Roche Analyst Meeting
EULAR 2007

Barcelona, Spain

Friday, June 15, 2007
Forward-looking statements

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3. delay or inability in obtaining regulatory approvals or bringing products to market;
4. fluctuations in currency exchange rates and general financial market conditions;
5. uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
6. increased government pricing pressures;
7. interruptions in production;
8. loss of or inability to obtain adequate protection for intellectual property rights;
9. litigation;
10. loss of key executives or other employees; and
11. adverse publicity and news coverage.

Any statements regarding earnings per share growth is not a profit forecast and should not be interpreted to mean that Roche’s earnings or earnings per share for this year or any subsequent period will necessarily match or exceed the historical published earnings or earnings per share of Roche.
Introduction

Dr. Karl Mahler
Head of Investor Relations
Agenda

• **Actemra: The OPTION trial results**
  Prof. Andrea Rubbert-Roth, Professor of Medicine, University of Cologne, Germany

• **MabThera: Longer-term repeat treatment studies**
  Prof. Paul Emery, arc Professor of Rheumatology, Academic Unit of Musculoskeletal Disease, University of Leeds, Leeds Teaching Hospitals Trust, UK

• **Roche’s emerging franchise in autoimmune diseases**
  Dr. Urs Schleuniger, Business Director, Hematology & Autoimmune Diseases, Roche

• **Q&A**
Roche’s key therapeutic areas
Current and future pillars of growth

**Oncology**
- Xeloda
- MabThera
- Herceptin
- Avastin
- Tarceva
- C.E.R.A.
- Pertuzumab
- ARQ
- 12 phase I compounds

**Autoimmune**
- MabThera
- Actemra
- CellCept
- Ocrelizumab
- Pamapimod (p38 kin inh)
- 2 phase I compounds

**Metabolic**
- R1440 GKA
- R1583 GLP-1
- R1658 CETP Inh
- R1439 dual PPAR

**Virology**
- Tamiflu
- Pegasys
- R1626 Polymerase Inhib.
- R7227 Protease Inhibitor
- R7128 Polymerase Inhib.
- R7025 next gen. IFN

**Neurology/ Psychiatry**
- 6 phase I compounds

**ON HAND**
- PROMISING
- LATE STAGE

**EMERGING**
- MID-TERM

**EARLY STAGE**
RA market continues to grow
Biologic therapies are the significant driver

Sales of RA treatments

Sources: Decision Resources, Evaluate Pharma, IMS, Wood Mackenzie
RA: A very concentrated market

<30% of EU doctors account for 80% of biologics prescriptions

Source: Synovate Healthcare
Biologics prescribers concentrated in urban centers
% of prescribing doctors by biologic product

Product 1
- Mixed office and hospital: 18%
- City/teaching/university hospital: 21%
- Urban hospital: 24%
- Rheumatology clinic: 7%
- Rural town hospital: 23%

Product 2
- Mixed office and hospital: 16%
- City/teaching/university hospital: 3%
- Urban hospital: 25%
- Office (non-hospital): 21%
- Rheumatology clinic: 5%
- Rural town hospital: 30%

Product 3
- Mixed office and hospital: 21%
- City/teaching/university hospital: 16%
- Urban hospital: 26%
- Office (non-hospital): 5%
- Rheumatology clinic: 25%
- Rural town hospital: 7%

Source: Synovate Healthcare
Increased penetration of biologics into mild-to-moderate market segments

Source: Synovate Healthcare
Roche in Autoimmune Diseases

Building a new therapeutic franchise

**MabThera**
**Rheumatoid Arthritis**
- Launched in RA anti-TNFα inadequate responders (IR) in US and EU
- Filing for RA in DMARD IR in 2008

**Multiple Sclerosis, Lupus, Vasculitis**
- Phase III in LN, ANCA ass. vasculitis and SLE ongoing

**Actemra**
**Rheumatoid Arthritis**
- Filed in Japan
- Broad international phase III program ongoing
- Global filing in 2007

**CellCept**
**Lupus**
- Phase III in Lupus Nephritis (LN)
- Filing 2007

**Ocrelizumab**
**Rheumatoid Arthritis, Multiple Sclerosis, Lupus**
- Phase II trial in RA met primary and secondary endpoints, presented at ACR ’06
- Phase III program in RA initiated
- Trials in LN, SLE, and MS to start in 2007

