# Patisiran: Autonomic Outcomes

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## SUMMARY

- APOLLO was a multicenter, international, randomized, double-blind, placebo-controlled, phase 3 study designed to assess the efficacy and safety of IV patisiran in patients with hATTR-PN.[1]
- An analysis of the autonomic outcomes was assessed from the APOLLO trial, which included the COMPASS-31 questionnaire, Norfolk QOL-DN questionnaire, mBMI, and mNIS+7.[2]
- Patisiran treatment showed improvements compared with placebo in all assessments of autonomic function at 18 months.[2]
- Orthostatic hypotension was reported as an AE in 1 out of 77 (1.3%) patients in the placebo group and 3 out of 148 (2.0%) patients in the patisiran group.[3]

## INDEX

## CLINICAL DATA

### 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 hATTR-PN. The primary endpoint was the change from baseline in the mNIS+7 at 18 months.[1]

An analysis was conducted to assess autonomic outcomes from the APOLLO trial. Autonomic symptoms were measured with the COMPASS-31 questionnaire and Norfolk QOL-DN questionnaire. Nutritional status and wasting due to GI dysfunction was measured with mBMI. Postural BP was measured as a component of the mNIS+7.[2]

### Results
Patient Demographics & Baseline Characteristics
There were 225 patients randomized to receive patisiran [n=148; 138 (93.2%) completed the trial] or placebo [(n=77; 55 (71.4%) completed the trial]. The two groups were generally well balanced with

respect to baseline characteristics and disease severity. Baseline assessments of COMPASS-31, the autonomic neuropathy domain of Norfolk QOL-DN, the postural BP component of mNIS+7, and mBMI are presented 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) |
| Vasomotor (range 0–5), mean (±SD) | 1.0 (1.4) | 0.9 (1.44) | 1.0 (1.4) |
| Secretomotor (range 0–15), mean (±SD) | 4.9 (3.7) | 4.2 (3.7) | 4.4 (3.7) |
| Gastrointestinal (range 0–25), mean (±SD) | 8.1 (3.5) | 8.2 (4.3) | 8.1 (4.1) |
| Bladder (range 0–10), mean (±SD) | 1.9 (2.7) | 2.0 (2.5) | 2.0 (2.5) |
| Pupillomotor (range 0–5), mean (±SD) | 1.1 (1.1) | 1.2 (1.2) | 1.2 (1.2) |
| mBMI (kg/m$^2$ x g/L), mean (±SD) | 989.9 (214.2) | 969.7 (210.5) | 976.6 (211.5) |
| BMI (kg/m$^2$), mean (±SD) | 23.6 (4.3) | 23.0 (4.4) | 23.2 (4.4) |
| Albumin (g/dL), mean (±SD) | 41.8 (3.4) | 42.1 (3.5) | 42.0 (3.5) |
| Weight (kg), mean (±SD) | 67.5 (15.7) | 67.3 (16.6) | 67.4 (16.3) |
| mNIS + 7 total score (range 0–304), mean (±SD) | 74.6 (37.0) | 80.9 (41.5) | 78.8 (40.1) |
| Postural BP (range 0–2), mean (±SD) | 0.6 (0.7) | 0.7 (0.8) | 0.6 (0.8) |
| Norfolk QOL-DN total score (range -4 to 136), mean (±SD) | 55.5 (24.3) | 59.6 (28.2) | 58.3 (27.0) |
| Autonomic neuropathy domain (range 0–12), mean (±SD) | 2.9 (2.9) | 3.0 (2.8) | 3.0 (2.8) |

Abbreviations: BMI = body mass index; COMPASS-31 = Composite Autonomic Symptom Score-31; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy.

