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

*Roadshow London, September 6th, 2006*





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- 6 increased government pricing pressures;
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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>

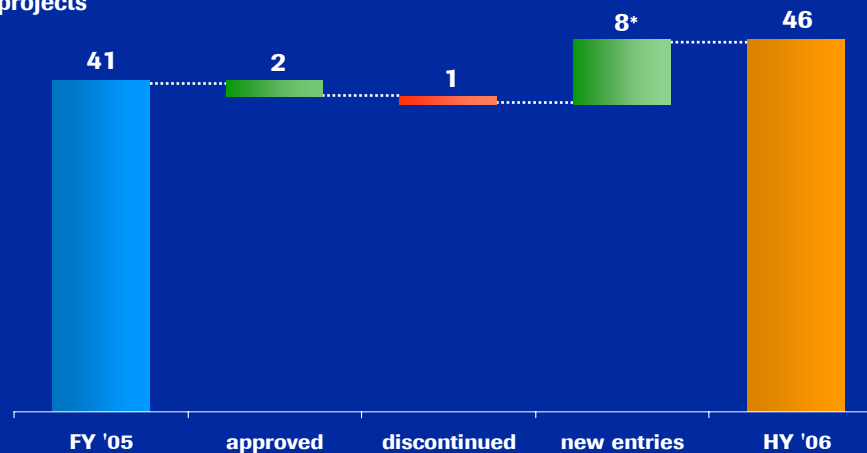
Phase I progress	
<b>5 new entries</b> (moved from phase 0 or newly entered)	R1664 - dyslipidemia
	R1450 - Alzheimer's
	R1507 - solid tumors
	Trastuzumab DM1 (GNE) - mBC
	R3477 (S1P1, Actelion) <sup>1</sup> - autoimmune diseases
<b>2 moved forward to phase II</b>	Topical VEGF (GNE) - diabetic foot ulcers
	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

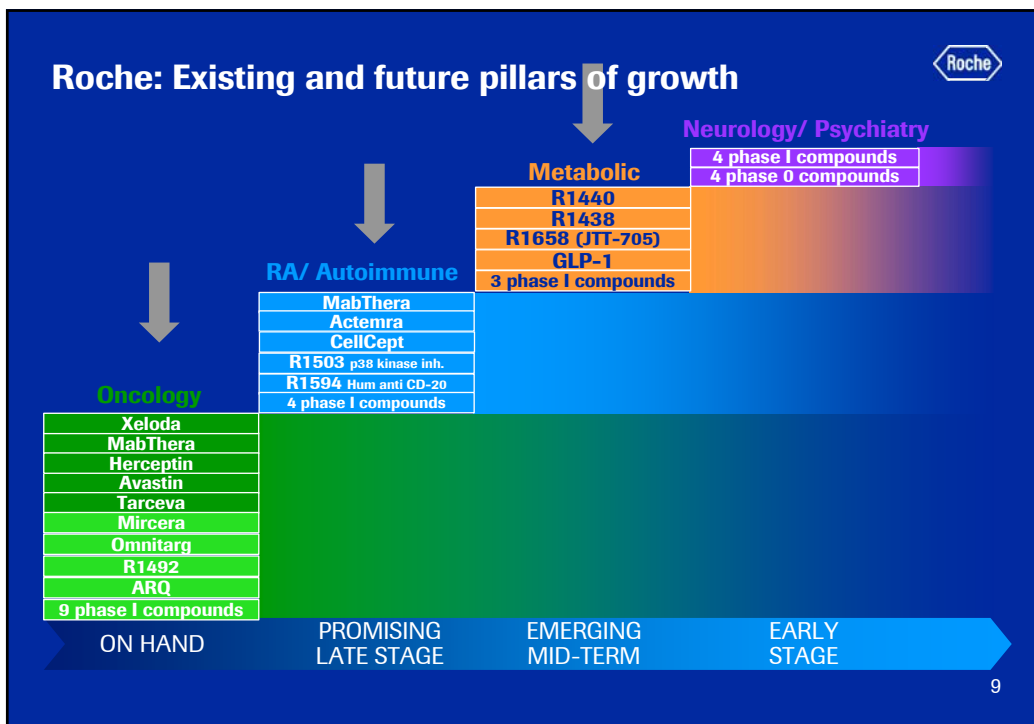
## An industry leading late stage pipeline

