Lipid Lowering Efficacy of Bococizumab Among 4,449 High Risk Patients
The SPIRE Lipid Lowering Trials

Safety and Cardiovascular Efficacy of Bococizumab Among 27,438 High Risk Patients
The SPIRE 1 and SPIRE 2 Cardiovascular Outcome Trials

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Brigham and Women’s Hospital, Boston MA

on behalf of the worldwide investigators and participants in the
Studies of PCSK9 Inhibition and the Reduction in vascular Events (SPIRE)
Bococizumab Development Program
Monoclonal Antibodies to PCSK9 and Recycling of the LDL Receptor: Cardiovascular Outcomes Trials

Evolocumab (Amgen)  
FOURIER  
NCT 01764633

Alirocumab (Sanofi/Regeneron)  
ODYSSEY  
NCT 01663402

Bococizumab (Pfizer)  
SPIRE-1, SPIRE-2  
NCT 01975376  
NCT 01975389

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The SPIRE Bococizumab Clinical Development Program

SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) N = 31,887

SPIRE Lipid Lowering Trials (N=4,449)
- SPIRE HR (n = 711)
  On maximally tolerated statin
  High risk of CV event
  LDL-C ≥70 mg/dL

- SPIRE FH (n = 370)
  HeFH (genetic diagnosis or Simon Broome Criteria),
  LDL ≥70 mg/dl

- SPIRE SI (n = 184)
  Statin intolerant
  LDL-C ≥70 mg/dL

SPIRE LDL (n = 2,139)
- On maximally tolerated statin
- High risk of CV event
- LDL-C ≥70 mg/dL

SPIRE LL (n = 746)
- On statin High / very high risk of CV event
- LDL-C ≥100 mg/dL

SPIRE AI (n = 299)
- Statin intolerant
- Hyperlipidemia

SPIRE CV Outcome Trials (N=27,438)
- SPIRE-1 (n=16,817)
  High Risk Primary and Secondary Prevention
  LDL-C ≥70 mg/dL
  on highly effective statin
  (or partially statin intolerant)

- SPIRE-2 (n=10,621)
  High Risk Primary and Secondary Prevention
  LDL-C ≥100 mg/dL
  on highly effective statin
  (or statin intolerant)

Ridker et al, Am Heart J 2016;178:135-144
The Six SPIRE Lipid Lowering Trials (N=4,449)

- **Screen 4 weeks**
  - Randomize
  - **R**
  - **Bococizumab 150 mg SC Q2 Weeks + maximally tolerated statin**
  - **Placebo SC Q2 Weeks + maximally tolerated statin**
  - **Treatment Period (52 weeks)**
  - **Safety follow-up (6 weeks)**
  - **12 week and 52 week Change in Lipid Levels**

The SPIRE 1 and SPIRE 2 Cardiovascular Outcome Trials (N = 27,438)

- **Patients with or at high risk for cardiovascular events**
  - SPIRE-1: LDLC >70 mg/dL or non-HDLC >100mg/dL
  - SPIRE-2: LDLC >100 mg/dL or non-HDLC >130mg/dL

- **Pre-screen ≤30 days**
  - **Screen ≤14 days**
  - **Run-in 3 visits**
  - **Randomize**
  - **R**
  - **Bococizumab 150 mg SC Q2 Weeks + maximally tolerated statin**
  - **Placebo SC Q2 Weeks + maximally tolerated statin**
  - **Treatment Period (>2 years)**
  - **Safety follow-up (6 weeks)**
  - **CV Events***

*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death*

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Evolution and Humanization of Therapeutic Monoclonal Antibodies

- **Murine (0% human)**
  - Tositumomab (Bexxar)

- **Chimeric (65% human)**
  - Abciximab (ReoPro)
  - Infliximab (Remicade)
  - Rituximab (Rituxan)

- **Humanized (> 90% human)**
  - Bococizumab
  - Tocilizumab (Actemra)

