The latest intervention in ACS: the monoclonal antibody against PCSK9

Henry Ginsberg MD
Irving Professor of Medicine
Columbia University, New York
Impact of PCSK9 Inhibitory mAbs on LDL Receptor Expression

LDL=low-density lipoprotein; LDL-R=LDL receptor; mAbs=monoclonal antibodies; PCSK9=proprotein convertase subtilisin/kinexin type 9; SREBP-2=sterol regulatory element-binding protein-2.
Statin + anti-PCSK9 mAb MOA

LDL=low-density lipoprotein; LDL-R=LDL receptor; PCSK9=proprotein convertase subtilisin/kinexin type 9; SREBP-2=sterol regulatory element-binding protein-2.
PCSK9 Clinical Trials: What’s new?

New = presented and/or published from Sept 2014

PCSK9 inhibitors: monoclonal antibodies (mAbs)

⇒ Evolocumab
⇒ Alirocumab
⇒ Bococizumab
A  

Phase 1a: AMG 145 or Placebo, Single Ascending Doses in Healthy Subjects

B  

Phase 1b: AMG 145 or Placebo, Multiple Ascending Doses in Subjects with Hypercholesterolemia

Clapton S. Dias, Adam J. Shaywitz, Scott M. Wasserman, Brian P. Smith, Bing Gao, Dina S. Stolman, Caroline P...

Effects of AMG 145 on Low-Density Lipoprotein Cholesterol Levels: Results From 2 Randomized, Double-Blind, Placebo-Controlled, Ascending-Dose Phase 1 Studies in Healthy Volunteers and Hypercholesterolemic Subjects on Statins

Evolocumab

PROFICIO Programme
Evolocumab (AMG 145): Programme PROFICIO

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>Combo-therapy</td>
<td>(N = 631)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Monotherapy</td>
<td>(N = 411)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Statin-intolerant</td>
<td>(N = 157)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>HeFH</td>
<td>(N = 161)</td>
</tr>
<tr>
<td>Phase 2/3</td>
<td>HoFH/Severe HeFH</td>
<td>(N ≤ 67)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Open-label Extension</td>
<td>(N &gt; 1000)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Secondary Prevention</td>
<td>(N = 22500)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>IVUS Plaque Atherome</td>
<td>(N = 900)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Phase 3</td>
<td>(N = 1700)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Phase 3</td>
<td>(N = 600)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Phase 3</td>
<td>(N = 300)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Phase 3</td>
<td>(N = 300)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Phase 3</td>
<td>(N ≤ 3800)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Phase 3</td>
<td>(N = 75)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Phase 3</td>
<td>(N ≤ 3800)</td>
</tr>
</tbody>
</table>
RUTHERFORD-2 : Study Design

Screening Period with Placebo Injection → Randomization → Evolocumab 140 mg SC Q2W N = 111
   → Evolocumab 420 mg SC QM N = 110
   → Placebo SC Q2W N = 55
   → Placebo SC QM N = 55

End of Study

Max. 6 weeks

Day 1 Week 2 Week 4 Week 6 Week 8 Week 10 Week 12 Week 14

Evolocumab or placebo SC Q2W
Evolocumab or placebo SC QM

\(^a\) N's are number of patients randomized. One patient in each of the placebo Q2W and evolocumab Q2W groups did not receive any doses of the study drug and were not included in the analyses

\(^b\) Injections at weeks 4 and 6 were done at home

\(^c\) Week 14 was a follow-up call for Q2W patients to capture adverse events and concomitant medications

