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**Roche Pharma Development**  
*Guido Magni*  
*Global Head of Medical Sciences*

*Roadshow Paris, September 5th, 2006*





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## Overview on value adding propositions

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**Roche in oncology**

**Roche in rheumatoid arthritis**

**Poised to re-enter cardiovascular and metabolic diseases**

**Summary**

**Appendix**

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## H1 '06: Sales outgrowing market over three times Highest increase in operating profit<sup>1</sup> ever

- Oncology franchise continues to grow rapidly (+48 %<sup>2</sup>)
- Autoimmune franchise starting off in Europe and US following approval of MabThera/ Rituxan in first RA indication
- Boniva continues successful rollout in US, already 42 countries launched
- Operating profit<sup>1</sup> increased 35 %<sup>2</sup>
- 11 approvals received, 11 filings submitted
- Six phase III trials met primary endpoint
- Four phase II trials met primary endpoint

<sup>1</sup> before exceptional items

<sup>2</sup> local growth

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## H1 '06: Progress report on a leading late stage pipeline

|   | Phase III results   | Status                          |
|---|---|---------------------------------|
| ✓ | <b>Mircera</b> – renal anemia in dialysis patients (AMICUS)     | Filed EU and US April '06       |
| ✓ | <b>Mircera</b> – renal anemia in pre-dialysis patients (ARCTOS) | Filed EU and US April '06       |
| ✓ | <b>Xeloda</b> – gastric Ca (ML17032)                            | Filing H2' 06                   |
| ✓ | <b>Xeloda</b> – oesophagogastric Ca (REAL2)                     | Filing H2' 06                   |
| ✓ | <b>Actemra</b> – RA (Japanese S&S)                              | Filed Jp April '06              |
| ✓ | <b>Herceptin</b> – mBC combo hormonal (TAnDEM)                  | Filing EU H2' 06                |
| ✓ | <b>Herceptin</b> – adjuvant BC (HERA FU)                        | Approved EU H1'06               |
| ✓ | <b>MabThera</b> – RA TNF IR (REFLEX FU)                         | Approved EU and US H1 '06       |
| - | <b>Avastin</b> – pancreatic Ca (CALGB 80303)                    | AVITA continues, Filing EU '08  |
| ✗ | <b>Bondronat</b> – Metastatic Bone Pain                         | Stopped due to slow recruitment |

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## H1 '06: Progress report on early stage pipeline

*Major additions to support growth beyond 2010/ 2015*

| Phase II results                            | Status  |
|---|---|
| ✓ <b>Ocrelizumab</b> - RA (Action)          | Phase III to start soon   |
| ✓ <b>Avastin + Tarceva</b> - NSCLC 2nd line | Phase III ongoing   |
| ✓ <b>R1658</b> - dyslipidemia (efficacy)    | Safety phase II trial ongoing   |
| ✓ <b>Ipsen BIM 51077</b> - T2D              | Opted in, phase II (sustained release formulation) to start early '07 |
| ✗ <b>Insulin sensitizer</b> - T2D           | <i>Discontinued</i>   |

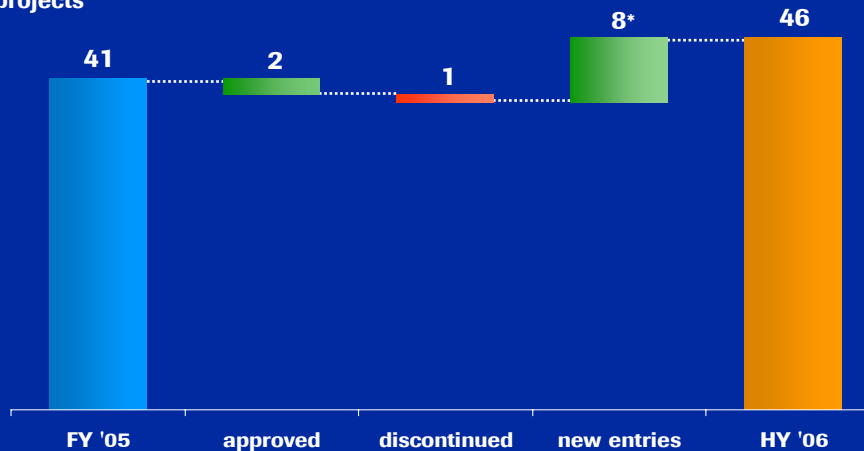
| Phase I progress  |   |
|---|---|
| <b>5 new entries</b><br>(moved from phase 0 or newly entered) | R1664 - dyslipidemia                                      |
|   | R1450 - Alzheimer's                                       |
|   | R1507 - solid tumors                                      |
|   | Trastuzumab DM1 (GNE) - mBC                               |
|   | R3477 (S1P1, Actelion) <sup>1</sup> - autoimmune diseases |
| <b>2 moved forward to phase II</b>                            | Topical VEGF (GNE) - diabetic foot ulcers                 |
|   | Opt-in (ARQ 501) - solid tumors                           |
| <b>3 terminated</b>   | Raptiva (GNE) - adult atopic dermatitis                   |
|   | CHC 12103 (CHU) - solid tumors                            |
|   | R1550 (Antisoma)- mBC                                     |

<sup>1</sup> partnered in July '06

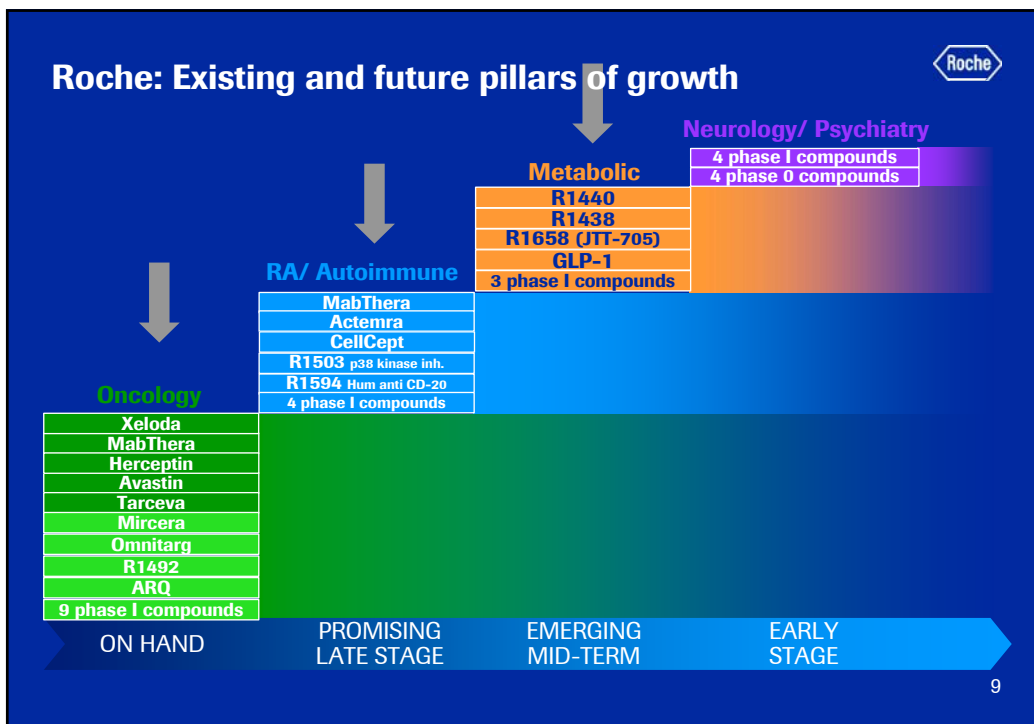
## An industry leading late stage pipeline