**Pamapimod (p38 kinase inhibitor)**
**Rheumatoid Arthritis**
- In Phase II in RA
- Data in 2007

**In phase 1**
- 6 compounds for autoimmune diseases

7 phase III projects
2 phase II projects
Actemra: The OPTION trial results

Prof. Andrea Rubbert-Roth
Professor of Medicine, University of Cologne, Germany
IL-6 contributes to chronic inflammation in RA

- Monocytes/macrophages
- Endothelial cells
- T cell activation
- B cells
- Mesenchymal cells, fibroblasts/synoviocytes
- Hepatocytes
- Acute-phase proteins (hepcidin, CRP)
- Osteoclast activation
- Bone resorption
- Maturation of megakaryocytes
- Thrombocytosis
- Auto-antibodies (RF)
- Hyper γ-globulinaemia

Elevated IL-6 plays central role in RA

- IL-6 has a central role in RA
  - Induction of auto-antibodies
  - Activation of osteoclasts
  - Induction of acute-phase proteins
  - Maturation of megakaryocytes leads to thrombocytosis
  - Suppression of T-regulatory cells
- Produced by a range of cells (macrophages, fibroblasts, T cells and B cells)
- Expression induced by a variety of inflammatory factors, including TNF-α, IL-1β, and IL-175
**Actemra**
*A humanised anti-IL-6 receptor antibody*

- Binds to membrane-bound and soluble forms of IL-6 receptor
- Inhibits IL-6 binding to its receptor
- Blocks IL-6 signalling and gene activation
The OPTION study
TOcilizumab Pivotal Trial in methotrexate Inadequate respONders

Study population and objectives

• Patients with moderate-to-severe rheumatoid arthritis with an inadequate response to methotrexate (MTX)
  – Patients could have been on TNFα-antagonists but not necessarily TNF-failures

• Efficacy: reduction in signs and symptoms of RA, in combination with MTX vs placebo infusion (maintaining stable dose of MTX)
  – Primary endpoint: proportion of patients achieving ACR20 response at week 24

• Safety: adverse events; laboratory assessments; immunogenicity

• To explore pharmacokinetics and pharmacodynamics (hsCRP, IL-6, sIL-6R, DAS)
Study design

- Tocilizumab or placebo q4wk iv (6 infusions) maintaining stable dose of MTX
- Total randomised: 623 patients
- Early withdrawals and patients entering escape were classified as non-responders for the ACR and EULAR analyses

* One patient was randomised to tocilizumab 4 mg/kg + MTX but was not dosed
§ Includes one patient who was randomised to tocilizumab 4 mg/kg + MTX but who received tocilizumab 8 mg/kg + MTX through study
## Demographics

*Intent-to-treat population*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (MTX only) (n=204)</th>
<th>Tocilizumab 4 mg/kg + MTX (n=213)</th>
<th>Tocilizumab 8 mg/kg + MTX (n=205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>78</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>Age (mean, yrs)</td>
<td>50.6</td>
<td>51.4</td>
<td>50.8</td>
</tr>
<tr>
<td>RF positive (%)</td>
<td>74</td>
<td>82</td>
<td>87</td>
</tr>
<tr>
<td>Mean MTX dose (mg/wk)</td>
<td>14.9</td>
<td>14.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Previous DMARDs (mean number)*</td>
<td>1.7</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Prior anti-TNF treatment (%)**</td>
<td>9</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Concomitant steroids (%)</td>
<td>54</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Concomitant NSAIDs (%)</td>
<td>68</td>
<td>68</td>
<td>66</td>
</tr>
</tbody>
</table>

*Not counting MTX

**Discontinued for reasons other than lack of efficacy
Patients’ baseline disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (MTX only) (n=204)</th>
<th>Tocilizumab 4 mg/kg + MTX (n=213)</th>
<th>Tocilizumab 8 mg/kg + MTX (n=205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (mean, yrs)</td>
<td>7.8</td>
<td>7.4</td>
<td>7.5</td>
</tr>
<tr>
<td>SJC (mean)</td>
<td>20.7</td>
<td>20.0</td>
<td>19.5</td>
</tr>
<tr>
<td>TJC (mean)</td>
<td>32.8</td>
<td>33.2</td>
<td>31.9</td>
</tr>
<tr>
<td>CRP (mean, mg/dL)</td>
<td>2.36</td>
<td>2.79</td>
<td>2.61</td>
</tr>
<tr>
<td>ESR (mean, mm/h)</td>
<td>49.7</td>
<td>49.2</td>
<td>51.2</td>
</tr>
<tr>
<td>DAS28 (mean)</td>
<td>6.82</td>
<td>6.78</td>
<td>6.82</td>
</tr>
</tbody>
</table>
Results: Efficacy and safety
Significant clinical benefit with tocilizumab

