Evaluation of Quality of Life and Disability in Patients with Hereditary Transthyretin-Mediated (hATTR) Amyloidosis with Polyneuropathy Following Treatment with Patisiran, an Investigational RNAi Therapeutic: Results from the Phase 3 APOLLO Study

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Hereditary ATTR (hATTR) Amyloidosis

Disease Overview and Introduction to Patisiran, an Investigational RNAi Therapeutic

• hATTR Amyloidosis
  ◦ Rare, inherited, rapidly progressive, debilitating, life-threatening, often fatal disease caused by mutations in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract\(^1\)\(^-\)\(^5\)
  ◦ Median survival 4.7 years following diagnosis\(^6\); reduced survival (3.4 years) for patients presenting with cardiomyopathy\(^6\)\(^-\)\(^8\)

• Multisystem disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms\(^2\)\(^,\)\(^9\)\(^,\)\(^10\)
  ◦ Disease continuum includes patients who present with predominantly polyneuropathy symptoms (formerly FAP) or cardiomyopathy symptoms (formerly FAC), yet many patients experience a variety of symptoms
    – Clinical manifestations (e.g., disease penetrance and rate of progression) is influenced by TTR genotype and geographical region

• Limited treatment options
  ◦ Liver transplant for early-stage disease and TTR tetramer stabilizers
    – Tafamidis approved in EU for Stage 1 hATTR amyloidosis\(^11\) and certain other countries outside U.S.
    – Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study\(^12\)

• Continued high unmet medical need for novel therapeutics

• Patisiran, an Investigational RNAi Therapeutic
  ◦ Lipid nanoparticle formulated RNAi, administered by IV infusion, targeting hepatic production of mutant and wild-type TTR

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Patisiran Therapeutic Hypothesis

![Diagram of Patisiran Therapeutic Hypothesis]

- Production of mutant and wild-type TTR
- Unstable circulating TTR tetramers reduced
- Organs deposition of monomers, amyloid fibrils prevented/clearance promoted
- Neuropathy, cardiomyopathy stabilization or improvement
Patisiran Phase 3 APOLO Study Design

**Patient Population**
- hATTR amyloidosis: any TTR mutation, FAP Stage 1 or 2
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

**ClinicalTrials.gov Identifier**: NCT01960348

**Primary Endpoint**
- Change in mNIS+7 from baseline at 18 months

**Secondary Endpoints**
- Norfolk QOL-DN
- NIS-weakness
- R-ODS
- 10-meter walk
- mBMI
- COMPASS-31

**Select Exploratory Endpoint**
- EQ-5D QOL

†Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous tetramer stabilizer use

*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine).

Patients who completed study were eligible for patisiran treatment on Global OLE Study (NCT02510261)
Patisiran Phase 3 APOLO Study Endpoints

Primary Endpoints

- **mNIS+7**: a composite measure of neurological impairment
  - Higher score indicates worsening of neuropathy

Select Secondary Endpoints

- **Norfolk QOL-DN**: 35-item QOL questionnaire that is sensitive to small fiber, large fiber, and autonomic nerve function
  - Higher score indicates worsening of QOL
- **R-ODS**: 24-item questionnaire used to capture activity and social participation (disability)
  - Lower score indicates worsening disability
- **10-meter walk test (m/sec)**: assessment of ambulation that measures gait speed
  - Lower score indicates worsening
- **COMPASS 31**: 31-item questionnaire used to evaluate patient reported autonomic neuropathy symptoms
  - Higher score indicates worsening of autonomic neuropathy symptoms

Select Exploratory Endpoints

- **EQ-5D-5L**: 5-item standardized instrument to measure quality of life
  - Lower score indicates worsening of QOL
- **EQ-VAS**: assessment of patient’s own global impression of their overall health
  - Lower score indicates worsening of QOL
# Patisiran Phase 3 APOLO Study Results

