Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)
Baseline Demographics from the Phase 3 APOLLO Study
Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

• Also known as familial amyloidotic polyneuropathy (FAP)
• Autosomal dominant hereditary amyloidosis caused by deposition of mutant and wild-type transthyretin (TTR) in nerves, gastrointestinal tract, heart, and eyes
  ◦ Median survival 5-15 years
• Polyneuropathy is symmetrical with motor, sensory and autonomic components
  ◦ 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
  ◦ Tetramer stabilizers
    – Tafamidis approved in the EU for Stage 1 FAP and certain other countries outside the U.S.
    – Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study
• Continued high unmet medical need for novel therapeutics

Patisiran
Hereditary ATTR Amyloidosis with Polyneuropathy (hATTR-PN)

- International Nonproprietary Name designation for ALN-TTR02 = Patisiran (Pa-TEE-sa-ran)
- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR
- Administered by IV infusion
- Positive Phase 1 results in human volunteers
  - Data published in New Engl J Med\(^1\)
- Positive multi-dose Phase 2 results in patients with hATTR-PN
  - Data published in Orphanet J Rare Dis\(^2\)
- Phase 2 Open-Label Extension (OLE) study ongoing
  - Includes clinical endpoints measured every 6 months
  - Positive interim data reported at ISA, April 2014; ANA, Oct. 2014; AAN, March 2015; ANA, Sept. 2015; EC-ATTR, Nov 2015; AAN, April 2016
- APOLLO Phase 3 trial: enrollment complete, trial ongoing
- APOLLO-OLE ongoing

---
Patisiran Phase 3 Study Design

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

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

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

Exploratory Endpoints
- EQ-5D QOL
- NIS+7
- Serum TTR levels
- Cardiac assessments
- Grip strength
- Rasch-built Overall Disability Scale

Patients who complete the study may be eligible for patisiran treatment on Phase 3 OLE study (APOLLO-OLE), ClinicalTrials.gov Identifier: NCT02510261
<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor strength/weakness</td>
<td>192</td>
<td>Neurologic exam of lower limbs, upper limbs, and cranial nerves*</td>
</tr>
<tr>
<td>QST</td>
<td>80</td>
<td>Measures heat pain and touch pressure at multiple sites over entire body</td>
</tr>
<tr>
<td>Reflexes</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Σ NCS</td>
<td>10</td>
<td>Measures motor and sensory nerve function with focus on number of nerve fibers (action potentials)†</td>
</tr>
<tr>
<td>PBP</td>
<td>2</td>
<td>Measures autonomic function to address risk of orthostasis</td>
</tr>
<tr>
<td>Nerve Conduction Studies (NCS)</td>
<td>10</td>
<td>Measures motor and sensory nerve function with focus on number of nerve fibers (action potentials)†</td>
</tr>
</tbody>
</table>

* *NIS includes sensory competent; while mNIS+7 accounts for sensory within QST"
A total of 225 patients with hATTR-PN enrolled from December 2013 – January 2016
Patients with hATTR-PN enrolled at 44 sites in 19 countries

- United States: 19%
- France: 16%
- Taiwan: 8%
- Spain: 8%
- Japan: 7%
- Germany: 7%
- Mexico: 7%
- Portugal: 4%
- South Korea: 4%
- Sweden: 4%
- Italy: 4%
- Canada: 4%
- Turkey: 4%
- Cyprus: 4%
- Brazil: 2%
- Netherlands: 2%
- United Kingdom: 1%
- Argentina: <1%

N=225

*Data as of 01March2016
# Phase 3 Placebo-Controlled hATTR-PN Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment, N</th>
<th>Study Sites, N</th>
<th>Enrolling Countries, N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patisiran¹*</td>
<td>225</td>
<td>44</td>
<td>19</td>
</tr>
<tr>
<td>IONIS-TTR&lt;sub&gt;Rx&lt;/sub&gt;²</td>
<td>172</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Diflunisal³</td>
<td>130</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Tafamidis⁴</td>
<td>128</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

¹ClinicalTrials.gov Identifier: NCT01960348
²ClinicalTrials.gov identifier: NCT01737398
*Data as of 01March2016
## Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>225</td>
</tr>
<tr>
<td>Median Age, years (range)</td>
<td>62 years (24-82)</td>
</tr>
<tr>
<td>Gender, n (%) males</td>
<td>167 (74)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>51 (23)</td>
</tr>
<tr>
<td>Black/African or African American</td>
<td>6 (3)</td>
</tr>
<tr>
<td>White / Caucasian</td>
<td>162 (72)</td>
</tr>
<tr>
<td>Other/Missing</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>
### Patisiran Phase 3 Study*

#### Baseline Demographics, continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TTR Genotype</strong></td>
<td></td>
</tr>
<tr>
<td>V30M</td>
<td>95 (42)</td>
</tr>
<tr>
<td>nonV30M†</td>
<td>130 (58)</td>
</tr>
<tr>
<td><strong>FAP Stage</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>104 (46)</td>
</tr>
<tr>
<td>2</td>
<td>119 (53)</td>
</tr>
<tr>
<td>3</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>PND Score</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>57 (25)</td>
</tr>
<tr>
<td>II</td>
<td>65 (29)</td>
</tr>
<tr>
<td>IIIA</td>
<td>63 (28)</td>
</tr>
<tr>
<td>IIIB</td>
<td>38 (17)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Previous tetramer stabilizer use</strong></td>
<td>119 (53)</td>
</tr>
</tbody>
</table>

†Represents 57 different mutations, including GLU-89-GLN (n=13); THR-60-ALA (n=13); ALA-97-SER (n=15); SER-50-ARG (n=8), as well as numerous other mutations with ≤5 patients per group.

