Pcsk9 inhibitors: second revolution in CV disease

(the first was the revolution of statins)

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Professor of Medicine
Georgetown University
Recently the Food and Drug Administration (FDA) approved alirocumab and evolocumab, PCSK9 inhibitors, for the treatment of hyperlipidemia.

More specifically these to be used as an:

“adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL [low-density lipoprotein]-cholesterol.”

A third PCSK9 inhibitor-Bococizumab- is under intensive investigation
Why is this so important?

- Are very potent LDL reducing agents
- Lower LDL to levels we have never seen before
- Their mechanism of action is favorable, work well with statins and work like statins
- Have the potential of eliminating CV events ?
- Have the potential of eliminating atherosclerosis ??

BUT

- Have issues and Limitations:
- They are injectable proteins/antibodies
- May cause side effects
What are the Pcsk9 inhibitors

- PCSK9 is a protein
- Proprotein convertase subtilisin kexin 9 (PCSK9) is produced predominantly in the liver
- Its job is to tag the LDL receptors for destruction
- PCSK9 inhibitors prevent that by binding PCSK9

- Another small molecule the “interfering RNA (siRNA)”, can cause direct degradation of messenger RNA that leads to production of PCSK9
- It is currently under intense investigation. A single dose of siRNA resulted in 70% reduction of circulating PCSK9 and 40% reduction in LDL cholesterol
The first suggestion of a link between PCSK9 and hypercholesterolemia was published in 2003.

The progress from PCSK9 discovery to the development of targeted treatment has been unprecedented in terms of scale and speed.

PCSK9 inhibition is now considered an exciting and revolutionary approach in the reduction of residual risk of cardiovascular disease.

Can reduce LDL to its infancy levels.
Total Cholesterol Levels Increase During Development and Remain Higher Than Those in Hunter-Gatherer Populations

**TC Changes During Fetal Development Through Adulthood**

- **Birth**
- **Weaned**
  - Breast fed
  - Formula diet
  - High fat
  - Low fat

**Distribution of Total Serum Cholesterol Levels in ~34,000 US Adults From NHANES III (1988–1994)**

Cholesterol levels for modern hunter-gatherer populations range from: 3
- 101 mg/dL–146 mg/dL

LDL-C Levels Rise After Adulthood and Remain Higher Than Those in Early Development

**Mean LDL-C by Age**

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33–34</td>
<td>49</td>
</tr>
<tr>
<td>41–42</td>
<td>28</td>
</tr>
<tr>
<td>4–5</td>
<td>48</td>
</tr>
<tr>
<td>4–5</td>
<td>83</td>
</tr>
<tr>
<td>20–39</td>
<td>113</td>
</tr>
<tr>
<td>40–59</td>
<td>124</td>
</tr>
<tr>
<td>60–74</td>
<td>123</td>
</tr>
</tbody>
</table>

**Average LDL-C Levels in the US**

<table>
<thead>
<tr>
<th>Years</th>
<th>Average LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988–1994</td>
<td>129</td>
</tr>
<tr>
<td>1999–2002</td>
<td>123</td>
</tr>
<tr>
<td>2007–2010</td>
<td>116</td>
</tr>
</tbody>
</table>

**Notes:**

- In utero: wk = 79, n = 79
- Infants: mo = 18
- Adults: y = 8,174

Formulas: fed, breastfed, umbilical cord plasma concentrations

NHANES trends in mean LDL-C serum levels of U.S. adult respondents from 1999–2006; estimates are age adjusted to the 2000 standard U.S. population using the direct method. *Mean age-adjusted LDL-C levels; approx. 15,000 U.S. adults from NHANES (1988–2010)

Almost two decades the 4S first showed that simvastatin effectively improve survival in patients with cardiovascular disease (CVD), and initiated a revolution in the treatment of atherosclerotic heart disease.

Results with other statins confirmed and enhanced these results.

Other newer and/or novel compounds were abandoned either because of lack of efficacy or unacceptable side effects.

Recently ezetimibe-in the IMPROVE-IT study- showed further improvement of outcomes when added to a statin.

Yet the incremental reduction of LDL-C was modest and additional benefits small, but the study confirmed the impression that “Lower is better”.

That’s where PCSK9 come into play.
Why are Psck9 inhibitors important?