Q2W, biweekly; QM, monthly; SC, subcutaneous

# Rutherford-2: Baseline Lipids

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Q2W (N = 54)</th>
<th>Evolocumab 140 mg Q2W (N = 110)</th>
<th>Placebo QM (N = 55)</th>
<th>Evolocumab 420 mg QM (N = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C&lt;sup&gt;a&lt;/sup&gt; (mg/dL), mean (SD)</td>
<td>151 (37)</td>
<td>161 (51)</td>
<td>152 (43)</td>
<td>154 (43)</td>
</tr>
<tr>
<td>ApoB (mg/dL), mean (SD)</td>
<td>114 (30)</td>
<td>119 (31)</td>
<td>110 (22)</td>
<td>115 (26)</td>
</tr>
<tr>
<td>HDL-C (mg/dL), mean (SD)</td>
<td>53 (17)</td>
<td>50 (16)</td>
<td>49 (13)</td>
<td>52 (16)</td>
</tr>
<tr>
<td>ApoA1 (mg/dL), mean (SD)</td>
<td>145 (28)</td>
<td>142 (34)</td>
<td>135 (24)</td>
<td>143 (29)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL), median (Q1, Q3)</td>
<td>96 (75, 143)</td>
<td>119 (87, 161)</td>
<td>102 (79, 151)</td>
<td>113 (85, 157)</td>
</tr>
<tr>
<td>Lp(a) (nmol/L), median (Q1, Q3)</td>
<td>44 (24, 105)</td>
<td>78 (29, 206)</td>
<td>87 (36, 219)</td>
<td>61 (17, 194)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL. Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); Q2W, biweekly; QM, monthly; SD, standard deviation.
RUTHERFORD-2: Mean % change in LDL-C\textsuperscript{a} from Baseline to the Mean of weeks 10 and 12, and week 12 alone

\textsuperscript{a} Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL.

\textsuperscript{b} \textit{P} < 0.001; placebo-adjusted treatment difference analyzed using repeated measures model which included treatment group, stratification factors (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates. LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly; SE, standard error
Evolocumab (AMG 145): Programme PROFICIO

**Combo-therapy**
- Phase 2 (N = 631)

**Mono-therapy**
- Phase 2 (N = 411)

**Statin-intolerant**
- Phase 2 (N = 157)

**HeFH**
- Phase 2 (N = 161)

**HoFH/Severe HeFH**
- Phase 2/3 (N ≤ 67)

**Open-label Extension**
- Phase 2 (N > 1000)

**Secondary Prevention**
- Phase 3 (N = 22500)

**IVUS Plaque Atherome**
- Phase 3 (N = 900)
Evolocumab in HoFH: TESLA (part B)

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n=16)</th>
<th>Evolocumab group (n=33)</th>
<th>All patients (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LDL-C (UC) mmol/L</td>
<td>8.7 (337)</td>
<td>9.2 (356)</td>
<td>9.0 (348)</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lipid-lowering therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Statin</td>
<td>100 %</td>
<td>100 %</td>
<td>100 %</td>
</tr>
<tr>
<td>- Ezetimibe</td>
<td>94 %</td>
<td>91 %</td>
<td>92 %</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LDL receptors mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True homozygous</td>
<td>7 (44 %)</td>
<td>15 (45 %)</td>
<td>22 (45 %)</td>
</tr>
<tr>
<td>Compound heterozygous</td>
<td>7 (44 %)</td>
<td>16 (48 %)</td>
<td>23 (47 %)</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>0</td>
<td>1 (3 %)</td>
<td>1 (2 %)</td>
</tr>
<tr>
<td>- Apolipoprotein B</td>
<td>2 (13 %)</td>
<td>0</td>
<td>2 (4 %)</td>
</tr>
<tr>
<td>- Autosomal recessive hypercholesterolemia</td>
<td>0</td>
<td>1 (3 %)</td>
<td>1 (2 %)</td>
</tr>
</tbody>
</table>
Evolocumab in HoFH: TESLA (part B)

Mean % in UC LDL-C from baseline to week 12

Evolocumab in HoFH : TESLA (part B)

% change in LDL-C at week 12 according to receptor mutation status

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Evolocumab group</th>
<th>Treatment difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>n = 16</td>
<td>n = 33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (UC)</td>
<td>7.9 %</td>
<td>-23.1 %</td>
<td>-30.9 %</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LDL-R mutations status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defective in one or both alleles</td>
<td>n = 8</td>
<td>n = 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (UC)</td>
<td>11.2 %</td>
<td>-29.6 %</td>
<td>-40.8 %</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Defective/defective status</td>
<td>n = 5</td>
<td>n = 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (UC)</td>
<td>15.1 %</td>
<td>-31.8 %</td>
<td>-46.9 %</td>
<td>0.0006</td>
</tr>
<tr>
<td>Defective/negative status</td>
<td>n = 3</td>
<td>n = 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (UC)</td>
<td>3.5 %</td>
<td>-21.0 %</td>
<td>-24.5 %</td>
<td>0.0128</td>
</tr>
<tr>
<td>Unclassified mutation status</td>
<td>n = 6</td>
<td>n = 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (UC)</td>
<td>3.8 %</td>
<td>-17.9 %</td>
<td>-21.7 %</td>
<td>0.13</td>
</tr>
<tr>
<td>Negative/negative mutation status</td>
<td>n = 0</td>
<td>n = 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (UC)</td>
<td>10.3 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-R heterozygous status</td>
<td>n = 0</td>
<td>n = 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (UC)</td>
<td>-55.7 %</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evolocumab (AMG 145): Programme PROFICIO

