Research and Development at Shionogi

March 10, 2011

SHIONOGI & CO., LTD.

Forward-Looking Statements

- **This presentation contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements.**

- **Risks and uncertainties include general domestic and international economic conditions such as general industry and market conditions, and changes of interest rate and currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials and entry of competitive products.**

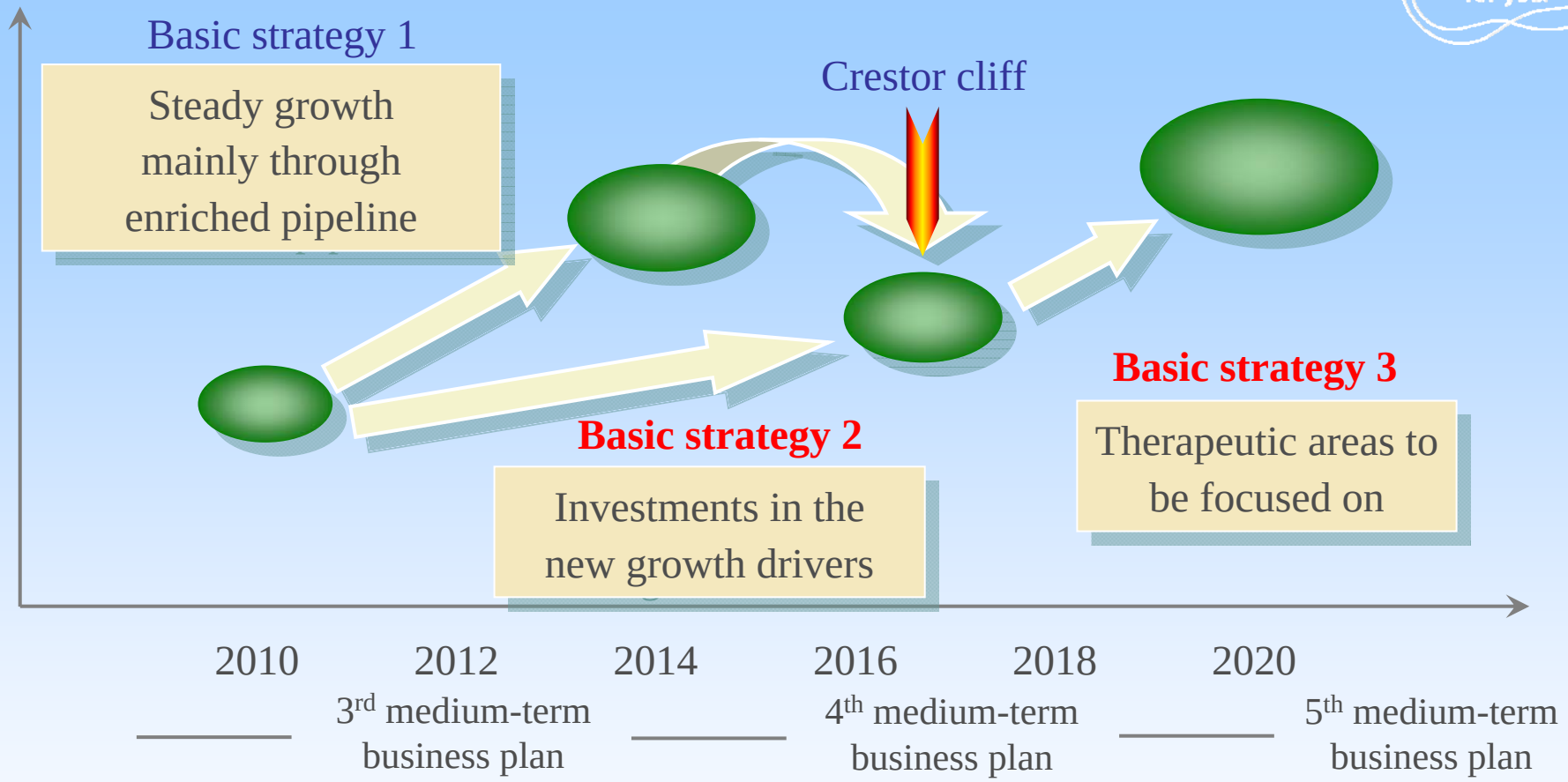
- **The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.**

- **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 kinds.**

Agenda

1. **Research : Kohji Hanasaki, Ph.D.**
   Executive General Manager, Pharmaceutical Research Division
2. **Development : Takuko Sawada**
   Executive General Manager, Pharmaceutical Development Division
3. **Summary : Isao Teshirogi, Ph.D.**
   Chief Executive Officer and Representative Director
4. **Q&A**

Basic Strategy in the 3rd Medium-Term Business Plan



Pursuing basic strategies 2 and 3 by further stepping up R&D activities will be crucial if we are to overcome the Crestor cliff and return to a growth trajectory

【Research】Goals for the 3rd Medium-Term Business Plan

Our Goal：World Top-Level Research Productivity

- Create NMEs with success rate of 50% or more in POC study
- Select four or more NMEs for DCS per year
  (Aim to establish a system to realize 5 or more DCS in 2015)

Enhancement of early phase research-portfolio

Improvement of predictive performance for clinical efficacy

Centralization of functions and strengthening of flexibility

Points to be strengthened during the 3rd Medium-Term Business Plan

Strengths in Shionogi drug discovery research acquired through the 2nd medium-term business plan

"Highly efficient low molecular SAR-engine"

NME: New molecular entity
SAR: Structure-activity relationship

【Development】Goals for the 3rd Medium-Term Business Plan

Our Goal: Speed-Up of Global Clinical Development

Decide and carry out quickly---"When, Where, Who, What studies at what cost"

Enhancement of strategic decision making function

Establishment of 3 regional development footholds worldwide

Points to be Strengthened during the 3rd Medium-Term Business Plan

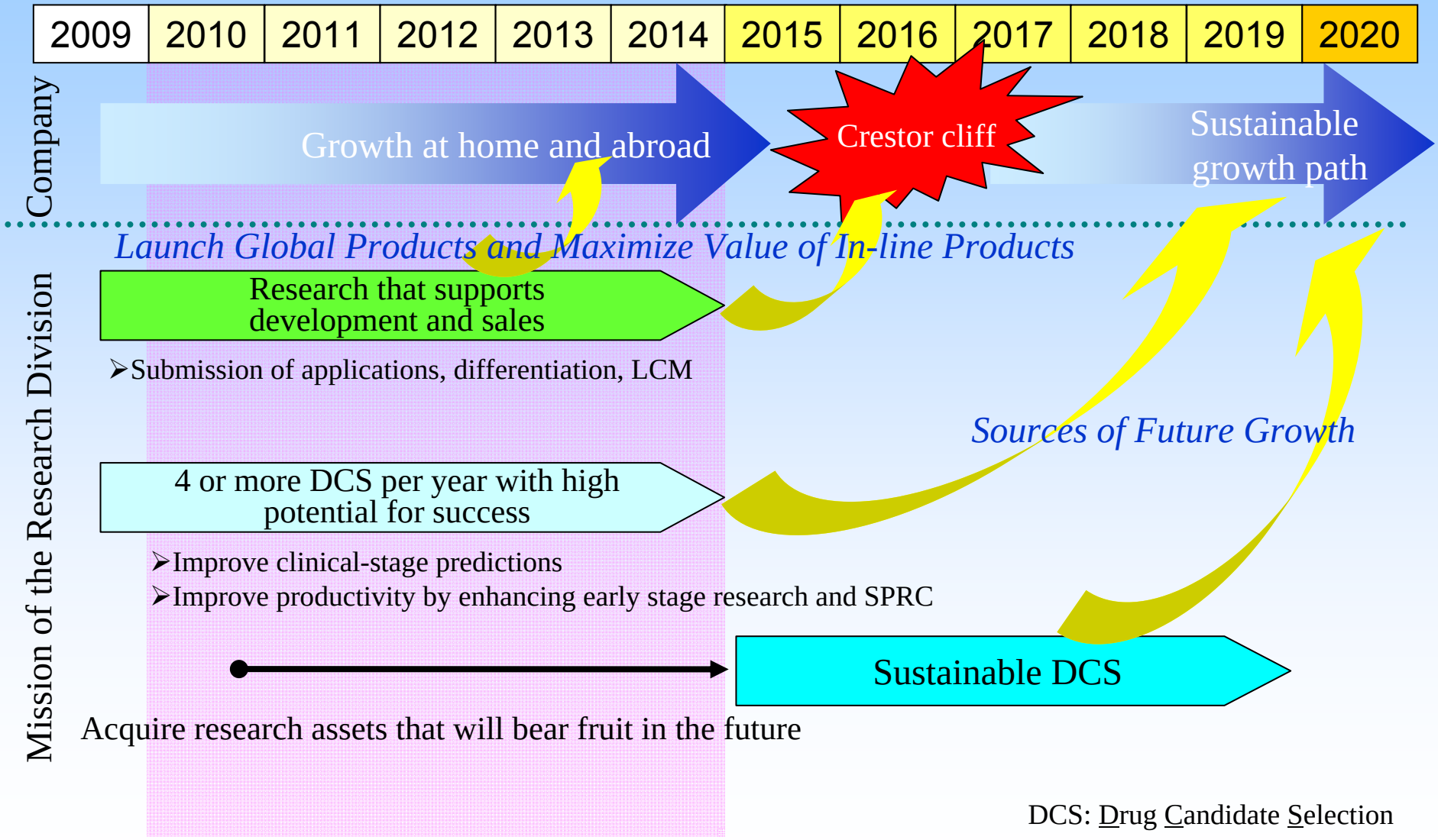
Strengths in Shionogi clinical development capability acquired through the 2nd Medium-Term Business Plan

"High success rate on the domestic clinical development "

Research

Kohji Hanasaki, Ph.D.
Executive General Manager
Pharmaceutical Research Division
Shionogi & Co., Ltd.

Mission of the Research Division



DCS: Drug Candidate Selection

Goals for the 3rd Medium-Term Business Plan

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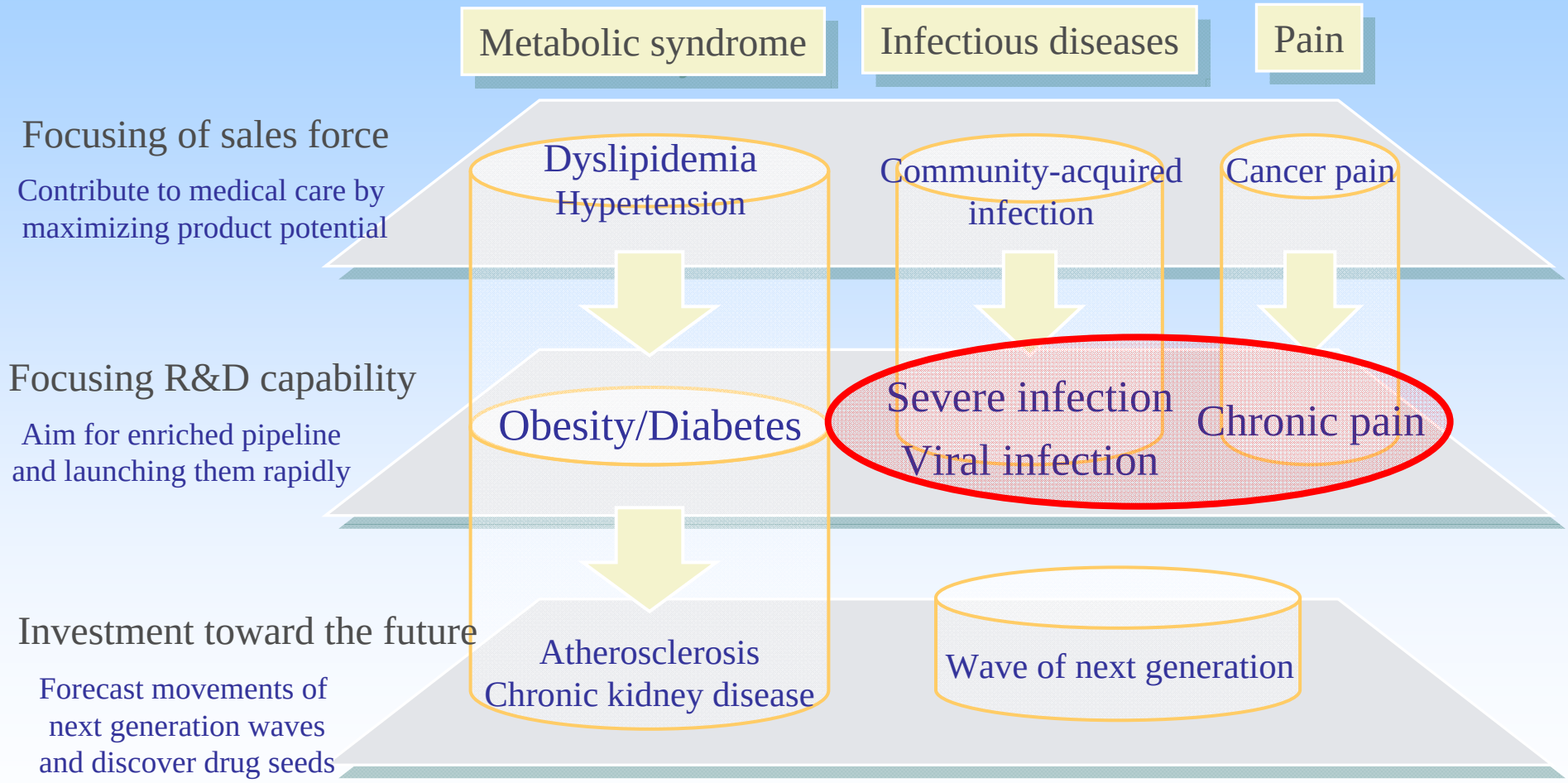
Research

Therapeutic Areas to Be Focused on



Achievement in FY2010

- Continuous creation of compounds for Phase I and DCS

Selected 2 compounds for DCS
- Anti-severe infectious disease drug (Gram-positive)
- Anti-severe infectious disease drug (Gram-negative)

Final evaluations of 2 compounds for DCS

Pre-clinical status in DCS
- Anti-pain drug <Phase I in FY2011>
- Central nervous system drug <Phase I in FY2011>
- Anti-skin disorders drug（NF-kB decoy oligo）

Advanced 2 compounds to Phase I
- HIV integrase inhibitor：S-265744LAP
- Esophagus cancer vaccine：S-488410

Research — Injectable Cephem Antibiotic Drug (Collaborative Project with GSK)

Unmet needs in Infectious Diseases

- Outbreaks of antibiotic-resistant Gram-negative infections reported in global.
- The need for new treatments to combat multi-resistant Gram-negative infections is increasing.

Shionogi's Strengths

- Leading domestic manufacturer of therapeutics for infectious diseases
- Shionogi possesses actual achievement in development and research asset in antibiotics infections.

