# Roche Pharma Development

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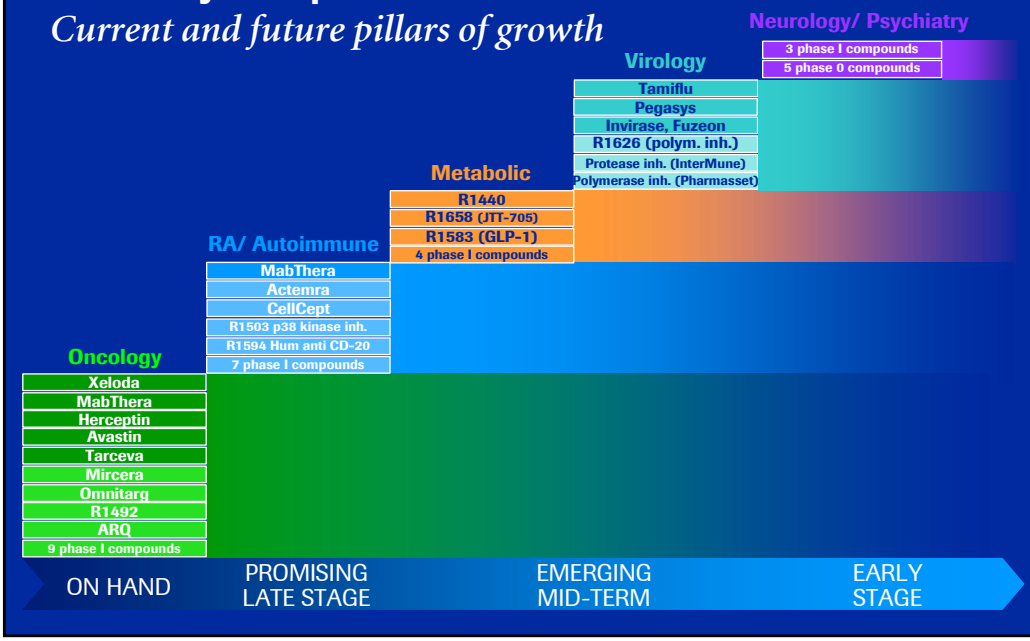
## Roche key therapeutic areas

*Current and future pillars of growth*

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***Oncology*** **– main current growth driver**

***Rheumatoid arthritis*** **– emerging disease area for growth**

***Anemia*** **– expanding a strong presence**

***Metabolic diseases*** **– therapeutic area for future growth**

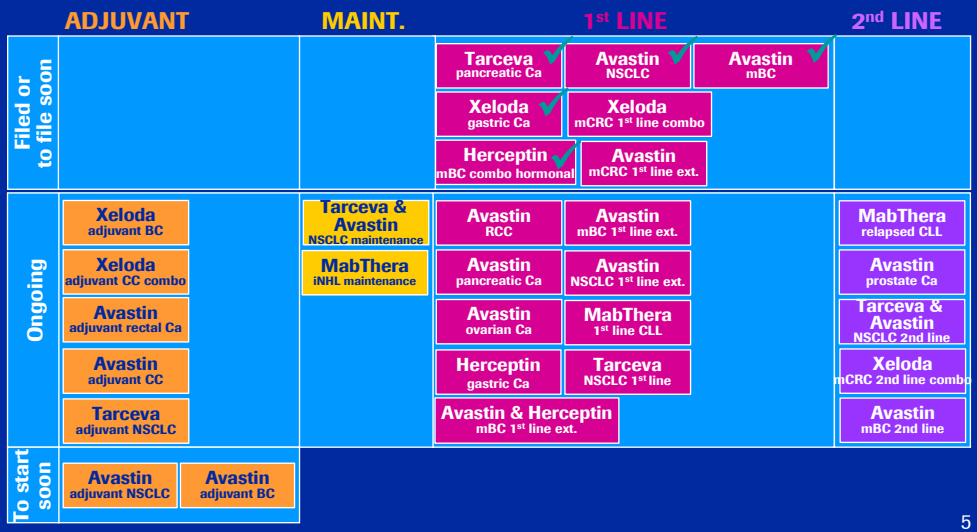
***HCV*** **– expanding current portfolio**