*Again strengthened*

Phase III/ filed projects



\* Including one project previously combined and now listed as two single indications  
As of June 30, 2006



## Overview on value adding propositions

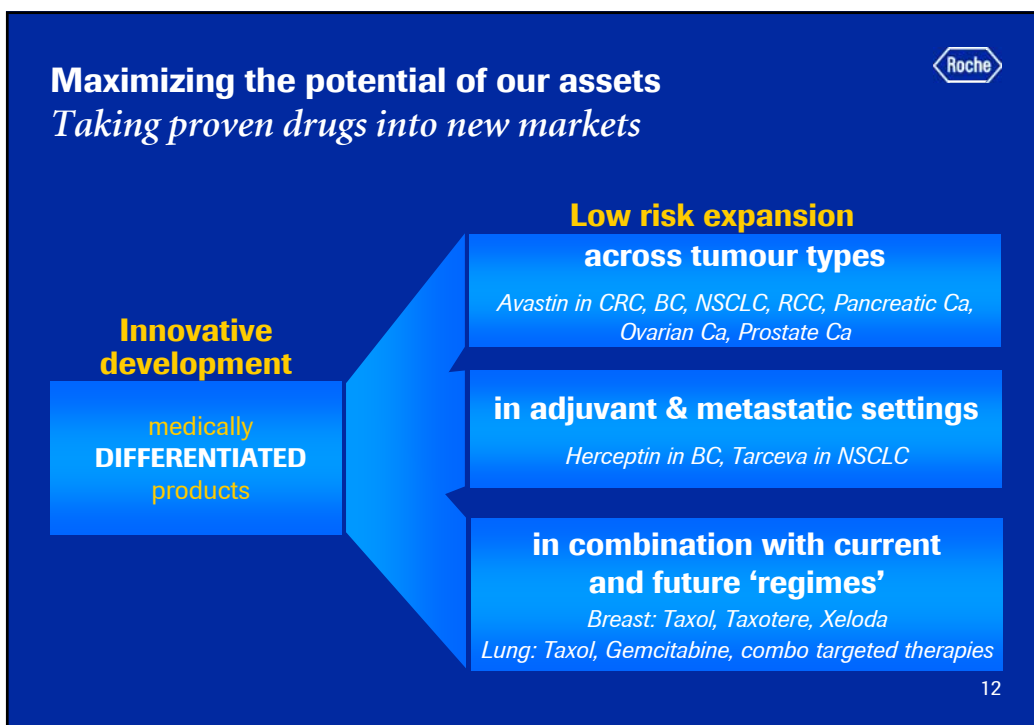
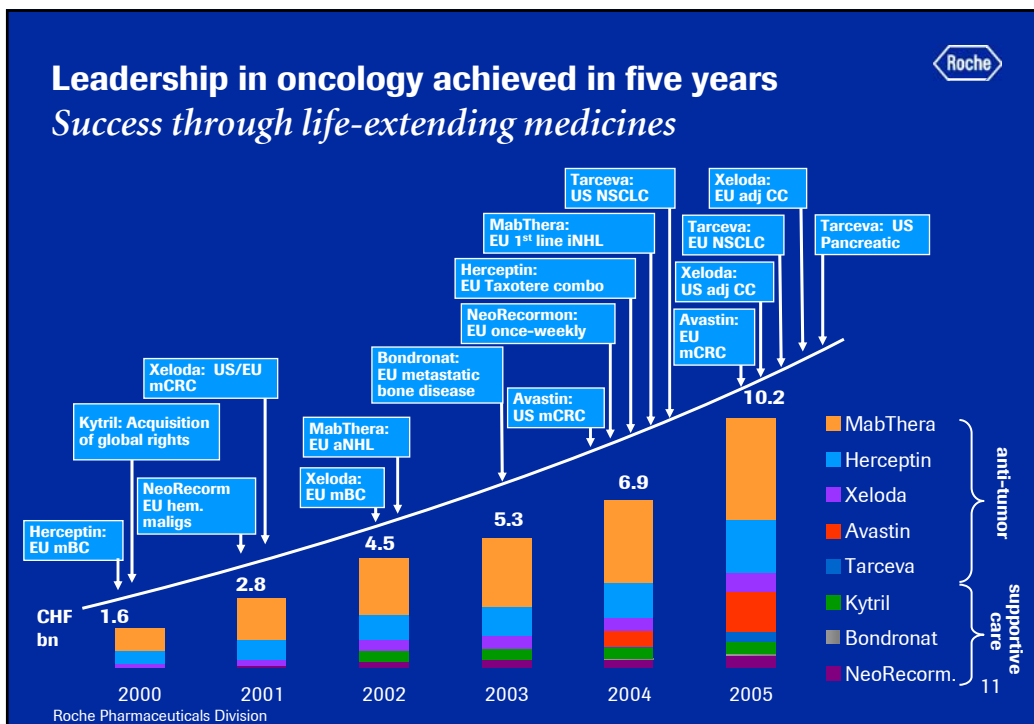
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- Roche in oncology**

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- Roche in rheumatoid arthritis**
- Poised to re-enter cardiovascular and metabolic diseases**
- Summary**
- Appendix**

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# A rich phase III pipeline targeting all main tumor types and early intervention



|                       | ADJUVANT  | MAINT.                                 | 1 <sup>st</sup> LINE   |   |                         | 2 <sup>nd</sup> LINE  |  |
|-----------------------|---|--|--|---|-------------------------|---|--|
| Filed or to file soon |   |  | Tarceva<br>pancreatic Ca<br>Xeloda<br>mCRC 1 <sup>st</sup> line combo<br>Avastin<br>mCRC 1 <sup>st</sup> line ext. | Avastin<br>NSCLC<br>Xeloda<br>gastric Ca<br>Herceptin<br>mBC combo hormonal   | Avastin<br>mBC          |   |  |
| Ongoing               | Xeloda<br>adjuvant BC<br>Xeloda<br>adjuvant CC combo<br>Avastin<br>adjuvant rectal Ca | Tarceva & Avastin<br>NSCLC maintenance | Avastin<br>RCC<br>Avastin<br>pancreatic Ca<br>Avastin<br>ovarian Ca  | Avastin<br>mBC 1 <sup>st</sup> line ext.<br>MabThera<br>1 <sup>st</sup> line CLL<br>Tarceva<br>NSCLC 1 <sup>st</sup> line | Herceptin<br>gastric Ca | MabThera<br>relapsed CLL<br>Avastin<br>prostate Ca<br>Tarceva & Avastin<br>NSCLC 2nd line | Xeloda<br>mCRC 2nd line combo<br>Avastin<br>mBC 2nd line |
| To start soon         | Tarceva<br>adjuvant NSCLC<br>Avastin<br>adjuvant NSCLC<br>Avastin<br>adjuvant BC      |  |  |   |                         |   |  |

