ALN-PCSsc, an RNAi Investigational Agent That Inhibits PCSK9 Synthesis With the Potential for Effective Bi-Annual Dosing: Interim Results

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Declaration of Interest: Employees of Alnylam Pharmaceuticals¹
Employees of The Medicines Company²
PCSK9 Therapeutic Hypothesis

PCSK9 Synthesis Inhibitors
Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

Anti-PCSK9 Mabs
Transiently block PCSK9 binding To LDL receptor (LDLR)
ALN-PCSsc Phase 1 Study  
Healthy Subjects with LDL-C >100mg/dl, On or Off Statins

**Primary objectives**  
- Safety, tolerability

**Secondary objectives**  
- PK, PCSK9, and LDL-C reduction

### Part A: Single Dose (SAD)  
Randomized 3:1, Single blind, Placebo controlled

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Mean PCSK9</th>
<th>Mean LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 mg</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 mg</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Part B: Multi-dose (MD)  
Randomized 3:1, Single blind, Placebo controlled

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Mean PCSK9</th>
<th>Mean LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>125mg qW</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250mg q2W</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300mg qM</td>
<td>6</td>
<td>+/- Statin</td>
<td></td>
</tr>
<tr>
<td>500 mg qM</td>
<td>6/5</td>
<td>+/- Statin</td>
<td></td>
</tr>
</tbody>
</table>
Safety Summary

ALN-PCSsc was generally well tolerated following single and multiple dosing:

- No SAE’s and no discontinuations due to AE’s
- Most common AE’s (>10% or more of ALN-PCSsc subjects)
  - Single dose (N=18): cough, musculoskeletal pain, nasopharyngitis
  - Multiple dose (N=33): headache, back pain, diarrhea, nausea
- All AE’s mild or moderate in severity
- AE profile generally similar with or without concomitant statins
- At higher drug exposures, 4 subjects experienced mild, localized, injection site reactions
- One subject developed clinically significant changes in LFT’s
  - ALT ~4x ULN without rise in bilirubin
  - Attributed to concomitant statin therapy; resolved on D/C of statin, recurred on statin re-challenge

Data reported is from database transfer Sept.24th 2015
Initial ALN-PCSsc Phase 1 Study Results
SAD PCSK9 Knockdown Relative to Baseline

Max PCSK9 knockdown of 88.7% with mean max of 82.3% (+/- 2.0)

Day/Treatment combinations where N=1 not displayed

Data reported is from database transfer Sept.24th 2015
Initial ALN-PCSsc Phase 1 Study Results
MD PCSK9 Knockdown Relative to Baseline

Mean (+/- SEM) PCSK9 Knockdown Relative to Baseline

Max PCSK9 knockdown of 94.4% with mean max of 88.5% (+/- 1.6)

S^ = On stable dose of statin
Two MD subjects excluded:
One placebo subject elected to discontinue;
One subject in 300 mg statin group was incarcerated on Day 14

Data reported is from database transfer Sept 24th 2015
Initial ALN-PCSsc Phase 1 Study Results
SAD LDL-C Lowering Relative to Baseline

Max LDL-C reduction of 78.1% with mean max of 59.3% (+/-5.0)

Data reported is from database transfer Sept.24th 2015
Initial ALN-PCSsc Phase 1 Study Results
MD LDL-C Lowering Relative to Baseline

Mean (+/- SEM) LDL-C Reduction Relative to Baseline

-20
-10
0
10
20
30
40
50
60
70
80
0 1 2 3 4 5 6 7

S^\* = On a stable dose of statins
Two MD subjects excluded:
One placebo subject elected to discontinue;
One subject in 300 mg statin group was incarcerated on Day 14

Max LDL-C reduction of 83.0% with mean max of 64.4% (+/- 5.4)

Data reported is from database transfer Sept. 24th 2015
## Initial ALN-PCSsc Phase 1 Study Results
Least Square Mean % Change in LDL-C by Beta Quantification