- Combo-therapy
  - Phase 2 (N = 631)
  - Phase 3 (N = 1700)

- Monotherapy
  - Phase 2 (N = 411)
  - Phase 3 (N = 600)

- Statin-intolerant
  - Phase 2 (N = 157)
  - Phase 3 (N = 300)

- HeFH
  - Phase 2 (N = 161)
  - Phase 3 (N = 300)

- HoFH/Severe HeFH
  - Phase 2/3 (N ≤ 67)
  - Phase 3 (N = 75)

- Open-label Extension
  - Phase 2 (N > 1000)
  - Phase 3 (N ≤ 3800)

- Secondary Prevention
  - Phase 3 (N = 22500)

- IVUS Plaque Atherome
  - Phase 3 (N = 900)
4465 patients (74%) elected to enroll into OSLER extension study program
1324 from Ph2 trials into OSLER-1
3141 from Ph3 trials into OSLER-2

Randomized 2:1
Evolocumab plus standard of care (n=2976)
Standard of care alone (n=1489)

Median follow-up of 11.1 months (IQR 11.0-12.8)
7% discontinued evolocumab early
96% completed follow-up

Trial Sponsor: Amgen
**LDL Cholesterol**

**Standard of care alone**
- Median LDL-C (mg/dL)
- 61% reduction (95%CI 59-63%), P<0.0001
- Absolute reduction: 73 mg/dL (95%CI 71-76%)

**Evolocumab plus standard of care**

<table>
<thead>
<tr>
<th>Time</th>
<th>N (Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4465</td>
</tr>
<tr>
<td>4 weeks</td>
<td>1258</td>
</tr>
<tr>
<td>12 weeks</td>
<td>4259</td>
</tr>
<tr>
<td>24 weeks</td>
<td>4204</td>
</tr>
<tr>
<td>36 weeks</td>
<td>1243</td>
</tr>
<tr>
<td>48 weeks</td>
<td>3727</td>
</tr>
</tbody>
</table>

(Sabatine et al. N Engl J Med 2015; March 15: online)
Other Lipid Parameters

52% ↓ in Non-HDL-C

47% ↓ in ApoB

26% ↓ in Lp(a)

13% ↓ in Triglycerides

7% ↑ in HDL-C

4% ↑ in ApoA1

Week 12 data; values are means except for TG and Lp(a) which are medians.

Standard of care alone
Evolocumab plus standard of care
Cardiovascular Outcomes

Composite Endpoint: Death, MI, UA → hosp, coronary revasc, stroke, TIA, or CHF → hosp

Evolocumab plus standard of care (N=2976)

Standard of care alone (N=1489)

HR 0.47
95% CI 0.28-0.78
P=0.003

Cumulative Incidence (%)

Days since Randomization

Sabatine et al. N Engl J Med 2015; March 15: online
## Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab + stnd of care (N=2976)</th>
<th>Standard of care alone (N=1489)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>All CV Events</td>
<td>29</td>
<td>0.95</td>
<td>31</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
<td>0.14</td>
<td>6</td>
</tr>
<tr>
<td>Coronary Events (MI, hosp for UA, or revasc)</td>
<td>22</td>
<td>0.75</td>
<td>18</td>
</tr>
<tr>
<td>Cerebrovasc Events (Stroke or TIA)</td>
<td>4</td>
<td>0.14</td>
<td>7</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>1</td>
<td>0.03</td>
<td>1</td>
</tr>
</tbody>
</table>

% are KM event rates at 1 year except for HF, which is a crude %

Sabatine et al. N Engl J Med 2015; March 15; online
## Safety

<table>
<thead>
<tr>
<th>Adverse events (%)</th>
<th>Evolocumab + std of care (N=2976)</th>
<th>Standard of care alone (N=1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>69.2</td>
<td>64.8</td>
</tr>
<tr>
<td>Serious</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Leading to discontinuation of evolocumab</td>
<td>2.4</td>
<td>n/a</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>4.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>6.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>0.9</td>
<td>0.3</td>
</tr>
</tbody>
</table>

