Patisiran: Use in Patients with Wild-type ATTR

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SUMMARY

- In the APOLLO study, patients with wtATTR were excluded from the study. All patients enrolled were required to have a diagnosis of hATTR-PN with a documented pathogenic variant in TTR.[1]
- In the APOLLO-B study, 80% of patients in the patisiran arm had a diagnosis of wtATTR.[2]
  - The overall study results include both patients with hATTR and patients with wtATTR.[2]
  - The APOLLO-B study met the primary endpoint of change from baseline in the 6-MWT at 12 months compared with placebo (patisiran, -8.15 m vs. placebo, -21.35 m; H-L estimate of median difference: 14.69 m [95% CI: 0.69, 28.69]; p=0.02).[2]
  - The study also met the first secondary endpoint of change from baseline in health status and quality of life at 12 months compared with placebo, as measured by the KCCQ-OS score (patisiran, 0.3 points vs. placebo, -3.4 points; LS mean difference, 3.7 points [95% CI: 0.2, 7.2]; p=0.04).[2]
  - Subgroup analyses of 6-MWT and KCCQ-OS showed consistent benefit with patisiran compared with placebo across prespecified patient subgroups at 12 months.[2]
  - In the overall population of both hATTR and wtATTR patients, the majority of AEs observed were mild or moderate. AEs that were reported in ≥5% of patients in the patisiran arm and seen ≥3% more frequently with patisiran than with placebo were IRRs, arthralgia, and muscle spasms.[2]

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APOLLO-B

APOLLO-B was a multicenter, randomized (1:1), double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=181) vs. placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR. Randomization was stratified by baseline tafamidis (yes vs. no), genotype (hATTR vs. wtATTR), and NYHA Class I or II and age < 75 years vs. all other. The primary endpoint was the change from baseline in the 6-MWT at 12 months. After the 12-month double-blind treatment period, all eligible patients received patisiran in an open-label extension period.[2]

Patient Demographics & Baseline Characteristics

In the APOLLO-B study, 144 patients (80%) in the patisiran arm and 144 patients (81%) in the placebo arm had a diagnosis of wtATTR.[2]

Efficacy Results

The overall study results include both patients with hATTR and patients with wtATTR.[2]

Primary Endpoint

Patisiran demonstrated a statistically significant difference compared with placebo in the primary endpoint of change from baseline in 6-MWT at 12 months (patisiran, -8.15 m [95% CI, -16.42 to 1.50] vs. placebo, -21.35 m [95% CI, -34.05 to -7.52]. The H-L estimate of median difference was 14.69 m (95% CI: 0.69, 28.69; p=0.02).[2]

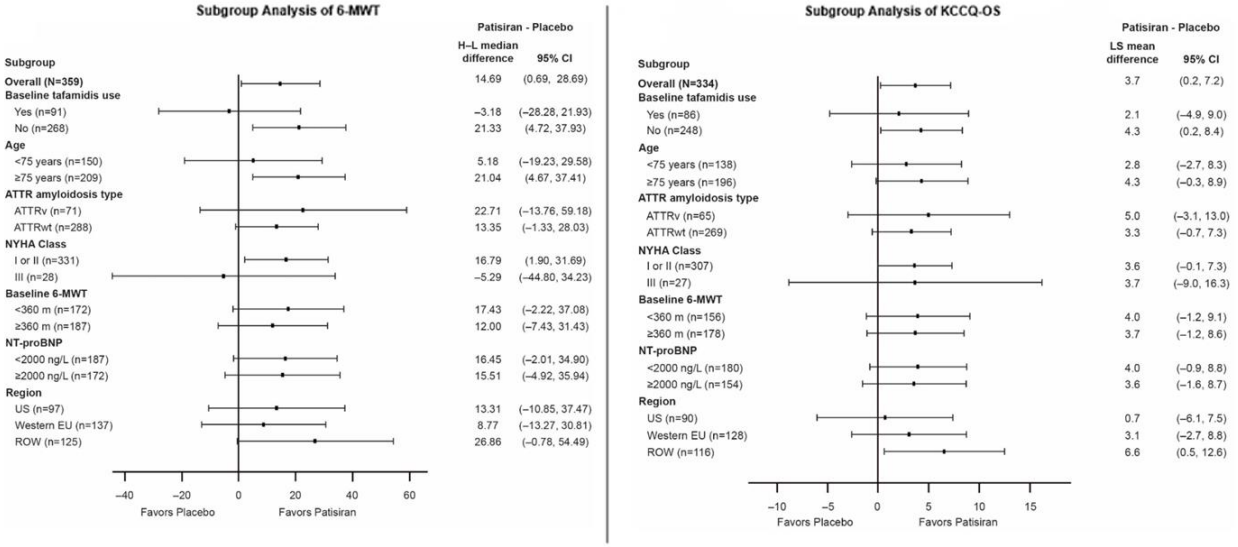
A sensitivity analysis was conducted using MMRM to confirm the primary endpoint results for change from baseline in 6-MWT at 12 months for patisiran compared with placebo. The analysis found an LS mean difference of 18.15 m (95% CI: 2.48, 33.82). A consistent difference in the 6-MWT was observed with patisiran treatment across prespecified subgroups defined according to baseline demographic and disease characteristics, including hATTR and wtATTR.[2]

