SHIONOGI & CO., LTD.

Research and Development at Shionogi

S-O-N-G
for you!

March 22, 2007 13:00-15:00

At Tokyo Branch Office




Speakers

Overview: **Isao Teshirogi, Ph.D.**
Director of the Board; Senior Executive Officer
Executive General Manager
Pharmaceutical Research & Development Division

Research: **Hirosato Kondo, Ph.D.**
Corporate Officer
General Manager, Discovery Research Laboratories

Development: **Takuko Sawada**
General Manager
Strategic Development Department




Realization of the 2nd Medium-Term Business Plan and sustainable growth

Achieving growth by continuously launching new products

Shionogi's R&D is committed to

- **Securing the continuous discovery of drug seeds**
- **Enhancing R&D productivity in stages from Drug Candidate Selection (DCS) to Proof of Concept (POC)**
- **Accelerating clinical development in Japan, the USA and EU**




Progress toward the goals of the 2nd Medium-Term Business Plan (1)

- **Enrich the product line for infectious diseases and add pain and metabolic syndrome to new target areas**

Infectious diseases:	**Expanded scope to include antiviral agents, etc. while concentrating on antibacterial infectious diseases**
Pain:	**Made progress in the development of novel pain treatment**
Metabolic syndrome:	**Developed S-2367 as a global strategic product**
Frontier areas:	**Progressed steadily in selected R&D programs**

- **Advance at least 5 new chemicals entities to Phase II or more advanced stages by the end of FY 2009 to introduce blockbuster to succeed Crestor®**

S-2367 (Anti-obesity: in Phase II)

S-364735 (Anti-HIV: in Phase II)

S-777469 (Antipruritic treatment: in Phase I)

Promote continuous global development for multiple products




Progress toward the goals of the 2nd Medium-Term Business Plan (2)

- **Establish the pipeline stream through active licensing activities**

  Adapalene (Acne vulgaris), Peramivir (Anti-Influenza): In-licensing

- **Increase R&D efficiency and success probability by forming active alliances with outside resources**

  Enriched R&D pipeline (Purdue Pharma L.P. in the USA, Hokkaido University)
  To be out-licensed a product in an unfocused research area through an optional agreement (S-0373)
  Out-licensed phospholipase A2 program (Anthera Pharmaceuticals, Inc. in the USA)
  Joint development agreement with Eli Lilly Japan K.K. (Duloxetine; Diabetic neuropathic pain)

- **Maximize product potential through life-cycle management from early development stage**

  Addition of new formulations: OxiNorm, Finibax® kit product, Claritin® dry syrup, Cetrotide® sustained release formulation (NS75B)
  Expansion of indications: Duloxetine, NS75B, Finibax®
  Clinical trials for evidence: Crestor®, Finibax®, Imunace®




Achieving the goals set for FY2006 (1)

- **Further advancement in R&D activities**

  Visualized R&D activities

  Promoted information sharing through open-frame monitoring system for R&D progress

  Established TA conference to maximize product value through MPDR (Marketing, Production, Development, Research)

- **Research**

  Advance 3 out of 4 compounds from DCS to FTIH

  Advanced S-777469 (Antipruritic treatment) to FTIH

  Evaluating back-up compounds of broad-spectrum cephem antibiotic, pain treatment and alleviator of opioid-induced adverse effects

  Advance 4 or more compounds from late discovery stage to DCS

  Advanced 3 out of 4 compounds from DCS to FITH: Prostaglandin D2 antagonist (backup for S-5751), Molecular-targeted anti-cancer drug, Small molecule TPO mimetic

FTIH: First trial in human




Achieving the goals set for FY2006 (2)

- **Development**

Launch 4 products

Launched: Cetrotide®, OxiNorm, Finibax® kit product

To be approved in FY2007: Claritin® dry syrup

File NDAs for 2 products

Filed: Irbesartan, Pirfenidone

Move Phase II products to the next clinical stage

S-2367 (Anti-obesity): Demonstrated POC in the USA; Phase IIb clinical study is in progress

S-013420 (Novel macrolide antibiotic): Advanced clinical phase: Phase IIb is in progress

Duloxetine (Diabetic peripheral neuropathic pain): Advanced clinical phase; preparing for Phase IIb/III

S-5751 (Prostagrandin D2 receptor antagonist): Discontinued development Back-up compound is in progress

Other products

S-364735 (Anti-HIV): Completed phase I; Phase II is in progress

NS75B (Benign prostatic hypertrophy): Completed Phase I/II; Phase IIb is in progress




New challenges based on past achievement

- **Enrich pipeline in the targeted therapeutic areas**
- **Advance stages from DCS to FTIH in timely and solid manner**
- **Develop human resources for global development**




Main targets for the period from FY2007 to FY2009

- **Secure continuous source for drug seeds through alliances**
- **Rapidly set up simultaneous development system in Japan, the USA and EU for accelerated new drug development**
- **Concentrate resources on the targeted therapeutic areas and achieve the highest R&D productivity in the pharmaceutical industry while accelerating the speed of development for in-house drug candidates from DCS to POC**

Challenge the objectives in a flexible, systematic and efficient manner, develop world-class human resources; and generate high R&D productivity




R&D Organization (Effective April 1, 2007)

Pharmaceutical Research Division

- Discovery Research Laboratories
- Developmental Research Laboratories
- Intellectual Property

Secure drug seeds continuously

Pharmaceutical Development Division

- Strategic Development
- Clinical Research
- Biostatistics

Develop in-house drug candidates globally




Desired R&D image for the end of FY2009

Aggressive R&D approach with spirit of venture companies

- mobility, planning & commitment -

Research

Continuously discover globally competitive drugs

Ensure FTIH for 2 or more new in-house drug candidates each year

Development

Simultaneously develop multiple in-house products in Japan, the USA and EU

Secure either one to two Phase IIb and one Phase III products or three Phase IIb products




Targeted milestones for FY2007

Research

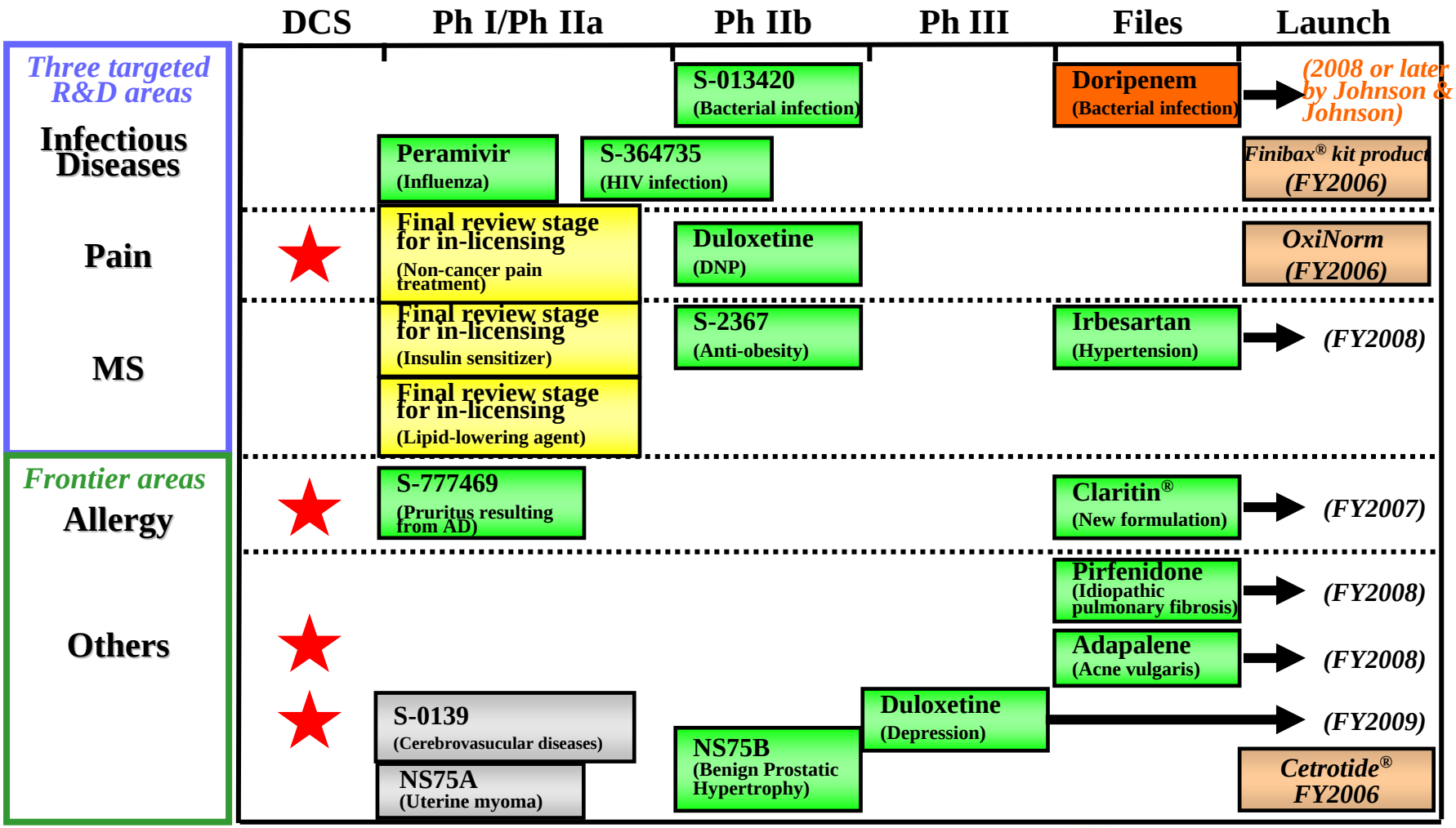
- **Advance 2 compounds currently in DCS to FTIH**
- **Advance 4 or more compounds in late discovery stage to DCS**
- **Strengthen the discovery research for drug "seeds"**
  - Hold 'Pharma-Innovation Discovery Competition Shionogi' to collect ideas from the public
  - Build a collaborative research facility in Hokkaido University campus
- **Promote global research alliances on the targeted 3 research areas**

Development

- **Launch Claritin® dry syrup**
- **File an NDA for Duloxetine (Depression)**
- **Respond properly to NDA review for Irbesartan and Pirfenidone**
- **Promote global development for compounds in late development stage**
  - **S-2367** → Conduct interim analysis for Phase IIb study
  - **S-777469** → Initiate POC study simultaneously both in Japan and the USA (Pruritus resulting from atopic dermatitis)
  - **S-013420** → Make a 'go/no-go' decision to enter Phase III study (Domestic)




Development status and launch schedule for new drugs (As of March 2007)



DNP: Diabetic Neuropathic Pain, AD: Atopic Dermatitis

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Research Division




Research goals for the 2nd Medium-term Business Plan

Three Targeted Areas

Infectious Diseases	*Metabolic Syndrome*	*Pain*

Frontier Area (Allergy and respiratory diseases, etc.)

