PCSK9 Inhibitors: A View of Clinical Studies

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PCSK9 Inhibitors : A View of Clinical Studies

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Disclosure

• Honoraria for consulting and speaker activities from
  – Amgen, Biolab, Boehringer-Ingelheim
  – Genzyme, Eli-Lilly, Merck, Pfizer, Praxis, Kowa, Jansen, Torrent & Sanofi/Regeneron
PCSK9 Inhibitors: A View of Clinical Studies

• Efficacy
  – General high risk population
  – Familial Hypercholesterolemia
  – Statin intolerant

• Safety

• CVD prevention?


**PCSK9 Inhibitors:**
From Target Discovery to Phase III in 10 Years

- **2003**
  - PCSK9 (NARC-1) discovered
  - PCSK9 GOF mutations associated with ADH*

- **2004**
  - PCSK9 LOF Mutations found with 28% ↓ LDL-C and 88% ↓ CHD risk
  - Humans null for PCSK9 have LDL-C ~15 mg/dL
  - Plasma PCSK9 binds to LDL-R

- **2005**
  - First Patients with FH / non-FH treated with PCSK9i mAb

- **2006**
  - Adenoviral ↑ expression in mice
  - PCSK9 KO mouse LDL-C

- **2007**
  - First subject treated with PCSK9 mAb
  - ↓ LDL-C in mice and non-human primates treated with anti-PCSK9 mAb

- **2008**
  - First publication POC in patients

- **2009**
  - 1st FDA / EMEA PCSK9i filing

- **2010**
  - First Patients with FH / non-FH treated with PCSK9i mAb

- **2011**
  - 1st FDA / EMEA PCSK9i filing

- **2012**
  - First Patients with FH / non-FH treated with PCSK9i mAb

- **2013**
  - First Patients with FH / non-FH treated with PCSK9i mAb

- **2014**
  - First Patients with FH / non-FH treated with PCSK9i mAb

PCSK9 Promotes Degradation of LDLRs

PCSK9 Promotes Degradation of LDLRs

LDL-C=low-density lipoprotein cholesterol; LDLR=low-density lipoprotein receptor.
Phase 3 Program to Support LDL-C Reduction in Targeted Populations

• **High CV Risk Patients**
  – Patients not at LDL-C goal with currently available LLT (even high doses of potent statins) = persistent risk

• **Familial Hypercholesterolemia**
  – LDL-C levels often far from goal, even with potent statins and combination Tx
  – Life-long exposure to high LDL-C; considered high risk even w/o additional risk factors

• **Statin Intolerant Patients**
  – LDL-C levels often far from goal, due to intolerance
  – Definition: unable to tolerate at least 2 statins, including one at the lowest dose
**Overview of ODYSSEY Phase 3 clinical trial program**

12 global phase 3 trials
Including more than 23,500 patients across more than 2,000 study centers

<table>
<thead>
<tr>
<th>HeFH population</th>
<th>HC in high CV risk population</th>
<th>Additional populations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Add-on to max tolerated statin (± other LMT)</td>
<td>Add-on to max tolerated statin (± other LMT)</td>
</tr>
<tr>
<td><strong>ODYSSEY FH I (EFC12492)</strong> N=471</td>
<td><strong>ODYSSEY COMBO I (EFC11568)</strong> N=306</td>
<td><strong>ODYSSEY MONO (EFC11716)</strong> N=100</td>
</tr>
<tr>
<td>LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL</td>
<td>LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL</td>
<td>Patients on no background LMTs</td>
</tr>
<tr>
<td>18 months</td>
<td>12 months</td>
<td>LDL-C ≥ 100 mg/dL</td>
</tr>
<tr>
<td><strong>ODYSSEY FH II (CL1112)</strong> N=250</td>
<td><strong>ODYSSEY COMBO II (EFC11569)</strong> N=660</td>
<td><strong>ODYSSEY ALTERNATIVE (CL1119)</strong> N=250</td>
</tr>
<tr>
<td>LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL</td>
<td>LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL</td>
<td>Patients with defined statin intolerance</td>
</tr>
<tr>
<td>18 months</td>
<td>24 months</td>
<td>LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL</td>
</tr>
<tr>
<td><strong>ODYSSEY HIGH FH (EFC12732)</strong> N=105</td>
<td><strong>ODYSSEY OUTCOMES (EFC11570)</strong> N=18,000</td>
<td><strong>ODYSSEY OPTIONS I (CL1110)</strong> N=350</td>
</tr>
<tr>
<td>LDL-C ≥ 160 mg/dL</td>
<td>LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL</td>
<td>Patients not at goal on moderate dose atorvastatin</td>
</tr>
<tr>
<td>18 months</td>
<td>12 months</td>
<td>LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL</td>
</tr>
<tr>
<td><strong>ODYSSEY LONG TERM (LTS11717)</strong> N=2,100</td>
<td><strong>ODYSSEY OUTCOMES II (CL1118)</strong> N=300</td>
<td><strong>ODYSSEY OPTIONS II (CL1110)</strong> N=350</td>
</tr>
<tr>
<td>LDL-C ≥ 70 mg/dL</td>
<td>LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL</td>
<td>Patients not at goal on moderate dose rosvuvalstatin</td>
</tr>
<tr>
<td>18 months</td>
<td>12 months</td>
<td>LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL</td>
</tr>
</tbody>
</table>

