Effect of alirocumumab on the frequency of lipoprotein apheresis: A randomised Phase III trial


Declaration of Interest

- Regeneron
- Sanofi
- Amgen
- Duke
- Esperion
- Aegerion
- Kowa
- Ionis
- Eliaz Therapeutics
- Alexion
- Catabasis
- Pfizer
- Novartis
- Kaneka
- Research contracts (Genzyme
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Genzyme
Background

- Untreated heterozygous familial hypercholesterolemia (HeFH) is associated with severely elevated LDL-C levels and a high risk for premature CHD¹
- Despite LDL-C-lowering therapy, many patients with FH do not reach their target LDL-C levels²
- Apheresis = Greek for ‘taking away’; lipoprotein apheresis is removal of LDL-C³,⁴
- This trial was designed to clarify whether adding alirocumab could reduce or eliminate apheresis therapy

ESCAPE: Study Design

Male and female patients ≥18 years of age with HeFH undergoing QW/Q2W lipoprotein apheresis therapy

- Screening (2 weeks)
- Double-blind treatment period (18 weeks)
- FU 8 weeks/OLE

Patients with HeFH were on stable background treatment (statins, ezetimibe, etc.) and had undergone consistent lipoprotein apheresis QW for ≥4 weeks or Q2W for ≥8 weeks (14 study sites in US & Germany)

Standardized Apheresis Treatment Rates from Week 7–18

Standardised apheresis treatment rate in the period:
Hodges-Lehmann estimate of median treatment difference (95% CI):
Weeks 7–18: 0.75 (0.67 to 0.83)  p<0.0001
Weeks 15–18: 0.50 (0.50 to 1.00)  p<0.0001

An apheresis rate of 0 indicates that the patient skipped all planned apheresis treatments and an apheresis rate of 1 indicates that the patient received all planned apheresis treatments between Week 7 and Week 18 (apheresis rate of 0.75; the patient received 75% of planned apheresis treatments).

Hodges-Lehmann estimate of median treatment difference (95% CI):

p-value versus placebo:

Weeks 7–18: 0.75 (0.67 to 0.83)  p<0.0001
Weeks 15–18: 0.50 (0.50 to 1.00)  p<0.0001

Dr. Patrick M. Moriarty
### Time-Averaged Cholesterol Concentrations

**LDL-C % change from baseline (%), LS mean (SE):**

<table>
<thead>
<tr>
<th>Interval</th>
<th>Alirocumab</th>
<th>Placebo</th>
<th>p-value versus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>-53.7 (2.3)</td>
<td>1.6 (3.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Week 18</td>
<td>-42.5 (4.7)</td>
<td>3.9 (6.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data labels are expressed in both measurements; 1Kroon Formula; Kroon AA et al. Atherosclerosis. 2000;152:519–526. LS, least squares

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**Average LDL-C value, mean, mmol/L**

- **Alirocumab 150 mg Q2W (n=41):**
  - 4.5/175.1
  - 4.5/174.7
  - 4.5/172.6
  - 4.3/165.0
  - 4.5/175.2

- **Placebo (n=21):**
  - 5.0/191.6
  - 4.3/166.0
  - 2.4/92.1
  - 2.5/98.1
  - 2.4/93.6
  - 2.5/95.2
  - 2.4/94.3

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**Interval (weeks):**

- 0
- 8–10
- 10–12
- 12–14
- 14–16
- 16–18

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# Safety: Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>% (n)</th>
<th>Alirocumab 150 mg Q2W (n=41)</th>
<th>Placebo (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>75.6 (31)</td>
<td>76.2 (16)</td>
</tr>
<tr>
<td>Treatment emergent SAE</td>
<td>9.8 (4)</td>
<td>9.5 (2)</td>
</tr>
<tr>
<td>TEAE leading to death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAE leading to permanent treatment discontinuation</td>
<td>4.9 (2)</td>
<td>4.8 (1)</td>
</tr>
<tr>
<td>TEAE of interest:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>2.4 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4.9 (2)</td>
<td>4.8 (1)</td>
</tr>
<tr>
<td>TEAE occurring in ≥5% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7.3 (3)</td>
<td>19.0 (4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14.6 (6)</td>
<td>9.5 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.9 (2)</td>
<td>14.3 (3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9.8 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9.8 (4)</td>
<td>4.8 (1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9.8 (4)</td>
<td>9.5 (2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7.3 (3)</td>
<td>9.5 (2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.9 (2)</td>
<td>9.5 (2)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0</td>
<td>9.5 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>7.3 (3)</td>
<td>4.8 (1)</td>
</tr>
</tbody>
</table>

TEAE, treatment-emergent adverse event; SAE, serious adverse event
Conclusions

• HeFH occurs in approx. 1:200 patients
  • Without effective treatment there is a high risk of premature CVD
  • In ODYSSEY ESCAPE, alirocumab significantly reduced the need for apheresis treatment by 75% vs. placebo
• In patients receiving alirocumab:
  • Apheresis was discontinued in 63% of patients
  • LDL-C was reduced by approximately 50% from baseline (vs. 2% increase for placebo)
• Treatment with alirocumab 150 mg Q2W may allow patients with HeFH to terminate or reduce the frequency of lipoprotein apheresis