Full update on activities in oncology given at **Roche Oncology Day**, June 19, 2006

## Overview on value adding propositions

Roche in oncology

Roche in rheumatoid arthritis

Poised to re-enter cardiovascular and metabolic diseases

Summary

Appendix



## Roche in RA

*Poised for a leadership role*



### MabThera / Rituxan (rituximab)

- Launched in RA anti-TNF inadequate responders in US and EU
- Phase III in RA DMARD inadequate responders ongoing
- Phase III for repeated treatment courses ongoing

### Actemra (tocilizumab)

- Japanese phase III in DMARD inadequate responders met primary endpoints - filed in Japan
- Phase III in RoW ongoing

### Ocrelizumab

- First phase II trial met primary and secondary endpoints
- Phase III program to be finalized and initiated soon

### R1503

- Phase II initiated in Q4'05



## REFLEX: Randomised Evaluation of Long-term Efficacy of MabThera in RA

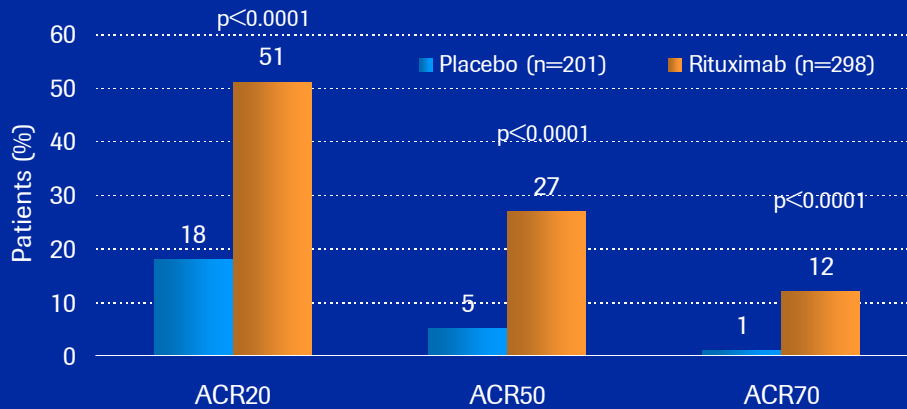


- Multi-centre, randomized, double-blind, placebo-controlled phase III study enrolling 514 patients
- Primary Endpoint:
  - proportion of patients with an **ACR20 response at Week 24**
- Secondary and exploratory radiographic endpoints:
  - secondary: Change in modified Sharp radiographic total score, erosion score, and **joint space narrowing score at Week 56**
  - exploratory: Change in modified Sharp radiographic total score, erosion score, and **joint space narrowing score at Week 24**





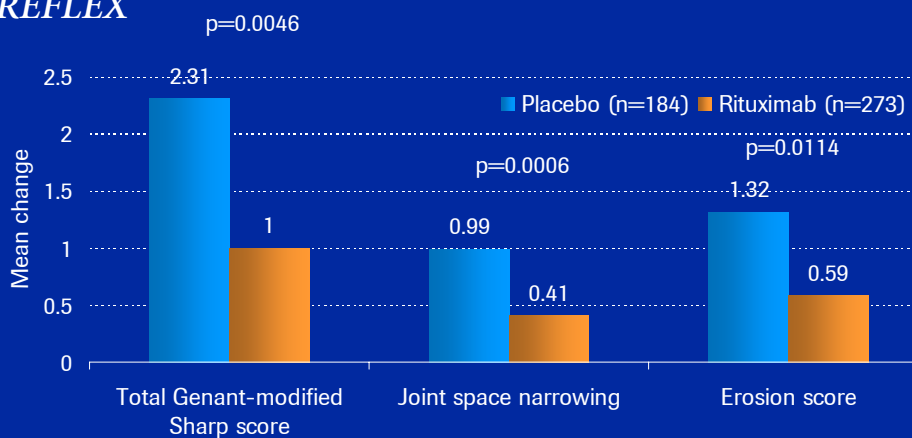
## Significant ACR responses at Week 24 *REFLEX*



Cohen et al. Arthritis Rheum. 2006 [in press]

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## Significant inhibition of radiographic progression at Week 56 *REFLEX*



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

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

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## Summary and outlook

### *MabThera/ Rituxan*

- Data from the REFLEX study provide first indication that a **B cell-targeted therapy can inhibit radiographic progression**
  - also represent first significant evidence of 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 course with no change in the safety profile
- Further phase III development program in patients with RA who have had an **inadequate response to disease modifying anti-rheumatic drugs (DMARDs)** ongoing
  - enrolling more than 1,700 patients
  - recruitment started end 2005/early 2006
  - all trials including a repeated treatment course after six months
  - EU filing planned in 2008

