Treatment of severe Familial Hypercholesterolemia
PCSK9 inhibitors

Identifying and Treating Severe Familial Hypercholesterolemia
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Disclosure

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  – Astra Zeneca, Pfizer, Sanofi/Regeneron.
Cardiovascular Disease (CVD) remains the biggest killer worldwide.

Reducing levels of low-density lipoprotein (LDL) cholesterol is a cornerstone of the prevention of CVD.

Despite the proven efficacy of statins in lowering CV events, many patients fail to reach recommended LDL-C goals.
Putting Into Perspective the Hazards of Untreated Familial Hypercholesterolemia

Figure. Cumulative probability of developing coronary artery disease (CAD) in men (left) and women (right) with heterozygous familial hypercholesterolemia (FH) as compared with unaffected relatives or the general population (non-FH). Relative risk (Rel Risk), as the ratio of cumulative CAD risk in FH divided by non-FH, is shown below each curve.

Paul N. Hopkins, J Am Heart Assoc. 2017;6:e006553
Focus on treatment of blood cholesterol to reduce ASCVD risk in adults

No LDL-C (and non-HDL-C) treatment goals

Statin centric

Identification of 4 patient groups most likely to benefit from statin therapy

ACC=American College of Cardiology; AHA=American Heart Association; ASCVD=arteriosclerotic cardiovascular disease; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol

- Clinical ASCVD
- LDL > 190 mg/dL
- DM 1 or 2 and age 40-75
- ASCVD 10 y risk > 7.5 % and age 40-75

- High intensity statin unless > 75 years old or intolerant
- High intensity statin unless intolerant
- High intensity statin unless 10 year ASCVD < 7.5 %
- Moderate to high intensity statin
The Actual Evidence

- At that time Statin drugs are the only class with actual mortality and morbidity benefits studied in randomized controlled trials
- No RCT evidence that adjuncts to statin therapy add clinical benefit
- Actually evidence to the contrary:
  - AIM HIGH: niacin added to statin when LDL < 80 mg/dL provides no benefit
  - ACCORD: adding fenofibrate to statin in patients with DM provides no benefit
- Focus Shift from LDL lowering to mortality and morbidity benefit
- No evidence for target LDL levels in terms of ASCVD event risk reduction
- High intensity statin therapy ( > 50 % LDL reduction) provides more clinical benefit than moderate intensity therapy ( 30-50 % LDL reduction)
Are Statins Enough?

- Statins are effective, potent, inexpensive and generally well tolerated
- Residual Risk
Major lipid trials
What is the LDL-cholesterol level we should aim for?

**Prim. Prev.**

- Equation: $y = 0.0599x - 3.3952$
- $R^2 = 0.9305$
- $p = 0.0019$
- LDL $57\text{mg/dL} = 1.5\text{mmol/L}$

**Sec. Prev.**

- Equation: $y = 0.1629x - 4.6776$
- $R^2 = 0.9029$
- $p < 0.0001$

O'Keefe, JACC 2004; 2142-6
Is a low LDL better and is a low LDL-C safe?
How low is too low LDL-c?

- Persons born with defective PCSK9 gene have very low LDL
  - They are protected from CVD
  - No depression
  - No cognitive abnormalities
  - They are generally healthy

- They have LDL-c <30mg/dL
  - Have no particular side effects
  - Appear to benefit from low LDL-c
Loss-of-Function PCSK9 Mutations in AA Are Associated with Low LDL-C and Low Prevalence of CHD Events

Adapted from Cohen JC. N Engl J Med 2006;354:1264-72. ARIC=Atherosclerosis Risk in the Community
The Role of PCSK9 in the Regulation of LDL Receptor Expression