1. Enrich product line for infectious diseases and add pain and metabolic syndrome to new target areas
2. Move at least 5 new chemical entities to Phase II or more advanced stages by the end of FY2009
3. Establish an unbroken pipeline stream through strategic development of licensing activity
4. Increase the R&D efficiency and success rate by forming active alliances with outside resources
5. Maximize product potential through life cycle management from an early development stage




Desired R&D image for the end of FY2009

Continuously discover globally competitive drugs

Ensure FTIH for 2 or more in-house new drug candidates each year

Achieve the highest R&D productivity in the pharmaceutical industry

- ➔ **through agile footwork**
- ➔ **by developing outstanding drug discovery technologies**




To realize the desired R&D image

Research framework at Shionogi

- Plan cross-divisional strategy by MPDR and provide feedback to each division
- Develop and in-license frontier key technologies
- Discover novel and original drug “seeds”
- Enrich back-up/contingency plan
- Utilize strategic alliances

Keep framework functioning efficiently = Realize high productivity

For the efficiency of the framework, organize mechanisms to harmonize each function and promote drug discovery




Mechanisms to promote drug discovery

- **Portfolio Management of Research Program**
  - **Promote program selection and focusing to enhance success probability**
  - **Keep a balance BIC with FIC while producing novel drugs continuously as well as innovative drugs**
- **Resource allocation**
  - **Optimize resources timely and flexibly including optimization for strategic outsourcing**
- **Develop human resources**
  - **Develop future leaders by promoting young researchers**
  - **Develop world-class human resources**

FIC: First in class, BIC: Best in class




Achievement in FY2006

- **Advanced 1 out of 4 compounds from DCS to FTIH**
  - **Advanced S-777469 (Antipruritic treatment) to FTIH**
  - **For the remaining 3 DCS compounds in infection and pain areas, evaluations of back-up compounds are under way**
- **Selected 3 new compounds to DCS**
  - **Prostaglandin D2 inhibitor (back-up of S-5751)**
  - **Molecular targeted anti-cancer drug**
  - **Small molecule TPO mimetic**
- **Agreed to establish collaborative research institute with Hokkaido University**




Milestone targets and measures for FY2007

- **Ensure FTIH for 2 compounds and DCS for 4 compounds**
  - **Promote further program selection and focusing**
  - **Expand capabilities to predict compound risk accurately at earlier stage**
- **Strengthen the discovery research for drug "seeds"**
  - **Hold 'Pharma-Innovation Discovery Competition Shionogi' to collect ideas from the public**
  - **Build a collaborative research facility in Hokkaido University campus**
- **Promote global research alliances on the targeted 3 research areas**



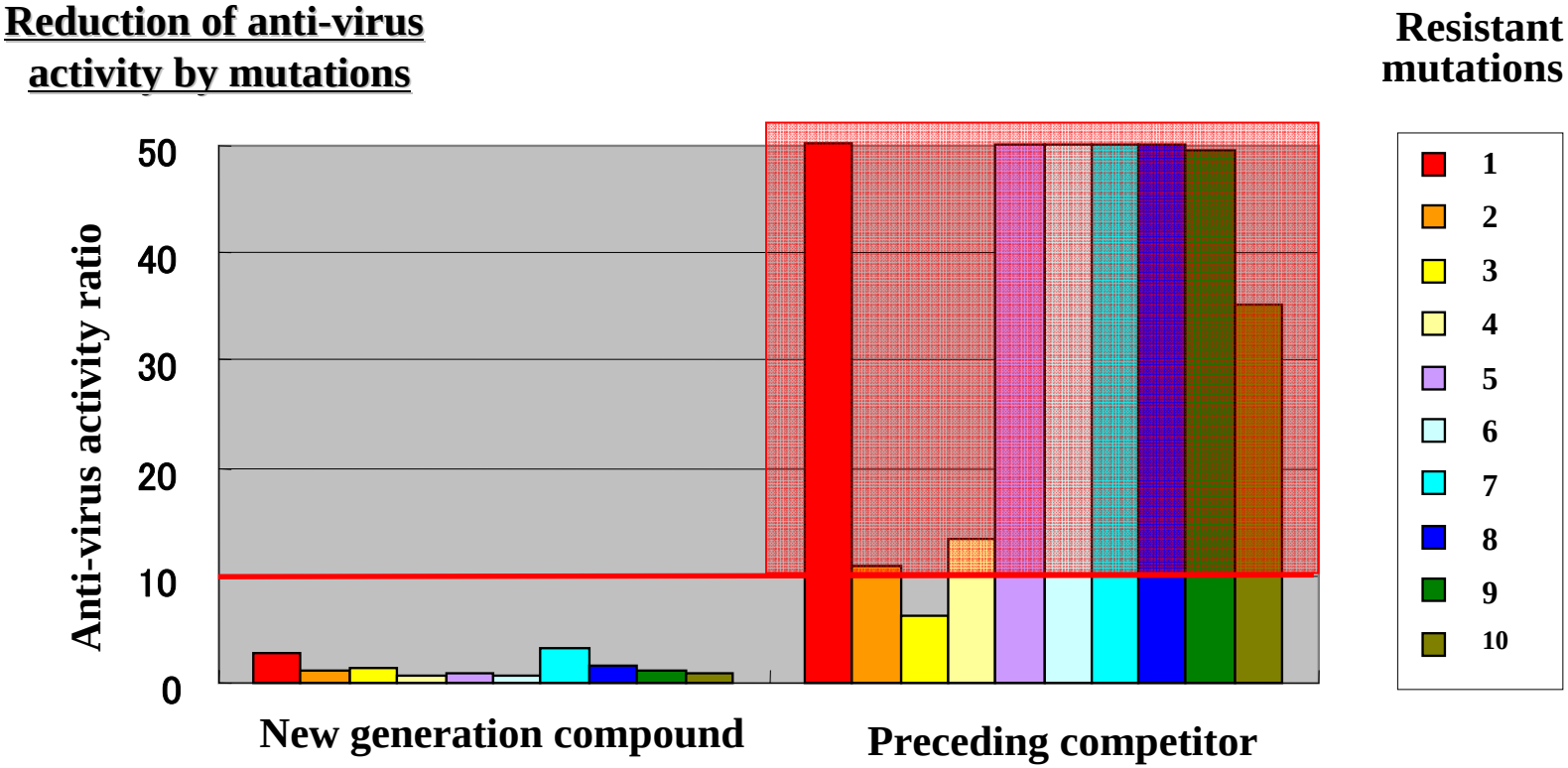

Topics in Research Division during FY2006

- **Profile of drug candidates**
- **Other topics**




Infectious Diseases area: New generation of HIV integrase inhibitors next to S-364735

Efficacy against highly resistant viruses for the preceding competitor



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Infectious Diseases area: Strengthen drug discovery research for influenza virus

Focus on anti-influenza and anti-HIV research as two main pillars

- **In-licensing of Peramivir**
  - **Neuraminidase inhibitor**
  - **Shows strong efficacy against pathogenic H5N1 virus (including avian flu) as well as seasonal influenza virus (both type A and type B)**
  - **Applicable not only against community acquired influenza infection but also against serious influenza infection requiring hospitalization**
- **Initiated drug discovery research for new generation compound**

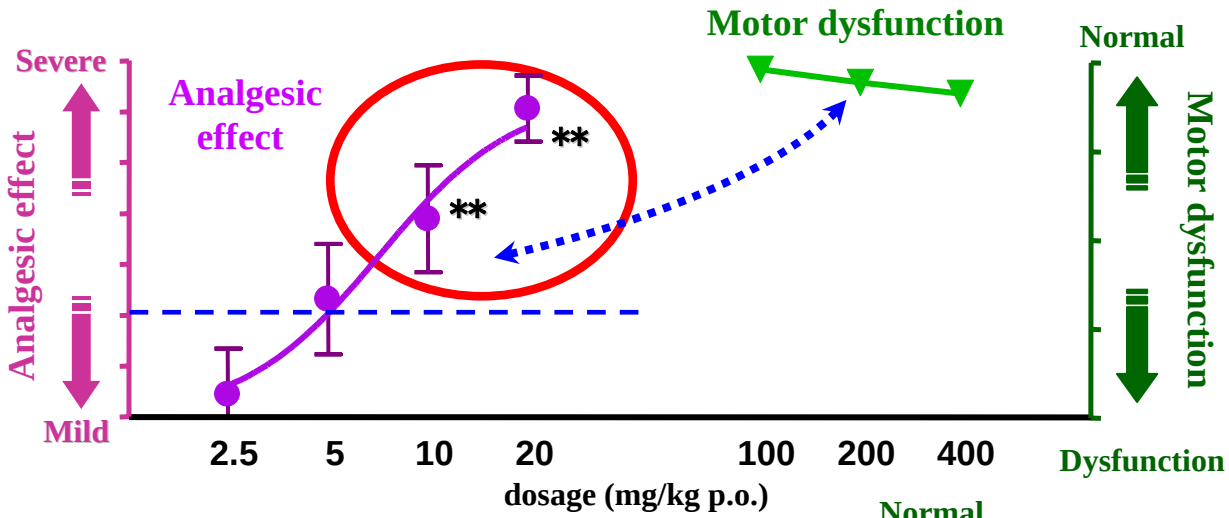



Pain area: Novel anti-neuropathic pain compound with alleviated side effect profile

Analgesic effect and motor dysfunction in neuropathic pain model

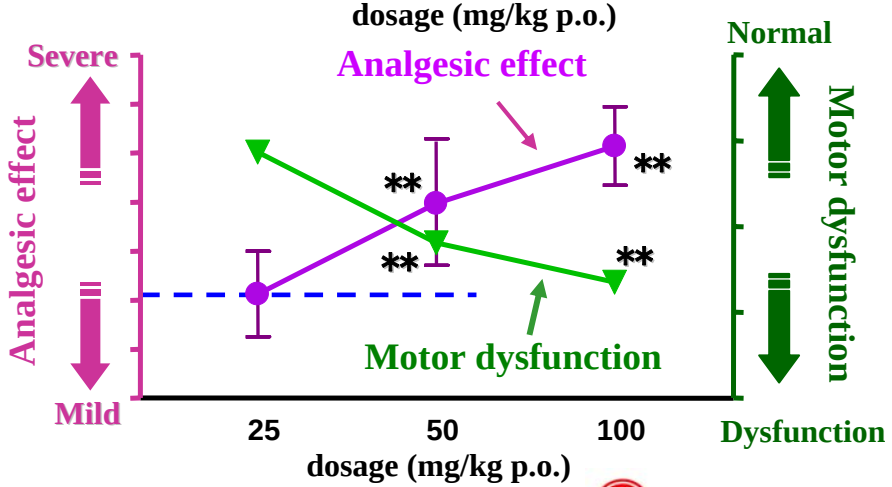
Compound X

No observation of motor dysfunction with wide dosage range



Gabapentine

First-line therapy:
Observation of motor dysfunction in the effective dosage range