- "Are considered a breakthrough in the management of dyslipidemias because"
  - Are safe and
  - Very-very effective
Safe because are Humanized monoclonal antibodies

Monoclonal Antibody Evolution

- **e.g. ibritumomab**
  - Highly immunogenic
  - 100% Mouse

- **e.g. rituximab and abciximab**
  - Still immunogenic
  - ~30% Mouse

- **e.g. trastuzumab and bevacizumab**
  - Still immunogenic
  - ~5-10% Mouse

- **e.g. adalimumab and panitumumab**
  - Least immunogenic

<table>
<thead>
<tr>
<th>Fully Mouse</th>
<th>Chimeric</th>
<th>Humanised</th>
<th>“Fully” Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st generation</td>
<td>2nd generation</td>
<td>3rd generation</td>
<td>4th generation</td>
</tr>
</tbody>
</table>
How LDL particles are cleared

LDL Particles Are Cleared From the Plasma by Binding to LDL Receptors and Being Internalized by the Hepatocyte

1. LDL binds to LDL receptor
2. LDL/LDL receptor complex internalized by hepatocyte
3. LDL degraded in lysosome
4. LDL receptor recycled to cell surface
Psck9 tags ldl-r for destruction

PCSK9 Binds to the LDL Receptor and Targets the LDL Receptor for Degradation

1. PCSK9 is made in hepatocyte and secreted
2. PCSK9 binds to LDL receptor
3. Internalization of entire complex
4. LDL receptor as part of entire complex is degraded
5. LDL receptor not recycled
Evoculhub binds to pcSK9
preventing it from binding the LDL receptors

LDL receptors can recycle to hepatocyte surface to clear more plasma LDL
Another caveat: Statins increase PCSK9 levels

Meta-analysis from 15 studies with 19 treatment arms
-A total of 2691 subjects, with 1973 in the statin arm and 718 in the control arm
-Changes in PCSK9 levels were irrespective of the type of statin

*Diabetes, Obesity and Metabolism 17: 1042–1055, 2015.*
Change in PCSK9 levels after statin therapy

<table>
<thead>
<tr>
<th>Study name</th>
<th>Differences in means</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15.00</td>
<td>20.373</td>
<td>25.873</td>
<td>0.000</td>
</tr>
<tr>
<td>B</td>
<td>20.00</td>
<td>19.242</td>
<td>25.000</td>
<td>0.005</td>
</tr>
<tr>
<td>C</td>
<td>15.00</td>
<td>6.499</td>
<td>23.877</td>
<td>0.001</td>
</tr>
<tr>
<td>D</td>
<td>78.00</td>
<td>1.742</td>
<td>77.742</td>
<td>0.001</td>
</tr>
<tr>
<td>E</td>
<td>6.00</td>
<td>4.815</td>
<td>10.205</td>
<td>0.005</td>
</tr>
<tr>
<td>F</td>
<td>6.00</td>
<td>4.815</td>
<td>10.205</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Grouped by Type of Statin**

<table>
<thead>
<tr>
<th>Group by Type of Statin</th>
<th>Study name</th>
<th>Differences in means</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Badhwar et al.</td>
<td>13.00</td>
<td>8.329</td>
<td>23.177</td>
<td>0.001</td>
</tr>
<tr>
<td>A</td>
<td>Darabi et al.</td>
<td>15.00</td>
<td>25.342</td>
<td>25.873</td>
<td>0.000</td>
</tr>
<tr>
<td>A</td>
<td>Tsai et al.</td>
<td>48.00</td>
<td>41.057</td>
<td>55.083</td>
<td>0.000</td>
</tr>
<tr>
<td>A</td>
<td>Bao et al.</td>
<td>19.00</td>
<td>45.306</td>
<td>103.095</td>
<td>0.000</td>
</tr>
<tr>
<td>A</td>
<td>Crouse et al.</td>
<td>47.00</td>
<td>44.583</td>
<td>89.916</td>
<td>0.000</td>
</tr>
<tr>
<td>A</td>
<td>Meyre et al.</td>
<td>44.00</td>
<td>41.057</td>
<td>50.092</td>
<td>0.000</td>
</tr>
<tr>
<td>A</td>
<td>Bhatnagar et al</td>
<td>45.00</td>
<td>35.200</td>
<td>55.700</td>
<td>0.000</td>
</tr>
<tr>
<td>A</td>
<td>Cold et al.</td>
<td>47.00</td>
<td>24.927</td>
<td>70.023</td>
<td>0.000</td>
</tr>
<tr>
<td>B</td>
<td>Grunewald et al.</td>
<td>36.00</td>
<td>13.573</td>
<td>59.073</td>
<td>0.000</td>
</tr>
<tr>
<td>B</td>
<td>Thatha et al.</td>
<td>30.00</td>
<td>45.010</td>
<td>105.010</td>
<td>0.000</td>
</tr>
<tr>
<td>B</td>
<td>Dufour et al.</td>
<td>36.00</td>
<td>53.735</td>
<td>61.459</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Pre-statin**