- **Fully Human (100% human)**
  - Evolocumab (Repatha)
  - Alirocumab (Praluent)
  - Canakinumab (Ilaris)

Potential for immunogenicity:
- **High**
- **Low**

Adapted from Foltz IN, Karow M, Wasserman SM. Circulation 2013; 127:2222-2230.
# The SPIRE Bococizumab Lipid Lowering Trials: Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Trials (N=4449)</th>
<th>SPIRE-HR (N=711)</th>
<th>SPIRE-LDL (N=2139)</th>
<th>SPIRE-FH (N=370)</th>
<th>SPIRE-LL (N=746)</th>
<th>SPIRE-SI (N=184)</th>
<th>SPIRE-AI (N=299)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>61.3</td>
<td>61.3</td>
<td>62.0</td>
<td>56.1</td>
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<td>Female (%)</td>
<td>43.7</td>
<td>37.4</td>
<td>40.6</td>
<td>41.9</td>
<td>44.2</td>
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<td>Diabetes (%)</td>
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<td>49.4</td>
<td>62.9</td>
<td>20.3</td>
<td>56.4</td>
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<td>FH (%)</td>
<td>12.1</td>
<td>7.2</td>
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<td>7.0</td>
<td>10.9</td>
<td>1.3</td>
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<tr>
<td>Statin Use (%)</td>
<td>99.8*</td>
<td>100.0</td>
<td>99.7</td>
<td>99.5</td>
<td>99.9</td>
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<td>LDLC (mg/dL)</td>
<td>122</td>
<td>115</td>
<td>112</td>
<td>147</td>
<td>136</td>
<td>174</td>
<td>112</td>
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<td>Apo B (mg/dL)</td>
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<td>95</td>
<td>93</td>
<td>114</td>
<td>107</td>
<td>129</td>
<td>90</td>
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<td>TG (mg/dL)</td>
<td>145</td>
<td>138</td>
<td>147</td>
<td>124</td>
<td>168</td>
<td>166</td>
<td>120</td>
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<tr>
<td>Lp(a) (mg/dL)</td>
<td>22</td>
<td>23</td>
<td>21</td>
<td>29</td>
<td>23</td>
<td>14</td>
<td>NA</td>
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<tr>
<td>hsCRP (mg/L)</td>
<td>1.8</td>
<td>1.6</td>
<td>2.0</td>
<td>0.9</td>
<td>2.2</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>

*Does not include SPIRE-SI
The SPIRE Bococizumab Lipid Lowering Trials:
Large Reductions in LDLC with PCSK9 inhibition at 12 weeks

55.2% reduction in LDLC at 12 weeks

- 12 weeks, 150 mg
- 12 weeks, 75 mg

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The SPIRE Bococizumab Lipid Lowering Trials: Unanticipated Attenuation of LDLC Reductions at 52 weeks

55.2% reduction in LDLC at 12 weeks
42.5% reduction in LDLC at 52 weeks

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The SPIRE Bococizumab Lipid Lowering Trials: Unanticipated Attenuation of Efficacy for All Lipid Parameters at 52 weeks
The SPIRE Bococizumab Lipid Lowering Trials: Development of Antidrug Antibodies (ADAs) and Attenuation of LDL Response Over Time

![Graph showing LDL cholesterol levels and the development of ADAs over time.](image)

- **Placebo**: ADA < 1:1,176 (ADA negative)
- **ADA > 1:1,176 (1 in 6)**
- **ADA > 1:5,674 (1 in 20)**

**ADA Positive (%)**
- Weeks 0: 5%
- Weeks 4: 5%
- Weeks 8: 21%
- Weeks 12: 38%
- Weeks 24: 39%
- Weeks 36: 44%
- Weeks 48: 45%
- Weeks 52: 46%
- EOS: 48%