### Laboratory results (%)

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab + std of care (N=2976)</th>
<th>Standard of care alone (N=1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT or AST &gt;3×ULN</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Creatine kinase &gt;5×ULN</td>
<td>0.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Summary for Evolocumab

↓ LDL-C by 61% at 12 weeks
  ▪ Absolute decrease of 73 mg/dL
  ▪ Median achieved LDL-C of 48 mg/dL

↓ CV outcomes by 53% over 1 year
  ▪ Prespecified, exploratory outcome with relatively few events
  ▪ Event curves diverged early & continued to separate over time
  ▪ Consistent effect on death, coronary, and cerebrovasc. events
  ▪ Consistent effect in major subgroups

Appeared to be well-tolerated
  ▪ AEs largely balanced, good tolerability in this extension study
  ▪ No gradient in incidence of any AE by achieved LDL-C, including in those with LDL-C < 25 mg/dL
Mean Percent Change from Baseline in LDL Cholesterol Values among Healthy Volunteers in Single-Dose Studies.

Alirocumab

ODYSSEY Programme
Overview of ODYSSEY Phase 3 Clinical Trial Program

<table>
<thead>
<tr>
<th>HeFH population</th>
<th>HC in high CV risk population</th>
<th>Additional populations</th>
</tr>
</thead>
</table>
| **Add-on to max-tolerated statin (± other LMT)** | **Add-on to max-tolerated statin (± other LMT)** | **ODYSSEY MONO (NCT01644474; EFC11716)**
Patients on no background LMTs
LDL-C ≥100 mg/dL
N=100; 6 months |
| ODYSSEY FH I (NCT01623115; EFC12492) | ODYSSEY COMBO I (NCT01644175; EFC11568) | ODYSSEY ALTERNATIVE (NCT01709513; CL1119)
Patients with defined statin intolerance
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=250; 6 months |
| LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=471; 18 months | LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=306; 12 months | *ODYSSEY COMBO II (NCT01644188; EFC11569)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=660; 24 months |
| ODYSSEY FH II (NCT01709500; CL1112) | *ODYSSEY COMBO II (NCT01644188; EFC11569) | ODYSSEY CHOICE I (NCT01926782; CL1308)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=700; 12 months |
| LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=250; 18 months | LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=660; 24 months | ODYSSEY CHOICE II (NCT02023879; EFC13786)
Patients not treated with a statin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=200; 6 months |
| ODYSSEY HIGH FH (NCT01617655; EFC12732) | ODYSSEY MONO (NCT01644474; EFC11716) | ODYSSEY OPTIONS I (NCT01730040; CL1110)
Patients not at goal on moderate dose atorvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=350; 6 months |
| LDL-C ≥160 mg/dL
N=105; 18 months | ODYSSEY ALTERNATIVE (NCT01709513; CL1119) | ODYSSEY OPTIONS II (NCT01730053; CL1118)
Patients not at goal on moderate dose rosvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=300; 6 months |
| ODYSSEY OLE (NCT01954394; LTS 13463) | ODYSSEY CHOICE I (NCT01926782; CL1308)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=700; 12 months | ODYSSEY OPTIONS II (NCT01730053; CL1118) | Open-label study for FH from EFC 12492,
CL 1112, EFC 12732 or LTS 11717
N=1000; 30 months |
| Open-label study for FH from EFC 12492,
CL 1112, EFC 12732 or LTS 11717
N=1000; 30 months | *For the ODYSSEY COMBO II other LMT not allowed at entry. |
| LDL-C ≥70 mg/dL
N=2,100; 18 months | LDL-C ≥70 mg/dL
N=1000; 30 months | FH=familial hypercholesterolemia; HC=hypercholesterolemia; LMT=lipid-modifying therapy; OLE=open-label extension. |
| ODYSSEY COMBO II (NCT01644188; EFC11569) | ODYSSEY OLE (NCT01954394; LTS 13463) | *ODYSSEY COMBO II (NCT01644188; EFC11569)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=660; 24 months |
| LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=660; 24 months | LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=660; 24 months | ODYSSEY OUTCOMES (NCT01663402; EFC11570)
LDL-C ≥70 mg/dL
N=18,000; 64 months |
| ODYSSEY OUTCOMES (NCT01663402; EFC11570) | ODYSSEY OLE (NCT01954394; LTS 13463) | ODYSSEY OPTIONS II (NCT01730053; CL1118) | LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=300; 6 months |
| LDL-C ≥70 mg/dL
N=18,000; 64 months | LDL-C ≥70 mg/dL
N=18,000; 64 months | ODYSSEY OPTIONS II (NCT01730053; CL1118) | LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=300; 6 months |