## 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><strong>Median Age, years (range)</strong></td>
<td>63 (34, 80)</td>
<td>62 (24, 83)</td>
</tr>
<tr>
<td><strong>Gender, males</strong></td>
<td>58 (75.3)</td>
<td>109 (73.6)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>25 (32.5)</td>
<td>27 (18.2)</td>
</tr>
<tr>
<td>Black/African or African American</td>
<td>1 (1.3)</td>
<td>4 (2.7%)</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>50 (64.9)</td>
<td>113 (76.4)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>10 (13.0)</td>
<td>37 (25.0)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>36 (46.8)</td>
<td>62 (41.9)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>31 (40.3)</td>
<td>49 (33.1)</td>
</tr>
<tr>
<td><strong>hATTR Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since hATTR diagnosis, mean (min, max)</td>
<td>2.60 (0.0, 16.5)</td>
<td>2.39 (0.0, 21.0)</td>
</tr>
<tr>
<td><strong>TTR Genotype</strong></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><strong>Previous tetramer stabilizer use</strong></td>
<td>41 (53.2)</td>
<td>78 (52.7)</td>
</tr>
<tr>
<td><strong>Disease Characteristics, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NIS</strong></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td>Mean (min, max)</td>
<td>57.0 (7.0, 125.5)</td>
<td>60.5 (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>&gt;100</td>
<td>9 (11.7)</td>
<td>23 (15.5)</td>
</tr>
<tr>
<td><strong>FAP Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: unimpaired ambulation</td>
<td>37 (48.1)</td>
<td>67 (45.3)</td>
</tr>
<tr>
<td>2: assistance with ambulation required</td>
<td>39 (50.6)</td>
<td>81 (54.7)</td>
</tr>
<tr>
<td>3: wheelchair bound or bedridden</td>
<td>1 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>PND Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I: preserved walking, sensory disturbances</td>
<td>20 (26.0)</td>
<td>36 (24.3)</td>
</tr>
<tr>
<td>II: impaired walking but can walk without stick or crutch</td>
<td>23 (29.9)</td>
<td>43 (29.1)</td>
</tr>
<tr>
<td>IIIa: walk with 1 stick or crutch</td>
<td>22 (28.6)</td>
<td>41 (27.7)</td>
</tr>
<tr>
<td>IIIb: walk with 2 sticks or crutches</td>
<td>11 (14.3)</td>
<td>28 (18.9)</td>
</tr>
<tr>
<td>IV: confined to wheelchair or bedridden</td>
<td>1 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiac Subpopulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td></td>
<td>36 (46.8)</td>
<td>90 (60.8)</td>
</tr>
</tbody>
</table>

**Blue, bolded text** indicated >10% difference in either group

†Other, patisiran N=1 (0.7%); More than one race, patisiran N=2 (1.4%); missing N=1 each for placebo (1.3%) and patisiran (0.7%)

*North America: USA, CAN; Western Europe: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; Rest of world: Asia: JPN, KOR, TWN, Eastern Europe: BGR, CYP, TUR; Central & South America: MEX, ARG, BRA

‡Represents 38 different TTR mutations

♯Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)
Patisiran Phase 3 APOLLO Study Results

mNIS+7: Change from Baseline

56.1% of patients in the patisiran group demonstrated improvement in mNIS+7 compared to 3.9% of patients on placebo (Odds ratio: 39.9; p=1.82 x 10^{-15}; improvement defined as <0 point increase from baseline to 18 months)
Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Change from Baseline

Norfolk QOL-DN reference range: -4 to 136

51.4% of patients in the patisiran group demonstrated improvement in Norfolk QOL-DN compared to 10.4% of patients on placebo (Odds ratio: 10.0; \( p=1.95 \times 10^{-10} \); improvement defined as <0 point increase from baseline to 18 months)
Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Change from Baseline in Individual Domains

- Patisiran demonstrated improvement across all domains of the Norfolk QOL-DN

**Norfolk QOL-DN: Change from Baseline in Individual Domains**

- MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Norfolk QOL-DN, Norfolk quality of life diabetic neuropathy questionnaire

**Graph Details**

- **Physical Functioning/Large Fiber**
  - Placebo: -1.9
  - Patisiran: 9
- **Activities of Daily Living (ADLs)**
  - Placebo: -1.2
  - Patisiran: 5.3
- **Symptoms**
  - Placebo: 0.5
  - Patisiran: 2.3
- **Small Fiber**
  - Placebo: -0.3
  - Patisiran: 2.8
- **Autonomic**
  - Placebo: 0.3
  - Patisiran: 0.8
• Overall, patients in the patisiran group consistently improved their quality of life as measured by EQ-5D-5L and EQ-VAS compared with placebo at 18 months; this improvement was evident as early as 9 months
Patisiran Phase 3 APOLO Study Results

R-ODS: Change from Baseline

- Patisiran demonstrated a significant improvement in disability at 18 months compared to placebo and nominal significance as early as 9 months.

MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; R-ODS, Rasch-built overall disability scale

R-ODS reference range: 0-48
Patients in the patisiran group demonstrated a significant improvement in gait speed compared to placebo; this improvement in gait speed was evident as early as 9 months.

**Patisiran Phase 3 APOLLO Study Results**

**10-MWT: Change from Baseline to Month 18**

- Patients in the patisiran group demonstrated a significant improvement in gait speed compared to placebo; this improvement in gait speed was evident as early as 9 months.

**Secondary endpoint; LS Mean**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
<th>Treatment Difference (Pati - PBO)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-MWT, m/sec</td>
<td>CFB to 18 mos</td>
<td>-0.24</td>
<td>0.08</td>
<td>0.311</td>
</tr>
</tbody>
</table>

MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; 10-MWT, 10-meter walk test; CFB, change from baseline; Pati, patisiran; PBO, placebo.

