Single dose safety, pharmacokinetics, and pharmacodynamics of a potent PCSK9 synthesis inhibitor, AZD8233, in subjects with elevated LDL cholesterol

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Introduction

PCSK9
- PCSK9 promotes degradation of LDL receptors in the liver, resulting in increasing circulating levels of LDL-C
- Monoclonal Abs and SiRNA that targets PCSK9 reduces LDL-C

AZD8233
- AZD8233 is a GalNAc-conjugated ASO (generation 2.5 cET) targeting the PCSK9 pre-mRNA to prevent production of PCSK9

\[ \text{Triantennary } N\text{-acetyl galactosamine (GalNAc)} \]

GalNAc-conjugation gives selective delivery to hepatocytes via the asialoglycoprotein receptor\(^1\)

\(^1\)Schmidt K et al. Nucleic acids Res., 2017 45:2294-2306, Acknowledgement: Knut Andersson for illustration

Abs, antibody; ASO, antisense oligonucleotide; cET, constrained ethyl; GalNAc, triantennary N-acetyl galactosamine; LDL-C, low-density lipoprotein-cholesterol; mRNA, messenger RNA; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA
• Single-dose, single-blind, randomized, placebo-controlled, dose escalation study
• Objective: to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single ascending doses in patients

Study design

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Placebo (n)</th>
<th>AZD8233 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>12 mg</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>20 mg</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>30 mg</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>60 mg</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>90 mg</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>120 mg</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

R, randomization; SC, subcutaneous
Safety and tolerability

- Well tolerated, no SAEs reported
- No clinically relevant safety lab signals
- No injection site or flu-like reactions

- AZD8233 had a biphasic plasma profile with a fast distribution and a long terminal half-life of 2–3 weeks

Pharmacokinetics

PK, pharmacokinetics; SAE, serious adverse event
Baseline levels for lipid biomarkers

- Patients included should be statin-naive and have an LDL-C \( \geq 100 \text{ mg/dL} \) and < 190 mg/dL

### Baseline levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo n = 14</th>
<th>4 mg n = 6</th>
<th>12 mg n = 6</th>
<th>20 mg n = 6</th>
<th>30 mg n = 6</th>
<th>60 mg n = 6</th>
<th>90 mg n = 6</th>
<th>120 mg n = 6</th>
<th>Total n = 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCSK9 (ng/mL)</td>
<td>241 (1.2)</td>
<td>256.1 (1.2)</td>
<td>230.3 (1.3)</td>
<td>247.7 (1.2)</td>
<td>230 (1.2)</td>
<td>221.9 (1.1)</td>
<td>267.7 (1.2)</td>
<td>248.6 (1.3)</td>
<td>242.3 (1.2)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>133.6 (1.2)</td>
<td>132.1 (1.1)</td>
<td>143 (1.1)</td>
<td>125.8 (1.1)</td>
<td>130.3 (1.1)</td>
<td>124.8 (1.1)</td>
<td>129.3 (1.1)</td>
<td>132.2 (1.2)</td>
<td>131.6 (1.1)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>208 (1.1)</td>
<td>207.4 (1.1)</td>
<td>236.7 (1)</td>
<td>200.2 (1.1)</td>
<td>202.5 (1.1)</td>
<td>212.1 (1.1)</td>
<td>196.5 (1.1)</td>
<td>194.9 (1.2)</td>
<td>207.1 (1.1)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>123 (1.3)</td>
<td>138.9 (1.6)</td>
<td>100.6 (1.5)</td>
<td>103.4 (1.4)</td>
<td>81.4 (1.7)</td>
<td>95.8 (1.4)</td>
<td>130.2 (1.3)</td>
<td>128.8 (1.2)</td>
<td>112.7 (1.5)</td>
</tr>
</tbody>
</table>

*aSummary statistics are given as geometric mean (SD), values below limit of quantification were set to limit of quantification in this analysis. SD, standard deviation.*
Potent and durable reduction of PCSK9 and LDL-C

Plots show geometric mean and SD of % change from baseline. n = 6 per AZD8233 cohort and n = 14 in placebo arm, PCSK9 measured as protein in plasma.
Reduction of total cholesterol, ApoB and non-HDL-C

Plots show geometric mean and SD of % change from baseline. n = 6 per AZD8233 cohort and n = 14 in placebo arm
ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol
Reduction of ApoB/ApoA1 ratio, but no significant effect on Triglycerides and HDL-C

Plots show geometric mean and SD of % change from baseline. n = 6 per AZD8233 cohort and n = 14 in placebo arm

ApoA1, apolipoprotein A-I
Conclusions (NCT03593785)

- Single subcutaneous doses of AZD8233 up to 120 mg were generally safe and well tolerated
- Substantial and durable reductions in PCSK9 and LDL-C were observed
  - This indicates potential superior reductions in PCSK9 and LDL-C, compared to approved and late-stage PCSK9-targeting drugs, using monthly or less frequent administration of doses below 100 mg
- Consistent with the LDL-C decrease, dose dependent reductions in total cholesterol, non-HDL-C and ApoB were observed
- Based on these encouraging safety and pharmacodynamic results, a multiple ascending dose study in statin treated patients with dyslipidemia and LDL-C > 70 mg/dL is in progress