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 Amyloidosis

- Rare, progressively debilitating, and fatal disease caused by a mutation in the transthyretin (TTR) gene resulting in misfolding and amyloidosis (e.g., in nerves, heart, and gastrointestinal tract) and subsequent dysfunctions across multiple organs.1-3

- Majority of patients develop a mixed phenotype of both amyloidosis and cardiomyopathy.1-3

- Effective -50% protein reduction by patisiran, median survival of 4 years for patients presenting with cardiomyopathy.2-3

- Orthostatic intolerance, caused by amyloid deposition in autonomic nerves of the cardiovascular system, is the development of symptoms after a sudden change in position, leading to dramatic symptoms including hypotension and syncope.4-5

- Orthostatic intolerance is commonly reported in patients but can go unnoticed or an uncommon autonomic neuropathy symptom of hATTR amyloidosis.2-3

- Orthostatic intolerance is associated with clinically significant events, such as near-syncope or syncope, hospitalization, or mortality.6-7

- 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 toilet).6-7

Patisiran

- Patisiran is a lipid nanoparticle-delivered RNAi therapeutic (RNAi therapy) that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing mutant and wild-type (wt) TTR proteins.1-3,8-9 (Figure 1)

- Patisiran is approved in select countries globally for the treatment of hATTR amyloidosis with cardiomyopathy by the US Food and Drug Administration (FDA) and the European Medicines Agency.10

- In the Phase 3 APOLLO study, patisiran demonstrated improvements in the primary endpoint of median time to first major cardiac event (MACE) (mMACE-7) and all secondary endpoints with an acceptable safety profile.10-11

- Endpoint used to evaluate patsiran’s effect on orthostatic hypotension and orthostatic intolerance symptoms in hATTR amyloidosis included the postural blood pressure (BP) component of mMACE-7 of the Confirmative Autonomic Symptoms Score (31-item questionnaire: COMPASS-31) study.12

Methods

APOLLO

- APOLLO (NCT01960348) was a Phase 3, randomised, placebo-controlled study of patisiran (0.3 mg/kg) vs placebo (n=201) every 3 weeks in patients with hATTR amyloidosis with cardiomyopathy.10-11

- Majority of patients in the APOLLO study (85% in the patsiran group and 79% in the placebo group) had single mutation hATTR amyloidosis 

- The primary endpoint was median time to first major adverse cardiac event (MACE) 24 months (mMACE-24) from randomisation.10

- Secondary endpoints included the postural BP domain, in which scoring was based on the change in systolic BP upon standing (maximum score: 2 points);10-11

- Decrease of 30 to <50 mmHg = 1 point

- Decrease of 20 to <30 mmHg = 1 point

- Decrease of ≥30 mmHg = 2 points

- COMPASS-31 contains the orthostatic intolerance domain (maximum score: 20 points); the specific questions assessed from this domain include:12

- “In the last 6 months, have you ever felt lightheaded, dizzy, or off? If yes, did this decrease the severity of your feelings or symptoms?” (mild, moderate, severe)

- “How has your orthostatic intolerance (OI) worsened over the last year?” (maximum score: 2 points):

- Improvement of ≤0.5 points = 0 points

- Improvement of >0.5 to ≤1 points = 1 point

- Improvement of >1 to ≤2 points = 2 points

- Apati in baseline OI was determined at baseline and endpoint using the COMPASS-31 orthostatic intolerance domain (Figure 2).

Results

Table 1: Patient Demographics and Clinical Characteristics in the APOLLO Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patisiran (n=103)</th>
<th>Placebo (n=98)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age, years</td>
<td>63 (44–83)</td>
<td>62 (44–83)</td>
<td>0.62</td>
</tr>
<tr>
<td>M/M: F</td>
<td>56:47</td>
<td>52:46</td>
<td>0.28</td>
</tr>
<tr>
<td>VSD, n (%)</td>
<td>40 (52)</td>
<td>56 (58)</td>
<td>0.19</td>
</tr>
<tr>
<td>Disease onset before 50 years of age, n (%)</td>
<td>10 (13)</td>
<td>15 (16)</td>
<td>0.57</td>
</tr>
<tr>
<td>Non-VSD, n (%)</td>
<td>47 (66)</td>
<td>37 (38)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean (SD) mMACE-7</td>
<td>27.0 (6.5)</td>
<td>26.9 (6.4)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

- There were 103 treated and 98 untreated patients in the COMPASS-31 study.12

- Median (range) time since diagnosis of hATTR amyloidosis, years: 10 (1–27)

- Mean (SD) mMACE-7 postural BP domain score: 0.6 (3.9)

- After 18 months, patients treated with patsiran were 5-fold more likely to report improvement in orthostatic intolerance symptoms than placebo-treated patients (10% vs 15%, respectively) (Figure 4)

Conclusions

- Following 18 months of treatment, improvements seen in postural BP were consistent with the change in orthostatic intolerance symptoms reported by the patsiran group.

- Patients treated with patsiran were 5-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 patsiran in addressing the impact of TTR amylodosis caused by amyloid deposition in the autonomic nerves of the cardiovascular system.