Patisiran: Orthostatic Hypotension

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SUMMARY

- A cross study analysis was conducted to evaluate the quantitative effect of patisiran and vutrisiran on orthostatic hypotension in patients with hATTR with polyneuropathy across the APOLLO, Global OLE, and HELIOS-A studies.[1]
  - In the APOLLO study, 91.2% of patients in the patisiran group with a PBP assessment had improvement or stabilization in PBP at Month 18 compared to baseline.[1]
  - In the Global OLE, 68.6% of patients in the APOLLO-placebo group, who received placebo during APOLLO and began patisiran during the Global OLE period, had improvement or stabilization in PBP at Month 18 compared to baseline. Rates of stabilization or improvement increased to 77.8% after 36 months of patisiran treatment in the Global OLE.[1]
  - In the HELIOS-A study, stabilization or improvement in PBP was seen in 81.6% of patients in the patisiran arm at Month 18.[1]
- During the APOLLO study, the impact of patisiran on orthostatic hypotension was assessed using the orthostatic intolerance domain of COMPASS-31.[2]
  - At Month 18, 30% of patients in the patisiran group experienced improvement in their orthostatic intolerance compared with baseline vs. 10% in the placebo group.[2]

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CROSS STUDY ANALYSIS OF PBP

A cross study analysis was conducted to evaluate the quantitative effect of patisiran and vutrisiran on orthostatic hypotension in patients with hATTR with polyneuropathy across the APOLLO, Global OLE, and HELIOS-A studies.[1]

Study Overviews

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. The primary endpoint was the change from baseline in the mNIS+7 at 18 months.[3]

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).[4]

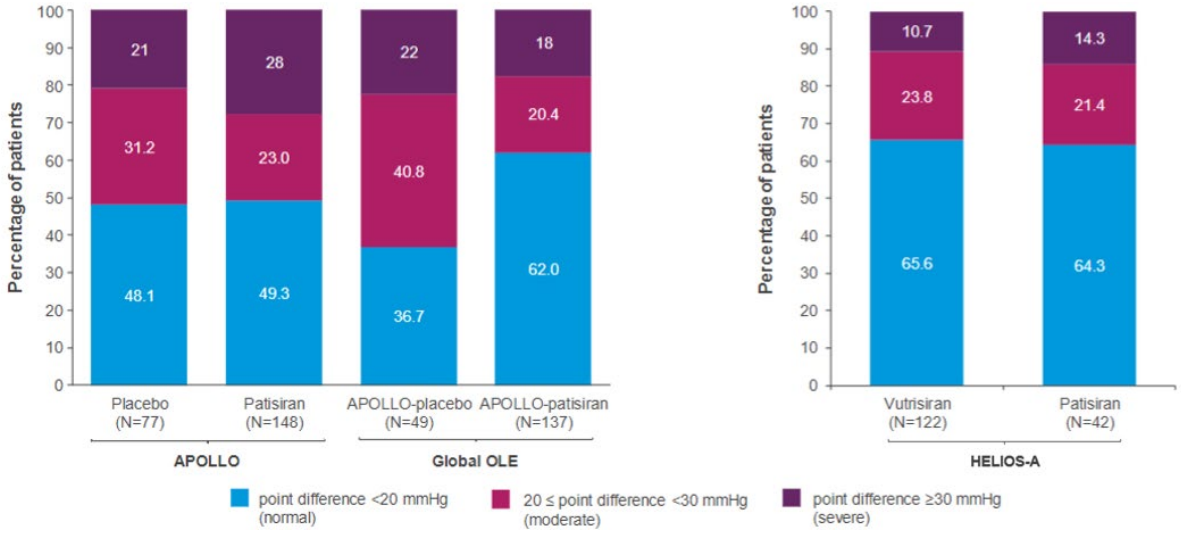
HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with the polyneuropathy of hATTR. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg 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]

Efficacy Results: mNIS+7-PBP Component

PBP was evaluated to assess the quantitative effect of patisiran on orthostatic hypotension. Orthostatic hypotension was calculated as the mean of 2 supine readings of SBP taken 15 minutes apart minus the lowest SBP upon standing at 1, 3, and 5 minutes. A smaller reduction in SBP between supine and upright positions indicated better PBP. The severity of orthostatic hypotension was categorized as follows: normal (<20 mmHg reduction), moderate (≥20–<30 mmHg reduction), and severe (≥30 mmHg reduction).[1]

The baseline assessments of PBP in the APOLLO, Global OLE, and HELIOS-A studies are presented in **Figure 1**.

