Clinical Efficacy and Safety of Achieving Very Low LDL-C Levels With the PCSK9 Inhibitor Evolocumab in the FOURIER Outcomes Trial

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Clinical Trial Update I
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Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Amgen, Bristol Myers Squibb, Merck, Pfizer, Daiichi Sankyo, GlaxoSmithKline)
- Research contracts (Amgen)
An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School

**Trial Design**

27,564 stable patients with CV disease (prior MI, stroke or PAD)
- age 40-85 years; additional CV risk factor(s)

Screening, Placebo Run-in, & Lipid Stabilization

Effective statin therapy (atorva ≥20 mg or ≈ statin dose ± ezetimibe)

LDL-C ≥ 1.8 mM
- non-HDL-C ≥ 2.6 mM

RANDOMIZED DOUBLE BLIND

Evolocumab SC
- 140 mg Q2W or 420 mg QM

Placebo SC
- Q2W or QM

Follow-up Q 12 weeks

Summary of FOURIER

- ↓ LDL-C by 59% (from 2.4 -> 0.8 [0.5, 1.2] mM)
- ↓ CV outcomes in patients already on statin therapy
- Evolocumab was safe and well-tolerated

Evolocumab was safe and well-tolerated.

LDL-C (mM)

- Median 0.78 mM
- IQR [0.49-1.27]

CV outcomes in patients already on statin therapy
- HR 0.85 (0.79-0.92)
- P<0.00001
- HR 0.80 (0.73-0.88)
- P<0.0001

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P<0.00001

HR 0.80 (0.73-0.88)
P<0.00001
Aims

To explore the clinical efficacy and safety associated with progressively lower achieved LDL-C levels
Methods - 1

- LDL-C assessed at 4 wks (ultracentrifugation if <1 mM)
- Analyzed 5 groups by achieved LDL-C at 4 weeks
  1) <0.5 mM (20 mg/dL)
  2) 0.5-1.3 mM (20-49 mg/dL)
  3) 1.3-1.8 mM (50-69 mg/dL)
  4) 1.8-2.6 mM (70-99 mg/dL)
  5) >2.6 mM (>100 mg/dL) was the referent group
- Pooled results across 2 Rx groups (evo, placebo)

1582 pts with events in first 4 wks or no LDL-C at week 4 were excluded
Methods - 2

- Prespecified 1° and 2° efficacy composite endpoints

- 10 safety adverse events evaluated:
  - Serious AE - AE->drug discon - AST/ALT>3x
  - Cancer - cataracts AEs - CK > 5x ULN
  - Hem stroke - Neurocognitive - Non-CV death
  - New onset diabetes (adjudicated by CEC)

- Cognition\(^1\) assessed using CANTAB tool and pt survey of everyday cognition (ECog)


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Achieved LDL-C at 4 Weeks

Median [IQR] LDL-C at 4 Weeks

- **Evo**: 0.8 mM [0.5-1.2]  
  32 mg/dL [21-45]

- **Pbo**: 2.2 mM [1.9-2.7]  
  87 mg/dL [74-104]

**Percent of Patients**

- **LDL (mM)**: <0.5 0.5-1.3 1.3-1.8 1.8-2.6 >2.6
- **%Evo**: 99.6% 96.5% 41% 10% 9.6%
- **%Placebo**: 0.4% 3.5% 59% 90% 90.4%

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Baseline Characteristics

<table>
<thead>
<tr>
<th>Achieved LDL-C in mM at 4 Weeks</th>
<th>&lt;0.5 (N=2669)</th>
<th>0.5-1.3 (N=8003)</th>
<th>1.3-1.8 (N=3444)</th>
<th>1.8-2.6 (N=7471)</th>
<th>&gt;2.6 (N=4395)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median), yrs*</td>
<td>64</td>
<td>63</td>
<td>62</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>Females*</td>
<td>16</td>
<td>23</td>
<td>27</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Caucasian race*</td>
<td>80</td>
<td>86</td>
<td>84</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>Current smoker*</td>
<td>26</td>
<td>27</td>
<td>29</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Prior MI</td>
<td>81</td>
<td>81</td>
<td>80</td>
<td>82</td>
<td>81</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>20</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Prior PAD</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78</td>
<td>80</td>
<td>82</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>TIMI Risk Score 2° Prevention*</td>
<td><strong>3.2</strong></td>
<td><strong>3.3</strong></td>
<td><strong>3.4</strong></td>
<td><strong>3.3</strong></td>
<td><strong>3.4</strong></td>
</tr>
</tbody>
</table>

Data shown are % patients unless otherwise specified

*Ptrend ≤ 0.0001

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### Lipids and Lipid Rx at Randomization