HC = hypercholesterolemia; LMT = lipid-modifying therapy  
*For the ODYSSEY COMBO II other LMT not allowed at entry
**Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations**

- **Combo-therapy**
  - Phase 3 (N = 1,700)\(^5\)

- **Monotherapy**
  - Phase 3 (N = 600)\(^5\)

- **Statin-intolerant**
  - Phase 3 (N = 300)\(^5\)

- **HeFH**
  - Phase 3 (N = 300)\(^5\)

- **HoFH**
  - Phase 3 (N = 125)\(^5\)

- **Open-label Extension**
  - Phase 3\(^†\) (N ~ 3,515)\(^5\)

- **Secondary Prevention**
  - Phase 3 (N = 905)\(^5\)

- **Athero**
  - Phase 3 (N = 950)\(^5\)

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*Subjects completed a qualifying Phase 2 study. \(^1\)Subjects completed a qualifying Phase 3 study.


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=300)**
  - On statin
  - High risk of CV event
  - LDL-C ≥70 or ≥100 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 LL (n=690)**
  - On statin
  - High / very high risk of CV event
  - LDL-C ≥100 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 statins (or statin intolerant)

- **SPIRE-2 (n=9,000)**
  - High Risk Primary and Secondary Prevention
  - LDL-C ≥100 mg/dL on statins (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
Studies in Patients at High CV Risk and Not at LDL-C Goal

ODYSSEY COMBO I
ODYSSEY COMBO II

## Baseline Characteristics: COMBO I and II

<table>
<thead>
<tr>
<th>All patients on background maximally tolerated statin ± other LLT</th>
<th>COMBO I</th>
<th>COMBO II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>63.0 (9.5)</td>
<td>63.0 (8.8)</td>
</tr>
<tr>
<td><strong>Male, % (n)</strong></td>
<td>62.7% (131)</td>
<td>72.0% (77)</td>
</tr>
<tr>
<td><strong>Race, white, % (n)</strong></td>
<td>81.3% (170)</td>
<td>82.2% (88)</td>
</tr>
<tr>
<td><strong>BMI, kg/m², mean (SD)</strong></td>
<td>32.6 (6.3)</td>
<td>32.0 (7.1)</td>
</tr>
<tr>
<td><strong>CHD history, % (n)</strong></td>
<td>78.5% (164)</td>
<td>77.6% (83)</td>
</tr>
<tr>
<td><strong>Hypertension, % (n)</strong></td>
<td>88.5% (185)</td>
<td>88.8% (95)</td>
</tr>
<tr>
<td><strong>Type 2 diabetes, % (n)</strong></td>
<td>45.0% (94)</td>
<td>39.3% (42)</td>
</tr>
<tr>
<td><em><em>Any statin</em>, % (n)</em>*</td>
<td>99.5% (208)</td>
<td>100% (107)</td>
</tr>
<tr>
<td><strong>High-intensity statin†, % (n)</strong></td>
<td>61.7% (129)</td>
<td>64.5% (69)</td>
</tr>
<tr>
<td><strong>LDL-C, calculated mean (SD), mg/dL</strong></td>
<td>100.2 (29.5)</td>
<td>106.0 (35.3)</td>
</tr>
</tbody>
</table>

LDL-C Reductions and Goal Achievement

**COMBO I**

- **ITT**
  - n=205
  - LS mean (SE) % change from baseline to Week 24: -48.2%
  - LS mean % difference (SE) vs placebo: **-45.9 (3.3)**
  - *P<0.0001

- **On-treatment analysis**
  - n=204
  - LS mean (SE) % change from baseline to Week 24: -50.7%
  - LS mean % difference (SE) vs placebo: **-49.9 (3.2)**
  - *P<0.0001

**COMBO II**

- **Primary Endpoint:** Percent Change from Baseline to Week 24 in LDL-C
  - n=467
  - LS mean (SE) % change from baseline to Week 24: -50.6%
  - LS mean difference (SE) vs. ezetimibe: -20.7% (-29.8 (2.3); *P<0.0001

- **Proportion of Patients Reaching LDL-C <1.81 mmol/L (70 mg/dL) at Week 24**
  - **ITT**
    - 75.0%
    - 9.0%
    - *P<0.0001
  - **On-treatment analysis**
    - 77.5%
    - 8.0%