*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

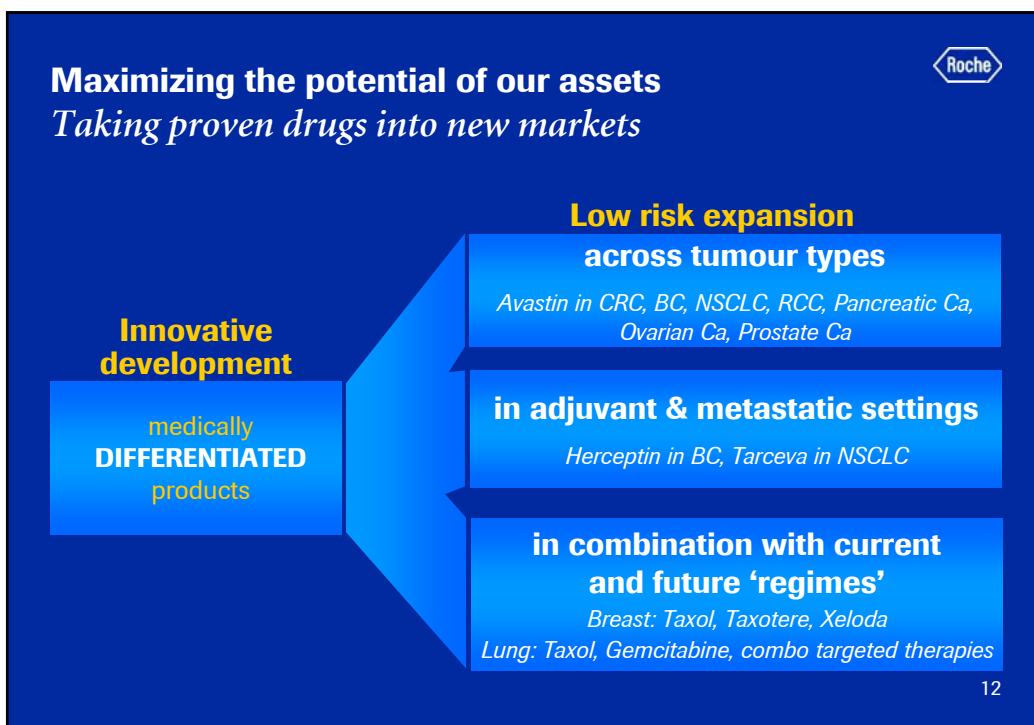
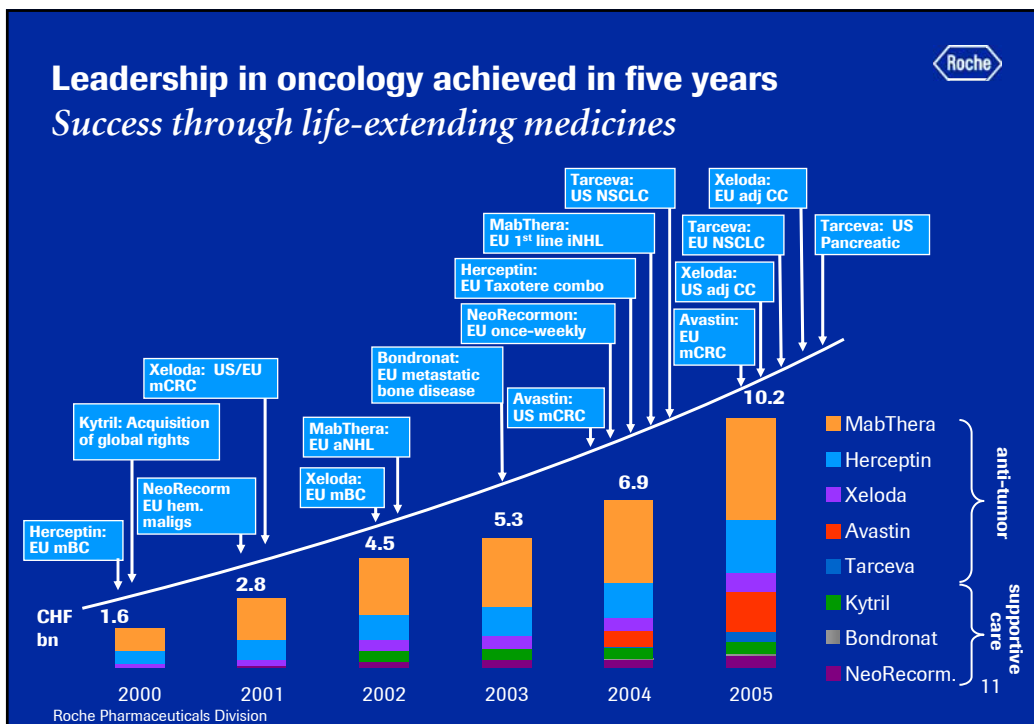
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- Roche in oncology**