- Pre-statin
- Post-statin

**Difference in means and 95% CI**

- **Pre-statin**: Difference in means 15.00, 95% CI (20.373, 25.873), p-value 0.000
- **Post-statin**: Difference in means 20.00, 95% CI (19.242, 25.000), p-value 0.005
Psck9 inhibitors have been approved for ascvd and fh
Evolocumab trials

as an adjunct to diet in: adults with HeFH or clinical ASCVD on maximally tolerated statin therapy OR patients with HoFH on other LDL-lowering therapies

COMBINATION WITH STATIN THERAPY IN CLINICAL ASCVD

LAPLACE-2 (Study 1)
Mean Baseline LDL-C: 108 mg/dL
N = 296

52-WEEK EFFICACY AND SAFETY IN CLINICAL ASCVD

DESCARTES (Study 2)
Mean Baseline LDL-C: 105 mg/dL
N = 139

FAMILIAL HYPERCHOLESTEROLEMIA

RUTHERFORD-2 (Study 3) and TESLA (Study 4)
Mean Baseline LDL-C:
Study 3: 156 mg/dL, N = 329
Study 4: 349 mg/dL, N = 49

*Maximally tolerated includes patients who have been optimized on statins or cannot tolerate any statin type or dose.
Laplace-2 study (ascvd)
n=296, baseline, Ldl=108 mg/dl

4-Week, Lipid-Stabilization Period

Double-Blind, 12-Week Study Period

Patients who needed additional LDL lowering

RANDOMIZATION TO STATIN

STATIN THERAPY
Atorvastatin 80 mg QD
Rosuvastatin 40 mg QD
Simvastatin 40 mg QD

RANDOMIZATION TO STUDY DRUG

Repatha™ Q2W 140 mg SC (fixed dose) + Statin

Placebo Q2W SC + Statin

Primary Endpoint
Mean percent change from baseline in LDL-C at week 12

Secondary Endpoints
Included percent of patients achieving LDL-C < 70 mg/dL and percent change from baseline in other lipid parameters at week 12

QD = once daily; Q2W = every 2 weeks; SC = subcutaneous.

*Key exclusion criteria: patients who experienced one of the following within prior 6 months were excluded: MI/UA, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or stroke and planned cardiac surgery or revascularization; baseline was measured after the lipid-stabilization period and before administration of first dose of study drug. 

1 Patients with clinical ASCVD on QD, doses of atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg; n=296.
Evolocumab + statin
up to 77% LDL reduction

Mean % Change in LDL-C From Baseline to Week 12

- Atorvastatin 80 mg: -1%
- Rosuvastatin 40 mg: 2%
- Simvastatin 40 mg: 13%

N = 147

Repah™ 140 mg Q2W + statin
Placebo + statin

P < 0.0001 for all arms represented

Estimates based on a multiple imputation model that accounts for treatment adherence.
Up 90% of patients achieved LDL-c <70mg/dl
Intensive LDL-C Reduction With Repatha™ Was Maintained Over 52 Weeks

**Percent Change in LDL-C at Week 52: Placebo vs Repatha™**

- **Placebo QM + background therapy**
- **Repatha™ 420 mg QM + background therapy**

**N = 139**

- Multicenter, double-blind, randomized, placebo-controlled, 52-week study of Repatha™ in 139 patients with clinical ASCVD
- In this study, Repatha™ was administered as the 420 mg once monthly dose. The 140 mg every 2 weeks or 420 mg once monthly doses yield similar reductions in LDL-C

*QM = once monthly.

Error bars indicate 95% CI; LDL-C measured via ultracentrifugation; Estimates based on a multiple imputation model that accounts for treatment adherence.