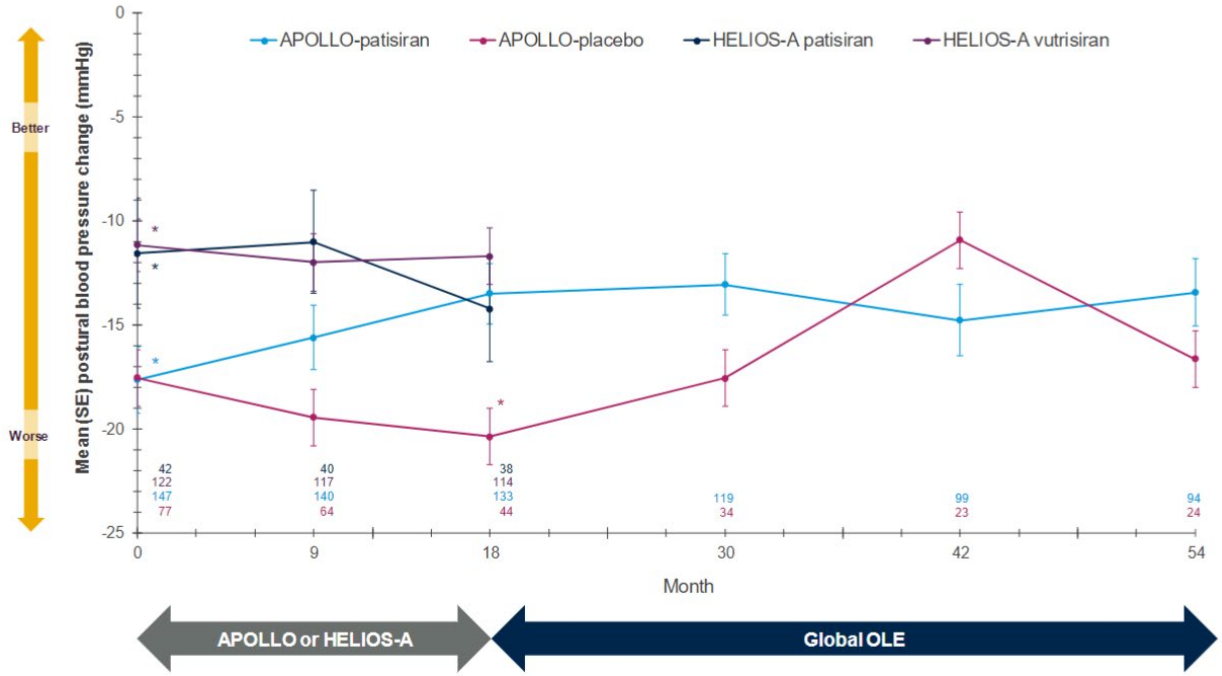
Figure 1. Percentage of Patients in Each PBP Category at Baseline of the APOLLO, Global OLE, and HELIOS-A Studies.[1,a]



Abbreviations: OLE = open-label extension; PBP = postural blood pressure.
[a]PBP is the categorized difference between (the average of 2 supine measurements taken 15 minutes apart) and (the lowest of upright measurements taken at 1, 3, and 5 minutes)
From Slama et al[1]

In the APOLLO-placebo arm, the proportion of patients with normal PBP decreased from APOLLO baseline to Global OLE baseline. However, in the APOLLO-patisiran arm, there was an increase in the proportion of patients with normal PBP from APOLLO baseline to Global OLE baseline. **Figure 2** shows the change in observed PBP across all 3 studies.[1]

Figure 2. Change in Observed PBP across the APOLLO, Global OLE, and HELIOS-A Studies.[1,a]



Abbreviations: OLE = open-label extension; PBP = postural blood pressure; SBP = systolic blood pressure; SE = standard error.
*Denotes the start of active treatment for specified studies.
[a]Change in PBP indicates the change in SBP between a supine and a standing position. Improvement indicated by a smaller decline in the SBP between supine and upright readings
From Slama et al[1]

At Month 18 in the APOLLO study, 91.2% of patients in the patisiran group with a PBP assessment had improvement or stabilization in PBP compared to baseline. The majority of patients in the APOLLO-patisiran group also showed improvement or stabilization during patisiran treatment after 36 months of patisiran treatment in the Global OLE (76.5%).[1]

At Month 18 in the Global OLE, 68.6% of patients in the APOLLO-placebo group, who received placebo during APOLLO and began patisiran during the Global OLE period, had improvement or stabilization in PBP compared to baseline. Rates of stabilization or improvement increased to 77.8% after 36 months of patisiran treatment in the Global OLE.[1]