Developing new cephem antibiotics that are efficacious against multi-resistant Gram-negative infections

Collaboration with GSK

- Proven relationship based on joint research and joint development of infectious diseases
- Best partner for maximizing the value of products in global

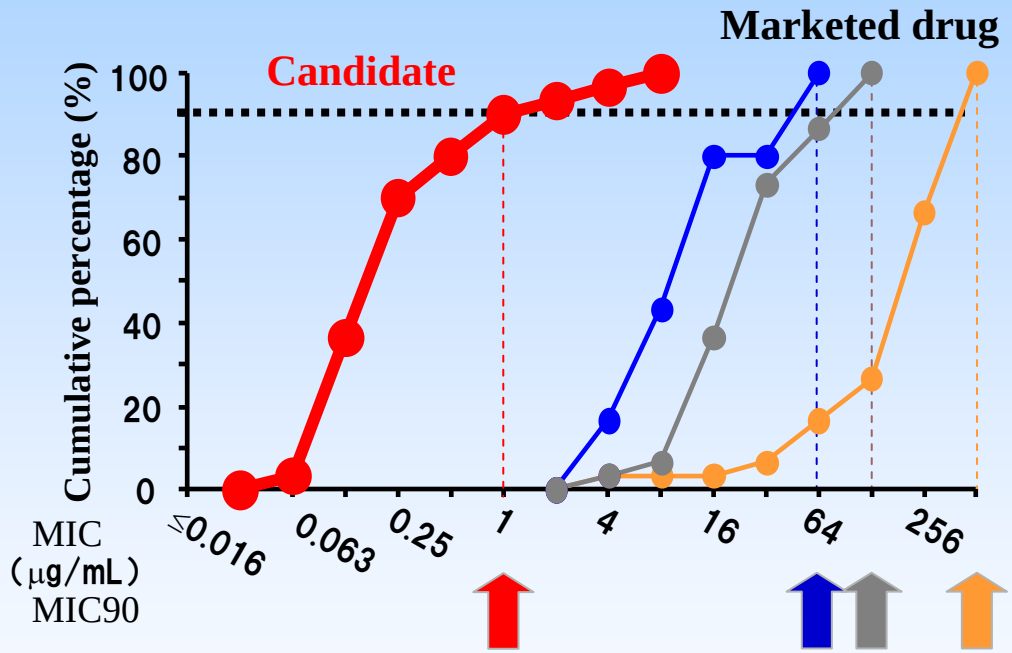
Contribution to infectious disease treatment worldwide

Benefits of Collaboration

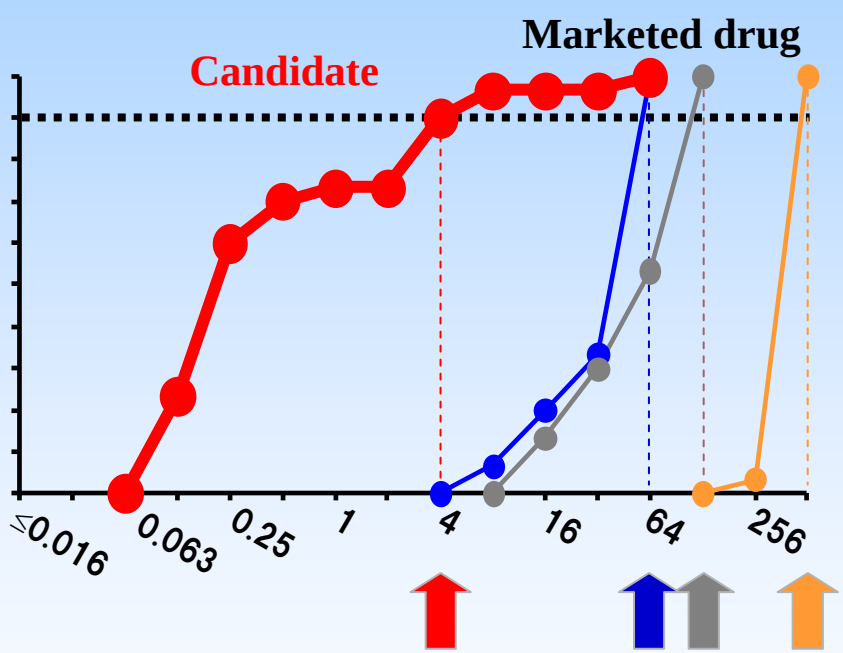
- Maximize the value of existing products and globalize operations for infectious diseases, one of Shionogi's priority therapeutic areas
- Enhanced evaluation of global clinical isolates.

Research　Injectable Cephem Antibiotic Drug (Collaborative Project with GSK)

Antibacterial Activity Against MDRP (number of strains；33)



Antibacterial Activity Against Multidrug-resistant A. baumannii (number of strains；29)

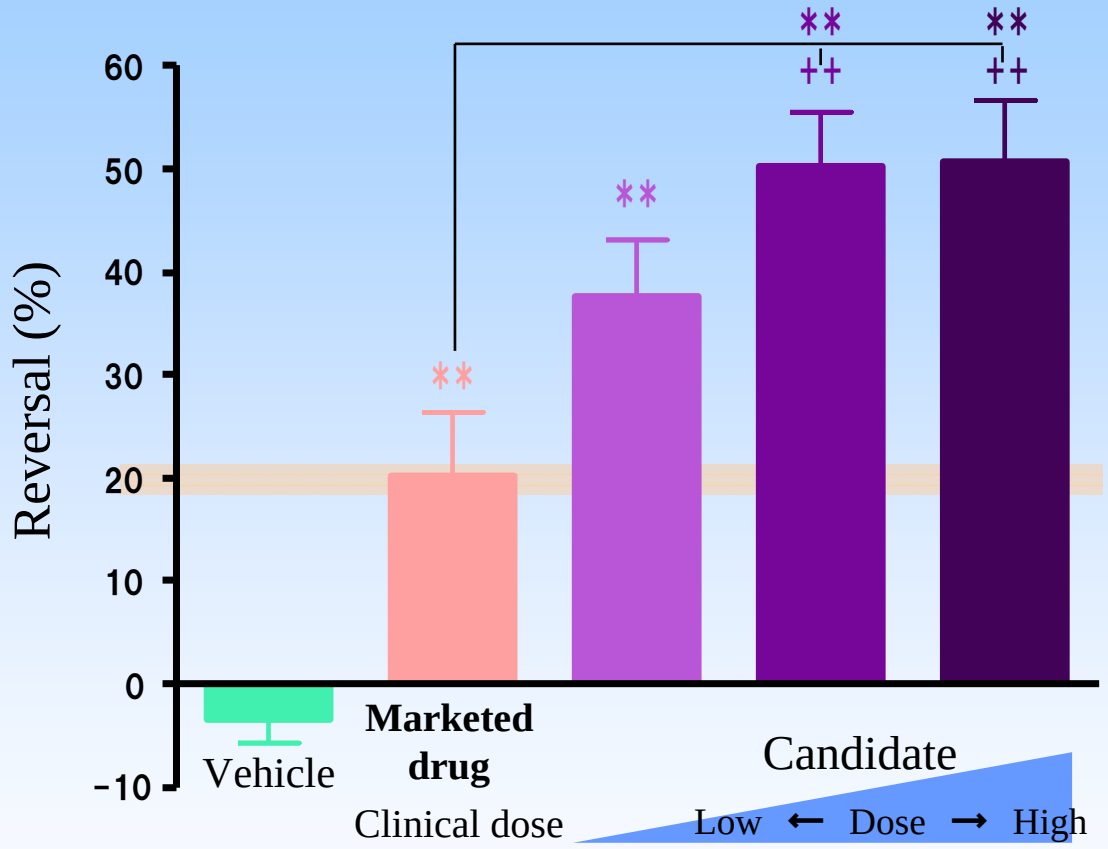


Strong antibacterial activity shown against MDRP and multidrug-resistant A. baumannii which are problematic in clinical settings.

Research Analgesic (with Purdue Pharm.)

Analgesic effect in a rat neuropathic pain model

(Phase I in FY2011)

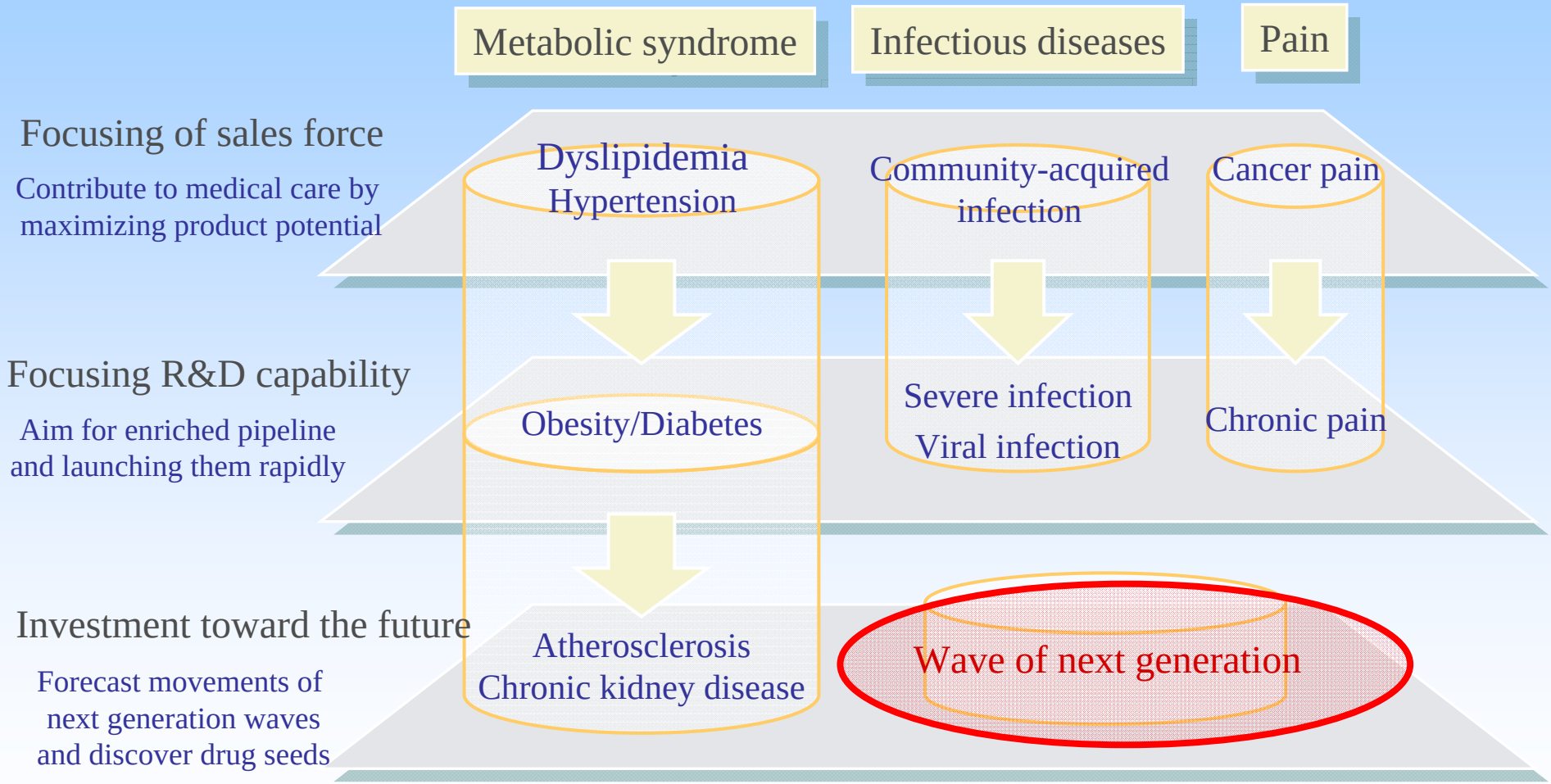


Maximum effect at Putative clinical dose

Higher efficacy than maximum effect of a marketed drug at the putative clinical dose.

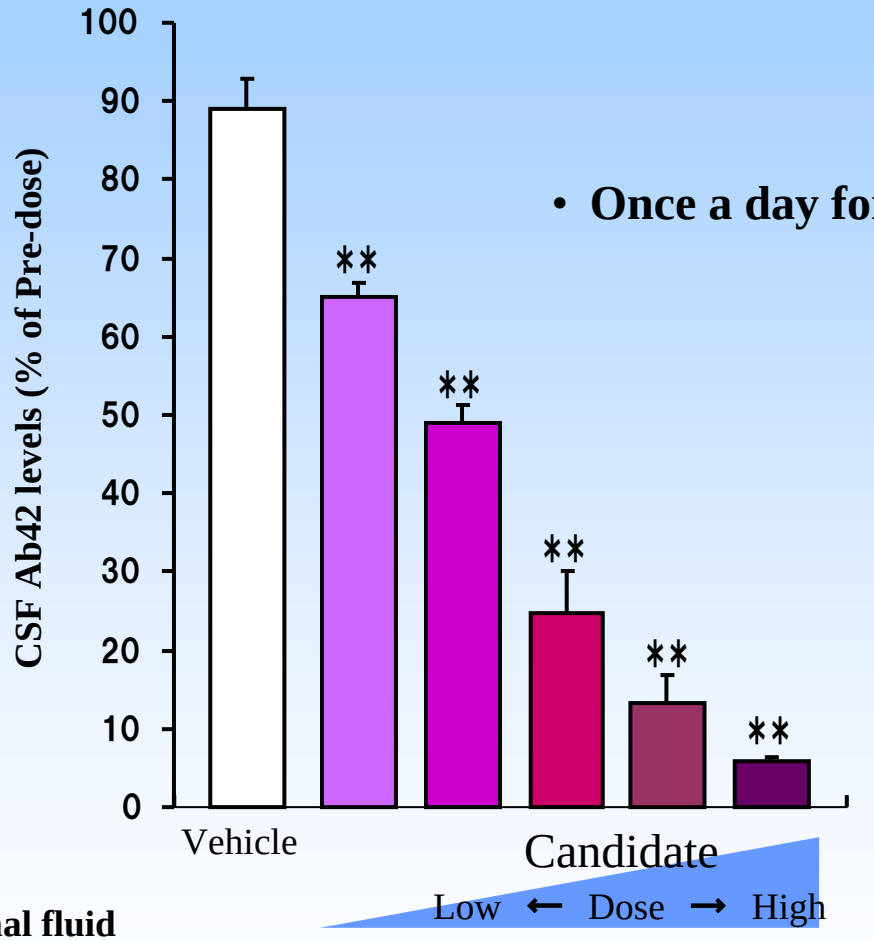
∗p<0.05, ∗∗p<0.01 vs. Vehicle.
+p<0.05, ++p<0.01 vs. Marketed drug

Therapeutic Areas to Be Focused on



Reduction of CSF* amyloid-β_{42} protein ($A\beta_{42}$) in dogs

(Phase I in FY2011)



- **Once a day for 14 days, p.o.**

***CSF: cerebrospinal fluid**

Strong decreasing effect of $A\beta_{42}$ at a low starting dose

**p<0.01 vs. Vehicle

Research

Point of Reinforcement 1: Exploration of early-stage seeds and technologies and acceleration of external collaboration to continuously improve outcomes

- Partnering to Create Drug Candidates

Collaboration in areas of focus

GSK: Cephem Antibiotic Drug

Purdue: Pain

Collaboration for next-gen therapies

Onco Therapy Science: Cancer peptide vaccine

Stallergenes: Allergy immune therapy

AnGes MG: NFkB decoy (dermatitis)

Collaboration with academia

Osaka University
PET Molecular Imaging Center

Hokkaido University
Shionogi Innovation Center

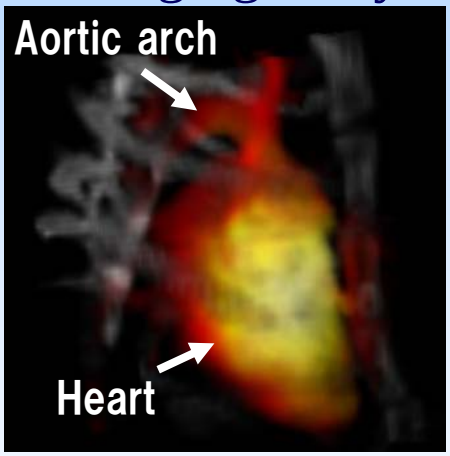
- Development of drug-seeds and novel technologies
- Translational research

FINDS-FLASH
(drug discovery competition)
Shionogi Science Program
(UK, Sweden, etc.)

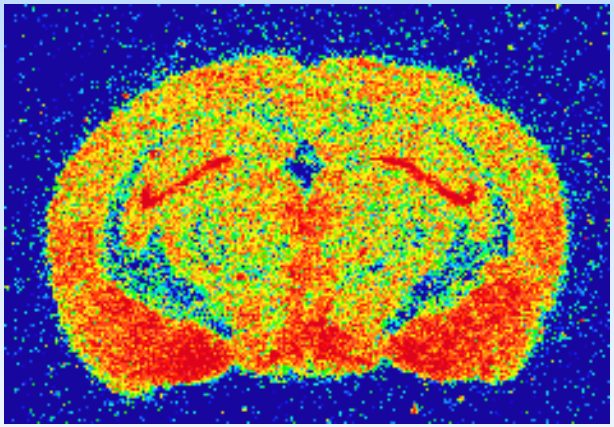
- Seed discovery through fundamental research collaboration

Point of Reinforcement 2: Improvement of clinical-stage predictions

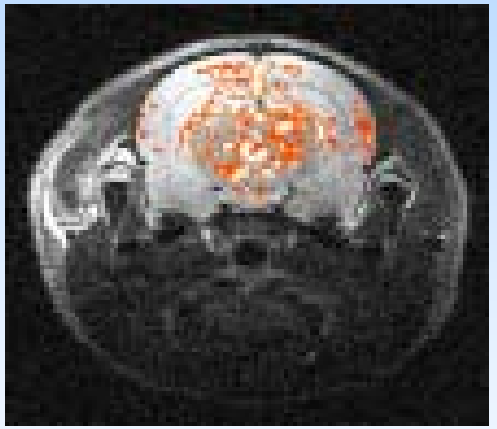
- **Osaka University *PET molecular imaging center*** (May, 2010)
  - Latest cyclotron, radio/image analysis devices
  - Synthesis of novel positron probe
  - Imaging analysis of pharmacokinetics and disease-model animals



Rat arteriosclerosis model
^{18}F-FDG unstable plaque imagaing



Distribution imaging by using Shionogi original probe in mouse brain



fMRI brain function imaging in formalin-induced pain model

Improvement of predictive performance for clinical efficacy by applying molecular imaging technology to clinical/non-clinical studies.