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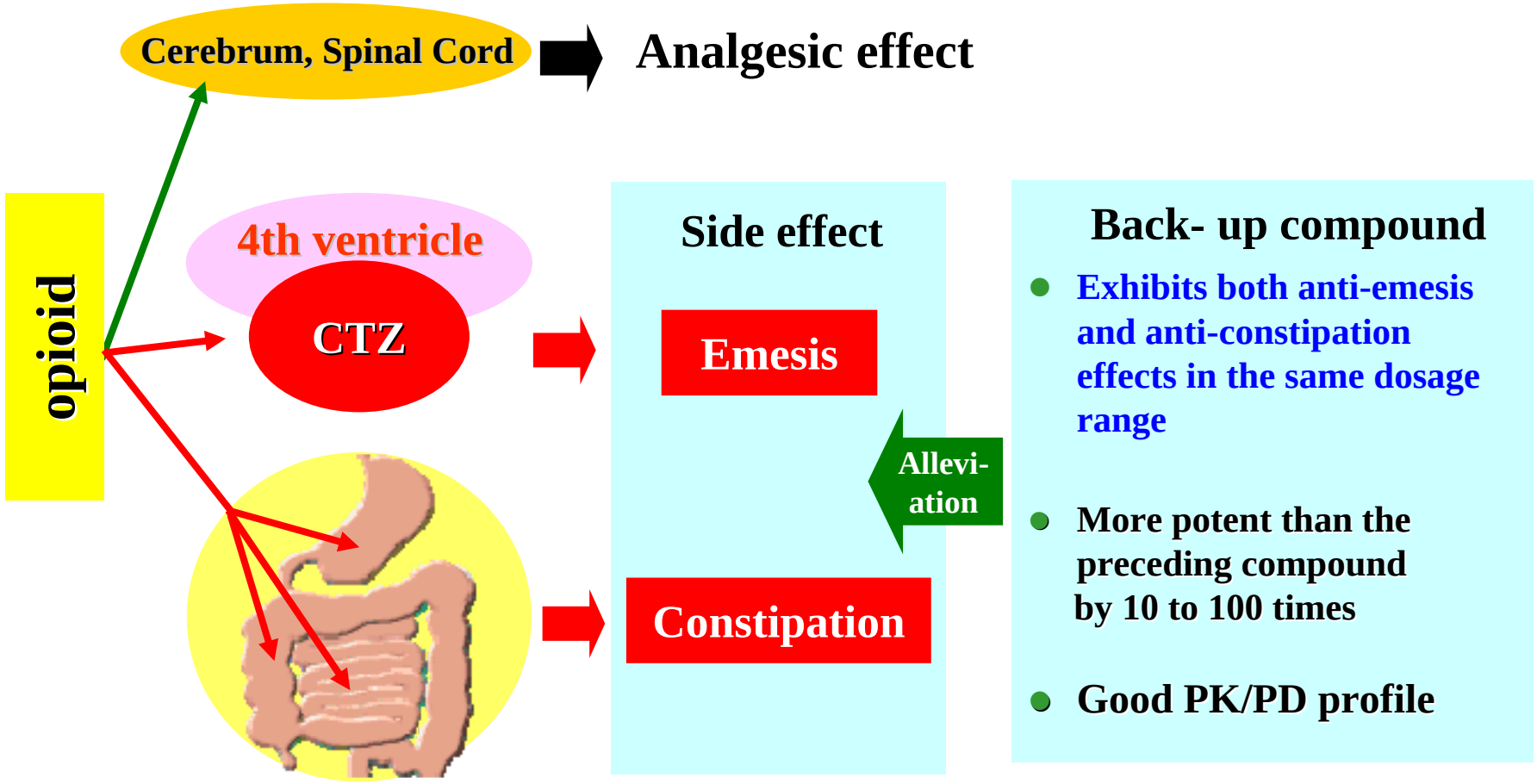
Pain area: Alleviator of opioid-induced adverse effects



CTZ: Chemoreceptor trigger zone




MS area: Post Crestor® Strategy

Pipeline for prevention/treatment of cardiovascular events

Diabetic

- Products
  - Dimelin®

Research program/In-licensing under review
Insulin sensitizer

Obesity

- Under development
  - S-2367

Research program
S-2367 follow up

Metabolic Syndrome

Hypertension

- Products
  - Fluitran®
  - Longes®
  - Landel®
- Under development
  - Irbesartan

Lipid disorder

- Shionogi products
  - Crestor®

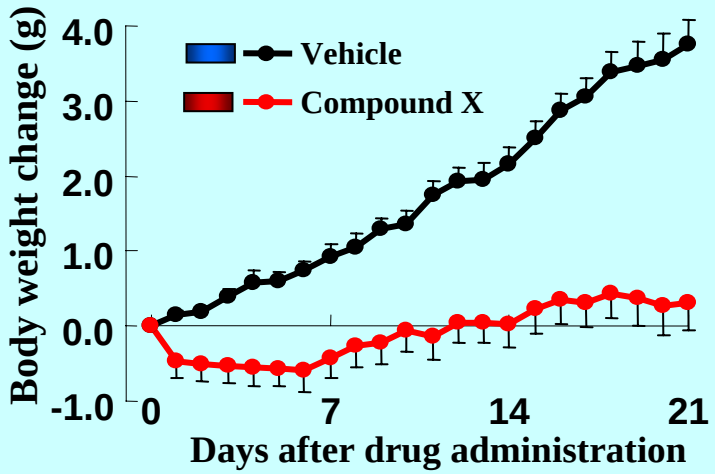
Research program/In-licensing under review
Drugs for HDL-C elevation
Drugs for LDL-C reduction

Arteriosclerosis Diseases
Diabetic Complication

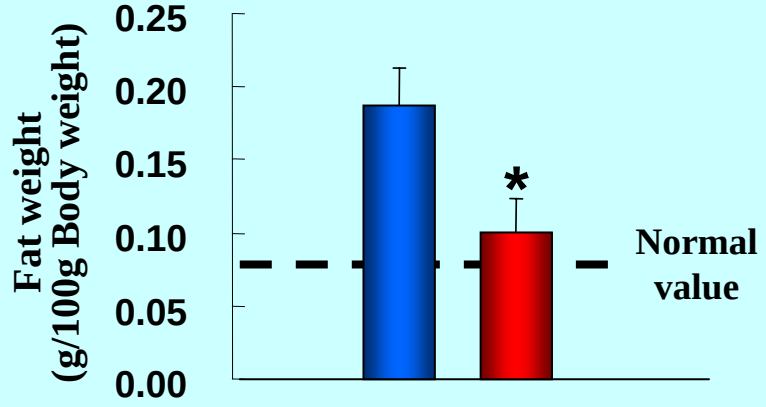



MS area: Drug discovery for novel anti-diabetic compound with weight-reducing potency

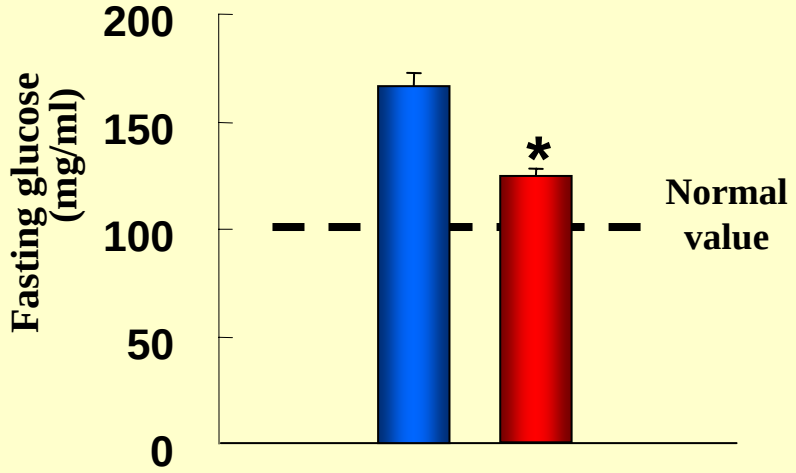
Inhibitory effect on body weight increase

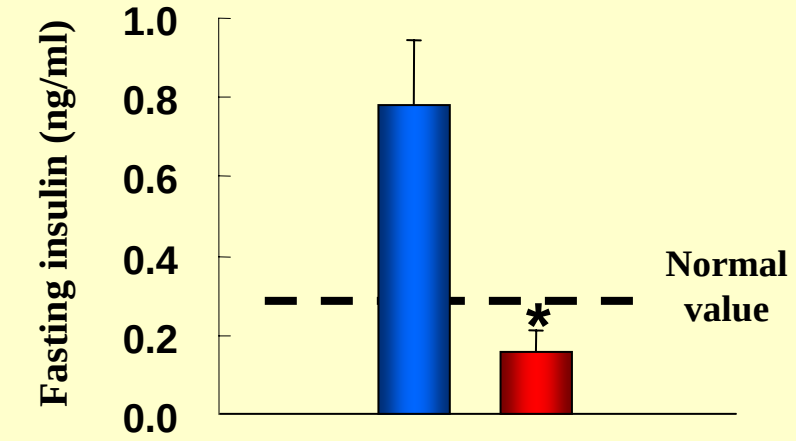


Mesenteric adipose mass



Fasting glucose & insulin level





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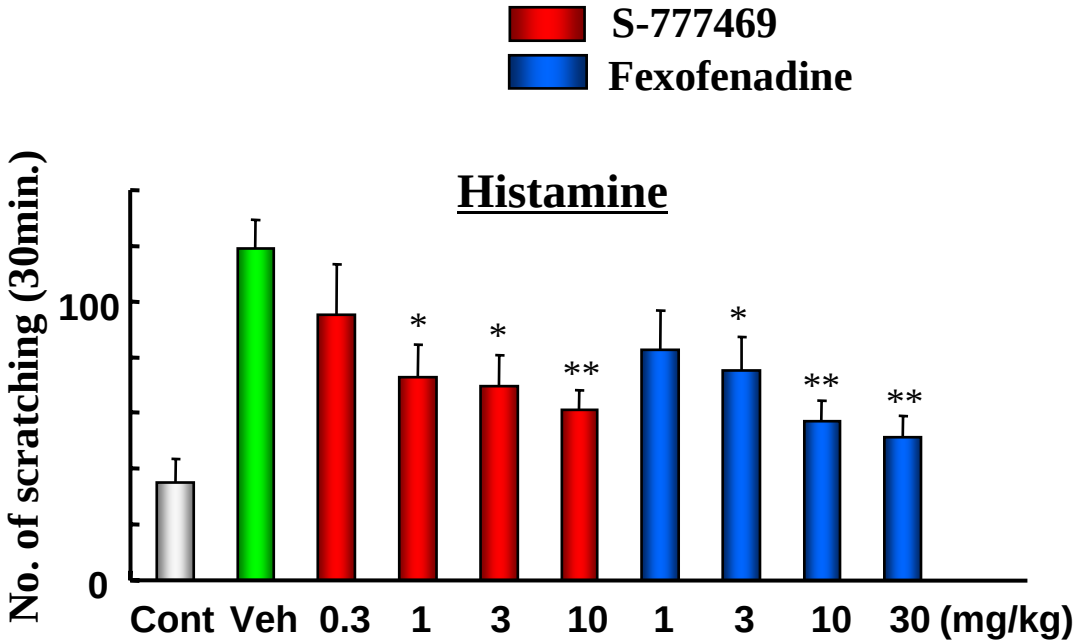
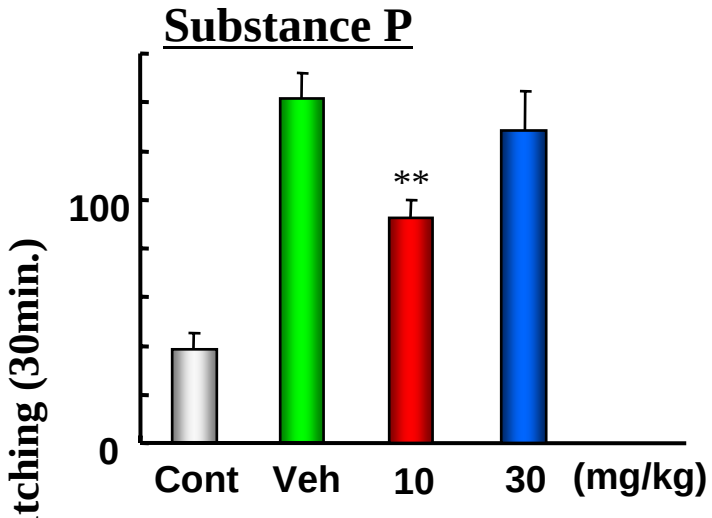
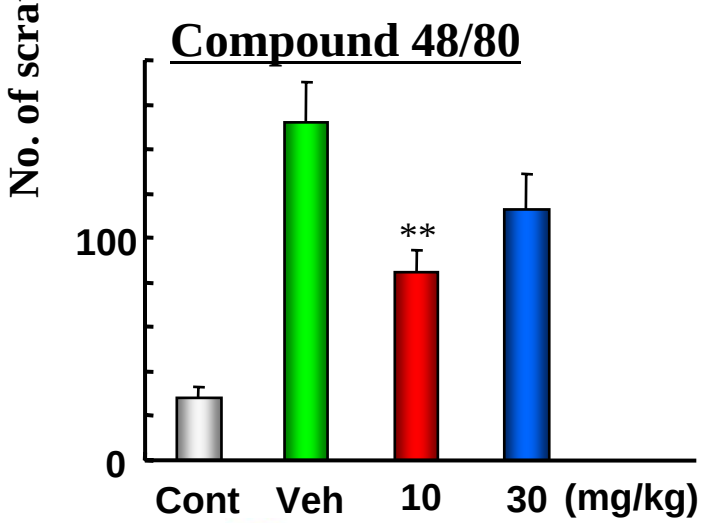
Frontier area: Pharmacological effects of S-777469 (1)

