Impact of Patisiran, an RNAi Therapeutic, on Orthostatic Intolerance in Patients with Hereditary Transthyretin-Mediated Amyloidosis

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Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, progressively debilitating, and fatal disease caused by a mutation in the transthyretin (*TTR*) gene that results in multisystem accumulation of amyloid fibrils (e.g., in nerves, heart, and gastrointestinal tract) and subsequent dysfunction across these multiple organs[1–5]
  - Majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[6–9]
  - Affects ~50,000 people worldwide[4]; median survival of 4.7 years following diagnosis, with a reduced survival of 3.4 years for patients presenting with cardiomyopathy[10–13]
- Orthostatic intolerance, caused by amyloid deposition in autonomic nerves of the cardiovascular system, is the development of symptoms after a sudden change in position[14]
- Orthostatic intolerance is commonly reported in patients but can go unnoticed as an autonomic neuropathy consequence of hATTR amyloidosis
  - Orthostatic intolerance is associated with clinically significant events, such as presyncope, syncope, fatigue, blurred vision, and falls[15,16]
  - Patients have reported the effects of orthostatic intolerance have a substantial negative impact on daily life (i.e., getting out of bed or standing after toileting)[17]

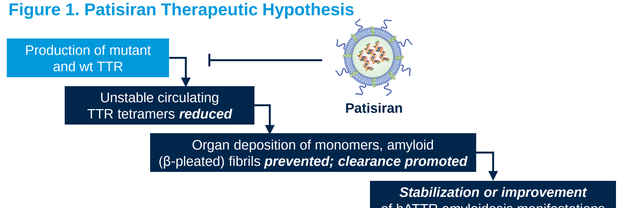
Patisiran

- Patisiran, a lipid nanoparticle-delivered RNA interference (RNAi) therapeutic, reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing mutant and wild-type (wt) TTR proteins[18,19] (**Figure 1**)
- Patisiran is approved in select countries globally for the treatment of hATTR amyloidosis with polyneuropathy[20–23]
- In the Phase 3 APOLLO study, patisiran demonstrated improvements in the primary endpoint of modified Neuropathy Impairment Score+7 (mNIS+7) and all secondary endpoints with an acceptable benefit:risk profile[6]
  - Endpoints used to evaluate patisiran's effect on orthostatic hypotension and orthostatic intolerance symptoms in hATTR amyloidosis included the postural blood pressure (BP) component of mNIS+7 and the orthostatic intolerance domain of the Composite Autonomic Symptom Score 31-item questionnaire (COMPASS-31)

Objective

- Describe the impact of patisiran on orthostatic hypotension and orthostatic intolerance symptoms

Figure 1. Patisiran Therapeutic Hypothesis



Methods

APOLLO

- APOLLO (NCT01960348) was a Phase 3, randomized, placebo-controlled study of patisiran 0.3 mg/kg intravenously (IV) every 3 weeks in patients with hATTR amyloidosis with polyneuropathy
- mNIS+7 contains postural BP domain, in which scoring was based on the change in systolic BP upon standing (maximum score: 2 points):
  - Decrease of <20 mmHg = 0 points
  - Decrease of 20–<30 mmHg = 1 point
  - Decrease of ≥30 mmHg = 2 points
- COMPASS-31 contains the orthostatic intolerance domain (maximum score, weighted: 40 points); the specific questions assessed from this domain include:
  - "In the past year, have you ever felt faint, dizzy, 'goofy', or had difficulty thinking soon after standing up from a sitting or lying position?" (yes, no)
  - If yes, "How would you rate the severity of these feelings or symptoms?" (mild, moderate, severe)
- Evaluated the least-squares (LS) mean change in the postural BP domain of mNIS+7 compared with baseline in patisiran vs placebo in the modified intention-to-treat (mITT) population
- Evaluated change in orthostatic intolerance domain of COMPASS-31 at 18 months compared with baseline in patisiran vs placebo (mITT population)
- Evaluated change in presence and severity of orthostatic intolerance symptoms evaluated descriptively using question-level analyses of the orthostatic intolerance domain in COMPASS-31 (mITT population)

Baseline Characteristics

- Placebo and patisiran groups were generally balanced with respect to baseline demographics and clinical characteristics in the APOLLO study (**Table 1**):