Targets and measures for FY2011

- Again turn out 4 or more DCS over the course of the year
  - Prioritize core programs in Shionogi's therapeutic areas of focus
  - Expand external research collaboration
  - Accelerate development of large molecule drugs in order to correspond medical unmet needs
- Establish drug discovery technologies to improve clinical POC ratio
  - Drug technologies that close the gap between clinical and non-clinical
    - Utilize imaging technology, primarily at Osaka University's molecular imaging center, in clinical and non-clinical fields
    - Build research system that benefits from clinical results feedback
- Concentrate research functions at newly completed research laboratory
  - Endeavor to improve research innovation
  - Enhance research outcomes by encouraging active communication between researchers

Point of Reinforcement 3: Concentrating functions and enhancing flexibility to improve research outcomes

- Concentrate research assets at the SPRC and improve facilities
  (scheduled completion: Aug. 2011)

Conceptual image

- Hokkaido University
- Shionogi Innovation Center
- Aburahi Laboratories

- Osaka University PET Molecular Imaging Center

- Academia
- External research institutes

- Mega-pharmaceutical companies
- Bio-ventures

Toward Top Class Global Research Productivity

SPRC: Shionogi Pharmaceutical Research Center

Development

Takuko Sawada

Executive General Manager

Pharmaceutical Development Division

Shionogi & Co., Ltd.

Agenda

- **Development Division Goals under the Third Medium-Term Business Plan**
- **Achievements in FY2010**
- **Target Milestones for FY2011**
- **Core Development Products**

Goals under the 3rd Medium-Term Business Plan

Speed Up Global Clinical Development

- **Globally develop at least 5 late stage (Phase IIb and beyond) products**
- **Submit NDAs overseas for 4 products (originate from Shionogi or Japanese research institutes) and launch at least one product by FY2014**

- **Establish a Global Development Office in April 2011**
  - **Unify global clinical development strategy**
- **Enhance development functions worldwide**
  - **Unify development function in the USA: Completed**
  - **Establish development footholds in EU**
  - **Enhance clinical developments in Asia**

Enhance Strategic Decision Making Function: What is the Global Development Office?

Global Project Management Department

- **Establishing Global Development Plans (GDPs)**
  - **Strategic planning of development compounds for speedy and efficient global development in 3 regions (Japan, USA, EU)**
- **Control and progress management of development compounds by Global Project Leaders (GPL)**
  - **GPLs will be assigned to global compounds once POC has been obtained for them**
  - **Global development according to GDPs**

New Product Planning Department

- **Market research on each therapeutic area, research into competitive product trends, and strategic planning to build a competitive advantage after launch of new products**

POC: Proof of concept

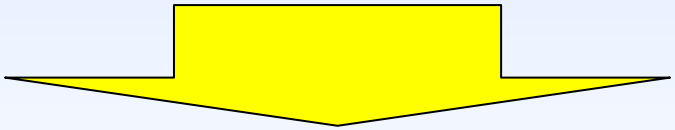
Enhance Strategic Decision Making Function: Decision-Making Process

- **Global Steering Committee (GSC)**

  Approval of development strategy and clinical trial plans for global compounds

- **Global Product Strategy Meeting (GPSM)**

  Evaluation and prioritization of the global portfolio



- **Make efficient investments by selection and concentration and promote partnering and in-licensing aggressively**

Selection and Concentration (1): Suspension of Development of S-2367 in Obesity in US/EU

- **The study aimed at showing 6% or more weight reduction compared to placebo in consideration of the gastrointestinal symptoms resulting from the use of orlistat and the effect of S-2367 on the red blood cells**
- **The combination of the two agents reduced the body weight significantly compared to placebo as well as to each of the two agents but fell short of the above goal**
- **The combination of the two agents were well tolerated with the main adverse events being gastrointestinal symptoms and effects on red blood cells such as anemia and reduction in the red blood cell count**
- **No untoward effects have been seen in the cardiovascular or neuropsychiatric system nor adverse events due to combined use of the two agents**
- **In consideration of regulatory reviews of our competitors' products, marketability and the cost required for further development, we have concluded that the development of S-2367 in the US and EU should be suspended**
- **S-234462, a back-up compound, showed weight reduction effects in two-week administration without affecting red blood cells. There were, however, reports of liver impairment and investigation is on-going to figure out the etiology**
- **Our Research Division has been working on the development of follow-up compounds**

S-2367: NDA Status Update for Anti-Obesity Agents

FDA rejected the initial commercial applications for three anti-obesity drugs

- **Qnexa (Phentermine/Topiramate, Vivus)**
  - **FDA advisory committee against approval (6 to 10)**
  - **Teratogenic potential assessment requested by FDA**
- **Lorqess (Lorcaserin, Arena)**
  - **FDA advisory committee against approval (5 to 9)**
  - **Further assessment of carcinogenesis in animal & final report of diabetic/overweight patients requested by FDA**
- **Contrave (Naltrexone/Bupropion, Orexigen)**
  - **FDA advisory committee for approval (13 to 7)**
  - **Sufficient CV study requested by FDA**

Selection and Concentration (2): Discontinued Development of S-888711 for Immune Thrombocytopenia

- **Dose finding study failed to show the expected efficacy among the selected doses**
- **The open-label extension study demonstrates encouraging efficacy results, but expansion of study and lengthening of development period are inevitable in the program due to external environment**
- **Considering the crowded situation with TPO products in the limited ITP market, and there is low business profitability in the market**
- **Focusing on liver associated thrombocytopenia could be expected higher business profitability**

ITP: Immune thrombocytopenia
TPO: Thrombopoietin

Achievements in FY2010 (1): Approvals and Launches and Life Cycle Management Progress

Approved or Launched	
Cymbalta®	Launched in April 2010 (Japan: Depression)
Rapiacta®	Additional indication for pediatric patients approved in October 2010 (Japan: Influenza virus infection)
KAPVAY™	Launched in January 2011(US: Attention-Deficit/Hyperactivity Disorder in pediatric patients)
CUVPOSA™	To be launched in spring 2011 (US: Chronic severe drooling in pediatric patients)
Development for new dosing route	
S-811717 (Oxycodone for injection)	Clinical studies by intravenous injection and subcutaneous injection completed: NDA

Achievements in FY2010 (2): Phase I–III

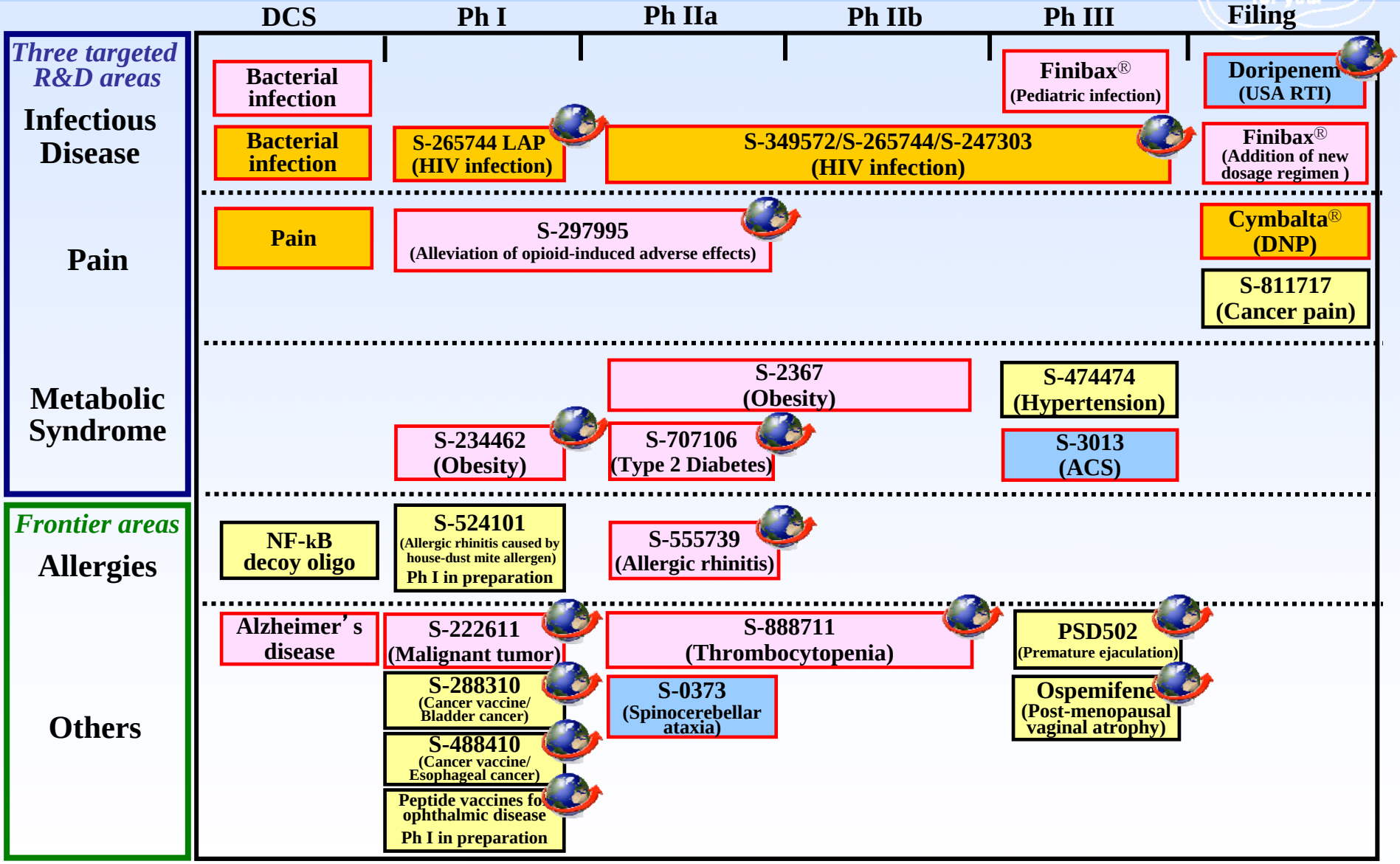
Progress in development status	
S-349572 (Dolutegravir)*	Global: Phase IIb completed, Phase III initiated
S-474474	Japan: One Phase III trial completed, next Phase III trial in preparation
S-2367	US: Phase II with Orlistat completed → Discontinued Japan: Phase II to be completed
S-297995	US: Phase IIa (POC) in progress US/Japan: Next Phase trial in preparation
S-707106	US: Phase Ib completed, Phase II (POC) initiated
S-888711	US/EU: Phase II (ITP) discontinued to review clinical dosage → Discontinued Japan: Phase IIa (Chronic liver disease) initiated
S-265744 LAP*	US: Phase I initiated
S-488410	Japan: Phase I/II initiated

POC: Proof of concept ITP: Immune thrombocytopenia
LAP: Long-acting parenteral formulation
* Developed by Shionogi-ViiV Healthcare LLC

Achievements in FY2010(3): In-Licensing

Details of In-Licensed Products	
S-524101	Sublingual allergen immunotherapy tablets (Allergic rhinitis caused by house-dust mite allergen)
NF-κB decoy oligo	Nucleic acid drug (Atopic dermatitis and other skin disorders)
Peptide vaccines for ophthalmic disease	Peptide vaccines for ophthalmic disease (Age-related macular degeneration and other retinal disorders)

Development Pipeline Enrichment (as of March 2011)



LAP: Long-acting parenteral formulation, RTI: Respiratory tract infection,
DNP: Diabetic peripheral neuropathic pain, ACS: Acute coronary syndrome,
DCS: Drug candidate selection

Developing products globally

In-house | Co-development | Out-licensed | In-licensed

Development

Steadily Advance the Development of Global Compounds and Create the Company's New Growth Drivers

Securing paths to growth in Japan, the USA, and the EU

S-349572 (Dolutegravir)
PSD502
Ospemifene

S-297995
S-888711
S-707106
S-555739

S-265744 LAP
S-222611
S-288310
S-488410
S-524101
Peptide vaccines for ophthalmic disease

DCS
NF-kB decoy oligo

Constructing a strategic pipeline that incorporates in-licensing products

LAP: Long-acting parenteral formulation
DCS: Drug candidate selection

Target Milestones for FY2011 (1): Approval, NDA filing

Approval	
Finibax®	**Severe infection in adult (dose regimen: 1g *t.i.d.*)**
S-811717	**Cancer-related pain of moderate to severe grade**
Cymbalta®	**Diabetic peripheral neuropathic pain**
NDA filing	
Finibax®	**Additional indication for pediatric infection**
Ospemifene	**Post-menopausal vaginal atrophy (US)**

Target Milestones for FY2011 (2): Phase I–III (1/2)

Progress in development status	
S-349572 (Dolutegravir)*	Global: Phase III enrollment completed
S-2367 (Japan), S-234462	Go/No-Go decision
Ospemifene	US: BE study completion, NDA filing
S-555739	Japan: Phase IIa completion, Go/No-Go decision
S-297995	US: Phase IIa completion, Phase IIb initiation Japan: Phase IIb initiation
S-707106	US: Phase IIa completion, Go/No-Go decision

* Developed by Shionogi-ViiV Healthcare LLC

Target Milestones for FY2011 (3): Phase I–III (2/2)

Progress in development status	
S-888711 (chronic liver disease)	Japan: Phase IIa completion, Go/No-Go decision
S-288310	Japan: Phase I/II in progress (enrollment completed)
S-488410	Japan: Phase I/II in progress (enrollment completed)
S-222611	US/EU: Phase Ib in progress (enrollment completed)
S-265744 LAP*	US: Phase I completion
FTIH: more than 3 compounds	

LAP: Long-acting parenteral formulation, FTIH: First trial in human

* Developed by Shionogi-ViiV Healthcare LLC

Development of Unapproved and Off-label Drugs of High Medical Need

Status of progress	
Endoxan®	Approved in February 2011: Refractory rheumatic disease
Endoxan®	NDA filing: Minimal change nephrotic syndrome in children
Flagyl®	NDA filing: Infections caused by anaerobic bacteria, amebiasis, giardiasis and bacterial vaginosis
Longes®	NDA filing: Childhood hypertension
Ifomide	NDA filing: Malignant lymphoma in childhood
Baktar®	NDA filing: Pneumocystis carinii
Vancomycin	NDA filing in preparation: Gram-positive bacteria-associated bloodstream infection
OxyContin®, OxiNorm®	Clinical trial in preparation: Moderate to severe chronic pain
Cymbalta®	Clinical trial in preparation: Fibromyalgia

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for you!

Core Development Products

Infectious Disease Area

SHIONOGI & CO., LTD.

