Outcomes of Patients with Hereditary Transthyretin-Mediated Amyloidosis with Early Onset V30M versus All Other Mutations in APOLLO, a Phase 3 Study of Patisiran

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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\(^1\)\(^-\)\(^5\)
    – V30M is most common mutation worldwide, with early age of symptom onset (< 50 years) seen in regions where the mutation is endemic\(^6\)\(^,\)\(^7\)
  ◦ Median survival 4.7 years following diagnosis\(^6\)\(^;\) reduced survival (3.4 years) for patients presenting with cardiomyopathy\(^8\)\(^-\)\(^10\)

• 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.
    – Diflunisal (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

Patisiran Phase 3 APOLLO Study Results
Study Design, Baseline Demographics and Characteristics

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

Randomization
2:1 RATIO

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

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

<table>
<thead>
<tr>
<th>Patient Population</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, n (%)</td>
<td>58 (75.3)</td>
<td>109 (73.6)</td>
</tr>
<tr>
<td>TTR Genotype, n (%)</td>
<td>V30M: 40 (51.9)</td>
<td>V30M: 56 (37.8)</td>
</tr>
<tr>
<td></td>
<td>Non-V30M: 37 (48.1)</td>
<td>Non-V30M: 92 (62.2)</td>
</tr>
<tr>
<td>Genotype Class, n (%)</td>
<td>Early Onset V30M (&lt;50 years of age at onset):</td>
<td>10 (13.0)</td>
</tr>
<tr>
<td></td>
<td>All Other Mutations (including late onset V30M and non-V30M):</td>
<td>67 (87.0)</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>1: 37 (48.1); 2: 39 (50.6); 3: 1 (1.3)</td>
<td>1: 67 (45.3); 2: 81 (54.7)</td>
</tr>
</tbody>
</table>

† 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).

Early Onset V30M By Country

ClinicalTrials.gov Identifier: NCT01960348
Patisiran Phase 3 APOLLO Study Endpoints

Primary Endpoint

• **mNIS+7**: a composite measure of neurological impairment
  - Higher score indicates worsening of neuropathy

Secondary Endpoints

• **Norfolk QOL-DN**: 35-item QOL questionnaire that is sensitive to small fiber, large fiber, and autonomic nerve function
  - Higher score indicates worsening of QOL

• **NIS-W**: motor function/strength assessment
  - Higher score indicates worsening of strength

• **R-ODS**: 24-item questionnaire used to capture activity and social participation (disability)
  - Lower score indicates worsening disability

• **10-meter walk test (m/sec)**: assessment of ambulation that measures gait speed
  - Lower score indicates worsening

• **mBMI (kg/m² x albumin [g/mL])**: nutritional status
  - Lower score indicates worsening of nutritional status

• **COMPASS 31**: 31-item questionnaire used to evaluate patient reported autonomic neuropathy symptoms
  - Higher score indicates worsening of autonomic neuropathy symptoms

All primary and secondary endpoints achieved statistical significant difference in favor of patisiran at 18 months. Nominal statistical significance was achieved as early as month 9 for mNIS+7, Norfolk QOL-DN, NIS-W, R-ODS, 10-MWT and mBMI.
Patisiran Phase 3 APOLLO Study Results

**mNIS+7: Early Onset V30M Subgroup Analysis**

<table>
<thead>
<tr>
<th>Group Description</th>
<th>Placebo n</th>
<th>Patisiran n</th>
<th>LS Mean Difference (SEM)</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (≤50 years of age at onset)</td>
<td>77</td>
<td>148</td>
<td>28.0 (2.60)</td>
<td>9.26 x 10^{-24}</td>
<td>-39.9, -28.1</td>
</tr>
<tr>
<td>Early Onset V30M (&lt;50 years of age at onset)</td>
<td>8</td>
<td>13</td>
<td>14.0 (4.74)</td>
<td>1.67 x 10^{-3}</td>
<td>-35.0, -9.5</td>
</tr>
<tr>
<td>All Other Mutations, including Late Onset V30M (≥50 years of age at onset)</td>
<td>43</td>
<td>124</td>
<td>31.5 (2.76)</td>
<td>5.7 x 10^{-22}</td>
<td>-42.6, -29.6</td>
</tr>
</tbody>
</table>

**Improvement in polyneuropathy with patisiran versus placebo was seen for all TTR mutation types, including early/late onset V30M and a range of non-V30M mutations.**

CI, confidence interval; LS, least squares; mNIS, modified neurological impairment score; SEM, standard error of the mean.
Improvement in QOL with patisiran versus placebo was seen across all TTR mutation types, including early/late onset V30M and a range of non-V30M mutations.
Patisiran Phase 3 APOLLO Study Results

Safety and Tolerability

<table>
<thead>
<tr>
<th>Type of Adverse Event, number of patients (%)</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
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</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

The safety profile of patisiran was similar in V30M and nonV30M patients

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, number of patients (%)</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>Asthenia</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 APOLO Study

Summary

- hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening, often fatal disease with high morbidity and mortality and limited therapeutic options
- Patisiran treatment improved neuropathy and QOL at 18 months
  - In the prespecified early onset V30M subgroup, consistent efficacy was observed compared to patients with other mutations, including late onset V30M and non-V30M genotypes combined
- Patisiran showed an encouraging safety and tolerability profile
  - Frequency of deaths trended lower in the patisiran group versus placebo arm
  - Key patisiran safety findings include mild to moderate peripheral edema and IRRs with only one treatment discontinuation due to these events
  - No safety signals with regard to thrombocytopenia, hepatic or renal dysfunction
- 99% of eligible APOLO patients enrolled into Global OLE study
Acknowledgments

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