Roche Science Events: ACC 2008
Conference Call for Investors and Analysts

HDL raising as a new therapeutic intervention and Roche’s CETP inhibitor R1658

Chicago, April 2, 2008
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Agenda

HDL raising and Roche’s CETP inhibitor

• **Introduction**
  
  Dr. Karl Mahler, Head of Investor Relations, Roche

• **Metabolic Diseases Patterns and Market**
  
  Luke Miels, Strategic Marketing Head Metabolic Diseases and Anemia, Roche

• **HDL raising: The new target**
  
  Prof. Dr. Philip Barter, Director, Heart Research Institute, Sydney

• **Safety data for Roche’s CETP inhibitor**
  
  Dr. Fouzia Laghrissi-Thode, Life Cycle Leader for R1658, Roche

• **Phase III Morbi-Mortality (M&M) study**
  
  Dr. Fouzia Laghrissi-Thode, Life Cycle Leader for R1658, Roche

• **Next steps**
  
  Luke Miels, Strategic Marketing Head Metabolic Diseases and Anemia, Roche
Dyslipidemia: Future growth driven by HDL treatment

CETP inhibitors and other HDL raising drugs will be responsible for the majority of market value

Sources: Wood MacKenzie, IMS therapy forecaster, Roche assumptions
Decision Resources, Cardium Study#4, 2007; Datamonitor Pipeline Insight dyslipidemia 2007
Metabolic diseases patterns and market

**HDL raising: The new target**

**Safety data for Roche’s CETP inhibitor**

**Phase III Morbi-Mortality (M&M) study**

**Next steps**
Global Statin Market - CHF 31bn

Mio LC CHF

IMS MIDAS (PADDS), Roche panels
The Market Today

**HDL as an emerging target in dyslipidemia**

**Short Term**
- Currently 6 million TRx/year in the US
- Market growth will be driven by Niacin based combinations
  - Moderate to severe flushing occurs in more than 30% of patients

**Medium Term**
- Entry of the CETPi class
- CETPi class will launch with M&M data in high risk populations
- CETPi are expected to be prescribed on top of statins to treat cardiovascular residual risk

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**US Niacin and Fibrate Scripts (MM TRx)**

**Percentage of Cardiovascular Events Prevented or Not Prevented in Major Clinical Studies**

Events Prevented  ▪️  Events Not Prevented

<table>
<thead>
<tr>
<th>Study</th>
<th>Events Prevented</th>
<th>Events Not Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S, CARE, WOS, LIPID, AF-CAPS</td>
<td>HPS</td>
<td>PROSPER</td>
</tr>
</tbody>
</table>

![Graph showing US Niacin and Fibrate Scripts (MM TRx)](image1)

![Graph showing Percentage of Cardiovascular Events Prevented or Not Prevented in Major Clinical Studies](image2)
High / Medium-Risk CHD patients in US
Patients potentially benefiting from HDL raising

**Hyperlipidemia**

- **Hyperlipidemic**: 87 mn
- **Statin Treated**: 31 mn

**High/medium-risk CHD**

- **High-risk CHD**: 8 mn
- **High/medium-risk CHD**: 78 mn

**Source**: Decision Resources
The Dyslipidemic Market

*Differences between LDL and HDL hypothesis*

**LDL**
- Validated surrogate marker
- Established scientific understanding of the LDL particle
- M&M data is not a launch requirement for LDL compounds
- Mature market
- Generics (statins)

**HDL**
- Non-validated surrogate marker
- Evolving scientific understanding of the HDL particle
- M&M data is a launch requirement for CETP class
- Emerging market
- Few compounds to raise HDL in phase III clinical development
Metabolic diseases patterns and market

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Phase III Morbi-Mortality (M&M) study

Next steps
FRAMINGHAM: Low HDL-C is an independent factor of CHD risk even when LDL-C is low

A highly significant correlation in more than 10’000 individuals, across two generations.

