PCSK9: Background summary

- LDL receptor (LDL-R) plays a key role in maintenance of intracellular and plasma cholesterol and LDL cholesterol (LDL-C).
- PCSK9 discovered as regulator of the hepatic LDL-R in 2003.
- PCSK9 in the plasma binds to LDL-Rs, reduces recycling, effectively down-regulating LDL-R activity and resulting in increased plasma LDL-C.
- Humans with gain-of-function mutations have higher plasma LDL-C and increased coronary artery disease risk, while those with loss-of-function mutations have lower plasma LDL-C and reduced CAD risk.
- PCSK9 levels increased with statin treatment.
- Appears an exciting new target for treating hypercholesterolemia.

Disclosures

- Research grants to the institution from and consultant: Abbott, Biosensors, Boston Scientific, Biotronik, Medtronic, Astra Zeneca
- Speaker honoraria from: Abbott, Biosensors, Boston Scientific, Biotronik, Medtronic, Astra Zeneca

The Role of PCSK9 in the Regulation of LDL Receptor Expression

Impact of an PCSK9 mAb on LDL Receptor Expression
Inhibition of PCSK9 with mAb

- Is there a limit to LDL-C reduction with a mAb?
  - Yes, approximately 60% – 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
Evolocumab OSLER Trial: Cumulative Incidence of Cardiovascular Events

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

HR 0.47
95% CI 0.28-0.78
P=0.003

Vascular outcomes (prespecified, exploratory) adjudicated by TIMI Study Group CEC, blinded to treatment

HR 0.65 (95% CI 0.40-0.99)
P=0.04

Follow-up (8 weeks)

Placebo Q2W SC

Alirocumab 150 mg Q2W SC

Study Design

Evlucumab OSLER Trial: Cumulative Incidence of Cardiovascular Events

¶

CVD clinical outcomes (prespecified, exploratory) adjudicated by TIMI Study Group CEC, blinded to treatment

3.3%*

1.7%**

*27/1550

**26/788

3.3%**

1.7%*

Summary: PCSK9 monoclonal antibodies and safety of very low LDL-C

- The safety data from two large phase 2/3 programs with alirocumab and evolocumab in >10,000 patients for period of up to 2 years shows;
- Evaluation of patients achieving very low LDL-C levels (<25 mg/dL) do not show any increase in clinical or laboratory side effects compared to those with higher LDL-C or control groups
- The CVD event data shows potential benefit from low and very low LDL-C and increased CVD events if LDL-C remains elevated

Risk Reduction of Major Cardiovascular Events by Achieved LDL-C Concentration with statins

LDL-C Levels and Risk of CV Events

Major CVD and Composite Events Rates in Various LDL-C Levels

Summary: PCSK9 monoclonal antibodies and safety of very low LDL-C

- The safety data from two large phase 2/3 programs with alirocumab and evolocumab in >10,000 patients for period of up to 2 years shows;
- Evaluation of patients achieving very low LDL-C levels (<25 mg/dL) do not show any increase in clinical or laboratory side effects compared to those with higher LDL-C or control groups
- The CVD event data shows potential benefit from low and very low LDL-C and increased CVD events if LDL-C remains elevated

Risk Reduction of Major Cardiovascular Events by Achieved LDL-C Concentration with statins

LDL-C Levels and Risk of CV Events

Major CVD and Composite Events Rates in Various LDL-C Levels

Summary: PCSK9 monoclonal antibodies and safety of very low LDL-C

- The safety data from two large phase 2/3 programs with alirocumab and evolocumab in >10,000 patients for period of up to 2 years shows;
- Evaluation of patients achieving very low LDL-C levels (<25 mg/dL) do not show any increase in clinical or laboratory side effects compared to those with higher LDL-C or control groups
- The CVD event data shows potential benefit from low and very low LDL-C and increased CVD events if LDL-C remains elevated

Risk Reduction of Major Cardiovascular Events by Achieved LDL-C Concentration with statins

LDL-C Levels and Risk of CV Events

Major CVD and Composite Events Rates in Various LDL-C Levels

Summary: PCSK9 monoclonal antibodies and safety of very low LDL-C

- The safety data from two large phase 2/3 programs with alirocumab and evolocumab in >10,000 patients for period of up to 2 years shows;
- Evaluation of patients achieving very low LDL-C levels (<25 mg/dL) do not show any increase in clinical or laboratory side effects compared to those with higher LDL-C or control groups
- The CVD event data shows potential benefit from low and very low LDL-C and increased CVD events if LDL-C remains elevated
The 1 million dollar question:

Will PCSK9 inhibitors reduce CV events safely in high-risk patients?