**Summary**

**Q&A**

## Oncology: A rich phase III pipeline

*Targeting main tumor types and use in early intervention*



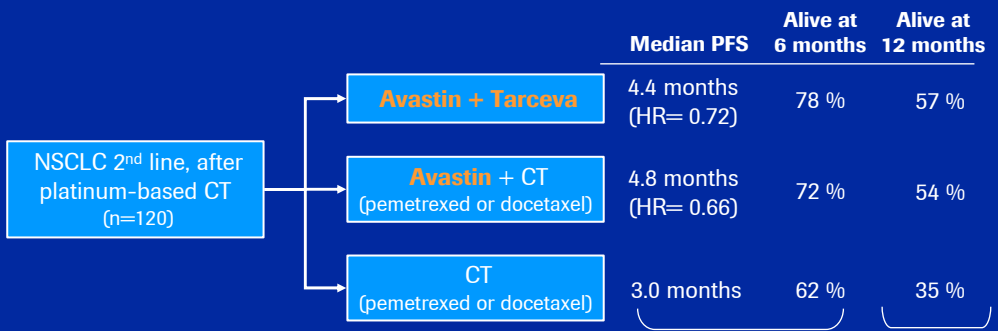



## Our commitment to develop Avastin in metastatic breast cancer

| | HER 2 +ve | HER 2 -ve | | | |
|---|---|---|---|---|---|
| **Study** | **AVEREL** phase III | **E2100** phase III | **AVADO** phase III | **RIBBON-1** phase III | **RIBBON-2** phase III |
| **Patient population** | 1st line | 1st line | 1st line | 1st line | 2nd line |
| **Treatment regimen** | Herceptin + Docetaxel ± Avastin | Paclitaxel ± Avastin | Taxotere ± Avastin 7.5mg/Kg or 15mg/Kg both q3weeks | Anthracyclines based or Xeloda or Taxanes based ± Avastin | CT (taxane based, Gemcitabine, Vinorelbine, Capecitabine) ± Avastin |
| **No of patients** | 320 | 722 | 705 | 900-1050 | 630 |
| **Status** | Started in Sep '06 | Completed – superior PFS and improved OS with addition of Avastin | Ex US Started Q1'06 | Started Q4'05 | Started Q1'06 |

## Combining targeted therapies without chemo

*Promising efficacy and favorable safety profile*




- Exploratory phase II trial
- Primary endpoint: PFS vs. chemotherapy alone
- No unexpected side effects