**ADA Positive (%)**
- Weeks 0: 0%
- Weeks 4: 0%
- Weeks 8: 25%
- Weeks 12: 25%
- Weeks 24: 40%
- Weeks 36: 45%
- Weeks 48: 45%
- Weeks 52: 45%
- EOS: 50%
The SPIRE Bococizumab Lipid Lowering Trials:
Impact of Antidrug Antibodies (ADAs) on Plasma Bococizumab Concentration Over Time

ADA titer-dependent reductions in bococizumab concentration is likely due to increased target-mediated clearance of unbound bococizumab and accelerated clearance of ADA bound bococizumab.
The SPIRE Bococizumab Lipid Lowering Trials:
Wide Individual Variation in Percent Change in LDLC at 52 Weeks with Bococizumab, Even Among Those Who Are Antidrug Antibody Negative*

* Analysis excludes non-compliant participants
On the basis of the completed SPIRE Lipid Lowering trials, the sponsor elected on November 1, 2016 to discontinue further development of bococizumab.

As a consequence of the data in the SPIRE Lipid Lowering trials, the sponsor elected to prematurely stop the ongoing SPIRE-1 and SPIRE-2 outcome trials which had, at that time, randomized 27,438 patients worldwide.

That decision was made with no knowledge by the sponsor or the investigators of any unblinded data within the SPIRE-1 or SPIRE-2 trials.
The Six SPIRE Lipid Lowering Trials (N=4,449)

**Treatment Period (52 weeks)**
- **Bococizumab 150 mg SC Q2 Weeks + maximally tolerated statin**
- **Placebo SC Q2 Weeks + maximally tolerated statin**

**Safety follow-up (6 weeks)**
- **12 week and 52 week Change in Lipid Levels**

The SPIRE 1 and SPIRE 2 Cardiovascular Outcome Trials (N = 27,438)

**Patients with or at high risk for cardiovascular events**
- **SPIRE-1**: LDLC >70 mg/dL or non-HDLC >100mg/dL
- **SPIRE-2**: LDLC >100 mg/dL or non-HDLC >130mg/dL

**Pre-screen ≤ 30 days**  **Screen ≤14 days**  **Run-in 3 visits**  **Randomize**

Pre-screening, Screening, and Three Run-in Visits

**SPIRE-1**: N=16,817  **SPIRE-2**: N=10,621

**Treatment Period (>2 years)**
- **Bococizumab 150 mg SC Q2 Weeks + maximally tolerated statin**
- **Placebo SC Q2 Weeks + maximally tolerated statin**

**Safety follow-up (6 weeks)**

*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death*

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# The SPIRE-1 and SPIRE-2 Cardiovascular Outcomes Trials: Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SPIRE-1 Bococizumab (N=8408)</th>
<th>SPIRE-1 Placebo (N=8409)</th>
<th>SPIRE-2 Bococizumab (N=5212)</th>
<th>SPIRE-2 Placebo (N=5309)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>63.3</td>
<td>63.3</td>
<td>62.2</td>
<td>62.6</td>
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<tr>
<td>Female (%)</td>
<td>26.3</td>
<td>26.5</td>
<td>34.1</td>
<td>35.1</td>
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<tr>
<td>Diabetes (%)</td>
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<td>46.1</td>
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<td>Smokers (%)</td>
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<td>23.0</td>
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<td>FH (%)</td>
<td>1.7</td>
<td>1.8</td>
<td>7.0</td>
<td>7.6</td>
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<tr>
<td>Statin Use (%)</td>
<td>99.1</td>
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<td>83.1</td>
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<tr>
<td>Primary Prevention (%)</td>
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<td>LDLC (mg/dL)</td>
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<td>94</td>
<td>134</td>
<td>133</td>
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<tr>
<td>Apo B (mg/dL)</td>
<td>80</td>
<td>80</td>
<td>106</td>
<td>106</td>
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<td>TG (mg/dL)</td>
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<td>125</td>
<td>157</td>
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<tr>
<td>Lp(a) (mg/dL)</td>
<td>19</td>
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<td>20</td>
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<tr>
<td>hsCRP (mg/L)</td>
<td>1.8</td>
<td>1.7</td>
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<td>2.3</td>
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<tr>
<td>Absolute risk (MACE+)*</td>
<td>3.02 per 100 person-years</td>
<td></td>
<td>4.19 per 100 person-years</td>
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* Placebo group event rate
The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Confirmation of Attenuation in LDLC Reduction Over Time