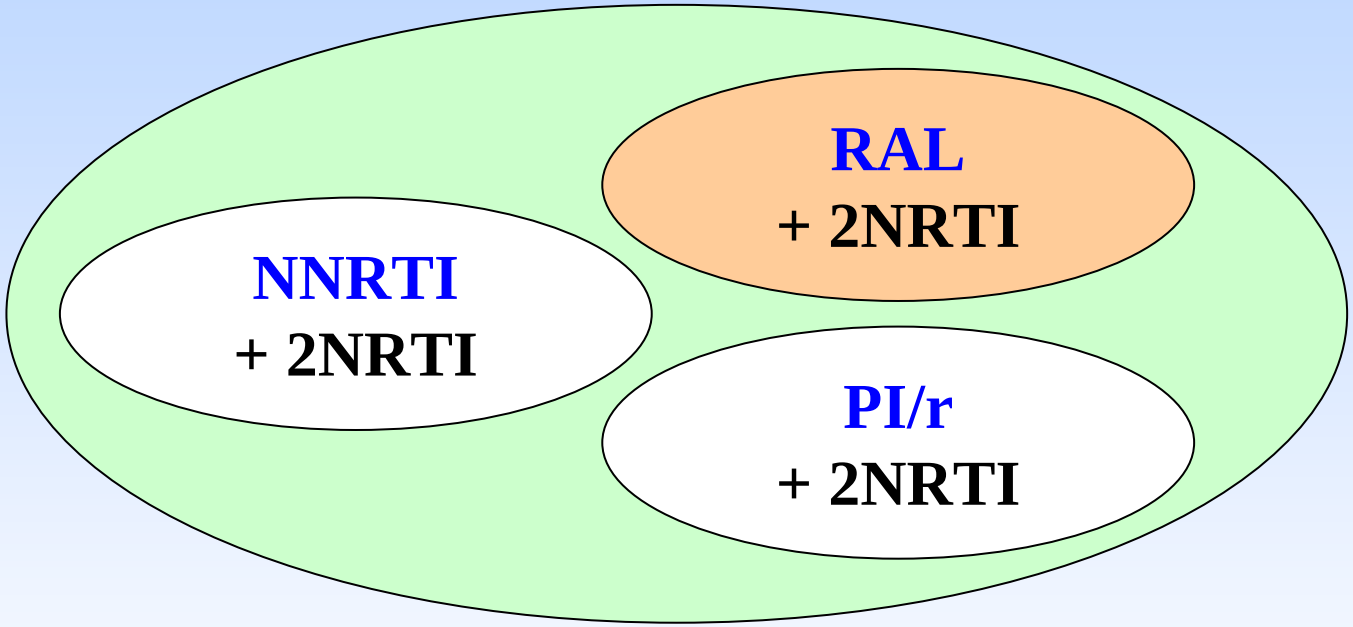
S-349572 (Dolutegravir: DTG): Anti-HIV Market (1)

- **Number of Patients**
  - **HIV patients (worldwide): about 33.4 M**
- **2009 Market**
  - **Global sales : US$14,300 million**
  - **US: about US$7,000 million (+13%),5EU: about US$4,000 (-0.2%)**
    RoW: about US$3,200 (+27%)
  - **African market is growing rapidly**
- **Anti-HIV drug sales trends**
  - **Sales of NRTIs and Protease inhibitors are flat**
  - **The first Integrase inhibitor, Isentress (raltegravir), was launched at the end of 2007. Sales were US$361 million in 2008, US$752 million in 2009, and US$780 million from Jan. to Sept. 2010**

*** DTG: Dolutegravir**

Dolutegravir: Anti-HIV Market (2)

First Line Therapy (For Naive Patients)

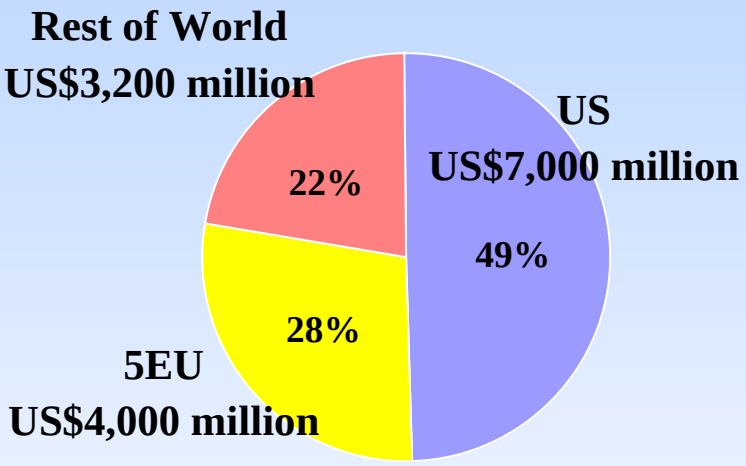


- **RAL was added as preferred option for naive patients in 2009 (Dec.)**
- **Both efficacy and safety profile of integrase inhibitor have been appreciated, and its use has expanded**

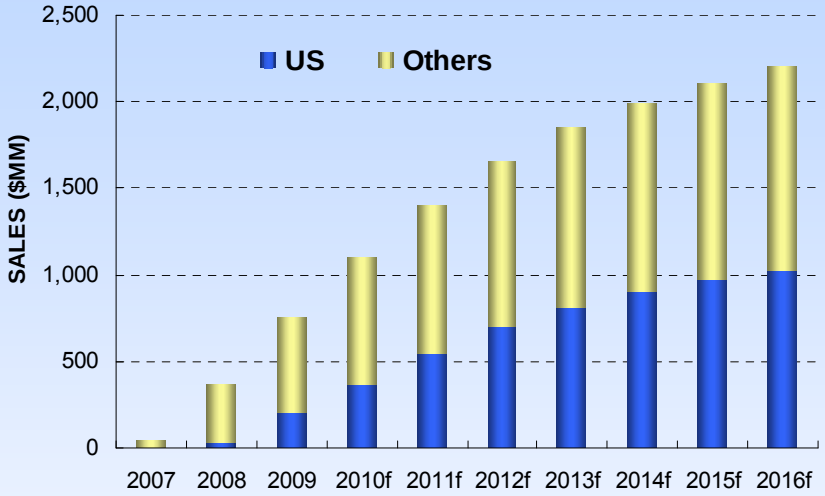
RAL: Raltegravir (Integrase Inhibitor)
NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI: Nucleoside Reverse Transcriptase Inhibitor
PI/r: Protease Inhibitor with Ritonavir

Dolutegravir: Anti-HIV Market (3)

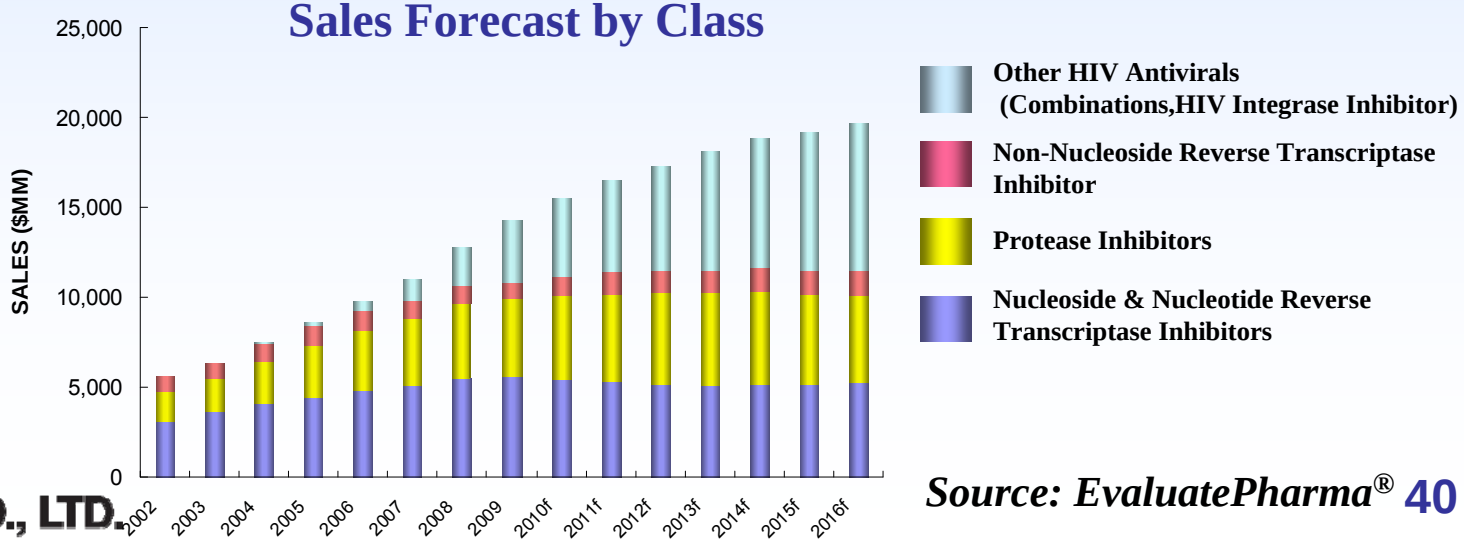
Sales by region (2009)



Raltegravir Sales Forecast



Sales Forecast by Class



Source: EvaluatePharma®

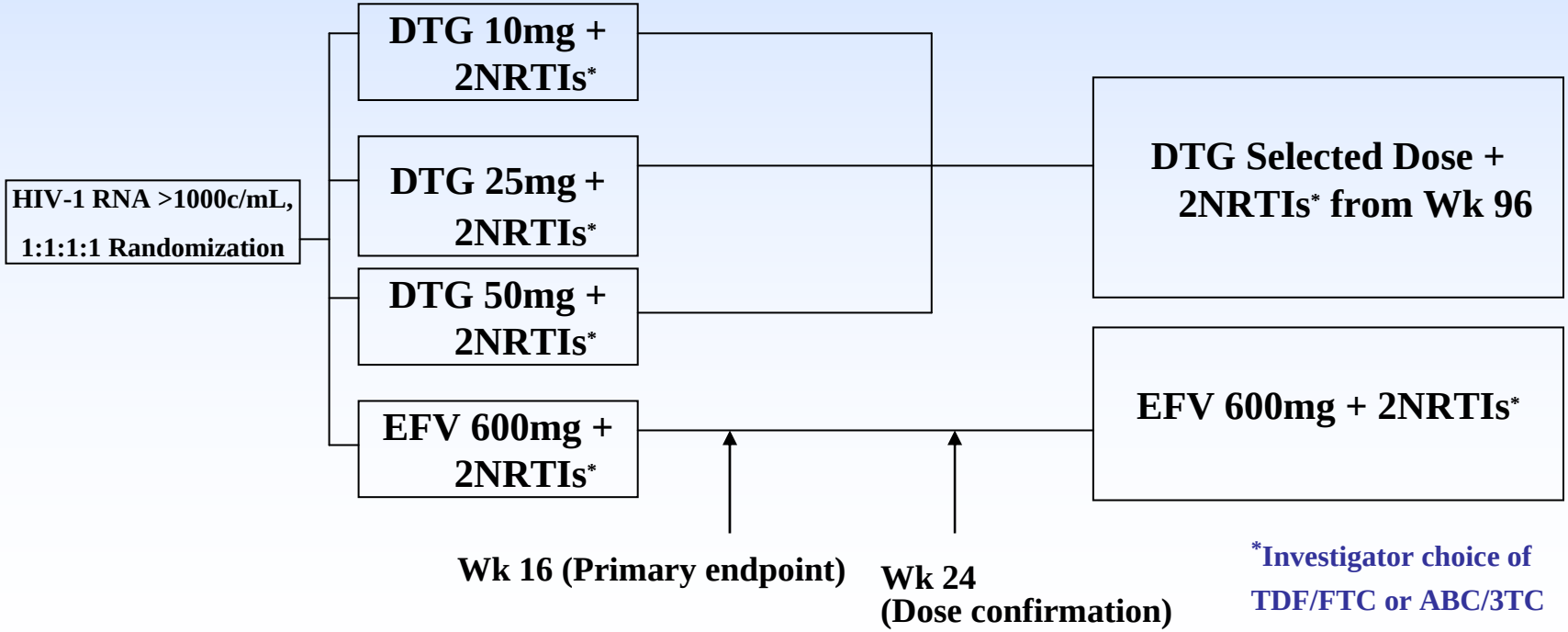
Dolutegravir: Profile

- **Developed by Shionogi-ViiV Healthcare LLC**
- **HIV integrase inhibitor (oral)**
- **Characteristics of Dolutegravir**
  - **10mg-50mg QD achieved HIV RNA <50 c/mL at 24 weeks for ≥90% of subjects in Phase IIb SPRING-1 study**
  - **No DTG resistant mutants emerged in SPRING-1 (high genetic barrier to resistance)**
  - **Active against patients with RAL resistance mutations (VIKING)**
  - **Clear PK/PD relationship**
  - **Can administer with most anti-HIV drugs without dose adjustment**
- **Dolutegravir: Global Phase III ongoing**

DTG: Dolutegravir, RAL: Raltegravir (Integrase inhibitor)

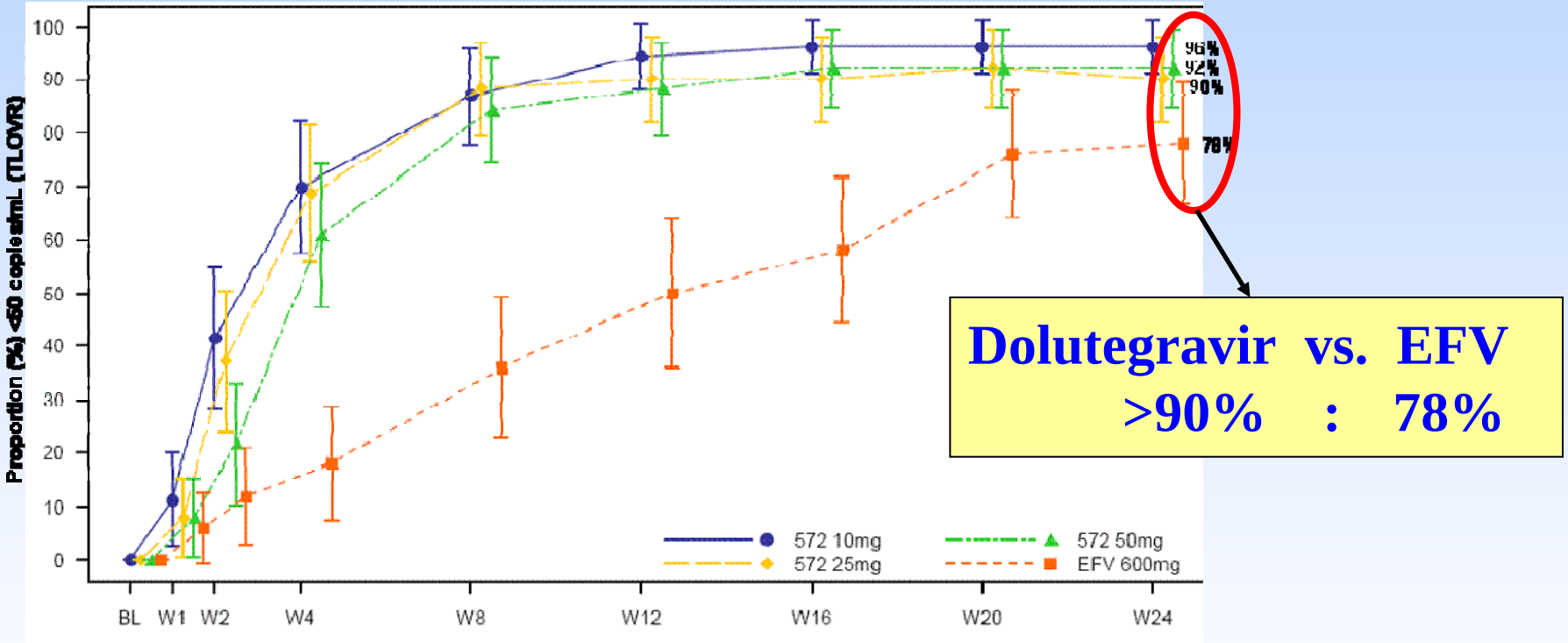
Dolutegravir: ING112276 (Phase IIb Naive Patients Study)

- **Phase IIb dose-ranging, partially-blinded trial**
- **N=200 therapy-naive patients**
- **Primary endpoint: % <50 c/mL at 16 weeks (TLOVR)**
- **All arms (n=50) include 2NRTI* backbone given once daily**



*Investigator choice of TDF/FTC or ABC/3TC
DTG: Dolutegravir

Dolutegravir: Once-Daily DTG Combination Therapy in Antiretroviral-Naive Adults: Rapid and Potent 24-week Antiviral Responses in SPRING-1 (ING112276)



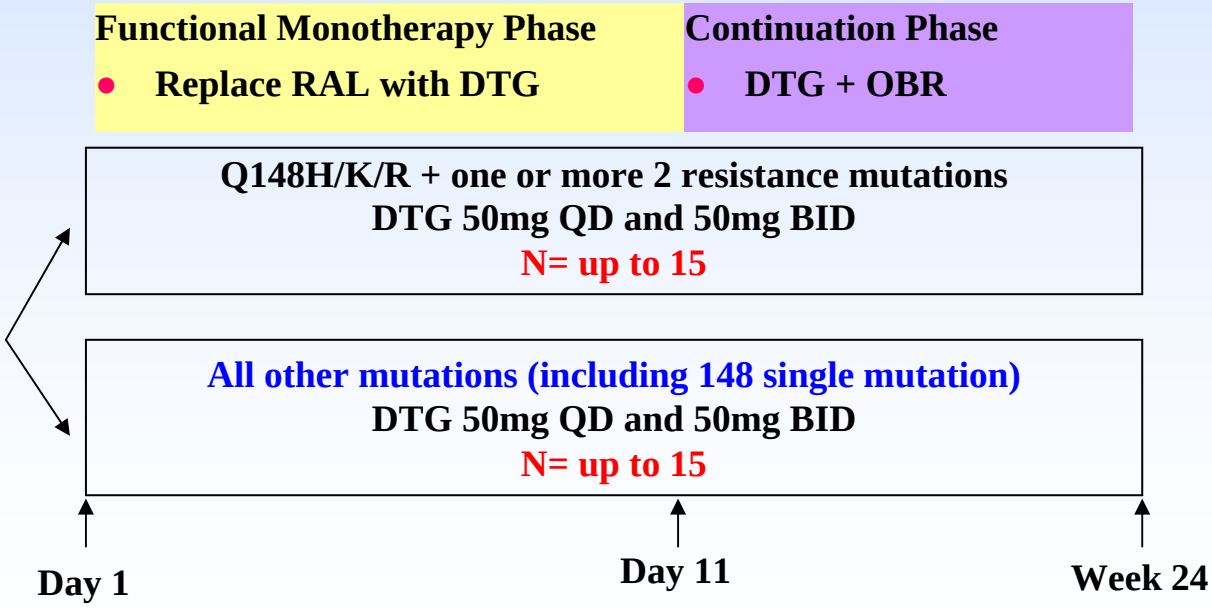
- **Dolutegravir administered once-daily without a PK booster was efficacious at all doses explored**
- **Dolutegravir was well tolerated with less impact on lipid parameters than EFV**