*Data as of 01March2016
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathy Impairment Scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mNIS+7</td>
<td>225</td>
<td>78.8 (8.0-165.0)</td>
</tr>
<tr>
<td>NIS</td>
<td>225</td>
<td>59.3 (6.0-141.6)</td>
</tr>
<tr>
<td>Patients with Cardiac Involvement†</td>
<td>122</td>
<td>(54%)</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>115</td>
<td>1461 (40-7895)</td>
</tr>
<tr>
<td>Troponin, ng/mL</td>
<td>116</td>
<td>0.1 (0.1-1.0)</td>
</tr>
<tr>
<td>LV wall thickness, cm</td>
<td>122</td>
<td>1.67 (1.3, 2.6)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>120</td>
<td>60.6 (31.8, 82.4)</td>
</tr>
<tr>
<td>mBMI, kg/m² x albumin [g/dL]</td>
<td>221</td>
<td>978.7 (522.1-1530.0)</td>
</tr>
</tbody>
</table>

†Definition of Cardiac Involvement: LV wall thickness ≥1.3cm; no history of hypertension or aortic valve disease

*Data as of 01 March 2016
Patisiran Phase 3 Study*
Baseline Correlation Data

Baseline mNIS+7 vs FAP Stage

Baseline Norfolk QOL vs FAP Stage

*Data as of 01March2016
Patisiran Phase 3 Study*
Baseline Correlation Data

Baseline mNIS+7 vs PND Score

Baseline Norfolk QOL vs PND Score

*Data as of 01March2016
APOLLO is the largest, controlled study of patients with hATTR-PN to date (N=225)

- Globally representative patient population (19 countries; 44 sites)

Patients with hATTR-PN enrolled represent a wide range of TTR mutations and disease severity

- Study includes a substantial proportion of patients with cardiac involvement (54%), enabling assessment of patisiran effects on other disease manifestations, including cardiac

Results expected in mid-2017
Acknowledgments

Thank you to the patients, investigators, study staff and collaborators participating in the Phase 3 APOLLO study

Study Investigators

- Adams, David: CHU Bicetre, France
- Arouns-Driess, Senda: Northwestern University, USA
- Attarian, Shahram: Hôpital de La Timone, France
- Barrosio, Fabio: Instituto FLENI Montaneses, Argentina
- Berk, John: Boston University, USA
- Brannagan, Thomas: Columbia University Medical Center, USA
- Buades Reines, Juan: Hospital Son Llatzer, Spain
- Campistol, Josep: Hospital Clinic, ICNU, Spain
- Coelho, Teresa: Hospital de Santo António, Portugal
- Conceicao, Isabel: Hospital de Santa Maria, Portugal
- Marques Junior, Wilson: Hospital das Clinicas da USP de Ribeirao, Brazil
- Dispenzieri, Angela: Mayo Clinic, USA
- Galan Davila, Lucia: Hospital Clinic San Carlos, Spain
- Gonzalez-Duarte, Alejandra: National Institute of Med Sciences, Mexico
- Gorevic, Peter: Mount Sinai Medical Center, USA
- Hazenberg, Bouke: UMC, Netherlands
- Ito, Mizuki: Nagoya University Hospital, Japan
- Kim, Byoung-Joon: Samsung Medical Center, South Korea
- Kristen, Arnt: Heidelberg University Hospital, Germany
- Kyriakides, Theodoros: CING, Cyprus
- Lin, Kon-Ping: Taipei Veterans General Hospital, Taiwan
- Lopate, Glenn: Washington University School of Medicine Center, USA
- Mezei, Michelle: Vancouver General Hospital, Canada
- Munoz Beamud, Francisco: Juan Ramon Jimenez Hospital, Spain
- Obici, Laura: Fondazione IRCCS Policlinico San Matte, Italy
- Oh, Jeeyoung: Konkuk University Hospital, South Korea
- O’Riordan, William: eStudySite, USA
- Parman, Yesim: Istanbul University, Turkey
- Plante-Bordeneuve, Violaine: CHU Henri, France
- Polydefkis, Michael: Johns Hopkins Bayview Medical Center, USA
- Quan, Dianna: University of Colorado - Aurora, USA
- Sabatelli, Mario: Universita Cattolica del Sacro Cuore Institute of Neurology, Italy
- Schmidt, Hartmut: University Hospital of Muenster, Germany
- Sekijima, Yoshiki: Shinshu University Hospital, Japan
- Suhr, Ole: Umea University Hospital, Sweden
- Tard, Celine: CHRU de Lille, France
- Taubel, Jorg: St George’s University of London, UK
- Tournef, Iqvato: UMHAT Aleksandrovska, Bulgaria
- Tuchman, Sascha: Duke University Medical Center, USA
- Vita, Giuseppe: Policlinico Universitario, Italy
- Yamashita, Taro: Kumamoto Univ. Hospital, Japan
- Yang, Chih-Chao: National Taiwan University Hospital, Taiwan
- Zonder, Jeffrey: Karmanos Cancer Institute, USA
- Waddington-Cruz, Marcia: Hospital Universitario Clementino Fraga Filho, Brazil

Study Collaborators

- Peter Dyck: Mayo Clinic, Rochester, MN USA

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