Dose response; Strength at higher ACR score

Cochran-Mantel-Haenszel analysis was used to calculate p-values

All comparisons are to placebo + MTX
Rapid onset of action with tocilizumab (DAS28)

2 out of 3 patients showed improvement in DAS28 within 2 weeks
Rapid and sustained improvement in HAQ score

Mean change in HAQ score over weeks for Placebo, TCZ 4 mg/kg + MTX, and TCZ 8 mg/kg + MTX treatments. The minimal clinical important difference (MCID) is set at -0.22.
Tocilizumab induces rapid CRP normalisation

[Graph showing mean CRP levels (mg/dL) over 24 weeks for Placebo, TCZ 4 mg/kg + MTX, and TCZ 8 mg/kg + MTX]

Tocilizumab increases haemoglobin levels
75% of improvement within 2 weeks

Analysis of variance of change from baseline haemoglobin (ANCOVA). All comparisons are to placebo + MTX.
## Most frequently reported AEs

**Incidence ≥5%**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Placebo (MTX only) (n=204)</th>
<th>Tocilizumab 4 mg/kg + MTX (n=213)</th>
<th>Tocilizumab 8 mg/kg + MTX (n=205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>URT infection</td>
<td>13 (6.4)</td>
<td>12 (5.7)</td>
<td>17 (8.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (4.4)</td>
<td>15 (7.1)</td>
<td>14 (6.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (4.9)</td>
<td>11 (5.2)</td>
<td>12 (5.8)</td>
</tr>
<tr>
<td>RA worsening</td>
<td>13 (6.4)</td>
<td>7 (3.3)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>ALT increase</td>
<td>3 (1.5)</td>
<td>12 (5.7)</td>
<td>11 (5.3)</td>
</tr>
</tbody>
</table>
## Serious adverse events: Infections

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Placebo + MTX (n=204)</th>
<th>Tocilizumab 4 mg/kg + MTX (n=212)</th>
<th>Tocilizumab 8 mg/kg + MTX (n=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with at least 1 AE</td>
<td>2 (1)</td>
<td>3 (1.4)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>-</td>
<td>-</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>-</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Empyema</td>
<td>-</td>
<td>-</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>-</td>
<td>1 (0.5)</td>
<td>-</td>
</tr>
<tr>
<td>Ovarian abscess</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peridiverticular abscess</td>
<td>-</td>
<td>-</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em></td>
<td>-</td>
<td>1 (0.5)</td>
<td>-</td>
</tr>
<tr>
<td>URI</td>
<td>-</td>
<td>-</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Adverse events
*Consistent with those seen in previous studies*

- Infusions generally well tolerated
- Low incidence of adverse GI events (1 peridiverticular abscess, 1 gastroenteritis)
- Transient ALT elevation – no evidence of clinical hepatitis or hepatic failure
- Lipid levels initially increased and subsequently stabilised at the upper level of normal - no relevant change in atherogenic risk index
- Slight increase in infections (including serious infections) over placebo
  - No occurrence of TB
Conclusions

**Rapid and significant improvements in signs and symptoms of RA**

- Dose response observed
- Strength of tocilizumab at more clinically relevant ACR 50/70 scores
- CRP normalised with 8 mg/kg dose – Suggests benefit in reducing inflammatory cascade

**Safety: Tocilizumab is well tolerated**

- Increases in LDL cholesterol within normal limits accompanied by increases in HDL - Leading to neutral impact on atherogenic index
- Occurrence of infections is at lower end seen with biologic agent

**IL-6 receptor inhibition with tocilizumab may offer a promising future therapeutic approach to RA**
MabThera: Longer-term repeat treatment studies