DTG: Dolutegravir, EFV: Efavirenz (NNRTI)

Dolutegravir: ING112961 (RAL Rescue Pilot Study)

- **Objectives:**
  - To assess the short-term antiviral activity of DTG 50mg once daily when replacing RAL in failing regimen
  - To assess BL mutations associated with lack of response to DTG
  - GT/PT at BL and in subjects with VF or subjects with VL => 400 at time of exit or completion of study
- **Primary endpoint: change from BL to Day 11 in HIV RNA**

- ART-exp, 3-class resistance (includes INI)
- On INI therapy with INI-resistance (per genotype at screen)
- Viral Load ≥ 1000 c/mL



DTG: Dolutegravir, RAL: Raltegravir (Integrase inhibitor),
OBR: Optimized background regimen

Dolutegravir: VIKING Study (ING112961): Virologic Response (Day 11) by Mutational Pathway

*Primary endpoint: <400c/mL and/or ≥ 0.7log decline	DTG 50mg QD (N=27)	DTG 50mg BID (N=24)
All subjects: Primary endpoint*	21/27 (78%)	23/24 (96%)
With Q148 +≥1	3/9 (33%)	11/11 (100%)
With other pathways	18/18 (100%)	12/13 (92%)
All subjects: <400 c/mL	11/27 (41%)	13/24 (54%)

- A better response rate for the primary endpoint at Day 11 was observed (23/24, 96%) in Cohort II
- A comparable safety profile was observed between Cohort I and II

DTG: Dolutegravir, 50mg QD: Cohort I, 50mg BID: Cohort II

Dolutegravir: VIKING Study: Change from Baseline in Plasma HIV-1 RNA log10 c/mL Between Cohort I and II at Day 11

		DTG 50mg QD (N=27)	DTG 50mg BID (N=24)
Baseline	Mean	4.4	4.4
	SD	0.79	0.74
Change from Baseline*	Mean	-1.5	-1.8
Adjusted Treatment	SD	0.77	0.54
Difference Cohort II vs. Cohort I	Mean (95% CI)	-0.32 (-0.57, -0.06)	
	p-value	0.017	

* The means (SDs) of change from baseline did not change after adjusting for baseline viral load, DTG FC, PSS of day1-10 regimen, and IN mutational pathway using the linear regression model.

- **Better efficacy at Day 11 in 50mg BID than 50mg QD (-1.8log copy/mL vs. -1.5log copy/mL decline of HIV RNA from baseline)**
- **DTG 50mg BID has been selected for Phase III INI-resistant study**

DTG: Dolutegravir (S/GSK1349572, 572),
50mg QD: Cohort I, 50mg BID: Cohort II

Dolutegravir: Phase III (Pivotal Studies)

Study No.	Patient Population	Study Design	Start
ING113086 SPRING-2	Treatment-naive	ART-naive pts (n~788) DTG vs. RAL (+ NRTIs of choice) non-inferiority design	2010 Oct
ING111762 SAILING	Treatment-experienced but INI-naive	ART-experienced, INI-naive pts (n~688) DTG vs. RAL (+ OBR) non-inferiority design	2010 Oct
ING114467 SINGLE	Treatment-naive	ART-naive pts (n~800) 572 Trii vs. Atripla non-inferiority design	2011 Feb

DTG: Dolutegravir, RAL: Raltegravir (Integrase inhibitor),
OBR: Optimized background regimen, Trii: DTG/ABC/3TC

S-O-N-G for you!

Core Development Products

Metabolic Syndrome Area

SHIONOGI & CO., LTD.

S-2367: Profile

- **Anti-obesity**
- **NeuropeptideY Y5 receptor antagonist (oral)**
- **Key findings from non-clinical studies**
  - **Increased energy consumption**
  - **Suppressed visceral fat accumulation and improved blood glucose and serum lipid levels**
  - **Sustainable weight suppression without rebound**
  - **Confirmed excellent safety (influence on heart rate & blood pressure was not observed)**
- **Key findings from clinical studies to date**
  - **Combo POC study with orlistat (US): The development of S-2367 in the US and EU was suspended, and the development of follow-up compounds to be proceeded**
  - **One of two Phase II studies in Japan has completed: Studies in Japan to be continued**

POC: Proof of concept

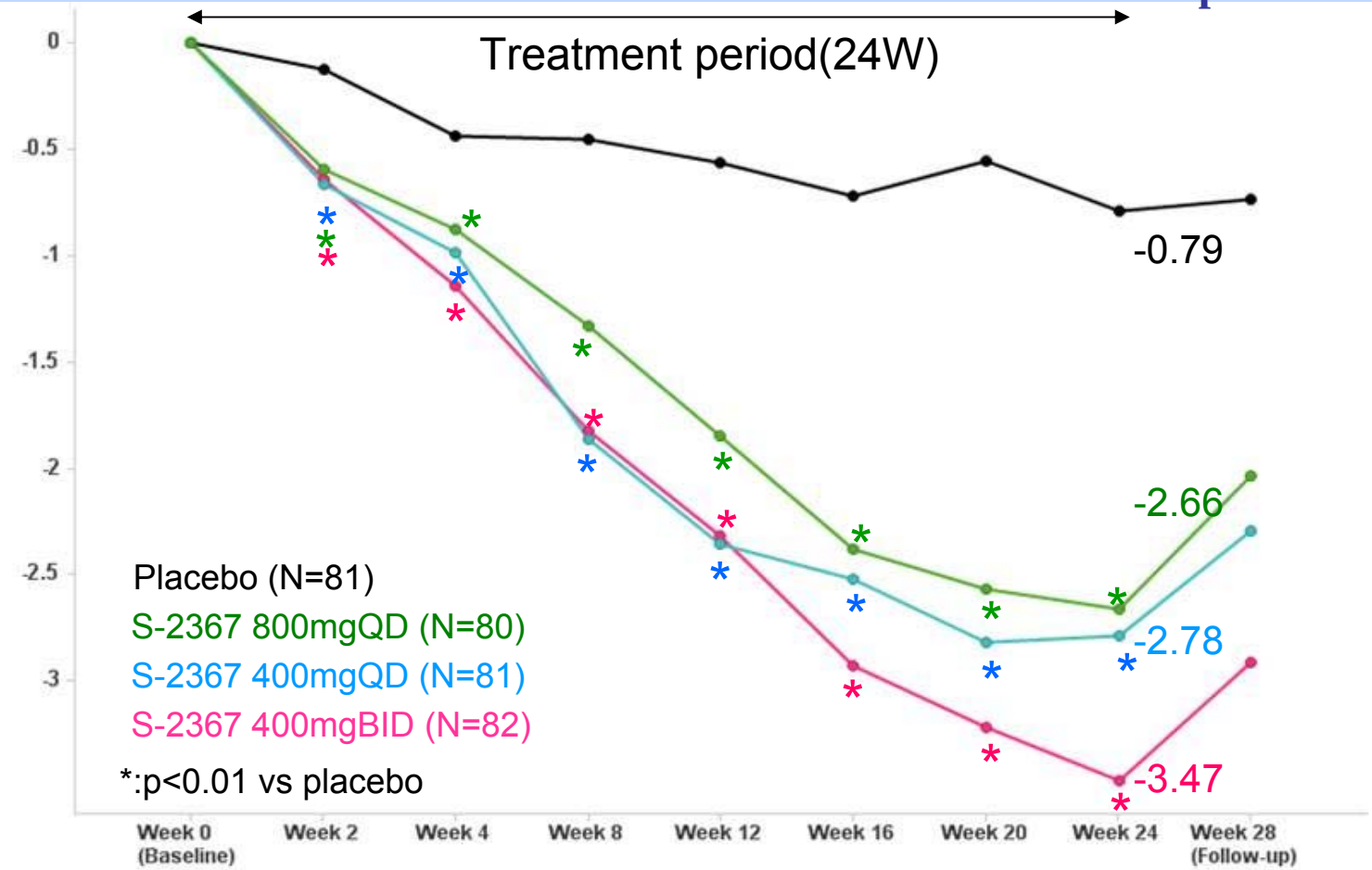
S-2367: Phase II Studies in Japan

- **Objective:**
  To evaluate S-2367 with respect to the effect on weight loss and the safety in obese subjects who have two or more of the following: diabetes mellitus, dyslipidemia, and hypertension
- **Study population:**
  - **BMI ≥ 25 kg/m^2**
  - **Visceral fat area ≥ 100 cm^2**
- **Two studies have been designed:**
  - **Obesity with diabetes mellitus and dyslipidemia (completed)**
  - **Obesity with hypertension and dyslipidemia (to be completed within FY2010)**

S-2367: Percent Change from Baseline in Body Weight

(Repeated Measures Analysis /FAS)

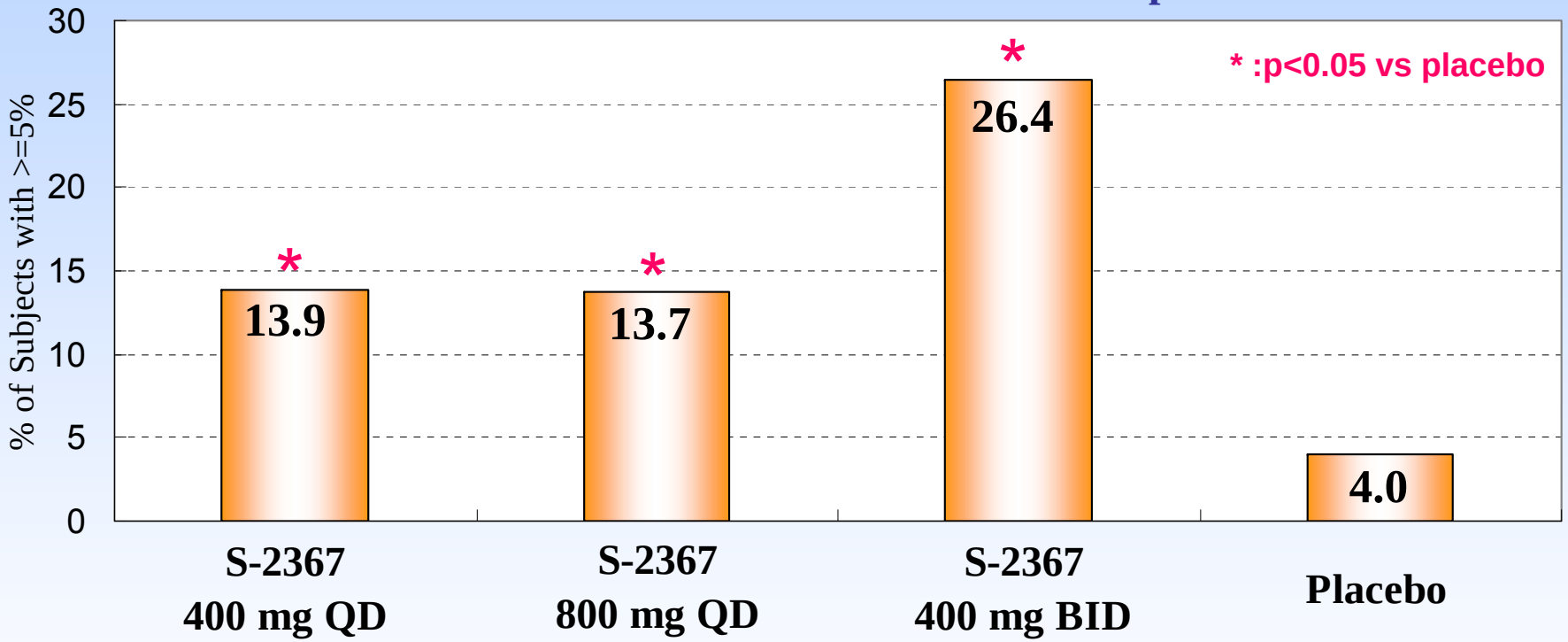
Japanese Phase II Data



S-2367 showed statistically significantly greater weight loss compared to placebo throughout the trial in all active groups

S-2367: Proportion of Subjects with >=5% Body Weight Loss at Week 24

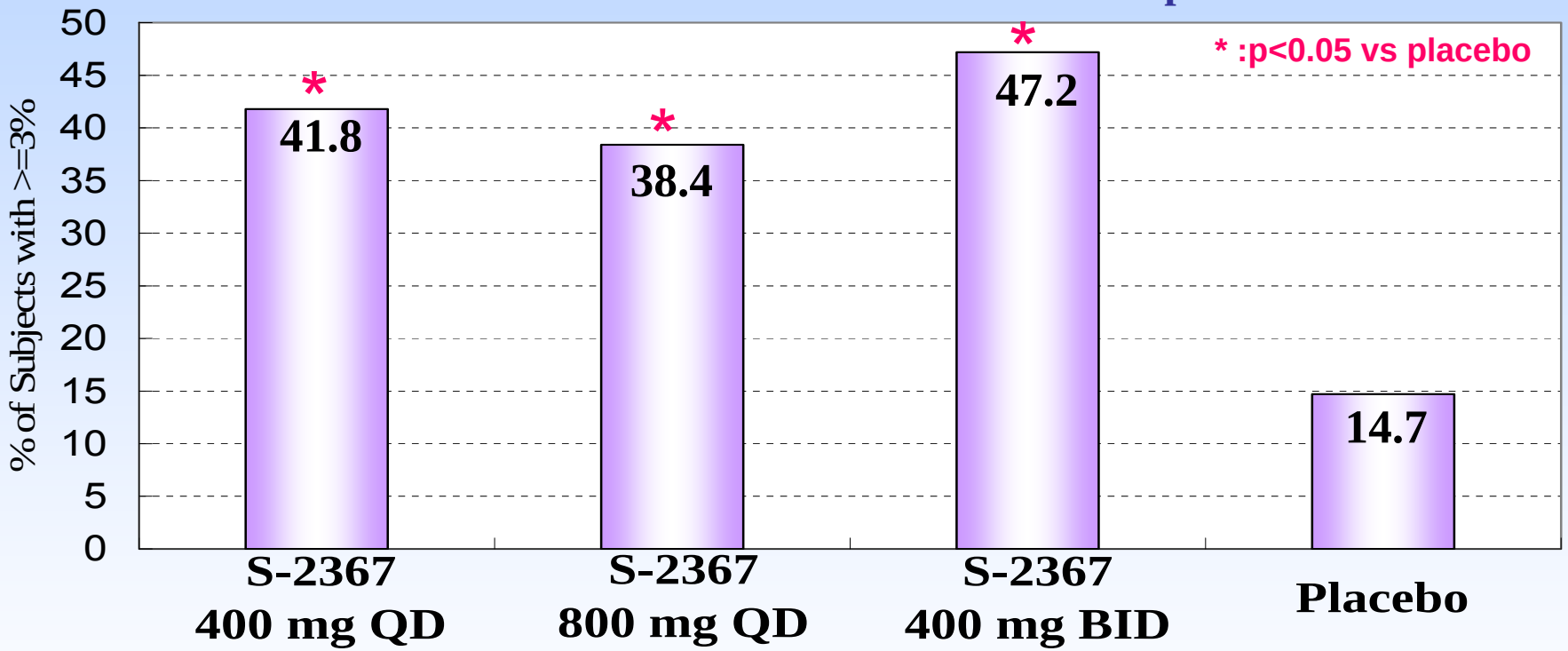
Japanese Phase II Data



S-2367 had statistically significantly greater proportions of subjects achieving 5% or more weight loss compared to placebo at week 24 in all active groups

