Impact of Baseline Polyneuropathy Severity on Vutrisiran Treatment Response in the Phase 3 HELIOS-A Study

Marco Luigetti1,2,*, Dianna Quan3, John L. Berk4, Isabel Conceição5, Yohei Misumi6, Chi-Chao Chao7, Shaun Bender, Emre Aldinc8, John Vest9, David Adams10

Background & Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis
- Rare, rapidly progressive, debilitating, and fatal disease caused by variants in the TTR gene1,2
- Pathogenic TTR variants cause the TTR protein to misfold and accumulate as amyloid deposits in multiple organs and tissues3
- Patients have significant impairment across multiple areas of health, with disease progression leading to poor quality of life, loss of physical function, and death4,5

Vutrisiran
- An RNAi therapeutic that targets hepatic production of variant and wild-type TTR
- Vutrisiran utilizes enhanced stabilization chemistry, designed for increased potency and high metabolic stability, allowing for subcutaneous injection every 3 months
- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on mNIS+7 compared with external placebo, first evident at Month 9 and continued to Month 18 (Figure 2)
- In general, patients with less severe disease at baseline had lower impairment in neuropathy-related QOL at Month 18 (Figure 3)

Conclusions
- Vutrisiran treatment demonstrated a beneficial effect on neurologic function and other key disease measures through 18 months, compared with external placebo, over a wide range of baseline polyneuropathy severities, as assessed by baseline Polyneuropathy Impairment Score (NIS)
- These benefits of vutrisiran versus external placebo, observed across all baseline NIS quartiles for polyneuropathy, quality of life, gait speed, disability, and nutritional status measures, highlight the impact of vutrisiran across the spectrum of hereditary transthyretin-mediated (hATTR) amyloidosis disease severity
- Overall, patients who were in lower NIS quartiles (less severe disease) at vutrisiran initiation maintained better scores compared with those in higher NIS quartiles
- The external placebo group progressively in worsened in all measures by Month 18
- The HELIOS-A randomized treatment extension period is ongoing and may inform the longer-term efficacy and safety of vutrisiran in patients with hATTR amyloidosis with polyneuropathy

Methods
- HELIOS-A is a Phase 3, global, open-label study of vutrisiran 25 mg SC Q3M in patients with hATTR amyloidosis with polyneuropathy
- In the primary analysis, efficacy and safety of up to 18 months of vutrisiran treatment were compared with the external APOLLO placebo group
- Post Hoc Analysis by Baseline Polyneuropathy Severity
- Patients were divided into quartiles based on baseline Neuropathy Impairment Score (NIS) severity
- Q1: NIS ≥5.0 to ≤20.5 Q2: NIS >20.5 to ≤44.1 Q3: NIS >44.1 to ≤73.1 Q4: NIS >73.1 to ≤127.0
- Patients with less severe disease at baseline had lower impairment in gait speed at Month 18
- In general, patients with less severe disease at baseline had lower impairment in neuropathy-related QOL at Month 18
- In general, patients with less severe disease at baseline had lower impairment in nutritional status at Month 18
- In general, patients with less severe disease at baseline had lower impairment in disability status at Month 18

Results

Quality of Life (Norfolk QOL-DN)
- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on Norfolk QOL-DN compared with external placebo, first evident at Month 9 and continued to Month 18
- In general, patients with less severe disease at baseline had less impairment in neuropathy-related QOL at Month 18 (Figure 3)

Gait Speed (10-MWT, m/s)
- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on 10-MWT compared with external placebo at Month 18
- In general, patients with less severe disease at baseline had higher gait speed at Month 18 (Figure 4)

Disability (R-ODS)
- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on R-ODS compared with external placebo, first evident at Month 9 and continued to Month 18
- In general, patients with less severe disease at baseline had lower impairment in disability status at Month 18 (Figure 5)

Nutritional Status (mBMI)
- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on mBMI compared with external placebo at Month 18 (Figure 6)
- In general, patients with less severe disease at baseline had lower impairment in nutritional status at Month 18

Results (cont.)

Results from Baseline to Month 18

Baseline Demographic and Disease Characteristics
- Across baseline NIS quartiles, vutrisiran patients and external placebo patients were generally clinically comparable