Prof. Paul Emery
arc Professor of Rheumatology, Academic Unit of Musculoskeletal Disease, University of Leeds, Leeds Teaching Hospitals Trust, UK
Rituximab: A novel biological agent for rheumatoid arthritis

- Rituximab (RTX) is a novel genetically engineered anti-CD20 therapeutic monoclonal antibody that selectively targets CD20+ B cells

Rituximab selectively targets CD20-positive B cells

**Efficacy: Radiographic outcomes**

*Patients with inadequate response (IR) to prior TNF inhibitors*
Rituximab: Advancing in RA

Initial approvals in RA
- US approval: TNF IRs
- EU approval: TNF IRs

Regulatory progress
- US filing: X-Ray in TNF IRs
- EU SmPC: X-Ray in TNF IRs

Global filing:
- MTX-Naive / X-Ray (IMAGE)
- DMARD-IRs

Score Trial: MRI data in DMARD-IRs

US approval:
- Feb 2006
- Jul 2006

Global filing:
- Feb 2007
- Apr 2007

2008 and beyond…
Treatment schema of the REFLEX study

- **RTX 1 g x 2 + MTX**
  - Week 24
  - Week 56
  - Repeat courses
  - Rescue (RTX 1 g x 2)

- **Placebo + MTX**
  - Week 16
  - Week 24
  - Week 56
Inhibition of radiographic progression
First evidence in patients with inadequate response to TNF inhibitors

Mean change at Week 56

- Total Genant-modified Sharp score: Placebo (n=184) - 2.31, RTX (n=273) - 1.0
- Joint space narrowing: Placebo (n=184) - 0.99, RTX (n=273) - 0.41
- Erosion score: Placebo (n=184) - 1.32, RTX (n=273) - 0.59

Primary analysis: Radiographs within time window, linear extrapolation from Week 24 for missing values

Keystone et al. EULAR 2007 (Abstract No. SAT0011)
Inhibition of radiographic progression

*Even in patients who do not achieve an ACR20 response (week 24)*

Primary analysis: Radiographs within time window, linear extrapolation from Week 24 for missing values

Keystone et al. EULAR 2007
Efficacy: Repeat treatment courses

Patients with inadequate response to DMARDs or prior TNF inhibitors
Study design

Open-label extension study of rituximab in RA

Phase II/III

Placebo

Rituximab 2 x 1000 mg

Rituximab 2 x 1000 mg + cyclophosphamide

Rituximab 2 x 1000 mg + methotrexate

Placebo

Rituximab 2 x 1000 mg

Rituximab 2 x 1000 mg + methotrexate

Rituximab 2 x 500 mg + methotrexate

Rituximab 2 x 1000 mg + methotrexate

Placebo

Rituximab 2 x 1000 mg + methotrexate

Timing of repeat treatment courses was variable, depending on clinical need

Rituximab 2 x 1000 mg

Long-term follow-up

All patients in the open-label extension study received weekly methotrexate (10–25 mg) and methylprednisolone 100 mg iv on Days 1 and 15 plus oral prednisone 60 mg/day on Days 2–7 and 30 mg/day on Days 8–14.
Patient exposure to repeat courses of rituximab

<table>
<thead>
<tr>
<th>Course</th>
<th>As of September 2006 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Course</td>
<td>1053</td>
</tr>
<tr>
<td>2nd Course</td>
<td>684</td>
</tr>
<tr>
<td>3rd Course</td>
<td>400</td>
</tr>
<tr>
<td>4th Course</td>
<td>142</td>
</tr>
<tr>
<td>5th Course</td>
<td>41</td>
</tr>
<tr>
<td>6th Course</td>
<td>11</td>
</tr>
<tr>
<td>7th Course</td>
<td>1</td>
</tr>
</tbody>
</table>

van Vollenhoven et al. EULAR 2007 (Abstract OP0119)
Efficacy with repeat treatment

*In DMARD and TNF inadequate responders*

- 1 or more courses of RTX
- 2 or more courses of RTX
- 3 or more courses of RTX
- $\geq 3$ courses of RTX ($1 \text{ g x } 2 \text{) + MTX with an IR to TNF inhibitors}^*$

Patients receiving $\geq 3$ courses of rituximab ($1 \text{ g x } 2 \text{) + MTX with an IR to DMARDs}^*$

