Innovations in lipid management:
Evolving insights and implications from PCSK9 research

PCSK9 inhibition: Novel insights into a new therapeutic approach for the lowering of LDL-C: the PCSK9 saga

Prof. Evan Stein, MD
Metabolic and Atherosclerosis Research Center, Cincinnati, USA

Presented - August 30, 2014
PCSK9 Inhibition: Mechanistic insights into a new therapeutic approach for the lowering of LDL cholesterol

- Role of PCSK9 in LDL cholesterol homeostasis
- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Non familial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin adverse patients
  - Heterozygous familial hypercholesterolemia
  - Homozygous familial hypercholesterolemia
- Effect on Lp(a)
- Safety and tolerability
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Approaches to Reducing PCSK9 interaction with LDL receptor

- Bind plasma PCSK9
  - Monoclonal antibodies (Regeneron/Sanofi, Amgen, Pfizer, Lily)
  - Adnectins (Adnexis/BMS)

- Reduce PCSK9 synthesis
  - siRNA (Alnylam)
Impact of an PCSK9 mAb on LDL Receptor Expression
Impact of an PCSK9 synthesis inhibition on LDL Receptor Expression
Dynamic Relationship Between mAb Levels, PCSK9 and LDL-C

Total REGN727/SAR236553 Concentration vs. Time

Free/Total PCSK9 Conc. (ng/mL) vs. Time (hours)

Time (hours)

Total REGN727/SAR236553
Dynamic Relationship Between mAb Levels, free PCSK9 and LDL-C

Free PCSK9, Total REGN727 /SAR236553 Concentration, and LDL-c mean % change vs. Time
Dynamic Relationship Between mAb Levels, free PCSK9 and LDL-C

Free PCSK9, Total REGN727 /SAR236553 Concentration, and LDL-c mean % change vs. Time

- Total REGN727/SAR236553
- free PCSK9
- LDL-c
PCSK9 Inhibition: Mechanistic insights into a new therapeutic approach for the lowering of LDL cholesterol

- Role of PCSK9 in LDL cholesterol homeostasis
- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Non familial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin adverse patients
  - Heterozygous familial hypercholesterolemia
  - Homozygous familial hypercholesterolemia
- Effect on Lp(a)
- Safety and tolerability
# Dose Groups

<table>
<thead>
<tr>
<th>REGN727 Dose</th>
<th>Patient Group</th>
<th>Total # Pts (R727:Pbo)</th>
<th>HeFH Status</th>
<th>Screening LDL-C (mg/dL)</th>
<th>Atorvastatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>50mg</td>
<td>1</td>
<td>7 (5:2)</td>
<td>HeFH</td>
<td>&gt;100</td>
<td>10-40 mg QD</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10 (8:2)</td>
<td>Non-FH</td>
<td>&gt;100</td>
<td>10-40 mg QD</td>
</tr>
<tr>
<td>100mg</td>
<td>3</td>
<td>7 (5:2)</td>
<td>HeFH</td>
<td>&gt;100</td>
<td>10-40 mg QD</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10 (8:2)</td>
<td>Non-FH</td>
<td>&gt;100</td>
<td>10-40 mg QD</td>
</tr>
<tr>
<td>150mg</td>
<td>5</td>
<td>7 (5:2)</td>
<td>HeFH</td>
<td>&gt;100</td>
<td>10-40 mg QD</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>10 (8:2)</td>
<td>Non-FH</td>
<td>&gt;100</td>
<td>10-40 mg QD</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>10 (8:2)</td>
<td>Non-FH</td>
<td>&gt;130</td>
<td>None (Diet alone)</td>
</tr>
</tbody>
</table>

Stein et al NEJM 2012; 366:1108-18
LDL-C and Apolipoprotein B Response
Mean % Change from Baseline with alirocumab

* P < 0.0001 vs. Placebo
† P < 0.01 vs. Placebo

Stein et al NEJM  2012; 366:1108-18
Inhibition of PCSK9 with mAb

- Is there a limit to LDL-C reduction with a mAb?
- How long will effect last?
Evolocumab (AMG 145) Every 2 Weeks: LDL-C Percentage Change From Baseline

Mean percentage change from baseline in calculated LDL-C.