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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 pancreatic Ca Xeloda mCRC 1 <sup>st</sup> line combo Avastin mCRC 1 <sup>st</sup> line ext.	Avastin NSCLC Xeloda gastric Ca Herceptin mBC combo hormonal	Avastin mBC		
Ongoing	Xeloda adjuvant BC Xeloda adjuvant CC combo Avastin adjuvant rectal Ca	Tarceva & Avastin NSCLC maintenance	Avastin RCC Avastin pancreatic Ca Avastin ovarian Ca	Avastin mBC 1 <sup>st</sup> line ext. MabThera 1 <sup>st</sup> line CLL Tarceva NSCLC 1 <sup>st</sup> line	Herceptin gastric Ca	MabThera relapsed CLL Avastin prostate Ca Tarceva & Avastin NSCLC 2nd line	Xeloda mCRC 2nd line combo Avastin mBC 2nd line
To start soon	Tarceva adjuvant NSCLC Avastin adjuvant NSCLC Avastin adjuvant BC						

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

## Overview on value adding propositions

Roche in oncology

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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

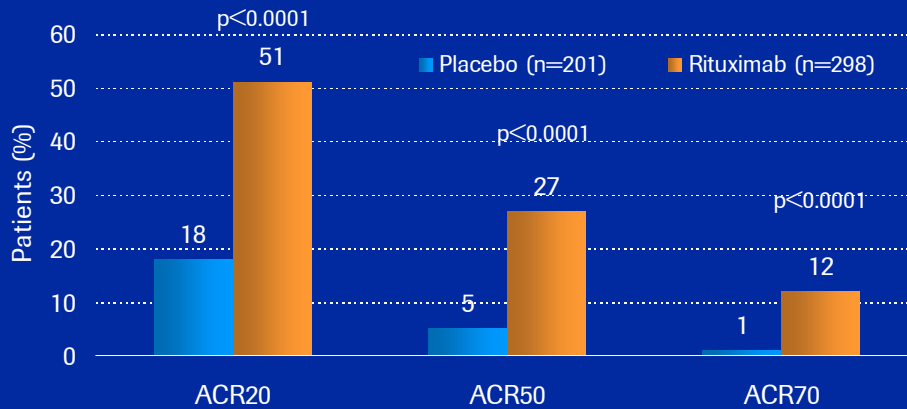


- Multi-centre, randomized, double-blind, placebo-controlled phase III study enrolling 514 patients
- Primary Endpoint:
  - proportion of patients with an **ACR20 response at Week 24**
- Secondary and exploratory radiographic endpoints:
  - secondary: Change in modified Sharp radiographic total score,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