FH=familial hypercholesterolemia; HC=hypercholesterolemia; LMT=lipid-modifying therapy; OLE=open-label extension.

*For the ODYSSEY COMBO II other LMT not allowed at entry.

ODYSSEY COMBO I : Study Design

Clinicaltrials.gov identifier: NCT01644175

Stratified by Hx MI or ischemic stroke, intensity of statin Rx (high vs not high)

High CV risk on maximally tolerated statin ± other LLT

I. LDL-C ≥70 mg/dL (manifest CVD)
   or
II. LDL-C ≥100 mg/dL (DM + other risk factors/CKD)

Assessments

W0 W4 W8 W12 W16 W24 W36 W52 W60

Dose ↑ if LDL-C ≥70 mg/dL at W8

Primary endpoint

End of treatment visit

Double-blind treatment period (52 weeks)
All patients on background maximally tolerated statin ± other LLT

Follow-up (8 weeks)

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

N=209

N=107

Placebo Q2W SC
Primary Endpoint Analysis: % Reduction in LDL-C from Baseline to Week 24 (vs Placebo)

All patients on background of maximally tolerated statin ± other LLT

LS mean (SE) % change from baseline to Week 24:

- Placebo: -2.3%
- Alirocumab: -48.2%

ITT:
- Placebo: -0.8
- Alirocumab: -50.7

On-treatment analysis:
- Placebo: -49.9 (3.2)*
- Alirocumab: -45.9 (3.3)*

*P<0.0001

LS mean % difference (SE) vs placebo:

16.8% received 150 mg Q2W at W12

Kereiakes, AHA 2014
LDL-C Levels Over Time by Treatment (ITT)

All patients on background of maximally tolerated statin ± other LLT

ITT analysis.
Per-protocol dose increase (n=32, 16.8%)
LDL-C Levels Over Time for Alirocumab-Treated Patients With/Without Dose Increase at Week 12

Per-protocol dose increase

% values indicated at Weeks 12, 24, and 52 show % change from baseline.
Clinicaltrials.gov identifiers: ODYSSEY FH I: NCT01623115; ODYSSEY FH II: NCT01709500.

**ODYSSEY FH I and FH II Study Design**

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)

**Placebo Q2W SC**

**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=167 (FH II)

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

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

**Assessments**

<table>
<thead>
<tr>
<th>W0</th>
<th>W8</th>
<th>W16</th>
</tr>
</thead>
<tbody>
<tr>
<td>W4</td>
<td>W12</td>
<td>W24</td>
</tr>
<tr>
<td>W36</td>
<td>W52</td>
<td>W64</td>
</tr>
<tr>
<td>W78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dose ↑ if LDL-C >70 mg/dL at W8

Primary efficacy endpoint

**Pre-specified analysis**

Efficacy: All Patients To W52
Safety: Baseline-W78 (all patients at least W52)
Patients should receive either rosuvastatin 20-40 mg, atorvastatin 40-80 mg daily, or simvastatin 80 mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator.

High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily.

### Lipid Medication and LDL-C at Baseline

<table>
<thead>
<tr>
<th>All patients on background of max-tolerated statin ± other lipid-lowering therapy</th>
<th>FH I</th>
<th>FH II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alirocumab (N=323)</td>
<td>Placebo (N=163)</td>
</tr>
<tr>
<td>Any statin†, % (n)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>High-intensity statin‡, % (n)</td>
<td>80.8% (261)</td>
<td>82.8% (135)</td>
</tr>
<tr>
<td>Ezetimibe, % (n)</td>
<td>55.7% (180)</td>
<td>59.5% (97)</td>
</tr>
<tr>
<td>LDL-C, mean (SD), mmol/L [mg/dL]</td>
<td>3.7 (1.3) [144.7 (51.2)]</td>
<td>3.7 (1.2) [144.4 (46.8)]</td>
</tr>
</tbody>
</table>

†Patients should receive either rosuvastatin 20-40 mg, atorvastatin 40-80 mg daily, or simvastatin 80 mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator.