- No. patients with $\geq 24$ weeks FU post 3rd course

1053 68 400 210 97
94 57

*Patients who had initially received rituximab ($0.5 \text{ g x } 2 \text{) + MTX or rituximab monotherapy were excluded from the efficacy analyses*
ACR scores are sustained
Repeated courses in patients with prior IR to TNF inhibitors

Keystone et al, EULAR 2007 (Abstract No. SAT0012)

Week 24, n=96
Improved outcomes with repeated courses

In patients with prior IR to TNF inhibitors

Keystone et al. EULAR 2007 (Abstract SAT0012)
Consistent time intervals between treatment courses

Suggests optimal repeat treatment at 6 – 12 month intervals

- Median time to repeat course (weeks)
  - TNF-IR (n=210): 37.9 (Course 1 to Course 2), 42.1 (Course 2 to Course 3)
  - DMARD-IR (n=94): 48.7 (Course 1 to Course 2), 56.2 (Course 2 to Course 3)

Course 1 to Course 2 | Course 2 to Course 3
Pooled safety results
More than 2400 patient-years
As of September 2006

<table>
<thead>
<tr>
<th>Duration of observation</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (any duration)</td>
<td>1053</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>1014</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>957</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>701</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>120</td>
</tr>
<tr>
<td>Total exposure (patient-years)</td>
<td>2438 patient-years</td>
</tr>
</tbody>
</table>
Infusion-related reactions

Acute reactions reduced with subsequent courses

Acute infusion reactions defined as pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough, bronchospasm, hypotension or hypertension

van Vollenhoven et al. EULAR 2007
No increase in infection rates with repeat treatment

- Course 1 (n=1053)
- Course 2 (n=684)
- Course 3 (n=400)
- Course 2 (n=142)

Infections/100 pt-yrs

- Course 1 (n=1053): 80, 85, 97, 101
- Course 2 (n=684): 5.4, 4.6
- Course 3 (n=400): 6.3
- Course 2 (n=142): 5.4

Serious infections

- Course 1 (n=1053): 80, 85, 97, 101
- Course 2 (n=684): 5.4, 4.6
- Course 3 (n=400): 6.3
- Course 2 (n=142): 5.4
Proportions of patients with IgM < LLN by treatment course

*Insufficient data beyond Week 24
IgM RF levels by treatment course over time

- 1st course
- 2nd course
- 3rd course
- 4th course

Mean IgM RF over weeks from 0 to 24.
Proportions of patients with IgG < LLN by treatment course

*Insufficient data beyond Week 24
Rates of serious infection
Similar in patients with low and normal Ig levels

<table>
<thead>
<tr>
<th></th>
<th>All exposure n=1053</th>
<th>Patients with normal IgG and IgM n=761</th>
<th>Patients with low IgG at any time n=67</th>
<th>Patients with low IgM at any time n=261</th>
<th>Patients with IgM &lt;0.4g/L and IgG &lt;3g/L n=2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with low Ig at anytime</td>
<td>-</td>
<td>-</td>
<td>67/1053 (6.3%)</td>
<td>261/1053 (24.7%)</td>
<td>2/1053 (&lt;1%)</td>
</tr>
<tr>
<td>Number of patients with a serious infection (SI)*</td>
<td>104 (9.9%)</td>
<td>66 (8.7%)</td>
<td>12 (17.9%)</td>
<td>32 (12.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Rate of SIs per 100 patient years 95% CI</td>
<td>5.4 (4.53, 6.38)</td>
<td>4.9 (3.93, 6.06)</td>
<td>6.8 (4.03, 11.49)</td>
<td>6.4 (4.74, 8.68)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Defined as serious AE and/or requiring iv antibiotics

van Vollenhoven et al. EULAR 2007 (Abstract OP0119)
MabThera – Conclusions

**Sustained or improved efficacy with repeat treatment**

- Benefits of rituximab are sustained with repeated courses
- Stopping joint damage progression remains a priority in inadequate responders to TNF inhibitors
- REFLEX study provides first and only evidence of inhibition of structural joint damage in this patient population
- This is independent of achieving a clinical response with rituximab

**Overall safety profile consistent with prior studies**

- Similar serious infection rates with repeat treatment courses – No opportunistic infections, viral reactivations or tuberculosis reported
- No lymphoproliferative malignancies and no increased risk of malignancy with additional courses of treatment were observed
- Long-term follow-up of RA patients receiving rituximab showed safety profile similar with each course
Roche’s franchise in autoimmune disorders

