International Symposium on Familial Amyloidotic Polyneuropathy

Clinical Updates on ALN-TTR Programs
Patisiran (ALN-TTR02) and ALN-TTRsc for the Treatment of Transthyretin Amyloidosis

November 10-13, 2013
**RNAi Therapeutics**

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

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
- ALN-TTR siRNA suppresses hepatic production of mutant and WT TTR
RNAi Delivery to Liver Solved
IV and SC Platforms: Pre-clinical

**Enables advancement of innovative medicines to patients**
- Potent, rapid, and durable target gene silencing with lipid nanoparticle (LNP) technology and IV dosing
- Potent, rapid, and durable target gene silencing with proprietary GalNAc-conjugate technology and SC dosing with wide therapeutic index

![Graph showing % TTR mRNA silencing (Relative to Control)](image1)

![Graph showing % TTR mRNA silencing (Relative to Control)](image2)

RNAi Therapeutic Hypothesis for Treatment of ATTR

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 and recovery,

Patisiran (ALN-TTR02) and ALN-TTRsc act to knock down both mutant and wild type TTR production.
Patisiran (ALN-TTR02)
Familial Amyloidotic Polyneuropathy (FAP)

Patisiran in clinical development

- International Nonproprietary Name designation for ALN-TTR02 = Patisiran (pa-TEE-sa-ran)
- Positive Phase I results in human volunteers
  » Data published in *New England Journal of Medicine*
- Positive multi-dose Phase II results in FAP patients
- Phase II Open-Label Extension (OLE) study initiated
  » Includes clinical endpoints measured every 6 months
- APOLLO Phase III trial initiated
Patisiran 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

Patisiran 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
Patisiran 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

Primary Objective
- Evaluate safety and tolerability of multiple doses of patisiran

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

Status
- Dosing completed
## Patisiran 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=29 (Cohorts 1-9)</td>
</tr>
<tr>
<td>Median Age</td>
<td>62 years (range 28-76)</td>
</tr>
<tr>
<td>Gender</td>
<td>20 males, 9 females</td>
</tr>
<tr>
<td>Enrollment by Country</td>
<td>• Portugal = 9</td>
</tr>
<tr>
<td></td>
<td>• France = 8</td>
</tr>
<tr>
<td></td>
<td>• Sweden = 6</td>
</tr>
<tr>
<td></td>
<td>• Spain = 3</td>
</tr>
<tr>
<td></td>
<td>• Germany = 1</td>
</tr>
<tr>
<td></td>
<td>• Brazil = 1</td>
</tr>
<tr>
<td></td>
<td>• USA = 1</td>
</tr>
<tr>
<td>TTR Genotype</td>
<td>• Val30Met (V30M) = 22</td>
</tr>
<tr>
<td></td>
<td>• Ser77Tyr (S77Y) = 2</td>
</tr>
<tr>
<td></td>
<td>• Ser77Phe (S77F) = 2</td>
</tr>
<tr>
<td></td>
<td>• Tyr116Ser (Y116S) = 1</td>
</tr>
<tr>
<td></td>
<td>• Phe64Leu (F64L) = 1</td>
</tr>
<tr>
<td></td>
<td>• Arg54Thr (R54T) = 1</td>
</tr>
<tr>
<td>FAP Stage</td>
<td>Stage 1 = 25</td>
</tr>
<tr>
<td></td>
<td>Stage 2 = 4</td>
</tr>
<tr>
<td>Concurrent Tetramer Stabilizer</td>
<td>14 tafamidis, 6 diflunisal, 9 none</td>
</tr>
<tr>
<td>Mean Serum TTR at Study Entry</td>
<td>246 µg/mL (range 163-397)</td>
</tr>
</tbody>
</table>
# Patisiran Phase II Study Results

## Safety and Tolerability - TEAEs Related or Possibly Related

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>0.01 mg/kg q4w (n=4)</th>
<th>0.05 mg/kg q4w (n=3)</th>
<th>0.15 mg/kg q4w (n=3)</th>
<th>0.30 mg/kg q4w (n=7)</th>
<th>0.30 mg/kg q3w (n=12)</th>
<th>Overall Patisiran (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (42.9%)</td>
<td>0</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>Cellulitis due to drug extravasation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (14.3%)</td>
<td>0</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Polyuria</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (14.3%)</td>
<td>0</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Facial erythema</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8.3%)</td>
<td>1 (3.4%)</td>
</tr>
</tbody>
</table>