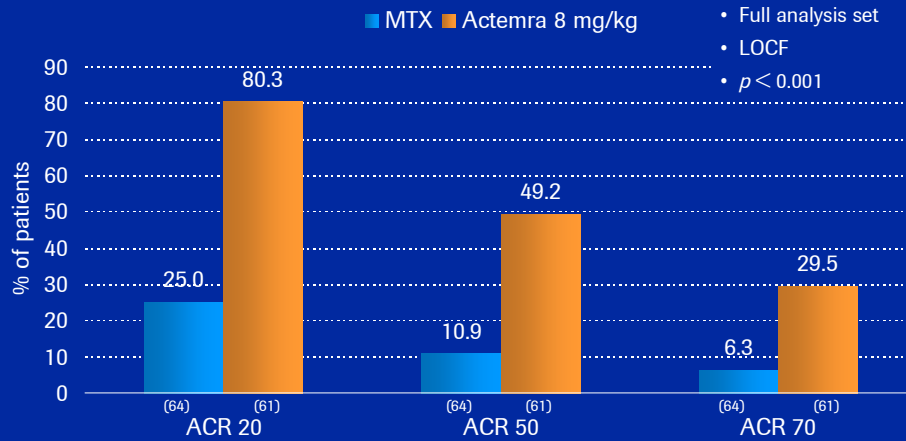
## Actemra

### *Japanese phase III results*

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

## Strong ACR scores (SATORI)

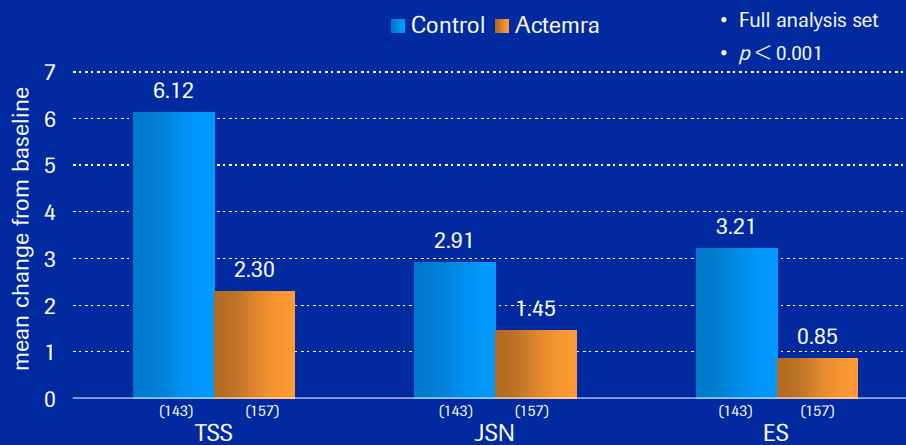
*Actemra shows consistent high efficacy*



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## Actemra substantially reduces joints damage (SAMURAI)

*Radiographic data, mean scores*



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

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## Summary and outlook

### *Actemra*

- Actemra monotherapy is **effective in controlling both**:
  - **signs and symptoms of RA** (excellent ACR scores achieved)
  - **progression of structural damage**
- The effectiveness of Actemra is **sustained over time**
- Actemra is in **general well tolerated**
- Already **filed in Japan**
- The **large phase III program being conducted in the US and Europe** is expected to confirm outstanding Japanese results - more than 4,000 patients to be enrolled
  - filing planned for 2007
- Actemra, through its **novel mechanism of action**, might become soon a new option for patients suffering from RA

## Overview on value adding propositions

### Roche in oncology

### Roche in rheumatoid arthritis

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### Poised to re-enter cardiovascular and metabolic diseases

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### Summary

### Appendix

# Global burden of cardiovascular disease

## Clinical care of CVD is costly and prolonged

### In 2002

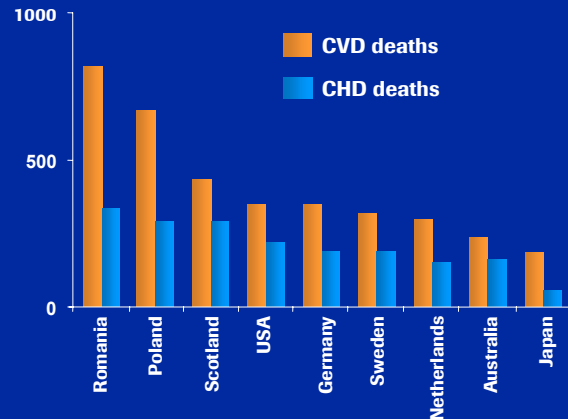
- CVD contributed to approximately one-third of all global deaths (17 million)
- 80% of burden is in low- and middle-income countries

### By 2020

- CHD and stroke will become the leading causes of death and disability worldwide
- Mortality from CVD will increase to 20 million

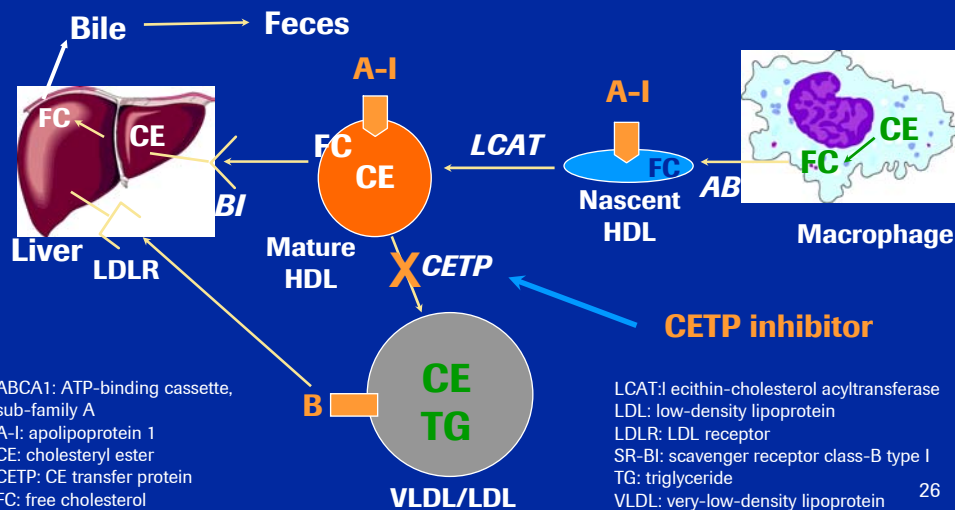
### Mortality from CVD and CHD in selected countries

Mortality rate per 100,000 population <sup>1</sup>



International Cardiovascular Disease Statistics 2003, 2005; AHA  
<sup>1</sup> Men aged 35-74 years CHD: coronary heart disease

# CETP inhibition as a novel strategy to raise HDL



ABCA1: ATP-binding cassette, sub-family A  
 A-I: apolipoprotein 1  
 CE: cholesteryl ester  
 CETP: CE transfer protein  
 FC: free cholesterol

LCAT: lecithin-cholesterol acyltransferase  
 LDL: low-density lipoprotein  
 LDLR: LDL receptor  
 SR-BI: scavenger receptor class-B type I  
 TG: triglyceride  
 VLDL: very-low-density lipoprotein

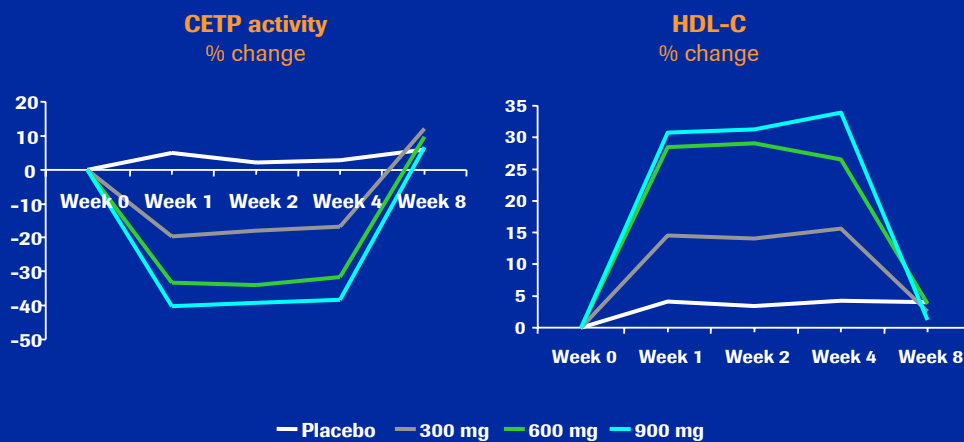
## Phase IIa PoC studies



- **Phase II study in healthy subjects with mild hyperlipidemia (N=198)**
  - 0, 300, 600, 900 mg qd for 4 weeks
  - *de Grooth GJ et al. Circulation 2002;105:2159-65*
- **Phase II study in subjects with Type II dyslipidemia (N=155)**
  - 0, 300, 600 mg qd with pravastatin 40 mg qd for 4 weeks
  - *Kuivenhoven JA et al. Am J Cardiol 2005;95:1085-8*

