Impact of Patisiran on Overall Health Status in hATTR Amyloidosis: Results from the APOLLO Trial

Sara Almquist-Driver,1 David Adams,2 Teresa Coelho,1 Michael Polydefkis,3 Alejandra Gonzalez-Duarte,4 Dianna Quan,5 Arnt Kristen,1 John L Berk,6 Angela M Partisano,6 Jared Gollob,8 Marianne Sweeney,6 Jihong Chen,3 Sonalee Aryanwal,6 Ole B Suhu1

1Northwestern University, Chicago, United States of America; 2CHU Brédière, Le Kremlin Bicêtre, France; 3Hospital de Santos António, Porto, Portugal; 4Johns Hopkins University, Baltimore, MD, USA; 5Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico City, Mexico; 6University of Colorado, Denver, United States of America; 7Heidelberg University Hospital, Heidelberg, Germany; 8Boston University, Boston, United States of America; 9A NYAM Pharmaceuticals, Cambridge, United States of America; 10Umeå University, Umeå, Sweden

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 gastrointestinal tract.1-16

• Affecting approximately 50,000 people worldwide,2-4; median survival of 4.7 years following diagnosis with a reduced survival of 3.4 years for patients with cardiomyopathy4,8

• Multisystem disease with heterogenous clinical presentation; amyloid accumulation often leads to dysfunction in multiple organs, including the peripheral nervous system, heart, gastrointestinal tract, and kidneys.2,4,11

• More than 120 pathologic TTR mutations have been identified, with V30M mutation as the most common worldwide.1,2

• Limited treatment options, such as tetramer stabilizers, are available; continued high unmet medical need for novel therapeutic options

Patisiran

• Investigational RNAi therapeutic in development for the treatment of hATTR amyloidosis

• Patisiran demonstrated rapid and sustained reduction of mutant and wild-type TTR (wTTR) by inhibiting the synthesis of disease-causing protein (Figure 1)

• Phase 3, APOLLO: study met the primary efficacy endpoint of modified Neuruphysy Impairment Score (mNIS+7) and all secondary endpoints with favorable safety profile.1,15

Objective

• Evaluate the impact of patisiran on overall health in patients enrolled in APOLLO

Methods

APOLLO Phase 3 Study Design

• Phase 3, randomized (2:1), double-blind study of patisiran 0.3mg/kg or placebo IV q3w in patients with hATTR amyloidosis with polyneuropathy1,13 (Figure 2)

• Primary endpoint was change in mNIS+7 from baseline at 18 months

• mNIS+7 is a quantitative and referenced assessment to quantify motor, sensory, and autonomic components of polyneuropathy in patients with hATTR amyloidosis; higher score indicates worsening neuropathy (range 0–345)

• Norfolk Quality Of Life - Diabetic Neuropathy (Norfolk QOL-DN) questionnaire was the key secondary endpoint sensitive to small fiber, large fiber, and autonomic nerve function

• Range of possible scores is 4 to 136; decrease from baseline score represents improvement in QOL

• Overall health status was an exploratory endpoint assessed using EuroQol-5-dimension 5-level (EQ-5D-5L) and EuroQol visual analogue scale (EQ-VAS)

• EQ-5D-5L is a standardized measure of health status based on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression

• EQ-VAS is a patient’s global impression of their overall health and is improved (2.4 average point increase) from Baseline to 18 months

• Endpoints were analyzed using the MMRM method in the mITT population

Results

APOLLO Baseline Demographics

225 patients with hATTR amyloidosis with polyneuropathy from 44 sites in 19 countries enrolled between December 2013 and January 2016 (Table 1)

Table 1: APOLLO Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Demographic, n (%)</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, males</td>
<td>58 (75.3)</td>
<td>109 (73.6)</td>
</tr>
<tr>
<td>hATTR Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since hATTR diagnosis, (mean, min, max)</td>
<td>2.6 (0.0, 16.5)</td>
<td>2.4 (0.0, 21.0)</td>
</tr>
<tr>
<td>TTR Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V30M</td>
<td>40 (51.9)</td>
<td>56 (37.8)</td>
</tr>
<tr>
<td>nonV30M</td>
<td>37 (48.1)</td>
<td>92 (62.2)</td>
</tr>
<tr>
<td>Previous tetramer stabilizer use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41 (53.3)</td>
<td>78 (52.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>26 (34.6)</td>
<td>49 (33.3)</td>
</tr>
<tr>
<td>NHG Mean (min, max)</td>
<td>57 (7.0, 125.5)</td>
<td>61 (6.0, 141.6)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>35 (45.5)</td>
<td>62 (41.9)</td>
</tr>
<tr>
<td>≥50 &lt;100</td>
<td>33 (42.9)</td>
<td>63 (42.6)</td>
</tr>
<tr>
<td>≥100</td>
<td>9 (11.7)</td>
<td>23 (15.5)</td>
</tr>
<tr>
<td>Cardiac Subpopulation</td>
<td>36 (46.8)</td>
<td>90 (60.8)</td>
</tr>
</tbody>
</table>

Results (continued)

Primary Endpoint: mNIS+7

Statistically significant improvement in neuropathy, as measured by change from baseline in mNIS+7, was seen for patisiran relative to placebo at 18 months, with a LS mean difference of -3.40 (3.0) points (Figure 3)

Secondary Endpoint: Norfolk QOL-DN

• Patisiran treatment led to statistically significant improvements in Norfolk QOL-DN compared with placebo at 18 months, with an LS mean (SEM) difference of -21.1 (3.1) points

• Patients on placebo had worsening QOL over time, demonstrated by a LS mean (SEM) 14.4 (2.7) point increase in Norfolk QOL-DN compared with baseline, while patisiran group improved compared with baseline with an LS mean (SEM) change of -6.7 (1.8) points at 18 months

Safety and Tolerability

• Majority of adverse events (AEs) were mild or moderate in severity (Table 2)

• Peripheral edema (22.1%, placebo; 29.7% patisiran): decreased over time; did not result in treatment discontinuation

• Infusion-related reactions (IRRs) (9.1%, placebo, 18.9% patisiran); majority mild with no severe or serious IRRs, decreased over time, 1 patient discontinued treatment

Summary

• hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening, often fatal disease with high morbidity and mortality and limited therapeutic options

• Patients in the patisiran group in APOLLO consistently experienced improvement in overall health status as measured by EQ-SD-5L and EQ-VAS

• A greater number of patisiran patients reported preservation or improvement in EQ-SD-5L domains compared to placebo treated patients

• Improvement in overall health status in patients treated with patisiran was consistent with improvement in other measures of efficacy such as mNIS+7 and Norfolk QOL-DN

• Patisiran showed an encouraging safety and tolerability profile