Phase I Safety, Pharmacokinetic and Pharmacodynamic Results for ALN-TTR01
Preliminary Study Results

Dinah Sah, Ph.D.
November 21, 2011
ALN-TTR Program Agenda

- Background and Preclinical Data
- ALN-TTR01 Phase 1 Trial Study Design
- Safety and Pharmacokinetic Data
- Pharmacodynamic and Clinical Activity Data
- Summary
RNA Interference (RNAi)
A New Class of Innovative Medicines

RNAi Therapeutics

- Harness natural pathway
  - Catalytic mechanism
  - Mediated by small interfering RNAs or “siRNAs”
- Treat disease with therapeutic gene silencing
  - Any gene in genome
TTR Amyloidosis Program
ALN-TTR01

First RNAi drug for ATTR
- Targets wild-type and all mutant forms of TTR

Lead siRNA candidate selected
- Potent, *in vitro* IC$_{50}$ = 3 pM
- Highly specific for TTR
  - Both wild-type and mutant TTR
- Non-immunostimulatory

Formulated with 1$^{st}$ generation LNP
- LNP is multi-component formulation
  - Includes cationic lipid, fusogenic lipid, PEG lipid, and cholesterol
- Highly efficient for liver delivery
  - Achieves robust, reproducible hepatocyte-specific gene silencing
ALN-TTR01 Therapeutic Efficacy
V30M TTR Transgenic Mouse Model

ALN-TTR01 promotes regression of pathogenic mutant human TTR deposits in peripheral tissues

- >90% Regression of existing V30M hTTR tissue deposits
- Multi-dose i.v. bolus of ALN-TTR01 or control siRNA, 3 mg/kg (d0, 14, 28, 42, 56, and 70)
- Quantitation of TTR deposition by immunohistochemistry (day 77)

![Graph showing relative TTR tissue levels in various tissues](image)

**Control siRNA**

**ALN-TTR01**

- Esophagus: 100%
- Colon: 99%
- Stomach: 99%
- Sciatic nerve:
  - 97%
- Dorsal root ganglion:
  - 99%

XII International Symposium on Amyloidosis, 2010
Collaboration with M. Saraiva
ALN-TTR01 Activity
Non-Human Primates

ALN-TTR01 shows dose-dependent silencing of TTR mRNA and protein

- Single i.v. infusion of ALN-TTR01 or control siRNA
- Liver mRNA levels measured 48hr post-dose, serum protein levels measured over 28d post-dose

Keystone RNAi, Feb 2009
ALN-TTR01 Phase I Study

Study Design
- Randomized, placebo-controlled, single-blind, single-dose escalation study
  - 3:1 randomization
  - 4 patients/cohort
- Up to 36 patients with ATTR
  - Conducted in Portugal (T. Coelho, A. Silva), Sweden (O. Suhr), France (D. Adams, P. Lozeron) and UK (T. Mant, P. Hawkins)

Primary Objective
- Evaluate safety and tolerability of ALN-TTR01

Secondary Objective
- Characterize plasma PK
- Assess preliminary pharmacodynamics and clinical activity
  - Serum TTR, RBP, Vitamin A levels

Study Status
- Dose escalation completed; accruing additional patients at top dose
ALN-TTR01 Phase I Study Design

Dose levels and dosing schedule
- 0.01, 0.03, 0.1, 0.2, 0.4, 0.7 and 1.0 mg/kg
  » Option of enrolling up to 2 additional cohorts at top planned dose to further assess safety, PK and PD/clinical activity
- Single 15-min i.v. infusion; premedication including corticosteroid
ALN-TTR01 Phase I Study Results
Baseline Characteristics

- Total Patients N=31
  - ALN-TTR01: Placebo = 23:8
- Median Age = 38 years (range 21-76)
- Male:Female = 17:14
- Enrollment by Country
  - Portugal = 22
  - Sweden = 5
  - France = 3
  - UK = 1
- TTR Genotype
  - Val30Met = 28
  - Ser77Tyr = 2
  - Ser77Phe = 1
- Stage of Disease
  - 1 (Early) = 31
  - ≥ 2 = 0
- Mean BMI = 23.9 kg/m² (range 18.5-31.7)
- Mean Serum TTR at Study Entry = 266.6 μg/mL (range 117.2-393.5)

Preliminary, Study Ongoing
# ALN-TTR01 Phase I Study Results

## Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>ALN-TTR01 Dose Level (mg/kg)</th>
<th>All ALN-TTR01 (n=23)</th>
<th>Placebo** (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 (n=3)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0.03 (n=3)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0.10 (n=3)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0.20 (n=3)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0.40 (n=3)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0.70 (n=3)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>1.00 (n=5)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TEAE*</th>
<th>Infusion-Related Reaction</th>
<th>Fatigue</th>
<th>Headache</th>
<th>Constipation</th>
<th>Nausea</th>
<th>1st Degree A-V Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>0 (0.0)</td>
<td>1 (33.3)</td>
<td>0 (0.0)</td>
<td>1 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>n (%)</td>
<td>0 (0.0)</td>
<td>1 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>n (%)</td>
<td>1 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>n (%)</td>
<td>1 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>n (%)</td>
<td>1 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

No SAEs related to study drug administration

*Includes TEAEs probably or possibly related to study drug: all mild-moderate in severity. No significant increases in liver function tests (LFTs).

