Clinical Update on Patisiran Phase 2 Trials in Familial Amyloidotic Polyneuropathy

April 30, 2014
Dr. Ole Suhr
RNA Interference (RNAi)
A New Class of Innovative Medicines

RNAi Therapeutics

- Harness natural pathway
  » Catalytic mechanism
  » Mediated by small interfering RNA or “siRNA”
- Therapeutic gene silencing
  » Any gene in genome
  » Distinct mechanism of action vs. other drug classes
  » Unique opportunities for innovative medicines
- Clinically validated platform
Patisiran (ALN-TTR02)
Familial Amyloidotic Polyneuropathy (FAP)

Patisiran in clinical development

- International Nonproprietary Name designation for ALN-TTR02 = Patisiran (Pa-TEE-sa-ran)
- Orphan drug status in US/EU
- Fast track designation by FDA
- Positive Phase 1 results in human volunteers
  - Data published in New England Journal of Medicine\(^1\)
- Positive multi-dose Phase 2 results in FAP patients\(^2\)
- Phase 2 Open-Label Extension (OLE) study ongoing
  - Includes clinical endpoints measured every 6 months
- APOLLO Phase 3 trial ongoing

\(^1\)Coelho et al., *N Engl J Med*;369:819-29 (2013)
\(^2\)Int'l Symp. FAP, Nov. 2013
Robust knockdown of both wild-type and mutant TTR in ATTR patients

- Open label, multi-center, multi-dose, dose escalation study
- Results (n=29) show up to 96% TTR knockdown; 84% and 87% mean TTR knockdown after 1\textsuperscript{st} and 2\textsuperscript{nd} doses in 0.30 mg/kg q3w cohort (p<0.001 vs. 0.01 mg/kg)
- 1:1 Knockdown of wild-type and mutant TTR; Similar efficacy in patients with TTR stabilizers

*Excludes post-day 28 data from one patient that experienced drug extravasation during second infusion
Patisiran Open-Label Extension (OLE) Study

FAP patients dosed on Phase 2 trial eligible to roll over onto Phase 2 OLE study

- Up to 2 years of dosing, with clinical endpoints evaluated every 6 months
  - Clinical endpoints include those in APOLLO Phase 3 study
  - Dosing at 0.30 mg/kg every 3 weeks
  - After 2 years, patients may continue treatment on another extension study
  - Subjects with left ventricular wall thickness of 13 mm or greater on transthoracic echocardiogram eligible to take part in cardiac subgroup
    - Echo and cardiac biomarkers taken every 6 months

- Study objectives
  - Primary: Safety and tolerability of long-term dosing with patisiran
  - Secondary: Effects on neurologic impairment (mNIS+7), quality of life, mBMI, disability, mobility, nerve fiber density in skin biopsies, and serum TTR levels

- Status
  - 23 Patients in current analysis based on April 3, 2014 data cut-off
  - 25 Patients enrolled to date
  - Expect enrollment to be completed in May with final N=27
# Patisiran Phase 2 OLE Preliminary Study Results*

## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>N=23</td>
</tr>
<tr>
<td>Median age</td>
<td>65.5 years (range 30-77)</td>
</tr>
<tr>
<td>Gender</td>
<td>16 males, 7 females</td>
</tr>
<tr>
<td>TTR genotype</td>
<td>Val30Met (V30M) = 16, Ser77Tyr (S77Y) = 2, Ser77Phe (S77F) = 2,</td>
</tr>
<tr>
<td></td>
<td>Tyr116Ser (Y116S) = 1, Phe64Leu (F64L) = 1, Arg54Thr (R54T) = 1</td>
</tr>
<tr>
<td>FAP stage/PND score</td>
<td>Stage 1: 20, Stage 2: 3</td>
</tr>
<tr>
<td>Concurrent tetramer stabilizer</td>
<td>10 tafamidis, 7 diflunisal, 6 none</td>
</tr>
<tr>
<td>Total doses administered to date</td>
<td>81</td>
</tr>
<tr>
<td>Median doses/patient to date</td>
<td>4 (range 1-8 doses)</td>
</tr>
</tbody>
</table>

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*Preliminary results as of April 3, 2014*
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result (mean, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum TTR (µg/mL)</td>
<td>241.4 (179.2 – 313.7)</td>
</tr>
<tr>
<td>NIS (max impairment: 244 points)</td>
<td>35.4 (4.0 - 93.4)</td>
</tr>
<tr>
<td>mNIS+7 (max impairment: 304 points)</td>
<td>55.0 (3.0 – 122.5)</td>
</tr>
<tr>
<td>mBMI</td>
<td>1030.3 (747.8 – 1410.9)</td>
</tr>
<tr>
<td>EQ-5D-5L (max impairment: 0)</td>
<td>0.8 (0.3-1.0)</td>
</tr>
<tr>
<td>10-Meter walk test (sec)</td>
<td>10.7 (5.3-22.0)</td>
</tr>
</tbody>
</table>