**Phase III Tarceva + Avastin in 2nd line NSCLC ongoing, data available 2008**



*Oncology* – the main current growth driver

***Rheumatoid arthritis*** **– emerging disease area for growth**

*Anemia* – expanding a strong presence

*Metabolic diseases* – therapeutic area for future growth

*HCV* – expanding current portfolio

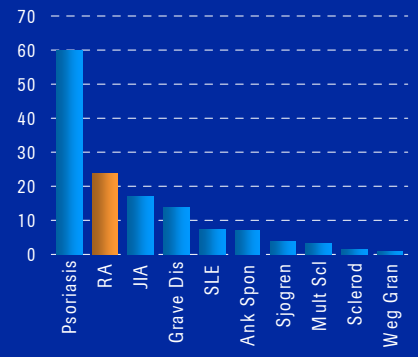
Summary

Q&A

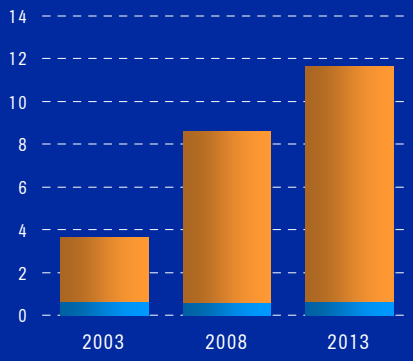
## Autoimmune diseases

*Among the leading causes of death in young and middle aged women*

**Global incidence autoimmune diseases**
**Per 10,000 Patient years (PY)**




**Global sales to treat RA ($bn)[1]**




**Autoimmune diseases: female predominance (~65%)**
**Affects ~5 to 8% of the population**

[1] Source : Decision Resources, March 2005



## Roche in autoimmune diseases

*Building a new therapeutic franchise*

**MabThera - RA**

**Actemra - RA, sJIA**

**CellCept - Lupus Nephritis**

**MabThera - LN, PPMS, ANCA ass. vasculitis, SLE**

**Ocrelizumab - RA**

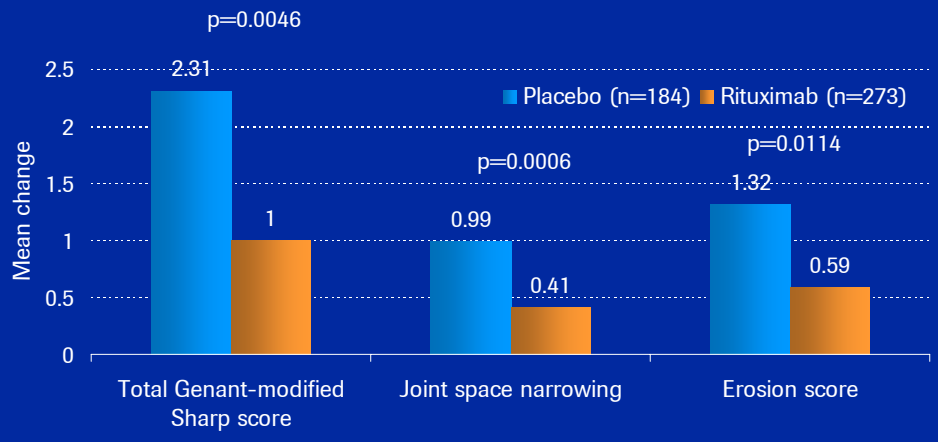
**R1503 (p38 kinase inhibitor) - RA**

**MabThera - RRMS**

**Phase 1 - 7 compounds in development**

## MabThera in RA: REFLEX (anti-TNF inadequate responders)

*Significant inhibition of radiographic progression at Week 56*




Keystone et al, EULAR 2006 (Abstract No. OPO016)



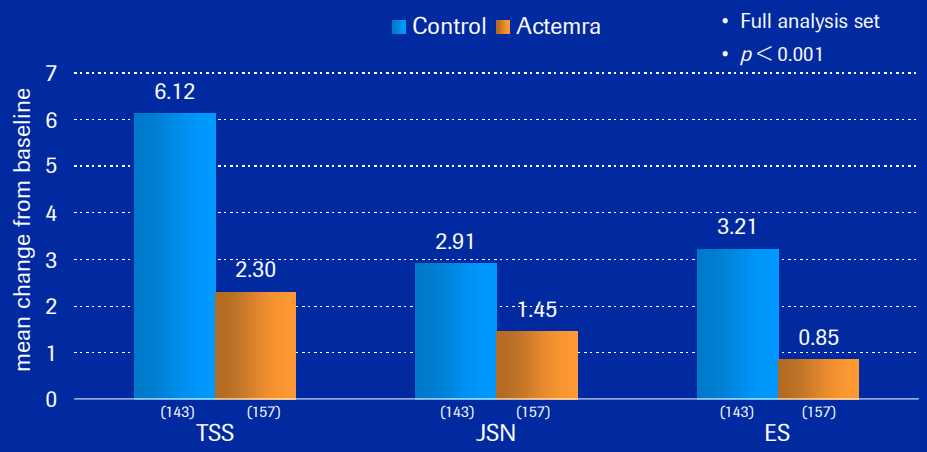
## MabThera/ Rituxan

*Summary and outlook*

- REFLEX study provides first indication that a B cell-targeted therapy can inhibit radiographic progression
  - the only compound to show inhibition of radiographic progression in patients with an inadequate response to 1 or more TNF inhibitors
- Repeated courses of MabThera treatment show similar or improved efficacy compared with the first treatment course with no change in the safety profile
- Phase III development program in patients with RA who have had an inadequate response to disease modifying anti-rheumatic drugs (DMARDs) ongoing
  - enrollment of more than 1,700 patients ongoing
  - EU filing planned in 2008

## Actemra in RA: SAMURAI, PJD study

*Substantial reduction of joint damage*




TSS: Total Sharp Score; JSN: Joint Space Narrowing; ES: Erosion Score



## Actemra in RA

*Summary and outlook*

- Actemra monotherapy is effective in controlling
  - signs and symptoms of RA (excellent ACR scores)
  - progression of structural damage
- Effectiveness sustained over time
- Generally well tolerated
- Filed in Japan
- The large phase III program being conducted in the US and Europe is expected to confirm excellent Japanese results
  - more than 4,000 patients to be enrolled
  - filing planned for 2007

## R1594 (Ocrelizumab): Phase I/II ACTION

*Phase III to start in 2007*

### Study design

- 237 patients with moderate-severe RA
- Phase I/II dose-escalation: MTX + ocrelizumab (IV days 1 and 15)
- Primary endpoint: safety and tolerability

### Results

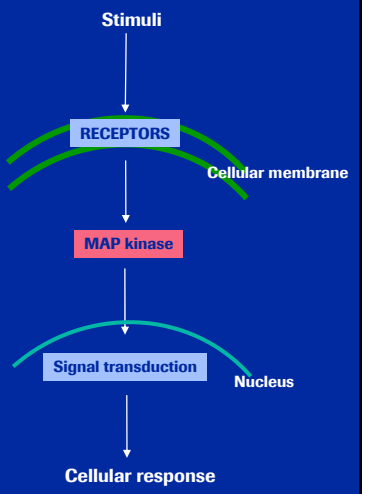
- **Well tolerated at all doses**
  - most frequent AEs: infusion-associated grade 1/2 headaches, nausea, chills, pyrexia, and dizziness
  - rate of SAEs and infection-related SAEs was similar in the groups
  - low immunogeneicity at doses 200mg and higher (HAHA)
- **Clinical activity at all doses**



