Primary Results from APOLLO-B Open-label Extension Study of Patisiran in Patients with Transthyretin Cardiac Amyloidosis

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Conclusions

- Patients with transthyretin-mediated (ATTR) cardiac amyloidosis treated with patsiran for 24 months demonstrated sustained benefit across endpoints (6-minute walk test [6MWT], Kansas City Cardiomyopathy Questionnaire-Overall summary [KCCQ-OS]) and cardiac biomarkers (NT-proBNP and troponin I).
- Placebo-treated patients who initiated patsiran displayed relative stabilization or slowing of progression across multiple endpoints (6MWT, KCCQ-OS, NT-proBNP, troponin I) at Month 24 compared with results at Month 12.
- Composite outcome and mortality analyses across the DB and OLE periods did not show significant differences; however, favorable trends were observed.
- Patisiran demonstrated an acceptable safety profile.
- The overall benefit-risk profile of patsiran in patients with ATTR cardiac amyloidosis continued to be favorable through Month 24.

Introduction

ATTR Amyloidosis

- Protein accumulation and tissue damage caused by accumulation of transthyretin (TTR) amyloid in multiple organs and tissues, including the heart and autonomic nervous system, leading to cardiomyopathy in patients with transthyretin type transthyretin (ATTRtTR) amyloidosis.
- The primary cardiomyopathy is driven by ongoing cardiac TTR amyloid deposition, which begins in the heart before affecting other organs.
- The amyloidosis is a deadly disease with a high mortality rate.

Methods

- **Patient Selection**: The APOLLO-B study enrolled patients with ATTRtTR cardiac amyloidosis, including the amyloidotic event sub-type (syringomyelia or polyneuropathy).
- **Randomization**: Patients were randomized to receive patisiran or placebo in a 1:1 ratio, regardless of baseline proBNP level.
- **Primary Endpoints**: The primary endpoints were change from baseline in 6MWT distance at Month 24 and KCCQ-OS score at Month 24.

Results

**Baseline Demographics and Disease Characteristics**

Table 1. Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patisiran (n=178)</th>
<th>Placebo (n=179)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69.3 (13.4)</td>
<td>69.4 (12.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>Sex, female</td>
<td>52 (29.3)</td>
<td>54 (30.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>TTR genotype</td>
<td>ATTRwt (95.8)</td>
<td>ATTRwt (95.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Baseline proBNP level, ng/L, median (IQR)</td>
<td>3.7 (4.9)</td>
<td>3.0 (1.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline transcranial ultrasound score</td>
<td>0.2 (0.9)</td>
<td>0.1 (0.3)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

**Results, continued**

Figure 1. APOLLO-B Study Design

Figure 2. Cardiac SAEs (Cardiac disorders SOC) – Overall Summary; MedDAR

**KCCQ-OS Score**

Figure 3. Change from Baseline in KCCQ-OS at Month 24

**6MWT Distance**

Figure 4. Change from Baseline in 6MWT at Month 24

**Troponin I**

Figure 5. Annual Adjusted Geometric Mean Field Change in Troponin I over 24 Months

**NT-proBNP**

Figure 6. Annual Adjusted Geometric Mean Field Change in NT-proBNP over 24 Months

**Baseline proBNP and troponin I levels**

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Baseline proBNP (ng/L), median (IQR)</th>
<th>Baseline troponin I (ng/L), median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.7 (4.9)</td>
<td>0.1 (0.3)</td>
</tr>
<tr>
<td>12</td>
<td>1.2 (1.5)</td>
<td>0.1 (0.3)</td>
</tr>
<tr>
<td>24</td>
<td>1.2 (1.5)</td>
<td>0.1 (0.3)</td>
</tr>
<tr>
<td>Change from Month 12</td>
<td>−2.5 (3.0)</td>
<td>−0.1 (0.3)</td>
</tr>
</tbody>
</table>

**AEs leading to study drug discontinuation**

Table 2. Summary of AEs in Patients Receiving Patisiran

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Patients</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allcause AEs</td>
<td>113 (63.5)</td>
<td>63.9</td>
</tr>
<tr>
<td>Cardiac AEs</td>
<td>9 (5.1)</td>
<td>5.2</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>16 (9.1)</td>
<td>9.1</td>
</tr>
</tbody>
</table>

**KCCQ-OS Score**

Table 3. Summary of Cardiac Settings

<table>
<thead>
<tr>
<th>Cardiac Setting</th>
<th>Patisiran (n=347)</th>
<th>Placebo (n=347)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR ≥60 mL/min/1.73 m2</td>
<td>137 (40.0)</td>
<td>129 (37.5)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Troponin I and NT-proBNP levels**

<table>
<thead>
<tr>
<th>Level</th>
<th>Patisiran (n=347)</th>
<th>Placebo (n=347)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30%</td>
<td>144 (80.9)</td>
<td>137 (39.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>103 (19.1)</td>
<td>200 (60.5)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Exploratory Analyses**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR amyloidosis with polyneuropathy</td>
<td>0.54</td>
</tr>
<tr>
<td>Transcranial ultrasound score</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Discussion

- Patisiran demonstrated sustained benefit in multiple endpoints across the DB and OLE periods.
- The mean change from baseline in 6MWT distance at Month 24 was −7.8 m, similar to the maintained treatment benefit on both functional capacity and heart rate variability after Month 12.
- The adjusted geometric mean field change in NT-proBNP from baseline to Month 24 was −4.9 (95% CI: −6.7 to −3.3) in the patsiran group compared with placebo (−0.8, 95% CI: −2.6 to 0.8).
- The adjusted geometric mean field change in troponin I from baseline to Month 24 was −2.0 (95% CI: −3.3 to −0.7) in the patsiran group compared with placebo (0.2, 95% CI: −0.4 to 0.4).
- Patisiran was associated with a decrease in KCCQ-OS score, with a mean change from baseline of −12.0 (95% CI: −17.4 to −6.5) at Month 24.
- The proportion of patients with ≥1 death at Months 12 and 24 was lower in the patsiran group (6.2% and 11.3%) compared with placebo (13.1% and 16.7%).
- Patisiran was associated with a decrease in proBNP level from baseline to Month 24 in patients with ATTRtTR amyloidosis.

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