*Ascorvastatin 80 mg with or without 10 mg ezetimibe daily.*
Adverse reactions occurring in ≥ 3% of Repatha™-treated patients and more frequently than with placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Repatha™ (n=599)</th>
<th>Placebo (n=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>4.0%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2.1%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.8%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.8%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Cough</td>
<td>1.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Influenza</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Contusion</td>
<td>1.0%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

*Repatha™ 140 mg Q2W and 420mg QM combined.*
## Adverse Events in the DESCARDES trial: 52 week F/U

<table>
<thead>
<tr>
<th>Adverse reactions occurring in ≥ 3% of Repatha™-treated patients and more frequently than with placebo</th>
<th>Repatha™ (n=599)</th>
<th>Placebo (n=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>10.5%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9.3%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Influenza</td>
<td>7.5%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Back pain</td>
<td>6.2%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Injection site reactions†</td>
<td>5.7%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Cough</td>
<td>4.5%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.5%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4.2%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Headache</td>
<td>4.0%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>3.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.2%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.0%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3.0%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

*Repatha™ 420mg QM; †includes erythema, pain, bruising*
Low LDL-C Levels

- In a pool of placebo- and active-controlled trials, as well as open-label extension studies that followed them, a total of 1,609 patients treated with Repatha™ had at least one LDL-C value < 25 mg/dL.
- Changes to background lipid-altering therapy were not made in response to low LDL-C values, and Repatha™ dosing was not modified or interrupted on this basis.
- Although adverse consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C induced by Repatha™ are unknown.

An integrated analysis of phase 2 and 3 randomized, placebo- and active-controlled studies of Repatha™ for up to 52 weeks’ duration

<table>
<thead>
<tr>
<th></th>
<th>Any LDL-C &lt; 25 mg/dL</th>
<th>Any LDL-C &lt; 40 mg/dL</th>
<th>All LDL-C &gt; 40 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repatha™ + SoC n = 1,609</td>
<td>51.3%</td>
<td>51.0%</td>
<td>52.0%</td>
</tr>
<tr>
<td>Repatha™ + SoC n = 2,665</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SoC n = 1,339</td>
<td>51.0%</td>
<td>52.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>SoC n = 2,038</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

SoC = standard of care; AE = adverse event.
Across Four Clinical Trials, Repatha™ Demonstrated Significant LDL-C Reduction

As an adjunct to diet in: adults with HeFH or clinical ASCVD on maximally tolerate statin therapy* OR patients with HoFH on other LDL-lowering therapies

**COMBINATION WITH STATIN THERAPY IN CLINICAL ASCVD**

LAPLACE-2 (Study 1)
Mean Baseline LDL-C: 108 mg/dL
N = 296

**52-WEEK EFFICACY AND SAFETY IN CLINICAL ASCVD**

DESCARTES (Study 2)
Mean Baseline LDL-C: 105 mg/dL
N = 139

**FAMILIAL HYPERCHOLESTEROLEMIA**

RUTHERFORD-2 (Study 3) and TESLA (Study 4)

Mean Baseline LDL-C:
Study 3: 156 mg/dL, N = 329
Study 4: 349 mg/dL, N = 49

*Maximally tolerated includes patients who have been optimized on statins or cannot tolerate any statin type or dose.*
Repatha™ Provided Additional Lowering of LDL-C in Two Studies of Patients With FH

<table>
<thead>
<tr>
<th>HeFH (Study 3)¹</th>
<th>HoFH (Study 4)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Design:</strong> Multicenter, double-blind, randomized, placebo-controlled, 12-week trial</td>
<td></td>
</tr>
<tr>
<td><strong>Population:</strong> 329* patients with HeFH diagnosed by Simon Broome criteria† on statins with or without other lipid-lowering therapies</td>
<td></td>
</tr>
<tr>
<td>- 38% had clinical ASCVD</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline LDL-C:</strong> 156 mg/dL</td>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong> Mean % change in LDL-C vs placebo: −61% (P &lt; 0.0001) in Q2W group (n = 164)</td>
<td></td>
</tr>
<tr>
<td><strong>Trial Design:</strong> Multicenter, double-blind, randomized, placebo-controlled, 12-week trial</td>
<td></td>
</tr>
<tr>
<td><strong>Population:</strong> 49 patients with HoFH‡</td>
<td></td>
</tr>
<tr>
<td>- Not on lipid-apheresis therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline LDL-C:</strong> 349 mg/dL</td>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong> Mean % change in LDL-C vs placebo: −31% (P &lt; 0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

The safety and effectiveness of Repatha™ have not been established in pediatric patients with primary hyperlipidemia or HeFH.

The safety and effectiveness of Repatha™ have not been established in pediatric patients with HoFH who are younger than 13 years old.