## R1503: p38 kinase inhibitor

*First oral "anti-TNF" treatment*

- **P38 kinase**
  - the newest member of MAP kinase family
  - it is activated in response to inflammatory cytokines and endotoxins
- **R1503 phase II**
  - randomized, double-blind, placebo-controlled
  - dose-ranging
  - First data available mid-2007
- **Filing planned in post 2009**



*Oncology* – the main current growth driver

*Rheumatoid arthritis* – emerging disease area for growth

***Anemia* – expanding a strong presence**

*Metabolic diseases* – therapeutic area for future growth

*HCV* – expanding current portfolio

Summary

Q&A



## Chronic Kidney Disease (CKD)
*A global problem*

**Prevalence / Incidence**

> 500 million people worldwide

~ 1 in 10 of the general population have some degree of CKD[1]

~ 250,000 new patients are diagnosed with CKD each year[2]

**High medical need**

- 2/3 of patients are not maintained within target Hb range
- 9 out of 10 patients experience Hb "cycling"
- dosing - majority of patients still receive TIW (3x/wk) or QW (1x/wk) dosing

1. International Federation of Kidney Foundations. http://www.ifkf.net/resources.php, 2. Moeller et al Nephrol Dial Transplant 2002; 17:2071-2076.

## Overview of MIRCERA phase III trials

*A comprehensive renal clinical program - 2700 patients in 29 countries*

| ESA-naïve patients | | ESA-treated patients | | | |
|---|---|---|---|---|---|
| CKD† SC ARCTOS Study (BA16738) | Dialysis IV AMICUS Study (BA16736) | Dialysis IV MAXIMA Study (BA16739) | Dialysis SC PROTOS Study (BA16740) | Dialysis IV STRIATA Study (BA17283) | Dialysis IV/SC PFS RUBRA Study (BA17284) |
| MIRCERA 1x/2wk 1x/4wk | MIRCERA 1x/2wk 1x/4wk | MIRCERA 1x/2wk 1x/4wk | MIRCERA 1x/2wk 1x/4wk | MIRCERA 1x/2wk | MIRCERA 1x/2wk |
| Darbepoetin 1x/wk | Epoetin 3x/wk | Epoetin 1-3x/wk | Epoetin 1-3x/wk | Darbepoetin 1x/wk, 1x/2wk | Epoetin 1-3x/wk |

†Patients with CKD not on dialysis

Schedule for conversion

Presented at ERA-EDTA 2006

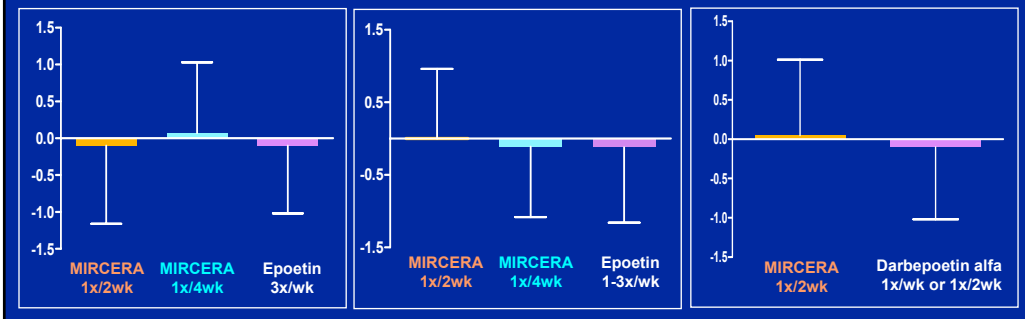
Presented at ASN 2006



## Phase III in maintenance: Primary endpoint met

*No change in mean Hb levels*

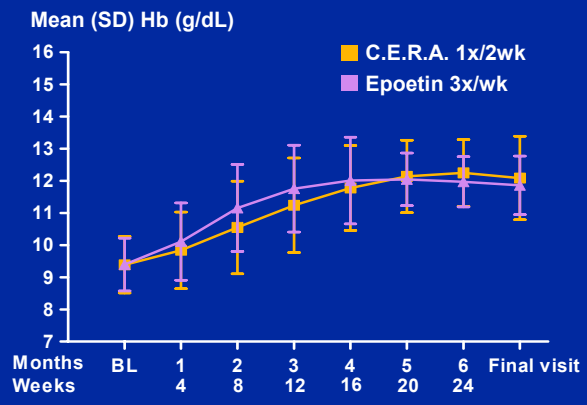
Mean (SD) Hb change between baseline and evaluation periods (g/dL)