S-2367: Proportion of Subjects with >=3% Body Weight Loss at Week 24

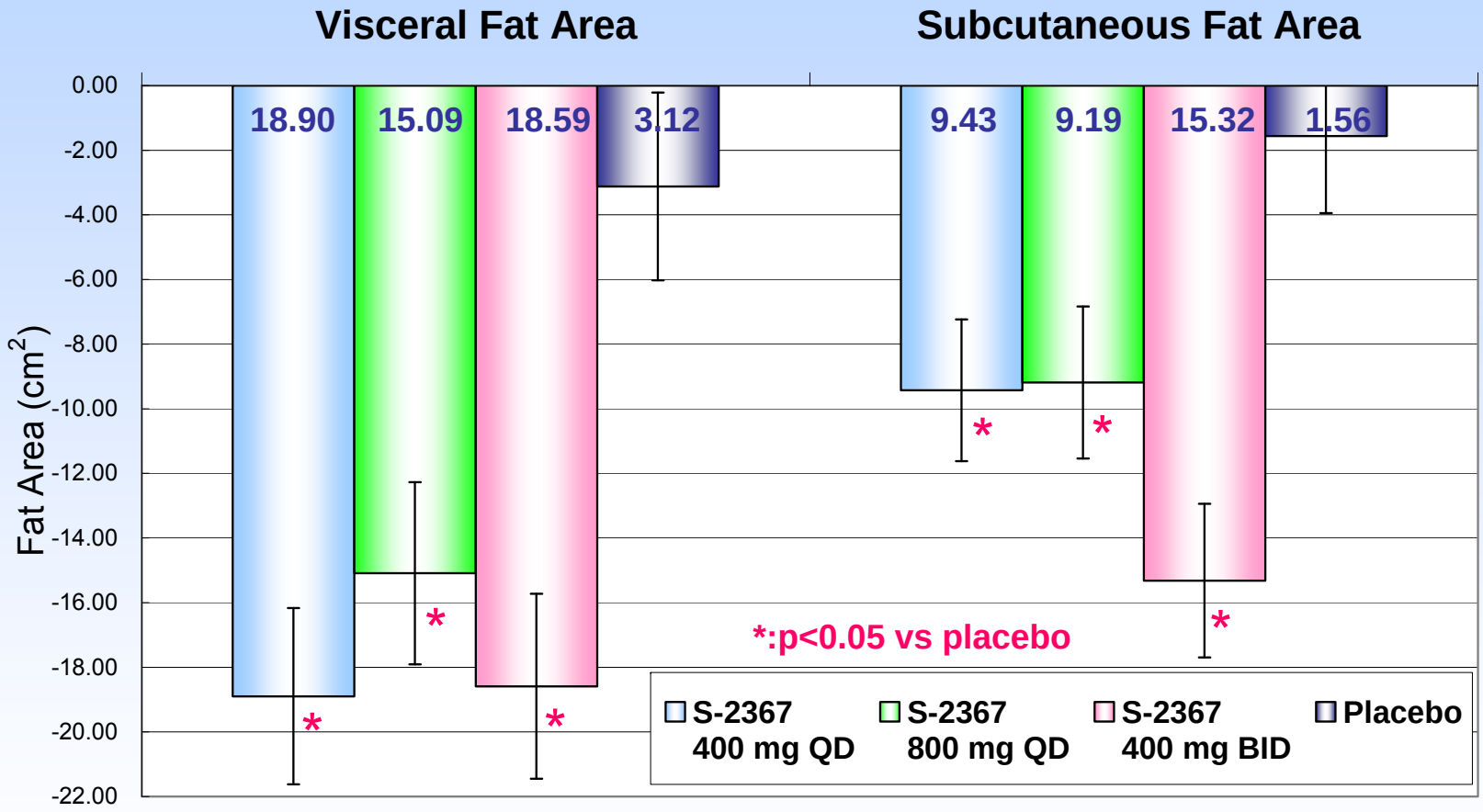
Japanese Phase II Data



S-2367 had statistically significantly greater proportions of subjects achieving 3% or more weight loss compared to placebo at week 24 in all active groups

S-2367: Change in Visceral Fat Area and Subcutaneous Fat Area (cm^2) at Week 24

Japanese Phase II Data



S-2367 increased the visceral fat area and the subcutaneous fat area with statistical significance at week 24 compared to placebo in all active groups

S-2367: Summary of Phase II Study in Japan
(Obesity with Type II Diabetes / Dyslipidemia Study)

- **S-2367 achieved statistically significant weight loss and reduction in visceral and subcutaneous fat area in Japanese obesity patients with Type II diabetes and dyslipidemia**
- **No evidence of increased depression, anxiety, suicidality or cardiovascular risk**
- **Similar frequency of adverse events leading to the study discontinuation between active groups and placebo group**
- **Anemia and hemolysis findings were seen in active groups; changes in red blood cell parameter reached to a steady state by Week 12 and no further changes were seen until the end of dosing period**

Core Development Products

Pain Area

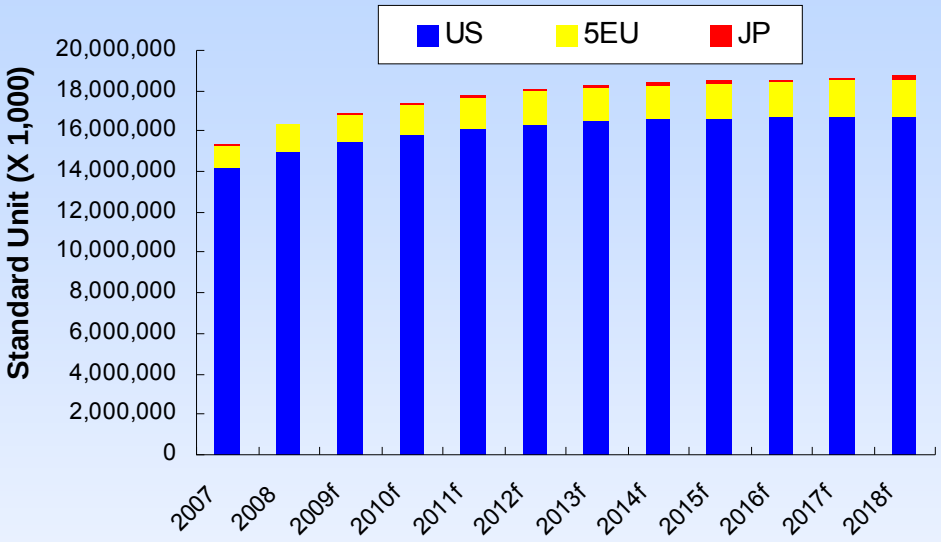
SHIONOGI & CO., LTD.

S-297995: Profile

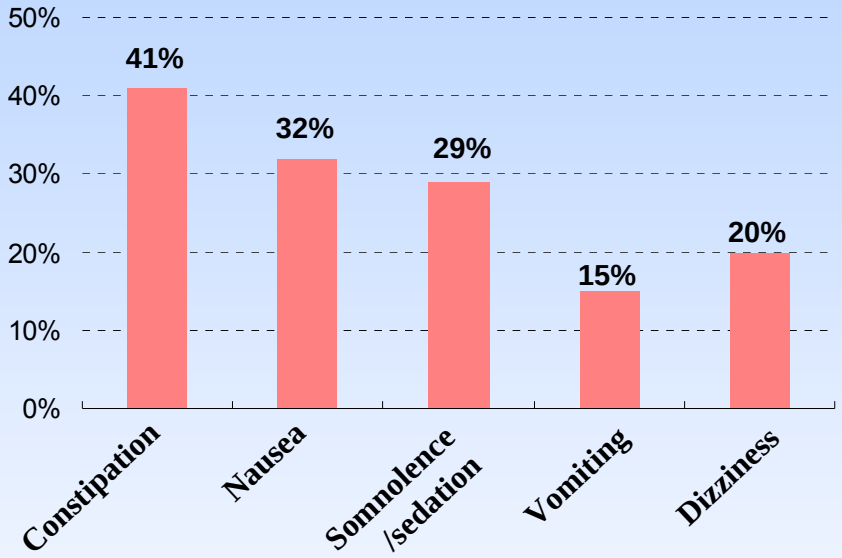
- **Indication: Relief of opioid-induced gastrointestinal symptoms such as nausea, vomiting and constipation**
- **Positioning: S-297995 is effective not only for opioid-induced constipation but for nausea/vomiting, which are difficult to alleviate with the existing treatments**
- **Mechanism: Orally active peripheral opioid receptor antagonist**
- **Pharmacological characteristics (non-clinical study):**
  - **Suppressed morphine-induced nausea and vomiting in ferret model**
  - **Suppressed morphine-induced small intestinal hypomotility in rat model**
  - **Showed anti-emetic and anti-constipation effect at a similar exposure level**
  - **No effect on the analgesic effect of morphine due to low propensity to permeate the blood-brain barrier**
- **Development stage: Phase I study completed in Japan**
  Phase IIa study on-going in the USA
- **Future plan: Phase IIb study to be conducted in the USA and Japan**

S-297995: Opioid Market

Sales Volume Trend in Opioids

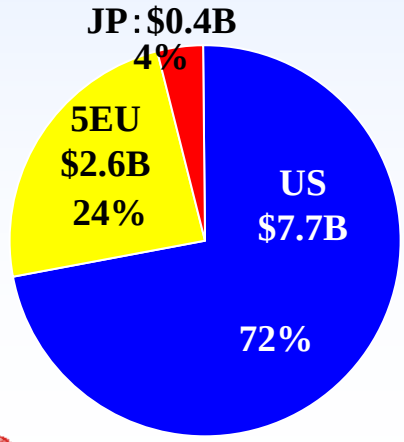


Side effect in Opioids



Source: Pain 112 (2004) 372-380

Opioids Sales value 2010

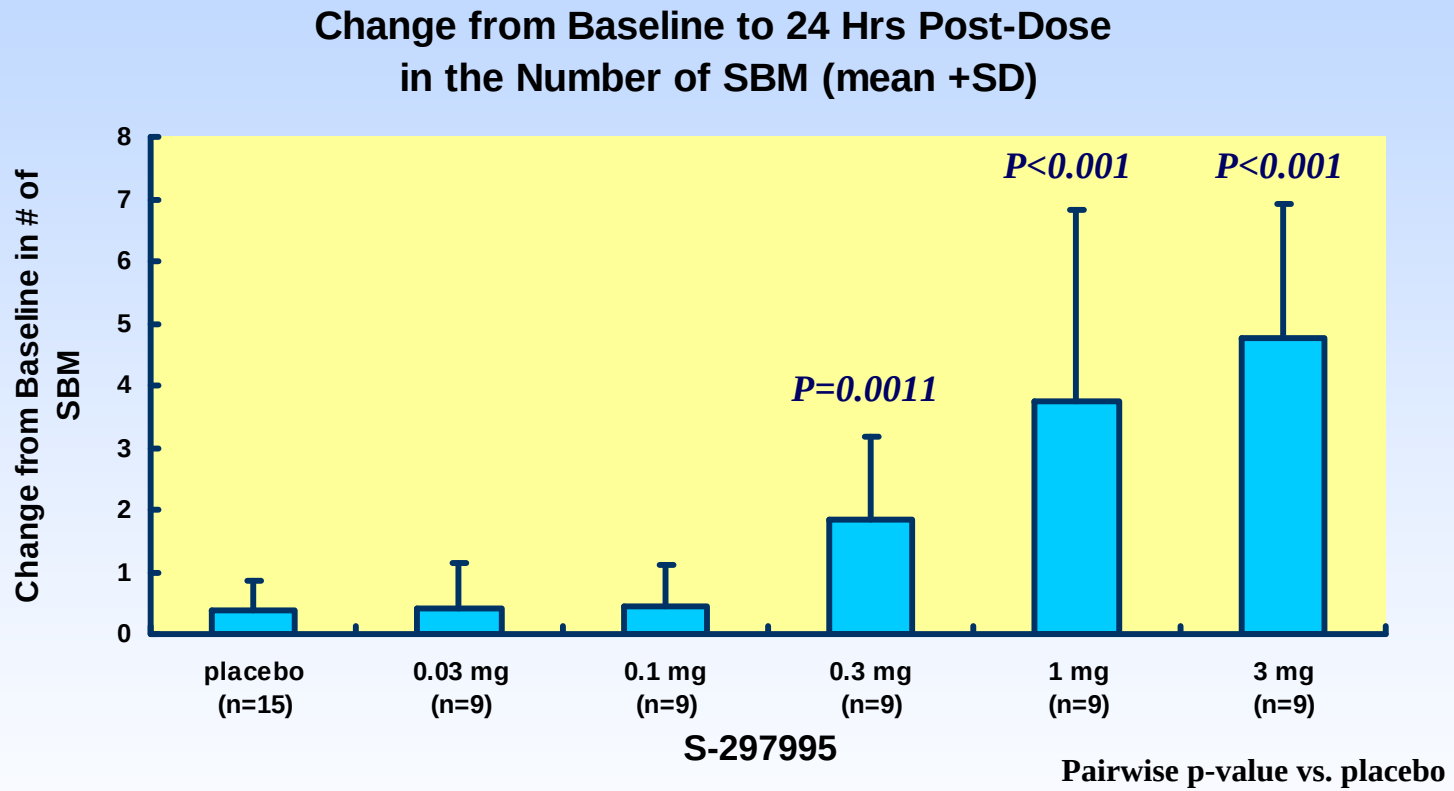


- **Opioids are administered for patients with moderate to severe pain including cancer or chronic pain. The amount of worldwide sales of opioids was around US$11 billion in 2010, and sales volume are still now increasing**
- **Side effects, such as nausea/vomiting and constipation, are occurred in more than 40% of opioid users**

S-297995: Phase IIa Study Synopsis in the USA

- **Primary objective**
  - **To evaluate the safety and efficacy of single dose S-297995 for treatment of opioid induced constipation (OIC) in subjects physically dependent on opioids**
- **Study design**
  - **Single center, randomized, double-blind, placebo-controlled, single-ascending dose**
- **Subjects**
  - **72 adult subjects (Age 18 – 65 yrs)**
  - **Diagnosis of chronic pain, OIC and opioid physical dependence**
  - **Morphine equivalent ≥90 mg daily and receiving opioid therapy ≥3 months**
- **Dosing regimen**
  - **Single oral dose administered under fasted conditions**
  - **6 dosage levels tested (0.01 mg, 0.03 mg, 0.1 mg, 0.3 mg, 1 mg, 3 mg)**

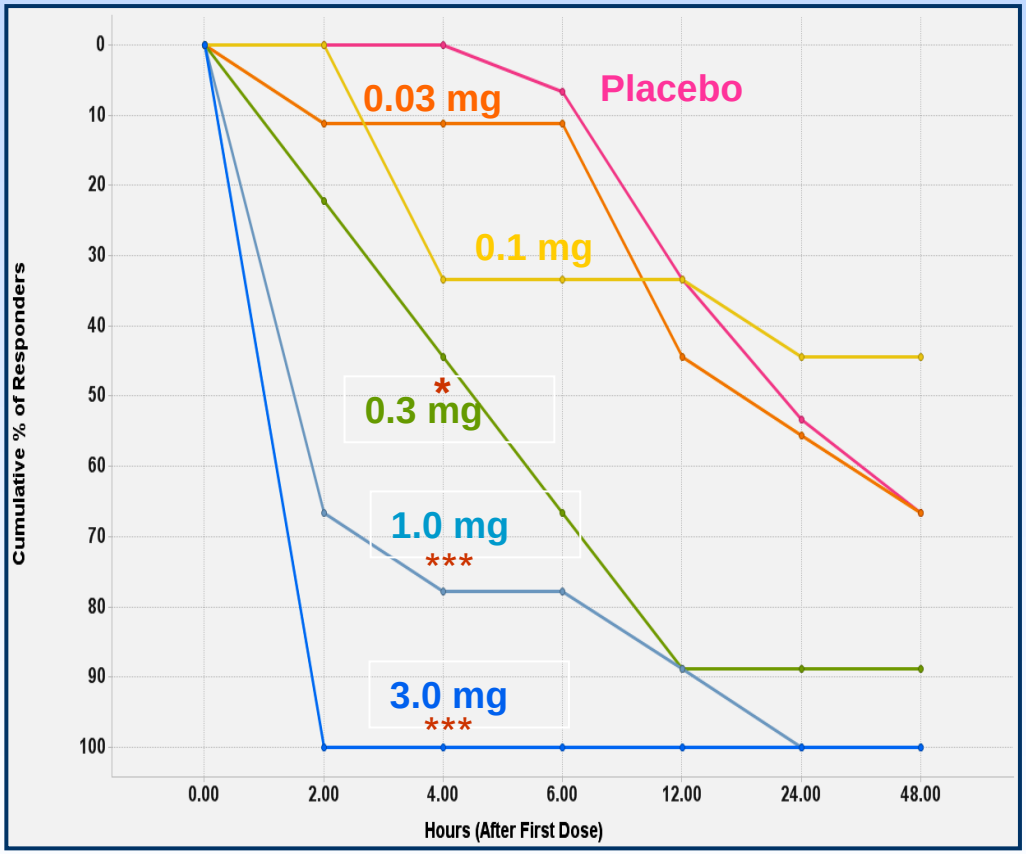
S-297995: Preliminary Data of Phase IIa Study in the USA