### Cardiac subgroup: n = 9

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result (mean, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>911.6 (105.0-2070.0)</td>
</tr>
<tr>
<td>Troponin I (ng/mL)</td>
<td>0.16 (0.0–0.7)</td>
</tr>
<tr>
<td>LV wall thickness (cm)</td>
<td>1.5 (1.3-1.7)</td>
</tr>
<tr>
<td>V30M/non-V30M (N)</td>
<td>6/3</td>
</tr>
</tbody>
</table>

*Preliminary results as of April 3, 2014*
Patisiran Phase 2 OLE Preliminary Study Results*
Correlation of mNIS+7 with 10m walk, FAP stage, PND score

*Preliminary results as of April 3, 2014
Patisiran Phase 2 OLE Preliminary Study Results*
Safety and Tolerability - TEAEs Related or Possibly Related

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>0.30 mg/kg q3w (n=23)</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction**</td>
<td>1 (4.3%)</td>
<td>Mild</td>
</tr>
<tr>
<td>Increase of diarrhea</td>
<td>1 (4.3%)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Impairment of taste</td>
<td>1 (4.3%)</td>
<td>Mild</td>
</tr>
</tbody>
</table>

**Single patient had mild, transient reactions after 2nd and 3rd doses not requiring dose interruption

- All TEAEs mild to moderate in severity
- No SAEs
- No changes in liver function tests, renal function, or hematologic parameters

*Preliminary results as of April 3, 2014
Patisiran Phase 2 OLE Preliminary Study Results*
Reduction in IRR Rate with 70-minute Microdosing Regimen

*Preliminary results as of April 3, 2014

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>60 min (# of patients)</th>
<th>70 min (# of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Phase 2 OLE</td>
<td>--</td>
<td>23</td>
</tr>
</tbody>
</table>

Patisiran
0.30 mg/kg

% Doses Associated with IRR

<table>
<thead>
<tr>
<th>Infusion Time</th>
<th>% Doses Associated with IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 min</td>
<td>1/20</td>
</tr>
<tr>
<td>70 min</td>
<td>2/99</td>
</tr>
</tbody>
</table>

*p = 0.03
Fisher’s Exact Test
Patisiran Phase 2 OLE Preliminary Study Results*

Phase 2 and Phase 2 OLE Study: TTR Knockdown After First Dose

*Preliminary results as of April 3, 2014
Patisiran Phase 2 OLE Preliminary Study Results*
Sustained TTR Knockdown of ~80% at Pre-Dose Measurement

*Preliminary results as of April 3, 2014
Phase 3 Trial of Patisiran in FAP
Study Ongoing

Randomized, double-blind, placebo-controlled, global study

- Sample size and randomization
  » N=200
  » 2:1, Patisiran vs. placebo

- Key eligibility criteria
  » V30M and non-V30M FAP
  » Baseline NIS 10-100 (FAP stages 1 and 2)

- Treatment regimen
  » Patisiran 0.30 mg/kg vs. placebo IV q3w for 18 months
  » All completers eligible for patisiran treatment on Phase 3 OLE study

Primary Endpoint
- mNIS+7 at 18 months

Secondary Endpoints
- Norfolk QOL-DN, NIS-weakness, mBMI, timed 10-meter walk, COMPASS-31 autonomic symptom score

Statistical Considerations
- Placebo mNIS+7 progression rate of 17.8 points/yr derived from natural history study of 283 FAP patients
- Study with 90% power to detect as little as 37.5% difference in ΔmNIS+7 between treatment groups with 2-sided alpha = 0.05
- Blinded interim analysis of variability planned for potential sample size re-estimation
Robust and durable TTR knockdown demonstrated in patients with multi-dose regimen in Phase 2

- Similar activity against mutant and wild-type TTR as well as both V30M and non-V30M
- Favorable safety profile to date

Phase 2 OLE study ongoing with enrollment expected to be completed in May

- Safety profile encouraging to date with significant reduction in IRR rate using 70-minute microdosing infusion regimen
- Mean baseline NIS of 35.4, in line with inclusion criteria for APOLLO Phase 3
- Preliminary assessment of TTR knockdown with 0.30 mg/kg dosed every 3 weeks shows results consistent with Phase 2 data
  - Superimposable 1st dose TTR knockdown in Phase 2 OLE (n=19) as compared to patients treated at 0.30 mg/kg dose in Phase 2 (n=19)
  - Sustained TTR knockdown of approximately 80% based on pre-dose samples with data available out to 168 days
- Interim 6-month data on approximately 20 patients, including mNIS+7 and other clinical activity endpoints, expected to be presented in late 2014

APOLLO Phase 3 study ongoing
Acknowledgments

Patisiran (ALN-TTR02) Phase 2 Investigators

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  » Umea University Hospital, Umea, Sweden
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TTR Program - Scientific Collaborators

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- Yukio Ando and Hiro Jono
  » Kumamoto University, Japan

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