Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy: Results from the Phase 3 APOLLO Study

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Hereditary ATTR (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, debilitating, life-threatening, often fatal disease caused by mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract\(^1-^5\)
  - Median survival 2-15 years\(^1-^3\)

- Multi-systemic disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms\(^2,^6,^7\)
  - 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) influenced by TTR genotype and geographical region

- Limited treatment options
  - Liver transplant for early-stage disease
  - TTR tetramer stabilizers
    - Tafamidis approved in EU for Stage 1 hATTR amyloidosis\(^8\) and certain other countries outside U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study\(^9\)

- Continued high unmet medical need for novel therapeutics

Patisiran: Investigational RNAi Therapeutic for hATTR Amyloidosis

Therapeutic Hypothesis

- Lipid nanoparticle formulated RNAi, administered by IV infusion, targeting hepatic production of mutant and wild-type TTR

Production of mutant and wild type TTR

Unstable circulating TTR tetramers reduced

Organ deposition of monomers, amyloid (β-pleated) fibril prevented, clearance promoted

Neuropathy, cardiomyopathy stabilization or improvement
Patisiran: Investigational RNAi Therapeutic for hATTR Amyloidosis
Clinical Development Program

Positive results in human healthy volunteers (N=17)
- Single dose
- 0.01–0.5 mg/kg by IV infusion

Positive multi-dose results in adult patients with hATTR amyloidosis (N=29)
- Multiple doses
- Multiple schedules

Positive results in adult patients with hATTR amyloidosis with polyneuropathy who participated in the Phase 2 study (N=27)
- 0.3 mg/kg every 3 weeks by IV infusion for up to 2 years

Adults with hATTR amyloidosis with polyneuropathy (N=225)
- 0.3 mg/kg every 3 weeks by IV infusion for 18 months
- Randomized, double-blind, placebo-controlled

Adults with hATTR amyloidosis with polyneuropathy who participated in the Ph 2 OLE or Ph 3 study (N=211 enrolled)
- 0.3 mg/kg every 3 weeks by IV infusion
- Includes some patients with over 3 years treatment

Patisiran: Investigational RNAi Therapeutic for hATTR Amyloidosis
Phase 2 OLE Study Summary

Objectives:
• Primary: Safety and tolerability of long-term dosing with patisiran
• Secondary / Exploratory: Effects on neurologic impairment, QoL, mBMI, disability, mobility, grip strength, autonomic symptoms, nerve fiber density in skin biopsies, cardiac biomarkers and echo (in cardiac subgroup), serum TTR levels

Results:
• Generally well tolerated in patients with hATTR amyloidosis with polyneuropathy out to 25 months with sustained mean serum TTR knockdown of ~80% for over 24 months and improvement in neuropathy impairment score which was consistent with therapeutic hypothesis that patisiran can potentially halt or improve neuropathy progression

Natural History (N=283)\(^*\)

<table>
<thead>
<tr>
<th>Mean ΔmNIS+7 at 24mos</th>
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<tbody>
<tr>
<td>Mean ΔmNIS+7 at 24mos</td>
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</table>

Patisiran Phase 2 OLE (N=26)\(^2\)

<table>
<thead>
<tr>
<th>20 out of 27* patients (74%) with no change or an improvement in mNIS+7 at month 24 compared to baseline</th>
</tr>
</thead>
</table>

*One patient discontinued prior to the Month 24 assessment and is included in the denominator
\(^1\)Adams D, et al., Neurology. 85:675-682 (2015); \(^*\)Predicted progression of median NIS value from Gompertz curve fit
\(^2\)Adams D, et al, AAN 2017
Patisiran Phase 3 APOPOLO 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

**2:1 Randomization†**
- Patisiran 0.3 mg/kg IV q3w*
- Placebo IV q3W*

**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 Endpoints**
- EQ-5D QOL
- NIS+7
- Serum TTR levels
- Cardiac assessments
- Grip strength
- Skin biopsies for nerve fiber density and amyloid

†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 may be eligible for patisiran treatment on Global OLE Study

OLE, open-label extension; ClinicalTrials.gov Identifier: NCT02510261
Adams D, et al. BMC Neurology 2017