**One placebo patient underwent elective hospitalization for liver transplant, scored as SAE unrelated to study drug.

Preliminary, Study Ongoing
**ALN-TTR01 Phase I Study Results**

**Plasma PK Data Summary**

<table>
<thead>
<tr>
<th>ALN-TTR01 (mg/kg)</th>
<th>0.01 (n=3)</th>
<th>0.03 (n=3)</th>
<th>0.1 (n=3)</th>
<th>0.2 (n=3)</th>
<th>0.4 (n=3)</th>
<th>0.7 (n=3)</th>
<th>1.0 (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>0.03</td>
<td>0.44</td>
<td>1.14</td>
<td>2.83</td>
<td>7.49</td>
<td>15.45</td>
<td>22.11</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-last&lt;/sub&gt; (min*µg/mL)</td>
<td>0.55</td>
<td>102</td>
<td>275</td>
<td>967</td>
<td>2,722</td>
<td>9,035</td>
<td>7,385</td>
</tr>
</tbody>
</table>

- C<sub>max</sub> and AUC<sub>0-last</sub> increase linearly in approximately dose-proportional manner
ALN-TTR01 Phase I Study Results
TTR Protein Time Courses, All Dose Groups

Preliminary, Study Ongoing
ALN-TTR01 Phase I Study Results
Dose-Dependent TTR Lowering at 0.4 to 1.0 mg/kg

ALN-TTR01 single dose results in rapid, dose-dependent, and durable lowering of serum TTR protein levels

- All patients show TTR lowering at 1.0 mg/kg, ranging 25-81%
- Average nadir at approximately Day 7 of 41% relative to placebo (geometric mean vs. placebo, p=0.02)

**Preliminary, Study Ongoing**
ALN-TTR01 Phase I Study Results
Robust RNAi in Patient at 1 mg/kg ALN-TTR01

- Single 1 mg/kg dose lowers serum TTR protein, RBP and vitamin A levels
- TTR protein reduced by 81% at nadir
- Rapid onset of effect with >50% lowering at day 2
- Nadir at ~day 7
- Durable effect with ~50% lowering at day 28

Preliminary, Study Ongoing
Human Proof of Concept for RNAi Therapeutics in ATTR Patients

- ALN-TTR01 is safe and well-tolerated
- Single dose results in rapid onset, dose-dependent, and durable lowering of serum TTR protein levels
  - At 1.0 mg/kg, all patients show evidence of TTR lowering, with average nadir of 41% relative to placebo at ~day 7 (p=0.02)
- Demonstration of human proof of concept with ALN-TTR01
  - 1st Demonstration of RNAi silencing of disease-causing protein in humans
  - Continued clinical development, including ALN-TTR02 which uses 2nd generation LNP
ALN-TTR01
• Phase I study to be completed

ALN-TTR02
• 2nd generation LNP with >10-fold enhanced potency *in vivo*
• On-track for clinical development
  » IND/IND equivalent ~YE ’11
  » Planned development to commercialization
2nd Generation ALN-TTR Program
ALN-TTR02

ALN-TTR02 shows >10-fold improved \textit{in vivo} efficacy in animal models

- ALN-TTR02 uses 2nd generation MC3 LNP formulation
- Single i.v. infusion; Serum TTR levels post-dosing
- Potent, dose-dependent, and durable TTR silencing
- On track to file IND/IND equivalent ~YE ’11

Serum TTR Concentration (% Control Pre-dose)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Graph showing serum TTR concentration over time for ALN-TTR01 and ALN-TTR02.}
\end{figure}

\textbf{Oligo Ther Soc., Sep 2011}
Acknowledgments

- **ALN-TTR01 Clinical Investigators**
  - David Adams, Pierre Lozeron
    - CHU Hospital Bicetre, Le Kremlin-Bicetre, France
  - Teresa Coelho, Ana Silva
    - Hospital Geral de Santo Antonio, Porto, Portugal
  - Philip Hawkins
    - National Amyloidosis Centre, Royal Free Hospital, London, U.K.
  - Tim Mant
    - Quintiles Drug Research Unit at Guy’s Hospital, London, U.K.
  - Ole Suhr
    - Umea, Sweden

- **TTR Program - Scientific Collaborators**
  - Maria Saraiva
    - Institute of Cellular and Molecular Biology, Porto, Portugal
  - Yukio Ando and Hiro Jono
    - Kumamoto University, Japan

- Medpace
- Tekmira Pharmaceuticals
- Alnylam Pharmaceuticals
Thank you