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## JTT-705/ R1658 phase IIa data *Monotherapy*

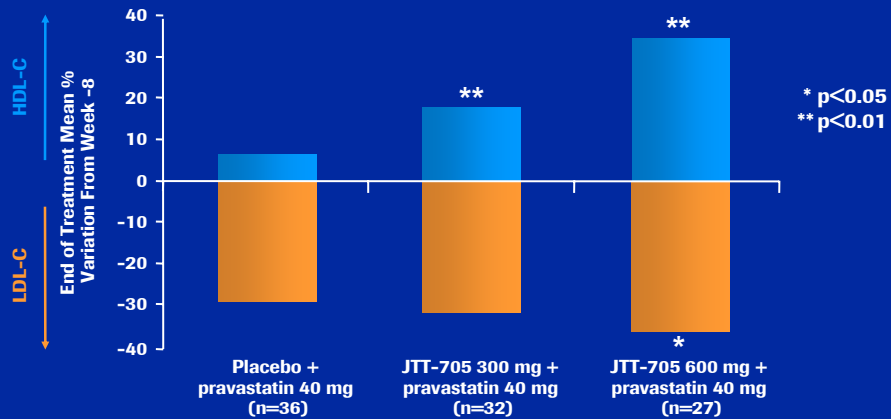


de Grooth GJ et al. Circulation 2002;105:2159-65

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## JTT-705/ R1658 in combination with pravastatin

### Lipid effects



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

Kuivenhoven JA et al. Am J Cardiol 2005;95:1085-8

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## Phase IIb efficacy and safety profile



- Two clinical trials initiated, one completed
- JTT-705/ R1658 up to 900 mg daily is well-tolerated, with a similar overall safety profile to placebo
- Most frequently reported adverse events were mild GI symptoms (e.g. diarrhea, nausea) which did not lead to discontinuation of treatment
- No increase in blood pressure observed (consistent with pre-clinical findings)
- Phase IIb **safety trial** continues, data expected in 2007

de Grooth GJ et al. Circulation 2002;105:2159-65; Data on file Roche Basel

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## Summary and outlook

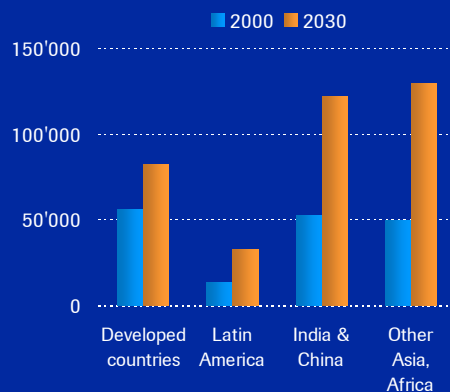
### *JTT-705/ R1658*

- Roche and Japan Tobacco signed agreement for development and commercialization of in October 2004
  - Roche has exclusive worldwide rights, excluding Japan and Korea
- Clinical efficacy **data confirms benefits of CETP inhibition** in hyperlipidemia/ dyslipidemia
- **Well-tolerated**, with a similar overall safety profile to placebo
- Phase II in dyslipidemia (combination with **pravastatin**)
  - primary endpoint: percentage and absolute change from baseline at Week 12 in HDL-C level (efficacy)
  - already seen **encouraging efficacy data**
  - safety trial ongoing
  - go/ no go decision for phase III in 2007

## Global prevalence of diabetes

### *Strongly driven by obesity and ageing*

#### Estimated number of people with diabetes by region



Source: Diabetes Care, Volume 27, May 2004

#### Major healthcare challenge

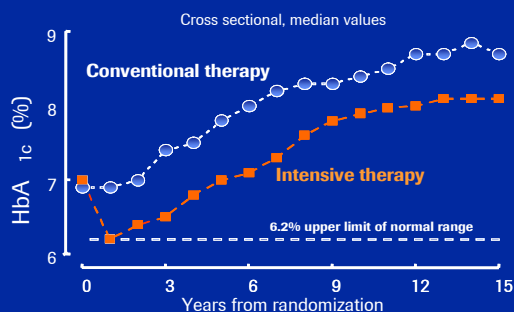
- Expanding prevalence > 350 mio by 2030
- Causing a number of vascular complications
- Significant burden to healthcare funding
  - US annual direct costs estimated at USD 92bn (2002, Lewin Group Study)
- 50% of all diabetics are unaware of their condition
- Type 2 diabetes accounts for 85% - 95% of all diabetics



# Type 2 Diabetes

## Disease progression despite intensive therapy

### United Kingdom Prospective Diabetes Study



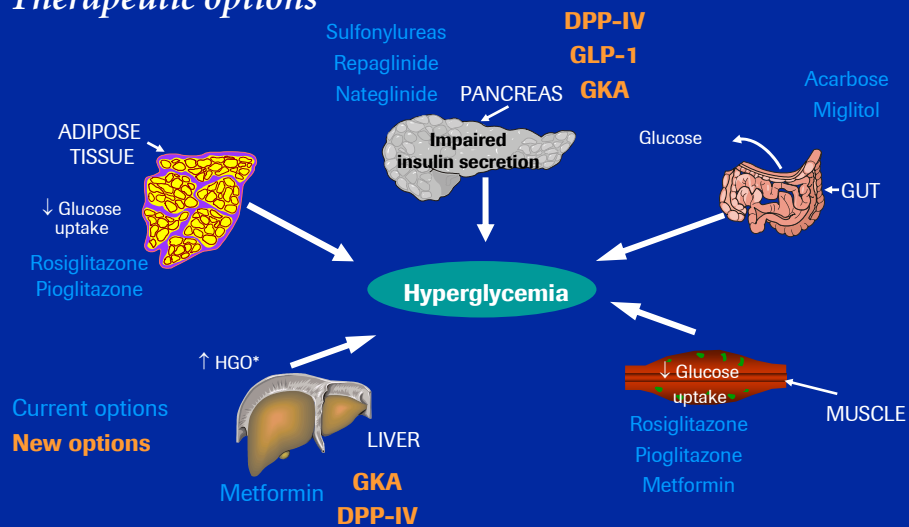
Conventional:  
FPG <15 mmol/L diet,  
pharmacotherapy

Intensive: FPG <6mmol/L  
(SUs, Metformin,  
insulin or combos)

- Multiple MOAs targeting underlying pathophysiologies,
  - greater and long-term efficacy
- Compliance for oral anti-hyperglycemic agents (OHAs) estimated at 60-70% (US)
  - restricted due to side effects (weight gain, nausea, CHF)
- Combination therapy & fixed combos
- Disease-modifiers
- New developments

# Type 2 Diabetes

## Therapeutic options



\*HGO=hepatic glucose output.



