Patisiran: Serum Transthyretin Levels

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SUMMARY

- In patisiran clinical studies, serum TTR levels were evaluated as a biomarker for PD assessment and were assessed using ELISA.[1–3]
  - In the phase 2 OLE study, patients treated with patisiran achieved a mean percent reduction in serum TTR level of 82% over 24 months.[1]
  - In the APOLLO study, patients treated with patisiran achieved a median percent reduction in serum TTR level of 81% (range, -38% to 95%) over 18 months.[2]
  - In the APOLLO-B study, patients treated with patisiran achieved a mean percent reduction in serum TTR level of 86.8% (SD, 13.6%) at 12 months.[3]
  - In the HELIOS-A study, patients treated with patisiran achieved a mean steady-state peak percent reduction in serum TTR of 86.0% (SD, 10.0%) at 18 months.[4]

INDEX

CLINICAL DATA

Phase 2 OLE

The phase 2 OLE study (N=27) was a multicenter, international study in patients with hATTR-PN. Patients who previously received and tolerated patisiran in the phase 2 study were eligible to enroll in the phase 2 OLE study. Patients received IV patisiran 0.3 mg/kg every 3 weeks for approximately 2 years.[1]

In the phase 2 OLE, serum TTR was used as a biomarker for PD assessment. Over 24 months, the mean percent reduction from baseline in the serum TTR level was 82%, with a mean maximal reduction of 93%. Concomitant TTR stabilizer use (patisiran and TTR stabilizer vs. patisiran alone), TTR genotype (V30M vs. non-V30M), sex, and age (<65 vs. ≥65 years) did not affect the PD activity of patisiran.[1]

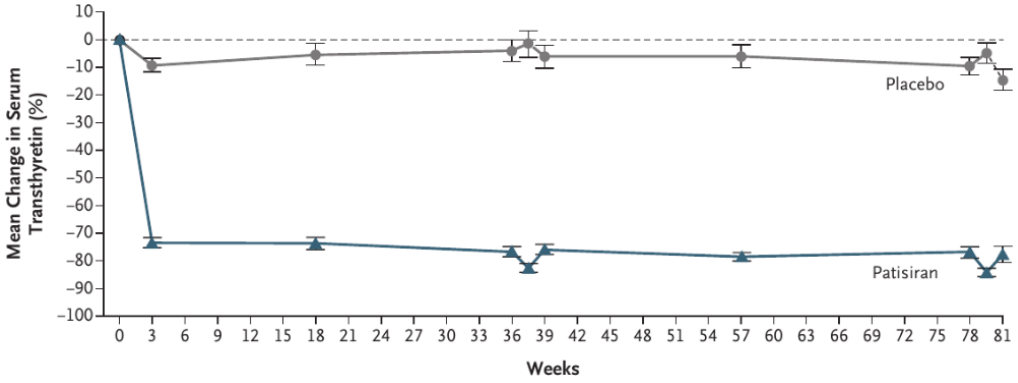
APOLLO Study

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 hATTR-PN. The primary endpoint was the change from baseline in the mNIS+7 at 18 months.[2]

In the APOLLO study, serum TTR was used as a biomarker for PD assessment. Over 18 months, the median percent reduction from baseline in the serum TTR level was 81% (range, -38 to 95) and was similar across

age, sex, or genotype. **Figure 1** shows the mean percent change in serum TTR levels from baseline to 18 months.[2]

Figure 1. Mean Percent Change from Baseline in Serum TTR Over Time in APOLLO.[2]



Abbreviations: TTR = transthyretin.
Footnotes: The nadirs in TTR reduction at 9 and 18 months correspond to the predose and postdose assessments.
From Adams et al.[2]

APOLLO-B Study

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) versus placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR. The primary endpoint was the change from baseline in the 6-MWT at 12 months. After the 12-month double-blind treatment period, all patients received patisiran in an open-label extension period.[3]

In the APOLLO-B study, serum TTR was used as a biomarker for PD assessment. At baseline, the mean (±SD) serum TTR level was 235.32±68.05 mg/L in the patisiran arm and 244.77±73.17 mg/L in the placebo arm. At 12 months, the mean serum TTR level was 30.93±33.60 mg/L in the patisiran arm and 229.40±77.15 mg/L in the placebo arm. In the patisiran group, the mean percent reduction from baseline in serum TTR was 86.8% (SD, 13.6%) at 12 months.[3]

HELIOS-A Study

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[5]

In the HELIOS-A study, serum TTR was used as a biomarker for PD assessment. Noninferiority of the percent reduction from baseline in serum TTR levels in the vutrisiran arm compared with the within-study patisiran arm through 18 months was evaluated as a secondary endpoint.[5] In patients treated with patisiran, the steady-state peak and trough mean percent reduction from baseline in serum TTR was 86.0% (SD, 10%) and 74.7% (SD, 14.7%), respectively.[4]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following sections of the ONPATTRO Prescribing Information[6]:

- CLINICAL PHARMACOLOGY Section 12.1 Mechanism of Action

- CLINICAL PHARMACOLOGY Section 12.2 Pharmacodynamics

ABBREVIATIONS

6-MWT = 6-minute walk test; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; ELISA = enzyme-linked immunosorbent assay; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PD = pharmacodynamic; SD = standard deviation; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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5. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):18-26. doi:10.1080/13506129.2022.2091985
6. ONPATTRO (patisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.