Evolocumab (AMG 145) Every 4 Weeks: LDL-C Percentage Change From Baseline

Mean percentage change from baseline in calculated LDL-C.

Inhibition of PCSK9 with mAb

- Is there a limit to LDL-C reduction with a mAb?
  - Yes – once all free PCSK9 is bound no additional LDL-C reductions occurs

- How long will effect last?
  - The larger the dose the longer the duration of the effect
  - ‘Rule of thumb’ is it requires 3 times higher dose to achieve same reduction in LDL-C when dosed every 4 weeks than is required for every 2 week dosing (e.g. 140 Q2W = 420 mg Q4W)
  - The physical limitation on the amount of mAb in 1 mL is ~150 mg, thus larger doses require larger injection volumes
PCSK9 Inhibition: Mechanistic insights into a new therapeutic approach for the lowering of LDL cholesterol

- Role of PCSK9 in LDL cholesterol homeostasis
- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Non familial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin adverse patients
  - Heterozygous familial hypercholesterolemia
  - Homozygous familial hypercholesterolemia
- Effect on Lp(a)
- Safety and tolerability
DESCARTES: % Change in LDL-C from baseline in patients on various background treatments

Error bars represent standard error for treatment difference
Treatment difference are least squares mean derived from a repeated measures model
UC LDL-C at week 52

Blom et al NEJM 2014:370:1809-19
DESCARTES: Long term stability of LDL-C reduction

FAS = Full analysis set, UC = Ultracentrifugation

Blom et al NEJM 2014:370:1809-19
GAUSS-2 Study Design

Screening and placebo run-in period
Fasting LDL-C 5–10 days before randomization
Subcutaneous injection of placebo

Randomization 2:2:1:1

- Evolocumab 140 mg SC Q2W + Placebo PO QD
  - N = 103

- Evolocumab 420 mg SC QM + Placebo PO QD
  - N = 102

- Placebo SC Q2W + Ezetimibe 10 mg PO QD
  - N = 51

- Placebo SC QM + Ezetimibe 10 mg PO QD
  - N = 51

Maximum 6 weeks

Time point
- 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

EOS* Q2W

EOS QM

Prior intolerance to ≥2 statins: LDL-C above NCEP ATP III risk category goal: Weekly dose 7 times the smallest available tablet strength or less

Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548
## GAUSS-2: Statin Intolerance History

<table>
<thead>
<tr>
<th></th>
<th>Biweekly</th>
<th>Monthly</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO Q2W + EZE QD (N = 51)</td>
<td>Evolocumab 140 mg Q2W + PBO QD (N = 103)</td>
<td>PBO QM + EZE QD (N = 51)</td>
</tr>
<tr>
<td>Number of intolerable statins, %</td>
<td>2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Worst muscle-related side effect*, %</td>
<td>Myalgia</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Myositis</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Any lipid-lowering therapy at baseline, %</td>
<td>29</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Any statin at baseline</td>
<td>18</td>
<td>18</td>
<td>20</td>
</tr>
</tbody>
</table>

*Data missing for one patient in the evolocumab Q2W arm. EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily.

Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548
### GAUSS-2: Key Baseline Lipids

