Results of the MILANO-PILOT Study

Effect of Infusion of ApoA-1\textsubscript{Milano} HDL Mimetic on Coronary Atherosclerosis in Acute Coronary Syndrome Patients

Stephen J Nicholls MBBS PhD and Steven E Nissen MD

Disclosure

Consulting: AstraZeneca, Amgen, Anthera, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Merck, Takeda, Roche, Kowa, LipoScience, Novartis, Sanofi-Regeneron.


The MILANO-PILOT study was sponsored by The Medicines Company.
Background

- Epidemiological studies suggest that high-density lipoproteins (HDL) protect against cardiovascular disease.

- However, HDL-cholesterol raising agents have not proven to reduce cardiovascular events in recent clinical trials.

- Infusing a HDL mimetic containing the naturally occurring variant ApoA-I_{Milano} (ETC-216) promoted plaque regression in a small intravascular ultrasound (IVUS) reported in 2003.

- Following refinements in the manufacturing process, the mimetic MDCO-216 was found to be well tolerated and produced expected increases in cholesterol efflux capacity.
Objective of Study

To perform a pilot proof of concept study to determine whether five infusions of a HDL mimetic containing ApoA-I_{Milano} (MDCO-216) at a dose of 20 mg/kg would provide a signal suggesting an impact on coronary atherosclerosis in patients with a recent acute coronary syndrome.
Trial Leadership

Steven E. Nissen MD  Study Co-Chair
Stephen J. Nicholls MBBS PhD  Study Co-Chair

Executive Committee

Christie Ballantyne MD (USA)
Wouter Jukema MD PhD (Netherlands)
John Kastelein MD PhD (Netherlands)
Wolfgang Koenig MD (Germany)
R Scott Wright MD (USA)
Peter Wijngaard PhD (Switzerland)*
David Kallend MBBS (Switzerland)*

* Sponsor representatives
126 patients at 22 global centers with an acute coronary syndrome. Coronary angiography showing 20-50% stenosis in a target vessel.

Intravascular ultrasound via motorized pullback at 0.5 mm/sec through >40 mm segment

120 patients underwent randomization stratified by hospital site and prior statin use

- Statin plus weekly IV saline placebo
  - 2 patients did not complete
  - 61 placebo completers

- Statin plus IV weekly MDCO-216 (20 mg/kg)
  - 5 patients did not complete
  - 52 MDCO-216 completers

Follow-up IVUS of originally imaged “target” vessel (n=113)
## Baseline Demographics and Statin Usage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=61)</th>
<th>MDCO-216 (n=52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.4</td>
<td>62.2</td>
<td>0.68</td>
</tr>
<tr>
<td>Male Gender</td>
<td>73.8%</td>
<td>76.9%</td>
<td>0.70</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>28.1</td>
<td>29.4</td>
<td>0.50</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56.7%</td>
<td>74.5%</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.0%</td>
<td>17.6%</td>
<td>0.75</td>
</tr>
<tr>
<td>Smoking</td>
<td>31.1%</td>
<td>38.5%</td>
<td>0.69</td>
</tr>
<tr>
<td>Baseline statin use</td>
<td>52.5%</td>
<td>48.1%</td>
<td>0.72</td>
</tr>
<tr>
<td>High intensity statins</td>
<td>44.3%</td>
<td>44.2%</td>
<td>0.99</td>
</tr>
<tr>
<td>Baseline LDL-C</td>
<td>76.0 mg/dL</td>
<td>87.0 mg/dL</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline HDL-C</td>
<td>41.0 mg/dL</td>
<td>44.0 mg/dL</td>
<td>0.62</td>
</tr>
</tbody>
</table>
### Percent Change in Biochemical Parameters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>MDCO-216</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>-19.0%</td>
<td>-21.2%</td>
<td>0.49</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>+8.0%</td>
<td>-7.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free cholesterol</td>
<td>-8.7%</td>
<td>-14.8%</td>
<td>0.27</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-8.4%</td>
<td>-5.1%</td>
<td>0.81</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>-17.2%</td>
<td>-13.7%</td>
<td>0.87</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>+5.6%</td>
<td>-5.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hsCRP</td>
<td>-62.1%</td>
<td>-53.9%</td>
<td>0.51</td>
</tr>
</tbody>
</table>

HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein
Primary Endpoint: Percent Atheroma Volume

Median Change in Percent Atheroma Volume (%)

Results expressed as median (interquartile range)
Secondary Endpoint: Total Atheroma Volume

Entire Vessel Length

Median Change Volume (mm$^3$)

-6.9 (-17.5, 2.2)  
P <0.01

-4.7 (-13.7, 1.7)  
P <0.01

Placebo  MDCO-216

Median Change Volume (mm$^3$)

-2.4 (-7.0, 0.7)  
P = 0.01

-2.4 (-4.6, 1.3)  
P = 0.04

Placebo  MDCO-216

Most Diseased 10-mm Segment

Results expressed as median (interquartile range)
Percent of Patients Showing Regression in PAV