COMPASS-31

Total COMPASS-31 scores improved in the patisiran group compared with the placebo group and reached statistical significance at 18 months, with an LS mean difference of -7.5 (95% CI: -11.9, -3.2; p=0.0008). Total COMPASS-31 scores improved from baseline in the patisiran group. At 9 months, the LS mean change (SEM) was -3.1 (1.2; 95% CI: -5.5, -0.7) in the patisiran group and 0.4 (1.7) in the placebo group. At 18 months, the LS mean change (SEM) was -5.3 (1.3; 95% CI: -7.9, -2.7) in the patisiran group and 2.2 (1.9; 95% CI: –1.6, 6.1) in the placebo group. Overall, mean values for each COMPASS-31 component were either similar to or improved from baseline in the patisiran group (**Figure 1**).[2]
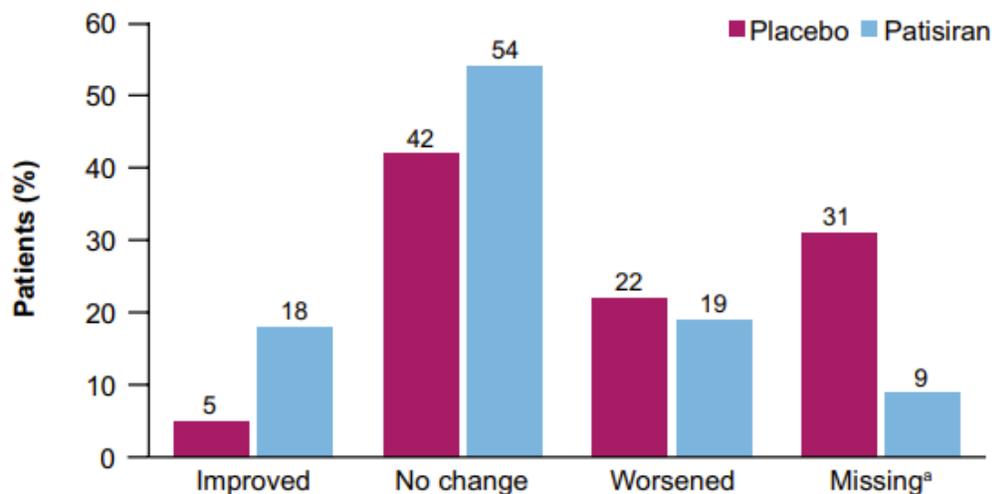
**Figure 1. LS Mean Change in COMPASS-31 at 18 Months.**[2]
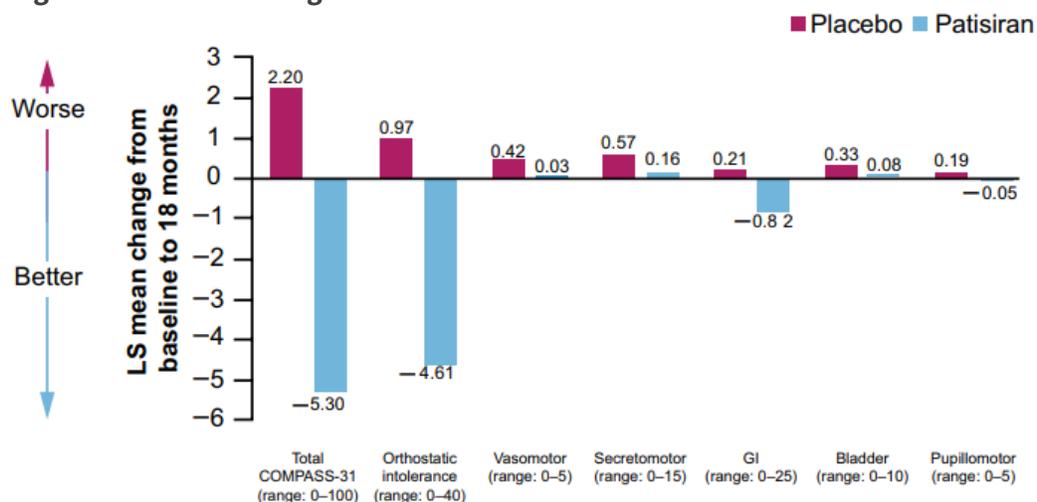


Abbreviations: COMPASS-31 = Composite Autonomic Symptom Score-31; GI = gastrointestinal; LS least squares.
From González-Duarte et al.[2]

After 18 months of treatment, a question-level analysis showed that patients in the patisiran group were 3.5 times more likely to report improvement in severity of diarrhea than patients in the placebo group (18% vs. 5%) and 3 times more likely than patients in the placebo group to report improvement in severity of orthostatic intolerance (30% vs. 10%). Patients in the patisiran group were also less likely to report worsening of orthostatic intolerance symptoms than patients in the placebo group after 18 months (14% vs. 23%), as seen in **Figure 2** and **Figure 3**.[2]

**Figure 2. Question-level Analysis of Change From Baseline in Diarrhea Presence and Severity at 18 Months from COMPASS-31.**[2]
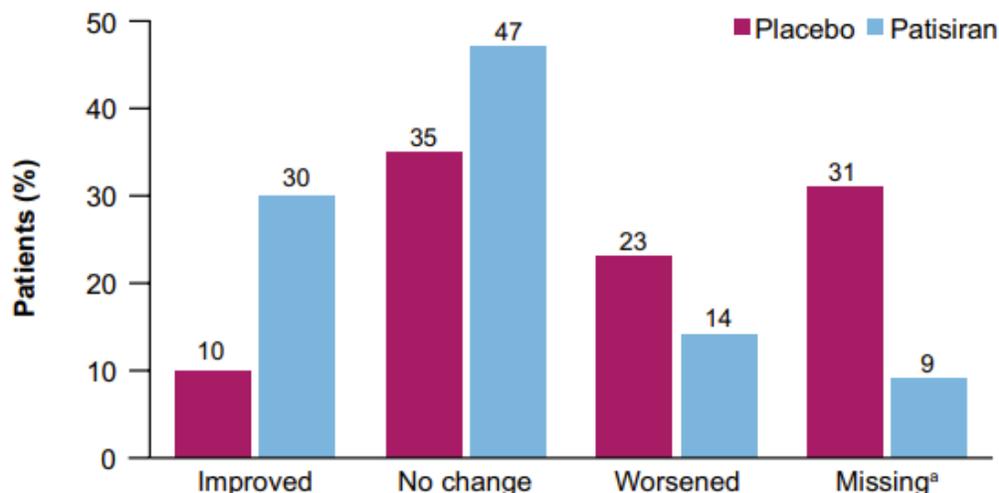