*OM and Q2W populations. In adults, the Simon Broome criteria include LDL-C ≥ 190 mg/dL (without therapy) plus clinical criteria (including patient or family history of tendon xanthomas, family history of early CAD, or family history of TC ≥ 250 mg/dL).‡ Diagnosis made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration ≥ 300 mg/dL, together with xanthoma before 10 years of age or evidence of HeFH in both parents.¹
Repata™ Was Studied in Patients With HeFH\(^1,2\)

4-Week, Lipid-Stabilization Phase

Patients with HeFH unable to achieve LDL-C <100 mg/dL despite statins with or without other lipid-lowering therapies and requiring additional LDL-C reduction

Background Therapy*

Double-Blind, 12-Week Study Period*

Repata™ Q2W 140 mg SC (fixed dose) + Background Therapy

Placebo Q2W SC + Background Therapy

**Randomization**

**Primary Endpoint**

Percent change from baseline in LDL-C at week 12

**Secondary Endpoints**

Included percent of patients achieving LDL-C <70 mg/dL and percent change from baseline in other lipid parameters at week 12

*At screening, eligible patients included those with HeFH diagnosed by the Simon Broome diagnostic criteria on a stable statin dose with or without other approved lipid-modifying therapy for at least 4 weeks before screening. Use of LDL or plasmapheresis within 16 weeks prior to enrollment and treatment with fibrates within 6 weeks of treatment were not allowed. Patients were stratified by other, non-statin lipid-lowering therapy and LDL-C level prior to randomization. In adults, the Simon Broome criteria include an LDL-C of ≥190 mg/dL (without therapy) plus clinical criteria (including patient or family history of tendon xanthomas, family history of early CAD, or family history of TC ≥290 mg/dL).\(^*\) Baseline was measured after the lipid-stabilization period and before administration of first dose of study drug.\(^*\)
In HeFH, Repatha™ Lowered LDL-C an Additional 61% vs Placebo When Combined With Background Therapy\textsuperscript{1,2}

68% of patients receiving Repatha™ + background therapy achieved LDL-C < 70 mg/dL compared with 2% of patients receiving placebo + background therapy\textsuperscript{†}

\textsuperscript{1} Estimates based on a multiple imputation model that accounts for treatment adherence.

\textsuperscript{2} Background therapy included statins with or without other lipid-lowering therapies, \textsuperscript{*}baseline LDL-C \textsuperscript{1}56 mg/dL.
Repatha™ Was Studied in Patients With HoFH\textsuperscript{1,2}

4-Week, Lipid-Stabilization Phase

Patients with HoFH (not on lipid-apheresis therapy) diagnosed by history of an untreated LDL-C > 500 mg/dL, together with either tendon xanthomas before 10 years of age or evidence of HoFH in both parents\textsuperscript{*}

RANDOMIZATION

Background Therapy\textsuperscript{†}

Double-Blind, 12-Week Study Period

Repatha™ QM 420 mg SC (fixed dose) + Background Therapy

Placebo QM + Background Therapy

N = 49

Primary Endpoint

Percent change from baseline in LDL-C at week 12

The safety and effectiveness of Repatha™ have not been established in pediatric patients with HoFH who are younger than 13 years old

\textsuperscript{*}Key exclusion criteria included New York Heart Association Class III or IV heart failure or last known left ventricular ejection fraction < 30\%, uncontrolled serious cardiac arrhythmia or MI within 3 months prior to enrollment, and uncontrolled hypertension. Patients who previously received Repatha™ or any other investigational therapy to inhibit PCSK9 were also excluded; \textsuperscript{†}Other lipid-lowering therapies (eg, statins, ezetimibe).\textsuperscript{3}
In HoFH, Repatha™ Lowered LDL-C 31% More Than Placebo When Combined With Background Therapy

- Repatha™ 420 mg QM + background therapy* (n = 33)
- Placebo + background therapy* (n = 16)

\[ P < 0.0001 \text{ for treatment difference} \]

**Mean % Change in LDL-C From Baseline to Week 12**

-22% (Repatha™)

-31% (treatment difference)

*Estimates based on a multiple imputation model that accounts for treatment adherence.
*Other lipid-lowering therapies (e.g., statins, ezetimibe)
Studies with alirocumab

- Long term studies and
- Studies in Familial hypercholesterolemia
Odyssey long term study
n=2,341

ODYSSEY LONG TERM
Study Design

Adults with HeFH
or at high-CV risk
On maximally tolerated statin
± other LLT
LDL-C ≥70 mg/dL
(1.81 mmol/L)