ClinicalTrials.gov Identifier: NCT01960348
Primary Endpoints

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

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

• NIS-W: motor function/strength assessment
  - Higher score indicates worsening of strength

• 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

• mBMI (kg/m² x albumin [g/L]): nutritional status
  - Lower score indicates worsening of nutritional status

• COMPASS-31: 31-item questionnaire used to evaluate patient reported autonomic neuropathy symptoms
  - Higher score indicates worsening of autonomic neuropathy symptoms

mNIS+7, modified neuropathy impairment scores +7; QOL, quality of life; NIS-W, neuropathy impairment score-weakness; R-ODS, Rasch-built Overall Disability Scale; mBMI, modified body mass index; COMPASS-31, Composite Autonomic Symptom Score questionnaire
## Patisiran Phase 3 APOLLO Study
### Primary and Secondary Endpoint Measures

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Domain</th>
<th>Range</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>mNIS+7</td>
<td>Neuropathy</td>
<td>0 – 304 points</td>
<td>Negative change</td>
</tr>
<tr>
<td>Norfolk QOL-DN</td>
<td>Quality of Life</td>
<td>-4 – 136 points</td>
<td>Negative change</td>
</tr>
<tr>
<td>NIS-W</td>
<td>Motor Strength</td>
<td>0 – 192 points</td>
<td>Negative change</td>
</tr>
<tr>
<td>R-ODS</td>
<td>Disability</td>
<td>0 – 48 points</td>
<td>Positive change</td>
</tr>
<tr>
<td>10-MWT</td>
<td>Ambulation (gait speed)</td>
<td>meters/second (m/sec)</td>
<td>Positive change</td>
</tr>
<tr>
<td>mBMI</td>
<td>Nutritional status</td>
<td>kg/m² x g/L</td>
<td>Positive change</td>
</tr>
<tr>
<td>COMPASS-31</td>
<td>Autonomic Symptoms</td>
<td>0 – 100 points</td>
<td>Negative change</td>
</tr>
</tbody>
</table>

mNIS+7, modified neuropathy impairment scores +7; QOL, quality of life; NIS-W, neuropathy impairment score-weakness; R-ODS, Rasch-built Overall Disability Scale; 10-MWT, 10 meter walk test; mBMI, modified body mass index; COMPASS-31, Composite Autonomic Symptom Score questionnaire
Patisiran Phase 3 APOLLO Study Results

Study Enrollment

225 patients with hATTR amyloidosis with polyneuropathy from 44 sites in 19 countries enrolled between Dec 2013 and Jan 2016

North America: 21%
Western Europe: 44%
Rest of World: 36%

*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; Asia: JPN, KOR, TWN; Central & South America: MEX, ARG, BRA
**Patisiran Phase 3 APOLLO Study Results**

**Enrollment and Disposition**

*Study populations: modified intent-to-treat (mITT) population: All patients who were randomized and received at least 1 dose of patisiran or placebo (placebo, N=77; patisiran, N=148)*

Discontinued (d/c) treatment: patients who permanently stopped treatment prior to the last scheduled dose (Week 78 visit);
Discontinued (d/c) study: patients who stopped the study before any Month 18 (Week 79-80) assessments were performed

Progressive disease: patients who stopped treatment due to rapid disease progression
Rapid disease progression: patients who have ≥24-point increase in mNIS+7 from baseline [based on an average of 2 measurements] and FAP Stage progression relative to baseline at 9 months and had no major protocol deviations

**Randomized (1:2) (N=225)**

- **Placebo (N=77)**
  - D/C Treatment (N=29; 37.7%)
    - AE 9.1%
    - Death: 5.2%
    - Progressive disease: 5.2%
    - Physician decision: 2.6%
    - Protocol deviation: 0%
    - Withdrawn by patient 15.6%
    - Study Withdrawal (N=22; 28.6%)

  - **Completed Study (N=55, 71.4%)**

- **Patisiran (N=148)**
  - D/C Treatment (N=11; 7.4%)
    - AE 2.0%
    - Death: 3.4%
    - Progressive disease: 0.7%
    - Physician decision: 0%
    - Protocol deviation: 0.7%
    - Withdrawn by patient 0.7%
    - Study Withdrawal (N=10; 6.8%)