Dr. Urs Schleuniger
Business Director, Hematology & Autoimmune Diseases, Roche
Roche’s autoimmune portfolio
Expanding breadth of indications

**RA**
- Oral DMARDs
  - R1295
  - R3421 (AI)
  - R3477 (AI)
  - BR3-FC (RA) GNE
  - PNP Inh (AI) Biocryst
  - S1P1 (MS) Actelion

**Biologics**
- MabThera (RA DMARD)
  - R1503 (RA)
  - MabThera (RRMS) GNE
  - Ocrelizumab (RA)
  - Actemra (RA)
  - Actemra (sJIA)
  - CellCept (LN)
  - Ocrelizumab (PPMS) GNE
  - MabThera (ANCA av) GNE
  - MabThera (SLE) GNE
  - MabThera (LN) GNE

**All Autoimmune**
- Pamapimod (p38 inh)
  - Ocrelizumab
  - MabThera

**Filed/Approved**
- MabThera (RA TNF)
## Overview of autoimmune disorders

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>PRIMARY PATHOLOGY</th>
<th>HIGH NEED?</th>
<th>PREVALENCE</th>
<th>PATIENTS</th>
<th>DISEASE PROGRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Joint/bone degeneration</td>
<td>Yes</td>
<td>1% global</td>
<td>+60 mln WW</td>
<td>Mild, moderate, severe</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Destruction of CNS myelin</td>
<td>Yes</td>
<td>&lt;&lt;1% global</td>
<td>0.6 - 1.1 mln WW</td>
<td>RRMS; SPMS; PPMS; PRMS *</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>Tissue damage from autoantibodies</td>
<td>Yes</td>
<td>&lt;0.5% global</td>
<td>0.5 mln US</td>
<td>Mild, intermittent, persistent, fulminant</td>
</tr>
<tr>
<td>Lupus Nephritis</td>
<td>Renal involvement in SLE</td>
<td>Yes</td>
<td>40 – 85% SLE patients</td>
<td>0.2 – 0.4 mln US</td>
<td>Class I - VI</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>Chronic intestinal inflammation</td>
<td>Yes</td>
<td>0.2% - 0.5% global</td>
<td>&gt; 5 mln</td>
<td>Mild, moderate, severe</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Autoimmune infiltration into skin</td>
<td>Yes</td>
<td>1 – 2% global</td>
<td>125 mln WW</td>
<td>Plaque-type: Mild, moderate, severe</td>
</tr>
</tbody>
</table>

* RRMS: Relapsing-Remitting Multiple Sclerosis; SPMS: Secondary-Progressive MS; PPMS: Primary Progressive MS; PRMS: Progressive Relapsing MS
RA patient cascade

Top 5 European countries

Source: Decision Resources
Not all patients respond to current therapy

Gold standard therapy
anti-TNF + MTX

Unmet Medical Need

Only 1 of 3 patients receives significant benefit

% ACR70 Responders

ACR 70 = 70% Improvement in:
- Global disease activity - patient
- Global disease activity - physician
- Patient assessment of Pain
- Physical disability
- Acute phase reactants - CRP, ESR
Majority patients still treated with DMARDs…
…but biologics account for majority sales

RA treated population in 2007

- 10% Conv. DMARDs & others
- 90% Biologics

RA sales in 2007

- 9% Conv. DMARDs & others
- 91% Biologics

Sources: US: SDI Longitudinal Data, IMS NSP Audit, SDI Longitudinal data
EU & RoW: Decision Resources, IMS MIDAS, Evaluate Pharma, Wood Mackenzie
Major players are active in this area…

…Yet opportunities remain for novel therapies

- **Enbrel** 1998
- **Remicade** J&J 1999
- **Humira** Abbott 2002
- **Orencia** BMS 2005
- **Actemra** Roche 2006

Phases:
- **Phase I/II**
  - **Denosumab** Amgen
  - **HuMax 20 GenMab**
  - **Belimumab** BGS/CAT/GSK
  - **Ocrelizumab** Roche
  - **Tru015 Trubion/Wyeth**