Orally active anti-pruritic drug with anti-inflammatory action via new mechanism of action

Anti-pruritic effect







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Frontier area: Pharmacological effects of S-777469 (2)

Anti-inflammatory effect

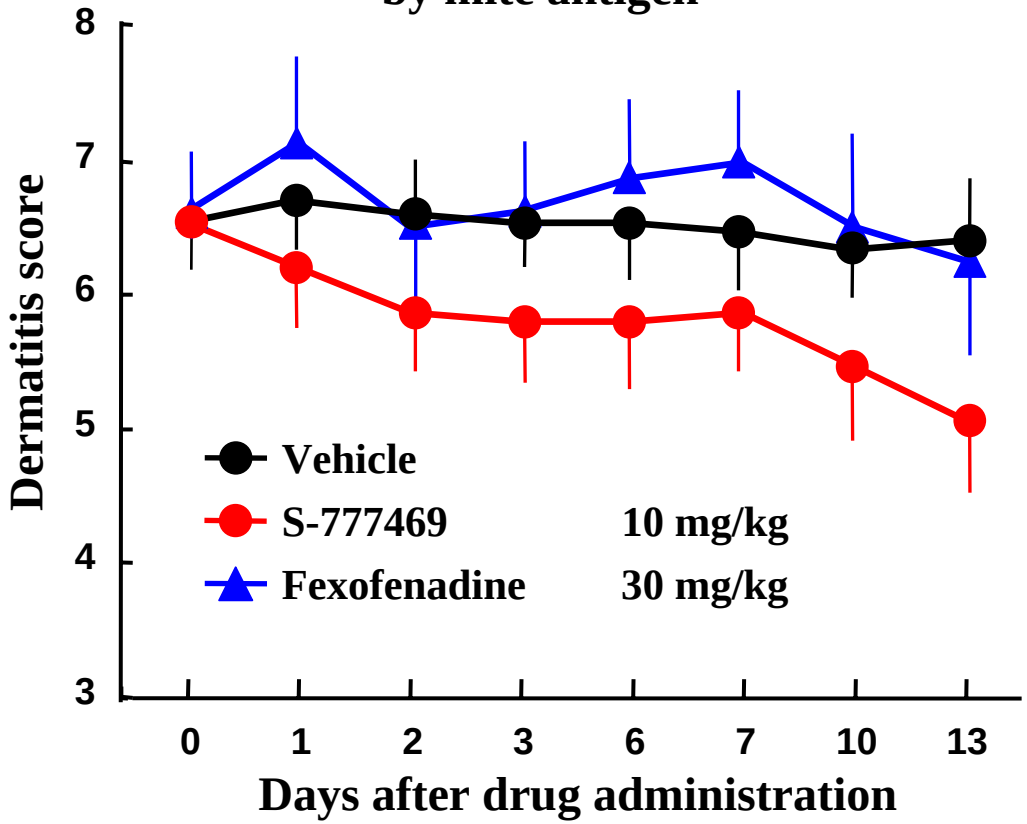
- **Dermatitis score:**
  Sum of severity in each item

- **Erythema/ hemorrharge**
- **Scarring/dryness**
- **Edema**
- **Excoriation/ erosion**

0: n.d.
1: mild
2: moderate
3: severe

n.d.: not detectable

Atopic dermatitis model induced by mite antigen



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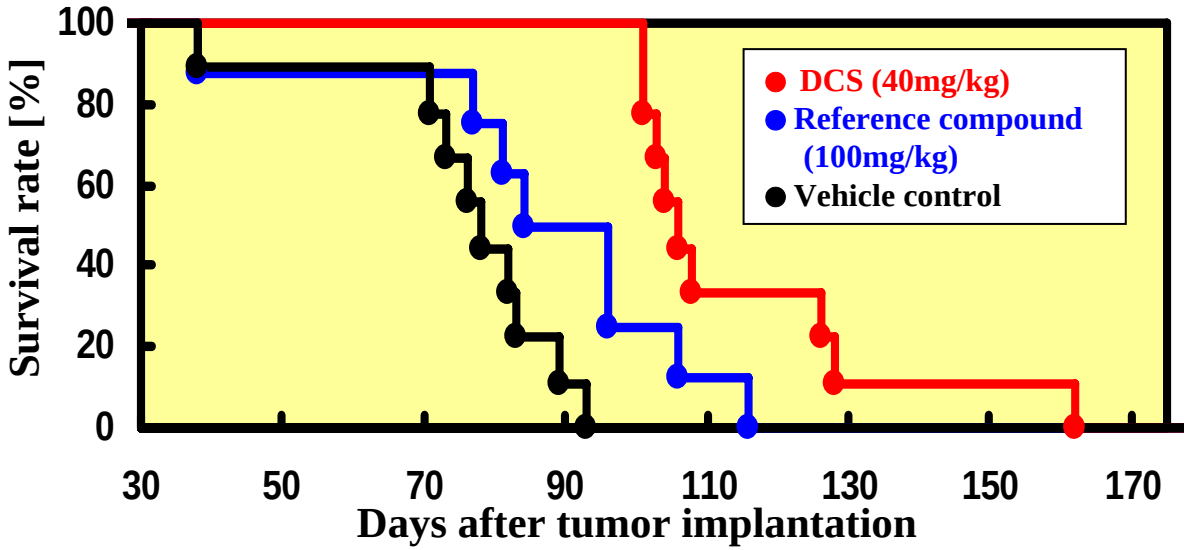
Frontier area: Molecular-targeted anti-cancer drug

Life prolongation effect in human tumor-bearing mouse



- Human cancer cells were implanted in the immuno-deficient mouse
- Drugs were orally administrated once daily (35 days ~)

Compound	Average survival days	Increased survival time [%]
Vehicle control	76	-
Reference compound (100 mg/kg)	87	14
DCS (40 mg/kg)	115*	52

** P<0.05 vs reference compound, Logrank test*

DCS potently prolonged survival time at the lower dose compared with reference compound

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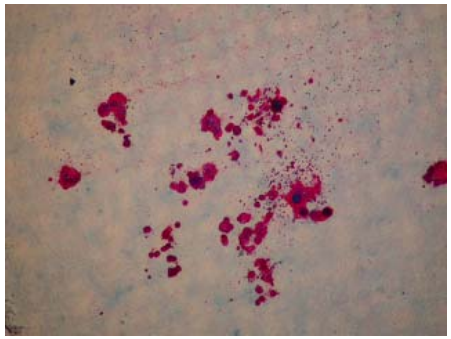
Frontier Area: Small molecule TPO mimetic

CFU-MK assay using human bone marrow-derived CD 34 positive cell

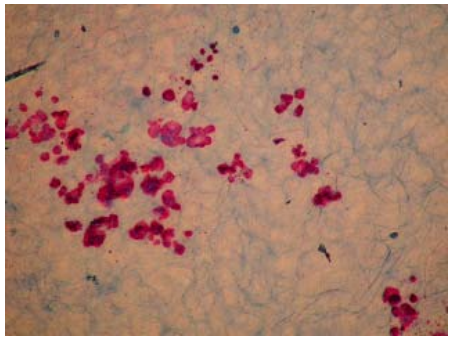
After culture for 12 days in the presence of drugs, megakayrocyte was stained with CD41 antibody

DCS compound induced differentiation/proliferation of hematoietic stem cell into megakaryocyte similar to hTPO

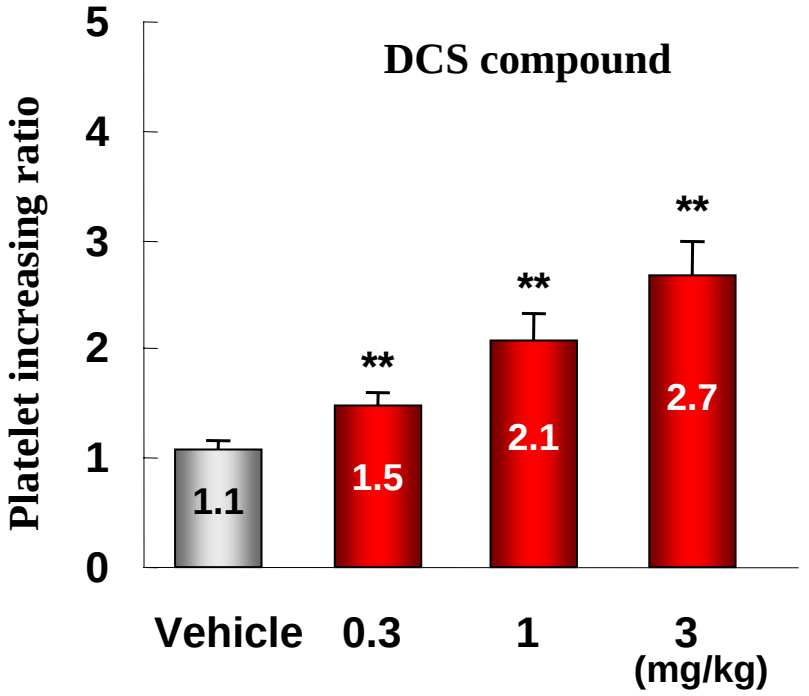
hTPO



DCS compound



Effective at 0.3mg/kg and more in *in-vivo* animal model



CFU-MK: Colony-forming units megakaryocyte

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Establish "Shionogi Innovation Center for Drug Discovery"

- ***The first research institute of a private company built in the Japanese national university campus***
- ***Accelerate drug discovery through the extensive alliance with Hokkaido University***

- **Research plan**
  - **Drug discovery research for biomedicine based on glycoengineering**
  - **Discovery research for novel drug "seeds"**
  - **Development of key technologies**
- **Action Plan**
  - **FY2007**
    - **Construction of facility**
    - **Start collaboration**
  - **FY2008**
    - **Start full-scale research**

Rendering of Research Facility

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Milestones of Research Division for FY2007

- **Ensure FTIH for 2 compounds and DCS for 4 compounds**
- **Strengthen the discovery research for drug “seeds”**
- **Promote globally collaborative research on the targeted 3 research areas**

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Development Division




Clinical Development

- **Realization of the 2nd medium-term business plan**
  - Targeted Development Division goals for the 2nd medium-term business plan
  - Desired image at the end of FY2009
  - Achievement of FY2006 goals
  - Main targets for the period from FY2007 to FY2009
  - Targeted milestones and measures for FY2007




Targeted Development Division goals for the 2nd Medium-term Business Plan

Three Targeted Areas

Infectious Diseases

Metabolic Syndrome

Pain

Frontier Area (Allergy and respiratory diseases, etc.)