Impact of a PCSK9 mAb on LDL Receptor Expression

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>% Change Apo B</th>
<th>% Change Non–HDL-C</th>
<th>% Change Lp (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.2</td>
<td>−2.2</td>
<td>0.0</td>
</tr>
<tr>
<td>SAR236553 50mg Q2W</td>
<td>−27.3*</td>
<td>−33.6*</td>
<td>−13.3†</td>
</tr>
<tr>
<td>SAR236553 100mg Q2W</td>
<td>−48.1*</td>
<td>−55.6*</td>
<td>−26.1*</td>
</tr>
<tr>
<td>SAR236553 150mg Q2W</td>
<td>−56.1*</td>
<td>−62.5*</td>
<td>−28.6*</td>
</tr>
<tr>
<td>SAR236553 200mg Q4W</td>
<td>−28.7*</td>
<td>−37.4*</td>
<td>−16.7†</td>
</tr>
<tr>
<td>SAR236553 300mg Q4W</td>
<td>−33.1*</td>
<td>−40.7*</td>
<td>−7.9†</td>
</tr>
</tbody>
</table>

*P<0.0001 for % change SAR236553 vs. placebo
†P=0.05 for % change SAR236553 vs. placebo

*P values are not adjusted for multiplicity (descriptive only)
Attainment of Prespecified LDL-C Levels at Week 12 (mITT Population)

% Patients Achieving Prespecified LDL-C Level

- Placebo: 16% (3% <100mg/dL, 0% <70mg/dL)
- 50mg Q2W: 93% (47% <100mg/dL, 0% <70mg/dL)
- 100mg Q2W: 97% (84% <100mg/dL, 0% <70mg/dL)
- 150mg Q2W: 100% (100% <100mg/dL, 100% <70mg/dL)
- 200mg Q4W: 89% (46% <100mg/dL, 0% <70mg/dL)
- 300mg Q4W: 97% (57% <100mg/dL, 0% <70mg/dL)

>70% decrease in LDL-C and 90-100% of patients reach predefined levels with 150 mg Q2W + 80 mg atorvastatin.

- SAR236553 + atorva 80 mg resulted in 73% reduction in mean LDL-C vs 17% for atorva 80 mg only.
- SAR236553 + stable dose of atorva 10 mg resulted in 66% LDL-C reduction.
- SAR236553 was generally well tolerated.

• p<0.0001 vs Placebo + A80
Most heFH Patients Receiving Alirocumab on Background Statin ± Other LLT Achieved LDL-C Goals

Proportion of patients reaching LDL-C goal† at Week 24

FH I

FH II

% patients

90
80
70
60
50
40
30
20
10
0

72.2%

81.4%

11.3%

2.4%

P<0.0001

Alirocumab

Placebo

†Very high-risk: <1.81 mmol/L (70 mg/dL); high-risk: <2.59 mmol/L (100 mg/dL). LLT = lipid-lowering therapy.

Intent-to-treat (ITT) Analysis
Most of These High CV-Risk Patients Receiving Alirocumab on Background Statin Achieved LDL-C Goal

Proportion of Patients Reaching LDL-C <1.8 mmol/L (70 mg/dL) at Week 24
All patients on background of maximally-tolerated statin

Intent-to-treat (ITT) analysis

P<0.0001
Who Needs Benefit?

- Very High LDL-C levels → FH
- Insufficient effects from statins
- Statin side effects
- Progression of Atherosclerosis
Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia Undergoing Lipoprotein Apheresis: the ODYSSEY ESCAPE Trial


This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

These joint authors contributed equally to this manuscript

Key Inclusion Criteria

- Diagnosis of HeFH by genotyping or clinical criteria (Simon Broome criteria or the WHO/Dutch Lipid Network criteria)
- Stable lipoprotein apheresis QW for ≥4 weeks or Q2W for ≥8 weeks
- Background LLT, diet and exercise level stable for ≥8 weeks
- Lipoprotein apheresis techniques: double membrane filtration, immunoadsorption, heparin-induced LDL precipitation, direct adsorption of lipids, dextran sulfate adsorption (plasma) and dextran sulfate adsorption (whole blood)