Patisiran Phase 3 APOLLO Study Results

COMPASS 31: Change from Baseline in Individual Domains

- Statistically significant improvement in autonomic neuropathy symptoms at 18 months for patients in the patisiran group compared to the placebo group

<table>
<thead>
<tr>
<th>Secondary endpoint; LS Mean</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
<th>Treatment Difference (Pati - PBO)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPASS 31</td>
<td>Baseline score, mean</td>
<td>30.31</td>
<td>30.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos</td>
<td>2.24</td>
<td>-5.29</td>
<td>-7.53</td>
</tr>
</tbody>
</table>

MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; CFB, change from baseline; COMPASS 31, composite autonomic symptom score 31
COMPASS 31 reference range: 0 - 100
Patisiran Phase 3 APOLLO Study Results

Safety and Tolerability

<table>
<thead>
<tr>
<th>Type of Adverse Event, number of patients (%)</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event (AE)</td>
<td>75 (97.4)</td>
<td>143 (96.6)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>28 (36.4)</td>
<td>42 (28.4)</td>
</tr>
<tr>
<td>Serious adverse event (SAE)</td>
<td>31 (40.3)</td>
<td>54 (36.5)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>11 (14.3)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>AE leading to study withdrawal</td>
<td>9 (11.7)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (7.8)</td>
<td>7 (4.7)</td>
</tr>
</tbody>
</table>

Overall, 13 deaths in APOLLO study; no deaths considered related to study drug
- Causes of death (e.g., cardiovascular, infection) consistent with natural history; frequency of death trended lower in the patisiran group compared with placebo group

Majority of AEs were mild or moderate in severity
- Peripheral edema
  - Did not result in any treatment discontinuations and decreased over time
- Infusion-related reactions (IRRs)
  - Majority mild in severity that decreased over time; led to treatment discontinuation in 1 patient
  - No severe, life-threatening or serious IRRs

No safety signals regarding cataracts, hyperglycemia, infection, or osteopenia/osteoporosis

No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

Safety in cardiac subpopulation comparable to overall study population

Adverse Events Occurring in ≥ 10% in Either Group

<table>
<thead>
<tr>
<th>Preferred AE Term, number of patients (%)</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>29 (37.7)</td>
<td>55 (37.2)</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>17 (22.1)</td>
<td>44 (29.7)</td>
</tr>
<tr>
<td>Infusion related reaction (IRR)</td>
<td>7 (9.1)</td>
<td>28 (18.9)</td>
</tr>
<tr>
<td>Fall</td>
<td>22 (28.6)</td>
<td>25 (16.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (18.9)</td>
<td>22 (14.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (20.8)</td>
<td>22 (14.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (14.3)</td>
<td>19 (12.8)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>14 (18.2)</td>
<td>19 (12.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (10.4)</td>
<td>18 (12.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (11.7)</td>
<td>16 (10.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (11.7)</td>
<td>15 (10.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (9.1)</td>
<td>15 (10.1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (7.8)</td>
<td>15 (10.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (10.4)</td>
<td>15 (10.1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (11.7)</td>
<td>14 (9.5)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>8 (10.4)</td>
<td>10 (6.8)</td>
</tr>
<tr>
<td>Muscular Weakness</td>
<td>11 (14.3)</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (10.4)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Syncope</td>
<td>8 (10.4)</td>
<td>3 (2.0)</td>
</tr>
</tbody>
</table>

Blue, bolded text: Indicates ≥5 percentage point difference in either group
Patisiran Phase 3 APOLLO Study

Summary

hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening, often fatal disease with limited therapeutic options

Patisiran treatment resulted in significant improvement in polyneuropathy relative to placebo

• Benefits seen in motor, sensory and autonomic neuropathy
• Positive effects observed across wide range of disease severity and TTR genotypes, including patients with cardiac involvement

Treatment with patisiran resulted in an improvement in QOL compared to placebo; treatment with patisiran demonstrated favorable impact on disability compared to placebo

• Patisiran treatment led to an improvement in Norfolk QOL-DN as well as EQ-5D-5L and EQ-VAS
• Decrease in autonomic symptoms and improvement in gait speed in patisiran-treated patients, thus potentially lessening the burden of disease

Patisiran showed an encouraging safety and tolerability profile

• Frequency of deaths trended lower in the patisiran group versus placebo arm
• Key patisiran safety findings include mild to moderate peripheral edema and IRRs with only one treatment discontinuation due to these events
• No safety signals with regard to thrombocytopenia, hepatic or renal dysfunction

99% of eligible APOLLO patients enrolled into Global OLE study
Acknowledgments

Thank you to the patients, their families, investigators, study staff and collaborators for their participation in the Phase 3 APOLLO study

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Alnylam has licenses to Arbutus Biopharma LNP intellectual property for use in RNAi therapeutic products using LNP technology