## Efficacy of Patisiran in Patients with hATTR Amyloidosis and Prior Tafamidis Use: Analysis of APOLLO

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### Introduction

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, progressively debilitating, and fatal disease caused by a mutation in the transthyretin (TTR) gene that results in multisystem accumulation of amyloid fibrils (e.g., in nerves, heart, and gastrointestinal tract) and subsequent dysfunction across these multiple organs.
- Affects ~50,000 people worldwide, median survival of 4.7 years following diagnosis, with a reduced survival of 3.4 years for patients presenting with cardiomyopathy.
- Non-specific heterogeneous clinical presentation, the majority of patients exhibit a mixed phenotype of both polyneuropathy and cardiomyopathy.

Patisiran

- A patiromer nanoparticle-delivered RNA interference (RNAi) therapeutic, reduces serum TTR levels by inhibiting hepatic transcription of the disease-causing mutant and wild TTR proteins.

### Primary Endpoint

- The key secondary endpoint was the change from baseline in the NIS+7 score at 18 months.
- Patisiran treatment significantly reduced the NIS+7 score compared with placebo (mean LS mean difference, −15.0; 95% CI, −24.9, −5.2; p < 0.001).

### Results

**Patient Demographics**

- Patisiran enrolled 225 patients, of whom 74% (32.3%) reported prior tafamidis use.
- Most patients with prior tafamidis use (n=46, 62.2%) discontinued tafamidis to enroll in APOLLO (25.1% enrolled vs n=33.3% discontinued due to disease progression (Figure 3).

**Tafamidis Use Prior to Enrolling in APOLLO**

- Early exposure to tafamidis was observed at 18 months with patisiran compared with placebo as seen as an LS mean difference (95% CI) of −21.1 (−27.2, −4.9).

### Safety and Tolerability

**Tafamidis Use Prior to Enrolling in APOLLO**

- Safety and tolerability in the prior tafamidis subgroup was consistent with that seen in the overall APOLLO population.
- Majority of adverse events (AEs) were mild or moderate in severity.
- Common AEs that occurred more frequently with tafamidis than placebo in the overall APOLLO population were peripheral edema (30% vs 22%) and inflation-related reactions (11% vs 13%).
- No safety concerns related to hepatic laboratory parameters (including bilirubin), hepatic dysfunction, or renal dysfunction.
- Causes of deaths were consistent with natural history of hATTR amyloidosis.

## Methods

**APOLLO Phase 3 Study Design**

- APOLLO (NCT01880844) was a Phase III, randomized, placebo-controlled study of patients 0.3 mg/kg intravenous (IV) every 3 weeks (q3w) in patients with ATTR amyloidosis with polyneuropathy (Figure 2).

**Figure 2. APOLLO Study Design**

### Conclusions

- Approximately one-third of patients enrolled in the randomized, placebo-controlled patiromer Phase 3 APOLLO study were previously treated with tafamidis.
- Reduction in patients with prior tafamidis use discontinued tafamidis due to disease progression; majority of other patients discontinued tafamidis to participate in the APOLLO study, although for discontinuation not specified.
- Patients with prior tafamidis use who received patisiran treatment for >1 year demonstrated a significant improvement from baseline in polyneuropathy and QOL compared with placebo, similar to that experienced by the overall APOLLO population.
- These data suggest that patients who discontinue tafamidis treatment due to disease progression or for other reasons may benefit from treatment with patisiran.
- Patisiran demonstrated an acceptable benefit-risk profile.

### Table 2. Safety Summary for the Overall APOLLO Population

<table>
<thead>
<tr>
<th>Event (%)</th>
<th>Prior Tafamidis Use</th>
<th>Overall APOLLO Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>28 (29)</td>
<td>38 (39)</td>
</tr>
<tr>
<td>Any severe AE</td>
<td>8 (8)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Any worsening AE</td>
<td>12 (12)</td>
<td>44 (46)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>4 (4)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Death*</td>
<td>2 (2)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>

*AEs related to tafamidis.