## Glucagon-like peptide (GLP-1)

### *Important therapeutic target for type 2 diabetes*

- Incretin hormone, produced by L-cells of intestine in response to food intake
- Dual mechanism of action: stimulates insulin secretion, inhibits glucagon release
- Induces pancreatic  $\beta$ -cell proliferation/ differentiation
- Delay in gastric emptying and appetite suppression
- Short half life: rapidly broken down by dipeptidyl peptidase (DPP IV)
  - protection against hypoglycemia
- Reduced GLP-1 response to food in T2D patients

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## BIM-51077/ R1583: Partnered with Ipsen

### *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

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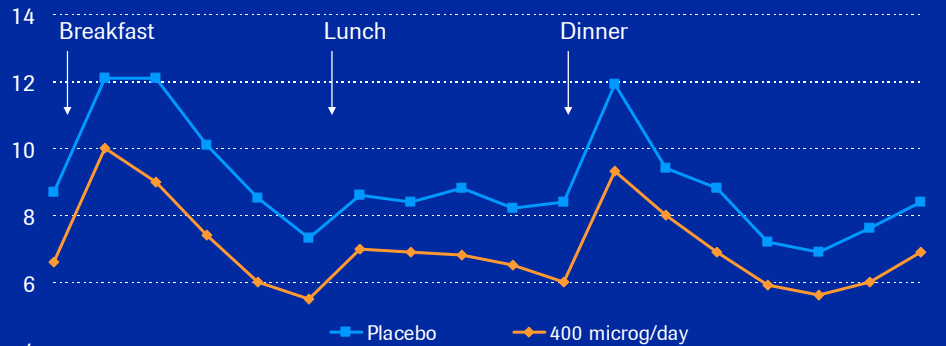
## BIM-51077/ R1583



### Phase II 28 days continuous infusion

#### 24h profile of blood glucose concentrations

Day 28, mean glucose concentration [mmol/L]



18 T2D patients treated with metformin, 12 active, 6 placebo, 28-day continuous subcutaneous infusion of BIM-51077 IRF

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## Summary and outlook



### BIM-51077/ R1583 (GLP-1)

- Greater binding potency than native protein
- Extended metabolic half life (22-fold more stable in plasma)
- Sustained improvement in blood glucose control over days by continuous infusion
- **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**

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## Type 2 Diabetes

### *Dipeptidyl peptidase (DPP IV) inhibitors*

- Protects GLP-1 from rapid degradation
- **Main benefits**
  - can be taken orally
  - potential for monotherapy and combination (sulfonylurea, metformin or glitazones)
- **Main disadvantages**
  - no weight loss
  - side effects?
  - 'rich' competitive environment

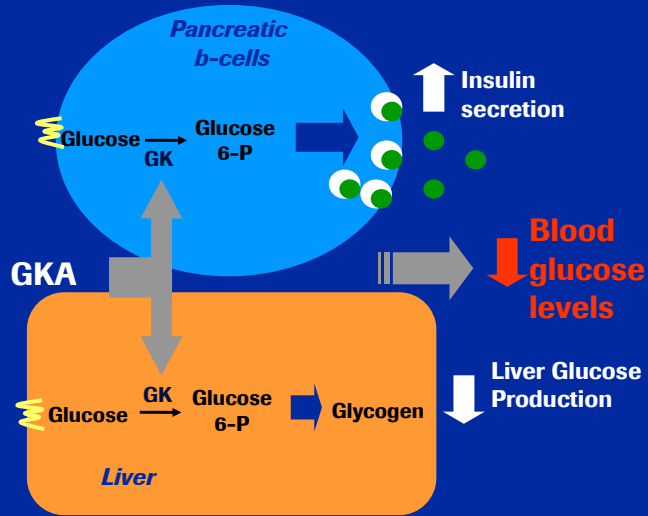
## Summary and outlook

### *R1438 (DPP -IV)*

- Potentially best in class molecule
- 2 phase II ongoing
  - mono and combo with metformin
  - to complete end 2006/ early 2007
  - filing planned in 2009
- Back-up compounds in earlier stages of development

## 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 address 2 of the underlying pathologies in T2D
  - impaired insulin secretion
  - increased liver glucose production



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## Summary and outlook R1440 (GKA)

- **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)
  - initiated in Q4'05
  - first data in 2007
  - filing planned in 2009
- **Main benefits of this class**
  - oral
  - addresses two underlying pathogenic mechanisms of type II diabetes

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## Overview on value adding propositions

Roche in oncology

Roche in rheumatoid arthritis

Poised to re-enter cardiovascular and metabolic diseases

Summary

Appendix

## Our objectives for 2006 - Pharmaceuticals

*Announced for 2006*

| Major clinical data | Compound          | Phase | Indication                        | Data    | Status H1 |
|---------------------|-------------------|-------|-----------------------------------|---------|-----------|
|                     | Mircera (CERA)    | III   | Renal anemia (correction)         | Final   | ✓         |
|                     | CellCept          | III   | Lupus nephritis (Induction phase) | Final   |           |
|                     | Herceptin         | III   | mBC combo hormonal (TAnDEM)       | Final   | ✓         |
|                     | Xeloda            | III   | mCRC 2nd line                     | Final   |           |
|                     | Avastin           | III   | NSCLC 1st line (AVAIL)            | Interim | ✓         |
|                     | Avastin / Xeloda  | III   | mCRC 1st line combo extension     | Final   |           |
|                     | R1658             | II    | Dyslipidemia                      | Final   | ✓         |
|                     | R873              | IIa   | MED                               | Final   |           |
|                     | Avastin / Tarceva | II    | NSCLC 2nd line                    | Final   | ✓         |
| R1594               | II                | RA    | Final                             | ✓       |           |

| Filings | Compound        | Indication              | Status H1 |
|---------|-----------------|-------------------------|-----------|
|         | Mircera (CERA)  | Renal anemia            | ✓         |
|         | Avastin         | NSCLC 1st line          | ✓ (US)    |
|         | Avastin         | mBC 1st line            | ✓         |
|         | Avastin/ Xeloda | mCRC 1st line extension |           |
|         | Herceptin       | Adjuvant BC             | ✓         |
|         | Xeloda          | mCRC 1st line combo     |           |

**Divisional sales growth**

**Double-digit growth in local currencies**

barring unforeseen events

## Summary

### *Building additional value propositions*

- Oncology - on hands
- Autoimmune diseases/ rheumatoid arthritis - in the 'late stage' of development/ launch
- Metabolic disease - a potential opportunity shaping up
- CNS - still in an early stage



