

# **Astellas R&D Meeting 2006**

**July 3, 2006  
Astellas Pharma Inc.**



## **Cautionary statement regarding forward-looking information**

**This material includes forward-looking statements based on assumptions and beliefs in light of the information currently available to management and subject to significant risks and uncertainties. Actual financial results may differ materially depending on a number of factors including adverse economic conditions, currency exchange rate fluctuations, adverse legislative and regulatory developments, delays in new product launch, pricing and product initiatives of competitors, the inability of the company to market existing and new products effectively, interruptions in production, infringements of the company's intellectual property rights and the adverse outcome of material litigation.**

**This material contains information on pharmaceuticals (including compounds under development), but this information is not intended to make any representations or advertisements regarding the efficacy or effectiveness of these preparations nor provide medical advice of any kind.**

# Astellas R&D Meeting 2006

July 3, 2006  
Masafumi Nogimori  
President and CEO



# My Mission as New CEO

- Achievement of O.P. target of ¥250 billion for FY2007
- Mid- / long-term growth offsetting patent expiry of Prograf/Harnal
- Reinforcement of domestic/global sales & marketing capabilities
- Enhancement of R&D capabilities
- Improvement of operational efficiency on a global basis  
(optimization of organization/ cost structure etc.)
- Increase of return to shareholders

**For sustainable improvement of enterprise value**

# Enhancement of R&D capabilities

## Research

- Pursuing drug discovery target for diseases with unmet medical needs
- Reorganization of drug discovery function:
  - Expansion of Tsukuba Research Center

## Development

- Maximization of products value on a global basis
- Speedy development and launch of new products
- Improvement of profitability of investment

## Product acquisition / In-licensing

- Reinforcement of pipeline in addition to in-house developed compounds
- Utilization and expansion of current sales infrastructure in Japan, US and Europe

# **Astellas**

# **R&D Meeting 2006**

July 3, 2006  
Masao Shimizu  
Senior Corporate Officer  
Senior Vice President, Development



# Mission of Astellas Development Division



## - Speedy and continuous launch of new products -

### Maximization of product value on a global basis

- Development plan to maximize product value  
=> Multinational study / Transatlantic study
- Acceleration of development of highly prioritized projects
- Promotion of life cycle management (additional indication/formulation)

### Speedy development and launch of new products

- Efficient development under global development system
- Strategic/efficient outsourcing

### Improvement of profitability of investment

- Prioritization of development projects
- Reinforcement of project management system (efficient resource allocation) <sup>6</sup>

# Global Organization of Development

Global development operations fully integrated since April 2005

**CEO/ Product Strategy Executive Committee**

Final decision at HQs

PESAP / proposal of master plan

**Development Div. /  
Global Development Committee (GDC)**

PESAP: Project  
Evaluation System in  
Astellas Pharma.

Decision from  
global aspects

Proposal from  
global aspects

**Global Project Team**

**Local Project Team**

R & D  
Sales & Marketing  
Medical  
Medical Affairs

**Europe**

(Headcount: around 500)

**Local Project Team**

R & D  
Sales & Marketing  
Medical  
Medical Affairs

**Japan/Asia**

(Headcount: Japan around 400  
Asia around 50)

**Local Project Team**

R & D  
Sales & Marketing  
Medical  
Medical Affairs

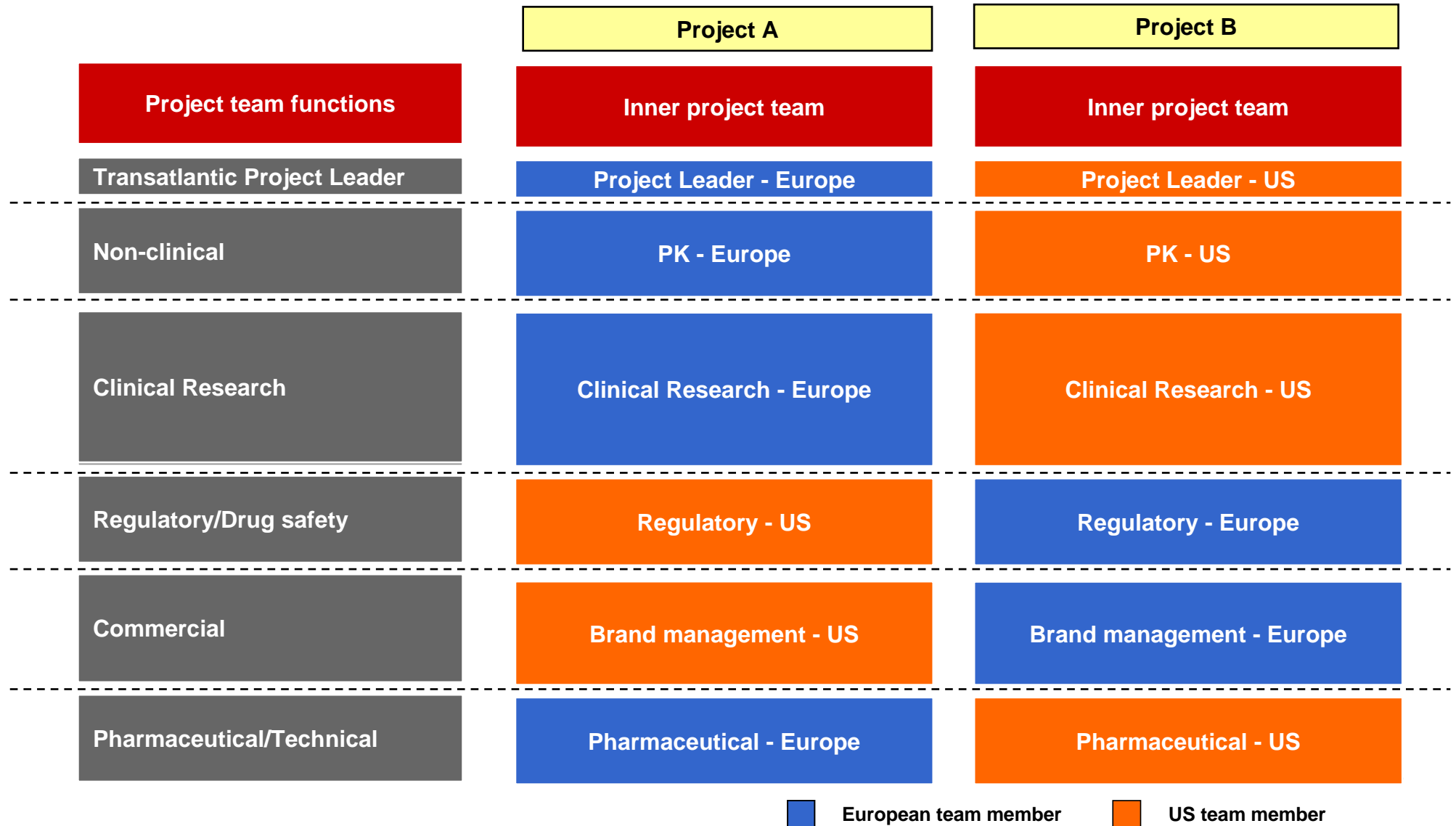
**US**

(Headcount: around 300)