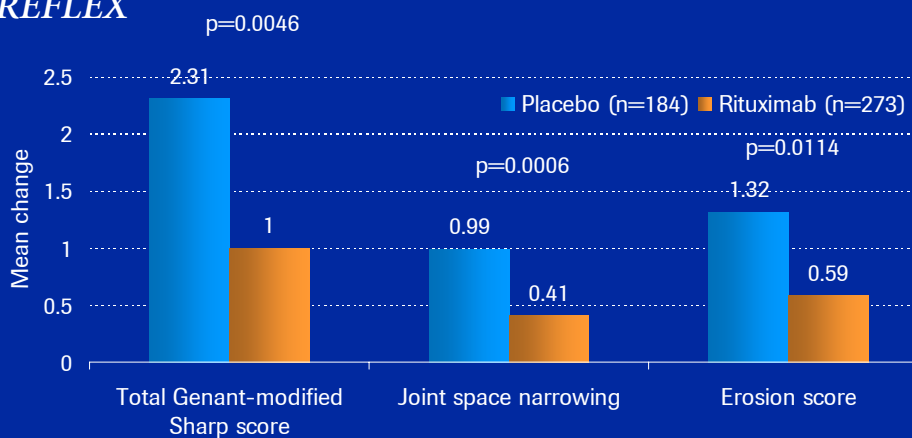
## Significant ACR responses at Week 24 REFLEX



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

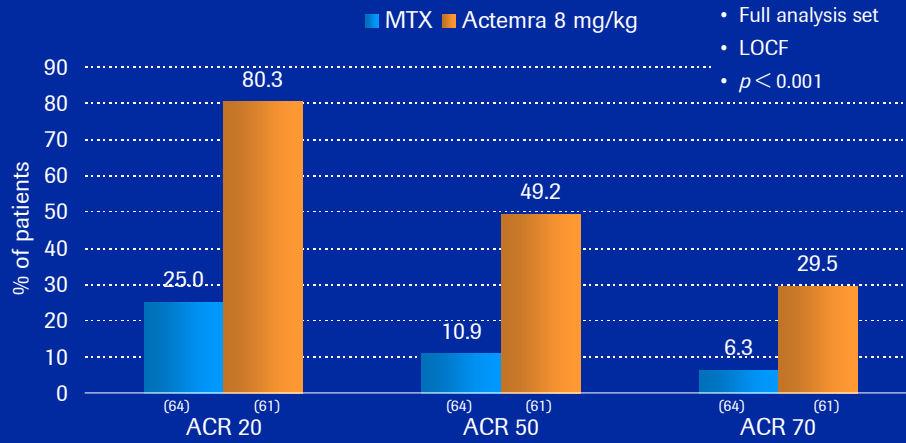
## Actemra

### *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)

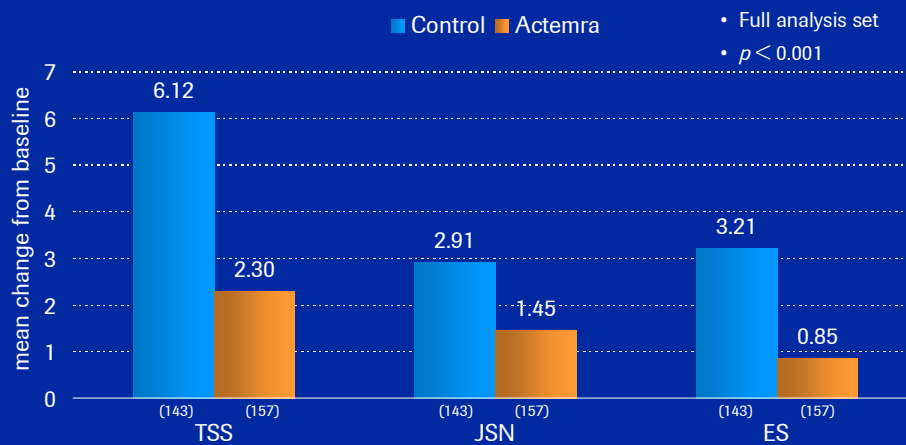
*Actemra shows consistent high efficacy*



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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