* Men aged 50-70

Relationship Between Changes in LDL-C and HDL-C Levels and CHD Risk

1% decrease in LDL-C reduces CHD risk by 1%

1% increase in HDL-C reduces CHD risk by 1%

TNT Trial: Major Cardiovascular Event Frequency by HDL level in group with LDL-C < 70 mg/dL

Barter et al, NEJM 2007, 357; 13, 1301-1310
Benefits of raising HDL

**Animal studies**

- Raising HDL-C either by infusing HDL or by increasing the synthesis of apoA-I by genetic manipulation greatly inhibits the development of atherosclerosis in both mice and rabbits

**Human Studies**

- Raising HDL-C by treatment with either niacin or fibrates in intervention trials is associated with a slowing of progression of CAD and a reduction in CV events.
- Infusion of reconstituted HDL reduces the atherosclerosis burden as assessed by IVUS.
Vascular protective properties of HDL

Promote cholesterol efflux from macrophages

- Anti-oxidant properties
- Anti-thrombotic properties
- Anti-inflammatory properties
- Improve endothelial function
- Promote endothelial repair
- Other
Effect of CETP inhibition on plasma cholesterol transport

- Liver
  - LDL-R
  - SR-B1
  - SR-B1
  - FC
- Bile
- HDL
- CETP
- CETP
- VLDL/LDL
- Extrahepatic tissues
- FC
- LCAT
Relationship between CETP and atherosclerosis

**Animal studies (Rodents)**
- Rodents naturally deficient in CETP
- Rodents naturally resistant to development of atherosclerosis
- Expression of CETP in transgenic mice and rats increases atherosclerosis in most (but not all) models

**Animal studies (Rabbits)**
- Rabbits have high level of activity of CETP
- Rabbits naturally highly susceptible to the development of atherosclerosis
- Inhibition of CETP in rabbits decreases atherosclerosis in all models
Relationship between CETP and atherosclerosis

**Human studies**

- Torcetrapib inhibits CETP in humans and raises HDL-C by about 60% and lowers LDL-C by more than 20%
- In human studies torcetrapib had no effect on atherosclerosis in three imaging trials
- In human studies torcetrapib increased both mortality and major cardiovascular events in a large end-point trial
Off-target pharmacological effects of torcetrapib unrelated to CETP inhibition

In patients receiving torcetrapib in the ILLUMINATE trial there was a significant:

• Increase in blood pressure
• Decrease in serum potassium
• Increase in serum bicarbonate
• Increase in serum sodium
• Increase in serum aldosterone

The adverse outcome in the ILLUMINATE trial may thus have been the consequence of an off-target pharmacology of torcetrapib unrelated to CETP inhibition.

Barter et al, NEJM 2007;357:1301-1310
The changes in potassium and bicarbonate predicted adverse outcome in the ILLUMINATE trial

Deaths by changes in K+ and HCO3- from baseline to month 1

### Decrease in serum potassium

<table>
<thead>
<tr>
<th></th>
<th>Decrease ≥ Median (≥ 0.1 mmol/L)</th>
<th>Decrease &lt; Median (&lt; 0.1 mmol/L)</th>
<th>N/C*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>3709</td>
<td>3629</td>
<td>195</td>
</tr>
<tr>
<td>Deaths (%)</td>
<td>54 (1.46)</td>
<td>35 (0.96)</td>
<td>4 (2.05)</td>
</tr>
</tbody>
</table>

### Increase in serum bicarbonate

<table>
<thead>
<tr>
<th></th>
<th>Increase &gt; Median (&gt; 0.7 mmol/L)</th>
<th>Increase ≤ Median (≤ 0.7 mmol/L)</th>
<th>N/C*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>3669</td>
<td>3695</td>
<td>169</td>
</tr>
<tr>
<td>Deaths (%)</td>
<td>54 (1.47)</td>
<td>35 (0.95)</td>
<td>4 (2.37)</td>
</tr>
</tbody>
</table>

N/C = not classified due to missing value

Barter et al, NEJM 2007;357:1301-1310
Cox proportional hazard model adjusted for age, gender and baseline HDL-C. Excludes 265 patients with missing month 3 HDL-C.

Hazard ratios for CHD Death or Non-Fatal MI by quintile of on-trial HDL-C (referent group is HDL-C < 60 mg/dL stratum)

<table>
<thead>
<tr>
<th>CHD Death or Non-Fatal MI (Hazard Ratio)</th>
<th>Quintiles of HDL-C (mg/dL) at Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>&lt;60</td>
</tr>
<tr>
<td>0.67</td>
<td>60-70</td>
</tr>
<tr>
<td>0.47*</td>
<td>71-80</td>
</tr>
<tr>
<td>0.57*</td>
<td>81-93</td>
</tr>
<tr>
<td>0.43*</td>
<td>&gt;93</td>
</tr>
</tbody>
</table>

*P<0.05

**ILLUMINATE trial:**
The higher the achieved HDL-C in the torcetrapib treated patients, the lower the event rate

Cox proportional hazard model adjusted for age, gender and baseline HDL-C. Excludes 265 patients with missing month 3 HDL-C.
What is the future of CETP inhibition as an anti-atherogenic strategy in humans?