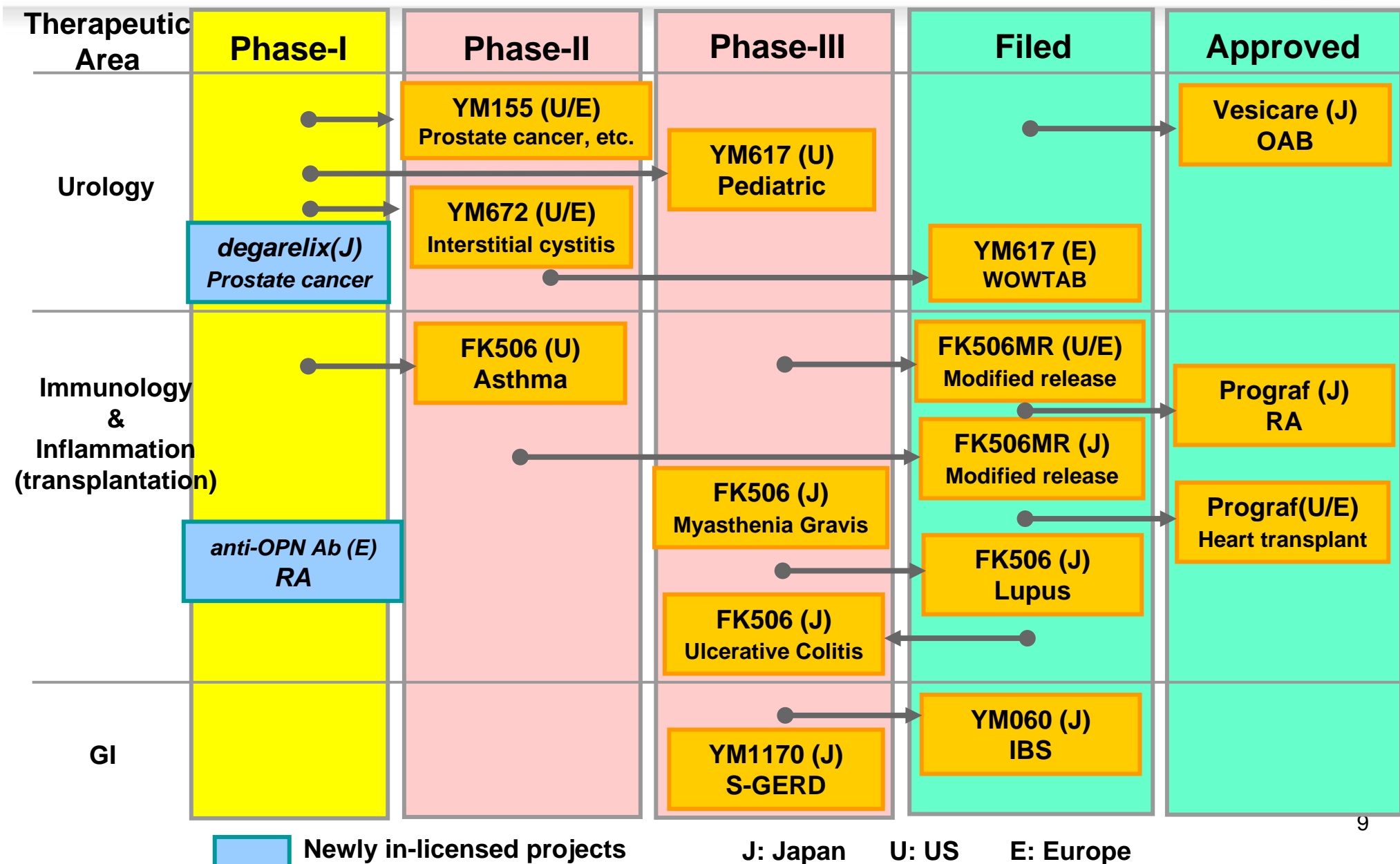
# Improvement of development system efficiency



## Transatlantic harmonization



# Progress of Projects (since April 2005)-(1)



# Progress of Projects (since April 2005)-(2)



Therapeutic Area	Phase-I	Phase-II	Phase-III	Filed	Approved
CV & Diabetes		YM758 (U/E) SA,AF	YM026 (J) Additional indication	RSD1235 (U) AF [preparation for filing] YM026 (J) Additional indication	Vaprisol(U) Euvolemic hyponatremia
Infection			telavancin(U/E) cSSSI, HAP	FK463 (J) Prophylaxis FK463 (E) Deep-seated fungal infection T-3811(J) Respiratory infections	Funguard(J) Pediatric Mycamine(U) 100mg Vial
CNS	XP13512(J) RSL, Neuropathic pain		FK199B (J) Modified release		Luvox (J) SAD
Kidney	YM311(FG-2216) (J) Anemia	YM311(FG-2216) (E) Anemia			
	ILY101(J) Hyperphosphatemia	YM533 (J) Renal failure		YM086(J) Diabetic nephropathy	

## Discontinued projects (since April 2005)

YM087	Acutely decompensated CHF	P-II (US/Europe)
FK352B	dialysis-related hypotension	P-II (Japan)
Aczone™	Acne	Filed (US)
FK506	Gel formulation (psoriasis)	P-III (US)
telithromycin	Skin and soft tissue infections & uterine infection	Filed (Japan)
FK614	NIDDM	P-II (US/Japan)
FK949	Behavioral and psychological symptoms of dementia	P-II (Japan)
FK506	Rheumatoid arthritis	P-III (US) P-II (Europe)
FK481	Osteoporosis	P-II (Japan)
FK778	Suppression of organ rejection in liver and kidney transplants	P-II (US/Europe)

## Number of Projects (Area / Development Stage)

Area \ Stage	Pre-Clinical /Phase-I	Phase-II	Phase-III	Filed
Japan	28	3	10	9
US		7	6 <sup>(*)</sup>	2
Europe		8	1	3

\* Including preparation of filing

## Three highly prioritized projects

Development code	Area Stage	Classification (Therapeutic Target)
YM060	Japan: Filed Europe: P-II	5-HT <sub>3</sub> antagonist (Irritable bowel syndrome)
YM150	Europe: P-II	Oral Factor Xa inhibitor (Prevention of thromboembolism)
YM311(FG-2216)	Europe: P-II Japan: P-I	Oral EPO inducer (Renal anemia)

# Projects to be discussed today

- YM060; 5-HT<sub>3</sub> receptor antagonist
- YM150; Oral Factor Xa inhibitor
- YM311(FG-2216); Oral EPO inducer
- **YM758; Cardiac I<sub>f</sub> channel inhibitor <Newly disclosed>**
- YM155; Survivin expression inhibitor
- YM086(BIBR277); Type 2 diabetic nephropathy
- Anti-human osteopontin antibody; Rheumatoid arthritis

# Project Review

July 3, 2006  
Masaharu Asano  
Corporate Officer  
Vice President, Project Management  
Development



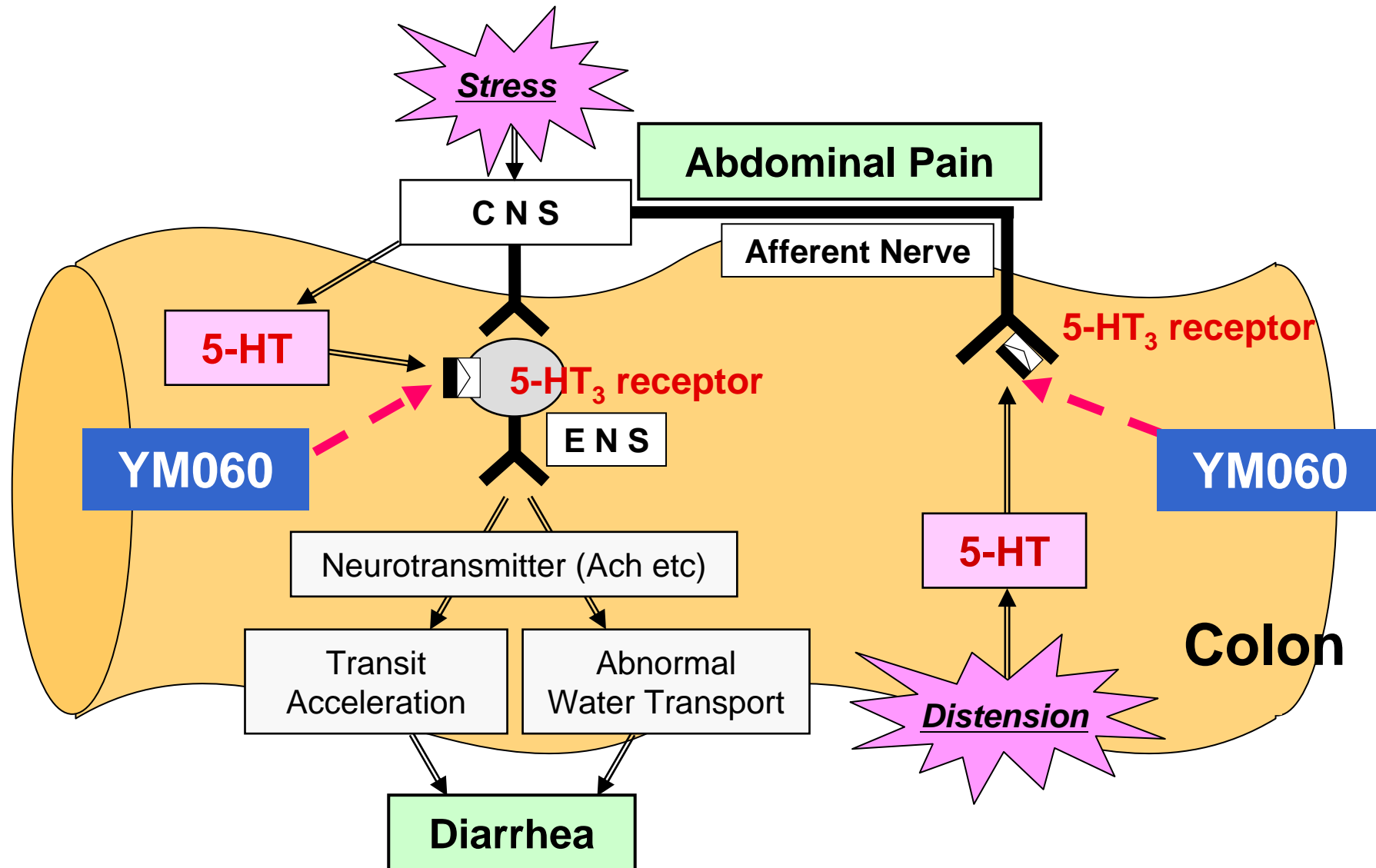
# Projects to be discussed today

- YM060; 5-HT<sub>3</sub> receptor antagonist
- YM150; Oral Factor Xa inhibitor
- YM311(FG-2216); Oral EPO inducer
- **YM758; Cardiac I<sub>f</sub> channel inhibitor <Newly disclosed>**
- YM155; Survivin expression inhibitor
- YM086(BIBR277); Type 2 diabetic nephropathy
- Anti-human osteopontin antibody; Rheumatoid arthritis

