A Randomized, Single-Blind, Placebo-Controlled, Phase 1/2 Study of ALN-AAT, an Investigational RNAi Therapeutic for the Treatment of Alpha-1 Antitrypsin Deficiency Associated Liver Disease: Interim Study Results

12th Annual Meeting of the Oligonucleotide Therapeutics Society (OTS)
28 September 2016
Alpha 1 Antitrypsin (AAT) Deficiency

Background

AAT is a serine proteinase inhibitor (serpin)
- Inhibits neutrophil elastase, trypsin, thrombin, chymotrypsin, etc
- Abundant plasma protein, primarily synthesized in hepatocytes

AAT deficiency
- “PiZZ” phenotype accounts for 95% of AAT-deficient patient population
- Z allele likely arose in N Europe, present in up to 5% of the population
- Z allele has point mutation Glu342Lys
- Autosomal codominant inheritance of disease

- PiZ has slow rate of protein folding, permitting polymerization of intermediate which accumulates in hepatocyte ER
- Failure of secretion results in peripheral deficiency
  - Lack of protease inhibition primarily manifests as lung disease: early onset emphysema
- Hepatocyte accumulation results in liver disease
  - Infantile cholestatic hepatitis - usually self-limiting, but progressive liver disease in minority
  - Progressive liver fibrosis
  - Cirrhosis
  - Hepatocellular carcinoma
Z-AAT mRNA expression in hepatocytes

Reduced Z-AAT polymers in hepatocytes

Suppression of hepatocyte Z-AAT protein production permits clearance of the accumulated abnormal protein from the liver, permitting stabilization and potentially reversal of liver disease

Reduced hepatocyte damage

Decrease in liver fibrosis and HCC
ALN-AAT Phase 1/2 Study Design


- **0.1 mg/kg x 1 SC, N=4**
- **0.3 mg/kg x 1 SC, N=4**
- **1.0 mg/kg x 1 SC, N=4**
- **3.0 mg/kg x 1 SC, N=4**
- **6.0 mg/kg x 1 SC, N=4**

Healthy adult volunteers
Outcome evaluations: Safety and Pharmacodynamic Response (reduction in plasma AAT level)

Part B: Multiple-Ascending Dose (MAD) | Randomized 4:2, Single-blind, Placebo-controlled

- **1.0 mg/kg, q28d ×4 SC, N=6**

Healthy adult volunteers
Outcome evaluations: Safety and Pharmacodynamic Response (reduction in plasma AAT level)

Clinicaltrials.gov identifier NCT02503683
# ALN-AAT Phase 1/2 Interim Study Results

**Demographics: Part A + B (Healthy Volunteers)**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Results</th>
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<tbody>
<tr>
<td>Number enrolled</td>
<td>N=26 (ALN-AAT:Placebo = 19:7)</td>
</tr>
<tr>
<td>Median Age</td>
<td>28 years (range: 18 - 60)</td>
</tr>
<tr>
<td>Gender, n</td>
<td>Female: 13</td>
</tr>
<tr>
<td></td>
<td>Males: 13</td>
</tr>
<tr>
<td>Race, n</td>
<td>White / Caucasian: 13</td>
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<tr>
<td></td>
<td>African: 5</td>
</tr>
<tr>
<td></td>
<td>Asian: 3</td>
</tr>
<tr>
<td></td>
<td>Other: 5</td>
</tr>
</tbody>
</table>
ALN-AAT Phase 1/2 Interim Study Results
Summary of Safety

ALN-AAT was generally well-tolerated in Parts A and B of Study ALN-AAT-001

No drug-related serious adverse events (SAEs) or discontinuations due to adverse events (AEs)

Part A: Total of 57 AEs reported in 5 placebo and 14 ALN-AAT subjects
• 15 related or possibly related AEs were reported in 7 subjects
  ◦ Diarrhea, dyspnea (normal spirometry), nasopharyngitis, elevated ALT/AST, elevated CK, influenza, worsening allergy, headache, injection site bruise, injection site dysesthesia, abdominal pain
• No injection site reactions were reported

Part B: Total of 23 AEs reported in 2 placebo and 4 ALN-AAT subjects
• 6 related or possibly related AEs were reported in 2 subjects*
  ◦ Nasopharyngitis, headache, injection site bruise, oropharyngeal pain, psoriasis, subacute spongiotic dermatitis
• No injection site reactions were reported

No clinically significant changes in vital signs or EKG

Data transfer: 30Jun2016
*One AE of ligament sprain with missing relatedness assessment is not included in this count
ALN-AAT Phase 1/2 Interim Study Results
Pharmacodynamics: Serum AAT Levels, Part A (Single Dose)

6.0 mg/kg dose group -
- Max AAT knockdown (KD): 88.9%
- Mean maximal KD: 83.9 ± 2.6%
- Mean AAT KD at ~6 months: 75.0 ± 1.2%
ALN-AAT Phase 1/2 Interim Study Results
Pharmacodynamics: Serum AAT Levels, Part B (Multiple Doses)

Data transfer: 30Jun2016
AAT Knockdown at 1mg/kg multidose comparable to 3 and 6 mg/kg single doses

Days since first dose

Mean [± SEM] AAT Level Relative to Baseline

- Single Dose 3.0 mg/kg
- Single Dose 6.0 mg/kg
- Multiple Doses 1.0 mg/kg q28d ×4

Data transfer: 30Jun2016
ALN-AAT Phase 1/2 Interim Study Results
Pharmacodynamics: Dichotomous Pattern Explained by Target SNP

SNP confers a single base mismatch between drug and target
Prevalence up to 30% in some populations
SNP is not co-inherited with Z allele

Data transfer: 30Jun2016
ALN-AAT Phase 1/2 Interim Study Results
Liver Transaminases, Part A

**Dose**
- Placebo
- 0.1 mg/kg
- 0.3 mg/kg
- 1.0 mg/kg
- 3.0 mg/kg
- 6.0 mg/kg

**ALT**
- Levels for each dose are shown with a 1x ULN threshold.

**AST**
- Levels for each dose are shown.

**Days Since Dose**
- Data transfer: 30Jun2016

**N**
- Placebo: 5
- 0.1 mg/kg: 3
- 0.3 mg/kg: 3
- 1.0 mg/kg: 3
- 3.0 mg/kg: 3
- 6.0 mg/kg: 3
ALN-AAT Phase 1/2 Interim Study Results
Liver Transaminases, Part B

Placebo

ALT

AST

1.0 mg/kg

Days Since First Dose

Data transfer: 30Jun2016
ALN-AAT Phase 1/2 Interim Study Results

Summary and Next Steps

ALN-AAT clinically well tolerated with single or multiple (4) doses

Dose-dependent, potent and durable suppression of AAT was observed

Diminution of PD effect in presence of SNP in target sequence demonstrates specificity of drug mechanism

Asymptomatic, reversible, dose-dependent increase in hepatic transaminase observed

Next Steps

• Since the target patient population has established liver disease, plan to hold further development of this molecule
• Identification of a 2nd generation molecule is in progress, CTA expected in 2017
Thank you