‡High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily.

Kastelein, ESC 2014
Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 versus Placebo

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C

All patients on background max-tolerated statin ± other lipid-lowering therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>LS Mean Difference (SE) vs. Placebo</th>
<th>% Change from Baseline to Week 24</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH I</td>
<td>-48.8% (2.7)</td>
<td>43.4% had dose increase at W12</td>
<td>N=322</td>
</tr>
<tr>
<td>FH II</td>
<td>-48.7% (3.4)</td>
<td>38.6% had dose increase at W12</td>
<td>N=166</td>
</tr>
</tbody>
</table>

Intent-to-treat (ITT) Analysis

Kastelein, ESC 2014
Alirocumab Maintained Consistent LDL-C Reductions Over 52 Weeks

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

<table>
<thead>
<tr>
<th>Placebo:</th>
<th>FH I</th>
<th>Alirocumab:</th>
<th>FH I</th>
<th>FH II</th>
</tr>
</thead>
</table>

- **LDL-C, LS mean (SE), mmol/L**
  - **Placebo:**
    - FH I: 4.5 mmol/L
    - FH II: 4.0 mmol/L
  - **Alirocumab:**
    - FH I: 3.5 mmol/L
    - FH II: 3.7 mmol/L

- **mg/dL**
  - **Placebo:**
    - FH I: 1.8 mmol/L
    - FH II: 1.9 mmol/L
  - **Alirocumab:**
    - FH I: 1.8 mmol/L
    - FH II: 1.7 mmol/L

- **Intention-to-treat (ITT) Analysis**
- **LLT = lipid-lowering therapy**

**Kastelein, ESC 2014**

- **Dose ↑ if LDL-C >70 mg/dL at W8**
HeFH or High CV-risk patients
On max-tolerated statin ± other lipid-lowering therapy
LDL-C ≥1.81 mmol/L [70 mg/dL]

Double-blind treatment (18 months)
Follow-up (8 weeks)

n=1553

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

n=788

Placebo Q2W SC

Assessments
W0 W8 W16 W24 W36 W52 W64 W78

Primary efficacy endpoint
Pre-specified analysis
Efficacy: All Patients To W52
Safety: Baseline-W78 (all patients at least W52)

86% (2011/2341) completed 52 weeks (both treatment arms)
26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) had completed 78 weeks by time of this analysis
Mean treatment duration: 65 weeks (both treatment arms)

ClinicalTrials.gov identifier: NCT01507831.
## Baseline Characteristics

<table>
<thead>
<tr>
<th>All patients on background of max-tolerated statin ± other lipid-lowering therapy</th>
<th>Alirocumab (n=1553)</th>
<th>Placebo (n=788)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>60.4 (10.4)</td>
<td>60.6 (10.4)</td>
</tr>
<tr>
<td><strong>Male, % (n)</strong></td>
<td>63.3% (983)</td>
<td>60.2% (474)</td>
</tr>
<tr>
<td><strong>Race, White</strong></td>
<td>92.8% (1441)</td>
<td>92.6% (730)</td>
</tr>
<tr>
<td><strong>BMI, kg/m², mean (SD)</strong></td>
<td>30.2 (5.7)</td>
<td>30.5 (5.5)</td>
</tr>
<tr>
<td><strong>HeFH, % (n)</strong></td>
<td>17.8% (276)</td>
<td>17.6% (139)</td>
</tr>
<tr>
<td><strong>CHD history, % (n)</strong></td>
<td>67.9% (1055)</td>
<td>70.1% (552)</td>
</tr>
<tr>
<td><strong>Type 2 diabetes, % (n)</strong></td>
<td>34.9% (542)</td>
<td>33.9% (267)</td>
</tr>
<tr>
<td><strong>Any statin†, % (n)</strong></td>
<td>99.9% (1552)</td>
<td>99.9% (787)</td>
</tr>
<tr>
<td><strong>High-intensity statin‡, % (n)</strong></td>
<td>44.4% (690)</td>
<td>43.4% (342)</td>
</tr>
<tr>
<td><strong>Any LLT other than statins, % (n)</strong></td>
<td>28.1% (437)</td>
<td>27.9% (220)</td>
</tr>
<tr>
<td><strong>Ezetimibe, % (n)</strong></td>
<td>13.9% (216)</td>
<td>15.0% (118)</td>
</tr>
<tr>
<td><strong>LDL-C, calculated mean (SD), mmol/L [mg/dL]</strong></td>
<td>3.2 (1.1) [122.7 (42.6)]</td>
<td>3.2 (1.1) [121.9 (41.4)]</td>
</tr>
</tbody>
</table>