# Overview of YM060

- **Mechanism:** 5-HT<sub>3</sub> receptor antagonist
- **Target Indications:** Diarrhea-predominant irritable bowel syndrome
- **Formulation:** Tablet (Once daily)
- **Status:**
  - Japan: Filed (January 2006)
  - EU: P-II completed (under data analysis)
  - Initiation of P-III in US and Europe in FY2006
  - Submission of NDA:1H of FY2008 (schedule)
- **Target Profile:**
  - More effective in diarrhea and lower bowel symptoms than competitors
  - Early onset for IBS symptoms
  - No gender difference

# YM060: Mechanism of Action



# YM060: Study Results

## ■ P-III study synopsis and results in Japan

**[Study design]**                      Duration:12 weeks                      Number of patients:539 patients  
Treatment:YM060 5 $\mu$ g, Placebo  
Primary endpoint: Responder rate of relief of overall IBS symptoms

### **[Results]**

- The responder rate in YM060 group was statistically significant higher than that in placebo group in the primary and secondary endpoints.
- No patients on YM060 had serious adverse drug event.

## ■ P-II study synopsis and results in Europe

**[Study design]**                      Duration:12 week                      Number of patient:691 patients  
Treatment:YM060 2.5, 5, 10, 20 $\mu$ g, Placebo  
Primary endpoint: Responder rate of relief of overall IBS and relief of abdominal pain/discomfort

### **[Results]**

- All YM060 dose groups showed numerically higher responder rates in 2 primary endpoints than placebo.
- All doses were well tolerated and no drug-related SAE was found in any group.

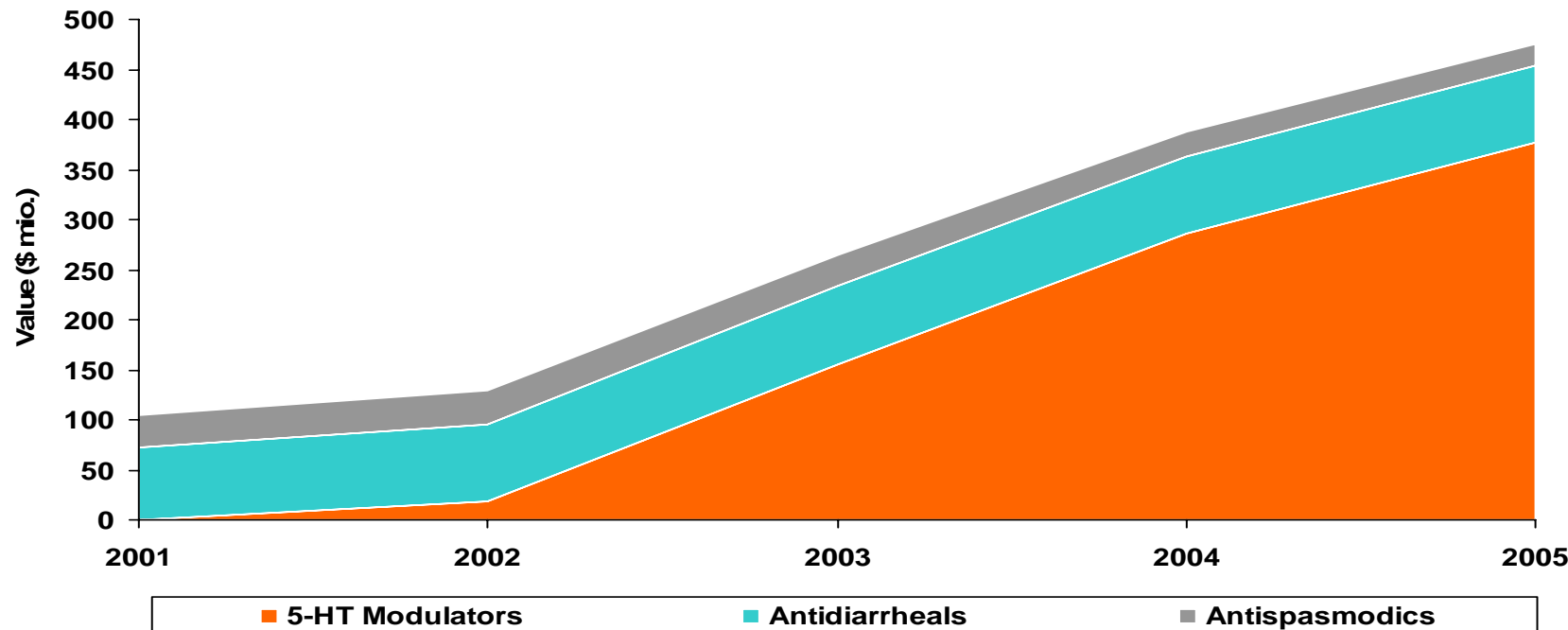
# YM060: IBS Market in US

## <5-HT Modulators>

Generic name	Mechanism of action Indication	Remarks
tegaserod	5-HT <sub>4</sub> receptor agonist IBS with constipation (only for women)	- Launch in 2002 in US - Twice a day
alosetron	5-HT <sub>3</sub> receptor antagonist Severe diarrhea-predominant IBS (only for women)	- Remarketed in 2002 in US - Twice a day
ramosetron (YM060)	5-HT <sub>3</sub> receptor antagonist Diarrhea-predominant IBS	- Filed in Japan, P-II in EU - Once a day

- US IBS market: \$475 mil (2005)
- 5-HT modulators account for 80% of the market.
- Treatment for IBS with constipation accounts for most of 5-HT modulators market.

\*5-HT Modulators: 5HT receptor antagonist/agonist



Source: IMS  
Health, IMS  
MIDAS™, 2006

# Overview of YM150

- **Mechanism:** Activated Factor Xa (FXa) inhibitor
- **Target Indications:** Prevention of venous thromboembolism (VTE) after major orthopedic surgery,  
Prophylaxis of thromboembolic complications associated with atrial fibrillation (AF)
- **Formulation:** Oral (Once daily)
- **Status:** VTE: P-IIb in Europe (Study completion anticipated in FY2007)  
AF: In preparation for P-II in US and Europe (Study initiation anticipated in FY2006)
- **Target Profile:** More convenient and safer than currently available therapies
- **Topics:** Dose dependent efficacy was shown in VTE P-II POC study. (YM150 3, 10, 30, 60mg o.d. were compared to enoxaparin 40mg)  
YM150 up to 240 mg was well tolerated without bleeding concern in healthy volunteer study.