Assessments
W0 W8 W16 W24 W52 W64 W78

Double-blind treatment (18 months)
N=1553
R
N=788

Follow-up (8 weeks)

Primary efficacy endpoint

Alirocumab 150 mg Q2W SC
(single 1-mL injection using prefilled syringe
for self-administration)

Placebo Q2W SC

CV=cardiovascular, HeFH=heterozygous familial hypercholesterolemia, LDL-C=low-density lipoprotein cholesterol, LLT—lipid-lowering therapy; Q2W—every 2 weeks; SC—subcutaneous; W—week.
ClinicalTrials.gov identifier: NCT01550831.
Calculated LDL-C Levels over Time

ITT Analysis

Placebo + maximally tolerated statin ± other LLT

Alirocumab + maximally tolerated statin ± other LLT

Least-squares mean calculated LDL-C Level (mg/dL)

140
120
100
80
60
40
20
0

No. of pts with data available:

Placebo  780  747  716  708  694  676  659  652

Alirocumab  1530  1458  1412  1386  1359  1349  1324  1269

Familial hypercholesterolemia
n=486

ODYSSEY FH I and FH II Study Design

Double-Blind Treatment Period (78 Weeks)

HeFH patients on max tolerated statin ± other lipid-lowering therapy

LDL-C ≥1.81 mmol/L [70 mg/dL] (history of CVD)
or
2.59 mmol/L [100 mg/dL] (no history of CVD)

Alirocumab 75 mg Q2W SC with potential ↑ to 150 mg Q2W SC
(single 1-ml injection using prefilled pen for self-administration)

n=323 (FH I); n=107 (FH II)

Per-protocol dose ↑ possible based on pre-specified LDL-C level

n=163 (FH I); n=82 (FH II)

Placebo Q2W SC

Assessments
WD  W8  W16  W36  W52  W64  W78

Dose ↑ if LDL C >70 mg/dL at W8

Primary efficacy endpoint

Pre-specified analysis
Efficacy: All Patients To W52
Safety: Baseline-W70 (all patients at least W52)

Long term efficacy in FH

**Alirocumab Maintained Consistent LDL-C Reductions Over 52 Weeks**

Achieved LDL-C Over Time on Background of Maximally-Tolerated Statin + Other LLT

- **Placebo:**
  - FH I
  - FH II

- **Alirocumab:**
  - FH I
  - FH II

- **Weeks 0-52**
  - LDL-C levels:
    - 4.0 mmol/L
    - 3.5 mmol/L
    - 1.9 mmol/L

**Dose ↑ if LDL-C >70 mg/dL at W8**

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D.,
Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D.,
Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H.,
Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D.,
Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D.,
and Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

ABSTRACT

The New England Journal of Medicine, March 15th, 2015
Enrolled 4465 patients from 12 phase 2,3 evolocumab trials.

Patients were randomly assigned in a 2:1 ratio to:

- evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard therapy or
- standard therapy alone.

Patients were followed for a median of 11.1 months with assessment of:

- lipid levels,
- safety, and
- Prespecified, adjudicated cardiovascular events: (death, myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure).
# Clinical Characteristics of the Patients at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Evolocumab Group (N = 2976)</th>
<th>Standard-Therapy Group (N = 1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ±SD — yr</td>
<td>57.8±11.0</td>
<td>58.2±10.9</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>1490 (50.1)</td>
<td>765 (51.4)</td>
</tr>
<tr>
<td>White race — no. (%)†</td>
<td>2559 (86.0)</td>
<td>1267 (85.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1545 (51.9)</td>
<td>777 (52.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>382 (12.8)</td>
<td>217 (14.6)</td>
</tr>
<tr>
<td>Known familial hypercholesterolemia</td>
<td>289 (9.7)</td>
<td>151 (10.1)</td>
</tr>
<tr>
<td>Moderately high risk or high risk on NCEP</td>
<td>1332 (44.8)</td>
<td>693 (46.5)</td>
</tr>
<tr>
<td>Statin.</td>
<td>2073 (69.7)</td>
<td>1055 (70.9)</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>376 (12.6)</td>
<td>229 (15.4)</td>
</tr>
</tbody>
</table>
Clinical Characteristics of the Patients at Baseline