1. **Enrich product line for infectious diseases and add pain and metabolic syndrome to new target areas**
2. **Move at least 5 new chemical entities to Phase II or more advanced stages by the end of FY2009**
3. **Establish an unbroken pipeline stream through strategic development of licensing activity**
4. **Increase the R&D efficiency and success rate by forming active alliances with outside resources**
5. **Maximize product potential through life cycle management from an early development stage**




Desired image for the end of FY2009

Simultaneously develop multiple in-house products in Japan, the USA and EU

Secure either one to two Phase IIb and one Phase III products or three Phase IIb products

- **In a position to establish the development base and start operation in EU in addition to the USA**
- **In a position to enable to file NDAs both in the USA and EU by ourselves or through alliances with business partner**




Achievement of FY2006 goals (1)

Achievement:

1. **Launched 3 products which were under NDA review (Cetrotide®, Finibax® kit product, OxiNorm)**
2. **Filed NDAs for Irbesartan and Pirfenidone**
3. **Made a 'go/no-go' decision for 4 products in Phase II (S-013420, Duloxetine; Diabetic peripheral neuropathic pain, S-2367, S-5751)**

Claritin® dry syrup: pending the progress of NDA review by authority




Achievement of FY2006 goals (2)

Since April 2006

- **Finibax® kit product NDA filed → Launched**
- **OxiNorm NDA filed → Launched**
- **Cetrotide® NDA filed → Launched → Post-marketing clinical study is in progress**
- **Irbesartan Phase III → NDA filed**
- **Pirfenidone Phase III → NDA filed**
- **Duloxetine Phase IIa → In preparation for Phase IIb/III**
  (Diabetic peripheral neuropathic pain)
- **S-013420 Phase IIa → Phase IIb**
- **S-2367 Phase IIa → Phase IIb**
- **NS75B Phase I/II → Phase IIb**
- **S-364735 * Phase I → Phase II**
- **S-777469 Pre-clinical → Phase I**

Advanced almost all the products to next phases

* *Shionogi -GSK (JV) Product*




Achievement of FY2006 goals (3)

- **Promoted further selection on development compounds and positively out-licensed compounds in unfocused areas**

  S-5920 (Acute chest syndrome in sickle cell disease)

  S-3013 (Arteriosclerosis)

  S-0373 (Spinocerebellar ataxia, Parkinson's disease)

  S-0139 (Cerebrovascular diseases)

- **In-licensed targeted area products**

  Peramivir (Influenza)

  LDL-C reducer

  Insulin sensitizer treatment

  Non-cancer pain treatment




Achievement of FY2006 goals (4)

- **Development of new formulations for approved products**

  Finibax® kit product, OxiNorm, Claritin® dry syrup,

  Cetrotide® sustained release formulation (NS75B)

- **Post-Marketing clinical studies: → Studies are in progress**

  Crestor® - Prevention of plaque extension in coronary arteries (IVUS study)

  Finibax® - Establish 3 times/day administration based on PK/PD theory

  Imunace® - Pharmacogenomics test with renal cell carcinoma

- **Additional indications:**

  Duloxetine - Diabetic neuropathic pain (In preparation for Phase III)

  NS75B (Cetrorelix pamoate) - Benign Prostatic Hypertrophy (Phase IIb is in progress)

  Finibax® - Pediatric use (Planning Protocol)




Main targets for the period from FY2007 to FY2009

Accumulate experience in overseas development and accelerate the speed of globalization

1. **Development of global strategic products**
   - Promote overseas activities with S-2367, S-364735 and S-777469
   - Continuously discover compounds competitive in global market to follow the above 3 products
2. **Construct a functional organization and intensify investment in R&D**
   - Streamline strategic core organization to promote simultaneous development in Japan/the USA/EU and develop human resources
   - Continuously increase investment in development
3. **Positively seek business opportunities**
   - Accelerate global development through strategic alliances




Targeted milestones and measures for FY2007

Set challenging goals and accomplish them steadily

- **NDA ~ Launch**

  Launch of Claritin® dry syrup

  Complete phase III and NDA filing for Duloxetine (Depression)

- **Go/No-Go Decisions**

  S-2367 **Conduct interim analysis for Phase IIb study**

  S-364735 **Make a go/no-go decision**

  S-777469 **Advance to Phase II and initiate development simultaneously in Japan and the USA**

  S-013420 **Make a go/no-go decision to enter Phase III study**

- **FTIH**

  3 products (2 in-house products and Peramivir)

- **Life Cycle Management**

  Finibax® **Complete post-marketing clinical study and initiate clinical study for pediatric use**




Targeted milestones and measures for FY2007

Optimize operating efficiency to enhance development capability

1. Resources

- Positively utilize outside resources in Japan and abroad
- Promote recruitment for mid-carrier specialists
- Enhance function of Shionogi USA, Inc.

2. Process and Infrastructure

- Reform and streamline the development processes to operate on a global basis
- Increase the number of products to be controlled under EDC (Electronic Data Capture) system
- Establish and operate clinical data base on a global basis
- Start electronic filing for NDA (eIND, eCTD)




Core Development Products

- **Product characteristics**
- **Indications**
- **Pre-clinical and clinical study data, etc.**




S-2367: Profile

- **Anti-obesity (Oral)**
- **Neuropeptide Y (NPY) Y5 receptor antagonist**
- **Key findings from pre-clinical studies**
  - Increased energy consumption
  - Suppressed visceral fat accumulation and improved blood glucose and serum lipid levels
  - Expected product profile without rebound
  - Confirmed excellent safety
- **Key findings from clinical studies to date**
  - Once-daily administration (T ½ : about 20 hours)
  - No serious adverse events observed
  - Achieved positive Phase IIa proof-of-concept achieved in US study

Phase IIb studies are under way in the USA




S-2367: Outline of Phase 2b Study

- Two Phase IIb Studies are under way.
  - Study 1
    - RCD (Reduced calorie diet)-lead in followed by RCD with S-2367 or placebo treatment
    - Number of patients: 750
    - Maximum dose:1600 mg
  - Study 2
    - LCD (Low calorie diet)-lead in followed by RCD with S-2367 or placebo treatment
    - Number of patients: 750
    - Maximum dose:1600 mg
- Year-long studies based on FDA Draft Guidance for “Developing Products for Weight Management”
- Interim analyses are planned 6 month later after study initiation




S-2367: Future Development

- **Phase IIb studies:**
  - **Studies 1 and 2:**
    - **Initiated patient enrollment in March for completion within 2007**
    - **Scheduled to conduct interim analysis within FY2007 (i.e. by March 2008)**
- **Other clinical studies:**
  - **Drug-drug interaction study**
    - **Successfully completed**
  - **MTD study (Maximum Tolerance Dose Study):**
    - **Smoothly ongoing and to be completed in 2Q 2007**

USA NDA scheduled for within FY2010




S-364735: Profile

- **Developed by Shionogi-GlaxoSmithKline Pharmaceuticals, LLC**
- **Integrase inhibitor (Oral)**
  (Novel anti-HIV drug with a different mechanism of action from existing drugs)
- **Strong anti-HIV activity in inhibiting virus replication (at 1nM level) *in vitro***
- **Resistant mutation slow to emerge**
- **Good pharmacokinetics profile**
- **Low risk of drug-drug interactions**
- **Confirmed no severe clinical adverse events in the studies**

Phase II study is under way in the USA



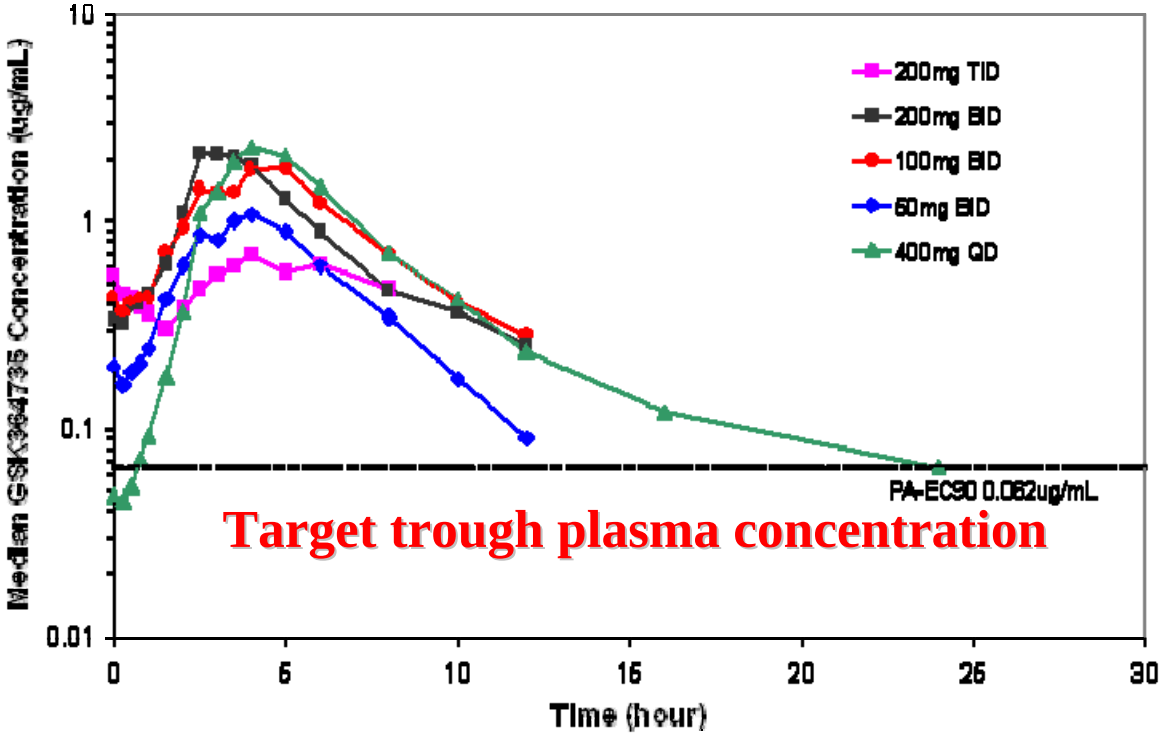

S-364735: Summary of Phase I and Outline of Phase II Study

- **Summary of Phase I study**
  - **Pharmacokinetics:**
    - **Plasma concentration exceeded the targeted treatment trough value**
    - **No drug inhibition/induction against metabolic enzyme**
    - **Food effect was observed for plasma concentration**
  - **Safety:**
    - **Confirmed safety, good tolerability and no severe adverse events**
- **Outline of Phase II study**
  - **Design of study:**
    - **Assess efficacy, safety, tolerability and pharmacokinetics by monotherapy for 10 days**




S-364735: PK data of multiple dose study (Median)

Target trough plasma concentration (Cmin), 62 ng/mL, for S-364735 was calculated from *in vitro* anti-HIV activity to achieve enough anti-viral activity in humans



Exceeded target trough value by administration of over 50mg BID

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S-777469: Profile

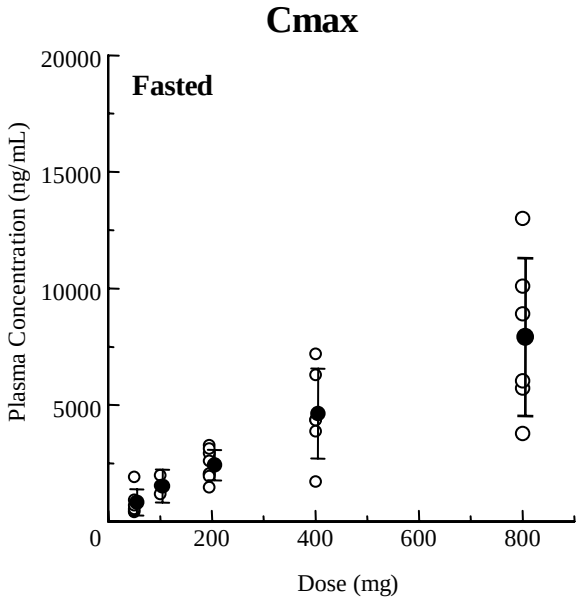
- **Target Indication: Atopic dermatitis**
- **Orally active drugs with anti-pruritic anti-inflammatory efficacy based on novel mechanism of action**
- **Inhibits scratching behavior induced by various pruritogenic agents in mouse model**
- **Demonstrated anti-inflammatory efficacy in chronic mouse model**
- **Good safety profile in GLP tox studies**
- **Phase I multiple dose study to be initiated simultaneously in Japan and the USA in 2Q FY2007**
- **POC study to be initiated in Japan and the USA by the end of 2007**