- Majority of TEAEs were mild or moderate
- Two SAEs reported
  - Episode of severe nausea/vomiting in patient with autonomic involvement by FAP; discontinued study after 1 dose
  - Episode of self-limiting cellulitis of the arm occurred as a result of drug extravasation at infusion site
- No changes in liver function tests, renal function, or hematologic parameters
Patisiran Phase II Study Results
Dose Response and Duration of TTR Knockdown

Robust knockdown of TTR in ATTR patients

- Results (n=28) show up to 96% TTR knockdown; 84% and 87% mean TTR knockdown after 1st and 2nd doses in 0.30 mg/kg q3w cohort (p<0.001 vs. 0.01 mg/kg)

* 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
# Patisiran 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>Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<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>22.1 ± 12.5</td>
</tr>
<tr>
<td>0.05 q4w (n=3)</td>
<td>58.0</td>
<td>48.4 ± 16.2</td>
</tr>
<tr>
<td>0.15 q4w (n=3)</td>
<td>81.7</td>
<td>74.5 ± 6.8***</td>
</tr>
<tr>
<td>0.30 q4w (n=6^)</td>
<td>87.5</td>
<td>82.6 ± 5.9***</td>
</tr>
<tr>
<td>0.30 q3w (n=12)</td>
<td>94.2</td>
<td>83.8 ± 5.1***</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 < 0.05 vs. 0.01 mg/kg group

*** p < 0.001 vs. 0.01 mg/kg group

*p values from ANCOVA models including baseline TTR and dose groups as factors; models significant at p < 0.001 for Dose 1, p < 0.001 for Dose 2
Patisiran Phase II Study Results
TTR Knockdown in V30M Patients: WT vs Mutant

Wild Type vs. Mutant
V30M Patients

TTR Knockdown by Patisiran
0.30 mg/kg qw4 cohorts

*1 of 6 subjects not V30M (no data)
Patisiran Phase II Study Results
TTR KD with Patisiran in Patients on Tetramer Stabilizer

**Baseline TTR Levels by Stabilizer Use**
All cohorts

- No stabilizer (n=9)
- Tafamidis (n=14)
- Diflunisal (n=6)

*p<0.001 by ANOVA*

**TTR Knockdown by Patisiran**
0.30 mg/kg cohorts

- Patisiran (n=5)
- Patisiran + diflunisal (n=3)
- Patisiran + tafamidis (n=10)

Mean Baseline Serum TTR (µg/mL)

% Mean Serum TTR Knockdown Relative to Baseline

Day
Patisiran Open-Label Extension (OLE) Study

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

- Up to 2 years of dosing, with clinical endpoints evaluated every 6 months
  - Clinical endpoints include those in APOLLO Phase III study
  - Dosing at 0.30 mg/kg every 3 weeks
  - After 2 years, patients may continue treatment on another extension study until drug commercially available

- 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
  - Open and enrolling
  - Plan to report data once annually, beginning 2014
Phase III Trial of Patisiran in FAP
Study Initiated

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

- Sample size and randomization
  - N=200
  - 2:1, Patisiran vs Placebo
  - Stratify for baseline NIS, early onset (age < 50) V30M vs all other mutations (including late-onset V30M), prior tafamidis/diflunisal use vs no prior use

- 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 q3 weeks x 18 months
  - All completers eligible for patisiran treatment on Phase III 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 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
ALN-TTRsc
Familial Amyloidotic Cardiomyopathy (FAC)

**ALN-TTRsc in clinical development**

- Subcutaneous delivery
- Positive Phase I study results
  - Normal healthy volunteer study in UK
  - Data presented at Annual Scientific Meeting of Heart Failure Society of America, September 2013
- Pilot Phase II study start expected in late 2013
- Phase III start planned for 2014
ALN-TTRsc Phase I Study

Study Design
- Randomized, double-blinded, placebo-controlled SAD and MAD study in healthy volunteers
  - 3:1 randomization (ALN-TTRsc:Placebo)
  - 4 subjects/cohort
  - Cohort 1-4: single doses of 1.25, 2.5, 5.0 and 10 mg/kg
  - Cohort 5-7: multiple doses of 2.5, 5.0 and 10 mg/kg
    - Multi-dose schedule: Daily x 5, followed by weekly x 5