At Month 18 in the HELIOS-A study, stabilization or improvement in PBP was seen in 81.6% of patients in the patisiran arm compared to baseline.[1]

APOLLO: ORTHOSTATIC INTOLERANCE COMPONENT OF COMPASS-31

During the APOLLO study, the impact of patisiran on orthostatic hypotension was assessed using the orthostatic intolerance domain of COMPASS-31. COMPASS-31 is a 31-question patient-reported outcome assessment that measures autonomic symptoms across six weighted domains: orthostatic intolerance (40 points); vasomotor (5 points); secretomotor (15 points); gastrointestinal (25 points); bladder (10 points); and pupillomotor (5 points), on a 100-point scale; a higher score indicates worse autonomic dysfunction.[2]

Baseline Disease Characteristics

Baseline values of the COMPASS-31 total score and the orthostatic intolerance domain are summarized in **Table 1**.[2]

Table 1. Baseline Disease Characteristics of Autonomic Endpoints.[2]

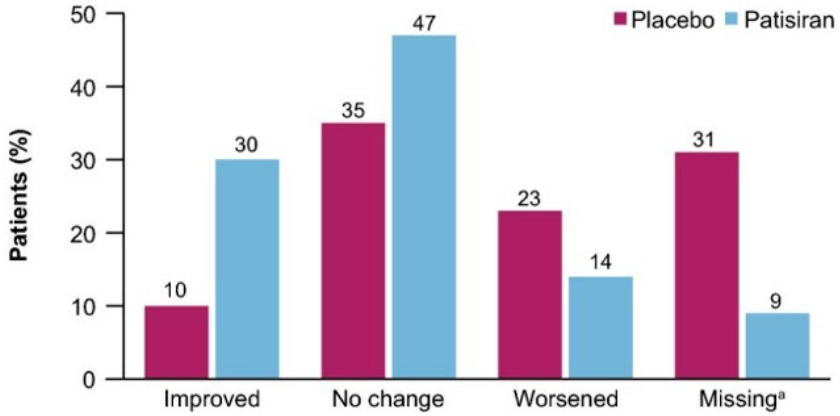
Characteristic	Placebo (n=77)	Patisiran (n=148)	Total (n=225)
COMPASS-31 total score (0–100), mean (±SD)	30.3 (16.4)	30.6 (17.6)	30.5 (17.1)
Orthostatic intolerance (range 0–40), mean (±SD)	13.2 (11.2)	14.2 (10.8)	13.8 (10.9)

Abbreviations: COMPASS-31 = Composite Autonomic Symptom Score-31 questionnaire; SD = standard deviation.

Efficacy Results

At Month 18, total COMPASS-31 scores improved in the patisiran group vs. the placebo group with a LSMD of -7.5 (95% CI: -11.9, -3.2; p=0.0008). An improvement was also observed across each of the six autonomic domains of COMPASS-31. As seen in **Figure 3**, at Month 18, 30% of patients in the patisiran group experienced improvement in their orthostatic intolerance vs. 10% in the placebo group.[2]

Figure 3. Question-Level Analysis of Orthostatic Intolerance Domain at Month 18 of the APOLLO Study.[2]



[a] Missing data at 18 months were more common in the placebo group (n=24, 31% overall) than the patisiran group (n=13, 9% overall). Reasons for the missing data in this analysis include: placebo–death (n=4), early withdrawal of subject (n=15), incomplete data at baseline (n=1), random missingness (n=4); patisiran: death (n=6), early withdrawal of subject (n=4), incomplete data at baseline (n=3).
From González-Duarte et al[2]

SAFETY RESULTS

Safety outcomes were not evaluated as part of the cross study PBP analysis.[1]

Safety Results: APOLLO

Across both treatment groups, 97% of patients reported AEs, of which the majority were mild or moderate in severity. 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.[3]

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%).[3]

The safety profile of patisiran in the Global OLE and HELIOS-A studies was consistent with that in the APOLLO study.[4,5]

ABBREVIATIONS

AE = adverse event; COMPASS-31 = Composite Autonomic Symptom Score-31 questionnaire; hATTR = hereditary transthyretin amyloidosis; IRR = infusion-related reaction; IV = intravenous; LS = least squares; LSMD = least squares mean difference; mNIS+7 = modified Neurologic Impairment Score +7; OLE = open-label extension; PBP = postural blood pressure; SBP = systolic blood pressure; SD = standard deviation; SE = standard error.

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