODS, 10-MWT, mBMI, and COMPASS-31.[1]
- Over 18 months, the median reduction in serum TTR level was 81% in patients treated with patisiran.[1]
- At 18 months of the exploratory analysis in the cardiac subpopulation, treatment with patisiran was associated with improved cardiac structure and function compared with placebo, including differences in longitudinal strain and left ventricular wall thickness.[1]
- During the study, 97% of patients reported AEs across both treatment groups, of which the majority were mild or moderate in severity. AEs which occurred more frequently in the patisiran group than the placebo group were peripheral edema (30% vs 22%) and IRRs (19% vs. 9%). There were no serious or severe IRRs, and the frequency of IRRs decreased over time.[1]

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STUDY DESIGN

APOLLO was a multicenter, international, randomized (2:1), double-blind, placebo-controlled, phase 3 study designed to assess the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=148) versus placebo (n=77) in patients with the polyneuropathy of hATTR. Randomization was stratified according to NIS (5 to 49 vs. 50 to 130), early onset of disease (age <50 years) with a V30M variant vs. other pathogenic variants (including late-onset disease with a V30M variant), and previous use of a transthyretin stabilizer (yes vs. no).[1] To minimize the risk of IRRs, patients received premedication at least 60 minutes prior to patisiran infusion.[1,2] The primary endpoint was the change from baseline in the mNIS+7 at 18 months.[1]

Select inclusion and exclusion criteria for the APOLLO study are presented in **Table 1**.[1,2]

Table 1. APOLLO Inclusion and Exclusion Criteria.[1,2]

Inclusion Criteria	Exclusion Criteria
• Age 18-85 years • Diagnosis of hATTR • NIS of 5-130 • PND score ≤IIIb • AST and ALT ≤2.5x ULN, total bilirubin within normal limits, albumin >3 g/dL, INR ≤1.2 • Serum creatinine ≤1.5x ULN	• Had a prior liver transplant or planning to undergo liver transplant during the study period • NYHA heart failure classification >2

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; hATTR = hereditary transthyretin amyloidosis; INR = international normalized ratio; NIS = Neuropathy Impairment Score; NYHA = New York Heart Association; PND = polyneuropathy disability; ULN = upper limit of normal.

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

A total of 225 patients were randomized (148 in the patisiran group and 77 in the placebo group) at 44 sites in 19 countries. The median age was 62 years in the patisiran group and 63 years in the placebo group; approximately 74% of patients were male. Most patients (72%) were white/Caucasian. Baseline characteristics for patients enrolled in APOLLO are presented in **Table 2**.[1]

Table 2. Baseline Demographic and Clinical Characteristics in APOLLO.[1,a]

Characteristic	Placebo (n=77)	Patisiran (n=148)
Median time since hATTR diagnosis — yr (range)	1.4 (0.0–16.5)	1.3 (0.0–21.0)
TTR genotype — no. (%)		
V30M	40 (52)	56 (38)
With onset of disease before 50 yr of age	10 (13)	13 (9)
non-V30M[b]	37 (48)	92 (62)
Previous use of TTR stabilizer — no. (%)	41 (53)	78 (53)
FAP stage — no. (%)		
1: unimpaired ambulation	37 (48)	67 (45)
2: assistance with ambulation	39 (51)	81 (55)
3: wheelchair bound or bedridden	1 (1)	0
PND score — no. (%)		
I: preserved walking, sensory disturbances	20 (26)	36 (24)
II: impaired walking without need for a stick or crutches	23 (30)	43 (29)
IIIA: walk with one stick or crutch	22 (29)	41 (28)
IIIB: walk with two sticks or crutches	11 (14)	28 (19)
IV: confined to wheelchair or bedridden	1 (1)	0
NYHA class — no. (%)		
I	40 (52)	70 (47)
II	36 (47)	77 (52)
Missing Data	1 (1)	1 (<1)

Abbreviations: FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; NYHA = New York Heart Association; PND = polyneuropathy disability, TTR = transthyretin.

[a]Differences in baseline demographic and clinical characteristics between the patisiran and placebo groups were tested with the use of t-tests for continuous variables (age and log-transformed years since diagnosis of hereditary transthyretin amyloidosis) and Fisher's exact tests for categorical variables (sex, race, geographic region, V30M or non-V30M *TTR* genotype, previous use or nonuse of tetramer stabilizer, and New York Heart Association class). A significant difference between the groups ($P<0.05$) was found for *TTR* genotype only.

[b] Represents 38 different *TTR* variants.