Secondary Endpoint

Patisiran demonstrated a statistically significant difference in the first secondary endpoint of change from baseline in patient-reported health status and quality of life as measured by the KCCQ-OS score at 12 months compared with placebo (patisiran, 0.3 vs. placebo, -3.4) with a LS mean difference of 3.7 (95% CI: 0.2, 7.2; p=0.04).[2]

Subgroup analyses of 6-MWT and KCCQ-OS showed consistent benefit with patisiran compared with placebo across prespecified patient subgroups at 12 months, as seen in **Figure 1**.[3]

Figure 1. Subgroup Analyses of 6-MWT and KCCQ-OS at 12 Months.[3]



Abbreviations: 6-MWT = 6-minute walk test; ATTR = transthyretin amyloidosis; CI = confidence interval; hATTR = hereditary transthyretin amyloidosis; H-L = Hodges-Lehmann; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; ROW = rest of world; wtATTR = wild-type transthyretin amyloidosis.
From Maurer et al.[3]

Serum TTR Reduction

Serum TTR reduction at 12 months was assessed as a pharmacodynamic endpoint of the APOLLO-B study. Patients treated with patisiran achieved a mean (SD) percent serum TTR reduction of 86.8 (13.6).[1]

Patients with hATTR and patients with wtATTR achieved a mean (SD) percent TTR reduction of 85.2 (12.7) and 87.2 (13.9), respectively.[1]

Safety Results

During the 12-month treatment period, AEs were reported in 91% of patients in the patisiran arm and 94% of patients in the placebo arm. The majority of AEs were mild or moderate in severity, and the frequency of serious and severe AEs was similar between the two arms. AEs that were reported in ≥5% of patients in the patisiran arm and seen ≥3% more frequently with patisiran than with placebo were IRRs (12% vs. 9%), arthralgia (8% vs. 4%), and muscle spasms (7% vs. 2%). A summary of AEs reported at 12 months is presented in **Table 1.**[2]

Table 1. Summary of Adverse Events in APOLLO-B at 12 Months.[2]

Event, n (%)	Patisiran (N=181)	Placebo (N=178)
Any AE	165 (91)	168 (94)
Any serious AE[a]	61 (34)	63 (35)
Any severe AE[b]	47 (26)	52 (29)
AEs leading to treatment discontinuation	5 (3)	5 (3)
Cardiac AEs[c]	82 (45)	100 (56)
Cardiac serious AEs[c]	32 (18)	28 (16)
Deaths (safety analysis)[d]	5 (3)	8 (4)

Abbreviations: AE = adverse event; HF = heart failure; MedDRA = Medical Dictionary for Regulatory Activities.
[a]Defined as AEs that resulted in death, were life-threatening, resulting in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators.
[b]All AEs were graded for severity. Severe AEs were defined as AEs for which more than minimal, local, or noninvasive intervention was received which had a severe effect on limiting self-care activities of daily living; or which had the potential for life-threatening consequences or death.
[c]Included all events selected according to the MedDRA, version 23.0, system organ class: Cardiac disorders.
[d]Deaths in the patisiran arm included sudden cardiac death (1 patient), death due to Covid-19, HF, pancreatitis (1 patient each), and undetermined cause (1 patient). Deaths in the placebo arm included death due to HF (3 patients), undetermined cause (2 patients), and death due to cholangitis, infection, pancreatic cancer (1 patient each). Heart transplantation and the implantation of left ventricular assist devices were counted as deaths in the efficacy analysis but were not counted as deaths in the safety analysis.

Cardiac Safety Summary

Table 2 below summarizes the cardiac safety findings from APOLLO-B, providing the number of events identified within Standardized MedDRA Queries.

Table 2. APOLLO-B Cardiac Safety Summary at 12 Months.[4]

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)

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

ABBREVIATIONS

6-MWT = 6-minute walk test; AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary

transthyretin amyloidosis with polyneuropathy; H-L = Hodges-Lehmann; IRR = infusion-related reaction; IV = intravenous; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS = least squares; m = meter; MedDRA = Medical Dictionaries for Regulatory Activities; MMRM = mixed model for repeated measures; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; QT = QT interval; ROW = rest of world; SD = standard deviation; SMQ = standardized MedDRA Query; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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