<table>
<thead>
<tr>
<th></th>
<th>Biweekly</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO Q2W</td>
<td>Evolocumab</td>
</tr>
<tr>
<td></td>
<td>EZE QD (N = 51)</td>
<td>140 mg Q2W + PBO QD (N = 103)</td>
</tr>
<tr>
<td><strong>LDL-C</strong>, mg/dL</td>
<td><strong>195 (64)</strong></td>
<td><strong>192 (57)</strong></td>
</tr>
<tr>
<td><strong>ApoB</strong>, md/dL</td>
<td><strong>140 (37)</strong></td>
<td><strong>140 (32)</strong></td>
</tr>
<tr>
<td><strong>Lp(a)</strong>, nmol/L</td>
<td><strong>57 (22, 205)</strong></td>
<td><strong>39 (10, 101)</strong></td>
</tr>
<tr>
<td><strong>TG</strong>, mg/dL</td>
<td><strong>170 (120, 243)</strong></td>
<td><strong>165 (123, 224)</strong></td>
</tr>
<tr>
<td><strong>PCSK9</strong>, ng/mL</td>
<td><strong>317 (125)</strong></td>
<td><strong>285 (80)</strong></td>
</tr>
</tbody>
</table>

*Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was <40 mg/dL (1.0 mmol/L) or triglyceride levels were >400 mg/dL (3.9 mmol/L).

EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily; TG, triglycerides.

Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548
GAUSS-2: Biweekly Evolocumab LDL-C Response

Number of subjects:

<table>
<thead>
<tr>
<th>Study Week</th>
<th>BL</th>
<th>Day 1</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Ezetimibe (N = 51)</td>
<td>51</td>
<td>51</td>
<td>100</td>
<td>99</td>
<td>98</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: Evolocumab 140 mg Q2W (N = 103)</td>
<td>103</td>
<td>100</td>
<td>99</td>
<td>98</td>
<td>98</td>
<td>98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean Percent Change in LDL-C from Baseline

-80 -60 -40 -20 0

Study drug administration
Biweekly SC

BL, baseline. Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values. P values are multiplicity adjusted.

Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548
GAUSS-2: Monthly Evolocumab LDL-C Response

Study drug administration
Monthly SC

Mean Percent Change in LDL-C from Baseline

Number of subjects:

BL Day 1 Week 2 Week 4 Week 6 Week 8 Week 10 Week 12
51 102 50 100 51 100 44 91 45 96

1: Ezetimibe (N = 51) 2: Evolocumab 420 mg QM (N = 102)

BL, baseline. Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values. $P$ values are multiplicity adjusted.

Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548
GAUSS-2: LDL-C Goal Achievement at Week 12

Proportion of Patients Achieving LDL-C Target Goal at Week 12, n (%)

- Lower Risk* < 160 mg/dL
  - Ezetimibe QD + PBO Q2W: 12 (92%)
  - Evolocumab 140 mg Q2W + PBO QD: 7 (70%)
  - Ezetimibe QD + PBO QM: 0 (0%)

- Moderately High Risk < 130 mg/dL
  - Ezetimibe QD + PBO Q2W: 28 (80%)
  - Evolocumab 420 mg QM + PBO QD: 3 (20%)
  - Ezetimibe QD + PBO QM: 1 (8%)

- High Risk < 100 mg/dL
  - Ezetimibe QD + PBO Q2W: 29 (91%)
  - Evolocumab 140 mg Q2W + PBO QD: 28 (91%)
  - Ezetimibe QD + PBO QM: 1 (4%)
  - Evolocumab 420 mg QM + PBO QD: 2 (7%)

*Combination of NCEP ATP III moderate and low risk categories.
Rate based on subjects with observed values at Week 12 and LDL-C above target goal at baseline.

Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548
PCSK9 Inhibition: Mechanistic insights into a new therapeutic approach for the lowering of LDL cholesterol

- Role of PCSK9 in LDL cholesterol homeostasis
- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Non familial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin adverse patients
  - Heterozygous familial hypercholesterolemia
  - Homozygous familial hypercholesterolemia
- Effect on Lp(a)
- Safety and tolerability
Reduction in Lipoprotein(a) With PCSK9 Monoclonal Antibody Evolocumab (AMG 145): a Pooled Analysis of More Than 1,300 Patients in 4 Phase II Trials

Error bars represent standard error.

