Investor science conference call from ADA 2009
New Orleans, 8 June 2009
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Introduction

Dr. Karl Mahler, Head of Investor Relations
Agenda

Diabetes management & cardiovascular risk reduction

- **Metabolism/Diabetes in Roche Pharma**
  - Luke Miels, Head of Strategic Marketing for Metabolic Diseases

- **R1439(aleglitazar) PPAR αγ co-agonist phase IIb SYNCHRONY data**
  - Michael Lincoff, MD, Professor of Medicine, Department of Cardiovascular Medicine, Cleveland Clinic, Ohio, USA

- **R1439(aleglitazar) PPAR αγ co-agonist phase III and future plans**
  - Dr. Klaus Hinterding, Aeglitazar Lifecycle Leader

- **R1583(taspoglutide) GLP-1 phase III update**
  - Dr. Rajiv Patni, Taspoglutide Lifecycle Leader

- **Metabolism/Diabetes franchise update**
  - Luke Miels, Head of Strategic Marketing for Metabolic Diseases

- **Questions & Answers (45 minutes)**

  Total duration: Up to 1½ hour
Roche pharma pipeline overview

*Five Disease Biology Areas*

- **Oncology**
  - Avastin
  - MabThera/Rituxan
  - Herceptin
  - Xeloda
  - Tarceva
  - R1273 (pertuzumab)
  - R1507 (IGF-1R mAb)
  - R3502 (trastuzumab-DM1)
  - R3616 (hedgehog inh.)
  - R7159 (3rd gen anti-CD20)
  - Apomab
  - Dacetuzumab
  - Dulanermin
  - 15 ph. I compounds

- **Inflammation**
  - MabThera/Rituxan
  - Actemra
  - R1594 (ocrelizumab)
  - Anti-IL 13
  - 9 ph. I compounds

- **Metabolism**
  - R1439 (agliptin)
  - R1583 (tasoglutide)
  - R1658 (dalcetrapib)
  - R7201 (SGLT-2 inh)
  - 6 ph. I compounds

- **Virology**
  - Pegasys
  - Tamiflu
  - R3484 (HPV16)
  - R7128 (HCV pol. inh.)
  - R7227 (HCV pro. inh.)

- **CNS**
  - R1594 (ocrelizumab)
  - R1678 (schizophrenia)
  - R3487 (Alzheimer’s)
  - 4 ph. I compounds

- **Today’s focus**

- **On hand Promising Emerging Early**
  - late stage mid-term stage
Roche in metabolic diseases
Growing need for innovative products

Diabetes: The epidemic continues; often accompanied by high blood pressure and obesity

Dyslipidemia: Silent danger on the rise; causes clogged arteries, heart disease and stroke over time

Source: Type 2 Diabetes: Global Epidemiology, Strategyst Consulting, 2004

Sources: Wood MacKenzie, IMS therapy forecaster, Roche assumptions, Decision Resources, Cardium Study#4, 2007; Datamonitor Pipeline, Insight dyslipidemia 2007
Metabolism/Diabetes in Roche Pharma

Luke Miels, Head of Strategic Marketing for Metabolic Diseases
Metabolism R&D strategy is focusing on targets with the potential to lower cardiovascular risk

Assumptions
• Type 2 diabetes is also a cardiovascular disease
• Glucose reduction alone is not sufficient

Target priorities
• Effects beyond pure glucose/HbA1c reduction
• Innovation that the market will reward
• Focused development plans including “Personalised Health Care” (PHC) approach
• First- and/or best-in-class potential
Roche: Promising outlook in Metabolism

Leading compounds with differentiated profiles…

**R1439 (aleglitazar) PPAR αγ co-agonist**
- Phase II data very encouraging
- Phase III transition and outline of the development strategy

**R1658 (dalcetrapib) CETP inhibitor**
- First-in-class, high unmet medical need
- Phase III progressing in line with expectations
- Scientific publications to differentiate its unique structure
Roche: Promising outlook in Metabolism
...and potential to be best-in-class

R1583 (taspoglutide) GLP-1 analogue
- Phase III status and plans to address updated FDA guidelines
- Roche perspective on GLP-1s and C-cell thyroid tumors

R7201 SGLT-2 inhibitor
- Goal to be best-in-class
- Phase II initiated
- Phase III decision by 1H 2010
R1439(aleglitazar) PPAR αγ co-agonist phase IIb SYNCHRONY data

