Phase I Safety, Pharmacokinetic and Pharmacodynamic Results for ALN-PCS
A Novel RNAi Therapeutic for the Treatment of Hypercholesterolemia

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Unmet need
- Multiple studies indicate that many patients (up to 80%) are not at LDL-C goals on statins\(^1,2\)

Genetics
- GOF mutations associated with hypercholesterolemia and premature CHD
- LOF mutations associated with hypocholesterolemia and decreased CHD risk\(^3,4\)

Animal models
- PCSK9 KD leads to increased LDLR and decreased LDL-C\(^5\)

Impact of current therapy
- Statins increase PCSK9 expression, which may limit their efficacy\(^6\)

\(^1\)Jacobson et al., NHANES II, Arch Intern Med; 160:1361-1369 (2000)
\(^3\)Abifadel et al., Nat Genet; 34:154-156 (2003)
\(^5\)Horton et al., J. Lipid Res; 50:S172-S177 (2009)
\(^6\)Welder et al., J Lipid Res; 51:2714-2721 (2010)
PCSK9 role in both intracellular and extracellular degradation of LDLR

A. Intracellular Pathway

B. Extracellular Pathway

PCSK9 Mechanism
PCSK9 Mechanism

PCSK9 role in both intracellular and extracellular degradation of LDLR

A. Intracellular Pathway

B. Extracellular Pathway

PCSK9 Blockers Inhibit only extracellular functions
PCSK9 Mechanism

PCSK9 role in both intracellular and extracellular degradation of LDLR

A. Intracellular Pathway
B. Extracellular Pathway

PCSK9 Blockers Inhibit only extracellular functions

PCSK9 Synthesis Inhibitors
Inhibit PCSK9 synthesis and both intracellular and extracellular functions
ALN-PCS Phase I Study
Design and Status

Study Design
- Randomized, single-blind, placebo-controlled, single-dose escalation study
  - 3:1 Randomization
  - 4 Subjects/cohort (except 0.250 and 0.400 mg/kg cohorts with 8 subjects, 6:2)
  - 6 Dose levels (0.015-0.400 mg/kg)
- Healthy volunteers with elevated baseline LDL-C (>116mg/dL), not on statin or lipid therapy

Dose levels and dosing schedule
- 0.015, 0.045, 0.090, 0.150, 0.250 (n=6), and 0.400 (n=6) mg/kg
- Single 60-min i.v. infusion
- Pre-medication including corticosteroid, H1/H2 blocker and acetaminophen

Primary objective
- Safety and tolerability

Secondary objectives
- Assess pharmacodynamics and clinical activity
  - Plasma PCSK9 protein and LDL-C levels
- Characterization of pharmacokinetics

Study Status
- Two study centers in the UK participating
- Active, but not recruiting
## ALN-PCS Phase I Subjects
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>N=32 (ALN-PCS:Placebo=24:8)</td>
</tr>
<tr>
<td>Median Age</td>
<td>46 years (range 25-61)</td>
</tr>
<tr>
<td>Gender</td>
<td>30 males, 2 females</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>28.5 (range 23.4-33.9)</td>
</tr>
<tr>
<td>Mean baseline PCSK9</td>
<td>1031 ng/mL (range 453-1556)</td>
</tr>
<tr>
<td>Mean baseline LDL-C</td>
<td>145.7 mg/dL (range 113.5-237.6)</td>
</tr>
</tbody>
</table>
ALN-PCS Safety and Tolerability

Overall TEAEs ≥ 10%

- All TEAEs mild or moderate in severity
- No SAEs related to study drug administration
  - One subject at 0.045 mg/kg dose level was diagnosed with bilateral PEs and DVTs; determined by PI to be unrelated to study drug given subject's prior history and symptoms prior to study drug administration
- No laboratory abnormalities (LFTs, CRP, cytokines, or complement)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>0.015 (n=3)</th>
<th>0.045 (n=3)</th>
<th>0.090 (n=3)</th>
<th>0.150 (n=3)</th>
<th>0.250 (n=6)</th>
<th>0.400 (n=6)</th>
<th>Overall ALN-PCS02 (N=24)</th>
<th>Placebo (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rash</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0 (00.0)</td>
<td>0 (00.0)</td>
<td>4 (66.7)</td>
<td>6 (100)</td>
<td>12 (50.0)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>headache</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>0 (00.0)</td>
<td>0 (00.0)</td>
<td>1 (16.7)</td>
<td>5 (20.8)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>hiccups</td>
<td>2 (66.7)</td>
<td>0 (00.0)</td>
<td>0 (00.0)</td>
<td>0 (00.0)</td>
<td>0 (00.0)</td>
<td>2 (33.3)</td>
<td>4 (16.7)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>cold symptoms</td>
<td>0 (00.0)</td>
<td>1 (33.3)</td>
<td>0 (00.0)</td>
<td>2 (66.7)</td>
<td>1 (16.7)</td>
<td>0 (00.0)</td>
<td>4 (16.7)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>paraesthesia</td>
<td>1 (33.3)</td>
<td>0 (00.0)</td>
<td>0 (00.0)</td>
<td>0 (00.0)</td>
<td>2 (33.3)</td>
<td>3 (12.5)</td>
<td>2 (25.0)</td>
<td></td>
</tr>
<tr>
<td>polyuria/dysuria</td>
<td>1 (33.3)</td>
<td>0 (00.0)</td>
<td>0 (00.0)</td>
<td>0 (00.0)</td>
<td>1 (16.7)</td>
<td>2 (8.4)</td>
<td>1 (12.5)</td>
<td></td>
</tr>
</tbody>
</table>