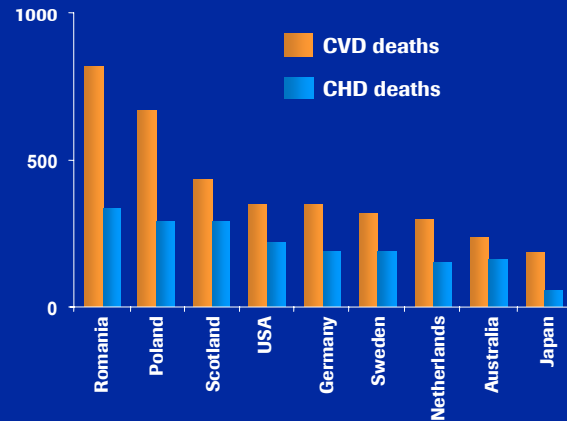
- CVD contributed to approximately one-third of all global deaths (17 million)
- 80% of burden is in low- and middle-income countries

#### By 2020

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

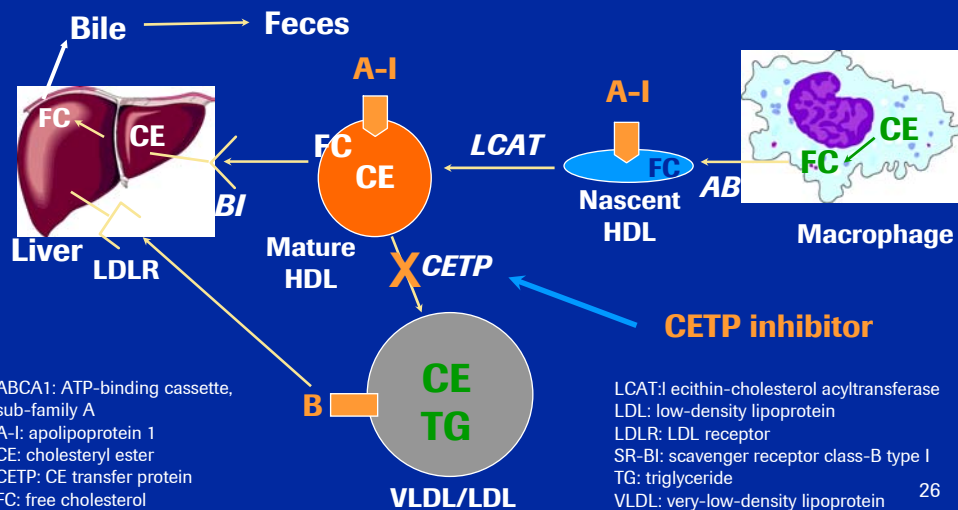
#### Mortality from CVD and CHD in selected countries