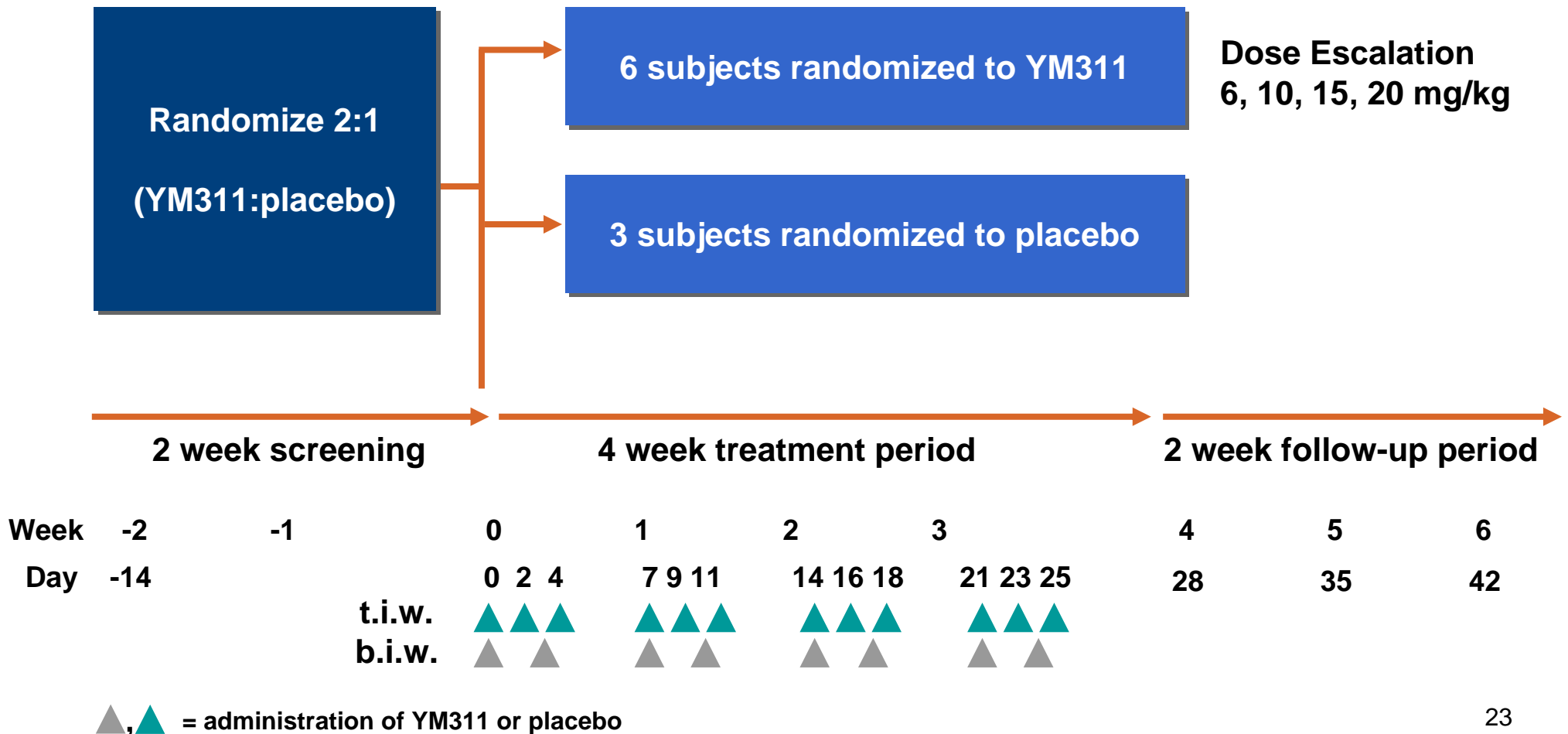
# Overview of YM311(FG-2216)

- **Mechanism** Induction of erythropoiesis by HIF-PH\* inhibition  
\*Hypoxia-inducible factor prolyl-4-hydroxylase:  
Degradation enzyme related to erythropoiesis
- **Target Indications:** Anemia in Chronic kidney disease (CKD)  
(dialysis and pre-dialysis)  
Chemotherapy-induced anemia (CIA)  
Anemia of cancer (AoC), etc.
- **Target Profile:** Effective in wide variety of anemia  
Patient friendly oral formulation  
Lower cost therapy
- **Areas:** Europe and Japan
- **Status:** **P-II in US and Europe**  
**(Astellas will join development program with FibroGen**  
**in the US and Europe in 1H of FY2006)**  
**Initiation of P-III study anticipated in 2008**  
  
**P-I in Japan (single dose YM311 showed dose dependent**  
**increase in plasma EPO)**  
**Initiation of P-II study anticipated in 2007**

# YM311: Anemia in CKD (Pre-dialysis) P-IIa Study in Europe : Study design



Treatment: 6 ~ 20 mg/kg t.i.w. or b.i.w. for 4 weeks



# YM311: Efficacy (Interim Results)

## EPO-naïve

Dosage	N	Mean Hb Change (g/dL) from Baseline
6 mg/kg, t.i.w.	6	1.1
10 mg/kg, b.i.w.	4	1.2
10 mg/kg, t.i.w.	5	0.9
Placebo	5	-0.3

## EPO-treated

Dosage	N	Mean Hb Change (g/dL) from Baseline
6 mg/kg, t.i.w.	6	-1.1
15 mg/kg, t.i.w.	3	0.2
20 mg/kg, t.i.w.	1	1.8
Placebo	5	-1.2

EPO-treated patients: Stable regimen of rHuEPO (recombinant human erythropoietin) for a minimum of eight weeks before the first dose of study drug, and a mean baseline hemoglobin concentration of 9.5 to 12.5 g/dL

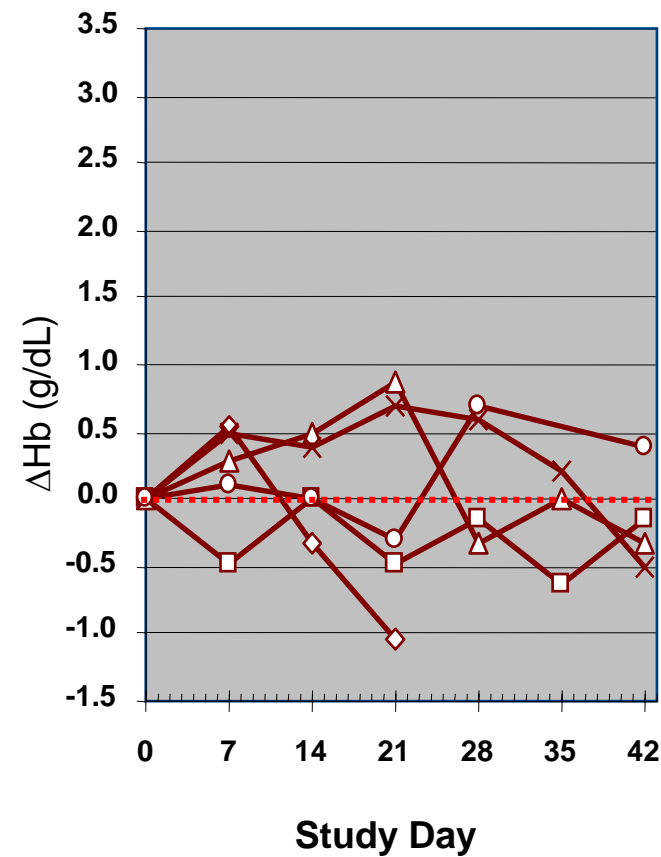
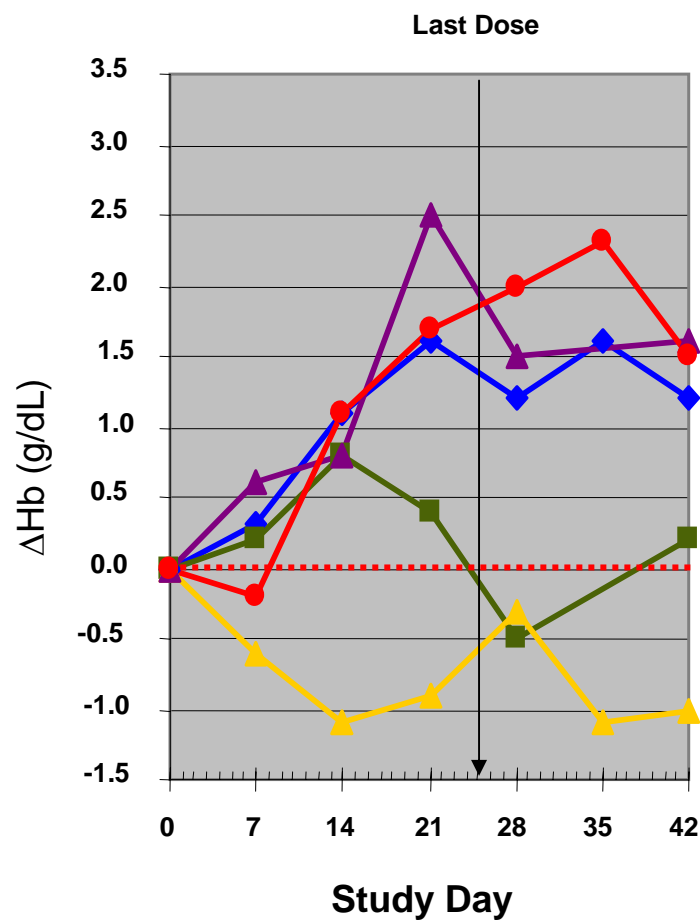
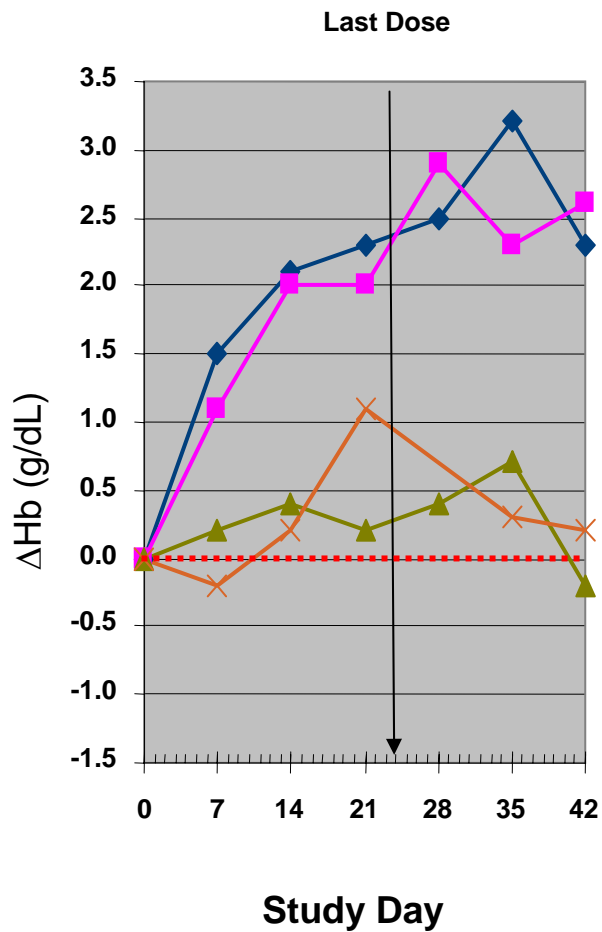
# YM311: EPO-naïve (10 mg/kg b.i.w. or t.i.w.): Hb