- **Proportion of Patients Reaching LDL-C <1.3 mmol/L (50 mg/dL) at Week 24**
  - Alirocumab
    - 77.0%
    - 45.6%
    - *P<0.0001
  - Ezetimibe
    - 60.3%
    - 14.2%
  - Post hoc
Consistent LDL-C Reductions Over 52 Weeks

- LDL-C ↓ from baseline maintained over 52 weeks with alirocumab
- Mean achieved LDL-C levels of 53.3 mg/dL in COMBO I and 53.3 mg/dL in COMBO II at week 52 with alirocumab
- Consistent effects of alirocumab vs comparator through 52 weeks

Alirocumab Dose Selection Based on Patient Needs

A flexible model to address:

- Different baseline LDL-C
- Different background LLT
- Treat to target approach

75 mg Q2W 1 ml  →  150 mg Q2W 1 ml

Additional offer Q4W:

- 300 mg (+ statins)
- 150 mg (- statins)
Percent Reduction from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels in the Evolocumab Group, as Compared with the Placebo Group, at Weeks 12 and 52, According to Background Lipid-Lowering Therapy.

Results of Bococizumab, A Monoclonal Antibody Against PCSK9, from a Randomized, Placebo-Controlled, Dose-Ranging Study in Statin-Treated Subjects With Hypercholesterolemia

Figure 2 Mean absolute change from baseline in LDL-C at week 12. The placebo and bococizumab Q14 days and Q28 days dose groups are shown, with the corresponding mean percent changes from baseline in italics.

Familial Hypercholesterolemia
Alirocumab Studies in Familial Hypercholesterolemia

ODYSSEY FH I
ODYSSEY FH II
ODYSSEY HIGH FH

Kastelein et al., ESC 2014 oral presentation, Efficacy and safety of alirocumab in patients with heFH not adequately controlled with current lipid-lowering therapy: Results of ODYSSEY FH I and FH II studies

Ginsberg et al. AHA 2014 oral presentation, ODYSSEY HIGH FH: Efficacy and Safety of Alirocumab in Patients with Severe Heterozygous Familial Hypercholesterolemia
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Diagnosis of HeFH*, % (n)</th>
<th>FH I</th>
<th>Placebo</th>
<th>FH II</th>
<th>Placebo</th>
<th>FH II</th>
<th>Placebo</th>
<th>HIGH FH</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotyping</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>39.9% (129)</td>
<td>38.0% (62)</td>
<td>70.1% (117)</td>
<td>81.7% (67)</td>
<td>19.4% (14)</td>
<td>14.3% (5)</td>
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</tr>
<tr>
<td>Genotyping</td>
<td></td>
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</tr>
<tr>
<td>59.8% (193)</td>
<td>62.0% (101)</td>
<td>29.9% (50)</td>
<td>18.3% (15)</td>
<td>80.6% (58)</td>
<td>85.7% (30)</td>
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<tr>
<td>Clinical criteria</td>
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<td></td>
</tr>
<tr>
<td>38.0% (62)</td>
<td>70.1% (117)</td>
<td>81.7% (67)</td>
<td>19.4% (14)</td>
<td>14.3% (5)</td>
<td></td>
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<tr>
<td>59.8% (193)</td>
<td>62.0% (101)</td>
<td>29.9% (50)</td>
<td>18.3% (15)</td>
<td>80.6% (58)</td>
<td>85.7% (30)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>52.1 (12.9)</td>
<td>51.7 (12.3)</td>
<td>53.2 (12.9)</td>
<td>53.2 (12.5)</td>
<td>49.8 (14.2)</td>
<td>52.1 (11.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, % (n)</td>
<td>55.7% (180)</td>
<td>57.7% (94)</td>
<td>51.5% (86)</td>
<td>54.9% (45)</td>
<td>48.6% (35)</td>
<td>62.9% (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race, white, % (n)</td>
<td>92.9% (300)</td>
<td>88.3% (144)</td>
<td>98.2% (164)</td>
<td>97.6% (80)</td>
<td>88.9% (64)</td>
<td>85.7% (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>29.0 (4.6)</td>
<td>30.0 (5.4)</td>
<td>28.6 (4.6)</td>
<td>27.7 (4.7)</td>
<td>28.8 (5.2)</td>
<td>28.9 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD history, % (n)</td>
<td>45.5% (147)</td>
<td>47.9% (78)</td>
<td>34.1% (57)</td>
<td>37.8% (31)</td>
<td>43.1% (31)</td>
<td>62.9% (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, % (n)</td>
<td>12.1% (39)</td>
<td>18.4% (30)</td>
<td>21.6% (36)</td>
<td>15.9% (13)</td>
<td>16.7% (12)</td>
<td>25.7% (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>43.0% (139)</td>
<td>43.6% (71)</td>
<td>34.1% (57)</td>
<td>29.3% (24)</td>
<td>55.6% (40)</td>
<td>60.0% (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes, % (n)</td>
<td>9.6% (31)</td>
<td>15.3% (25)</td>
<td>4.2% (7)</td>
<td>3.7% (3)</td>
<td>12.5% (9)</td>
<td>17.1% (6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Diagnosis of HeFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the Simon Broome criteria for definite FH or the WHO/Dutch Lipid Network criteria with a score of >8 points.