**Achieved LDL-C in mM at 4 Weeks**

<table>
<thead>
<tr>
<th>At Randomization</th>
<th>&lt;0.5 (N=2669)</th>
<th>0.5-1.3 (N=8003)</th>
<th>1.3-1.8 (N=3444)</th>
<th>1.8-2.6 (N=7471)</th>
<th>≥2.6 (N=4395)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Lipid values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C, mM</td>
<td>2.1</td>
<td>2.4</td>
<td>2.2</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Total cholesterol, mM</td>
<td>4.0</td>
<td>4.3</td>
<td>4.2</td>
<td>4.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Triglycerides, mM</td>
<td>1.5</td>
<td>1.5</td>
<td>1.6</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>HDL-C, mM</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Lipoprotein (a), nM</td>
<td>22</td>
<td>43</td>
<td>32</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>High potency statin, % (&gt; Atorvastatin 40 mg/d)</td>
<td>63</td>
<td>69</td>
<td>70</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Ezetimibe, %</td>
<td>4.1</td>
<td>5.0</td>
<td>5.4</td>
<td>4.6</td>
<td>7.4</td>
</tr>
</tbody>
</table>

\[P_{\text{trend}} \leq 0.0001 \text{ for each}\]

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LDL-C Over Time

LDL-cholesterol at 4 weeks in mM

- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- ≥ 2.6

Mean LDL-C (mM)

Weeks After Randomization

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CV Death, MI, Stroke, UA, or Coronary Revasc

LDL-C (mM) Adj HR (95% CI)

<0.5 0.76 (0.64-0.90)
0.5-1.3 0.85 (0.76-0.96)
1.3-1.8 0.94 (0.82-1.09)
1.8-2.6 0.97 (0.86-1.09)
> 2.6 referent

P = 0.0012
## CV Death, MI, or Stroke

**Table of LDL-C Levels and Adjusted Hazard Ratios (HR)**

<table>
<thead>
<tr>
<th>LDL-C (mM)</th>
<th>Adj HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>0.5-1.3</td>
<td>0.75 (0.64-0.86)</td>
</tr>
<tr>
<td>1.3-1.8</td>
<td>0.87 (0.73-1.04)</td>
</tr>
<tr>
<td>1.8-2.6</td>
<td>0.90 (0.78-1.04)</td>
</tr>
<tr>
<td>&gt; 2.6</td>
<td>referent</td>
</tr>
</tbody>
</table>

**Graph: LDL-C (mM) at 4 weeks**

**Graph Note:**
- Adjusted Event Rate (probability)
- LDL-C (mM) at 4 weeks

**Statistical Significance:**

\[ P = 0.0001 \]
Safety Events - 1

% pts

Adj P-values for trend >0.10 for each comparison

LDL-C (mM) at 4 wks
- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- ≥2.6

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Safety Events - 2

% pts

Adj P-values for trend >0.10 for each comparison

LDL-C (mM) at 4wks
- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- ≥2.6

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# Evaluation of Cognition

<table>
<thead>
<tr>
<th>CANTAB Tests</th>
<th>Adj $P_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function</td>
<td>0.11</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.61</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>0.61</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Global Score</strong></td>
<td><strong>0.30</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Everyday Cognition Self Survey</th>
<th>Adj $P_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>0.11</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.12</td>
</tr>
<tr>
<td>Planning</td>
<td>0.27</td>
</tr>
<tr>
<td>Organization</td>
<td>0.98</td>
</tr>
<tr>
<td>Divided attention</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td><strong>0.017</strong></td>
</tr>
</tbody>
</table>

Better scores at lower achieved LDL-C
Exploratory Analysis Pts with LDL-C <0.26 mM (<10 mg/dL) at 4 wks

N=504: Median [IQR] LDL-C 0.18 [0.13-0.23] mM = 7 [5-9] mg/dL

Cardiovascular Efficacy

- Adj HR 0.69 (0.49-0.97) P=0.03
- Adj HR 0.59 (0.37-0.92) P=0.02

Safety

- Adj HR 0.94 (0.74-1.20) P=0.61
- Adj HR 1.08 (0.63-1.85) P=0.78

Serious adverse event

- Adj HR 0.69 (0.49-0.97) P=0.03
- Adj HR 0.59 (0.37-0.92) P=0.02

AE -> drug discontinued

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Conclusions

- LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i ($<$ 1 mM)

- A strong progressive relationship of achieved LDL-C and CV events seen, down to LDL $<$0.26 mM ($<$10 mg/dL)

- No excess in safety events with very low achieved LDL-C $<$0.5 mM ($<$20 mg/dL) at 2.2 years

*These data suggest that we should target considerably lower LDL-C than is currently recommended for our patients with atherosclerotic CV disease*
Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial

Robert P Giugliano, Terje R Pedersen, Jeong-Gun Park, Gaetano M De Ferrari, Zbigniew A Gaciong, Richard Ceska, Kalman Toth, Joanna Gouni-Berthold, Jose Lopez-Miranda, François Schiele, François Mach, Brian R Ott, Estella Kanesky, Armando Lira Pineda, Ransi Somaratne, Scott M Wasserman, Anthony C Keech, Peter S Sever, Marc S Sabatine, on behalf of the FOURIER Investigators

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