†Patients should receive either rosvuastatin 20-40 mg, atorvastatin 40-80 mg daily, or simvastatin 80 mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator

‡High-intensity statin: atorvastatin 40-80 mg or rosvuastatin 20-40 mg daily.
Alirocumab Maintained Consistent LDL-C Reductions Over 52 Weeks

Achieved LDL-C Over Time

All patients on background of maximally tolerated statin ± other lipid-lowering therapy

![Graph showing LDL-C levels over time for Alirocumab and Placebo]

- **Alirocumab**
  - Week 0: 118.9 mg/dL (+0.8%)
  - Week 52: 53.1 mg/dL (−56.8%)

- **Placebo**
  - Week 0: 123.0 mg/dL (+4.4%)
  - Week 52: 53.1 mg/dL (−56.8%)

Intent-to-treat (ITT) analysis

Robinson et al. N Enl J Med 2015; March 15: online
*Post-hoc* Adjudicated Cardiovascular TEAEs
(Same as primary endpoint of ongoing ODYSSEY OUTCOMES trial†)

**Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event**
Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

Cox model analysis:
**HR=0.46 (95% CI: 0.26 to 0.82)**
Nominal p-value = <0.01

**Mean treatment duration: 65 weeks**

---

**Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event**

- **Placebo + max-tolerated statin ± other LLT**
- **Alirocumab + max-tolerated statin ± other LLT**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Placebo</th>
<th>Alirocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>788</td>
<td>1550</td>
</tr>
<tr>
<td>12</td>
<td>776</td>
<td>1534</td>
</tr>
<tr>
<td>24</td>
<td>731</td>
<td>1446</td>
</tr>
<tr>
<td>36</td>
<td>703</td>
<td>1393</td>
</tr>
<tr>
<td>48</td>
<td>682</td>
<td>1352</td>
</tr>
<tr>
<td>60</td>
<td>667</td>
<td>1335</td>
</tr>
<tr>
<td>72</td>
<td>321</td>
<td>642</td>
</tr>
<tr>
<td>84</td>
<td>127</td>
<td>252</td>
</tr>
<tr>
<td>96</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**No. at Risk**

- Placebo
  - 788
  - 776
  - 731
  - 703
  - 682
  - 667
  - 321
  - 127
  - 0

- Alirocumab
  - 1550
  - 1534
  - 1446
  - 1393
  - 1352
  - 1335
  - 642
  - 252
  - 0

†Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. LLT, lipid-lowering therapy

Cannon et al. Eur Heart J 2015; Feb 16: online
➡️ Bococizumab

SPIRE Programme
Results of Bococizumab, a Monoclonal Antibody Against Proprotein Convertase Subtilisin/Kexin Type 9, from a Randomized, Placebo-Controlled, Dose-Ranging Study in Statin-Treated Subjects With Hypercholesterolemia

Christie M. Ballantyne, MDa,b, Joel Neutel, MDC, Anne Cropp, PharmDd, William Duggan, PhD, Ellen Q. Wang, PhD, David Plowchalk, PhD, Kevin Sweeney, PhD, Nitin Kaila, PhD, John Vincent, MD, PhD, and Harold Bays, MD

aSection of Cardiovascular Research, Division of Atherosclerosis, Department of Medicine, Baylor College of Medicine, Houston, Texas; bCenter for Cardiovascular Research, Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas; cOrange County Research Center, Tustin, California; dClinical Sciences, Global Innovative Pharma Business, Pfizer Inc., Groton, Connecticut; eStatistics, Global Innovative Pharma Business, Pfizer Inc., Groton, Connecticut; fClinical Pharmacology, Global Innovative Pharma Business, Pfizer Inc., New York, New York; gClinical Pharmacology, Global Innovative Pharma Business, Pfizer Inc., Groton, Connecticut; hClinical Sciences, Global Innovative Pharma Business, Pfizer Inc., New York, New York; and iLouisville Metabolic and Atherosclerosis Research Center, Louisville, Kentucky
Objective

This dose-ranging phase 2b study (NCT01592240) evaluated the LDL-C–lowering effect of subcutaneous (SC) doses of bococizumab administered every 2 weeks (Q14 days) or monthly (Q28 days).