  - **Completed Study (N=138, 93.2%)**
## Patisiran Phase 3 APOLLO Study Results
### Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic, 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>
</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; Asia: JPN, KOR, TWN; Central & South America: MEX, ARG, BRA
‡Represents 38 different TTR mutations
### Baseline Disease Characteristics, continued

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Placebo (N=77)</th>
<th>Patisiran (fN=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIS, mean (SEM)</strong></td>
<td></td>
<td></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>≥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>NYHA Class I</td>
<td>16 (44.4)</td>
<td>34 (37.8)</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>20 (55.6)</td>
<td>56 (62.2)</td>
</tr>
</tbody>
</table>

*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 APOLO Study Results
Serum TTR Reduction

87.8% mean max serum TTR reduction from baseline for patisiran over 18 months

<table>
<thead>
<tr>
<th>TTR Change</th>
<th>Change from baseline at 9 months</th>
<th>Change from baseline at 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td>Mean (SEM) Serum TTR Knockdown</td>
<td>1.5% (4.47)</td>
<td>82.6% (1.36)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td></td>
<td>4.8% (3.38)</td>
<td>84.3% (1.48)</td>
</tr>
</tbody>
</table>

Placebo (N=77)
Patisiran (N=148)
Patisiran Phase 3 APOLLO Study Results
mNIS+7: Change from Baseline

Difference at 18 mos (Pati – PBO): -33.99
p-value: 9.26 \times 10^{-24}

MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline
mNIS+7 reference range: 0-304 points
Patisiran Phase 3 APOLLO Study Results
mNIS+7 Subcomponents: Change from Baseline to Month 18

**NIS-W**
Range: 0 to 192
Treatment Difference (Patisiran – Placebo): -17.87 (95% CI: -22.32, -13.43)

**NIS-R**
Range: 0 to 20
Treatment Difference (Patisiran – Placebo): -1.08 (95% CI: -2.00, -0.17)

**QST**
Range: 0 to 80
Treatment Difference (Patisiran – Placebo): -13.05 (95% CI: -16.33, -9.77)

**∑5 NCS**
Range: 0 to 10
Treatment Difference (Patisiran – Placebo): -1.04 (95% CI: -1.35, -0.74)

**Postural BP**
Range: 0 to 2
Treatment Difference (Patisiran – Placebo): -0.28 (95% CI: -0.47, -0.10)

**Legend:**
- Favors Patisiran
- Favors Placebo

**Note:**
- mITT, modified intent to treat; NIS-W, neuropathy impairment score-weakness; NIS-R, neuropathy impairment score-reflexes; QST, Quantitative Sensory Testing; NCS, Nerve Conduction Studies; BP, Blood Pressure
Patisiran Phase 3 APOLLO Study Results

mNIS+7: Change from Baseline to Month 18 in Subgroups

LS Mean Difference | 95% CI
--- | ---
Overall | -33.99 | (-39.86, -28.13)
Age | -30.63 | (-37.98, -23.28)
Age | -38.55 | (-48.27, -28.83)
Sex | -35.10 | (-41.82, -28.39)
Sex | -31.72 | (-44.64, -18.8)
Race | -33.89 | (-40.72, -27.05)
Race | -33.73 | (-46.49, -20.98)
Region | -46.95 | (-62.78, -31.11)
Region | -36.80 | (-45.37, -28.24)
Region | -27.70 | (-37.91, -17.49)
NIS | -28.00 | (-35.51, -20.49)
NIS | -39.09 | (-47.77, -30.42)
Genotype | -37.10 | (-44.83, -29.37)
V30M | -31.70 | (-40.64, -22.77)
Genotype | -22.25 | (-35, 9.5)
Genotype | -36.10 | (-42.58, -29.61)
Genotype Class | -38.30 | (-46.11, -30.49)
Early onset V30M | -39.94 | (-39.12, -20.77)
All other mutations | -29.94 | (-39.12, -20.77)
Previous Tetramer Stabilizer Use | -38.24 | (-47, -29.49)
Yes | -37.81 | (-46.73, -28.89)
No | -30.68 | (-38.33, -23.03)
FAP Stage | -29.65 | (-37.4, -21.91)
1 | -29.94 | (-39.12, -20.77)
2 & 3 | -38.24 | (-47, -29.49)
Cardiac Subpopulation | -37.81 | (-46.73, -28.89)
Yes | -30.68 | (-38.33, -23.03)
No | -29.65 | (-37.4, -21.91)

mITT, modified intent to treat
Patisiran Phase 3 APOLLO Study Results
Norfolk QOL-DN: Change from Baseline

MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline
Norfolk QOL-DN reference range: -4 to 136

Difference at 18mos (Pati – PBO): -21.1
p-value: $1.10 \times 10^{-10}$
Patisiran Phase 3 APOLO Study Results

Norfolk QOL-DN: Change from Baseline to Month 18 in Subgroups

### Treatment Difference (Patisiran – Placebo)

- **Overall**: -21.13 (95% CI: -27.24, -15.01)
- **Age**
  - <65: -22.09 (95% CI: -31.29, -12.89)
  - ≥65: -20.78 (95% CI: -29.42, -12.13)
- **Sex**
  - M: -22.02 (95% CI: -29.29, -14.76)
  - F: -20.63 (95% CI: -34.75, -6.51)
- **Race**
  - White: -21.28 (95% CI: -28.83, -13.74)
  - Non-White: -19.07 (95% CI: -33.67, -4.47)
- **Region**
  - North America: -20.92 (95% CI: -36.61, -5.24)
  - Western Europe: -21.69 (95% CI: -29.76, -13.62)
  - Rest of World: -22.50 (95% CI: -35.58, -9.42)
- **NIS**
  - <50: -22.96 (95% CI: -32.77, -13.15)
  - ≥50: -20.16 (95% CI: -28.53, -11.8)
- **Genotype**
  - V30M: -21.81 (95% CI: -31.11, -12.5)
  - Other: -20.84 (95% CI: -30.27, -11.4)
- **Genotype Class**
  - Early onset V30M: -21.05 (95% CI: -45.05, 2.95)
  - All other mutations: -21.54 (95% CI: -28.21, -14.88)
- **Previous Tetramer Stabilizer Use**
  - Yes: -17.56 (95% CI: -25.73, -9.39)
  - No: -25.88 (95% CI: -36.17, -15.58)
- **FAP Stage**
  - 1: -18.31 (95% CI: -26.61, -10.01)
  - 2 & 3: -24.16 (95% CI: -33.64, -14.67)
- **Cardiac Subpopulation**
  - Yes: -22.97 (95% CI: -31.94, -13.99)
  - No: -20.17 (95% CI: -29.88, -10.46)
Patisiran Phase 3 APOLLO Study Results
mNIS+7 and Norfolk QOL-DN: Binary Analysis

**Improvement in mNIS+7**
Odds ratio: 39.9 (11.0, 144.4)
\( p = 1.82 \times 10^{-15} \)

**Improvement in Norfolk QOL-DN**
Odds ratio: 10.0 (4.4, 22.5)
\( p = 1.95 \times 10^{-10} \)

**Percent of Patients (95% CI)**
- **mNIS+7**: 56.1% (48.1, 64.1)
- **Norfolk QOL-DN**: 51.4% (43.3, 59.4)

**Placebo** vs **Patisiran**

Improvement defined as patients with <0 point increase from baseline to 18 months

mITT, modified intent to treat;
*Post-hoc analysis; nominal p-value
Patisiran Phase 3 APOLLO Study Results
Additional Secondary Endpoints: Change from Baseline (CFB) to 18 Months

All secondary endpoints achieved statistical significance at 18 months
  • Nominal statistical significance was achieved as early as month 9 for NIS-W, R-ODS, 10-MWT and mBMI