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline NIS Quartile</th>
<th>NIS Score</th>
<th>Baseline Characteristics</th>
<th>Vutrisiran</th>
<th>External Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>NIS ≥5.0 to ≤20.5</td>
<td>Age, years</td>
<td>60.3 (7.7)</td>
<td>60.0 (7.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Q2</td>
<td>NIS &gt;20.5 to ≤44.1</td>
<td>Male, %</td>
<td>52 (54)</td>
<td>56 (55)</td>
<td>0.46</td>
</tr>
<tr>
<td>Q3</td>
<td>NIS &gt;44.1 to ≤73.1</td>
<td>Time from NIS diagnosis (years, mean ± SD)</td>
<td>17.7 (7.7)</td>
<td>17.7 (7.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>Q4</td>
<td>NIS &gt;73.1 to ≤127.0</td>
<td>Time to NIS diagnosis (years, mean ± SD)</td>
<td>17.7 (7.7)</td>
<td>17.7 (7.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>Q1</td>
<td>NIS ≥5.0 to ≤20.5</td>
<td>Serum TTR level (g/L, mean ± SD)</td>
<td>0.62 (0.42)</td>
<td>0.61 (0.42)</td>
<td>0.81</td>
</tr>
<tr>
<td>Q2</td>
<td>NIS &gt;20.5 to ≤44.1</td>
<td>Serum TTR level (g/L, mean ± SD)</td>
<td>0.61 (0.42)</td>
<td>0.61 (0.42)</td>
<td>0.81</td>
</tr>
<tr>
<td>Q3</td>
<td>NIS &gt;44.1 to ≤73.1</td>
<td>Serum TTR level (g/L, mean ± SD)</td>
<td>0.60 (0.42)</td>
<td>0.60 (0.42)</td>
<td>0.81</td>
</tr>
<tr>
<td>Q4</td>
<td>NIS &gt;73.1 to ≤127.0</td>
<td>Serum TTR level (g/L, mean ± SD)</td>
<td>0.60 (0.42)</td>
<td>0.60 (0.42)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

References:
1. Hanna.
2. Hawkins et al.
3. Mohty et al.
5. Adams et al.
6. Chai-Chao Chao.
7. Alnylam Pharmaceuticals, Cambridge, MA, USA.
8. Boston Medical Center, Boston, MA, USA.
9. Corinio Therapeutics.
10. Ionis Pharmaceuticals.

Post Hoc Analysis by Baseline Polyneuropathy Severity

- Patients were divided into quartiles based on baseline Neuropathy Impairment Score (NIS) severity
- Q1: NIS ≥5.0 to ≤20.5 Q2: NIS >20.5 to ≤44.1 Q3: NIS >44.1 to ≤73.1 Q4: NIS >73.1 to ≤127.0
- In general, patients with less severe disease at baseline had lower impairment in gait speed at Month 18
- In general, patients with less severe disease at baseline had lower impairment in disability status at Month 18
- In general, patients with less severe disease at baseline had lower impairment in nutritional status at Month 18

Results from Baseline to Month 18

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on mBMI compared with external placebo at Month 18 (Figure 6)
- In general, patients with less severe disease at baseline had lower impairment in nutritional status at Month 18

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on Norfolk QOL-DN compared with external placebo, first evident at Month 9 and continued to Month 18
- In general, patients with less severe disease at baseline had less impairment in neuropathy-related QOL at Month 18 (Figure 3)

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on 10-MWT compared with external placebo at Month 18
- In general, patients with less severe disease at baseline had higher gait speed at Month 18 (Figure 4)

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on R-ODS compared with external placebo, first evident at Month 9 and continued to Month 18
- In general, patients with less severe disease at baseline had lower impairment in disability status at Month 18 (Figure 5)

- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on mBMI compared with external placebo at Month 18 (Figure 6)
- In general, patients with less severe disease at baseline had lower impairment in nutritional status at Month 18

- Overall, patients who were in lower NIS quartiles (less severe disease) at vutrisiran initiation maintained better scores compared with those in higher NIS quartiles
- The external placebo group progressively in worsened in all measures by Month 18
- The HELIOS-A randomized treatment extension period is ongoing and may inform the longer-term efficacy and safety of vutrisiran in patients with hATTR amyloidosis with polyneuropathy

Figure 1. Study Design

Figure 2. Mean Change from Baseline in mNIS+7 Score

Figure 3. Mean Change from Baseline in Norfolk QOL-DN Total Score

Figure 4. Mean Change from Baseline in 10-mWT (m/s)

Figure 5. Mean Change from Baseline in R-ODS

Figure 6. Mean Change from Baseline in mBMI

Gait Speed (10-MWT, m/s)
- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on 10-MWT compared with external placebo at Month 18
- In general, patients with less severe disease at baseline had higher gait speed at Month 18 (Figure 4)

Disability (R-ODS)
- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on R-ODS compared with external placebo, first evident at Month 9 and continued to Month 18
- In general, patients with less severe disease at baseline had lower impairment in disability status at Month 18 (Figure 5)

Nutritional Status (mBMI)
- Across all baseline NIS quartiles, vutrisiran demonstrated a beneficial effect on mBMI compared with external placebo at Month 18
- In general, patients with less severe disease at baseline had lower impairment in nutritional status at Month 18

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the HELIOS-A study. Presented at Peripheral Neuropathy Annual Meeting, June 17–19, 2023, Copenhagen, Denmark.