† In FH I, one patient was categorized as “probable” FH by clinical criteria – genotyping results for this patient are pending.
## 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>
<th>HIGH FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab (N=323)</td>
<td>Placebo (N=163)</td>
<td>Alirocumab (N=167)</td>
<td>Placebo (N=82)</td>
</tr>
<tr>
<td><strong>Any statin</strong>, % (n)</td>
<td><strong>100%</strong></td>
<td><strong>100%</strong></td>
<td><strong>100%</strong></td>
</tr>
<tr>
<td><strong>High-intensity statin</strong>, % (n)</td>
<td><strong>80.8%</strong> (261)</td>
<td><strong>82.8%</strong> (135)</td>
<td><strong>86.2%</strong> (144)</td>
</tr>
<tr>
<td><strong>Ezetimibe</strong>, % (n)</td>
<td><strong>55.7%</strong> (180)</td>
<td><strong>59.5%</strong> (97)</td>
<td><strong>67.1%</strong> (112)</td>
</tr>
<tr>
<td><strong>LDL-C, mean (SD), mg/dL</strong></td>
<td><strong>144.7</strong> (51.2)</td>
<td><strong>144.4</strong> (46.8)</td>
<td><strong>134.6</strong> (41.3)</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.
LDL-C Reductions and Goal Achievement

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C
All patients on background max-tolerated statin ± other lipid-lowering therapy

FH I
- 48.8% increase at W12
- 57.9% (2.7) P<0.0001

Alirocumab
Placebo

N=322
N=163

FH II
- 48.7% increase at W12
- 51.4% (3.4) P<0.0001

Alirocumab
Placebo

N=166
N=81

High FH

LONG TERM
HeFH population with baseline LDL-C ≥160 mg/dL

LDL-C % change from baseline to Week 24: comparison with ODYSSEY LONG TERM HeFH patients with LDL-C baseline ≥160 mg/dL
All patients on background of maximally tolerated statin ± other LLT

ITT
Sensitivity analysis

n=71
n=35
n=62
n=31

-45.7%
-50.3%

-52.3%
-43.6%

Proportion of patients reaching LDL-C goal at Week 24
FH I
- 72.2%

Alirocumab
Placebo

FH II
- 81.4%

Alirocumab
Placebo

N=84
N=35

LDL-C <100 mg/dL
P<0.0001

LDL-C <70 mg/dL
P=0.0082

% patients reaching LDL-C goal at Week 24

Very high risk: ≥2.59 mmol/L (100 mg/dL); high risk: ≥1.81 mmol/L (70 mg/dL); LLT = lipid-lowering therapy
Consistent LDL-C Reductions Over 52 Weeks

- Significantly greater LDL-C ↓ vs placebo at week 24 in FH I, FH II, and HIGH FH (P<0.001 for all studies)
- Mean achieved LDL-C levels with alirocumab of 65.9-74.3 mg/dL at week 52 in FH I and II and 107 mg/dL at week 24 in HIGH FH
- In HIGH FH, percentage decrease from baseline informed by high baseline LDL-C (196.3 mg/dL):
  - The absolute mean decrease from baseline in LDL-C was –90.8 mg/dL at Week 24 with alirocumab versus 182 mg/dL with placebo
PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial

Frederick J Raal, Evan A Stein, Robert Dufour, Traci Turner, Fernando Civeira, Lesley Burgess, Gisle Langset, Russell Scott, Anders G Olsson, David Sullivan, G Kees Hovingh, Bertrand Cariou, Joanna Gouni-Berthold, Ranssi Somaratne, Ian Bridges, Rob Scott, Scott M Wasserman, Daniel Gaudet, for the RUTHERFORD-2 Investigators*

Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial

Frederick J Raal, Narimon Honarpour, Dirk J Blom, G Kees Hovingh, Feng Xu, Rob Scott, Scott M Wasserman, Evan A Stein, for the TESLA Investigators*

Figure 2: Mean percentage change in ultracentrifugation LDL cholesterol concentration from baseline to week 12

Vertical lines represent standard error around the mean. The plot is based on observed values and no imputation was used for missing values. Number of patients represents those analysed for this endpoint at each visit.
Individual Percent Change from Baseline to Week 12 in UC LDL-C (N = 94)

Abbreviations: ARH, autosomal recessive hypercholesterolemia.
Lipoprotein(a) is an independent risk factor for cardiovascular disease.