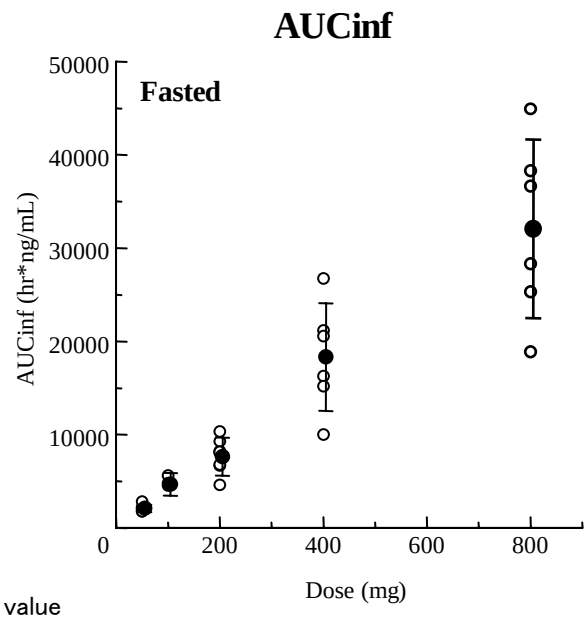
Phase I single dose study is under way




S-777469: Latest update on Japanese Phase I single dose study

- **Good tolerability**
- **Rapid elevation of blood concentration level**
- **Dose-dependent elevation of exposure up to 800 mg**





○: individual observed value
●: mean value ±standard deviation

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Pirfenidone: Profile

- **Licensed from MARNAC, INC. (USA) and KDL, Inc. (Japan)**
- **Idiopathic pulmonary fibrosis**
- **Anti-fibrosis (Oral)**
- **Designated as an orphan drug by Pharmaceuticals and Medical Devices Agency (PMDA)**
- **Completed Phase III clinical studies in November 2006**
- **With VC (vital capacity) change, significantly inhibited worsening of the condition compared with a placebo.**

NDA filed in March 2007




Pirfenidone: Design of Phase III clinical study

- **Design of the clinical trial: Double-blind placebo-controlled study**
  - **Study to compare efficacy of pirfenidone 1800mg versus placebo**
  - **Evaluated Risk/Benefit when the dose is reduced:**
    - Set Pirfenidone 1200mg (low dose) Group
  - **Target sample size: 250 patients (1800mg–100 patients: 1200mg-50 patients: placebo-100 patients)**
  - **FAS (Full analysis set):**
    - 267 patients (1800mg-108 patients: 1200mg-55patients: placebo-104patients)
  - **Significance level: 0.10 (Power 80%)**
- **Endpoints**
  - **Primary Endpoint: Change in Vital Capacity (VC)**
  - **Secondary Endpoint:**
    - **Distribution of progression-free survival**

      (definition of disease progression : death or more than 10% decrease in VC)
    - Change for lowest SpO_2 **(**arterial oxygen saturation**)** from beginning to 52nd week of administration




Pirfenidone: Results of Phase III clinical study (Efficacy: FAS)

- **Analysis of covariance for VC (Vital Capacity): 52 weeks**

Group	Number	Adjusted mean (L)	Difference with Group P(L)	2-sided p-value
Group H	104	- 0.09	0.07	0.0416
Group L	54	- 0.08	0.09	0.0394
Group P	103	- 0.16	–	–




Pirfenidone: Results of Phase III clinical study

- **Analysis of covariance for lowest SpO_2: 52 weeks**

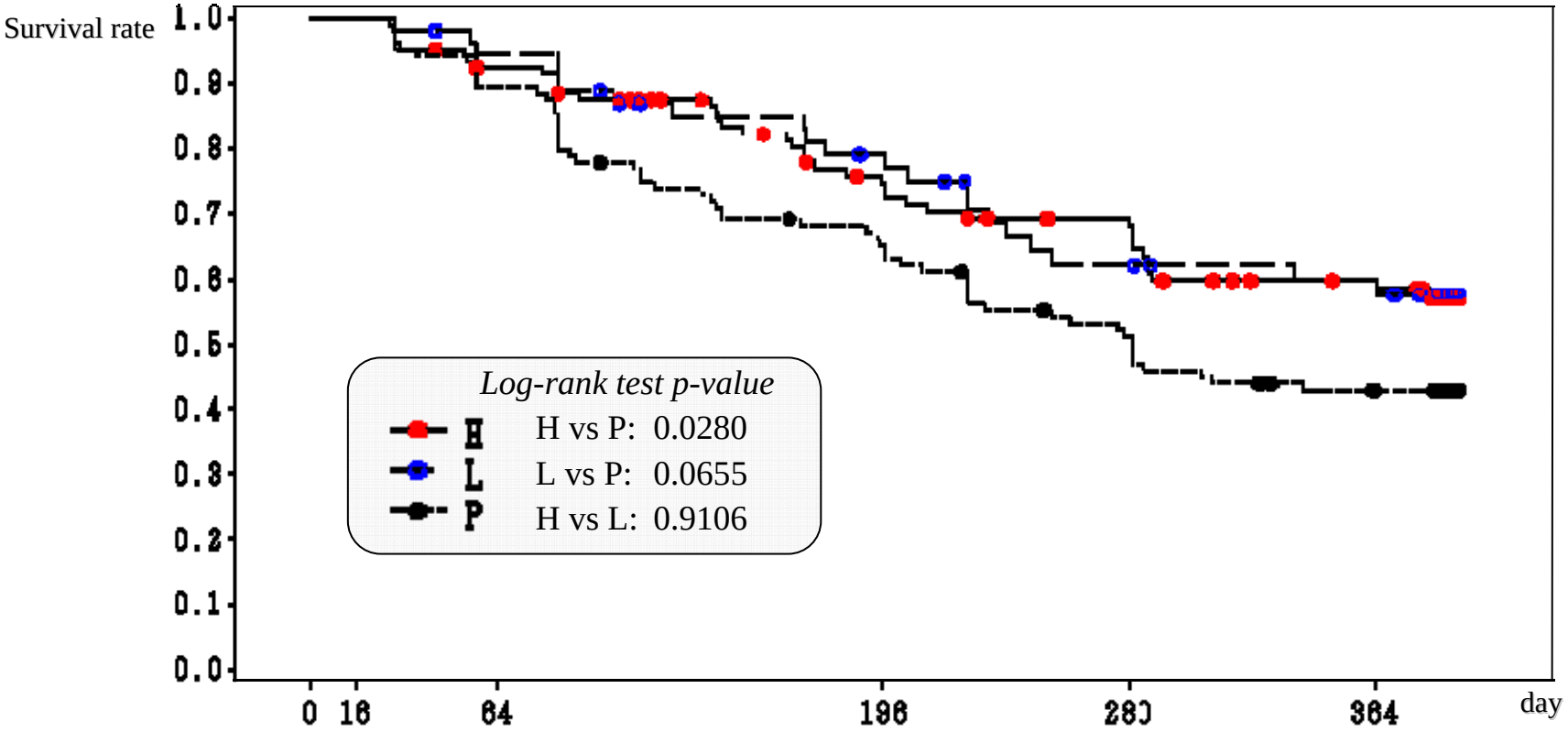
Group	Number	Adjusted mean (%)	Difference with Group P (%)	2-sided p-value
Group H	99	- 1.70	- 0.17	0.7393
Group L	53	- 0.84	0.69	0.2485
Group P	100	- 1.53	–	–




Pirfenidone: Results of Phase III clinical study

- **Distribution of progression-free survival (52 weeks)**

Definition of disease progression : death or more than 10% decrease in VC



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Peramivir: Profile

- **Licensed from BioCryst Pharmaceuticals, Inc. (the USA)**
- **Anti-influenza virus drug (neuraminidase inhibitor)**
- **Highly active against influenza A and B viruses**
  → Stronger activity against influenza B virus than Tamiflu
- **Strong activity against the highly pathogenic avian influenza virus (H5N1)**
- **Strong binding power with neuraminidase and difficult to dissociate**
  → Possibly effective even with only one administration
- **Possibly effective even if administered more than 48 hours after infection**
  (Delay Administration)
- **Broad indications from ordinary seasonal influenza to serious influenza that requires hospital care**
- **The U.S. Department of Health and Human Services (DHHS) awarded US$102.6 million to BioCryst for advanced development of Peramivir to treat seasonal and life-threatening influenza**
- **Phase II study is ongoing in USA (intramuscular injection)**

Phase I in preparation (Japan)



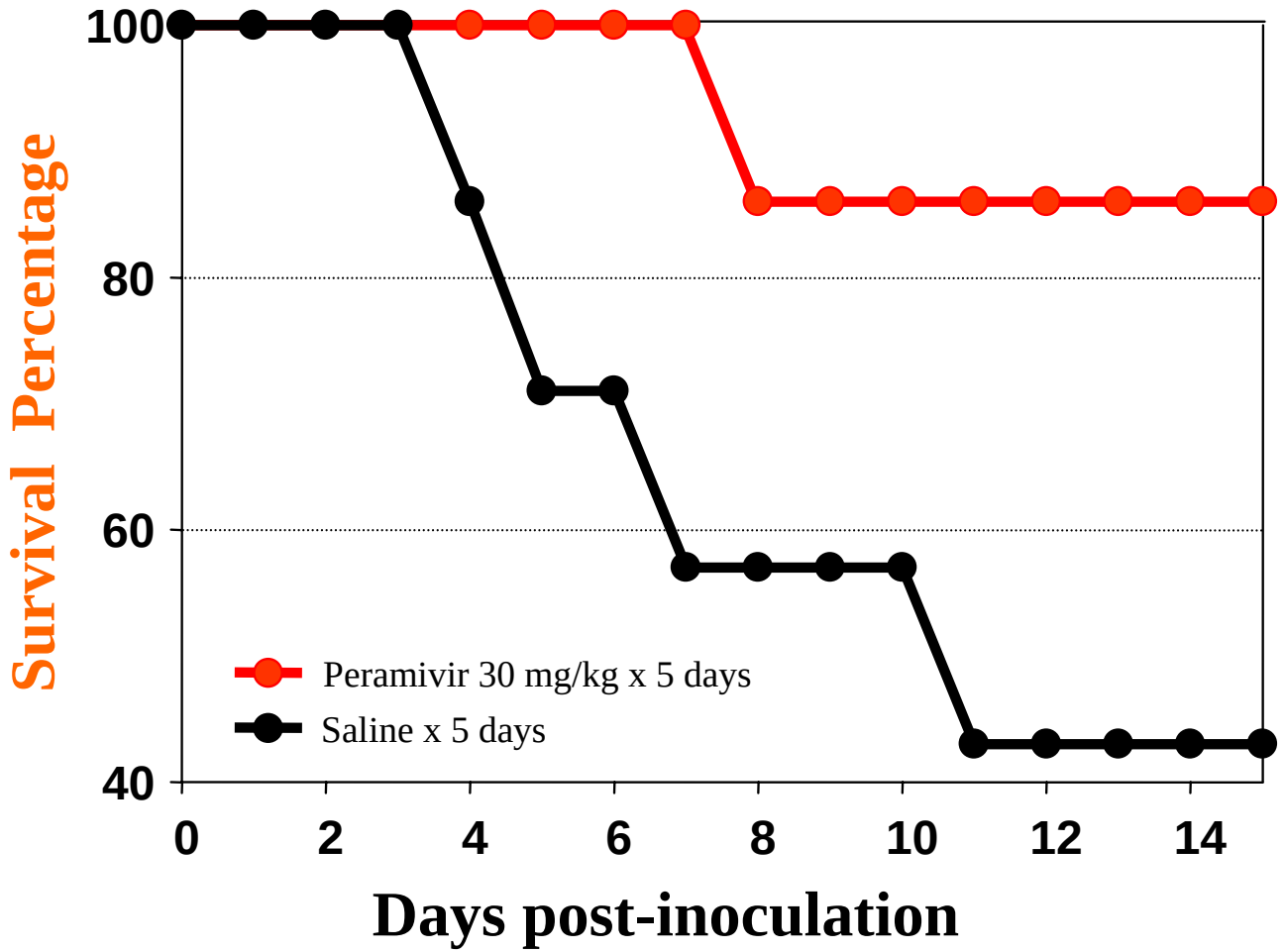

Peramivir: Anti-virus activities against influenza viruses

Virus type/ subtype	No. of Isolates	IC_{50}[nM]		
		Peramivir	(Tamiflu) Oseltamivir carboxylate	(Relenza) Zanamivir
A/H1N1	5	0.34 (0.26-0.43)	0.45 (0.45-0.60)	0.95 (0.73-1.05)
A/H3N2	6	0.60 (0.47-0.87)	0.37 (0.27-0.45)	2.34 (1.85-3.13)
B	8	1.36 (1.08-1.95)	8.50 (5.33-18.3)	2.70 (2.00-3.10)