Key Exclusion Criteria

- Diagnosis of homozygous FH
- Lipoprotein apheresis schedule other than QW and Q2W
Pre-apheresis LDL-C Over Time

Average LDL-C value (pre-apheresis), mean (SE), mmol/L

Alirocumab 150 mg Q2W (n=41)
Placebo (n=21)

Apheresis rate varied from Week 7 onwards

<table>
<thead>
<tr>
<th>Week 6</th>
<th>Week 18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alirocumab</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>-53.7 (2.3)</td>
<td>1.6 (3.1)</td>
</tr>
<tr>
<td>-42.5 (4.7)</td>
<td>3.9 (6.3)</td>
</tr>
</tbody>
</table>

*p-value versus placebo*<0.0001

Raw mean values are provided for baseline. SE, standard error.

Time-Averaged Cholesterol Concentrations†
(Kroon Formula¹)

†Time-averaged concentrations are widely regarded to provide the best estimate of the physiologically effective plasma cholesterol concentrations during long-term treatment with lipoprotein apheresis. Data labels are expressed in both measurements.


Standardized Apheresis Treatment Rates from Week 7–18

An apheresis rate of 0 indicates that the patient skipped all planned aphereses and an apheresis rate of 1 indicates that the patient received all planned aphereses; between Week 7 and Week 18 (apheresis rate of 0.75:, the patient received 75% of planned aphereses).

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

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Study Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

RANDOMIZED DOUBLE BLIND

Follow-up Q 12 weeks
**LDL-C Levels**

<table>
<thead>
<tr>
<th>LDL Cholesterol</th>
<th>Evolocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 70 mg/dL</td>
<td>87%</td>
<td>18%</td>
</tr>
<tr>
<td>≤ 40 mg/dL</td>
<td>67%</td>
<td>0.5%</td>
</tr>
<tr>
<td>≤ 25 mg/dL</td>
<td>42%</td>
<td>&lt; 0.1%</td>
</tr>
</tbody>
</table>
Primary Endpoint
Key Secondary Efficacy Endpoint
## Safety: Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events — no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>10,664 (77.4)</td>
<td>10,644 (77.4)</td>
</tr>
<tr>
<td>Serious</td>
<td>3410 (24.8)</td>
<td>3404 (24.7)</td>
</tr>
<tr>
<td>Thought to be related to the study agent and leading to discontinuation of study regimen</td>
<td>226 (1.6)</td>
<td>201 (1.5)</td>
</tr>
<tr>
<td>Injection-site reaction*</td>
<td>296 (2.1)</td>
<td>219 (1.6)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>420 (3.1)</td>
<td>393 (2.9)</td>
</tr>
<tr>
<td>Muscle-related event</td>
<td>682 (5.0)</td>
<td>656 (4.8)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>8 (0.1)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Cataract</td>
<td>228 (1.7)</td>
<td>242 (1.8)</td>
</tr>
<tr>
<td>Adjudicated case of new-onset diabetes†</td>
<td>677 (8.1)</td>
<td>644 (7.7)</td>
</tr>
<tr>
<td>Neurocognitive event</td>
<td>217 (1.6)</td>
<td>202 (1.5)</td>
</tr>
<tr>
<td>Laboratory results — no. of patients/total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminotransferase level &gt;3 times the upper limit of the normal range</td>
<td>240/13,543 (1.8)</td>
<td>242/13,523 (1.8)</td>
</tr>
<tr>
<td>Creatine kinase level &gt;5 times the upper limit of the normal range</td>
<td>95/13,543 (0.7)</td>
<td>99/13,523 (0.7)</td>
</tr>
</tbody>
</table>

* The between-group difference was nominally significant (P<0.001).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.
Study Conclusions