Lipoprotein(a) Levels in Familial Hypercholesterolemia: An Important Predictor of Cardiovascular Disease Independent of the Type of LDL Receptor Mutation

Figure 4 Kaplan-Meier Curves for CVD-Free Survival in Subjects With FH According to Lp(a) Levels and Type of Mutation. The black solid line indicates null mutations and Lp(a) levels $>50$ mg/dl; the black dashed line indicates null mutations and Lp(a)...
Evolocumab Reduces Lp(a) in Heterozygous FH

![Graph showing % Change From Baseline for Lp(a) with 350 mg and 420 mg doses.](image)

Raal F et al. Circulation 2012;126:2408-2417
Change from Baseline to Week 24:
Total Cholesterol, Non-HDL-C, Apo B and Lp(a) (ITT)

These are secondary endpoints in ITT analysis population. *Analyzed with the use of multiple imputation, followed by robust regression. A combined estimate for adjusted mean (±SE) is shown.

If proven to be safe and efficacious in the long term, as well as cost effective, PCSK9 monoclonal antibodies might be the best standard of care for many patients with severe forms of familial hypercholesterolaemia.

Santos RD & Watts G. Lancet. 2015;385:307-10
Studies in Statin Intolerance

ODYSSEY ALTERNATIVE

Moriarty et al. AHA 2014 oral presentation, ODYSSEY ALTERNATIVE: Efficacy and safety of alirocumab versus ezetimibe, in patients with statin intolerance defined by placebo run-in and statin rechallenge arm
ODYSSEY ALTERNATIVE Study Design

Statin intolerant patients* (by medical history) with LDL-C ≥70 mg/dL (very-high CV risk) or ≥100 mg/dL (moderate/high risk)

**Placebo**

**Double-Blind Treatment Period (24 Weeks)**

N=100

Alirocumab 75/150 mg SC Q2W + placebo PO QD
administered via single 1 mL injection using prefilled pen for self-administration

Per-protocol dose ↑ possible depending on W8 LDL-C

N=100

Ezetimibe 10 mg PO QD + placebo SC Q2W

N=50

Atorvastatin 20 mg PO QD + placebo SC Q2W

**Assessments**

W-4 W0 W4 W8 W12 W16 W24

Patients discontinued if muscle-related AEs reported with placebos during run-in

Per-protocol dose increase if Week 8 LDL-C ≥70 or ≥100 mg/dL (depending on CV risk)

Primary endpoint
(LDL-C % change from baseline, ALI and EZE only)
Safety analysis (all groups)

*Unable to tolerate at least two different statins, including one at the lowest dose, due to muscle-related symptoms

†4-week single-blind placebo run-in follows 2-week washout of statins, ezetimibe and red yeast rice.
OLTP: Alirocumab open-label treatment period; W, Week.
Patient Disposition

Entered placebo run-in (N=361)

Excluded (N=47)
- 25 due to muscle-related AE during placebo run-in (6.9% of those entering run-in)
- 22 due to other inclusion/exclusion criteria

Randomized (N=314)

Alirocumab (N=126) (all patients treated)
- Completed 24 weeks (N=96)
  - Discontinued: 23.8% (N=30)
  - Due to AE (N=23)

Primary analysis (N=126)
Safety analysis (N=126)

Ezetimibe (N=125) (1 patient not treated)
- Completed 24 Weeks (N=82)
  - Discontinued: 33.6% (N=42)
  - Due to AE (N=31)

Primary analysis (N=122)
Safety analysis (N=124)

Atorvastatin (N=63) (all patients treated)
- Completed 24 weeks (N=42)
  - Discontinued: 33.3% (N=21)
  - Due to AE (N=16)

Safety analysis only (N=63)
Alirocumab Significantly Reduced LDL-C From Baseline to Week 24 vs Ezetimibe

% change from baseline to Week 24 in LDL-C

ITT (primary endpoint)

- Alirocumab: -45.0%
  - LS mean (SE): -30.4 (3.1); P<0.0001
  - 49.5% of 109 patients who received at least one injection after Week 12 had dose increase.