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



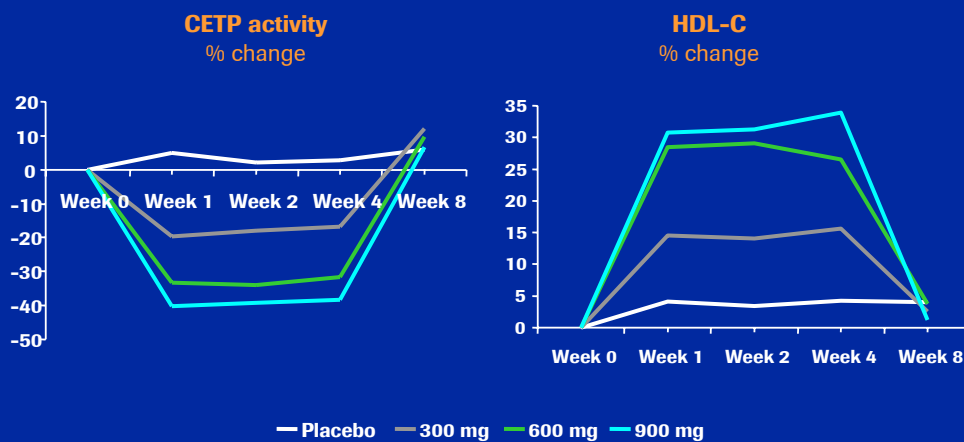
## Phase IIa PoC studies



- **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*

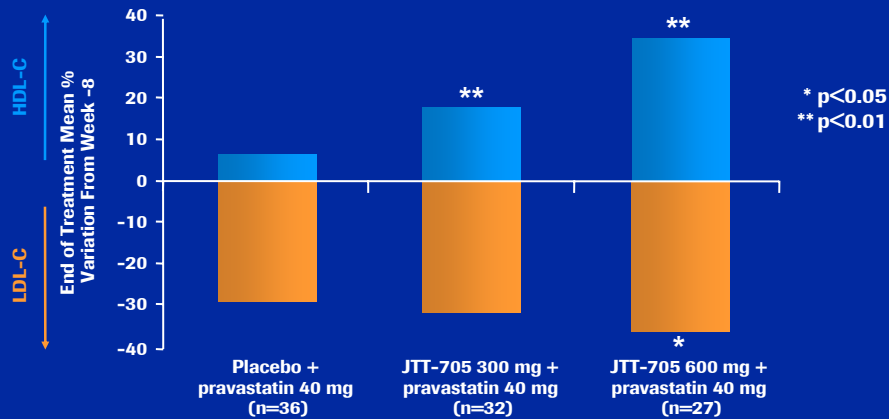


de Grooth GJ et al. Circulation 2002;105:2159-65

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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

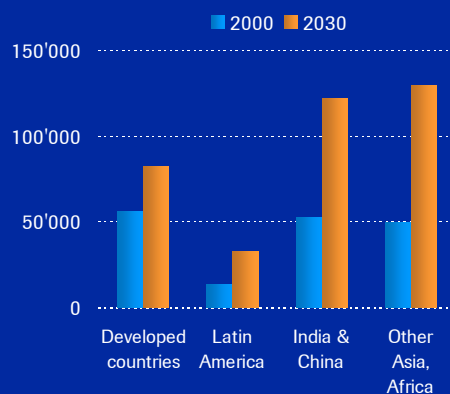
### *JTT-705/ R1658*

- 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

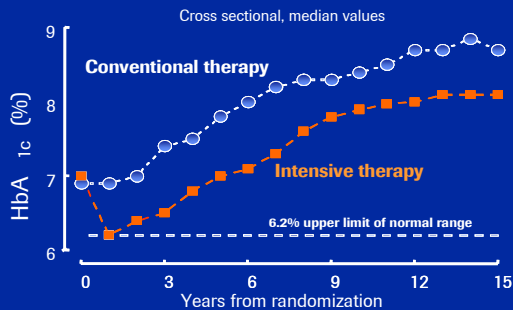
- Expanding prevalence > 350 mio by 2030
- Causing a number of vascular complications
- Significant burden to healthcare funding
  - US annual direct costs estimated at USD 92bn (2002, Lewin Group Study)
- 50% of all diabetics are unaware of their condition
- Type 2 diabetes accounts for 85% - 95% of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



# Type 2 Diabetes

## Disease progression despite intensive therapy

### United Kingdom Prospective Diabetes Study



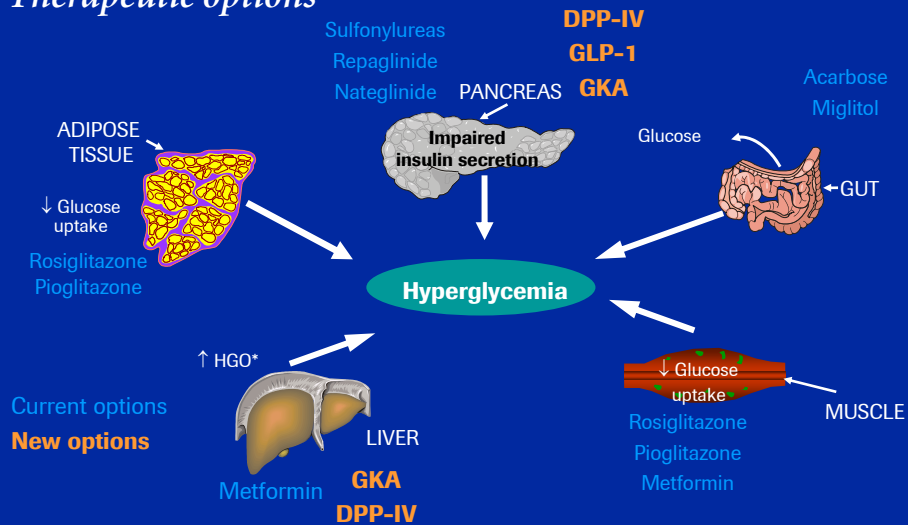
Conventional:  
FPG <15 mmol/L diet,  
pharmacotherapy