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Evolocumab</th>
<th>Alirocumab</th>
<th>Bococizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>FOURIER</td>
<td>ODYSSEY Outcomes</td>
<td>SPIRE I</td>
</tr>
<tr>
<td>Sample size</td>
<td>27,500</td>
<td>10,000</td>
<td>17,000</td>
</tr>
<tr>
<td>Patients</td>
<td>MI, stroke or PAD</td>
<td>4-52 wks post-ACS</td>
<td>High risk of CV event</td>
</tr>
<tr>
<td>Statin</td>
<td>Atorva ≥20 mg or equiv</td>
<td>Ezetimibe or cholest</td>
<td>Lipid-lowering Rx</td>
</tr>
<tr>
<td>LDL-C</td>
<td>≥70 (≥1.8)</td>
<td>≥70 (≥1.8)</td>
<td>≤&lt;50 (≤1.8)</td>
</tr>
<tr>
<td>PCSK9 Inhibitor Dosing</td>
<td>Q2W or Q4W</td>
<td>Q2W</td>
<td>Q2W</td>
</tr>
<tr>
<td>Endpoint 1°</td>
<td>CV death, MI, stroke, or urgent revasc for UA</td>
<td>CV death, MI, stroke, or urgent revasc for UA</td>
<td>CV death, MI, stroke, or urgent revasc for UA</td>
</tr>
<tr>
<td>Endpoint 2°</td>
<td>CV death, MI, stroke, or urgent revasc for UA</td>
<td>CV death, MI, stroke, or urgent revasc for UA</td>
<td>CV death, MI, stroke, or urgent revasc for UA</td>
</tr>
<tr>
<td>Recruitment Status</td>
<td>Completed June 2015</td>
<td>Projected for Dec 2015</td>
<td>?</td>
</tr>
<tr>
<td>Completion</td>
<td>2017</td>
<td>1/2018</td>
<td>8/2017</td>
</tr>
</tbody>
</table>

www.clinicaltrials.gov [accessed September 6, 2015]

The Impact of PCSK9 Inhibitors on Lipid Levels and Outcomes in Patients with Primary Hypercholesterolemia: A Network Meta-Analysis

Michael J. Lipinski, Umberto Benedetto, Ricardo O. Escarcega, Giuseppe Biondi-Zoccai, Thibault Lhermusier, Nevin C. Baker, Rebecca Torguson, H. Bryan Brewer, Ron Waksman

Cardiovascular Mortality

All-Cause Mortality

MACE

The Impact of PCSK9 Inhibitors on Lipid Levels and Outcomes in Patients with Primary Hypercholesterolemia: A Network Meta-Analysis

Michael J. Lipinski, Umberto Benedetto, Ricardo O. Escarcega, Giuseppe Biondi-Zoccai, Thibault Lhermusier, Nevin C. Baker, Rebecca Torguson, H. Bryan Brewer, Ron Waksman

Cardiovascular Mortality

All-Cause Mortality

MACE
Neurocognitive Events

Will patients tolerate injection and who will cover the cost?

Cholesterol-lowering Praluent and Repatha cost more than $14,000 a year per patient but would be cost-effective at $2,180, research group says.

Prospects and uncertainties

Prospects
- Major and sustained LDL-lowering efficacy
- Effective with or without statins
- May change management of cholesterol in
  - FH pts
  - Statin-intolerant patients
  - High risk pts not at goal, on top of statins

Uncertainties
- Clinical benefit?
- Tolerability of injections on the long term?
- Side effects?
  - Related to each molecule
  - Related to very low levels of LDL cholesterol

PCSK9 mAbs: When should they be used?
- ONLY after maximal tolerated dose of efficacious statins ± ezetimibe and
  - LDL-C is still above acceptable LDL-C ‘goal’ (HeFH and very high/low risk nonFH)
  - When patients cannot tolerate statins or effective dose of statin
  - In homozygous FH prior to mipomersen or lomitapide (tolerability, serious side effects and cost)
- Choice of dose and dosing regimen
  - Evolocumab 140 mg Q2w and QM the same for 60% efficacy and side effects
  - Alirocumab 75 mg Q2W sub-maximal PCSK9 suppression and LDL-C reduction ~50% versus 60% with 150 mg Q2W
- For patients on maximal efficacious statins ‘near goal’ (e.g. 70 for very high/low risk) ezetimibe should always be next step rather than PCSK9 mAb, even ‘lower dose’

Thank You