YM311 (10 mg b.i.w.)

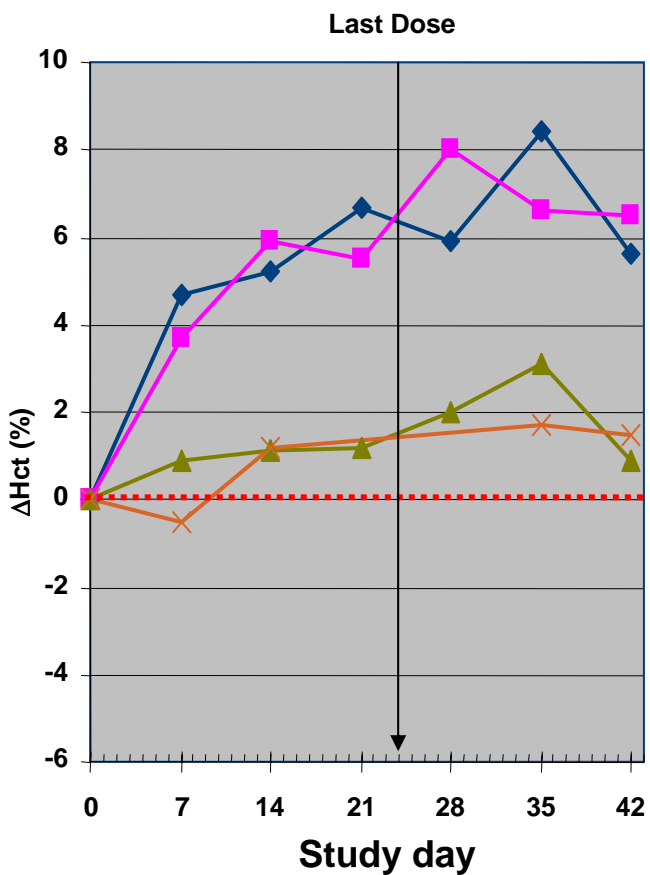
YM311 (10 mg t.i.w.)

