Impact of Patisiran on Norfolk Quality of Life Questionnaire Diabetic Neuropathy (QOL-DN) in Patients with Hereditary Transthyretin-Mediated Amyloidosis: Results from the Phase 3 APOLLO Study

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Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Disease Overview and Introduction to Patisiran, an Investigational RNAi Therapeutic

• hATTR Amyloidosis
  ◦ Rare, inherited, rapidly progressive, debilitating, life-threatening disease caused by mutations in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract\(^1\)-\(^5\)
  ◦ Median survival 4.7 years following diagnosis\(^6\); reduced survival (3.4 years) for patients presenting with cardiomyopathy\(^6\)-\(^8\)

• Multisystem disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms\(^2\)-\(^9\),\(^10\)
  ◦ Disease continuum includes patients who present with predominantly polynuropathy symptoms (formerly FAP) or cardiomyopathy symptoms (formerly FAC), yet many patients experience a variety of symptoms
  – Clinical manifestations (e.g., disease penetrance and rate of progression) are influenced by TTR genotype and geographical region

• Limited treatment options
  ◦ Liver transplant for early-stage disease and TTR tetramer stabilizers
    – Tafamidis approved in EU for Stage 1 hATTR amyloidosis\(^11\) and certain other countries outside U.S.
    – Diffunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study\(^12\)

• Continued high unmet medical need for novel therapeutics

• Patisiran, an Investigational RNAi Therapeutic
  ◦ Lipid nanoparticle formulated RNAi, administered by IV infusion, targeting hepatic production of mutant and wild-type TTR

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Patisiran Phase 3 APOLLO Study Results

Study Design, Baseline Demographics and Characteristics

**Patient Population**
- hATTR amyloidosis with documented TTR mutation
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

ClinicalTrials.gov Identifier: NCT01960348

### APOLLO Population (N=225)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years (range)</td>
<td>63 (34-80)</td>
<td>62 (24-83)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>58 (75.3)</td>
<td>109 (73.6)</td>
</tr>
<tr>
<td>TTR Genotype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V30M</td>
<td>40 (51.9)</td>
<td>56 (37.8)</td>
</tr>
<tr>
<td>NIS, mean (min, max)</td>
<td>57 (7, 125.5)</td>
<td>60.5 (6, 141.6)</td>
</tr>
<tr>
<td>FAP Stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: 37 (48.1)</td>
<td>1: 67 (45.3)</td>
<td></td>
</tr>
<tr>
<td>2: 39 (50.6)</td>
<td>2: 81 (54.7)</td>
<td></td>
</tr>
<tr>
<td>3: 1 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PND Score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I: 20 (26)</td>
<td>I: 36 (24.3)</td>
<td></td>
</tr>
<tr>
<td>II: 23 (29.9)</td>
<td>II: 43 (29.1)</td>
<td></td>
</tr>
<tr>
<td>IIIA: 22 (28.6)</td>
<td>IIIA: 41 (27.7)</td>
<td></td>
</tr>
<tr>
<td>IIIB: 11 (14.3)</td>
<td>IIIB: 28 (18.9)</td>
<td></td>
</tr>
<tr>
<td>IV: 1 (1.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Primary Endpoint**
- Change in mNIS+7 from baseline at 18 months

**Secondary Endpoints**
- Norfolk QOL-DN (quality of life)
- NIS-weakness (muscle weakness)
- R-ODS (disability)
- 10-meter walk (gait speed)
- mBMI (nutritional status)
- COMPASS-31 (autonomic symptoms)

**Stratification factors for randomization include:**
- neuropathy impairment score (NIS: < 50 vs. ≥ 50),
- early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous use.

*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine).

COMPASS-31, composite autonomic symptom score-31; EQ-5D-5L, EuroQol 5 dimensions-5L; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment scale +7; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; OLE, open-label extension; q3W, every 3 weeks; R-ODS, Rasch-built overall disability scale; Adams D et al. BMC Neurol 2017;17(1):181.
Patisiran Phase 3 APOLO Study Results

mNIS+7: Change from Baseline

56.1% of patients in the patisiran group demonstrated improvement in mNIS+7 compared to 3.9% of patients on placebo (odds ratio: 39.9; p=1.82 × 10^{-15}; improvement defined as <0 point increase from baseline to 18 months)
Norfolk QOL-DN: Change from Baseline