## Phase III in correction: Primary endpoint met

*Smooth and steady Hb increase with a high response rate*

**AMICUS (iv in dialysis)**



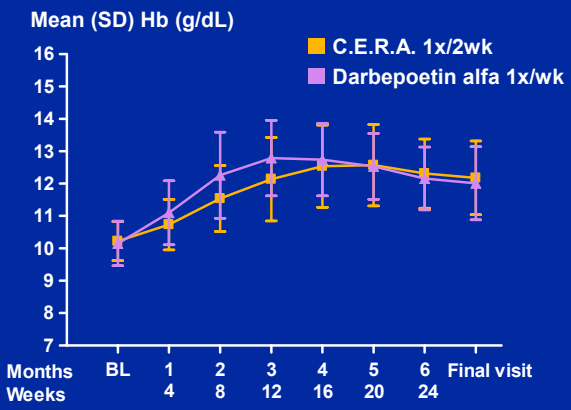

| | Response rate (%) | 95% CI |
|---|---|---|
| C.E.R.A. 1x/2wk | 93.3 | 87.7-96.9 |
| Epoetin 3x/wk | 91.3 | 79.2-97.6 |



## Phase III in correction: Primary endpoint met

*Smooth and steady Hb increase with a high response rate*

**ARCTOS (sc in pre-dialysis)**

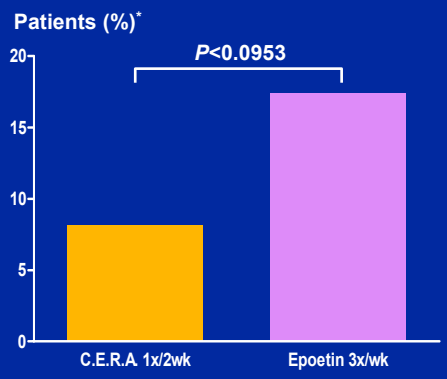



| | Response rate (%) | 95% CI |
|---|---|---|
| C.E.R.A. 1x/2wk | 97.5 | 93.8-99.3 |
| Darbepoetin alpha 1x/wk | 96.3 | 92.1-98.6 |

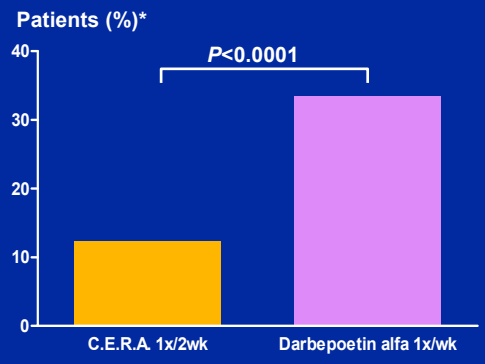
## Fewer patients exceed Hb 13 g/dL with Mircera

*Seen in both phase III correction trials*

**AMICUS (iv in dialysis)**




**ARCTOS (sc in pre-dialysis)**




*Patients with ≥1 Hb value >13 g/dL during first 8 weeks



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- *Oncology* – the main current growth driver
- *Rheumatoid arthritis* – emerging disease area for growth
- *Anemia* – expanding a strong presence
- ***Metabolic diseases* – therapeutic area for future growth**
- *HCV* – expanding current portfolio
- Summary
- Q&A

## Roche in metabolic/ cardiovascular diseases
*Major decision points within the near future*

**R1583 (GLP-1) – Type II Diabetes**

**R1440 (GKA) – Type II Diabetes**

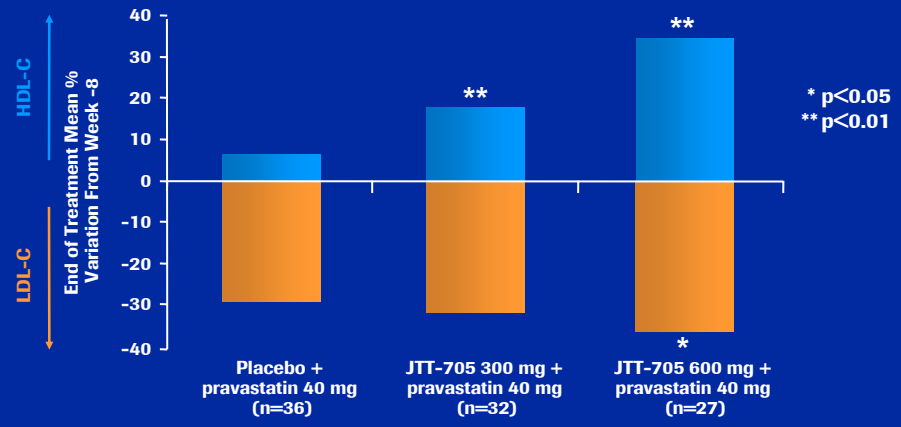
**R1658 (CETP inh) – Dyslipidemia**

**Phase I - 4 compounds in development**

**Phase 0 - 4 compounds in development**




## JTT-705/ R1658 (CETP inhibitor): Phase IIa
*Combination with pravastatin*




**Pravastatin administered for 12 weeks; JTT-705 administered for the last 4 weeks**

Kuivenhoven JA et al. Am J Cardiol 2005;95:1085-8, Phase II study in subjects with Type II dyslipidemia (N=155) 0, 300, 600 mg qd with pravastatin 40 mg qd for 4 weeks