Placebo

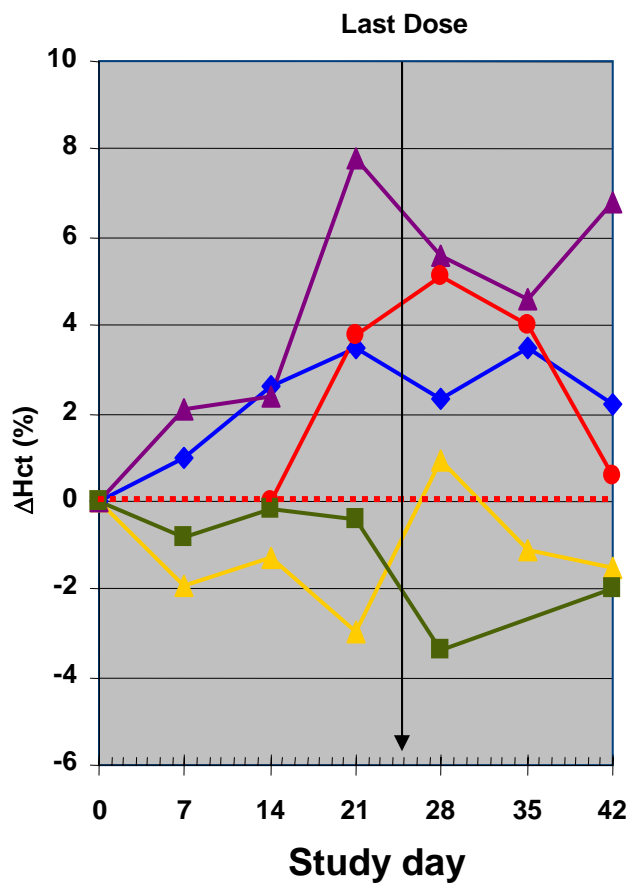


# YM311: EPO-naïve (10 mg/kg b.i.w. or t.i.w.): Hct

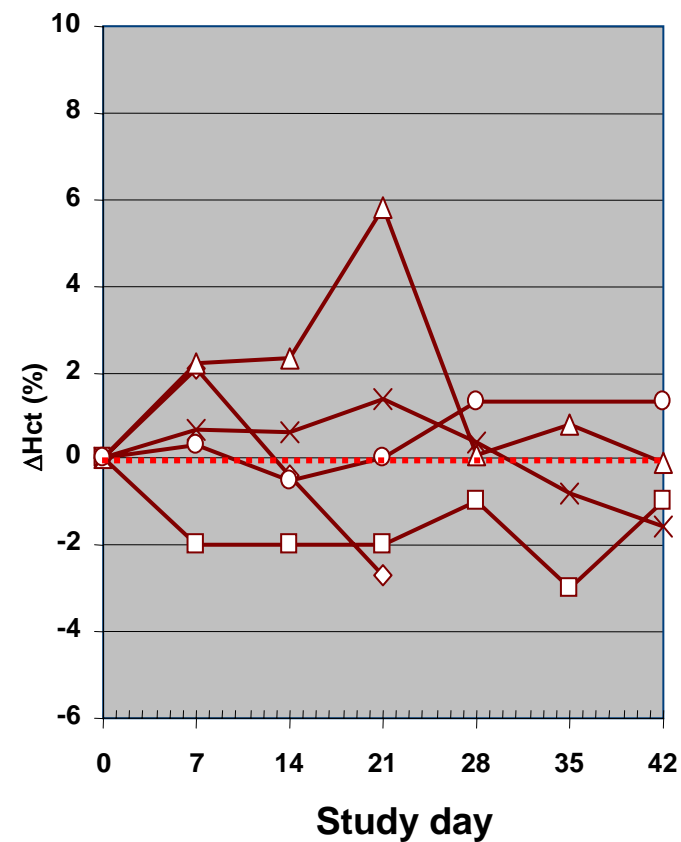
**YM311 (10 mg b.i.w.)**



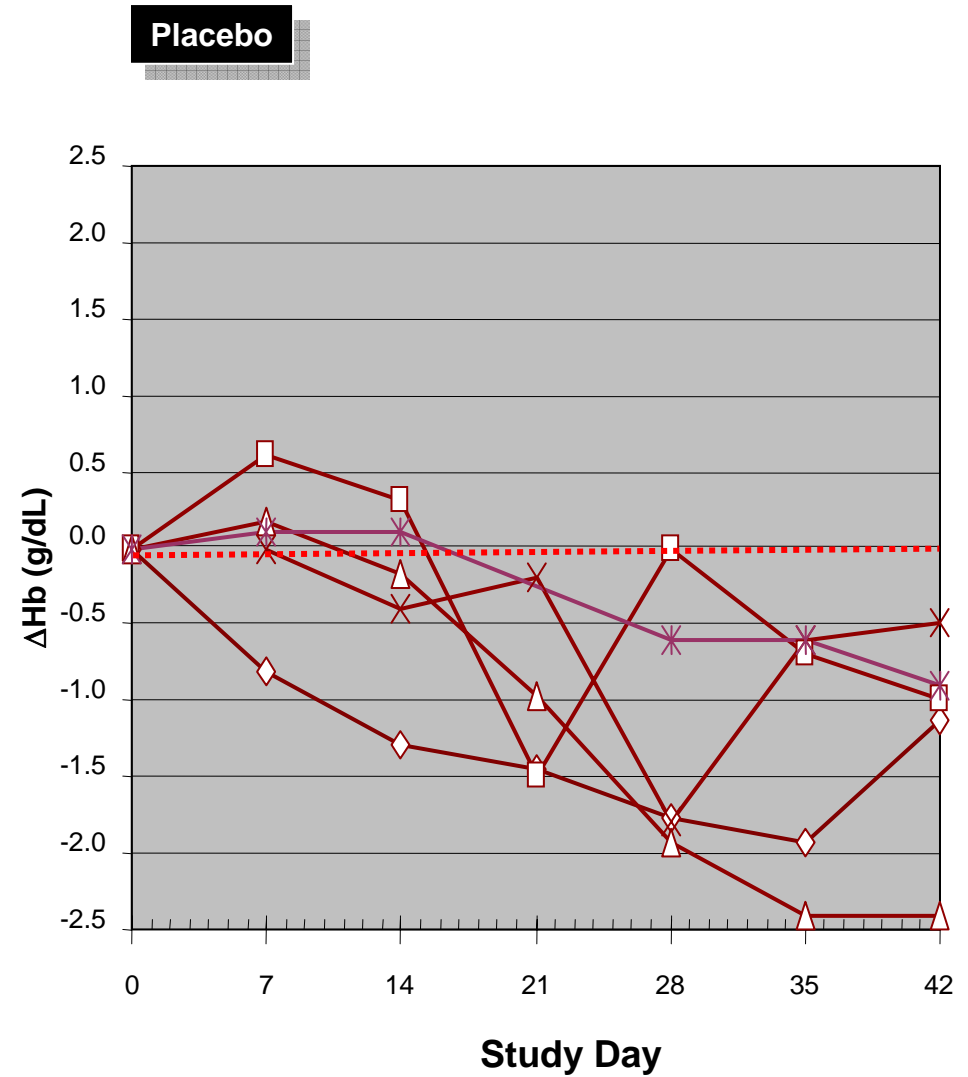
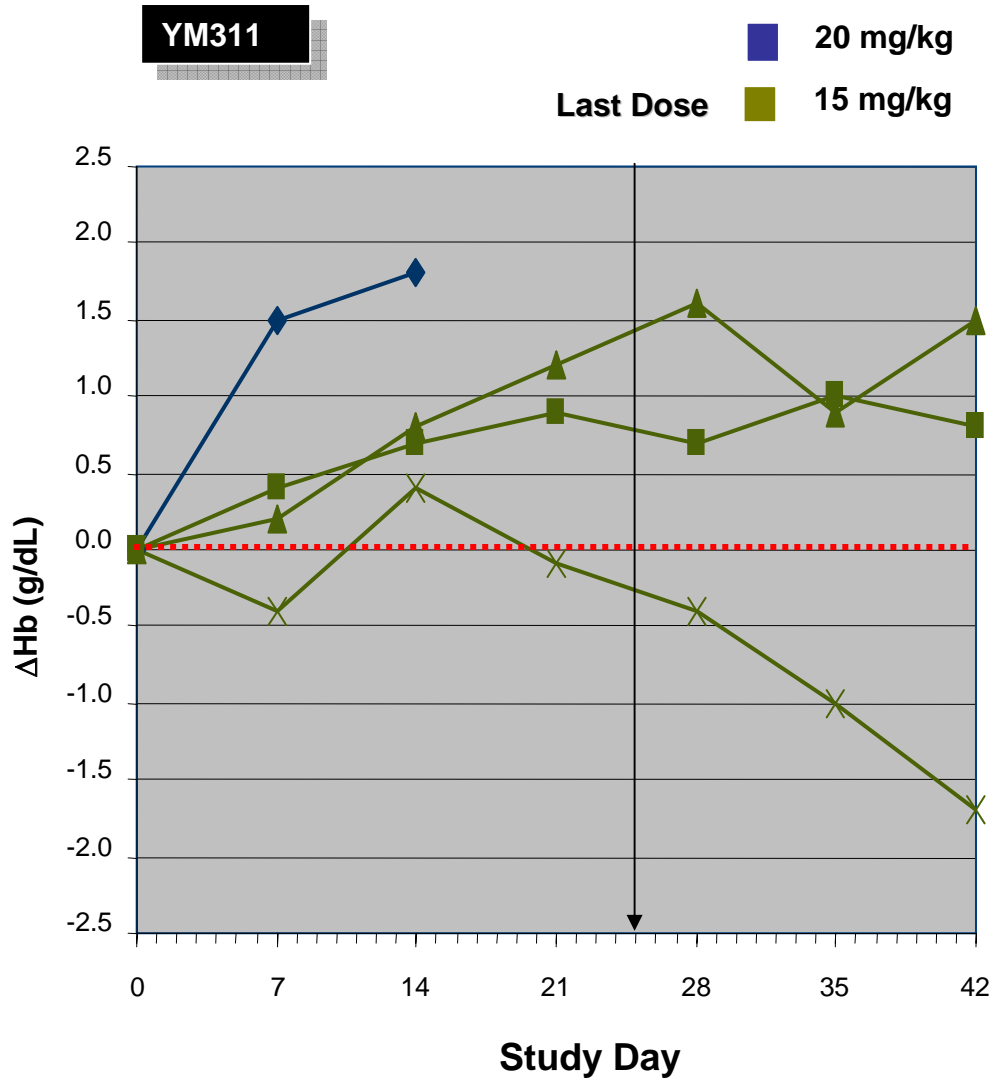
**YM311 (10 mg t.i.w.)**



**Placebo**



# YM311: EPO-treated (15 or 20 mg/kg t.i.w.): Hb

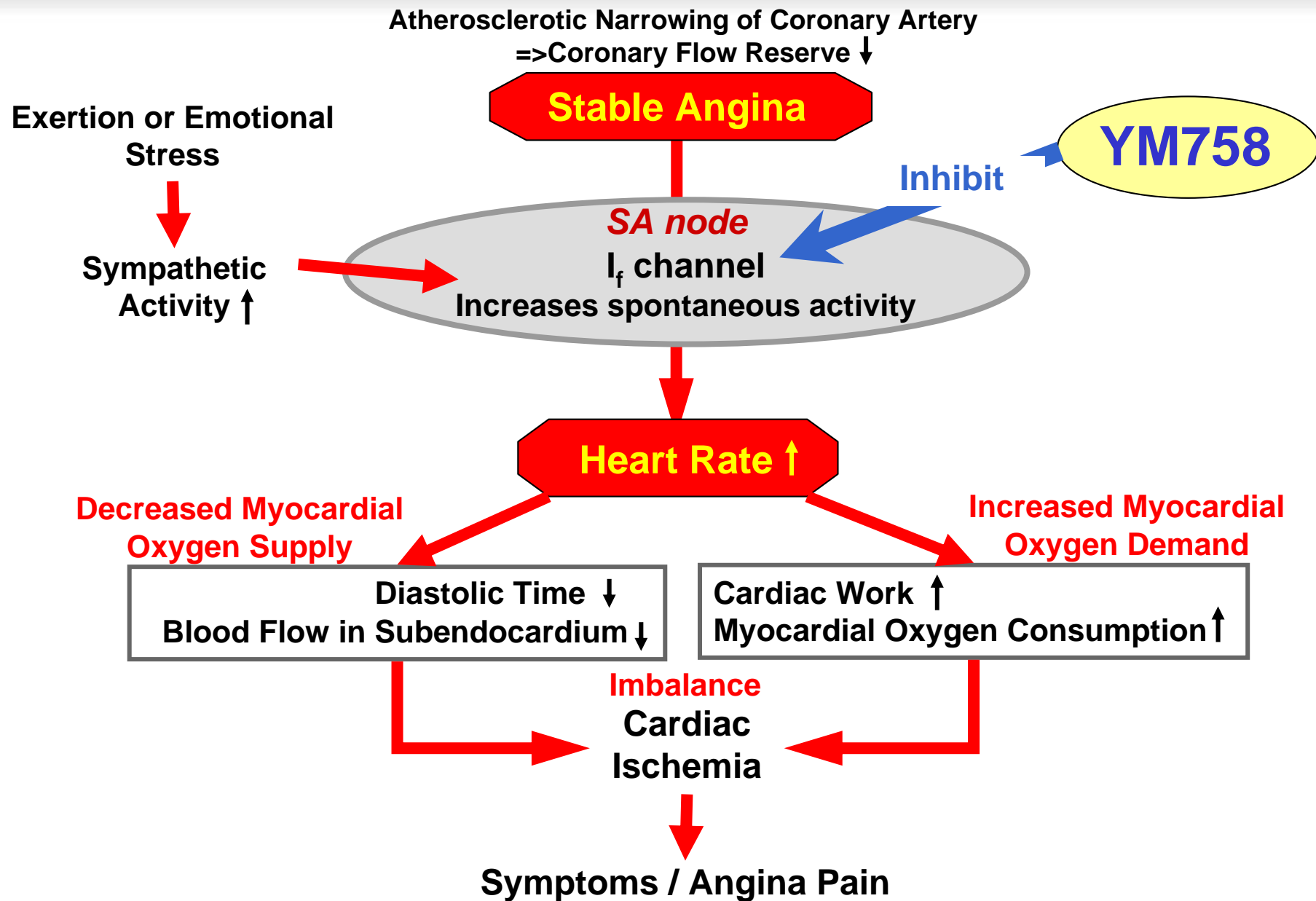


# Overview of YM758 (Stable Angina) <Newly disclosed>



- **Mechanism:** Cardiac I<sub>f</sub> channel inhibition
- **Target indications:** Stable Angina
- **Formulation:** Oral
- **Status:** P-II in Europe
- **Target profile:**
  - Heart rate lowering effect during exercise
  - No negative inotropic effect (vs. beta blockers, Ca<sup>2+</sup> channel blockers)
  - No hypotension (vs. beta blockers, Ca<sup>2+</sup> channel blockers)
  - No pro-arrhythmic effect (No effect on ECG parameters)
  - Once daily