Gubareva et al., 2001. Antimicrob. Agents Chemother. 45, 3403-3408




Peramivir: *Efficacy in a model (ferret) infected with highly pathogenic avian influenza A/Vietnam/1203/04(H5N1)*



Arnold, et al. ICAAC Poster V-2041b, (2006)

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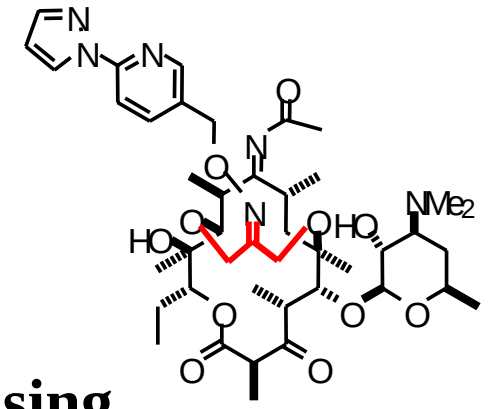
S-013420: Profile



- **Licensed from Enanta Pharmaceuticals (the USA)**
- **Novel macrolide antibiotic (Oral)**
  (Novel characteristic of bridged structure)
- **Broad spectrum enough to cover major causing bacteria causing respiratory infections**
- **Strong antibacterial activity against *S. pneumoniae* (including penicillin or macrolide resistant stains)**
- **Good PK profile**
- **Suitable for pediatric usage because of no bitterness**

Phase IIb study in progress



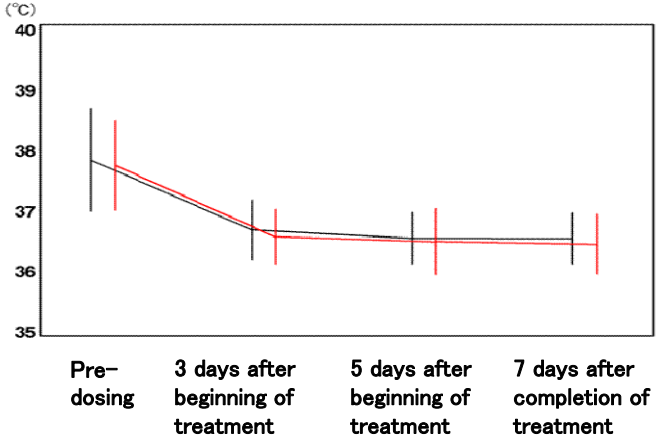

S-013420: Summary of Phase IIa Study and Outline of Phase IIb Study in Japan

- **Summary of Phase IIa study**
  - **Efficacy:**
    - **Confirmed high efficacy (clinical efficacy and bacteriological response) in a short dosing period (3 days)**
  - **Safety:**
    - **No serious adverse event; safe and well-tolerated**
    - **Transaminase elevation and digestive symptoms were major adverse events (similar to those of analog drugs)**
- **Outline of Phase IIb study**
  - **Targeted disease**
    - **Pneumonia caused by bacteria or atypical pathogen**
  - **Study design**
    - **Randomized double blinded dose finding study**
  - **Accumulate study cases to initiate Phase III study in the next winter season**



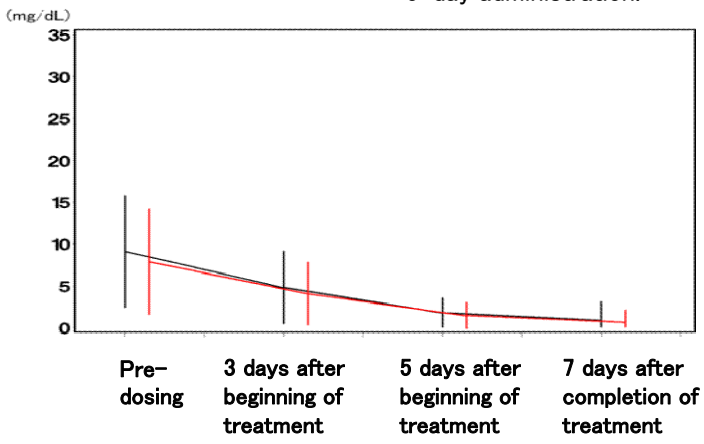

S-013420: Change of parameters for efficacy

【Body Temperature】

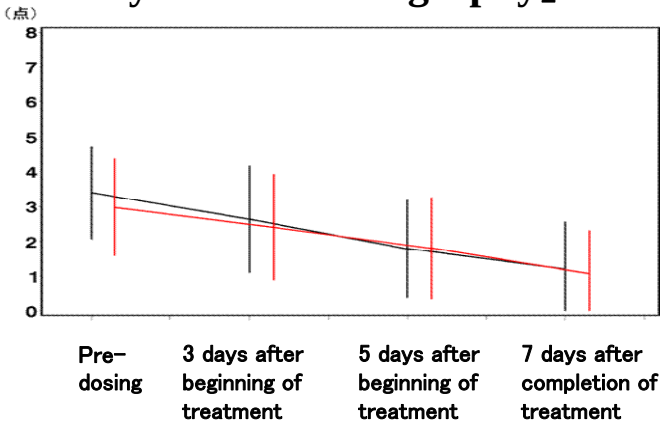


【CRP】

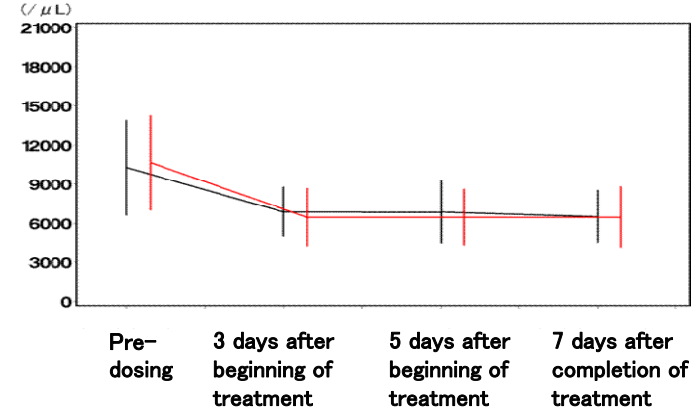
3-day administration:
5-day administration:



【Severity of chest radiography】



【WBC】



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Irbesartan: Profile

- **Licensed from Sanofi-Aventis (France)**
- **Currently co-developed by Dainippon Sumitomo Pharma Co., Ltd.**
- **Hypertension treatment**
- **Angiotensin II receptor antagonist (Oral)**
- **Approved for diabetic nephropathy (the USA & EU)**
- **Conducting Phase III study for heart failure (the USA & EU)**
- **Not pro-drug**

Proved non-inferiority to another angiotensin II receptor antagonist through double-blind study

NDA filed in December 2006




Duloxetine: Profile

- **Licensed from Eli Lilly and Company (the USA),**
  Shionogi and Eli Lilly Japan K.K. will co-market Duloxetine
- **Anti-depressant (Oral)**
- **SNRI:Serotonin & Norepinephrine Reuptake Inhibitor**
- **Side effects on autonomic nervous system induced by anticholinergic effects of Duloxetine are less than those of tricyclic antidepressants**

Conducting additional clinical trials with higher dosages to maximize the efficacy of Duloxetine, taking into account the dosage levels used abroad.

NDA filing is scheduled during FY 2007




Duloxetine:

Additional Indication - Diabetic peripheral neuropathic pain (DPNP)

- **Treatment of diabetic peripheral neuropathic pain (Oral)**
- **Shionogi and Eli Lilly Japan K.K. will co-develop and co-market Duloxetine for the indication**
- **First-line drug for DPNP; no approved drug with high efficacy is available in Japan.**
- **DPNP is a diabetes complication; Duloxetine will contribute to expanding and strengthening the pipeline in MS area and pain area**
- **Life Cycle Management after approval for depression**

Eli Lilly obtained an indication for DPNP in the USA in September 2004




Duloxetine (Diabetic peripheral neuropathic pain): Phase IIa study

- **Dose-response study**
  - Dosing period: 13 weeks
  - Target sample size: 200 patients
  - Study schedule:
    - FPI: November 2005
    - LPO: December 2006
    - Key Open: March 9, 2007

Go on to Phase IIb/III study

- **Continuation study following dose-response study**
  - Dosing period: 52 weeks
  - Target sample size: Patients proceeded from dose-response study
  - Study schedule:
    - FPI: March 2006
    - LPO: December 2007 (Planned)

FPI: First patient in, LPO: Last patient out



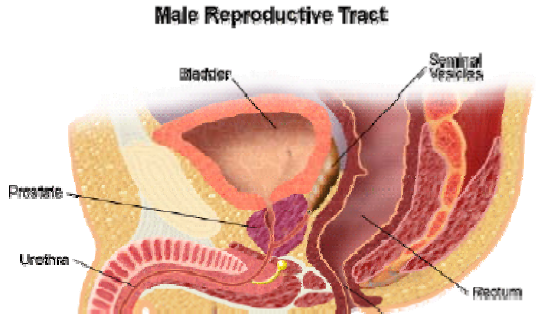

NS75B: Profile

- **Sustained-release formulation of Cetrotide®,**
  Licensed from Zentaris AG (Germany)
- **Generic name: Cetrorelix pamoate**
- **GnRH (Gonadotropin releasing hormone) antagonist (IM)**
- **Treatment for Benign Prostatic Hypertrophy (BPH)**
- **Good characteristics of both α_1 blocker and antiandrogenic agent**
- **Minor and temporary suppression of sexual function and that of markers for prostatic cancer**
- **Surgical treatment may be avoided**




NS75B: Current status of development

- **Phase I/II study completed**
  - Confirmed good sustained release curve from PK data
  - Suppression of testosterone is dose dependent
  - Confirmed suppression of markers for prostatic cancer (PSA)
  - Confirmed no serious adverse event, tolerability was comfortable
- **Phase IIb study started**
  - Primary Endpoint: Improvement of International Prostate Symptom Score (IPSS)
  - Number of patients: 300
  - Duration: 8 months
  - FPI: December 21, 2006
  - Key Open: April, 2008 (Planned)
  - Introduced Electronic Data Capture (EDC)