<table>
<thead>
<tr>
<th>SAD</th>
<th>LSM % change at group nadir (N)</th>
<th>LSM % change day 84 (N)</th>
<th>LSM % change day 140 (N)</th>
<th>LSM % change day 180 (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300mg</td>
<td>-50.0 (3)</td>
<td>-50.0 (3) **</td>
<td>-43.1 (3)</td>
<td>-47.0 (3)</td>
</tr>
<tr>
<td>500mg</td>
<td>-59.0 (3)</td>
<td>-50.5 (3) **</td>
<td>-38.8 (2)</td>
<td>-36.3 (2)</td>
</tr>
<tr>
<td>800mg</td>
<td>-52.8 (6)</td>
<td>-43.3 (5) **</td>
<td>-49.3 (4)</td>
<td>ongoing</td>
</tr>
</tbody>
</table>

Max LDL-C day 180; 53%

<table>
<thead>
<tr>
<th>MD</th>
<th>LSM % change at group nadir (N)</th>
<th>LSM % change day 84 (N)</th>
<th>LSM % change day 140 (N)</th>
<th>LSM % change day 208 (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300mg</td>
<td>-59.5 (6)</td>
<td>-59.5 (6) ***</td>
<td>-50.8 (6)</td>
<td>-44.4 (5)</td>
</tr>
<tr>
<td>300mg S</td>
<td>-53.4 (3)</td>
<td>-46.6 (3) *</td>
<td>-39.2 (3)</td>
<td>ongoing</td>
</tr>
<tr>
<td>500mg</td>
<td>-53.5 (6)</td>
<td>-51.9 (6) ***</td>
<td>-53.8 (6)</td>
<td>ongoing</td>
</tr>
<tr>
<td>500mg S</td>
<td>-59.9 (4)</td>
<td>-53.2 (5) ***</td>
<td>-53.0 (3)</td>
<td>ongoing</td>
</tr>
</tbody>
</table>

S = On stable dose of statin
*, P < 0.05; **, P < 0.01; ***, P < 0.001 (pairwise comparisons vs. Placebo)
LSMs and P values from baseline-adjusted ANCOVA model
Placebo subjects completed prior to day 140

Data reported is from database transfer Sept.24th 2015
**Initial ALN-PCSsc Phase 1 Study Results**

Least Square Mean % Change of Other Lipid Parameters: Day 84

<table>
<thead>
<tr>
<th>SAD Group (N)</th>
<th>LP(a)</th>
<th>Total Chol</th>
<th>ApoB</th>
<th>Non-HDL</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (5)</td>
<td>+ 2.2</td>
<td>- 4.7</td>
<td>-15.0</td>
<td>-10.6</td>
<td>+12.7</td>
</tr>
<tr>
<td>25mg (2)</td>
<td>+ 2.2</td>
<td>-16.8</td>
<td>-16.5</td>
<td>-23.5</td>
<td>+ 8.0</td>
</tr>
<tr>
<td>100mg (3)</td>
<td>-20.2</td>
<td>-17.8</td>
<td>-26.9</td>
<td>-28.3</td>
<td>+18.6</td>
</tr>
<tr>
<td>300mg (3)</td>
<td>-44.7</td>
<td>-30.8**</td>
<td>-47.3**</td>
<td>-48.9***</td>
<td>+39.5</td>
</tr>
<tr>
<td>500mg (3)</td>
<td>-34.7</td>
<td>-26.1</td>
<td>-39.2</td>
<td>-36.3</td>
<td>+ 6.9</td>
</tr>
<tr>
<td>800mg (6)</td>
<td>-24.5</td>
<td>-28.8**</td>
<td>-37.5</td>
<td>-37.0*</td>
<td>+ 0.6</td>
</tr>
</tbody>
</table>

Max. reductions: LP(a) (-77%); Total-C (-48%); ApoB (-72%); Non-HDL (-68%)

