Interim Results from Phase II Trial of ALN-TTR02
A Novel RNAi Therapeutic for the Treatment of Familial Amyloidotic Polyneuropathy

Biennial Meeting of the Peripheral Nerve Society
June 30, 2013
RNAi to treat genetic disease

- ATTR is significant orphan disease
  - ~50,000 Patients worldwide

- Clinical pathology
  - Onset ~40 to >60 yr
  - Two predominant forms
    - Familial amyloidotic polyneuropathy (FAP)
    - Familial amyloidotic cardiomyopathy (FAC)
  - Peripheral sensorimotor neuropathy, autonomic neuropathy, and/or cardiomyopathy
  - Fatal within 5-15 years

- Current treatments limited
  - Liver transplant current standard of care
    - <3,000 Patients eligible
  - EU approval of Pfizer’s Vyndaqel™ (tafamidis) for FAP
    - Complete Response Letter from FDA
Mutant TTR is genetic cause of ATTR

- Autosomal dominant with >100 defined mutations
- Misfolds and forms amyloid deposits in nerves, heart, other tissues
- Wild-type TTR also accumulates in amyloid plaques
  - Limits benefits of liver transplantation
TTR Knockdown and Clinical Outcomes

Rationale for Expected Benefit

TTR knockdown is validated endpoint

- ~50% Knockdown in other systemic amyloidoses
  » Disease improvement or stabilization
- Elimination of mutant TTR following liver transplantation
  » Disease improvement or stabilization
- Stabilization of TTR by tafamidis
  » Disease stabilization using NIS-LL endpoint
- V30M transgenic mouse model data
  » Complete amyloid regression with TTR knockdown

Gillmore et al., Lancet; 358:24-9 (2001)
ALN-TTR02 Phase I Study Results

Rapid, dose-dependent, durable, specific, and RNAi-mediated TTR knockdown
- Randomized, placebo-controlled, single-blind, single-dose escalation study in healthy volunteers (n=17)
- Up to 94% TTR knockdown at nadir and 77% knockdown sustained at 28 days
- RNAi mechanism of action confirmed by 5’RACE analysis of circulating mRNA

![Graph showing % Mean Serum TTR Knockdown Relative to Baseline over Study Days for different siRNA doses.](image)
ALN-TTR02 Multi-Dose Pharmacology
Non-Human Primate

ALN-TTR02 achieves robust TTR knockdown with q4w and q3w regimens
- NHP multi-dose study provides key data for dose/dose regimen selection in Phase III
- Nadir TTR levels of >85% with evidence for cumulative knockdown effects

% Mean Serum TTR Knockdown

Weeks

Days

Start New Dosing Paradigm
ALN-TTR02 Phase II Study

Study Design
- Open-label, multi-dose, dose escalation study in FAP patients
  - Cohorts of 3 subjects each
  - Cohorts 1-3: 0.01, 0.05, 0.15 q4w x 2 doses
  - Cohort 4-5: 0.30 mg/kg q4w x 2 doses
  - Cohort 6-9: 0.30 mg/kg q3w x 2 doses
  - Pre-medication regimen
    - Cohorts 1-6: Standard pre-medication regimen
    - Cohorts 7-9: Simplified/reduced pre-medication regimen

Primary Objective
- Evaluate safety and tolerability of multiple doses of ALN-TTR02

Secondary Objectives
- Assess preliminary clinical activity
  - Serum TTR, retinol binding protein (RBP), Vitamin A levels

Status
- Cohorts 1-6 completed/data analyzed
- Cohorts 7 and 8 patients dosed
- Cohort 9 patients scheduled
## ALN-TTR02 Phase II Study Results
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>N=19* (Cohorts 1-6)</td>
</tr>
<tr>
<td>Median age</td>
<td>64 years (range 28-76)</td>
</tr>
<tr>
<td>Gender</td>
<td>12 males, 7 females</td>
</tr>
<tr>
<td>Enrollment by country</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Portugal = 8</td>
</tr>
<tr>
<td></td>
<td>• Sweden = 6</td>
</tr>
<tr>
<td></td>
<td>• France = 5</td>
</tr>
<tr>
<td>TTR genotype</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Val30Met (V30M) = 15</td>
</tr>
<tr>
<td></td>
<td>• Ser77Tyr (S77Y) = 2</td>
</tr>
<tr>
<td></td>
<td>• Ser77Phe (S77F) = 1</td>
</tr>
<tr>
<td></td>
<td>• Tyr116Ser (Y116S) = 1</td>
</tr>
<tr>
<td>Stage of disease</td>
<td>1 (Early) = 19</td>
</tr>
<tr>
<td>Concurrent tetramer stabilizer</td>
<td>11 tafamidis, 5 diflunisal</td>
</tr>
<tr>
<td>Mean serum TTR at study entry</td>
<td>251 μg/mL (range 163-397)</td>
</tr>
</tbody>
</table>

*Additional patient enrolled in Cohort 1; received one dose due to protocol amendment*
All TEAEs mild or moderate in severity

- Mild infusion reaction in one subject at 0.3 mg/kg; completed dose with slowing of infusion rate
- An episode of self-limiting cellulitis of the arm (SAE) occurred as a result of drug extravasation at infusion site in a patient with poor IV access
- No changes in liver function tests, renal function, or hematologic parameters
ALN-TTR02 Phase II Study Results
Dose Response and Duration of TTR Knockdown

ALN-TTR02 Treatment Groups
- 0.01 mg/kg q4w (n=4*)
- 0.05 mg/kg q4w (n=3)
- 0.15 mg/kg q4w (n=3)
- 0.30 mg/kg q4w (n=6+)
- 0.30 mg/kg q3w (n=3)