SPIRE-1 (LDLC ≥ 70 mg/dL)

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Placebo</th>
<th>Bococizumab</th>
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<tbody>
<tr>
<td>BSL</td>
<td>94.2</td>
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<td>1</td>
<td>93.9</td>
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<td>2</td>
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<td>6</td>
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<td>9</td>
<td>93.0</td>
<td>92.4</td>
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<tr>
<td>12</td>
<td>92.1</td>
<td>92.2</td>
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<tr>
<td>16</td>
<td>92.4</td>
<td>92.2</td>
</tr>
<tr>
<td>24</td>
<td>94.1</td>
<td>92.4</td>
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</table>

Mean LDL Cholesterol (mg/dl)

SPIRE-2 (LDLC ≥ 100 mg/dL)

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<tr>
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<td>144.2</td>
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<tr>
<td>1</td>
<td>133.3</td>
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<td>2</td>
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<td>28</td>
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<td>143.2</td>
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Mean LDL Cholesterol (mg/dl)

Placebo

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<tr>
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<td>3</td>
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<td>6</td>
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<td>9</td>
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<td>24</td>
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<td>28</td>
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<td>30</td>
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Bococizumab

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<th>Bococizumab</th>
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<td>30</td>
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<td>47</td>
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 SPIRE -1 (LDLC ≥ 70 mg/dL)

 SPIRE -2 (LDLC ≥ 100 mg/dL)

 Placebo

 Bococizumab

Mean LDL Cholesterol (mg/dl)

SPIRE

SPIRE 1 (LDLC > 70 mg/dL)

SPIRE 2 (LDLC > 100 mg/dL)

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The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Confirmation of Wide Individual Variability in Percent LDLC Reduction

14 weeks

52 weeks

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The SPIRE-1 Cardiovascular Outcomes Trial: Baseline LDLC > 70 mg/dL Primary Pre-Specified Endpoint*

- Placebo: 173 events
- Bococizumab 150 mg: 173 events

Cumulative proportion with MACE + UARUR

Weeks

HR 0.99
95%CI 0.80-1.22
P = 0.94

Baseline LDLC 94 mg/dL
Placebo Event Rate 3.02 / 100-person years
Median follow-up 7 months

*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death

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The SPIRE-2 Cardiovascular Outcomes Trial: Baseline LDLC > 100 mg/dL
Primary Pre-Specified Endpoint*

**Placebo**
224 events
**Bococizumab 150 mg**
179 events

Cumulative proportion with MACE + UARUR

Weeks

Baseline LDLC 133 mg/dL
Placebo Event Rate 4.19 / 100-person years
Median follow-up 12 months

HR 0.79
95%CI 0.65-0.97
P = 0.021

*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death

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The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Combined Trials
Primary Endpoint*, Stratified By Magnitude of LDLC Reduction (%)

Placebo
Bococizumab 150 mg, < median % LDLC reduction
Bococizumab 150 mg, ≥ median % LDLC reduction

HR 0.94
95%CI 0.77-1.14
P = 0.51

HR 0.75
95%CI 0.61-0.92
P = 0.006

*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death

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The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Combined Trials
Primary Endpoint*, Stratified By Duration of Exposure