- A unique aspect of the trial design was the incorporation of bococizumab dose reductions if persistent LDL-C values ≤25 mg/dL were achieved.

- This was the first study of a PCSK9 inhibitor to report the impact on LDL-C reduction when a dose reduction strategy is used in an effort to prevent extremely low levels of LDL-C.
Adjusted LS-mean changes from baseline in LDL-C versus placebo* up to week 12 in subjects receiving bococizumab Q14 days

* Placebo Q14 days (n=44-48).

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least-squares.
Adjusted LS-mean changes from baseline in LDL-C versus placebo* up to week 12 in subjects receiving bococizumab Q28 days

* Placebo Q28 days (n=46-48).

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least-squares.
SPIRE Phase 3 Bococizumab Clinical Development Program: Designed to Address Unmet Needs in the Management of CVD in High Risk Patients

**SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) N=~30,000**

**SPIRE Lipid Lowering Studies**
- **SPIRE HR (n=600)**
  - On statin
  - High risk of CV event
  - LDL-C ≥70 mg/dL
- **SPIRE LDL (n=1,932)**
  - On statin
  - High risk of CV event
  - LDL-C ≥70 mg/dL
- **SPIRE FH (n=300)**
  - HeFH (genetic diagnosis or Simon Broome Criteria), LDL >70 mg/dL
- **SPIRE SI (n=150)**
  - Statin intolerant
  - LDL-C ≥70 mg/dL

**SPIRE CV Outcome Studies**
- **SPIRE-1 (n=17,000)**
  - High Risk Primary and Secondary Prevention
  - LDL-C ≥70 to <100 mg/dL on highly effective statin (or statin intolerant)
- **SPIRE-2 (n=9,000)**
  - High Risk Primary and Secondary Prevention
  - LDL-C ≥100 mg/dL on highly effective statin (or statin intolerant)

NCT#: https://clinicaltrials.gov
SPIRE HR: NCT01968954
SPIRE LDL: NCT01968967
SPIRE HF: NCT01968980
SPIRE-LL: NCT02100514
SPIRE-SI: NCT02135029
SPIRE-1: NCT01975376
SPIRE-2: NCT01975389
In Summary
Approximate LDL-C Reductions\textsuperscript{a} Across anti-PCKS9 monoclonal antibodies

- **High-risk patients on maximally lipid-lowering therapy**
  - 48-61\% \textsuperscript{1,2}

- **HeFH patients, in combination with statins**
  - 45-63\% \textsuperscript{3-5}

- **Statin-intolerant patients**
  - 50-60\% \textsuperscript{6,7}

\textsuperscript{a} Absolute reductions, not adjusted for placebo

Evaluating cardiovascular event reduction and safety on a background treatment with statin therapy in patients at very high risk of atherothrombotic event

<table>
<thead>
<tr>
<th>Name</th>
<th>Molecule</th>
<th>Number of patients</th>
<th>Type of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY-OUTCOMES¹</td>
<td>Alirocumab</td>
<td>18,000</td>
<td>Recently (&lt; 52 weeks) ACS</td>
</tr>
<tr>
<td>FOURIER²</td>
<td>Evolocumab</td>
<td>27,500</td>
<td>History of clinically evident cardiovascular disease at high risk for a recurrent event</td>
</tr>
<tr>
<td>SPIRE-1³</td>
<td>Bococizumab</td>
<td>17,000</td>
<td>High risk of a CV event</td>
</tr>
<tr>
<td>SPIRE-2⁴</td>
<td>Bococizumab</td>
<td>9,000</td>
<td>High risk of a CV event</td>
</tr>
</tbody>
</table>

CVD: Cardiovascular Disease

www.ClinicalTrials.gov identifiers: (last access March 2014)  
1. NCT 01663402; 2. NCT 01764633; 3. NCT 01975376; 4. NCT 01975398
Conclusion

All these data support for PCSK9 inhibitor as an effective strategy to reduce atherogenic lipoproteins and major CV events