# YM758: Mechanism of action -Stable Angina-

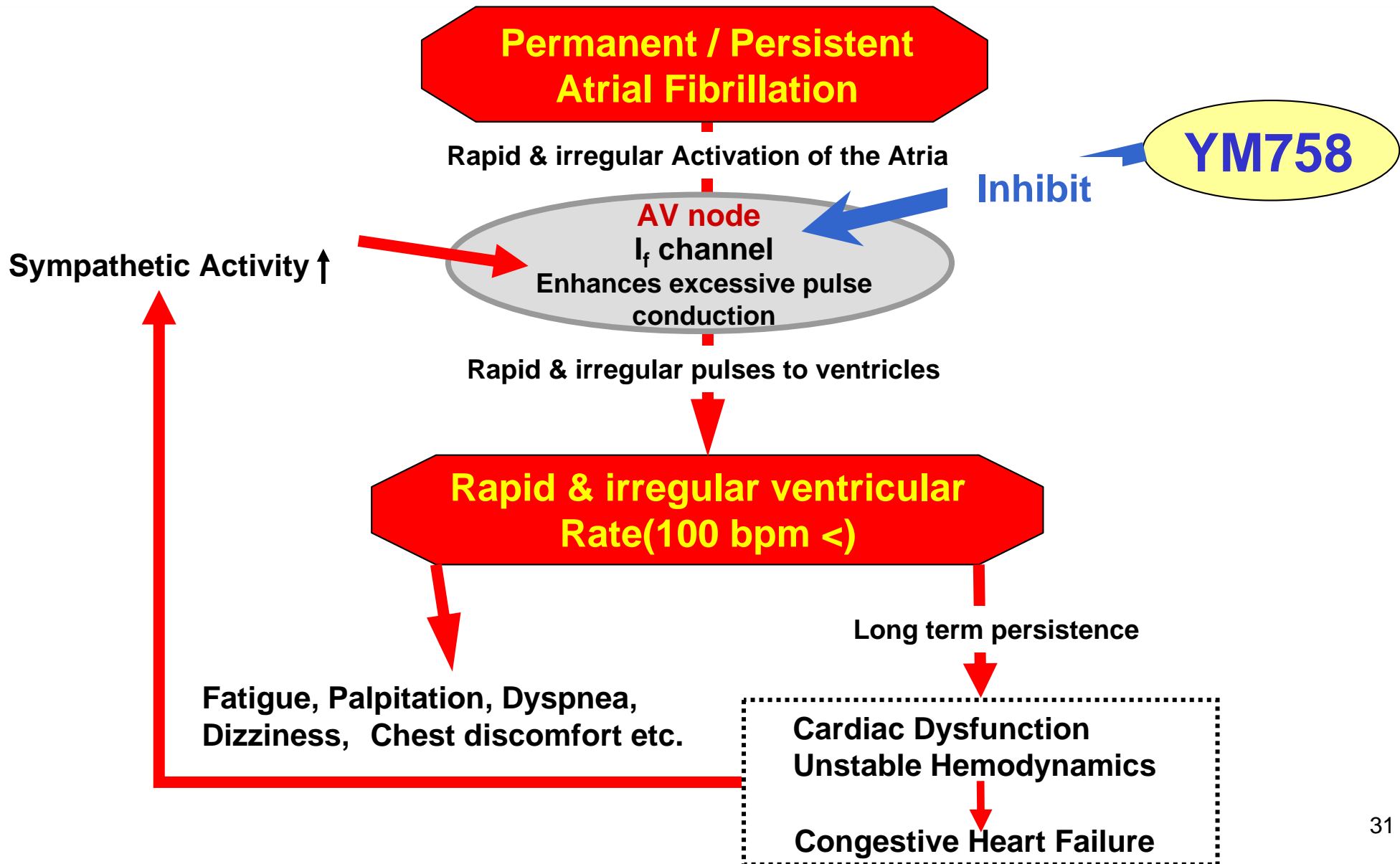


# Overview of YM758 (Atrial Fibrillation)

- **Mechanism:** Cardiac I<sub>f</sub> channel inhibition
- **Target indications:** Atrial Fibrillation (ventricular rate control therapy)
- **Formulation:** Oral
- **Status:**
  - P-II in US
  - P-I in Japan (in preparation)
- **Target Profile:**
  - Ventricular rate lowering effect during atrial fibrillation
  - Ventricular rate control during exercise (vs. digitalis)
  - No negative inotropic effect (vs. beta blockers, Ca<sup>2+</sup> channel blockers)
  - No hypotension (vs. beta blockers, Ca<sup>2+</sup> channel blockers)
  - No pro-arrhythmic effect (=No effect on ECG parameters)
  - Once daily

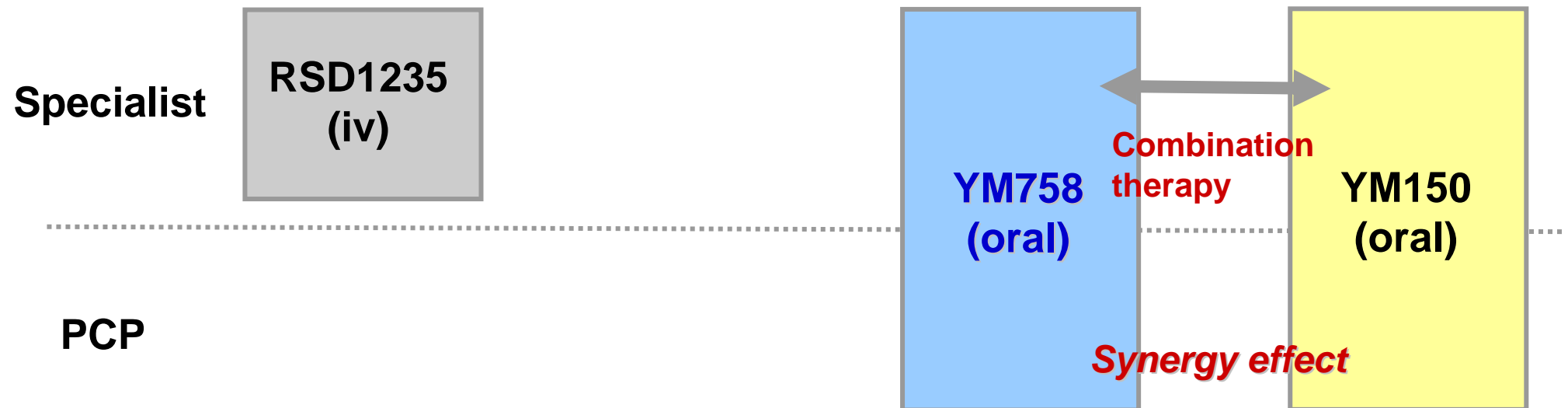
# YM758: Mechanism of action

## -Atrial Fibrillation (ventricular rate control)-



# Positioning of YM758 in 4 treatment modes of AF therapy

Drug Treatment	Cardioversion (converted to normal rhythm)	Sinus Rhythm Maintenance (Rhythm Control)	Ventricular Rate Control	Anti-thrombotics (Stroke Prevention)
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# Overview of YM155

- **Mechanism:** Survivin suppressant
- **Target Indications:** Hormone Refractory Prostate Cancer (HRPC), Non Small Cell Lung Cancer (NSCLC), Metastatic Melanoma (MM), etc.
- **Formulation:** Injection
- **Status:** P-II in US and Europe (HRPC, NSCLC, MM)  
P-I in Japan
- **Target profile:**
  - YM155 has a potent anti-cancer activity for which the novel mechanism of action based on its inhibitory effect on survivin expression.
  - In treatment of HRPC, NSCLC and MM etc., it is expected to improve patient's survival time and response rates when used alone or in combination with other treatments
- **Topics:** US P-I results are presented at 42th ASCO in June, 2006

# YM155: US Phase I study - Protocol synopsis -



## Protocol synopsis

- **Primary objective;** Determine the MTD and DLT
- **Population;** Advanced solid malignancies and NHL refractory to standard therapy
- **Dose;** 1.8, 3.6, 4.8, 6.0 (mg/m<sup>2</sup>/day)
- **Mode of administration;** 7days continuous IV infusion (21days/cycle)
- **Design;** Dose escalation were evaluated in cohorts 3-6 patients and MTD was defined as the dose preceding the dose at which 2 of up to 6 patients experience a DLT. Additional subjects, 12 or more, were enrolled at MTD to better define the safety profile at MTD
- **Definition of DLT;** Platelet count <25.000, ANC<500/mm<sup>3</sup> for longer than 5 days, Non-hematological toxicity  $\geq$  Grade 3, etc.