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

- Multiple MOAs targeting underlying pathologies,
  - 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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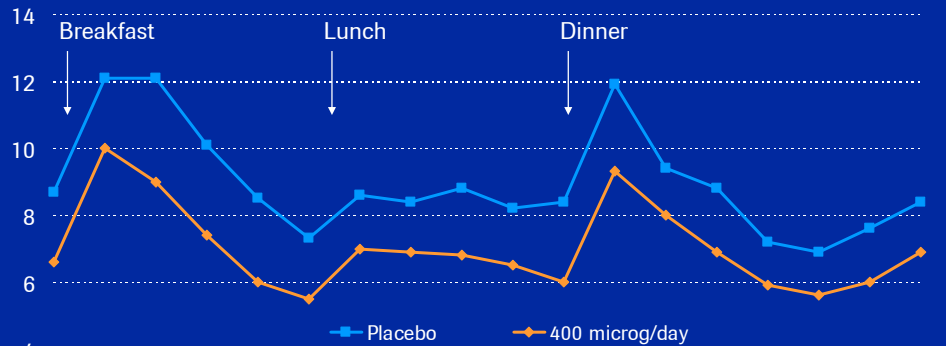
## BIM-51077/ R1583



### 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

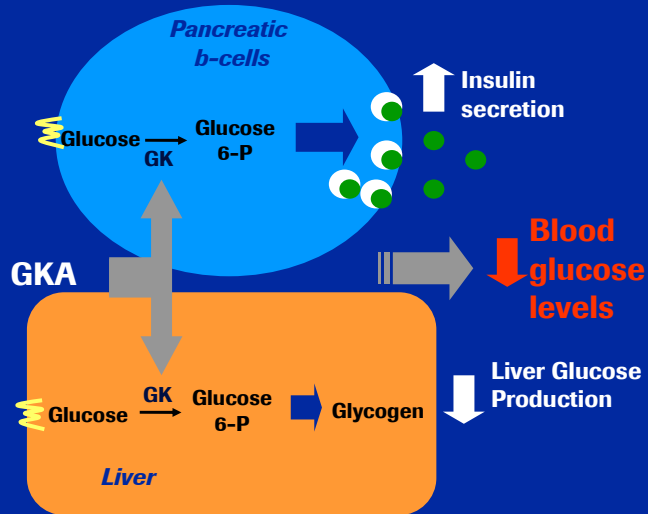
## Summary and outlook

### *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</b> <b>SERENE</b>	MTX + placebo vs. MTX + MabThera 1g vs. MTX + MabThera 2g	495	Reduction in signs and symptoms
<b>MTX naïve</b> <b>(X-ray study)</b> <b>IMAGE</b>	MTX vs. MTX + MabThera 1g vs. MTX + MabThera 2g	852	Reduction in signs and symptoms Inhibition of structural joint damage Improvement in physical function
<b>MTX-IR</b> <b>Dose escalation</b> <b>MIRROR</b>	Rituximab 1g retx 1g vs. Rituximab 1g retx 2g vs. 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 Actemra 8mg + MTX MTX <b>OPTION</b>	630	MTX partial responders	ACR 20 response at Wk 24
Actemra 4 mg + MTX Actemra 8 mg + MTX MTX <b>LITHE</b>	1'170	MTX partial responders	ACR 20 at Wk 24 Sharp Score at Wk 52 Sharp Score at Wk 104 Physical function at Wk 104
Actemra 8 mg + DMARDs DMARDs <b>TOWARD</b>	1'200	DMARD partial responders	ACR 20 response at Wk 24
Actemra 4 mg + MTX Actemra 8 mg + MTX MTX <b>RADIATE</b>	570	Anti-TNF $\alpha$ failures	ACR 20 response at Wk24
Actemra 8 mg 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