## JTT-705/ R1658 (CETP inhibitor)
*Summary and outlook*

- Benefits of CETP inhibition in hyperlipidemia/ dyslipidemia confirmed
- No increase in blood pressure
- Phase II in dyslipidemia (combination with pravastatin)
  - primary endpoint: percentage and absolute change from baseline at Week 12 in HDL-C level (efficacy)
  - encouraging efficacy data with once daily administration
  - safety trial ongoing
- Go/ no go decision for phase III in 2007



## BIM-51077/ R1583 (GLP-1): Partnered with Ipsen
*Promising data published*

**Immediate release formulation**

- Phase II: 28 days of continuous s.c. infusion
- Demonstrated linear dose/response curve, good HbA1c lowering, good tolerability, trend to increase insulin secretion and decrease body weight and appetite
- Presented at ADA '06

**Sustained release formulation**

- Preclinical data in beagle dog: s.c. injection with a small needle
- Achieved sustained release profile and long duration of release
- Presented at ADA '06

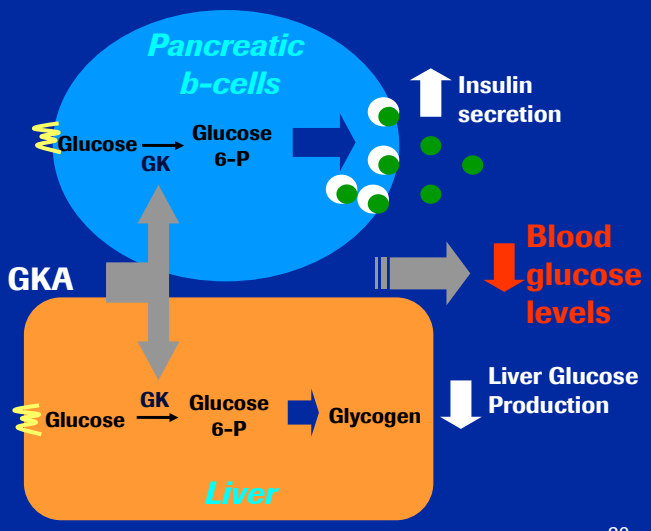
## BIM-51077/ R1583 (GLP-1)
*Summary and outlook*

- Extended metabolic half life (22-fold more stable in plasma)
- Good safety profile, no antibodies against BIM-51077
- Significant and rapid effect on 24h blood glucose following infusion
  - effect maintained over 28 days without desensitization
- Sustained effect on fasting blood glucose over 28 days
- Trend to increase insulin secretion, to decrease HbA1c, and decrease body weight and appetite
- Opted-in July 2006, start of phase II (sustained release formulation) early '07
- Frequency of administration planned to study: once a week and beyond



## Type 2 Diabetes
*Glucokinase Activator (GKAs)*

- Glucokinase: key enzyme regulating whole body glucose homeostasis
- Genetic loss of GK activity in humans leads to early diabetes
- GKAs targets 2 of the underlying pathologies in T2D
  - impaired insulin secretion
  - increased liver glucose production



## R1440 (GKA)
*Summary and outlook*

- First in class molecule
- Phase II ongoing in type II diabetes
  - four studies currently running (mono or combo with metformin, safety combo with sulfonylurea, titration study)
  - first data in 2007
  - filing planned in 2009
- Main differentiators
  - oral
  - targets two underlying pathogenic mechanisms of T2D



***Oncology* – the main current growth driver**

***Rheumatoid arthritis* – emerging disease area for growth**

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***HCV* – expanding current portfolio**

**Summary**

**Q&A**

## Roche in Hepatitis C
*Expanding current portfolio*

**R1626 (polymerase inhibitor)**
- Phase I full data presented at AASLD '06
- Phase II initiated October '06
- FDA fast track status granted

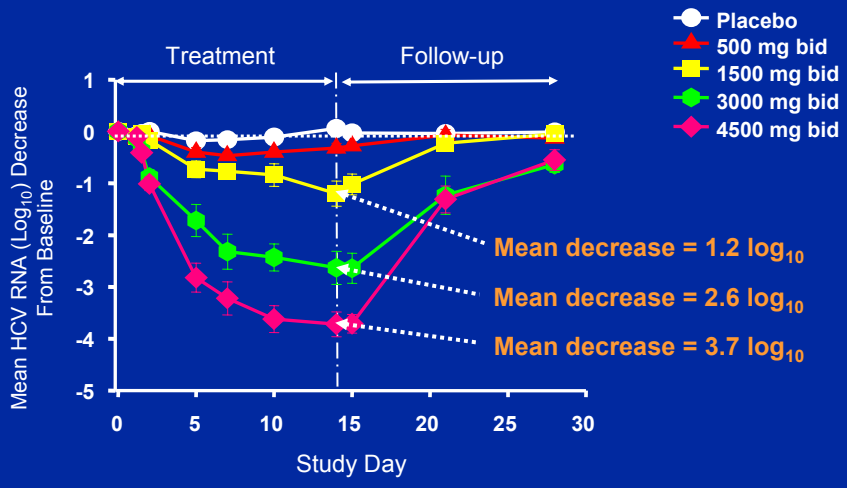
**R1656/R7128 Pharmasset (polymerase inhibitors)**
- Phase I ongoing