**Longer Duration of Exposure**
(Randomized before median date)
Mean exposure period 13.6 months

**Shorter Duration of Exposure**
(Randomized after median date)
Mean exposure period 5.6 months

*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death
The SPIRE-1 and SPIRE-2 Cardiovascular Outcomes Trials:
Incidence Rates of Adverse Events per 100 Person-Years of Exposure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bococizumab (N=13,707)</th>
<th>Placebo (N=13,697)</th>
<th>Incidence Rate Ratio or Incidence Difference</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Overall</td>
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<td></td>
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<tr>
<td>Any LDLC &lt;25 mg/dL</td>
<td>19.5</td>
<td>18.2</td>
<td>20.5</td>
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<td>No LDLC &lt;25 mg/dL</td>
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<tr>
<td>SAE</td>
<td>19.5</td>
<td>18.2</td>
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<td>SAE leading to drug DC</td>
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<td>4.8</td>
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<tr>
<td>Injection Site Reaction</td>
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<td>10.2</td>
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<td>Myalgia</td>
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<td>3.1</td>
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<td>3.4</td>
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<td>Diabetes</td>
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<td>4.9</td>
<td>3.5</td>
<td>4.2</td>
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<td>Cataract</td>
<td>1.1</td>
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<td>1.3</td>
<td>1.1</td>
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<tr>
<td>AST &gt; 3xULN</td>
<td>0.6</td>
<td>0.5</td>
<td>0.7</td>
<td>0.6</td>
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<tr>
<td>ALT &gt; 3x ULN</td>
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<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
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<tr>
<td>CK &gt; 3x ULN</td>
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<td>1.0</td>
<td>1.1</td>
<td>0.9</td>
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<tr>
<td>Glucose Change- wk 52 (mg/dL)</td>
<td>4.8</td>
<td>4.0</td>
<td>5.5</td>
<td>3.0</td>
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<tr>
<td>HbA1c Change- wk 52 (%)</td>
<td>0.09</td>
<td>0.07</td>
<td>0.10</td>
<td>0.06</td>
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</tbody>
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Ridker ACC 2017
Conclusions:
The SPIRE Lipid Lowering Trials and the SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials

1. PCSK9 inhibition with bococizumab reduces LDLC by 55 to 60% when given as an adjunct to statin therapy, but this effect is significantly attenuated over time in 10 to 15% of patients due to the development of anti-drug antibodies. This effect is specific to bococizumab (a humanized monoclonal antibody) and has not been seen with either evolocumab or alirocumab (fully human monoclonal antibodies). This immunogenicity also explains the higher rate of injection site reactions observed with bococizumab.

2. Bococizumab is also associated with wide individual variability in LDLC response even among those who do not develop anti-drug antibodies. This suggests that on-treatment measures of LDLC will be important for clinical practice. Whether similar individual variability in LDLC response is present for evolocumab and alirocumab is uncertain.
3. Despite anti-drug antibody production, variation in individual response, and early trial termination, bococizumab significantly reduced cardiovascular event rates in the higher-risk SPIRE-2 trial of those with LDLC >100 mg/dL, but not in the lower-risk SPIRE-1 trial of those with LDLC >70 mg/dL.

4. Consistent with the hypothesis that “lower is better for longer”, clinical benefits were greater and statistically significant in analyses of those who achieved and sustained greater absolute as well as relative reductions in LDLC. These data thus support the use of PCSK9 inhibitors in selected patients as an adjunct to aggressive statin therapy.
Conclusions:
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5. While bococizumab may not be available for clinical use, the public presentation of these data honors the altruism of our 31,887 trial participants and contributes to our understanding of PCSK9 inhibition and cardiovascular health.

6. In addition to thanking our dedicated investigators and coordinators in 35 countries worldwide, the SPIRE Executive Committee and Steering Committee wishes to give a special thanks to our research colleagues at Pfizer for their exceptional commitment to the rapid and fully transparent presentation of these data.
Lipid-Reduction Variability and Antidrug-Antibody Formation with Bococizumab

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Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients

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