* P < 0.001

Raal et al JACC 2014;(): doi:10.1016/j.jacc.2014.01.006 Online First
PCSK9 Inhibition: Mechanistic insights into a new therapeutic approach for the lowering of LDL cholesterol

- Role of PCSK9 in LDL cholesterol homeostasis
- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Non familial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin adverse patients
  - Heterozygous familial hypercholesterolemia
  - Homozygous familial hypercholesterolemia
- Effect on Lp(a)
- Safety and tolerability
# AMG 145 Pooled analysis >1300 patients: Clinical Adverse Effects

<table>
<thead>
<tr>
<th>AMG 145 – by dose and dose frequency</th>
<th>Placebo (n=333)</th>
<th>All AMG 145 (n=981)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 mg Q2W (n=124)</td>
<td>65 (52.4)</td>
<td>164 (49.2)</td>
</tr>
<tr>
<td>105 mg Q2W (n=125)</td>
<td>74 (59.2)</td>
<td>557 (56.8)</td>
</tr>
<tr>
<td>140 mg Q2W (n=123)</td>
<td>69 (56.1)</td>
<td>25 (7.5)</td>
</tr>
<tr>
<td>280 mg Q4W (n=156)</td>
<td>89 (57.1)</td>
<td>81 (8.3)</td>
</tr>
<tr>
<td>350 mg Q4W (n=210)</td>
<td>118 (56.2)</td>
<td>11 (3.3)</td>
</tr>
<tr>
<td>420 mg Q4W (n=213)</td>
<td>122 (57.3)</td>
<td>32 (3.3)</td>
</tr>
</tbody>
</table>

AEs:<sup>a</sup>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>All AMG 145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>11 (8.9)</td>
<td>25 (7.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (3.2)</td>
<td>11 (3.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (2.4)</td>
<td>11 (3.3)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (3.2)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0.0)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>8 (6.5)</td>
<td>32 (9.6)</td>
</tr>
<tr>
<td>AEs leading to discont</td>
<td>0 (0.0)</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>SAEs</td>
<td>0 (0.0)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Treatment-related SAEs</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**AMG 145 Pooled analysis >1300 patients: Lab of Interest**

<table>
<thead>
<tr>
<th>AMG 145 – by dose and dose frequency</th>
<th>Placebo</th>
<th>All AMG 145</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=333)</td>
<td>(n=981)</td>
</tr>
<tr>
<td>70 mg Q2W (n=124)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105 mg Q2W (n=125)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>140 mg Q2W (n=123)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>280 mg Q4W (n=156)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg Q4W (n=210)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>420 mg Q4W (n=213)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**AEs and labs of interest**

<table>
<thead>
<tr>
<th></th>
<th>AMG 145</th>
<th>Placebo</th>
<th>All AMG 145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site reaction</td>
<td>2 (1.6)</td>
<td>11 (3.3)</td>
<td>40 (4.1)</td>
</tr>
<tr>
<td>Muscle-related AEs</td>
<td>7 (5.6)</td>
<td>13 (3.9)</td>
<td>59 (6.0)</td>
</tr>
<tr>
<td>CK &gt; 5 x ULN&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (2.4)</td>
<td>3 (0.9)</td>
<td>14 (1.4)</td>
</tr>
<tr>
<td>ALT or AST &gt;3 x ULN</td>
<td>1 (0.8)</td>
<td>2 (0.6)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Binding antibodies</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Neutralizing antibodies</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

<sup>b</sup>5 patients in the AMG 145 treatment group had creatine kinase >10 x ULN, all of which were resolved at follow-up blood test.

Inhibition of PCSK9 with monoclonal antibodies is a very promising, and potentially the most effective, approach to reducing LDL-C including patients:

- With nonFH, HeFH and LDLr defective HoFH
- On statins or diet alone
- When added to all existing therapy
- Unable to tolerate statins, or effective doses of statins.
- SC delivery every 2 or 4 weeks

In large phase 2 and 3 program of 2 agents of over 6,000 patients no significant adverse effects have emerged so far

Four large CVD outcome trials are already underway with the Amgen (evolocumab), Sanofi (alirocumab) and Pfizer (bocomicizumab) monoclonal antibodies.