EFFICACY RESULTS

Primary Endpoint

mNIS+7

At baseline, the mean (±SD) mNIS+7 was 80.9±41.5 in the patisiran group and 74.6±37.0 in the placebo group. At Month 18, the change from baseline in mNIS+7 was significantly lower with patisiran than with placebo. The LS mean (±SE) change in mNIS+7 from baseline was -6.0±1.7 for patisiran and 28.0±2.6 for placebo, which resulted in a LS mean difference (95% CI) of -34.0 points between groups (-39.9, -28.1; *P*<0.001). More patients had a less than 10-point increase from baseline in the mNIS+7 at 18 months in the patisiran group (74%) as compared with the placebo group (14%). The treatment effect was significant for all subgroups and components of mNIS+7.[1]

At Month 18, 56% of patients in the patisiran group had an improvement in mNIS+7 compared with 4% of patients who received placebo. In patients that did not have an improvement in mNIS+7 and received patisiran (54 of 137 patients had available data), the median change from baseline in the mNIS+7 at 18 months was lower than that observed in all 51 patients who received placebo and had available data (9.9-point increase and 26.5-point increase, respectively).[1]

Secondary Endpoints

At Month 18, the change from baseline in the Norfolk QOL-DN score was significantly lower in the patisiran group compared with the placebo group. At baseline, the mean (±SD) Norfolk QOL-DN score in the patisiran group was 59.6±28.2 and in the placebo group was 55.5±24.3. At Month 18, the LS mean (±SE) change in the Norfolk QOL-DN score from baseline was -6.7±1.8 points in the patisiran group, and 14.4±2.7 in the placebo group (LS mean difference: -21.1 points; 95% CI: -27.2, -15.0; *P*<0.001). Across all subgroups, consistent effects in favor of patisiran were seen in Norfolk QOL-DN scores. At Month 18, 51% of patients in the patisiran group had improvement from their baseline Norfolk QOL-DN score compared with 10% in the placebo group.[1]

Significant between-group differences in favor of patisiran treatment were observed for all other secondary endpoints and are displayed in **Table 3**.[1]

Table 3. Secondary Endpoints in the Modified ITT Population.[1,a]

Endpoint	Placebo (n = 77)	Patisiran (n = 148)	LS Mean Difference (Patisiran – Placebo)	*P* Value
NIS-W[b]				
Mean (±SD) baseline score	29.0±23.0	32.7±25.2		
LS mean (±SE) change from baseline at 18 mo.	17.9±2.0	0.1±1.3	-17.9±2.3	<0.001
R-ODS[c]				
Mean (±SD) baseline score	29.8±10.8	29.7±11.5		
LS mean (±SE) change from baseline at 18 mo.	-8.9±0.9	0.0±0.6	9.0±1.0	<0.001
10-MWT, m/sec[d]				
Mean (±SD) baseline value	0.79±0.32	0.80±0.40		
LS mean (±SE) change from baseline at 18 mo.	-0.24±0.04	0.08±0.02	0.31±0.04	<0.001
mBMI[e]				
Mean (±SD) baseline value	989.9±214.2	969.7±210.5		
LS mean (±SE) change from baseline at 18 mo.	-119.4±14.5	-3.7±9.6	115.7±16.9	<0.001
COMPASS-31[f]				
Mean (±SD) baseline score	30.3±16.4	30.6±17.6		
LS mean (±SE) change from baseline at 18 mo.	2.2±1.9	-5.3±1.3	-7.5±2.2	<0.001

Abbreviations: 10-MWT = 10-meter walk test; BMI = body-mass index; COMPASS-31 = Composite Autonomic Symptom Score-31; ITT = intent-to-treat; LS = least squares; NIS = Neuropathy Impairment Score; NIS-W = Neuropathy Impairment Score-Weakness; R-ODS = Rasch-built Overall Disability Scale; SD = standard deviation; SE = standard error

[a]The ITT population included all the patients who underwent randomization and received at least one dose of patisiran or placebo.

[b]Scores on the weakness component of the NIS range from 0 to 192, with higher scores indicating more impairment. The number of patients who were assessed at 18 months was 51 in the placebo group and 137 in the patisiran group.

[c]Scores on the R-ODS range from 0 to 48, with lower scores indicating more disability. The number of patients who were assessed at 18 months was 54 in the placebo group and 138 in the patisiran group.

[d]A lower value indicates a slower gait speed. The number of patients who were assessed at 18 months was 55 in the placebo group and 138 in the patisiran group.

[e]The mBMI was the BMI (weight in kilograms divided by square of height in meters) × albumin level in grams per liter. The number of patients who were assessed at 18 months was 52 in the placebo group and 133 in the patisiran group.

[l]Values for the COMPASS-31 range from 0 to 100, with higher scores indicating more autonomic symptoms. The number of patients who were assessed at 18 months was 53 in the placebo group and 136 in the patisiran group.

Select Exploratory Endpoints

Serum TTR

Over 18 months, the median reduction in the serum TTR level in the patisiran group was 81% (range, −38 to 95) and was similar across age, sex, or genotype.[1]

Measures of Cardiac Structure and Function

The APOLLO study included 126 (56%) patients in the predefined cardiac subpopulation (baseline left ventricular wall thickness ≥13 mm in the absence of a history of aortic valve disease or hypertension). Treatment with patisiran was associated with better cardiac structure and function than placebo, including differences in longitudinal strain and mean left ventricular wall thickness at 18 months. **Table 4** contains results of the exploratory endpoints from the cardiac subpopulation.[1]

Table 4. Exploratory Endpoints from the Cardiac Subpopulation.[1]