Michael Lincoff, MD, Professor of Medicine, Department of Cardiovascular Medicine, Cleveland Clinic, Ohio, USA
High unmet need despite best standard of care

60-90% of CV events not prevented despite wide use of statins

Major clinical trials aiming at cardiovascular risk reduction

% event not prevented % event prevented

4S, The Lancet, 1994
Lipid, NEJM, 1998
Care, NEJM, 1996
HPS, The Lancet, 2002
WOSCOP, NEJM, 1999
AFCAPS/TexCAPS, JAMA, 1998
TNT, NEJM, 2005

Despite statin treatment a residual risk of >65% remains for major cardiovascular events

Aleglitazar: Proof of concept

*Pioglitazone has shown benefit on CV morbidity & mortality*

- PROACTIVE outcomes trial: Significant 16% relative-risk reduction on main secondary endpoint of death, myocardial infarction or stroke
- Beneficial and significant effects on CV outcomes confirmed by meta-analysis of randomized trials
- Beneficial and significant effects on atherosclerosis demonstrated in two imaging studies
  - PERISCOPE (IVUS\(^1\)) in patients with type 2 diabetes and coronary artery disease
  - CHICAGO (CIMT\(^2\)) in patients with type 2 diabetes
- Pioglitazone is not labeled for reduction of CV morbidity and mortality

\(^1\)IVUS: Intravascular ultrasound
\(^2\)CIMT: Carotid Intima-Media Thickness
Aleglitazar: A balanced and rationally-designed dual PPAR $\alpha/\gamma$ co-agonist

- Potential for dual PPAR agonists to reduce the cardiovascular risk in type 2 diabetes patients post acute coronary syndrome by improving
  - Lipid profile and
  - Glycemic control
- Other dual PPAR agonists have had a variety of safety concerns, likely due to an imbalance of effect on the $\alpha$ and $\gamma$ receptors
- Aleglitazar is rationally designed to have balanced activity on both the $\alpha$ and $\gamma$ receptors to optimize lipid and glucose levels and minimize adverse effects
- Favorable effects on dyslipidemia and glycemic control in pre-clinical, phase I & II studies, with a favorable toxicity profile

Aleglitazar: Potential to reduce cardiovascular risk in type 2 diabetes patients who had acute coronary syndrome
SYNCHRONY phase II study: Determine the optimal dose balancing efficacy, safety, and tolerability

4 weeks, single-blind, placebo run-in

Randomization: ~55 patients per treatment group (n=332)

16 weeks double-blind

- Placebo
- Aleglitazar 50 μg QD
- Aleglitazar 150 μg QD
- Aleglitazar 300 μg QD
- Aleglitazar 600 μg QD
- Pioglitazone 45 mg QD

16 weeks open label

4 weeks follow-up
Aleglitazar: Statistically significant dose-dependent reductions in HbA1c

Placebo

Aleglitazar

50 μg 150 μg 300 μg 600 μg

Pioglitazone

45 mg

P values vs. placebo.

Aleglitazar: Statistically significant reductions in fasting plasma glucose

Aleglitazar: Statistically significant reductions in triglycerides

Aleglitazar: Statistically significant reductions in atherogenic LDL cholesterol

Aleglitazar: Statistically significant increases in atheroprotective HDL cholesterol

Placebo

- 50 μg
- 150 μg
- 300 μg
- 600 μg

Aleglitazar

- 50 μg
- 150 μg
- 300 μg
- 600 μg

Pioglitazone

- 45 mg

Aleglitazar: Safety profile

Well tolerated with no unexpected toxicity

• Cardiac safety
  – No congestive heart failure in patients treated with 150 μg (phase III dose)
  – No myocardial infarction or coronary revascularization events during the study

• Aleglitazar saw less than half the increase in weight over placebo versus pioglitazone
  – Aleglitazar 150 μg: 0.52 kg
  – Pioglitazone: 1.06 kg

• Less edema was reported in patients receiving aleglitazar 150 μg (phase III dose) (4%) than in patients receiving pioglitazone (7%) [placebo 5%]

• No deaths reported in the SYNCHRONY study
SYNCHRONY phase II study: Aleglitazar improved glycemic control and lipid profile in patients with type 2 diabetes

- Dose-dependent beneficial effects on glucose control
- Dose-dependent improvements in lipid profiles

**Aleglitazar 150 μg the optimal dose for phase III**
- Lipid improvements better than pioglitazone at maximum dose
- Glycemic control similar to pioglitazone
- Potential ideal balance of efficacy and cardiovascular safety