- When added to statin therapy, evolocumab lowered LDL cholesterol levels by 59% from baseline compared to placebo, from a median of 92 mg/dL to 30 mg/dL.
- ↓ risk of the primary composite endpoint by 15% and ↓ risk of the key secondary endpoint by 20%.
- Magnitude of risk reduction shown to increase over time.
- No effect of additional LDL-C lowering on cardiovascular death or all-cause mortality.
- Injection-site reactions were significantly higher in the evolocumab group compared to the placebo group.
Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the ODYSSEY Outcomes trial

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Background Following acute coronary syndrome (ACS), the risk for future cardiovascular events is high and is related to levels of low-density lipoprotein cholesterol (LDL-C) even within the setting of intensive statin treatment. Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates LDL receptor expression and circulating levels of LDL-C. Antibodies to PCSK9 can produce substantial and sustained reductions of LDL-C. The ODYSSEY Outcomes trial tests the hypothesis that treatment with alirocumab, a fully human monoclonal antibody to PCSK9, improves cardiovascular outcomes after ACS.

Design This Phase 3 study will randomize approximately 18,000 patients to receive biweekly injections of alirocumab (75-150 mg) or matching placebo beginning 1 to 12 months after an index hospitalization for acute myocardial infarction or unstable angina. Qualifying patients are treated with atorvastatin 40 or 80 mg daily, rosuvastatin 20 or 40 mg daily, or the maximum tolerated and approved dose of one of these agents and fulfill one of the following criteria: LDL-C ≥ 70 mg/dL, non–high-density lipoprotein cholesterol ≥ 100 mg/dL, or apolipoprotein B ≥ 80 mg/dL. The primary efficacy measure is time to first occurrence of coronary heart disease death, acute myocardial infarction, hospitalization for unstable angina, or ischemic stroke. The trial is expected to continue until 1613 primary end point events have occurred with minimum follow-up of at least 2 years, providing 90% power to detect a 15% hazard reduction. Adverse events of special interest include allergic events and injection site reactions. Interim analyses are planned when approximately 50% and 75% of the targeted number of primary end points have occurred.

Summary ODYSSEY Outcomes will determine whether the addition of the PCSK9 antibody alirocumab to intensive statin therapy reduces cardiovascular morbidity and mortality after ACS. (Am Heart J 2014;168:682-689.e1.)
**ODYSSEY Outcome Trial**

**Patient population:**
- Recent ACS
- Inadequate control of atherogenic lipoproteins* despite optimal statin treatment†

**Primary endpoint:** Composite of
- Coronary heart disease death
- Non-fatal myocardial infarction
- Ischemic stroke
- Unstable angina requiring hospitalization

**Run-In Period (up to 16w)**
- Optimize statin; practice self-injection with placebo; complete planned revascularization
- 4-52 weeks

**Double-Blind Treatment Period (~ 2 to 5 years)**
- Until Month 2: 75 mg every 2 wks
- At Month 2 and beyond: 75 mg or 150 mg every 2 weeks adjusted in blinded fashion to achieve 15≤LDL-C<50 mg/dL
- M2
- Alirocumab (n=9000)
- Placebo (n=9000)

† **Optimal statin treatment:** Atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, or maximal tolerated dose of one of these statins, with or without non-statin lipid treatments. NCEP-ATPIII therapeutic lifestyle changes or equivalent throughout study.

* **Inadequate control of atherogenic lipoproteins.** At least one of the following: LDL-C ≥70 mg/dL (1.81 mmol/L), non-HDL-C ≥100 mg/dL (2.59 mmol/L), or apo B ≥80 mg/dL.
Recommended Use of PCSK9I’s

- Based on current guidelines, available evidence, and economic considerations:
  - Patients with FH or ASCVD and statin resistance (on max dose) for additional LDL lowering is a reasonable strategy.
    - Discuss with patient costs vs clinical benefit
  - In FH patients to avoid apheresis
  - 2nd line to addition of ezetimibe for statin intolerant patients
  - No evidence to support use of PCSK9I’s as monotherapy or for arbitrary reduction of statin dose
    - In complete statin intolerance, PCSK9I monotherapy should be considered only after careful risk assessment and patient preference
Questions ?