Table 1. Baseline Demographics and Clinical Characteristics in the APOLLO Study

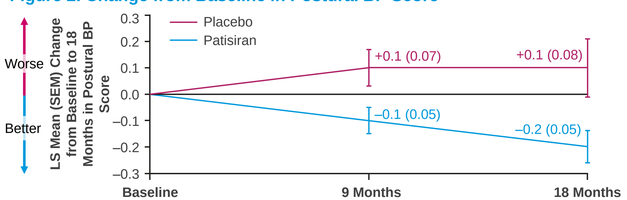
Characteristic	Placebo (n=77)	Patisiran (n=148)
Median (range) age, years	63 (34–80)	62 (24–83)
Male, n (%)	58 (75)	109 (74)
V30M, n (%)	40 (52)	56 (38)
Disease onset before 50 years of age	10 (13)	13 (9)
Non-V30M, n (%)	37 (48)	92 (62)
Mean NIS (min, max)	57 (7.0, 125.5)	61 (6.0, 141.6)
FAP stage, n (%)		
1: Unimpaired ambulation	37 (48)	67 (45)
2: Assistance with ambulation required	39 (51)	81 (55)
3: Wheelchair bound or bedridden	1 (1)	0
Median (range) time since diagnosis of hATTR amyloidosis, years	1.4 (0.0–16.5)	1.3 (0.0–21.0)
Mean (SD) COMPASS-31	30.3 (16.4)	30.6 (17.6)
Mean (SD) mNIS+7 postural BP domain score	0.6 (0.7)	0.7 (0.8)

Results

Postural BP Changes: mNIS+7 Postural BP Domain

- LS mean change from baseline to 18 months in postural BP domain score was −0.2 for the patisiran group and +0.1 for placebo (LS mean difference [standard error of the mean (SEM)] of −0.3 [0.1]) (**Figure 2**)

Figure 2. Change from Baseline in Postural BP Score



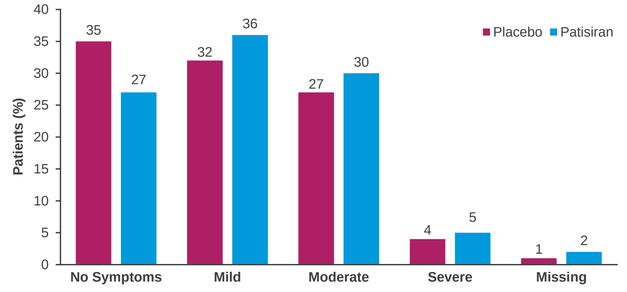
Dysautonomia Symptoms: Assessment of COMPASS-31 Orthostatic Intolerance Domain

- Patisiran demonstrated mean improvement compared with placebo at 18 months (−6.6); furthermore, the patisiran group improved overall compared with their own baseline (−3.8) vs overall worsening observed in the placebo group (+2.8)

Question-Level Analysis of Orthostatic Intolerance Symptoms: COMPASS-31

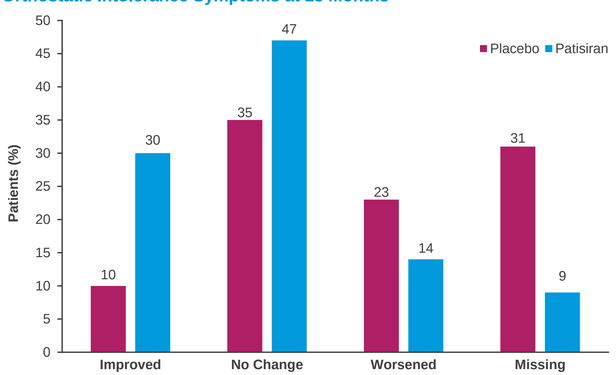
- At baseline, approximately two-thirds of all patients reported mild-to-severe symptoms of orthostatic intolerance in the past year (**Figure 3**)

Figure 3. COMPASS-31. Severity of Orthostatic Intolerance Symptoms at Baseline



- After 18 months, patisiran-treated patients were 3-fold more likely to report improvement in orthostatic intolerance symptoms than placebo-treated patients (30% vs 10%, respectively) (**Figure 4**)
  - Patisiran-treated patients were also less likely to experience worsening of these symptoms compared with placebo-treated patients (14% vs 23%, respectively)
- Missing data at 18 months were more common in the placebo group (n=24, 31% overall) than the patisiran group (n=13, 9% overall) with a higher proportion of missing data due to discontinuation (i.e., early withdrawal) in the placebo group than the patisiran group
  - Reasons for missing data in this analysis were (2:1 patisiran to placebo randomization):
    - Placebo: death (n=4); early withdrawal of subject (n=15); incomplete data at baseline (n=1); data missing at random (n=4)
    - Patisiran: death (n=6); early withdrawal of subject (n=4); incomplete data at baseline (n=3)

Figure 4. COMPASS-31. Change from Baseline in Presence and Severity of Orthostatic Intolerance Symptoms at 18 Months



Conclusions

- Following 18 months of treatment, improvements seen in postural BP were consistent with the change in orthostatic intolerance symptoms reported by the patisiran group
- Patients treated with patisiran were 3-fold more likely to report improvement in their orthostatic intolerance symptoms vs their own baseline compared with placebo
- These data illustrate the clinical benefit of patisiran in addressing the debilitating symptoms of hATTR amyloidosis caused by amyloid deposition in the autonomic nerves of the cardiovascular system

Abbreviations: BP, blood pressure; COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated; IV, intravenously; LS, least squares; mITT, modified intention-to-treat; mNIS+7, modified Neuropathy Impairment Score+7; NIS, Neuropathy Impairment Score; RNAi, RNA interference; SD, standard deviation; SEM, standard error of the mean; TTR, transthyretin; wt, wild-type.
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