Background and Rationale

Hereditary Transthyretin-mediated (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, life-threatening disease caused by a mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and GI tract. It is estimated that 50,000 people worldwide are affected.

- Multisystemic amyloidosis often leads to dysfunction in multiple organs, including the peripheral nervous system, heart, gastrointestinal tract, and kidneys.1-3

- Accumulation of fibrils in nerves can lead to manifestations of polyneuropathy, including peripheral neuropathy, autonomic dysfunction, and motor weakness causing fine and gross motor impairments whereas accumulation in heart can lead to cardiomyopathy.

Objective

- To describe the change in polyneuropathy disability (PND) scores and familial amyloidotic polyneuropathy (FAP) stage following 18 months of treatment with patisiran or placebo in APOLLO.

Methods

Phase 3 Study Design

- Multi-center, international, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy (Figure 2).

- Primary endpoint was the change in the modified Neuropathy Impairment Score (mNIS)-7 score from baseline at 18 months; secondary endpoints are shown in Figure 2.

- Exploratory endpoints included the polyneuropathy disability (PND) score and FAP stage, measures utilized to assess hATTR patient ambulation.

APOLLO Enrollment

- Patients enrolled had 39 different mutations and were divided into the following groups: North America, Western Europe and Rest of World (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=149)</th>
<th>Patisiran (N=146)</th>
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<tbody>
<tr>
<td>Median Age, years (range)</td>
<td>63 (34, 80)</td>
<td>62 (24, 83)</td>
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<tr>
<td>Gender (Male)</td>
<td>58 (75.3)</td>
<td>109 (73.6)</td>
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<tr>
<td>V30M</td>
<td>40 (51.9)</td>
<td>56 (37.8)</td>
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<tr>
<td>Non-V30M</td>
<td>37 (48.1)</td>
<td>92 (62.2)</td>
</tr>
<tr>
<td>NIS, Mean (min, max)</td>
<td>57 (7.0, 125.5)</td>
<td>61 (6.0, 141.6)</td>
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<tr>
<td>PND Score</td>
<td>3: impaired walking, sensory disturbances 20 (26.0) 36 (24.3) 2: impaired walking but can walk without stick or crutch 23 (29.9) 43 (29.1) 1: illa walk with 1 stick or crutch 22 (28.6) 41 (27.7) Ilb2: walk with 2 sticks or crutches 11 (14.3) 28 (18.9) 1: confined to wheelchair or bedridden 1 (1.3) 0</td>
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<tr>
<td>FAP Stage</td>
<td>1: unimpaired ambulation 37 (48.1) 67 (45.3) 2: assistant with ambulation required 39 (50.6) 81 (54.7) 3: wheelchair bound or bedridden 1 (1.3) 0</td>
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Stabilization or Improvement of PND Score

- Greater proportion of patients in the patisiran group had a stable or improved PND score relative to baseline compared with placebo at 18 months (Figure 3); improvement was only seen in the patisiran group.

- Among hATTR-treated patients, improvement in PND score was observed across all baseline severities (PND 1–IIIb).

- Of patients who improved in PND score (8.1%), 83% had an improvement from PND IIb to PND I, corresponding to a requiring walking aid to being able to perform unimpaired ambulation.

- Of the 30 patients on patisiran with a worsening PND stage, most worsened by 1 PND stage (28 patients; 93%), while 3 patients (10%) worsened by 2 PND stages and 2 (7%) worsened by 3 PND stages.

- Among the patients randomized to placebo, none demonstrated an improvement in PND score, while 23.8% showed no change and 45.6% worsened.

- Of the 32 patients on placebo with a worsening PND score, half of the patients worsened by 1 PND level, and the other half worsened by 2 PND levels.

- Larger percentage of placebo patients compared to patisiran patients had missing data at 18 months as a result of a higher study withdrawal rate.

Stabilization or Improvement of FAP Stage

- Greater proportion of patients in the patisiran group had a stable or improved FAP stage relative to baseline compared with placebo (Figure 4); improvement was only seen in the patisiran group.

- 117 patients (79.1%) in the patisiran group had stable or improved FAP stage compared with 32 (44.2%) in the placebo group.

- Larger percentage of placebo patients compared to patisiran patients had missing data at 18 months as a result of a higher study withdrawal rate in placebo patients.

Safety for Overall Population

- Majority of AEs were mild or moderate in severity

- Most common AEs were diarrhea and constipation

- Number of withdrawals due to AEs: 9 (6.8%)

- Number of serious AEs: 7 (4.7%)

- Number of deaths: 6 (7.8%)

Summary

APOLLO, the largest controlled study of patients with hATTR amyloidosis with polyneuropathy to date, is representative of the global patient population and included patients with various stages of polyneuropathy.

Patisiran treatment preserved ambulation in a larger proportion of patients compared to placebo, which improved ambulation, with some patients going from requiring walking aids to unassisted walking at 18 months; these results were consistent with the improvement in 10-meter walk test gait speed observed in the patisiran group compared to placebo.

Patisiran was generally well tolerated, with safety events similar in both groups.

These data further support the clinical benefit of patisiran compared to placebo in preserving or improving ambulation in patients with hATTR amyloidosis.