## 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  |
|--|--|-------------|--|
| <b>MTX-IR<br/>SERENE</b>                     | MTX + placebo vs.<br>MTX + MabThera 1g vs.<br>MTX + MabThera 2g              | 495         | Reduction in signs and symptoms  |
| <b>MTX naïve<br/>(X-ray study)<br/>IMAGE</b> | 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 |
| <b>MTX-IR<br/>Dose escalation<br/>MIRROR</b> | 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 <b>OPTION</b>   | 630         | MTX partial responders     | ACR 20 response at Wk 24  |
| Actemra 4 mg + MTX<br>Actemra 8 mg + MTX<br>MTX <b>LITHE</b>   | 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 <b>TOWARD</b>                  | 1'200       | DMARD partial responders   | ACR 20 response at Wk 24  |
| Actemra 4 mg + MTX<br>Actemra 8 mg + MTX<br>MTX <b>RADIATE</b> | 570         | Anti-TNF $\alpha$ failures | ACR 20 response at Wk24   |
| Actemra 8 mg<br>MTX <b>AMBITION</b>                            | 550         | MTX naive                  | ACR 20 response at Wk 24  |

Filing 2007

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## H1 '06: 11 approvals in major markets

*Pharmaceuticals Division*



| Product            | Indication                   | Region |
|--------------------|------------------------------|--------|
| Avastin            | 2nd line mCRC                | US     |
| Boniva/ Bonviva iv | Osteoporosis                 | US, EU |
| Herceptin          | Adjuvant BC                  | EU     |
| Femara             | BC                           | Japan  |
| Lucentis           | AMD                          | US     |
| MabThera/ Rituxan  | Rheumatoid arthritis         | US, EU |
| MabThera           | iNHL maintenance             | EU     |
| Rituxan            | 1st line aNHL                | US     |
| Tamiflu            | Influenza prophylaxis (ped.) | EU     |

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## A rich and low risk Phase III pipeline Keeping the high level of commitment

Filed or  
to file soon

- \* MabThera INHL maint relapse ✓
- Herceptin adjuvant BC ✓
- Mircera (CERA) renal anemia ✓
- Avastin NSCLC ✓
- Herceptin mBC combo hormonal ✓
- Antevas subarach. haemor ✓
- \* MabThera RA TNF nonresp. ✓
- Tarceva pancreatic Ca ✓
- Avastin mBC combo tax. ✓
- Xeloda gastric Ca ✓
- Sigmart acute heart failure ✓
- Epogin chemotherapy-induced anemia ✓

Ongoing

- MabThera 1st line CLL
- Xeloda mCRC 2nd line combo
- Avastin pancreatic Ca
- Avastin mBC 2nd line
- Tarceva & Avastin NSCLC 2nd line
- MabThera ANCA ass. vasculitis
- CellCept lupus nephritis
- MabThera relapsed CLL
- Xeloda adjuvant CC combo
- Avastin prostate Ca
- Avastin GIST
- Herceptin gastric Ca
- MabThera SLE
- CellCept MG/PV
- MabThera INHL maint 1st line
- Avastin mCRC 1st line ext.
- Avastin ovarian Ca
- Avastin adjuvant rectal Ca
- Actemra RA
- MabThera Lupus nephritis
- ED-71 osteoporosis
- Xeloda adjuvant BC
- Avastin adjuvant CC
- Avastin mBC combo non-taxanes
- Tarceva NSCLC 1st line
- Actemra sJIA
- MabThera PPMS
- Xolair pediatric asthma
- Xeloda mCRC 1st line combo
- Avastin RCC
- Avastin mBC combo Taxotere
- Tarceva & Avastin NSCLC maintenance
- MabThera RA DMARD failures
- Valcyte CMV ext.

To start soon

- Tarceva adjuvant NSCLC
- Avastin adjuvant NSCLC
- Avastin adjuvant BC

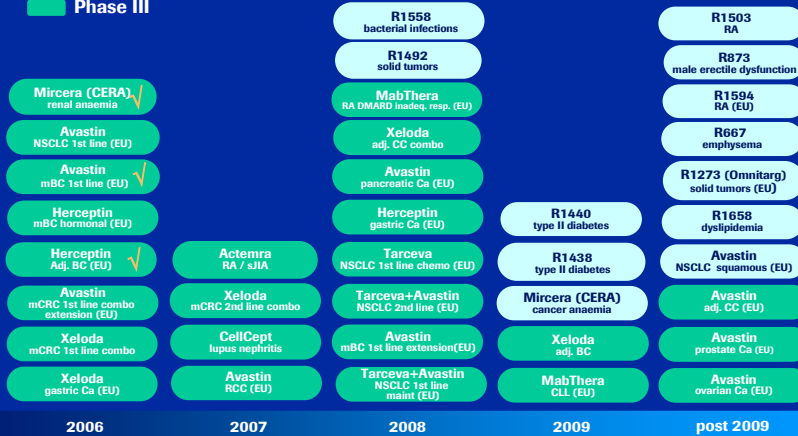
\* Approved in July 2006  
Status as of June 30, 2006

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## Major Roche managed projected submissions over the next years