**R7227 InterMune (protease inhibitor)**
- Phase I to start by end '06

**R7025 Maxygen (peg. interferon)**
- Phase I initiated in November '06



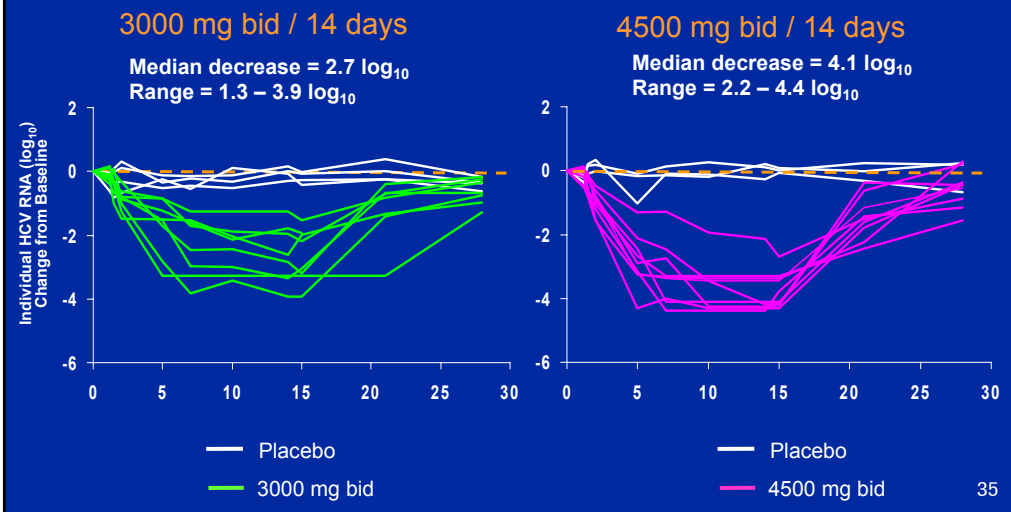

## R1626: Phase I data
*Robust antiviral effect*




– 8/9 BQL (<600 IU/mL) and 5/9 PCR negative (<50 IU/mL) at 4500 mg bid dose

## R1626: Phase I data

*Consistent drop in viral load across individual patients*






## R1626: Phase I data

*Summary*

- Greatest viral load reductions seen in this class
  - robust antiviral effect with mean viral load reductions of 1.2 – 3.7 $\log_{10}$ following 14 days of monotherapy
- No viral resistance observed
- Good tolerability
  - Increasing adverse events at higher dose levels
  - Reversible mild to moderate hematologic changes were treatment- and time-related

*Oncology* – the main current growth driver

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**Summary**

Q&A



## 2006/7: Further strong newsflow expected

**Oncology: 4 phase III, 2 phase II, 3 phase I**

**Avastin**
- EU filing mCRC label extension
- Phase III data available AVOREN, CALGB 90206 (RCC)
- Final analysis AVAIL (NSCLC)
- Recruitment completed AVANT (adj. CC), AVADO (mBC)
- Start of phase III in adj. NSCLC, ovarian Ca

**Xeloda**
- Global filing mCRC label extension
- Final analysis mCRC 2nd line

**MabThera**
- Recruitment completed PRIMA (iNHL 1st line maint.)

**Omnitarg**
- Phase II data available

**R1492/R1584 (EpoD)**
- Go/ No go decision for phase III and II

**R547 (CDK-inh)**
- Go/ No go decision for phase II

**R1530 (MAI)**
- Go/ No go decision for phase II

**Anemia**

**Mircera**
- Phase III correction data to be presented at ASN' 06

**Autoimmune diseases: 6 phase III, 1 phase II**

**Actemra**
- Final analysis of 4 phase III trials (RA)
- Recruitment completed LITHE (RA)

**MabThera**
- Recruitment completed SERENE and SUNRISE (RA)
- Phase II data (HERMES) in RRMS to be presented
- Go/ No go decision for phase III in RRMS