Endpoint	Placebo (n = 36)	Patisiran (n = 90)	LS Mean Difference (Patisiran – Placebo)	*P* Value
Left ventricular wall thickness — mm				
Mean (±SD) baseline value	16.4±2.1	16.8±2.6		
LS mean (±SE) change from baseline at 18 mo.	-0.1±0.3	-1.0±0.2	-0.9±0.4	0.02
Left ventricular longitudinal strain — %				
Mean (±SD) baseline score	-15.66±3.51	-15.13±3.41		
LS mean (±SE) change from baseline at 18 mo.	1.46±0.48	0.08±0.28	-1.37±0.56	0.02
NT-proBNP[a]				
Baseline value				
Geometric mean — pg/ml	711.1	726.9		
Coefficient of variation — %	190.8	220.3		
Ratio to baseline at 18 mo.[b]	1.97	0.89	0.45[c]	<0.001

Abbreviations: NT-proBNP = N-terminal pro-brain natriuretic peptide; SD = standard deviation; SE = standard error.

[a]NT-proBNP is a measure of cardiac stress that is an independent predictor of death in patients with transthyretin cardiac amyloidosis.

[b]Shown is the adjusted geometric mean ratio to baseline at month 18.

[c]Shown is the ratio of adjusted geometric mean ratio to baseline at month 18 between the two trial groups (patisiran:placebo).

Neuropathy Stage with PND Score

Compared with placebo, a greater proportion of patients in the patisiran group had a stable (n=96, 65%) or improved (n=12, 8%) PND score relative to baseline at 18 months. In the placebo group, no patients improved and 23 of 77 (30%) of patients had a stable score. Among patients whose PND score worsened, worsening by more than one level was observed in 5 of 30 patients (17%) in the patisiran group, as compared with 16 of 32 (50%) in the placebo group at 18 months.[1]

SAFETY RESULTS

Across both treatment groups, 97% of patients reported AEs, of which the majority were mild or moderate in severity. **Table 5** contains a summary of AEs from the 18-month treatment period. AEs which occurred more frequently in the patisiran group were peripheral edema (30% vs 22%) and IRRs (19% vs. 9%), which were mild or moderate in severity. One patient withdrew from the study due to a moderate IRR of flushing. IRR symptoms reported in ≥3% of patients in either group included back pain, flushing, abdominal pain, and nausea. There were no serious or severe IRRs, and the frequency of IRRs decreased over time.[1]

Death occurred in 7 patients (5%) in the patisiran group and in 6 patients (8%) in the placebo group. The causes of death were determined to be primarily cardiovascular in nature and were consistent with expected events in the hATTR population. The incidence of cardiac AEs (patisiran, 28%; placebo, 36%), cardiac serious AEs (patisiran, 14%; placebo, 13%), and cardiac failure (patisiran, 9%; placebo, 10%) was similar between the two groups. The incidence of cardiac arrhythmias was lower with patisiran (19%) than with placebo (29%).[1]

Table 5. Summary of AEs Reported in APOLLO at 18 Months.[1]

Preferred Term – no. (%)	Placebo (n=77)	Patisiran (n=148)
Any AE	75 (97)	143 (97)
Common AEs (occurring in ≥10% in either patient group)		
Diarrhea	29 (38)	55 (37)
Edema, peripheral	17 (22)	44 (30)
Fall	22 (29)	25 (17)
Nausea	16 (21)	22 (15)
Infusion-related reaction	7 (9)	28 (19)
Constipation	13 (17)	22 (15)
Urinary tract infection	14 (18)	19 (13)
Dizziness	11 (14)	19 (13)
Fatigue	8 (10)	18 (12)
Headache	9 (12)	16 (11)
Cough	9 (12)	15 (10)
Vomiting	8 (10)	15 (10)
Asthenia	9 (12)	14 (9)
Insomnia	7 (9)	15 (10)
Nasopharyngitis	6 (8)	15 (10)
Pain in extremity	8 (10)	10 (7)
Muscular weakness	11 (14)	5 (3)
Anemia	8 (10)	3 (2)
Syncope	8 (10)	3 (2)
AEs leading to treatment discontinuation	11 (14)	7 (5)
AE leading to withdrawal	9 (12)	7 (5)
Death	6 (8)	7 (5)
Any serious AE	31 (40)	54 (36)
Any severe AE	28 (36)	42 (28)

Abbreviations: AE = adverse event.

ABBREVIATIONS

10-MWT = 10-meter walk test; AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body-mass index; CI = confidence interval; COMPASS-31 = Composite Autonomic Symptom Score-31; FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; INR = international normalized ratio; IRR = infusion-related reaction; ITT = intent-to-treat; IV = intravenous; LS = least squares; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; NIS = Neuropathy Impairment Score; NIS-W = Neuropathy Impairment Score-Weakness;

NT-proBNP = N-terminal pro-brain natriuretic peptide; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NYHA = New York Heart Association; PND = polyneuropathy disability; R-ODS = Rasch-built Overall Disability Scale; SD standard deviation; SE = standard error; TTR = transthyretin; ULN = upper limit of normal.

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