Phase II  
Phase III



Status as of June 30, 2006

Unless stated otherwise, submissions will occur in US and EU

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# Roche R&D pipeline today

Total of 57 NME's + 55 Additional Indications



| phase 0<br>(14 NMEs)  | phase I<br>(21 NMEs + 3 AIs)        | phase II<br>(18 NMEs + 10 AIs)      | phase III<br>(2 NMEs + 34 AIs)         | Registration<br>(2 NMEs + 8 AIs)    |
|-----------------------|-------------------------------------|-------------------------------------|--|-------------------------------------|
| R1599 osteoarthritis  | R1541 IRD                           | R1558 bacterial infections          | R1569 Actemra RA                       | R744 Mircerca renal anaemia         |
| R1511 type 2 diabetes | R1295 RA                            | R1503 RA                            | CHU ED-71 osteoporosis                 | CHU Artervas subarach haemor        |
| R1579 type 2 diabetes | R3421 AI / transplant               | R1594 RA                            | R1569 Actemra sJIA                     | R597 Herceptin adj BC               |
| R1646 OAB             | R1439 type 2 diabetes               | R1440 type 2 diabetes               | R99 CellCept lupus nephritis           | R105* MabThera INHL maint relapse   |
| R1663 anticoagulant   | R1593 dyslipidemia                  | R1438 type 2 diabetes               | R99 CellCept MG/PV                     | R105* MabThera RA TNF nonresp       |
| R641 Alzheimer's      | R1664 dyslipidemia                  | R1658 dyslipidemia                  | R105 MabThera RA DMARD nonresp         | R435 Avastin NSCLC 1st line         |
| R1647 depression      | R1450 Alzheimer's                   | R873 MED                            | R105 MabThera CLL 1st line             | R435 Avastin mBC combo 1st/2nd line |
| R1551 schizophrenia   | R1678 schizophrenia                 | R1273 ovarian cancer                | R105 MabThera CLL relapsed             | R1415 Tarceva pancreatic ca         |
| R7118 schizophrenia   | R7090 anxiety                       | R1482 solid tumors                  | R105 MabThera INHL maint 1st line      | CHU Epogin cancer anaemia           |
| R7159 NHL             | R547 solid tumors                   | R667 emphysema                      | R1415 Tarceva NSCLC 1st line           | CHU Sigmart acute heart fail        |
| R1206 HIV             | R1454 solid tumors                  | R411 asthma                         | G1415-R435 T+A NSCLC 1st line maint    |                                     |
| R7025 HCV             | R1507 solid tumors                  | CHU gastroparesis                   | R340 Xeloda mCRC combo 1st line        |                                     |
| R7128 HCV             | R1530 solid tumors                  | CHU osteoporosis                    | R340 Xeloda adj CC combo               |                                     |
| CHU solid tumors      | R1645 solid tumors                  | CHU post-hepatectomy                | R340 Xeloda adj BC                     |                                     |
|                       | R1650 HCV                           | GEN diabetic foot ulcers            | R340 Xeloda gastric cancer             |                                     |
|                       | R1626 HCV                           | ISO renal transplant                | R435 Avastin adj CC                    |                                     |
|                       | GEN RA / Sjogrens syndrome          | IPS** type 2 diabetes               | R435 Avastin mBC combo Taxotere 1st    |                                     |
|                       | GEN basal cell carcinoma            | ARQ solid tumors                    | R435 Avastin mBC combo nonTaxotere 1st |                                     |
|                       | GEN cancer                          | R744 Mircerca cancer anaemia        | R435 Avastin pancreatic ca             |                                     |
|                       | GEN mBC                             | R435 Avastin NSCLC squamous         | R435 Avastin pancreatic ca             |                                     |
|                       | MEM Alzheimer's                     | R435 Avastin NSCLC mCNS treat       | R435 Avastin pancreatic ca             |                                     |
|                       | R127 Valganciclovir ulcerat colitis | R1415 Tarceva glioblastoma          | R435 Avastin pancreatic ca             |                                     |
|                       | R1594 NHL                           | R1273 Tarceva mBC                   | R435 Avastin pancreatic ca             |                                     |
|                       | R35 Daclizumab transp maint         | R35 Daclizumab asthma               | R435 Avastin pancreatic ca             |                                     |
|                       |                                     | GEN Lucentis diabetic macular edema | R435 Avastin pancreatic ca             |                                     |
|                       |                                     | GEN Avastin adj BC HER2-            | R435 Avastin pancreatic ca             |                                     |
|                       |                                     | GEN Avastin glioblastoma            | R597 Herceptin mBC combo               |                                     |
|                       |                                     | GEN MabThera BRMS                   | R597 Herceptin gastric ca              |                                     |
|                       |                                     | ** Opted-in July 2006               | R127 Valcyte CMV ext                   |                                     |
|                       |                                     |                                     | GEN Xolair pediatric asthma            |                                     |
|                       |                                     |                                     | GEN Avastin GIST                       |                                     |
|                       |                                     |                                     | GEN Avastin adj rectal cancer          |                                     |
|                       |                                     |                                     | GEN Avastin mBC 2nd line               |                                     |
|                       |                                     |                                     | GEN MabThera lupus nephritis           |                                     |
|                       |                                     |                                     | GEN MabThera PPMS                      |                                     |
|                       |                                     |                                     | GEN MabThera ANCA ass vessel           |                                     |
|                       |                                     |                                     | GEN MabThera SLE                       |                                     |

\* EU approval July 2006

### NME (New Molecular Entity)

- R Roche managed projects
- A Participations
- A Opt-in Opportunities

### AI (Additional Indication)

- R Roche managed projects
- A Participations
- A Opt-in Opportunities

- CHU Chugai
- GEN Genentech
- IPS Ipsen
- ISO Roche/Chugai
- MEM Memory
- ARQ Arctur

Status as of June 30, 2006

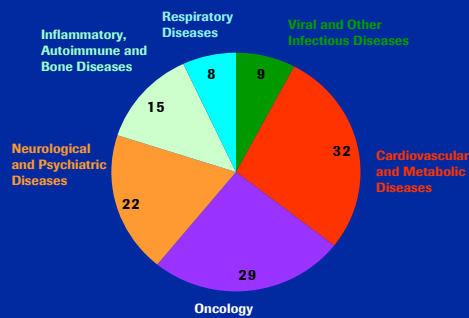
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# Roche managed R&D pipeline - overview

Projects by Therapeutic Area

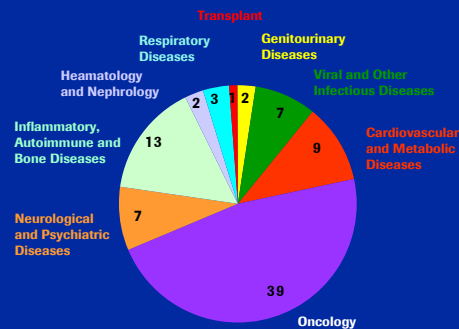


## Research



115 projects

## Development



83 projects

Status as of June 30, 2006

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## Cardiovascular disorders



### Atherosclerosis

- Damage to the arterial wall (large or medium-sized arteries) and subsequent creation of plaque consisting cholesterol on the damaged area (hardening of arteries)
- Can lead to coronary heart disease (CHD) and sudden death

### Hypertension

- Systolic blood pressure of 140mm Hg or above or diastolic blood pressure of 90mm Hg or above
- Increases risk of heart attack, stroke and renal failure

### Dyslipidemia

- Total cholesterol above 200mg/dl, LDL cholesterol above 130mg/dl
- Increased cholesterol level resulting in coronary arteries becoming clogged

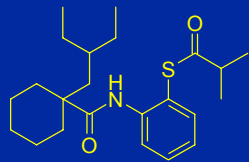
### Thrombosis

- Formation of blood clots in the blood system in the absence of bleeding
- Can arise following the rupture of an atherosclerotic plaque in arteries

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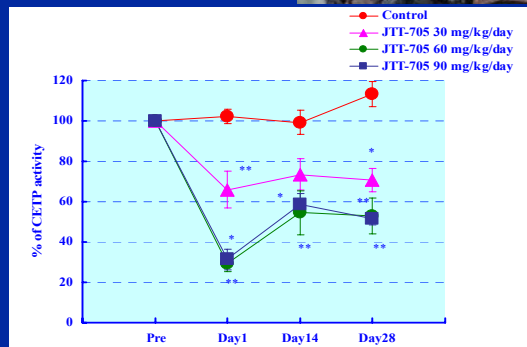
## JTT-705/ R1658

### Preclinical evaluation



- A thiol ester
- Forms a disulfide bond with CETP at cys 13
- Human, rabbit, hamster, cynomolgus monkey, marmosets: plasma IC<sub>50</sub> *in vitro*: 1 – 11.7 μM

### Effect of JTT-705 on serum CETP activity in marmosets



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