**CellCept**
- Final analysis phase III Lupus Nephritis
- Final analysis phase III Myasthenia Gravis

**Ocrelizumab**
- Phase II (ACTION) to be presented at ACR '06
- Start of phase III in RA

**R1503 (p38 kinase inh)**
- First phase II data available

**Metabolic/ Cardiovascular diseases: 2 phase II**

**R1440 (GKA)**
- First phase II data available

**R1658 (CETP inh)**
- Phase II completed
- Go/ No go decision for phase III

## 2006/7: Further strong newsflow expected

**Oncology: 4 phase III, 2 phase II, 3 phase I**

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- Recruitment com

**Omnitarg**
- Phase II data avai

**R1492/R1584 (Ep**
- Go/ No go decisi

**R547 (CDK-inh)**
- Go/ No go decision for phase II

**R1530 (MAI)**
- Go/ No go decision for phase II

**Anemia**

**Mircera**
- Phase III correction data to be presented at ASN' 06

**To be completed until mid '07:**

**10 phase III projects**

**5 phase II projects**

**Autoimmune diseases: 6 phase III, 1 phase II**

**Actemra**
- Final analysis of 4 phase III trials (RA)
- Recruitment completed LITHE (RA)

**MabThera**
- Recruitment completed SERENE and SUNRISE (RA)
- Phase II data (HERMES) in RRMS to be presented

RRMS

hritis

Gravis

at ACR '06

- First phase II data available

**Metabolic/ Cardiovascular diseases: 2 phase II**

**R1440 (GKA)**
- First phase II data available

**R1658 (CETP inh)**
- Phase II completed
- Go/ No go decision for phase III



## Summary

*Building additional value propositions*

- Oncology – worldwide leadership and continue to expand
- Autoimmune diseases/ rheumatoid arthritis – an emerging new growth area in late development stage – early launch
- Anemia – filed globally/ preparing for launch
- Metabolic disease - a potential opportunity for future growth shaping up
- HCV – new generation of drugs to be combined with Pegasys
- CNS – an attractive early portfolio

Oncology – the main current growth driver

Rheumatoid arthritis – emerging disease area for growth

Anemia –

Metabolic diseases – therapeutic area for future growth

HCV – expanding current portfolio

Summary

**Q&A**



Overview on value adding propositions

Roche in oncology

Roche in rheumatoid arthritis

Poised to re-enter cardiovascular and metabolic diseases

Summary

**Appendix**



## Roche's phase III program for MabThera in DMARD inadequate responders and MTX naïve patients

*All trials including a repeated treatment course after six months*

| Trial | Treatment | Sample Size | Endpoints |
|---|---|---|---|
| **MTX-IR**<br>**SERENE** | MTX + placebo vs.<br>MTX + MabThera 1g vs.<br>MTX + MabThera 2g | 495 | Reduction in signs and symptoms |
| **MTX naïve**<br>**(X-ray study)**<br>**IMAGE** | MTX vs.<br>MTX + MabThera 1g vs.<br>MTX + MabThera 2g | 852 | Reduction in signs and symptoms<br>Inhibition of structural joint damage<br>Improvement in physical function |
| **MTX-IR**<br>**Dose escalation**<br>**MIRROR** | Rituximab 1g retx 1g vs.<br>Rituximab 1g retx 2g vs.<br>Rituximab 2g retx 2g | 375 | Effect of further courses and dose escalation |

**EU Filing 2008**

## Roche's phase III program for Actemra
*Five trials ongoing*

| Treatment | Sample Size | Patient population | Endpoints |
|---|---|---|---|
| Actemra 4 mg + MTX<br>Actemra 8mg + MTX<br>MTX **OPTION** | 630 | MTX partial responders | ACR 20 response at Wk 24 |
| Actemra 4 mg + MTX<br>Actemra 8 mg + MTX<br>MTX **LITHE** | 1'170 | MTX partial responders | ACR 20 at Wk 24<br>Sharp Score at Wk 52<br>Sharp Score at Wk 104<br>Physical function at Wk 104 |
| Actemra 8 mg + DMARDs<br>DMARDs **TOWARD** | 1'200 | DMARD partial responders | ACR 20 response at Wk 24 |
| Actemra 4 mg + MTX<br>Actemra 8 mg + MTX<br>MTX **RADIATE** | 570 | Anti-TNFα failures | ACR 20 response at Wk24 |
| Actemra 8 mg<br>MTX **AMBITION** | 550 | MTX naive | ACR 20 response at Wk 24 |

**Filing 2007**



## Actemra in RA
*Japanese phase III results*

- Humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody
- Signs and symptoms (S&S) (SATORI)
  - Phase III clinical trial, double-blind randomized, 125 patients with inadequate response to methotrexate, Actemra monotherapy vs. MTX
  - Primary Endpoint: improvement of ACR20 response at Week 24
- PJD trial (SAMURAI)
  - Phase III, randomized, 306 patients with early active RA of less than 5 years, Actemra monotherapy vs. active comparator
  - Primary Endpoint: Sharp score at week 52