<table>
<thead>
<tr>
<th>Median lipid measure at baseline in parent study</th>
<th>Evolocumab Group (N = 2976)</th>
<th>Standard-Therapy Group (N = 1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>120 (97–148)</td>
<td>121 (97–151)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>202 (175–234)</td>
<td>205 (174–235)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>51 (42–62)</td>
<td>51 (42–62)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>120 (89–165)</td>
<td>119 (89–167)</td>
</tr>
</tbody>
</table>
Change in LDL cholesterol

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Baseline</th>
<th>4</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL Cholesterol (mg/dl)</td>
<td>Standard therapy</td>
<td>Evolocumab</td>
<td>Standard therapy</td>
<td>Evolocumab</td>
<td>Standard therapy</td>
<td>Evolocumab</td>
</tr>
<tr>
<td>No. at Risk</td>
<td>1489</td>
<td>394</td>
<td>1388</td>
<td>1376</td>
<td>402</td>
<td>1219</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>2976</td>
<td>864</td>
<td>2871</td>
<td>2828</td>
<td>841</td>
<td>2508</td>
</tr>
<tr>
<td>Absolute reduction (mg/dl)</td>
<td>60.4</td>
<td>73.4</td>
<td>70.4</td>
<td>72.7</td>
<td>70.5</td>
<td>70.5</td>
</tr>
<tr>
<td>Percentage reduction</td>
<td>45.3</td>
<td>60.9</td>
<td>58.8</td>
<td>54.0</td>
<td>58.4</td>
<td>58.4</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure 2. Cumulative Incidence of Cardiovascular Events.

Cumulative incidence of cv events

No. at Risk
Standard therapy 1489 1486 1481 1473 1467 1463 1458 1454 1447 1438 1428 1361 1361 407
Evolocumab 2976 2970 2962 2949 2938 2930 2920 2910 2901 2885 2871 2778 843

Hazard ratio, 0.47 (95% CI, 0.28–0.78)
P=0.003
### Adverse events and lab results

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Evolocumab Group (N = 2976)</th>
<th>Standard-Therapy Group (N = 1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>2060 (69.2)</td>
<td>2060 (69.2)</td>
</tr>
<tr>
<td>Serious</td>
<td>222 (7.5)</td>
<td>111 (7.5)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>71 (2.4)</td>
<td>N/A</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>190 (6.4)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Injection-site reaction</strong></td>
<td><strong>129 (4.3)</strong></td>
<td><strong>90 (6.0)</strong></td>
</tr>
<tr>
<td><strong>Neurocognitive event†</strong></td>
<td><strong>27 (0.9)</strong></td>
<td><strong>4 (0.3)</strong></td>
</tr>
<tr>
<td>Headache</td>
<td>106 (3.6)</td>
<td>32 (2.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>83 (2.8)</td>
<td>15 (1.0)</td>
</tr>
<tr>
<td><strong>ALT× ULN at any visit after</strong></td>
<td><strong>31 (1.0)</strong></td>
<td><strong>18 (1.2)</strong></td>
</tr>
<tr>
<td><strong>CK &gt;5× ULN at any visit after baseline</strong></td>
<td><strong>17 (0.6)</strong></td>
<td><strong>17 (1.1)</strong></td>
</tr>
</tbody>
</table>

*Note: N/A indicates data not available.*
Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*

ABSTRACT
Randomized 2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of >70 mg per deciliter and treated with statins at the maximum tolerated dose with or without other lipid-lowering therapy.

Patients were randomly assigned in a 2:1 ratio to receive

- **Alirocumab** (150 mg) or **placebo (standard therapy)** as a 1-ml subcutaneous injection every 2 weeks for 78 weeks.

The primary efficacy end point was the percentage change in calculated LDL cholesterol level from baseline to week 24.
### Baseline Characteristics of All Randomly Assigned Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alirocumab (N = 1553)</th>
<th>Placebo (N = 788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>60.4 (10.4)</td>
<td>60.6 (10.4)</td>
</tr>
<tr>
<td>Male sex</td>
<td>983 (63.3)</td>
<td>474 (60.2)</td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
<td>276 (17.8)</td>
<td>139 (17.6)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1055 (67.9)</td>
<td>552 (70.1)</td>
</tr>
<tr>
<td>Any statin</td>
<td>1552 (&gt;99.9)</td>
<td>787 (99.9)</td>
</tr>
<tr>
<td>Other lipid-lowering therapy</td>
<td>437 (28.1)</td>
<td>220 (27.9)</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>216 (13.9)</td>
<td>118 (15.0)</td>
</tr>
<tr>
<td>Calculated LDL cholesterol</td>
<td>122.4 (42.6)</td>
<td>121.9 (41.4)</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>101.9 (27.7)</td>
<td>101.4 (27.3)</td>
</tr>
</tbody>
</table>
Calculated LDL Cholesterol Levels over Time: Alirocumab vs placebo

Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).