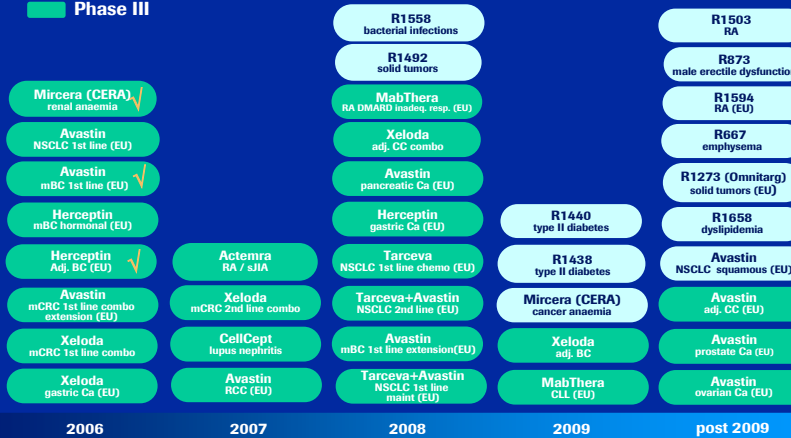
\* Approved in July 2006  
Status as of June 30, 2006

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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 (14 NMEs)	phase I (21 NMEs + 3 AIs)	phase II (18 NMEs + 10 AIs)	phase III (2 NMEs + 34 AIs)	Registration (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  
 FFS Ipsen  
 ISO Roche/Chugai  
 MEM Memory  
 ARQ Actelion

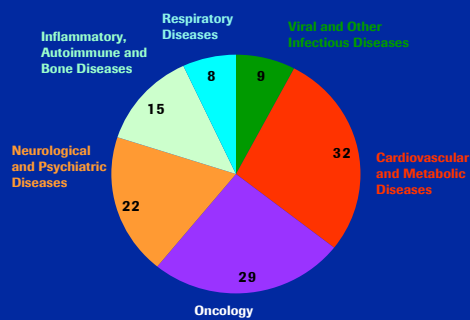
Status as of June 30, 2006

# Roche managed R&D pipeline - overview



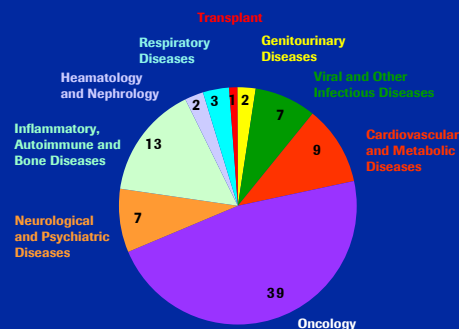
Projects by Therapeutic Area

## Research



115 projects

## Development



83 projects

Status as of June 30, 2006

## 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

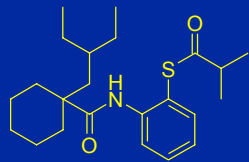
### Thrombosis

- 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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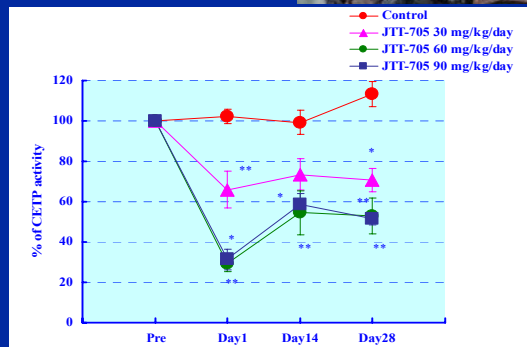
## JTT-705/ R1658

### 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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