- Ezetimibe: -14.6%
  - Absolute change of -33 (4.2) mg/dL
  - LS mean difference (SE) vs ezetimibe: -30.4 (3.1); P<0.0001

On-treatment (key secondary endpoint)

- Alirocumab: -52.2%
  - Absolute change of -96 (3.9) mg/dL
  - LS mean difference (SE) vs ezetimibe: -35.1 (2.8); P<0.0001

- Ezetimibe: -17.1%
  - Absolute change of -38 (4.2) mg/dL
### Safety Analysis

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Alirocumab (N=126)</th>
<th>Ezetimibe (N=124)</th>
<th>Atorvastatin (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEAEs</strong>*</td>
<td>82.5%</td>
<td>80.6%</td>
<td>85.7%</td>
</tr>
<tr>
<td>Treatment-emergent SAEs</td>
<td>9.5%</td>
<td>8.1%</td>
<td>11.1%</td>
</tr>
<tr>
<td>TEAEs leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TEAEs leading to discontinuation</strong></td>
<td>18.3%</td>
<td>25.0%</td>
<td>25.4%</td>
</tr>
<tr>
<td>Any skeletal-muscle related TEAE†</td>
<td>32.5%</td>
<td>41.1%</td>
<td>46.0%</td>
</tr>
<tr>
<td>HR (95% CI) alirocumab vs comparator</td>
<td>-</td>
<td>0.71 (95% CI: 0.47 to 1.06)</td>
<td>0.61 (95% CI: 0.38 to 0.99)</td>
</tr>
<tr>
<td><strong>P-value vs alirocumab‡</strong></td>
<td>-</td>
<td>0.096</td>
<td>0.042</td>
</tr>
<tr>
<td>Skeletal-muscle related TEAE leading to discontinuation</td>
<td>15.9%</td>
<td>20.2%</td>
<td>22.2%</td>
</tr>
<tr>
<td>HR (95% CI) alirocumab vs comparator</td>
<td>-</td>
<td>0.78 (95% CI: 0.43 to 1.41)</td>
<td>0.67 (95% CI: 0.34 to 1.32)</td>
</tr>
<tr>
<td><strong>P-value vs alirocumab‡</strong></td>
<td>-</td>
<td>0.409</td>
<td>0.240</td>
</tr>
</tbody>
</table>
Fewer Skeletal Muscle AEs With Alirocumab Than With Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event*

Cox model analysis:
HR ALI vs ATV = 0.61 (95% CI: 0.38 to 0.99), nominal P=0.042
HR ALI vs EZE = 0.71 (95% CI: 0.47 to 1.06), nominal P=0.096

*Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.
ALI=alirocumab; ATV= atorvastatin, EZE=ezetimibe.

Moriarty et al AHA 2014
GAUSS: % Change from Baseline in Calculated LDL-C* At All Visits

* Calculated LDL-C values.
Q4W, every 4 weeks; QD, daily, CI, confidence intervals
### GAUSS: Safety and Tolerability

<table>
<thead>
<tr>
<th>Adverse Events, Patient Incidence, n (%)</th>
<th>AMG 145 280 mg N = 32</th>
<th>AMG 145 350 mg N = 31</th>
<th>AMG 145 420 mg + Ezetimibe 10 mg N = 32</th>
<th>Placebo Q4W + Ezetimibe N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent AEs</td>
<td>22 (68.8)</td>
<td>15 (48.4)</td>
<td>18 (56.3)</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td>Serious AEs*</td>
<td>2 (6.3)</td>
<td>1 (3.2)</td>
<td>1 (3.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>8 (25.0)</td>
<td>3 (9.7)</td>
<td>6 (18.8)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Muscle-related AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (15.6)</td>
<td>1 (3.2)</td>
<td>1 (3.1)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Muscle fatigue</td>
<td>2 (6.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1 (3.1)</td>
<td>2 (6.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>0 (0.0)</td>
<td>1 (3.2)</td>
<td>1 (3.1)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Other most commonly reported AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (6.3)</td>
<td>2 (6.5)</td>
<td>1 (3.1)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (6.3)</td>
<td>1 (3.2)</td>
<td>1 (3.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (12.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

* Four serious adverse events were reported for AMG 145: acute pancreatitis, coronary artery disease, hip fracture, and syncope. None were considered treatment related.

AE: Adverse event. Some patients experienced more than 1 AE.
Safety
Pooled Safety Across ODYSSEY
TEAEs Occurring in ≥5% Patients in Any Group  
(Pool of 4x Phase 2 + 10x Phase 3 trials*)

<table>
<thead>
<tr>
<th>% (n) of patients All pts on background statin</th>
<th>Ezetimibe-controlled pool (N=1482)</th>
<th>Placebo-controlled pool (N=3752)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEAEs by preferred term in ≥5% patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5.4% (37)</td>
<td>11.3% (279)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6.7% (58)</td>
<td>4.2% (104)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5.9% (51)</td>
<td>6.1% (152)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>2.9% (25)</td>
<td>6.7% (166)</td>
</tr>
<tr>
<td>Influenza</td>
<td>3.7% (32)</td>
<td>5.7% (141)</td>
</tr>
<tr>
<td>Headache</td>
<td>3.9% (34)</td>
<td>4.8% (119)</td>
</tr>
</tbody>
</table>

*Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I), phase 2 (DF11565, DF11566, CL-1003, DF12361)  
Includes all data collected to last patient visit at 52 wks for COMBO, FH, HIGH FH and LONG TERM studies.
# Pooled Neurocognitive Disorders

## Safety Analysis – Total TEAEs

<table>
<thead>
<tr>
<th>% (n) of patients</th>
<th>Placebo-controlled pool</th>
<th>Ezetimibe-controlled pool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=1276)</td>
<td>Ezetimibe (N=618)</td>
</tr>
<tr>
<td></td>
<td>Alirocumab (N=2476)</td>
<td>Alirocumab (N=864)</td>
</tr>
<tr>
<td>% (n)</td>
<td>0.7% (9)</td>
<td>1.0% (6)</td>
</tr>
<tr>
<td></td>
<td>0.8% (21)</td>
<td>0.9% (8)</td>
</tr>
<tr>
<td>95% mid-p CI</td>
<td>0.3% to 1.3%</td>
<td>0.4% to 2.0%</td>
</tr>
<tr>
<td></td>
<td>0.5% to 1.3%</td>
<td>0.4% to 1.8%</td>
</tr>
<tr>
<td>Number of patients with an event per 100 patient years*</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.3 to 1.2</td>
<td>0.5 to 1.1</td>
</tr>
<tr>
<td>Hazard ratio versus control (95% CI)†</td>
<td>1.18 (0.54 to 2.58)</td>
<td>0.94 (0.32 to 2.74)</td>
</tr>
</tbody>
</table>

* Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period.
† Calculated using a Cox model stratified on the study.
Patients attaining very low LDL levels

Is it bad?
# TEAEs (≥2%) in Patients With 2 Consecutive LDL-C <25 mg/dL – by Organ Class

<table>
<thead>
<tr>
<th>Primary System Organ Class</th>
<th>Control (N=1894)</th>
<th>Alirocumab (N=3340)</th>
<th>Alirocumab LDL-C ≥25mg/dL (N=2544)</th>
<th>Alirocumab 2 LDL-C &lt;25mg/dL (N=796)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (%)</td>
<td>Rate/100 PY</td>
<td>Rate (%)</td>
<td>Rate/100 PY</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>687</td>
<td>36.3%</td>
<td>1286</td>
<td>38.5%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>478</td>
<td>25.2%</td>
<td>808</td>
<td>24.2%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>318</td>
<td>16.8%</td>
<td>567</td>
<td>17.0%</td>
</tr>
<tr>
<td>General and administration site conditions</td>
<td>282</td>
<td>14.9%</td>
<td>504</td>
<td>15.1%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>283</td>
<td>14.9%</td>
<td>497</td>
<td>14.9%</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>242</td>
<td>12.8%</td>
<td>428</td>
<td>12.8%</td>
</tr>
<tr>
<td>Respiratory, thoracic, mediastinal</td>
<td>172</td>
<td>9.1%</td>
<td>325</td>
<td>9.7%</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>159</td>
<td>8.4%</td>
<td>275</td>
<td>8.2%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>130</td>
<td>6.9%</td>
<td>270</td>
<td>8.1%</td>
</tr>
<tr>
<td>Investigations</td>
<td>127</td>
<td>6.7%</td>
<td>235</td>
<td>7.0%</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>120</td>
<td>6.3%</td>
<td>232</td>
<td>6.9%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>134</td>
<td>7.1%</td>
<td>211</td>
<td>6.3%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>110</td>
<td>5.8%</td>
<td>171</td>
<td>5.1%</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>71</td>
<td>3.7%</td>
<td>152</td>
<td>4.6%</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>84</td>
<td>4.4%</td>
<td>128</td>
<td>3.8%</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, and unspecified</td>
<td>48</td>
<td>2.5%</td>
<td>85</td>
<td>2.5%</td>
</tr>
<tr>
<td>Reproductive and breast</td>
<td>40</td>
<td>2.1%</td>
<td>77</td>
<td>2.3%</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td>46</td>
<td>2.4%</td>
<td>72</td>
<td>2.2%</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>53</td>
<td>2.8%</td>
<td>56</td>
<td>1.7%</td>
</tr>
<tr>
<td>Neurocognitive disorders - no. of patients (%)*</td>
<td>Alirocumab (N = 1550)</td>
<td>Alirocumab with 2 consecutive LDL cholesterol &lt;25 mg/dL (N = 575)</td>
<td>Placebo (N = 788)</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------------------</td>
<td>---------------------------------------------------------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Amnesia</td>
<td>5 (0.3)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Memory impairment</td>
<td>4 (0.3)</td>
<td>0</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Confusional state</td>
<td>4 (0.3)</td>
<td>1 (0.2)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Confusion postoperative</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>1 (&lt;0.1)</td>
<td>1 (0.2)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Disorientation</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>1 (&lt;0.1)</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Reading disorder</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Transient global amnesia</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vascular encephalopathy</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Neurocognitive events were selected with the use of a custom MedDRA query that was based on the