Given:

• the powerful evidence in animal studies that inhibiting CETP is anti-atherogenic and
• that off-target effects of torcetrapib unrelated to CETP inhibition may have been responsible for the adverse outcome in the ILLUMINATE trial

There is a compelling case for further testing of the hypothesis that inhibiting CETP will be anti-atherogenic in humans so long as the hypothesis is tested with a CETP inhibitor that does not share the off-target pharmacology of torcetrapib.
Metabolic diseases patterns and market

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Next steps
CETP Inhibitors

*R1658 is a unique CETPi*

- In contrast to the majority of other CETP inhibitors, R1658 has a different chemical backbone to Torcetrapib.
- In patients treated with R1658, HDL is of normal composition.
- In pre-clinical models and in clinical trials up to phase II, data showed that R1658 at therapeutic doses had a similar safety profile to placebo, including effects on blood pressure and RAAS activation.
Blood pressure and renin-angiotensin system genes

Stroes ESG et al, poster number 1021-204 presented at ACC 08

• Rat model to investigate the off-target toxicity of two CETP inhibitors

• Investigators reported
  – Torcetrapib dose-dependently increased blood pressure and the expression of renin-angiotensin-aldosterone system (RAAS) genes involved in regulating blood pressure
  – R1658 did not change blood pressure, heart rate or RAAS gene expression

• In contrast to torcetrapib, R1658 was not associated with the off-target toxicity on RAAS gene expression

• In this model, R1658, unlike torcetrapib, did not change blood pressure
General safety profile of R1658

Stein EA et al, poster number 1028-167 presented at ACC 08

• The safety profile of the CETPi R1658 was evaluated
  – data from five Phase 2 clinical trials
  – 561 patients received R1658; 277 received placebo
  – Treatment period of up to 12 weeks in duration

• There were no deaths in any of the studies
• Incidence of adverse events was similar in placebo and R1658 treatment groups
• Gastrointestinal side effects occur more frequently in R1658 treatment groups
• Incidence of adverse events did not increase with increasing dose
• Blood pressure remained stable over the study period
• R1658 was generally well tolerated in Phase 2 studies
Cardiovascular (CV) safety profile of R1658

Steiner G et al, poster number 1028-166 presented at ACC 08

- Specific CV safety and tolerability were assessed in a detailed analysis
  - data from five phase 2 clinical trials
  - 561 patients received R1658; 277 received placebo
  - Treatment period of up to 12 weeks in duration

- CV adverse events occurred at a similar low frequency in placebo and R1658 groups
- Severity and causality of CV adverse events were not related to R1658 dose
- No clinically relevant changes in blood pressure was observed.
- R1658 was generally well tolerated in phase 2 trials
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Phase III Morbi-Mortality (M&M) study

Next steps
M & M Study

Rationale

• Mortality and morbidity data: only true evaluation of the CV benefits of raising HDL-C by CETPi

• R1658 is being investigated to reduce CV risk on top of current recommended standard of care for CV risk factors

• Currently the only route to approval of CETPi
M&M Study

Patient population

• Roche trial will focus on high-risk CHD patients, after a recent event

• M&M study population
  – Selected after thorough consultation with medical/scientific experts and health authorities
  – Have the highest likelihood to benefit from treatment with CETPi
  – Will be closely monitored to detect, as early as possible, clinically meaningful differences between treated and controlled groups
M&M Study Design

*Trial in high-risk CHD patients, after a recent event*

- Approx 15’600 patients considered to have stable disease after a recent event
- Randomized to active treatment or placebo
- Optimized background therapy to assess “real” effect of raising HDL-C
- Study to run until final adjudicated event occurs
Metabolic diseases patterns and market

HDL raising: The new target

Safety data for Roche’s CETP inhibitor

Phase III M+M study

Next steps
CETPi – Development Plan

Step-wise investment – several key decision points

• Thorough, structured and step-wise phase III clinical programme implemented
• Strict safety monitoring through independent DSMB*: rapid assessment of findings in all studies throughout the phase III programme
• Key decision points incorporated to determine clinical trials progression
• Ongoing investment decisions matched to key decision points

* Data Safety Monitoring Board
CETPi – Development Plan

Step-wise investment – several decision points

![Graph showing step-wise investment with decision points labeled as data driven and CAP.](image-url)
Metabolic Portfolio
Promising Late-Stage Assets

• CETPi first phase III entry

• Compounds approaching phase III
  – GLP-1
  – DPP-IV
  – aleglitazar

• Update on Diabetes portfolio at ADA, June 2008
We Innovate Healthcare