<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>NIS-W</td>
<td>Baseline score, mean</td>
<td>29.03</td>
<td>32.69</td>
<td>-17.87</td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos</td>
<td>17.93</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>R-ODS</td>
<td>Baseline score, mean</td>
<td>29.8</td>
<td>29.7</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos</td>
<td>-8.9</td>
<td>0.0</td>
<td>4.07</td>
</tr>
<tr>
<td>10-MWT, m/sec</td>
<td>Baseline score, mean</td>
<td>0.79</td>
<td>0.80</td>
<td>0.311</td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos</td>
<td>-0.24</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>mBMI, kg/m² x albumin [g/L]</td>
<td>Baseline score, mean</td>
<td>990</td>
<td>970</td>
<td>115.7</td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos</td>
<td>-119.4</td>
<td>-3.7</td>
<td></td>
</tr>
<tr>
<td>COMPASS-31</td>
<td>Baseline score, mean</td>
<td>30.31</td>
<td>30.61</td>
<td>-7.53</td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos</td>
<td>2.24</td>
<td>-5.29</td>
<td></td>
</tr>
</tbody>
</table>

Pati, patisiran; PBO, placebo; NIS-W, neuropathy impairment score-weakness; CFB, change from baseline; R-ODS, Rasch-built Overall Disability Scale; 10-MWT, 10 meter walk test; mBMI, modified body mass index; COMPASS-31, Composite Autonomic Symptom Score questionnaire
Patisiran Phase 3 APOLLO Study
Exploratory Cardiac Endpoints

<table>
<thead>
<tr>
<th>Exploratory Endpoint</th>
<th>Measures</th>
<th>Normal Value</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>Cardiac stress</td>
<td>&lt;125*</td>
<td>Reduction</td>
</tr>
<tr>
<td>Troponin-I, mg/L</td>
<td>Myocardial injury</td>
<td>≤ 0.1</td>
<td>Reduction</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV wall thickness, cm</td>
<td>Cardiac amyloid burden</td>
<td>&lt; 1.2</td>
<td>Reduction</td>
</tr>
<tr>
<td>LV Mass, g</td>
<td>Cardiac amyloid burden</td>
<td>155 (M), 103 (F)</td>
<td>Reduction</td>
</tr>
<tr>
<td>Longitudinal Strain, %</td>
<td>Systolic function</td>
<td>-15.9 to -21.1</td>
<td>Reduction</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>Systolic function</td>
<td>&gt;50</td>
<td>Increase</td>
</tr>
<tr>
<td>Functional Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-MWT gait speed, m/sec</td>
<td>ambulation</td>
<td>1.1 – 1.3‡</td>
<td>Increase</td>
</tr>
</tbody>
</table>

M, Male; F, female; LV, left ventricular, 10-MWT, 10 meter walk test
*Age up to 75 years; ‡Age 10-79
# Patisiran Phase 3 APOLLO Study Results

## Exploratory Analysis: Cardiac Subpopulation

**Patients within cardiac subpopulation had substantial cardiac involvement**

<table>
<thead>
<tr>
<th>Exploratory endpoint</th>
<th>Placebo (N=36)</th>
<th>Patisiran (N=90)</th>
<th>Treatment Difference (Pati - PBO)</th>
<th>Nominal p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>Baseline, median</td>
<td>845.7</td>
<td>756.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, median‡</td>
<td>320.4</td>
<td>-49.9</td>
<td>-370.2</td>
</tr>
<tr>
<td>Troponin-I, mg/L</td>
<td>Baseline, mean</td>
<td>0.11</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, LS mean</td>
<td>0.0</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV wall thickness, cm</td>
<td>Baseline, mean</td>
<td>1.64</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, LS mean</td>
<td>-0.007</td>
<td>-0.100</td>
<td>-0.093</td>
</tr>
<tr>
<td>LV Mass, g</td>
<td>Baseline, mean</td>
<td>264.52</td>
<td>275.48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, LS mean</td>
<td>0.63</td>
<td>-15.12</td>
<td>-15.75</td>
</tr>
<tr>
<td>Longitudinal Strain, %</td>
<td>Baseline, mean</td>
<td>-15.66</td>
<td>-15.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, LS mean</td>
<td>1.46</td>
<td>0.08</td>
<td>-1.37</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>Baseline, mean</td>
<td>62.2</td>
<td>60.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos; LS mean</td>
<td>0.57</td>
<td>1.00</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Functional Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-MWT gait speed, m/sec</td>
<td>Baseline, mean</td>
<td>0.73</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos; LS mean</td>
<td>-0.35</td>
<td>0.01</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*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)

Pati, patisiran; PBO, placebo; CFB, change from baseline

‡P-value based on changes in log-transformed data
Patisiran Phase 3 APOLOLO Study Results