## Adverse Events and Achieved LDL-C: Evolocumab

### Supplemental Table S2 – Adverse Events and Laboratory Results by Achieved LDL Cholesterol

<table>
<thead>
<tr>
<th>Subject incidence, n (%)</th>
<th>Evolocumab subjects stratified by minimum post-baseline (achieved) LDL cholesterol</th>
<th>All evolocumab subjects (N = 2976)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25 mg/dL (N = 773)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>541 (70.0)</td>
<td>2060 (69.2)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>59 (7.6)</td>
<td>222 (7.5)</td>
</tr>
<tr>
<td>Muscle-related adverse event</td>
<td>38 (4.9)</td>
<td>190 (6.4)</td>
</tr>
<tr>
<td>CK &gt;5× ULN</td>
<td>3 (0.4)</td>
<td>17 (0.6)</td>
</tr>
<tr>
<td>ALT/AST &gt;3× ULN</td>
<td>7 (0.9)</td>
<td>31 (1.0)</td>
</tr>
<tr>
<td>Neurocognitive adverse event</td>
<td>4 (0.5)</td>
<td>27 (0.9)</td>
</tr>
<tr>
<td></td>
<td>25 to &lt;40 mg/dL (N = 759)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>517 (68.1)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>52 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Muscle-related adverse event</td>
<td>54 (7.1)</td>
<td></td>
</tr>
<tr>
<td>CK &gt;5× ULN</td>
<td>7 (0.9)</td>
<td></td>
</tr>
<tr>
<td>ALT/AST &gt;3× ULN</td>
<td>6 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive adverse event</td>
<td>9 (1.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;40 mg/dL (N = 1532)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>1058 (69.1)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>111 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Muscle-related adverse event</td>
<td>92 (6.0)</td>
<td></td>
</tr>
<tr>
<td>CK &gt;5× ULN</td>
<td>10 (0.7)</td>
<td></td>
</tr>
<tr>
<td>ALT/AST &gt;3× ULN</td>
<td>13 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive adverse event</td>
<td>13 (0.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥40 mg/dL (N = 1426)</td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>1000 (70.1)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>111 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Muscle-related adverse event</td>
<td>98 (6.9)</td>
<td></td>
</tr>
<tr>
<td>CK &gt;5× ULN</td>
<td>7 (0.5)</td>
<td></td>
</tr>
<tr>
<td>ALT/AST &gt;3× ULN</td>
<td>18 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive adverse event</td>
<td>14 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>

Cardiovascular Events ?
From: Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis

Effects of PCSK9 Antibodies in Adults With Hypercholesterolemia

Effects of PCSK9 inhibitors on All Cause Mortality

From: Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis

Effects of PCSK9 Antibodies in Adults With Hypercholesterolemia

Myocardial infarction

Unstable angina

From Genes to Medical Treatment: Effects of LDL-C Lowering on CVD


### Outcomes Trials for Alirocumab and Evolocumab

<table>
<thead>
<tr>
<th></th>
<th>ODYSSEY OUTCOMES</th>
<th>FOURIER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>ACS within the last 4 to 52 weeks; LDL-C ≥70 (on atorvastatin 40-80 mg or rosuvastatin 20-40 mg)</td>
<td>MI, stroke, or symptomatic PAD + at least 1 major RF or at least 2 minor RFs; LDL-C ≥70 (or non-HDL ≥100) (on atorvastatin 20 to 80 mg or equivalent)</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>18,000</td>
<td>27,500</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>CV death, MI, stroke, and hospitalization for UA</td>
<td>CV death, MI, stroke, coronary revascularization and hospitalization for UA</td>
</tr>
<tr>
<td><strong>Background Therapy</strong></td>
<td>Max tolerated doses of atorvastatin and rosuvastatin</td>
<td>Atorvastatin: 20 (at least), 40 (recommended where locally approved), 80 mg (or equivalent)</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>75 mg → 150 mg Q2W (based on w8 LDL-C level)</td>
<td>140 Q2W (1 ml pen) or 420 QM (3 x 1 ml pen or 3.5 ml via personal injector (9’ injection time)</td>
</tr>
</tbody>
</table>

SPIRE Program is only PCSK9i program with two CV Outcomes Studies testing different hypotheses.

SPIRE-2 is the only PCSK9i study explicitly assessing CV outcomes in high risk patients with an LDL-C >100 mg/dL despite the use of high intensity statins.


High risk Primary and Secondary Prevention
N=26,000
Conclusions

• PCSK9 inhibitors
  – Efficacious in lowering LDL-C and Lp(a)
  – Work in different clinical scenarios
  – Well tolerated
  – Will test barriers of clinical practice!!!!
  – Cost effectiveness !!!!!