- **Phase III**
  - **Cimzia** Celltech/UCB
  - **Golimumab** J&J
  - **Belimumab** HGS/CAT/GSK

- **Orals** e.g. p38

- **2008 and later**

- **Anti-TNF**
- **Other MoA**
- **Costimulation modulator**
- **B-Cell Targeted Therapy**

60
## MabThera: Roche’s ongoing phase III program

<table>
<thead>
<tr>
<th>Trial</th>
<th>Data timing</th>
<th>Treatment</th>
<th>Sample Size</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MTX-IR SERENE</strong></td>
<td>2008</td>
<td>MTX + placebo vs. MTX + MabThera 1g vs. MTX + MabThera 2g</td>
<td>495</td>
<td>Reduction in signs and symptoms</td>
</tr>
<tr>
<td><strong>MTX-IR Dose escalation MIRROR</strong></td>
<td>2008</td>
<td>Rituximab 1g retx 1g vs. Rituximab 1g retx 2g vs. Rituximab 2g retx 2g</td>
<td>375</td>
<td>Effect of further courses and dose escalation</td>
</tr>
<tr>
<td><strong>DMARD-IR SCORE</strong></td>
<td>2009</td>
<td>MTX + placebo vs. MTX + MabThera 1g vs. MTX + MabThera 2g</td>
<td>180</td>
<td>MRI changes at 6 months</td>
</tr>
</tbody>
</table>
| **MTX naïve (X-ray study) IMAGE** | 2010        | MTX vs. MTX + MabThera 1g vs. MTX + MabThera 2g                          | 852         | Reduction in signs and symptoms                                          
|                               |             |                                                                          |             | Inhibition of structural joint damage                                     |
|                               |             |                                                                          |             | Improvement in physical function                                         |

EU filing on track for 1H 2008
Actemra

Potential to become a significant new RA treatment

First-in-class agent

- Humanized monoclonal antibody blocking the activity of IL-6
- Conclusions from phase III Jap trials
  - Impressive efficacy in DMARD inadequate responders
  - Effective as monotherapy
  - Well tolerated

Large international phase III program

- 5 registration trials (>4,000 patients) - recruitment completed
- Mono and combo therapy
- Patient populations studied:
  - MTX inadequate responders
  - DMARD inadequate responders
  - TNFα inadequate responders
  - MTX naïve patients
- **First 2 trials (OPTION and TOWARD) met primary endpoint**
- Further clinical data during 2007

Filed in Japan in April 2006

Global filing 2007
### Actemra: Roche’s ongoing phase III program

*Additional international trials*

<table>
<thead>
<tr>
<th>TRAIL / Treatment Arms</th>
<th>Topline Data Timing</th>
<th>Sample Size</th>
<th>Patient population</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOWARD</strong>&lt;br&gt;Actemra 8 mg + DMARDs&lt;br&gt;DMARDs</td>
<td>Top line announced June 6, 2007</td>
<td>1’200</td>
<td>DMARD inadequate responders</td>
<td>ACR 20 response at Wk 24</td>
</tr>
<tr>
<td><strong>RADIATE</strong>&lt;br&gt;Actemra 4 mg + MTX&lt;br&gt;Actemra 8 mg + MTX&lt;br&gt;MTX</td>
<td>2007</td>
<td>570</td>
<td>Anti-TNFα inadequate responders</td>
<td>ACR 20 response at Wk 24</td>
</tr>
<tr>
<td><strong>AMBITION</strong>&lt;br&gt;Actemra 8 mg monotherapy&lt;br&gt;MTX</td>
<td>2007</td>
<td>550</td>
<td>MTX naive</td>
<td>ACR 20 response at Wk 24</td>
</tr>
<tr>
<td><strong>LITHE</strong>&lt;br&gt;Actemra 4 mg + MTX&lt;br&gt;Actemra 8 mg + MTX&lt;br&gt;MTX</td>
<td>2008</td>
<td>1’170</td>
<td>MTX inadequate responders</td>
<td>ACR 20 at Wk 24&lt;br&gt;Sharp Score at Wk 52&lt;br&gt;Sharp Score at Wk 104&lt;br&gt;Physical function at Wk 104</td>
</tr>
</tbody>
</table>