Abbreviations: COMPASS-31 = Composite Autonomic Symptom Score-31; GI gastrointestinal.
[a]Missing data at 18 months were more common in the placebo group (n=24, 31% overall) than the patisiran group (n=13, 9% overall). Reasons for the missing data in this analysis include: placebo–death (n=4), early 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]

**Figure 3. Question-level Analysis of Change From Baseline in Orthostatic Intolerance Presence and Severity at 18 Months from COMPASS-31.**[2]



Abbreviations: COMPASS-31 = Composite Autonomic Symptom Score-31.
[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).
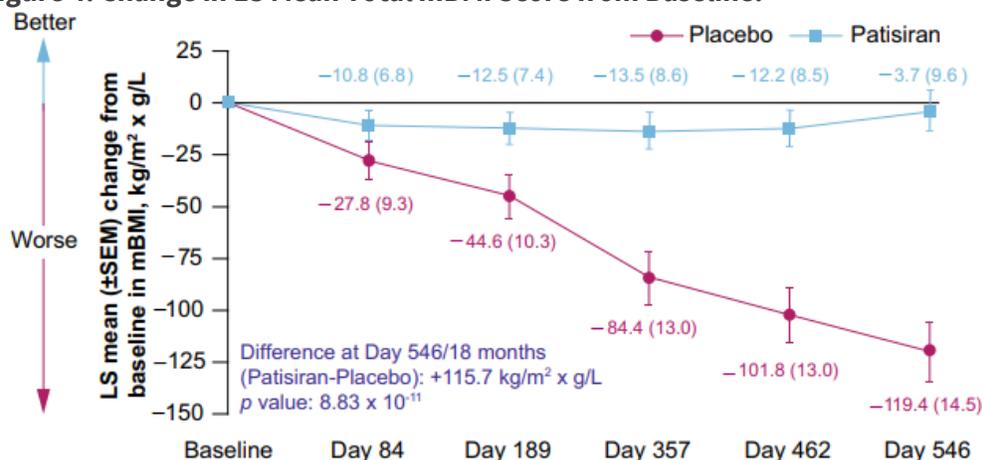From González-Duarte et al.[2]

## Norfolk QOL-DN: Autonomic Neuropathy Domain

At 18 months, the LS mean change from baseline (SEM) in the Norfolk QOL-DN autonomic neuropathy domain was -0.6 (0.2) in the patisiran group and 0.5 (0.3) in the placebo group, with an LS mean difference of -1.1 (95% CI: -1.8, -0.5; p=0.001). A question-level analysis showed that more patients in the placebo group reported moderate or severe diarrhea and/or loss of bowel control in the past 4 weeks at 18 months compared to baseline (43% vs. 33%). In the patisiran group, the analysis showed that fewer patients reported moderate or severe diarrhea and/or loss of bowel control in the past 4 weeks at 18 months compared to baseline (27% vs. 34%).[2]

## Modified Body Mass Index

At 18 months, there was a statistically significant difference in mBMI between the patisiran and placebo groups, favoring patisiran therapy with an LS mean difference of 115.7 (95% CI: -82.4, 149.0; p=8.83×10^{-11}), as seen in **Figure 4**. In the patisiran group, 41.2% demonstrated an increase from baseline in mBMI (kg/m$^2$ x g/L) at 18 months, compared with 6.5% in the placebo group.[2]

**Figure 4. Change in LS Mean Total mBMI Score from Baseline.**[2]



Abbreviations: LS = least squares; mBMI = modifed body mass index; SEM standard error of the mean.
From González-Duarte et al.[2]

mNIS+7: Postural BP Component

At 18 months, the LS mean change from baseline (SEM) in the postural BP component of the mNIS+7 was -0.2 (0.1) in the patisiran group and 0.1 (0.1) in the placebo group, favoring patisiran therapy with an LS mean difference of -0.3 points (95% CI: -0.5, –0.1).[2]

**Safety Results**

Across both treatment groups, 97% of patients reported AEs, of which the majority were mild or moderate in severity. Orthostatic hypotension was reported as an SAE in 1 out of 77 (1.3%) patients in the placebo group and 3 out of 148 (2.0%) patients in the patisiran group.[3] Common 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. 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.[1]

## ABBREVIATIONS

AE = adverse event; BP = blood pressure; CI = confidence interval; COMPASS-31 = Composite Autonomic Symptom Score-31; GI = gastrointestinal; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IRR = infusion-related reaction; IV = intravenous; LS = least squares; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN  = Norfolk Quality of Life-Diabetic Neuropathy; SAE = serious adverse event; SEM = standard error of the mean.

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## REFERENCES

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2.  González-Duarte A, Berk JL, Quan D, et al. Analysis of autonomic outcomes in APOLLO, a phase III trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis. *J Neurol*. 2020;267(3):703-712. doi:10.1007/s00415-019-09602-8
3.  Supplement to: Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153