ALN-PCSsc
Promising data with key questions yet to be addressed

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Unique approach for inhibition of PCSK9 aimed at single target organ

Small interfering (si) RNA conjugated to N-acetylgalactosamine targeting PCSK9 mRNA

N-acetylgalactosamine conjugate
Targets therapy to the liver only
Very efficient uptake and delivery

siRNA moiety
Short double stranded RNA modified to resist degradation
Specifically inhibits translation of PCSK9 mRNA
Efficacy

Protein expression and serum LDL-C

Multi-dose

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

- LDL-C reduction
  - Max of 83.0%
  - Mean max of 64.4% (+/- 5.4)
  - Apparent similar effects on LDL-C with or without concomitant statin
## Persistence of Effect

### Single dose

<table>
<thead>
<tr>
<th>Dose</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>

### Multi dose

<table>
<thead>
<tr>
<th>Dose</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>
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<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>
Key questions - Efficacy

Will liver specific targeting limit serum LDL-C lowering efficacy compared with monoclonal antibody approach?

Will liver specific targeting effect outcomes differently than a monoclonal antibody approach?

No direct effect on cells in the plaque

Statins – lower intracellular cholesterol
Mab – raise intracellular cholesterol
Ezetimibe and siRNA – No direct effect on intracellular LDL-c (sensing dependent)
Key questions PCSK9

Role other than LDL-R modulation in the hepatocyte?

- Trafficking of an the Alzheimer disease-associated BACE1 protein in mice

- Role in liver regeneration – mice knockout with impaired liver regeneration capacity

- Adult PCSK9 deficient mice exhibit glucose intolerance and may be at risk for diabetes
Safety

**Unintended consequences** – Theoretically could increase susceptibility to infection with certain viruses, such as HCV, vesicular stomatitis virus, the common cold rhino virus, and rous sarcoma virus.

**Dosing** - siRNA could elicit immune response if mistaken as foreign RNA.
Overall Impression

Intriguing Phase I data from a different approach to PCSK9 inhibition but represents only 42 healthy individuals

- Treatment is liver specific
- Effect on serum LDL-C that looks comparable to PCSK9 inhibition with monoclonal antibodies
- Dosing interval that could be as long as every 6 months
- Key potential safety questions still need to be explored