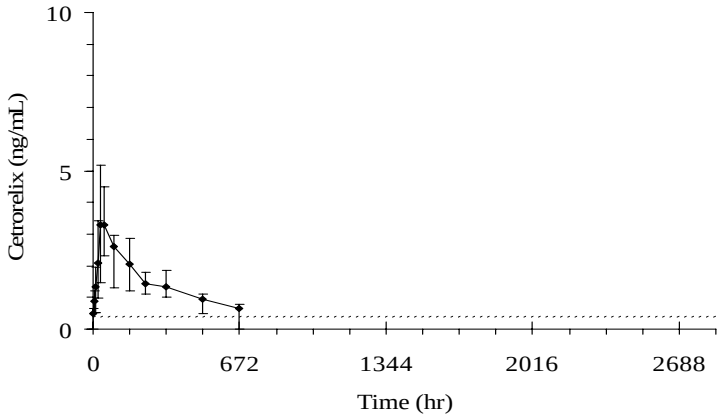
- **Co-development with Nippon Kayaku Co., Ltd. was discontinued**
  - Both companies focus on the areas where they have advantages
  - Shionogi expects synergy because it has products (antibiotics etc.) in urologic market
  - Shionogi expects acceleration of development due to centralization



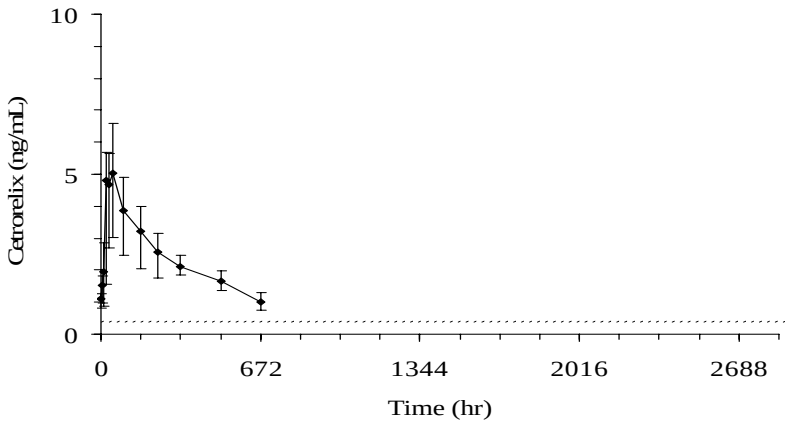

NS75B: PK in Phase I/II single dose study

- **Cmax and AUC were dose dependent**
- **Tmax was about 48 hrs and $T_{1/2}$ was over 10 days. Confirmed good sustained release curve**

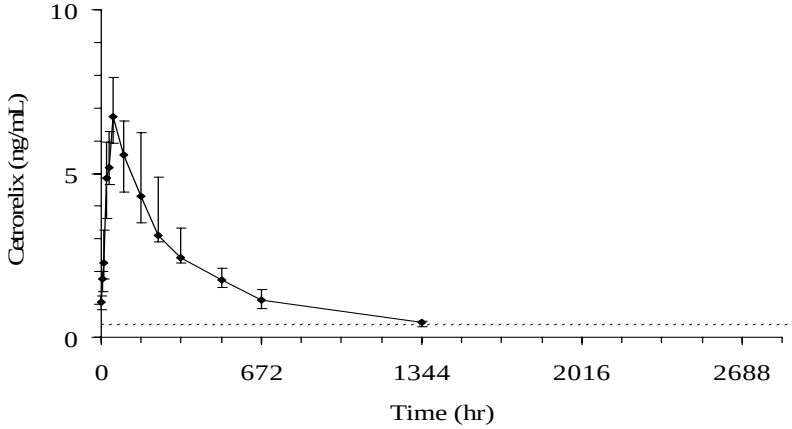
[30 mg single dose (n=8)]



[60 mg single dose (n=8)]



[90 mg single dose (n=8)]



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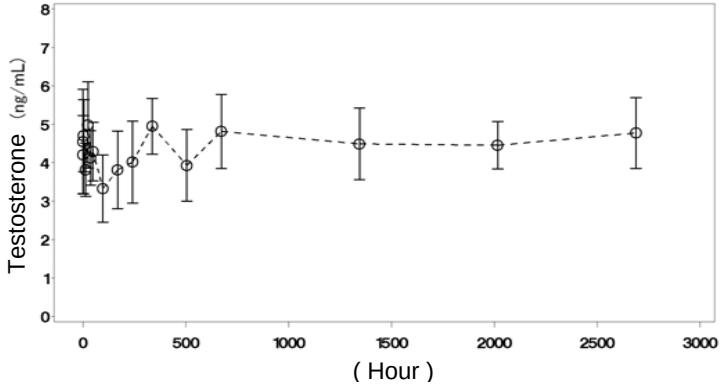
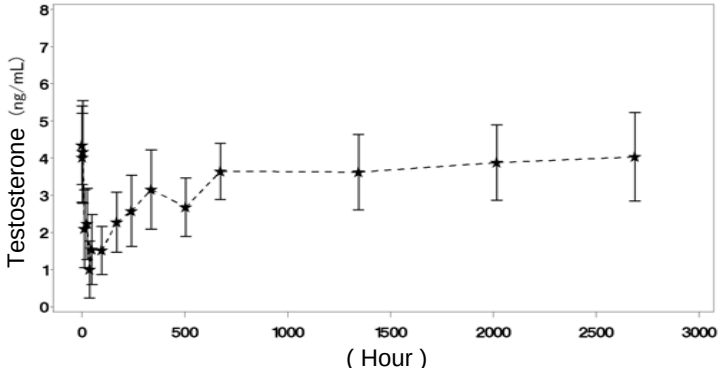
NS75B: Testosterone concentration change in Phase I/II single dose study

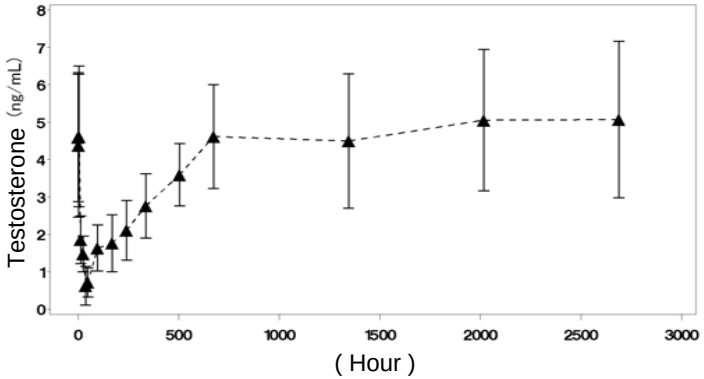
- **Suppression term and degree of testosterone was dose dependent**
- **The obtained results were similar to those in EU study; improvement of BPH can be expected**



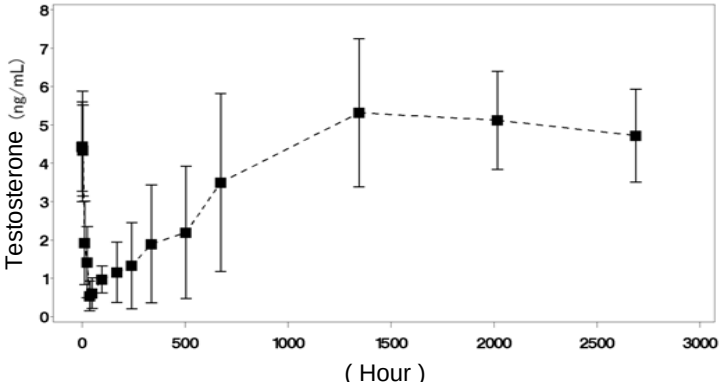
[placebo (n=6)]



[30 mg single dose (n=8)]



[60 mg single dose (n=8)]



[90 mg single dose (n=8)]

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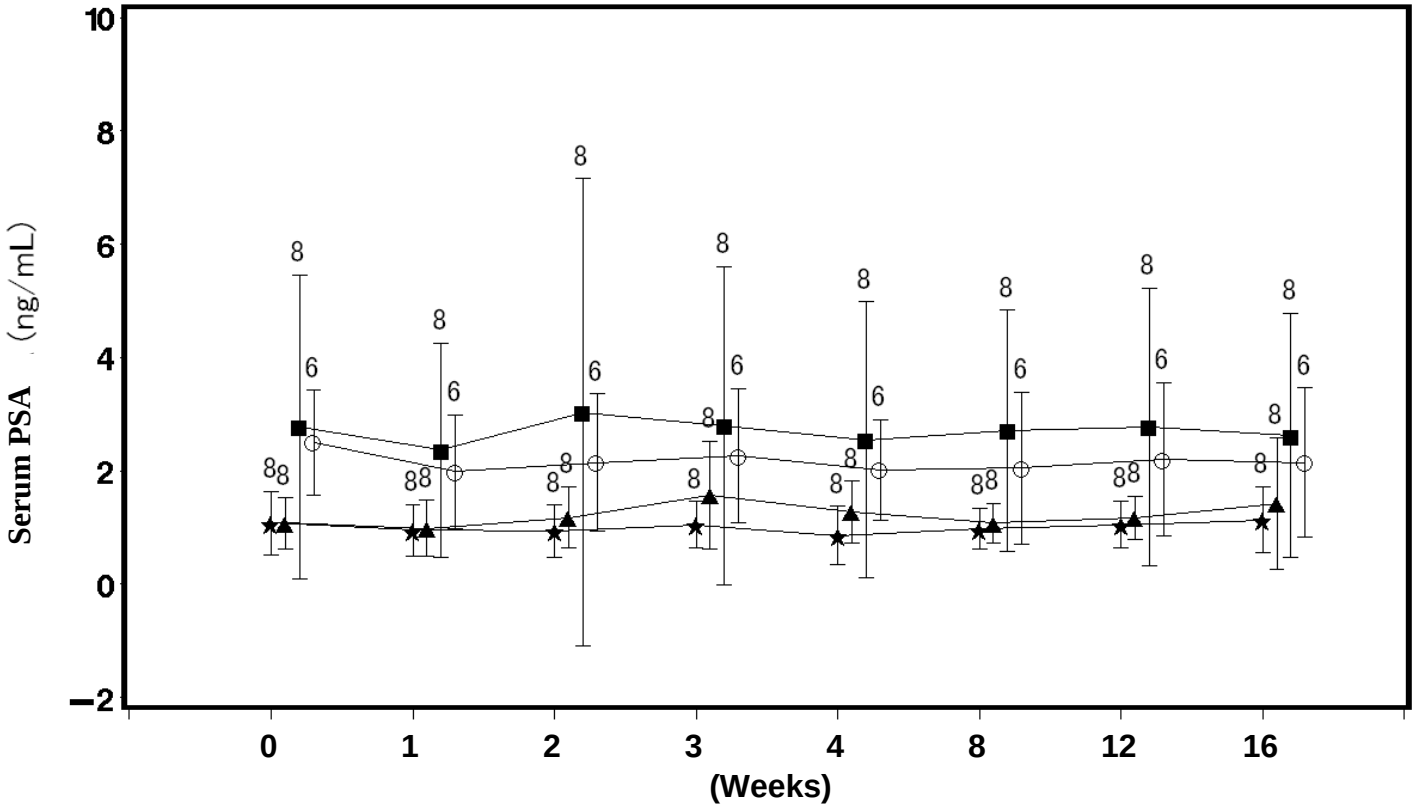
NS75B: Suppression of PSA in Phase I/II single dose study

- **Confirmed no suppression of markers for prostatic cancer (PSA)**






Targeted milestones for FY2007

Set challenging goals and accomplish them steadily

- **NDA ~ Launch**

  Launch Claritin® dry syrup

  Complete Phase III and NDA filing for Duloxetine (Depression)

- **Go/no-Go Decisions**

  S-2367 Conduct interim analysis for Phase IIb study

  S-364735 Make a go/no-go decision

  S-777469 Initiate POC study simultaneously in Japan and the USA

  S-013420 Make a go/no-go decision to enter Phase III study

- **FTIH**

  3 products (2 in-house products and Peramivir)

- **Life Cycle Management**

  Finibax® Complete post-marketing clinical study and initiate clinical study for pediatrics

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