Regressors

- Placebo: 67.2%
- MDCO-216: 55.8%

Progressors

- Placebo: 32.8%
- MDCO-216: 44.2%

\[ P = 0.21 \] for comparison to placebo group
Exploratory Analysis: Effect of Prior Statin Use

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=27)</th>
<th>MDCO-216 (n=25)</th>
<th>Placebo (n=29)</th>
<th>MDCO-216 (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Statin</td>
<td>-0.4</td>
<td>-0.9</td>
<td>-1.9</td>
<td>-0.1</td>
</tr>
<tr>
<td>Prior Statin</td>
<td>P=0.02</td>
<td>P=0.12</td>
<td>P=0.28</td>
<td>P=0.29</td>
</tr>
</tbody>
</table>

Results expressed as median (interquartile range)
Percent Change in HDL-Cholesterol Post Infusion

**Placebo**

- Day 1: -15%
- Day 8: -12%
- Day 15: -9%
- Day 22: -6%
- Day 29: -3%

**MDCO-216**

- Day 1: -15%
- Day 8: -12%
- Day 15: -9%
- Day 22: -6%
- Day 29: -3%

P <0.01 for comparison from day 1 to 29

**Graph Details**

- Placebo: n=60, n=58, n=58, n=59, n=56
- MDCO-216: n=55, n=52, n=51, n=48, n=48

**Notes**

- The graph shows the percent change in HDL-C post infusion for Placebo and MDCO-216, with a significant decrease from day 1 to 29 (P <0.01) for both groups.
### Adverse Clinical Events and Safety Findings

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=64)</th>
<th>MDCO-216 (n=58)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/AST &gt;2x ULN</td>
<td>1.7%</td>
<td>1.7%</td>
<td>1.0</td>
</tr>
<tr>
<td>Total Bilirubin &gt;2x ULN</td>
<td>0%</td>
<td>1.7%</td>
<td>0.49</td>
</tr>
<tr>
<td>CK &gt;5x ULN</td>
<td>1.7%</td>
<td>0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Change creatinine</td>
<td>+2.0%</td>
<td>-0.2%</td>
<td>0.23</td>
</tr>
<tr>
<td>Change glucose</td>
<td>+4.6%</td>
<td>+2.2%</td>
<td>0.84</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>10.9%</td>
<td>17.2%</td>
<td>0.32</td>
</tr>
<tr>
<td>Adverse events of special interest*</td>
<td>4.7%</td>
<td>15.5%</td>
<td>0.05</td>
</tr>
<tr>
<td>Infusion site reactions</td>
<td>3.1%</td>
<td>6.9%</td>
<td>0.34</td>
</tr>
</tbody>
</table>

ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine kinase; ULN: upper limit of normal

*acute renal failure, infusion reaction, thromboembolic event, non-infectious hepatitis, liver abnormalities requiring investigation
Conclusions

• Five infusions of MDCO-216 were well tolerated.

• HDL-C levels *increased* post-infusion in placebo patients and *decreased* with MDCO-216 as expected.

• However, MDCO-216 did not produce a significant effect on coronary disease progression measured by IVUS.

• These results occurred on a background of contemporary therapy in the post ACS setting.

• The findings from this pilot study do not provide the evidence required to proceed with further development.
Some Final Thoughts

- Favorable effects of HDL infusions in several prior imaging studies provided support for targeting HDL to favorably impact coronary atherosclerosis.

- However, the failure to demonstrate benefit with MDCO-216 in the setting of contemporary medical therapy will raise further skepticism that targeting HDL will prove protective.

- HDL mimetics differing in composition from MDCO-216 and a CETP inhibitor continue to undergo clinical evaluation.

- Unless one of these new agents demonstrates clinical benefits, the HDL modulation story may soon end.
Intravascular Ultrasound Efficacy Parameters

**Change in Percent Atheroma Volume**

\[
\text{Change in Percent Atheroma Volume} = \frac{\sum_n \text{Atheroma}_{\text{CSA}}}{\sum_n \text{EEM}_{\text{CSA}}} - \frac{\sum_n \text{Atheroma}_{\text{CSA}}}{\sum_n \text{EEM}_{\text{CSA}}} \quad \text{(Month 24)} - \frac{\sum_n \text{EEM}_{\text{CSA}}}{\sum_n \text{EEM}_{\text{CSA}}} \quad \text{(baseline)}
\]

**Normalized Atheroma Volume**

\[
\text{Normalized Atheroma Volume} = \frac{\sum_n \text{Atheroma}_{\text{CSA}}}{\text{Number of slices in patient’s pullback}} - \frac{\sum_n \text{Lumen}_{\text{CSA}}}{\text{Median number of slices in all pullbacks}}
\]

**Change in Atheroma Volume**

\[
\text{Change in Atheroma Volume} = \frac{\text{Atheroma Volume}}{\text{Month 24}} - \frac{\text{Atheroma Volume}}{\text{baseline}}
\]
Ultrasound Determination of Atheroma Area

Precise Planimetry of EEM and Lumen Borders