*Aleglitazar: Generally well tolerated, no unexpected toxicities*
R1439(aleglitazar) PPAR αγ co-agonist phase III and future plans

Dr. Klaus Hinterding, Aleglitazar Lifecycle Leader
Aleglitazar will not be developed as a traditional type 2 diabetes therapy

### Rationale

- Regulatory environment has changed; need for safety outcomes trial for diabetes therapies
- Several oral treatments for type 2 diabetes and dyslipidemia already available
- Generic thiazolidinediones
- Pioglitazone will have robust data set in type 2 diabetes

<table>
<thead>
<tr>
<th>Type 2 diabetes scenario</th>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
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<tr>
<td><strong>Endpoint / studies</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Targets</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Type 2 diabetes</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>A1c endpoint for registration, large safety database, post-approval outcomes study</strong></td>
</tr>
<tr>
<td><strong>Glycemic control in type 2 diabetes patients</strong></td>
</tr>
<tr>
<td><strong>Primary care physicians/internal medicine/family practice and endocrinologists</strong></td>
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</tbody>
</table>
Patients with type 2 diabetes are at high cardiovascular risk

- A patient with type 2 diabetes has the same cardiovascular event risk as a non-type 2 diabetes person with a previous cardiovascular event
- Diabetic patients post acute coronary syndrome are at highest risk of recurring CV events

Current hyperglycemic treatments do not significantly reduce the cardiovascular risk in type 2 diabetes

1Malmberg K et al. Circulation 2000;102:1014-1019
Indication for the reduction of morbidity & mortality in type 2 diabetics post acute coronary syndrome provides a strong platform for differentiation

<table>
<thead>
<tr>
<th>Reduction of morbidity &amp; mortality</th>
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<tbody>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Type 2 diabetes post acute coronary syndrome</td>
</tr>
<tr>
<td>Endpoint / studies</td>
</tr>
<tr>
<td>Composite cardiovascular morbidity &amp; mortality endpoint for registration</td>
</tr>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>Reduce cardiovascular morbidity &amp; mortality in patients who are stable following recent acute coronary syndrome and diagnosed with type 2 diabetes</td>
</tr>
<tr>
<td>Targets</td>
</tr>
<tr>
<td>Specialty care physicians</td>
</tr>
</tbody>
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**Rationale**

- Unmet need in this high-risk patient population
- Prescribers and payors realize value of aleglitazar to reduce residual risk on top of standard of care treatment
- Position aleglitazar as a “unique class” in a generic environment
- Aleglitazar has a unique cardio-metabolic profile beyond glucose control
**How we will develop aleglitazar**

*Phase III outcomes trial design* 

**Design**
- Double-blind, placebo-controlled study on top of standard of care
- Treatment duration: At least 2.5 years and until 950 events have occurred
- $N = 6,000$

**Patients**
- Type 2 diabetes (known and recently diagnosed)
- Hospitalized for acute coronary syndrome
- Randomization 2-6 weeks post index event

<table>
<thead>
<tr>
<th>Screening/placebo run-in period</th>
<th>Treatment period</th>
<th>Follow-up period</th>
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<tbody>
<tr>
<td><strong>Aleglitazar 150 µg or placebo</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Standard of care (diabetes and other cardiovascular risk factors)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At least 2.5 years</strong></td>
<td><strong>4 weeks</strong></td>
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**Primary endpoint**
- Composite endpoint of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke
How we will develop aleglitazar  
*Reduce cardiovascular risk in type 2 diabetes patients*

**Efficacy**
- Aleglitazar’s unique cardio-metabolic profile ideally addresses post acute coronary syndrome risk in type 2 diabetes patients
- In phase II, aleglitazar’s efficacy compared favorably with that of pioglitazone

**Safety**
- In phase II, aleglitazar has shown supportive safety data at the target dose
  - Weight gain and edema numerically less than with pioglitazone
- Non-clinical safety of aleglitazar is supportive of further development

**Regulatory**
- FDA and CHMP have agreed to proposed phase III outcomes trial, and support proposed development plan
Aleglitazar: Summary of rationale for moving into Phase III

• First-in-class opportunity
• Unique cardio-metabolic profile
• Development plan based on existing PPAR evidence
• Optimal benefit/risk balance for type 2 diabetes patients post acute coronary syndrome
• Niche indication in a population with significant unmet need
R1583(taspoglutide) GLP-1 phase III update