Primary Objective
- Evaluate safety and tolerability of subcutaneously administered single and multiple doses of ALN-TTRsc

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

Status
- Dosing completed; analysis ongoing
ALN-TTRsc Phase I Study
TTR Knockdown in Multi-Dose Cohorts

Rapid, dose-dependent, consistent, and durable knockdown of serum TTR
- Statistically significant knockdown of serum TTR at all doses evaluated (p<0.01)
- Consistent level of TTR knockdown with weekly dosing; durable effects lasting weeks after last dose
- Mean TTR knockdown of 87.5% and 92.4% at 5.0 and 10.0 mg/kg, respectively
  » Maximum TTR knockdown of up to 94%

Heart Failure Society of America, Sept. 2013
ALN-TTRsc Phase I Study
Human Translation of GalNAc-siRNA Conjugate Platform

- Excellent correlation of human to non-human primate TTR knockdown on mg/kg basis
- Demonstrates human translation of GalNAc-siRNA conjugate platform

Heart Failure Society of America, Sept. 2013
# ALN-TTRRsc Phase I Study
## Safety and Tolerability

### TEAEs Definitely or Possibly Related

<table>
<thead>
<tr>
<th>Reported AEs</th>
<th>Single Dose</th>
<th>Multiple Doses</th>
<th>Total TTRsc (n=21)</th>
<th>PBO (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.25 mg/kg</td>
<td>2.5 mg/kg</td>
<td>5.0 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td></td>
<td>(n=3)</td>
<td>(n=3)</td>
<td>(n=3)</td>
<td>(n=3)</td>
</tr>
<tr>
<td>Injection Site Reaction (ISRs)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>3 (100%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td></td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>3 (100%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (10%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Local Erythema</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
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<td>1 (33%)</td>
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<td>Local Bruise</td>
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<td></td>
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<td>0</td>
<td>1 (33%)</td>
<td>0</td>
</tr>
<tr>
<td>Local Tenderness</td>
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<td>Abdominal Tenderness</td>
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<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

*Adverse events through Day 28 (Cohorts 1-4), through Day 63 (Cohort 5-6) and through Day 42 (Cohort 7)*

- All TEAEs mild or moderate in severity; no SAEs
- ISRs: generally mild, resolving within ~2 hours of onset
- No study discontinuations, flu-like symptoms, or lab abnormalities
Patisiran and ALN-TTRsc Programs

**Summary**

**Patisiran (ALN-TTR02) for FAP**
- Robust and durable TTR knockdown demonstrated in patients with multi-dose regimen in Phase II
  - Similar activity against mutant and wild-type TTR
  - Favorable safety profile
- Phase II OLE study currently enrolling
  - Evaluating safety of long-term dosing and includes clinical endpoints
- APOLLO Phase III study in FAP initiated

**ALN-TTRsc for FAC**
- Positive data from Phase I trial in healthy volunteers
  - Human POC for GalNAc-siRNA delivery approach
- Pilot Phase II trial in FAC patients expected to start in Q4
- Phase III trial expected to start in 2014
Patisiran (ALN-TTR02) Phase II Investigators

- David Adams
  » CHU Hospital Bicetre, Le Kremlin-Bicetre, France
- Teresa Coelho, Ana Silva
  » Hospital Geral de Santo Antonio, Porto, Portugal
- Ole Suhr
  » Umea University Hospital, Umea, Sweden
- Isabel Conceicao
  » Centro Hospitalar Lisboa Norte-Hospital de Santa Maria, Lisboa, Portugal
- Juan Buades
  » Hospital Son Llatzer, Palma de Mallorca, Spain
- Josep Campistol
  » Hospital Clinic Barcelona Instituto, Barcelona, Spain
- Jean Pouget
  » Hôpital de La Timone, Marseille, France
- Hartmut Schmidt
  » University Hospital of Muenster, Muenster, Germany
- Marcia Waddington-Cruz
  » Hospital Universitário, Rio de Janeiro, Brazil
- John Berk
  » Boston University, Boston, MA USA

ALN-TTRsc Phase I Investigators

- Joseph Chiesa
  » Covance Clinical Research Unit, Leeds, United Kingdom
- Gary Peters
  » Hammersmith Medicines Research, London, United Kingdom

TTR Program - Scientific Collaborators

- Maria Saraiva
  » Institute of Cellular and Molecular Biology, Porto, Portugal
- 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