Change from baseline in number of SBM* became statistically significant at doses ≥ 0.3 mg

* SBM: Spontaneous Bowel Movement

S-297995: Preliminary Data of Phase IIa Study in the USA (Cumulative Response Rate of SBMs Over Time)



*P=0.024 ***P<0.0001

•Pair-wise p-value vs. placebo
•P-values based on Z test for two proportions

Statistical significance at doses ≥ 0.3 mg

S-297995: Summary of Phase IIa Study in the USA and Future Plan

- **Results of Phase II study for patients with opioid-induced constipation**
  - **No serious adverse events reported**
  - **Most common adverse events were mild or moderate gastrointestinal symptoms**
  - **No apparent CNS effect (analgesic interference or pupil size change) observed**
  - **Significantly increased in number of spontaneous bowel movements at 0.3 mg and more doses**
- **Future Plan**
  - **Phase IIb study in patients with opioid-induced constipation (US and Japan)**
  - **Phase I study for evaluation of anti-emetic effect (US)**

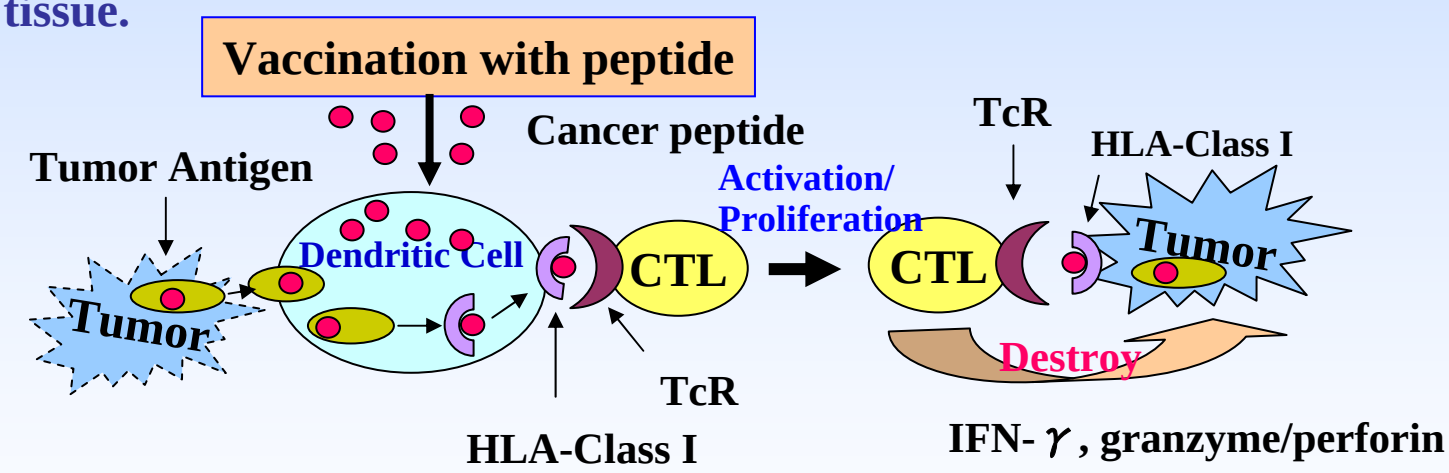
Core Development Products

Cancer and Other Areas

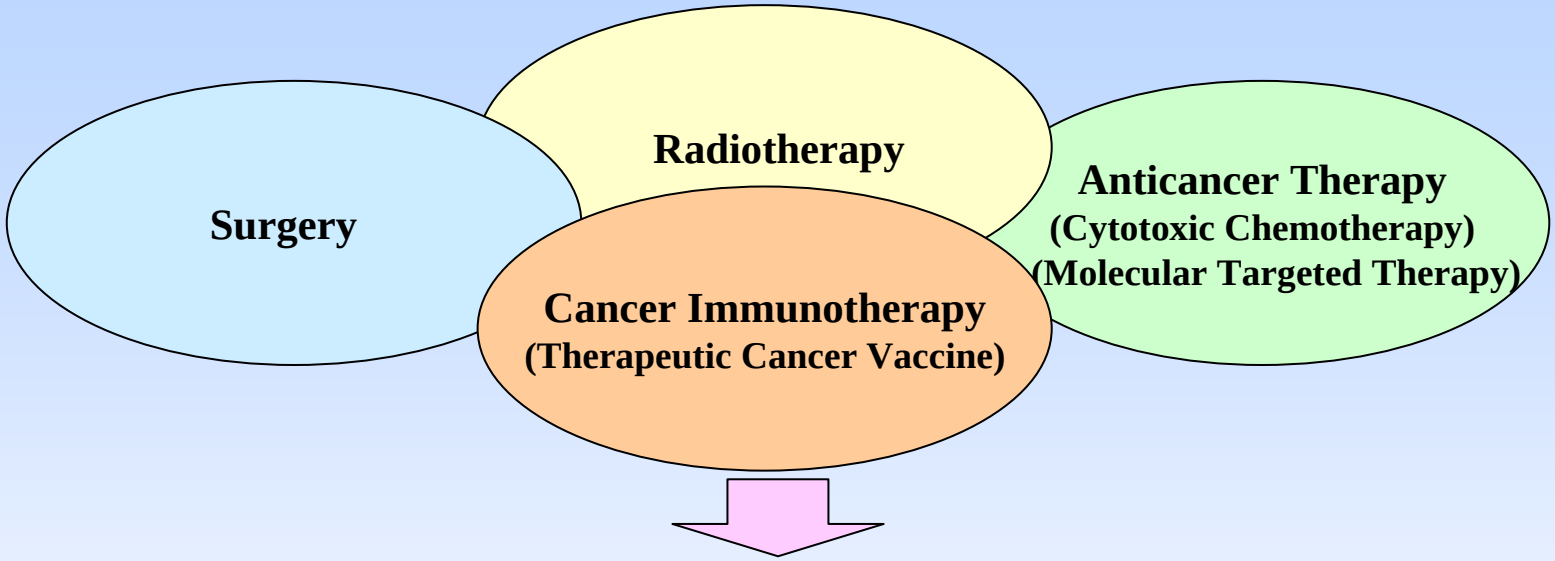
SHIONOGI & CO., LTD.

Mechanism of Action of Peptide Cancer Vaccine

- **Cytotoxic T-Lymphocytes (CTL) can be effectively and safely induced by vaccination with synthetic peptide derived from tumor-associated antigen (TAA) expressed by tumor cells but not by normal cells (except for testis). These CTLs are able to destroy tumor cells expressing HLA class I-presented epitopes.**
- **Each peptide used for vaccination is HLA-binding domain of TAA, therefore it is expected to induce CTL much more efficiently than full length proteins or lysate of tumor tissue.**



Peptide Cancer Vaccine Therapy



Peptide cancer vaccine therapy is anticipated to become the *forth major cancer treatment* alongside surgery, anticancer therapy and radiotherapy

- **Existing immunotherapies are mainly non-specific, the efficacy of which is, in general, insufficient in terms of anti-tumor activity**
- **In contrast, cancer vaccine using peptides derived from tumor-associated antigen can effectively induce cytotoxic T lymphocytes (CTL), which specifically destroy tumor cells expressing the epitope antigens**
- **Peptides used for vaccination are generally safe because they are endogenously expressed on tumor cells. So they could be used in combination with other therapies, such as chemotherapy and small molecules, without reducing quality of life (QOL)**

Peptide Cancer Vaccines (S-288310, S-488410): Profile

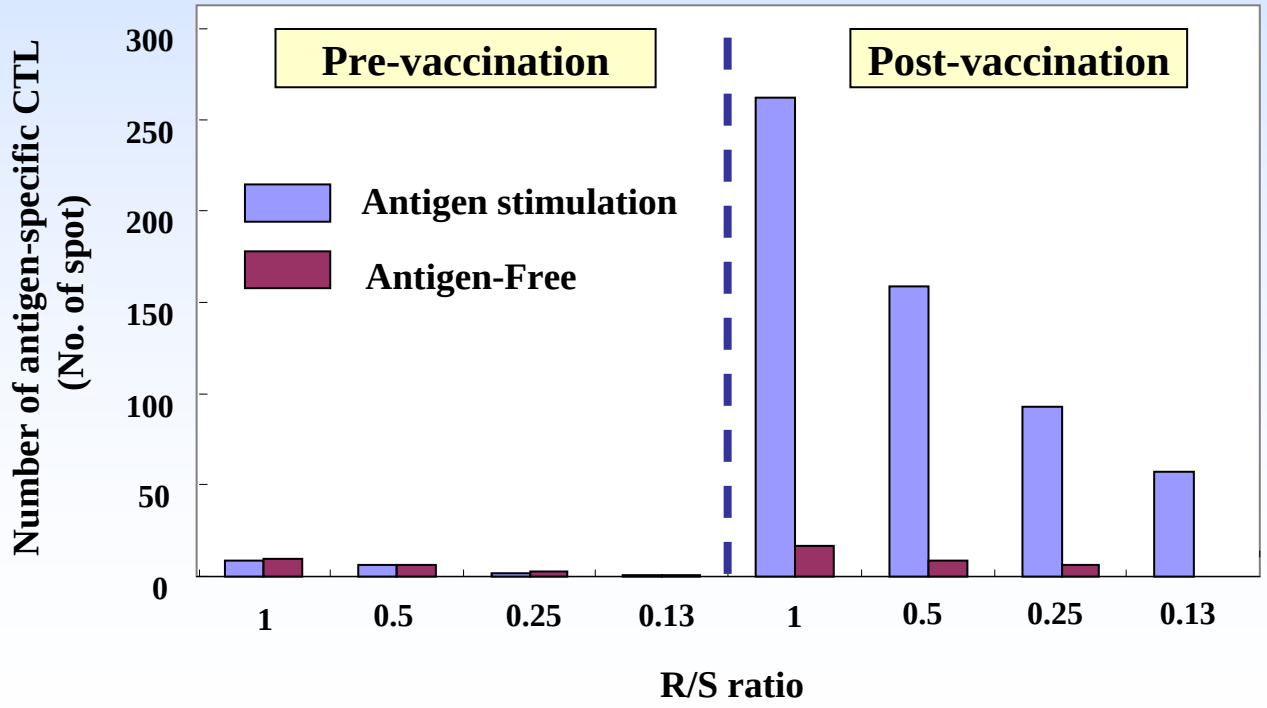
- **Licensed from OncoTherapy Science, Inc (Japan)**
- **Indication: S-288310 (bladder cancer), S-488410 (esophageal cancer, head and neck cancer, etc.)**
- **Mechanism: Therapeutic peptide cancer vaccine**
- **Characteristics:**
  - **Containing two or three HLA-A*24:02-restricted peptides**
  - **Peptides derived from proteins selectively expressed by tumor cells**
  - **Target proteins are critical for cancer cell growth**
  - **CTL induction is confirmed in patients with bladder or esophageal cancer who had failed standard therapy in translational research**
  - **These peptides bind to class I molecule HLA-A*24:02 on antigen presenting cells, thereby enabling a specific CTL response to be induced**

S-288310: CTL Induction in Phase I Study

【ELISPOT Assay】

- Assay for detection of antigen-specific CTL activity in peripheral blood lymphocytes
- CTL induction confirmed in 5 of 6 patients → To Phase II study

A case of patients who demonstrated CTL activity

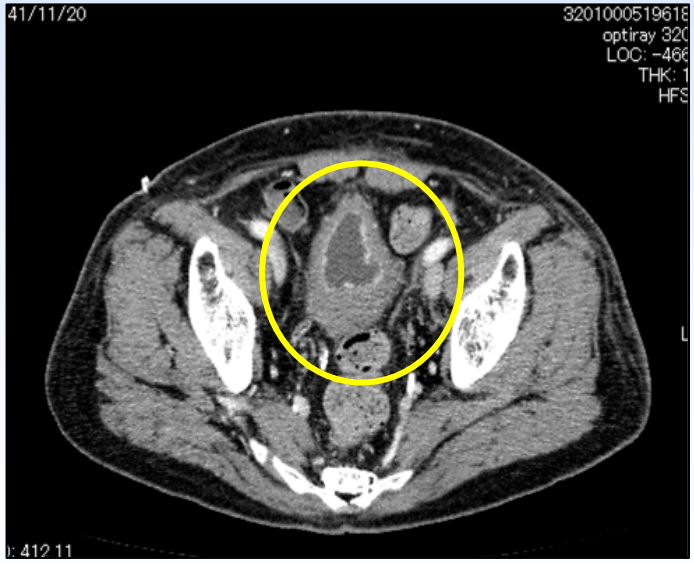


R/S ratio: Responder cells/Stimulator cells

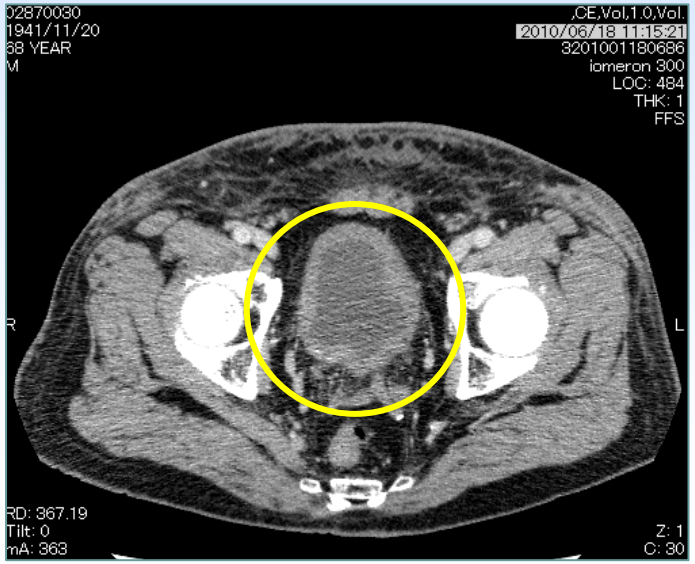
S-288310: Anti-Tumor Effect in Phase I Study

- **A patient with primary tumor and metastasis in lymph node**
- **At 12 weeks post-vaccination, the thickened wall of bladder was improved and the left inguinal lymph node shrunk, but growth of right inguinal lymph node and new lesion in para-aortic lymph node were observed**

Pre-vaccination



Post-vaccination

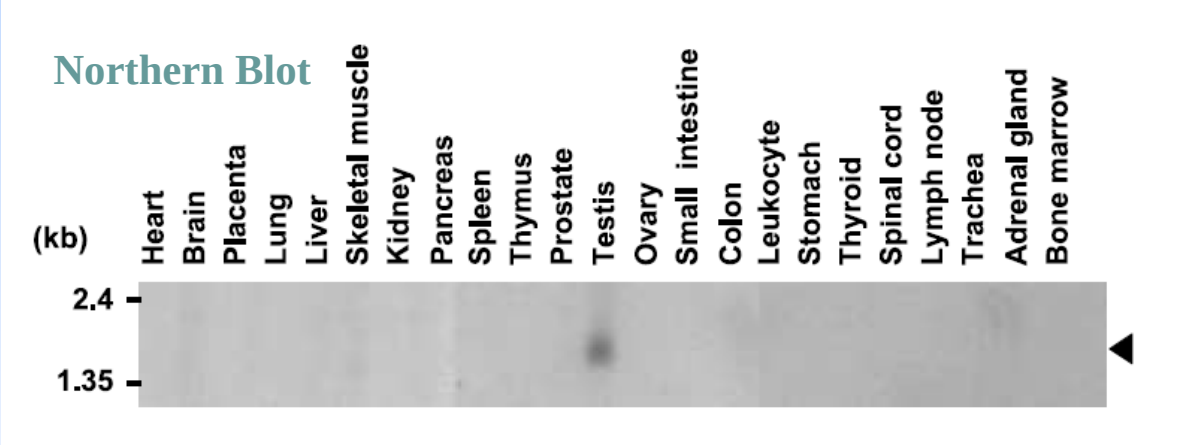


Improvement of thickened bladder wall

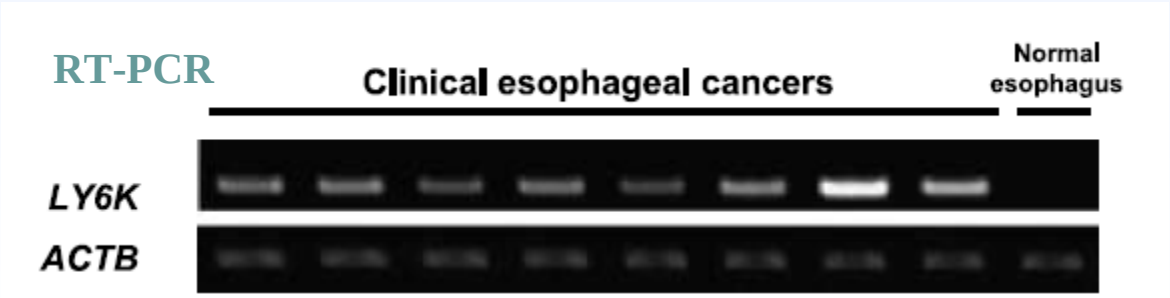
S-488410: Profile of Expression of Target Protein