Dr. Rajiv Patni, Taspoglutide Lifecycle Leader
# Taspoglutide global registration program: Over 6,000 patients

<table>
<thead>
<tr>
<th>Study name</th>
<th>Background treatment</th>
<th>Comparator</th>
<th>Sample size</th>
<th>Enrollment complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-emerge 1</td>
<td>Diet &amp; exercise</td>
<td>Placebo</td>
<td>330</td>
<td>Yes</td>
</tr>
<tr>
<td>T-emerge 2</td>
<td>Metformin, TZD</td>
<td>Byetta BID</td>
<td>990</td>
<td>Yes</td>
</tr>
<tr>
<td>T-emerge 3</td>
<td>Pioglitazone + metformin</td>
<td>Placebo</td>
<td>330</td>
<td></td>
</tr>
<tr>
<td>T-emerge 4</td>
<td>Metformin</td>
<td>Januvia</td>
<td>630</td>
<td>Yes</td>
</tr>
<tr>
<td>T-emerge 5</td>
<td>Metformin + SU</td>
<td>Lantus</td>
<td>990</td>
<td>Yes</td>
</tr>
<tr>
<td>T-emerge 6</td>
<td>SU ± metformin</td>
<td>Pioglitazone</td>
<td>650</td>
<td></td>
</tr>
<tr>
<td>T-emerge 7</td>
<td>Metformin (high BMI)</td>
<td>Placebo</td>
<td>260</td>
<td>Yes</td>
</tr>
<tr>
<td>T-emerge 8</td>
<td>History of cardiovascular event</td>
<td>Placebo</td>
<td>2000</td>
<td></td>
</tr>
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**Enrollment ahead of plan**
T-emerge 8 is a dedicated cardiovascular type 2 diabetes safety study

• Prospective study in 2,000 type 2 diabetes patients with history of cardiovascular event

• Taspoglutide + standard of care versus placebo + standard of care

• Primary endpoint: MACE\(^1\)

• Ensures that NDA will contain sufficient number of adjudicated, prospective cardiovascular events to satisfy new FDA guidance

• Pilot for a possible outcome trial to show cardiovascular benefit post approval

\(^1\)Major adverse cardiovascular event
Roche perspective on GLP-1s and C-cell thyroid tumors

• Taspoglutide carcinogenicity program ongoing
  – Preliminary incidence of C-cell hyperplasia and adenoma was observed in a small number of animals
  – Final safety data expected Q4 2009

• Clinical relevance of proliferative lesions in rodents under investigation
  – Working hypothesis: C-cell effects are rodent-specific
  – Appropriate pre-clinical mechanistic studies underway
  – Calcitonin monitoring in phase III
Taspoglutide filing: Aiming for late 2010
Phase III data Q4 2009 – Q1 2010

Replace frequent injections by once-weekly injection
Challenge oral anti-diabetic drugs (OAD) in early stage disease

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<tr>
<th></th>
<th>vs. exenatide</th>
<th>vs. liraglutide</th>
<th>vs. exenatide LAR</th>
<th>vs. insulin glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taspoglutide’s competitive advantage&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• Human GLP-1 analogue • Once weekly dosing • Over-all better efficacy</td>
<td>• Once weekly dosing • Potential for better efficacy • Effective starting dose • Simple titration regimen</td>
<td>• Human GLP-1 analogue • Auto injector, hidden needle • Ease of injection (needle size, no reconstitution) • Effective starting dose • Simple titration regimen</td>
<td>• Comparable A1c potency • Lower risk of hypoglycemia • Weight loss • Once weekly dosing • Auto injector • Simple titration regimen</td>
</tr>
</tbody>
</table>

Taspoglutide: Aiming for best-in-class

<sup>1</sup>Subject to completion of phase III clinical trials
Summary and key points

Luke Miels, Head of Strategic Marketing for Metabolic Diseases
Metabolism franchise summary

Early stage portfolio
• Focus on targets with the potential to lower cardiovascular risk vs. pure glucose lowering
• First- and/or best-in-class hurdle

Late stage portfolio
• R1439(aleglitazar) PPAR αγ co-agonist moves into phase III in a niche with a high unmet medical need
• R1583(taspoglutide) GLP-1 analogue phase III program expanded, recruitment ahead of plan, filing planned for late 2010
• R1658(dalcetrapib) CETP inhibitor phase III progressing well
Questions & Answers

Moderator: 
Dr. Karl Mahler, Head of Investor Relations
We Innovate Healthcare