* Includes first dose data from additional patient prior to protocol amendment
+ Excludes post-day 28 data from patient that experienced drug extravasation during second infusion
## ALN-TTR02 Phase II Study Results

### Summary of Serum TTR Knockdown by Dose Group

<table>
<thead>
<tr>
<th>Dose Group (mg/kg)</th>
<th>Dose 1</th>
<th></th>
<th></th>
<th>Dose 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum TTR KD (%)</td>
<td>TTR KD @ Nadir (Mean % ±SD)</td>
<td></td>
<td>Maximum TTR KD (%)</td>
<td>TTR KD @ Nadir (Mean % ±SD)</td>
</tr>
<tr>
<td>0.01 q4w (n=4+)</td>
<td>37.8</td>
<td>20.1 ± 13.2</td>
<td></td>
<td>34.4</td>
<td>32.9 ± 2.3</td>
</tr>
<tr>
<td>0.05 q4w (n=3)</td>
<td>58.0</td>
<td>48.4 ± 16.2</td>
<td></td>
<td>58.5</td>
<td>46.9 ± 15</td>
</tr>
<tr>
<td>0.15 q4w (n=3)</td>
<td>81.7</td>
<td>74.5 ± 6.8***</td>
<td></td>
<td>86.0</td>
<td>77 ± 7.8**</td>
</tr>
<tr>
<td>0.30 q4w (n=6^)</td>
<td>87.5</td>
<td>82.6 ± 5.9***</td>
<td></td>
<td>90.8</td>
<td>84.8 ± 10.5***</td>
</tr>
<tr>
<td>0.30 q3w (n=3)</td>
<td>83.8</td>
<td>83.1 ± 1.1***</td>
<td></td>
<td>92.8</td>
<td>87.4 ± 5.9***</td>
</tr>
</tbody>
</table>

+ Includes first dose data from additional patient prior to protocol amendment

^ Excludes post-day 28 data from patient that experienced drug extravasation during second infusion

**p < 0.01 vs. 0.01 mg/kg group; p values from ANCOVA models including baseline TTR as covariate and dose group as factor

*** p < 0.001 vs. 0.01 mg/kg group
ALN-TTR02 Phase II Study Results
TTR Knockdown in V30M Patients: WT vs Mutant

TTR-V30M (% remaining from baseline)

TTR-Wild Type (% remaining from baseline)

r² = 0.95
p < 10⁻¹⁵

0.30 mg/kg, q4w (n=5*)

0 10 20 30 40 50 60 70 80 90 100

Day

% Mean Serum TTR Knockdown Relative to Baseline

V30M  Wild Type

*1 of 6 subjects not V30M (no data)
ALN-TTR02 Phase II Study Results

TTR: Vit A/RBP Correlation

RBP: $r^2 = 0.85$, $p < 10^{-15}$
Vitamin A: $r^2 = 0.84$, $p < 10^{-15}$
ALN-TTR02 Phase II Study Results
TTR Knockdown at 0.30 mg/kg in Patients on Tetramer Stabilizer

0.30 mg/kg q4w and q3w Cohorts

% Mean Serum TTR Knockdown Relative to Baseline

- ALN-TTR02 (n=1)
- ALN-TTR02 + diflunisal (n=3)
- ALN-TTR02 + tafamidis (n=5)
Multiple doses of ALN-TTR02 generally safe and well tolerated

- No significant AEs associated with drug up through 0.30 mg/kg
- Favorable safety profile with 0.30 mg/kg administered either q3w or q4w
  - No abnormalities in liver function tests, renal function, or hematologic parameters
  - Mild infusion-related reaction seen in one subject
    - Able to complete dose with slowing of infusion rate
  - Single episode of self-limiting cellulitis of arm (SAE) due to drug extravasation in patient with poor IV access

Rapid and durable knockdown of serum TTR achieved with 0.30 mg/kg ALN-TTR02 dosed every 3 or 4 weeks

- Statistically significant knockdown of serum TTR at doses of 0.15 mg/kg (p<0.01) and 0.30 mg/kg (p<0.001)
- Mean TTR knockdown at nadir of 82.6% and 84.8% following doses 1 and 2, respectively, at 0.30 mg/kg q4w (p<0.001 vs. 0.01 mg/kg)
  - Maximum TTR knockdown of up to 90.8%
- Mean TTR knockdown at nadir of 83.1% and 87.4% following doses 1 and 2, respectively, at 0.30 mg/kg q3w (p<0.001 vs. 0.01 mg/kg)
  - Maximum TTR knockdown of up to 92.8%
- Both mutant and wild-type TTR suppressed to same extent (r2=0.95, p<0.001)
- Similar degree of TTR knockdown in patients on concurrent TTR stabilizers (e.g., tafamidis or diflunisal)
Next Steps

Ongoing Phase II Study in FAP

- Completion/data analysis of remaining 3 cohorts (cohorts 7-9)
  - 0.30 mg/kg q3w using simplified/reduced premedication regimen
    - To date, dosing in cohorts 7 and 8 with no reported infusion-related reactions
- Final Phase II data to be presented at IX\textsuperscript{th} International Symposium on FAP in Rio de Janeiro, Brazil
  - November 10-13, 2013
- Phase II extension study to start in Q3, 2013
  - Up to 2 years of dosing at 0.30 mg/kg for patients in Phase II
  - Includes clinical endpoints (e.g., NIS)

Phase III Study in FAP

- Plan to initiate by end of 2013
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ALN-TTR02 Phase II Investigators

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  » Kumamoto University, Japan

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