## Patient characteristics

- **Number of patients;** Total:41, <1.8 (8), 3.6 (6), 4.8 (25), 6.0 (2)>
- **Median # prior chemo regimens;** 5
- **Diagnosis;** Prostate(9), NHL(5), Colorectal(5), Sarcoma(4), Ovarian / Lung(3 each), etc.

# YM155: US Phase I study - RESULTS(1):Safety -



## ■ Hematological Toxicity

Dose	No. pts.	1 <sup>st</sup> cycle (All cycles)		
		ANC		Platelets
		Grade 3	Grade 4	Grade 3
1.8	8	0	0	0
3.6	6	0	0	0
4.8	25	0 (0)	1 (1)	0
6.0	2	0 (0)	1 (1)	0

## ■ Non-Hematological Toxicity

Dose	No. pts	Stomatitis				Nausea				Fever				Arthralgia				Creatinine				Renal Failure			
		Grade				Grade				Grade				Grade				Grade							
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1.8	8	1				1	1			3	2				1			1							
3.6	6					4				1				2											
4.8	25	5		1		5	2			10	2			6	2										
6.0	2	1		1			1			2					2			1							1

■ Responder in NHL

**Near CR in Recurrent DLBCL NHL  
Refractory to CHOP and RICE**



Oct 22, 2004



Dec 3, 2004

Pt treated with total 6 cycles YM155 then PSC transplant- now NED >18 mos<sup>26</sup>

# YM155: US Phase I study - CONCLUSION -



## ■ MTD and DLT;

- MTD; 4.8mg/m<sup>2</sup>/day
- DLT; Renal tubular necrosis and increased serum creatinine at 6.0mg/m<sup>2</sup>/day

## ■ Safety;

- Stomatitis, arthralgias, and fever were predominant toxicities at MTD but not severe

## ■ Efficacy;

- Impressive evidence of antitumor activity:
  - 3 partial responses in NHL
  - 2 PSA responses in docetaxel refractory HRPC
  - 1 minor response in NSCLC

## YM086(BIBR277) :Micardis Additional Indication



- **Generic name:** telmisartan
- **Target Indications:** Type 2 diabetic nephropathy
- **Mechanism:** Angiotensin II receptor blocker
- **Area:** Japan
- **Status:** Filed (June 30, 2006)
- **Origin:** Boehringer Ingelheim  
(development code: BIBR277)

# P-III(INNOVATION STUDY) - Study Outline -

- **Purpose:** To evaluate the effects of telmisartan on the progression of renal diseases from incipient nephropathy to overt nephropathy in type 2 diabetic patients
- **Primary Endpoints:** Time from baseline visit to first detection of overt nephropathy
- **Secondary Endpoints:** Urine albumin to creatinine ratio, Rate of progression of renal disease from incipient nephropathy to overt nephropathy, Restoration of normoalbuminuria, etc
- **Subjects:** 527 (hypertensive or normotensive Japanese patients with type 2 diabetes mellitus.)
- **Study design:** Randomized, double-blind, placebo-controlled trial  
527 patients were randomized to three groups (placebo, telmisartan 40mg or telmisartan 80mg)

**\* Study results are to be presented by the end of 2006**

# Overview of Anti-Human Osteopontin Antibody



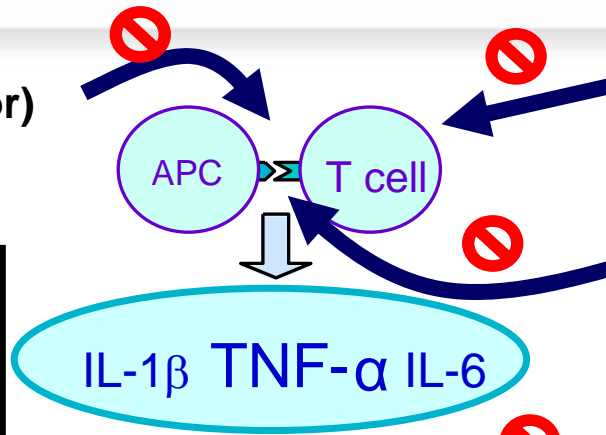
- **Agent:** Humanized anti-human osteopontin monoclonal antibody
- **Mechanism:** Neutralization of osteopontin
- **Formulation:** IV solution
- **Target indications:** Rheumatoid arthritis (RA)
- **Status:** P-I (preparation in Europe)
- **Origin:** In-license from Immuno-Biological Laboratories  
Co-development with Chemo-Sero Therapeutic Research Institute
- **Target profile:**
  - New mechanism of action (first in the class) for RA treatment
  - Superior efficacy and safety to other biological agents (e.g. TNF $\alpha$ -blocker), and other golden standard DMARDs (e.g. MTX, SSZ)

# Anti-Human Osteopontin Antibody: Mechanism of Action

- **CTLA4-Ig (T cell inhibitor)**

- abatacept (Orencia)

Unlike other agents working through systemic immunosuppressive effect, anti-OPN antibody inhibits OPN actively involved in inflammatory and bone destructive change within diseased joints.



- **Nucleic acid metabolism antagonist**

- methotrexate
  - leflunomide

- **Calcineurin inhibitor**

- tacrolimus (Prograph)
  - cyclosporin

- **TNF $\alpha$ -Blocker**

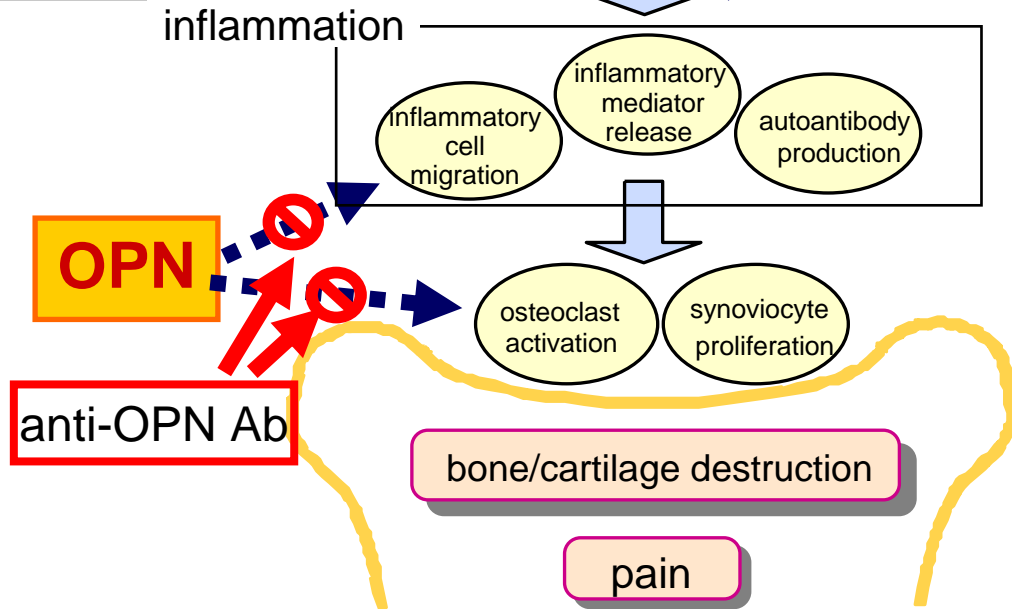
- infliximab (Remicade)
  - etanercept (Enbrel)
  - adalimumab (Humira)

- **IL-1 receptor antagonist**

- anakinra (Kineret)

- **IL-6 receptor antagonist**

- tocilizumab/MRA (Actemra)



**“Risk of Infection”**

due to systemic immunosuppression