NEJM March 15 2015
Adverse events with alirocumab
Cv events with alirocumab
Effects of Pcsk9 inhibiteores in Adults With Hypercholesterolemia

A Systematic Review and Meta-analysis

Elano Pio Navarese, MD, PhD; Michalina Kołodziejczak, MD; Volker Schulze, MD; Paul A. Gurbel, MD; Udaya Tantry, PhD; Yingfeng Lin, MD; Maximilian Brockmeyer, MD; David E. Kandzari, MD; Julia M. Kubica, MD; Ralph B. D’Agostino Sr., PhD; Jacek Kubica, MD, PhD; Massimo Volpe, MD; Stefan Agewall, MD; Dean J. Kereiakes, MD; and Malte Kelm, MD

Data from 22 phase 2 or 3 randomized, controlled trials (RCTs) comparing treatment using PCSK9 antibodies with no anti-PCSK9 therapy in adults with hypercholesterolemia were included.

A total of 10 159 patients were randomized to PCSK9 antibody or no antibody

## Treatment with PCSK9 antibodies (n=10,159 pts)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C reduction</td>
<td>-51%</td>
</tr>
<tr>
<td>All cause mortality</td>
<td></td>
</tr>
<tr>
<td>CV mortality</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td></td>
</tr>
</tbody>
</table>
## Primary Clinical End Points

\( n=10,159 \)

<table>
<thead>
<tr>
<th>Event</th>
<th>PCSK9 antib</th>
<th>control</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td>0.31% (19 of 6187 patients)</td>
<td>0.53% (21 of 3971 patients)</td>
<td>0.45 [95% CI, 0.23 to 0.86]</td>
<td>( P = 0.015 )</td>
</tr>
<tr>
<td><strong>Cardiovascular Mortality</strong></td>
<td>0.19% (12 of 6187 patients)</td>
<td>0.33% (13 of 3972 patients)</td>
<td>0.50 [95% CI, 0.23 to 1.10]</td>
<td>( P = 0.070 )</td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td>0.58% (19 of 3289 patients)</td>
<td>1.00% (19 of 1906 patients)</td>
<td>OR, 0.49 [CI, 0.26 to 0.93]</td>
<td>( P = 0.030 )</td>
</tr>
<tr>
<td><strong>Unstable Angina</strong></td>
<td>0.04% (1 of 2515 patients)</td>
<td>0.08% (1 of 1379 patients)</td>
<td>OR, 0.61 [CI, 0.06 to 6.14]</td>
<td>( P = 0.676 )</td>
</tr>
</tbody>
</table>
## Ongoing clinical outcome trials of PCSK9 inhibitors

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Study drug</th>
<th>Patient population</th>
<th>Primary outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOURIERNCT</td>
<td>Evolocumab</td>
<td>n = 27,000; h/o CVD high risk of CV; LDL-C $\geq$ 70 mg/dL on statin therapy</td>
<td>Time to cardiovascular death, CV event</td>
<td>5 years</td>
</tr>
<tr>
<td>ODYSSEY OUTCOME</td>
<td>Alirocumab</td>
<td>n = 18,000; ACS &lt; 52 weeks earlier; LDL-C $\geq$ 70 mg/dL or non-HDL-C $\geq$ 100 mg/dL; on statin therapy</td>
<td>Time to cardiovascular death CV event</td>
<td>64 months</td>
</tr>
<tr>
<td>SPIRE-1 NCT</td>
<td>Bococizumab</td>
<td>n = 17,000; high risk of CVD event, background lipid-lowering treatment; LDL-C 70–100 mg/dL</td>
<td>Time to composite major CV event</td>
<td>60 months</td>
</tr>
<tr>
<td>SPIRE-2 NCT</td>
<td>Bococizumab</td>
<td>n = 90000; high risk of CVD event; background lipid-lowering treatment; LDL-C $\geq$ 100 mg/dL</td>
<td>Time to composite major CV event</td>
<td>60 months</td>
</tr>
</tbody>
</table>
PCSK9 inhibitors represent a new revolution in Cardiovascular medicine and

It is happening “RIGHT HERE and RIGHT NOW”

Thank you very much!!!!!!