*Filing on track for 2007*
Ocrelizumab in autoimmune diseases

- Ocrelizumab is a humanized anti-CD 20 antibody
  - Roche is committed to studying B-cell therapy
  - Roche is studying ocrelizumab in rheumatoid arthritis, systemic lupus erythematosus (SLE), and multiple sclerosis (MS)
- Roche and Genentech are conducting global Phase III program for RA
  - First study began in December 2006
- Two global Phase III trials are being initiated in SLE (enrollment is expected to start in 4Q 2007)
- Roche and Genentech are also studying ocrelizumab in relapsing-remitting MS
  - Next steps are underway; findings from “proof of concept” rituximab study are being evaluated
Pamapimod (p38 inhibitor) for RA

- Pamapimod offers selective inhibition of p38α
- p38 regulates the production of the cytokines TNF, IL-1 and IL-6, which are inflammatory mediators that are overactive in RA
- Oral tablet formation
- Currently in Phase II
Multiple sclerosis
An emerging therapeutic area for Roche

- MS is a common neurological disease affecting more than 1 million people worldwide
- Multifocal inflammatory disease that damages the myelin of CNS and causes neurological impairment and, frequently, severe disability
- Commonest cause of neurological disability in young and middle-aged adults
- Prevalence of MS varies by geographical areas
  - high prevalence: Europe, Northern US, Canada, AUS
  - low prevalence: Japan and Africa
- More common in women (2:1), Caucasians

MRI allows clinicians to detect and follow pathological progression of disease & response to treatment
Multiple sclerosis therapies and treatment trends

Diagnosis and treatment rates for MS in major pharma markets

Prevalent population (thousands)

United States
France
Germany
Italy
Spain
United Kingdom
Japan

- Undiagnosed
- Diagnosed, not drug-treated
- Diagnosed, drug-treated

Source: Decision Resources
Prevalence of MS in Europe

~260,000 Patients Total

- RRMS: 65% (169’000 patients)
- SPMS: 25% (40’000 patients)
- PPMS: 10% (16’000 patients)

Diagnosed (81%)
137’000 patients

Treated (~66%)
90’000 patients

Source: Data Monitor
Multiple sclerosis therapy breakdown
*Role of biologics forecasted to grow substantially*

2005

- **25%** Altered peptide ligands
- **72%** Recombinant interferons
- **Other** < 1%

2020

- **45%** Recombinant interferons
- **19%** Oral immunomodulators
- **13%** MAbs
- **16%** Oral immunosuppressants
- **6%** Other
- **Other** < 1%

„Other“ includes corticosteroids, azathioprine and mycophenolate mofetil
„Other“ includes corticosteroids and chemotherapeutics
Source: Decision Resources Inc.
Development hurdles & treatment challenges

Unmet need: Remaining opportunity in MS

Reversing neuronal damage
Preventing disease progression
Improved therapy for chronic-progressive multiple sclerosis
More-convenient drug delivery
Improved diagnostic criteria
Improved animal models

Level of attainment
Source: Decision Resources Inc.

Area of highest medical need…

Low attainment/high opportunity
Medium attainment/medium opportunity
High attainment/low opportunity
Roche’s emerging multiple sclerosis portfolio
New approaches to MS therapy – multiple opportunities

**MabThera (anti CD-20)**
- Phase II (HERMES) in RRMS met primary endpoints
- Data presented at AAN ‘07
- Phase II/III in PPMS (OLYMPUS) – results in H1 2008

**Ocrelizumab (hum. anti CD-20)**
- Phase II / III in RRMS in preparation

**R1295**
- Orally active
- Phase II in preparation

**R3477 (S1P1 receptor agonist)**
- Phase I - joint development with Actelion
- Inhibits migration and recirculation of lymphocytes from lymph nodes
- Orally active
- In development for multiple autoimmune disorders, including MS

---

2 phase III projects (ongoing, in preparation)

2 phase I projects
Roche in autoimmune disorders

*Roche is well placed to address high unmet need and capitalize from large growth opportunity*

- Innovative pipeline with 2 first-in-class RA drugs in launch / pre-launch
- Large investment in development program (second only to oncology)
- Scientific and commercial collaboration with co-marketing partners Genentech and Chugai as well as other 3rd parties
- Strong corporate commitment to build up Autoimmune franchise
  - RA
  - MS
  - Lupus
  - Vasculitis

Roche poised to become a leader in Autoimmune Diseases