Data previously presented at the American Academy of Neurology (AAN) 2018; April 2018, Los Angeles, CA, USA

51.4% of patients in the patisiran group demonstrated improvement in Norfolk QOL-DN compared to 10.4% of patients on placebo (Odds ratio: 10.0; \( p=1.95 \times 10^{-10} \); improvement defined as <0 point increase from baseline to 18 months)
Patisiran Phase 3 APOLLO Study Results
Norfolk QOL-DN: Change from Baseline in Individual Domains

- Patisiran demonstrated improvement relative to placebo across all domains of the Norfolk QOL-DN
- Improvement compared to baseline was observed in physical functioning/large fiber, symptoms, and autonomic domains
- This improvement in QOL at 18 months in patients on patisiran was related to strength, digestive health, ability to perform everyday activities, and steadiness on their feet
**Patisiran Phase 3 APOLLO Study Results**

**Safety and Tolerability**

<table>
<thead>
<tr>
<th>Type of Adverse Event</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event (AE)</td>
<td>75 (97.4)</td>
<td>143 (96.6)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>28 (36.4)</td>
<td>42 (28.4)</td>
</tr>
<tr>
<td>Serious adverse event (SAE)</td>
<td>31 (40.3)</td>
<td>54 (36.5)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>11 (14.3)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>AE leading to study withdrawal</td>
<td>9 (11.7)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (7.8)</td>
<td>7 (4.7)</td>
</tr>
</tbody>
</table>

No deaths considered related to study drug
- Causes of death consistent with natural history

Majority of AEs were mild or moderate in severity
- **Peripheral edema**
  - Decreased over time
  - Did not result in any treatment discontinuations
- **Infusion-related reactions (IRRs)**
  - Majority mild in severity
  - Decreased over time
  - 1 patient discontinued treatment

No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

**Adverse Events Occurring in ≥ 10% in Either Group**

<table>
<thead>
<tr>
<th>Preferred AE Term</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>29 (37.7)</td>
<td>55 (37.2)</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>17 (22.1)</td>
<td>44 (29.7)</td>
</tr>
<tr>
<td>Infusion related reaction (IRR)</td>
<td>7 (9.1)</td>
<td>28 (18.9)</td>
</tr>
<tr>
<td>Fall</td>
<td>22 (28.6)</td>
<td>25 (16.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (16.9)</td>
<td>22 (14.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (20.8)</td>
<td>22 (14.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (14.3)</td>
<td>19 (12.8)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>14 (18.2)</td>
<td>19 (12.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (10.4)</td>
<td>18 (12.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (11.7)</td>
<td>16 (10.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (11.7)</td>
<td>15 (10.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (9.1)</td>
<td>15 (10.1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (7.8)</td>
<td>15 (10.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (10.4)</td>
<td>15 (10.1)</td>
</tr>
<tr>
<td>Aversion</td>
<td>9 (11.7)</td>
<td>14 (9.5)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>8 (10.4)</td>
<td>10 (6.8)</td>
</tr>
<tr>
<td>Muscular Weakness</td>
<td>11 (14.3)</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (10.4)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Syncope</td>
<td>8 (10.4)</td>
<td>3 (2.0)</td>
</tr>
</tbody>
</table>

Blue, bolded text: Indicates ≥5 percentage point difference in either group
Patisiran Phase 3 APOLLO Study

Summary

• hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening disease with limited therapeutic options

• Patisiran treatment resulted in significant improvement in polyneuropathy relative to placebo and baseline at 18 months
  o Benefits seen in motor, sensory and autonomic neuropathy
  o Positive effects observed across wide range of disease severity and TTR genotypes, including patients with cardiac involvement

• Patisiran also improved quality of life relative to placebo and baseline
  o The improvement in QOL at 18 months in patients on patisiran was related to strength, digestive health, ability to perform everyday activities, and steadiness on their feet
  o In contrast, patients on placebo worsened across all domains at 18 months

• Patisiran showed an encouraging safety and tolerability profile
  o Frequency of deaths trended lower in the patisiran group versus placebo arm
  o Key patisiran safety findings include mild to moderate peripheral edema and IRRs with only one treatment discontinuation due to these events
  o No safety signals with regard to thrombocytopenia, hepatic or renal dysfunction

• 99% of eligible APOLLO patients enrolled into Global OLE study

QOL, Quality of Life; IRRs, infusion related reactions; OLE, open label extension
Acknowledgments

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