*, P < 0.05; **, P < 0.01; ***, P < 0.001 (pairwise comparisons vs. Placebo)

LSMs and P values from baseline-adjusted ANCOVA model

Data reported is from database transfer Sept.24th 2015
# Initial ALN-PCSsc Phase 1 Study Results
## Least Square Mean % Change of Other Lipid Parameters: Day 84

<table>
<thead>
<tr>
<th>MD Group (N)</th>
<th>LP(a)</th>
<th>Total Chol</th>
<th>ApoB</th>
<th>Non-HDL-C</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (10)</td>
<td>-3.2</td>
<td>-5.5</td>
<td>-12.1</td>
<td>-7.1</td>
<td>-0.8</td>
</tr>
<tr>
<td>125mg qWx4 (6)#</td>
<td>-22.7</td>
<td>-23.6</td>
<td>-33.3</td>
<td>-36.8</td>
<td>+13.5</td>
</tr>
<tr>
<td>250mg q2Wx4 (6)</td>
<td>-27.1</td>
<td>-34.5***</td>
<td>-46.4***</td>
<td>-45.3***</td>
<td>+3.9</td>
</tr>
<tr>
<td>300mg (6)</td>
<td>-21.3</td>
<td>-40.4***</td>
<td>-52.5***</td>
<td>-56.9***</td>
<td>+11.2</td>
</tr>
<tr>
<td>300mg S (3)</td>
<td>-26.6</td>
<td>-25.9</td>
<td>-36.8</td>
<td>-36.7*</td>
<td>+9.1</td>
</tr>
<tr>
<td>500mg (6)</td>
<td>-28.4</td>
<td>-27.1**</td>
<td>-46.4***</td>
<td>-45.3***</td>
<td>+13.2</td>
</tr>
<tr>
<td>500mg S (5)</td>
<td>-39.5*</td>
<td>-30.5***</td>
<td>-41.7**</td>
<td>-46.4***</td>
<td>+5.8</td>
</tr>
</tbody>
</table>

Max. reductions: LP(a) (-76%); Total-C (-55%); ApoB (-68%); Non-HDL (-73%)

S = On stable dose of statin
*, P < 0.05; **, P < 0.01; ***, P < 0.001 (pairwise comparisons vs. Placebo)
LSMs and P values from baseline-adjusted ANCOVA models
# Day 91

Data reported is from database transfer Sept. 24th 2015
ORION-1 Phase 2 Clinical Study

480 ASCVD subjects with elevated LDL-C on maximal lipid lowering therapy

**Primary objectives**
- LDL-C levels at day 180

**Secondary objectives**
- Safety and tolerability, PCSK9 and LDL-C reduction and duration of effect qQ vs Bi-annual, proportion of patients reaching global lipid guidelines, changes in other lipoprotein levels

**Randomized 3:1, Double blind, Placebo controlled**

- Placebo x 1 SC: N=60
- 200 mg x 1 SC: N=60
- 300 mg x 1 SC: N=60
- 500 mg x 1 SC: N=60

**Open label extension**
- Placebo qQ x 2 SC: N=60
- 100 mg qQ x 2 SC: N=60
- 200 mg qQ x 2 SC: N=60
- 300 mg qQ x 2 SC: N=60

= dose
Summary

ALN-PCSsc is promising first-in-class PCSK9 synthesis inhibitor

- Generally well tolerated in this study
  - No SAE’s and no discontinuations due to AE’s
  - All AEs mild or moderate in severity
- Similar LDL-C reduction to published data reported for anti-PCSK9 Mabs* in subjects with and without statin co-medication
- Reductions in LP(a), total cholesterol, and non-HDL cholesterol, with no change in HDL
- Durability supports bi-annual, low volume SC dose regimen, to be confirmed in larger studies
- ALN-PCSsc advances in ORION Development Program
  - Phase 2 “ORION-1” study to begin Q4 2015