Data as of April 19

Alnylam Pharmaceuticals
Rapid, dose-dependent, and durable PCSK9 knockdown after single dose

- 68% mean reduction in 0.400 mg/kg (p<0.0001)
- Up to 84% reduction in 0.400 mg/kg group

* Data for n=6 from the 0.400 mg/kg group through Day 14 only
Rapid, dose-dependent, and durable LDL-C reduction after single dose

- 41% mean reduction in 0.400 mg/kg group (p<0.01)
- Up to 50% reduction in 0.400 mg/kg group

* Data for n=6 from the 0.400 mg/kg group through Day 14 only
### ALN-PCS Clinical Efficacy
#### Nadir and Target LDL-C

**Post-Dose Nadir LDL-C (mg/dL) Through Day 28***

<table>
<thead>
<tr>
<th>ALN-PCS Dose Groups (mg/kg)</th>
<th>Minimum LDL-C (mg/dL)</th>
<th>Mean Per Group Post-dose Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo n=8</td>
<td>0.045 n=3</td>
<td></td>
</tr>
<tr>
<td>0.015 n=3</td>
<td>0.090 n=3</td>
<td></td>
</tr>
<tr>
<td>0.150 n=6</td>
<td>0.250 n=6</td>
<td></td>
</tr>
<tr>
<td>0.400* n=6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANOVA: Dosed groups: p < 0.01

**Proportion Subjects Achieving LDL-C Target Levels**

<table>
<thead>
<tr>
<th>Dose Group mg/kg</th>
<th>100 mg/dL**</th>
<th>70 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3/8</td>
<td>0/8</td>
</tr>
<tr>
<td>0.015</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>0.045</td>
<td>1/3</td>
<td>0/3</td>
</tr>
<tr>
<td>0.090</td>
<td>1/3</td>
<td>0/3</td>
</tr>
<tr>
<td>0.150</td>
<td>3/3</td>
<td>0/3</td>
</tr>
<tr>
<td>0.250</td>
<td>5/6</td>
<td>1/6</td>
</tr>
<tr>
<td>0.400*</td>
<td>5/6</td>
<td>2/6</td>
</tr>
</tbody>
</table>

** p<0.05

* 0.400 mg/kg through Day 14

Data as of April 19
Correlation of PCSK9 and LDL-C Levels

Data as of April 19

ALN-PCS dose group

- Placebo
- 0.150 mg/kg
- 0.015 mg/kg
- 0.250 mg/kg
- 0.045 mg/kg
- 0.400 mg/kg
- 0.090 mg/kg

* Data for n=6 from 0.400 mg/kg group through Day 14 only
Efficacy Independent of Baseline PCSK9 Levels

Baseline PCSK9 Distribution

All Subjects

Baseline PCSK9 (ng/mL) SD Relative to mean

- < 0.5 below (n=13)
- within 0.5 (n=9)
- > 0.5 above (n=10)

PCSK9 and LDL-C Reduction by Baseline PCSK9 Levels
(0.150, 0.250, 0.400 mg/kg)

Maximum Per-Subject Percent Reduction

- Low
- Medium
- High

Baseline PCSK9 levels SD Relative to mean

Data as of April 19

Alnylam Pharmaceuticals
Effects on Total Cholesterol and HDL-C

Total Cholesterol (Day 14)
Relative to Baseline and Placebo

HDL-C (Day 14)
Relative to Baseline and Placebo

Data as of April 19
Summary

- ALN-PCS has unique mechanism of action
  - PCSK9 synthesis inhibitor vs. PCSK9 protein blocker
- Safe and well tolerated up to 0.400 mg/kg
  - No significant AEs associated with drug
  - No laboratory abnormalities (LFTs, CRP, cytokines, or complement)
- Achieved rapid, dose-dependent, and durable plasma PCSK9 protein knockdown up to 84%
  - 68% mean reduction (p<0.0001) at top dose of 0.400 mg/kg
- Achieved rapid, dose-dependent, and durable LDL-C lowering up to 50%
  - 41% mean reduction (p<0.01) at top dose of 0.400 mg/kg
- Achieved dose-dependent decrease in nadir LDL-C (p<0.01) and increased proportion of subjects at target LDL-C or better (p<0.05))
- Treatment resulted in close correlation of of PCSK9 plasma levels and LDL-C
- Treatment showed consistent effects across wide range of baseline PCSK9 levels
- Demonstrated dose-dependent lowering of total cholesterol (p<0.001) with no effect on HDL-C
Conclusions

- PCSK9 synthesis inhibition represents a novel and differentiated strategy for treatment of severe hypercholesterolemia
- ALN-PCS, an RNAi therapeutic targeting PCSK9, is a promising new PCSK9 synthesis inhibitor
  » Demonstrates rapid, dose-dependent, and durable knockdown of PCSK9 and lowering of LDL-C
- Future studies are warranted with ALN-PCS to further explore its potential for the treatment of severe hypercholesterolemia
  » Efficacy and durability with concomitant administration with statins
  » Efficacy in patients with high pre-treatment PCSK9 levels