- **Represents one of three target protein**

(1) Expressed in testis but not other organs



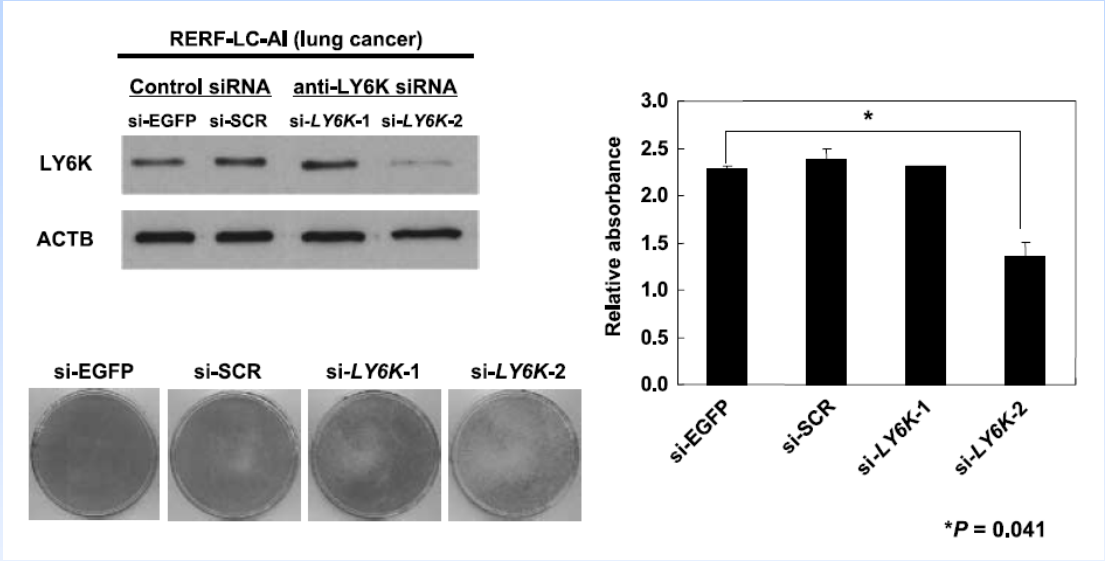
(2) Highly expressed in esophageal squamous cell carcinoma: Positive in 8 of 8 patients



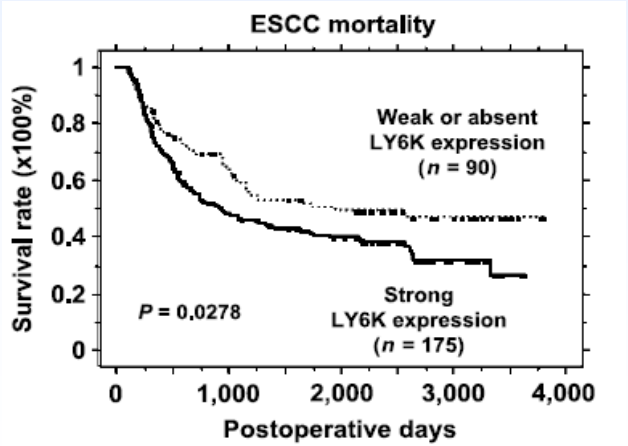
Ishikawa et al., Cancer Res 2007;67 11601-11611

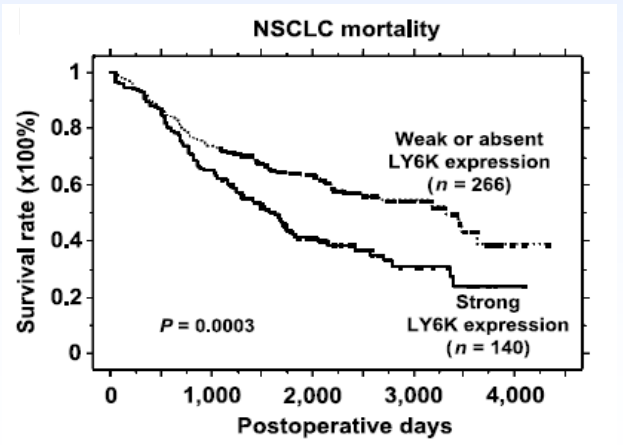
S-488410: Role of the Target Protein in Growth of Tumor Cells

(3) Growth inhibition of tumor cells by siRNA against the target



(4) Overexpression of the target associated with poor prognosis in cancer patients





Ishikawa et al., Cancer Res 2007;67 11601-11611

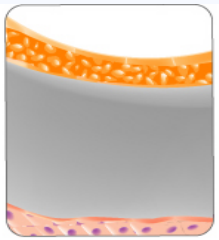
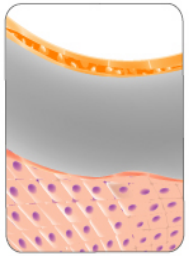
Ospemifene: Profile

- **Indication: Vulvar and vaginal atrophy (VVA)**
- **Under development in US. Licensed in from QuatRx in Mar, 2010**
- **Mechanism: Selective Estrogen Receptor Modulator (SERM)**
  - **Its estrogenic action in the vagina differentiates Ospemifene from the other currently available SERMs like raloxifene and tamoxifene**
  - **Ospemifene has significant antitumor activity in mammary cancer in rat. Ospemifene has estrogen receptor antagonistic in mammary gland**
- **Characteristics:**
  - **Oral, 60mg Tab. once-daily non-estrogen treatment for VVA**
  - **Favorable safety profile on risks highlighted by estrogen related products**
    - **Thromboembolism**
    - **Endometrial safety**
- **Status: Phase III studies were completed, then the bioequivalence study with commercial product is now underway**

Ospemifene: Vulvar and Vaginal Atrophy (VVA)

- **Estrogen plays an important role in maturation, proliferation, and function of urogenital mucosa, and affects thickness of vaginal epithelial cells, elasticity, and vaginal secretion**
- **VVA is a condition associated with declining estrogen levels after menopause, with symptoms that include dryness, burning, dyspareunia, vulvar pruritus, and atrophic change in genital and lower urinary tracts. VVA is also associated with urinary symptoms including frequency, over reactive bladder, and stress incontinence**
- **Reduced colonization of lactobacilli in vaginal epithelial cells increases vaginal pH, and then increases incidence of vaginal and urinary tract infections**
- **More than half of women aged 60 or older are suffering from VVA (Suckling JA, et al, The Cochrane collaboration 2008 Issue 4(1)) We estimate a total of 817,000 Ospemifene patients in the USA**

Vaginal epithelium

Pre menopause			Menopause		Post menopause
Superficial cells:		15%	→		1%
Intermediate cells:		80%			60%
Parabasal cells:		5%			39%

Ospemifene: Results of Pivotal Phase III study (1):
Placebo-Controlled Study 15-50310

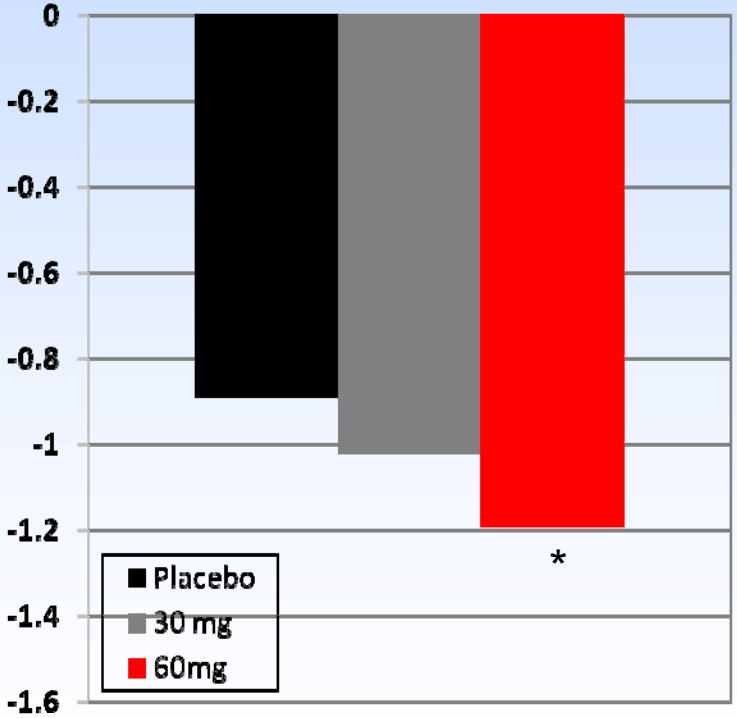
Co-primary endpoint (Change from baseline to week 12)	Ospemifene 60mg N = 276 (Comparison to placebo)
Increase in superficial cells from vaginal smear	p＜0.001
Decrease in parabasal cells from vaginal smear	p＜0.001
Decrease in vaginal pH	p＜0.001
Improvement in most bothersome moderate to severe symptom assessed on a 0-3 scale as recommended by FDA	Dyspareunia：p＜0.05 Dryness：p＜0.05

2nd placebo-controlled study 15–50821 successfully met four co-primary endpoints. The results show statistically significant difference from placebo in increase in superficial cells from vaginal smear, decrease in parabasal cells from vaginal smear, decrease in vaginal pH, and improvement in dyspareunia

Ospemifene: Results of Pivotal Phase III Study (2) :
Placebo-Controlled Study 15-50310

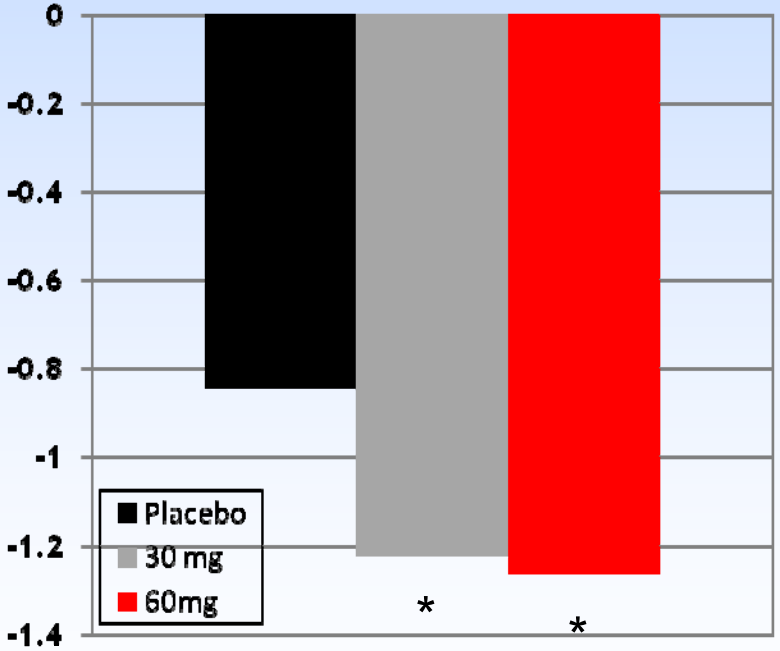
Most bothersome moderate to severe symptom

Dyspareunia



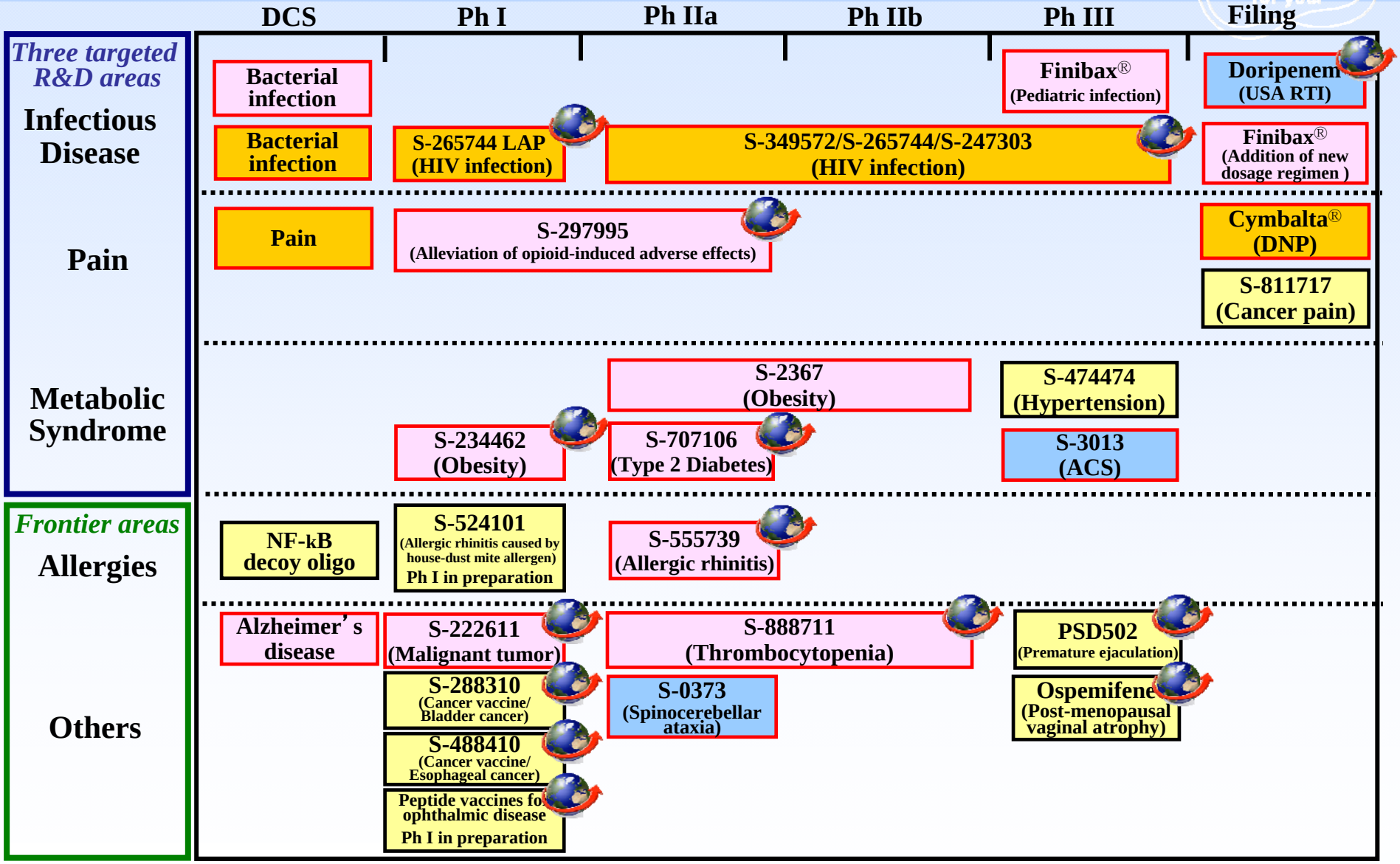
*** p < 0.05**

Dryness



*** p < 0.05**

Development Pipeline Enrichment (as of March 2011)



LAP: Long-acting parenteral formulation, RTI: Respiratory tract infection,
DNP: Diabetic peripheral neuropathic pain, ACS: Acute coronary syndrome,
DCS: Drug candidate selection

Developing products globally

In-house | Co-development | Out-licensed | In-licensed

Summary

Isao Teshirogi, Ph.D.
Chief Executive Officer and Representative Director
Shionogi & Co., Ltd.