Safety and Tolerability

Overall, 13 deaths in APOLOLO study; no deaths considered related to study drug

- Similar frequency of deaths in patisiran and placebo treatment groups
- Causes of death (e.g., cardiovascular, infection) consistent with natural history
APOLLO - Patisiran Phase 3 Study
Serious Adverse Events ≥ 2% in any Treatment Group

<table>
<thead>
<tr>
<th>Preferred Term; number of patients (%)</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 SAE</td>
<td>31 (40.3)</td>
<td>54 (36.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.3)</td>
<td>8 (5.4)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2 (2.6)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>2 (2.6)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>1 (1.3)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (3.9)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Atroventricular block complete</td>
<td>0</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>4 (5.2)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (3.9)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (3.9)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (5.2)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hereditary neuropathic amyloidosis</td>
<td>2 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia aspiration</td>
<td>2 (2.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Blue, bolded text indicated ≥3 percentage point difference in individual preferred terms in either group

No increases in observed frequency of events for patisiran compared to placebo group by system organ class:

- Cardiac disorders: 13.0% placebo, 13.5% patisiran
- Gastrointestinal disorders: 7.8% placebo, 8.8% patisiran
- Hepatobiliary disorders: 1.3% placebo, 0.7% patisiran
- Infections and infestations: 11.7% placebo, 5.4% patisiran
- Renal and urinary disorders: 6.5% placebo, 0.7% patisiran
Patisiran Phase 3 APOLLO Study Results
Safety and Tolerability: Common Adverse Events

**Majority of AEs were mild or moderate in severity**

- Peripheral edema
  - Did not result in any treatment discontinuations
  - Decreased over time
- Infusion-related reactions (IRRs)
  - Majority mild in severity
  - No severe, life-threatening or serious IRRs
  - Decreased over time
  - Led to treatment discontinuation in 1 patient

**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**

### 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 (16.9)</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 Results
Safety and Tolerability: Cardiac Subpopulation*

<table>
<thead>
<tr>
<th>Type of Adverse Event, number of patients (%)</th>
<th>Placebo (N=36)</th>
<th>Patisiran (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>35 (97.2)</td>
<td>86 (95.6)</td>
</tr>
<tr>
<td>Cardiac Disorders SOC</td>
<td>13 (36.1)</td>
<td>29 (32.2)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>18 (50.0)</td>
<td>31 (34.4)</td>
</tr>
<tr>
<td>Cardiac Disorders SOC</td>
<td>4 (11.1)</td>
<td>13 (14.4)</td>
</tr>
<tr>
<td>Cardiac Arrhythmias (HGLT)</td>
<td>11 (30.6)</td>
<td>17 (18.9)</td>
</tr>
<tr>
<td>Torsades de Pointes (SMQ)‡</td>
<td>5 (13.9)</td>
<td>7 (7.8)</td>
</tr>
<tr>
<td>Deaths</td>
<td>4 (11.1)</td>
<td>5 (5.6)</td>
</tr>
</tbody>
</table>

Blue, bolded text indicated >10 percentage point difference in either group

*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)
SOC, System Organ Class; HGLT, high-level group term; SMQ, standardized MedDRA queries
‡Torsades de Pointes SMQ is a search for reported events that may be associated with Torsades. It does not mean that these are confirmed events of Torsades de pointes; no cases of Torsades de pointes have been reported
Patisiran Phase 3 APOLLO Study Summary

hATTR amyloidosis is a multi-systemic, progressive, debilitating, life-threatening, often fatal disease with high morbidity and mortality and 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

Significant reduction in disease symptoms and disability, improvement in quality of life, nutritional status, strength, and ambulation seen with patisiran relative to placebo

Favorable and significant changes in exploratory cardiac measures in patisiran treated patients within cardiac subpopulation
• Clinically significant improvement in NT-proBNP, longitudinal strain and LV wall thickness and associated improvement in ambulation (10-MWT gait speed) relative to placebo

Patisiran was generally well tolerated in patients with hATTR amyloidosis for 18 months
• Similar frequency of deaths in patisiran and placebo groups; none were considered drug-related
• 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
• Safety in cardiac subpopulation comparable to overall study population

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

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

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