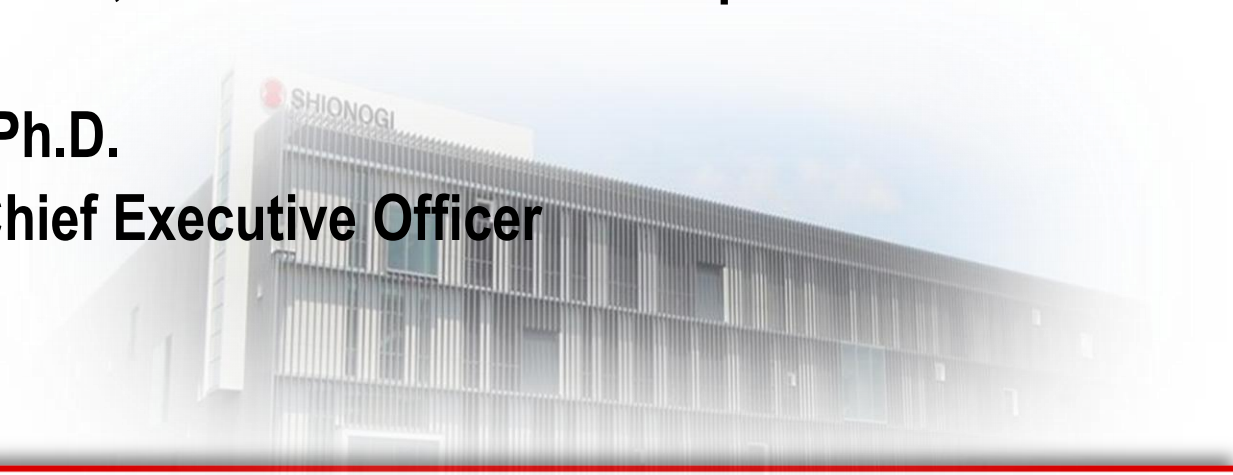
Research and Development at Shionogi

SHIONOGI & CO., LTD
March 19, 2014

SHIONOGI

Agenda

1. Research
   Kohji Hanasaki, Ph.D.
   Senior Vice President
   Pharmaceutical Research Division
2. Development
   Takuko Sawada
   Senior Vice President
   Global Development, Pharmaceutical Development Division
3. Summary
   Isao Teshirogi, Ph.D.
   President and Chief Executive Officer
4. Q&A



Research

Our Progress on the 3rd Medium-Term Business Plan and Our Action Plan for FY2014

Kohji Hanasaki, Ph.D.
Senior Vice President
Pharmaceutical Research Division

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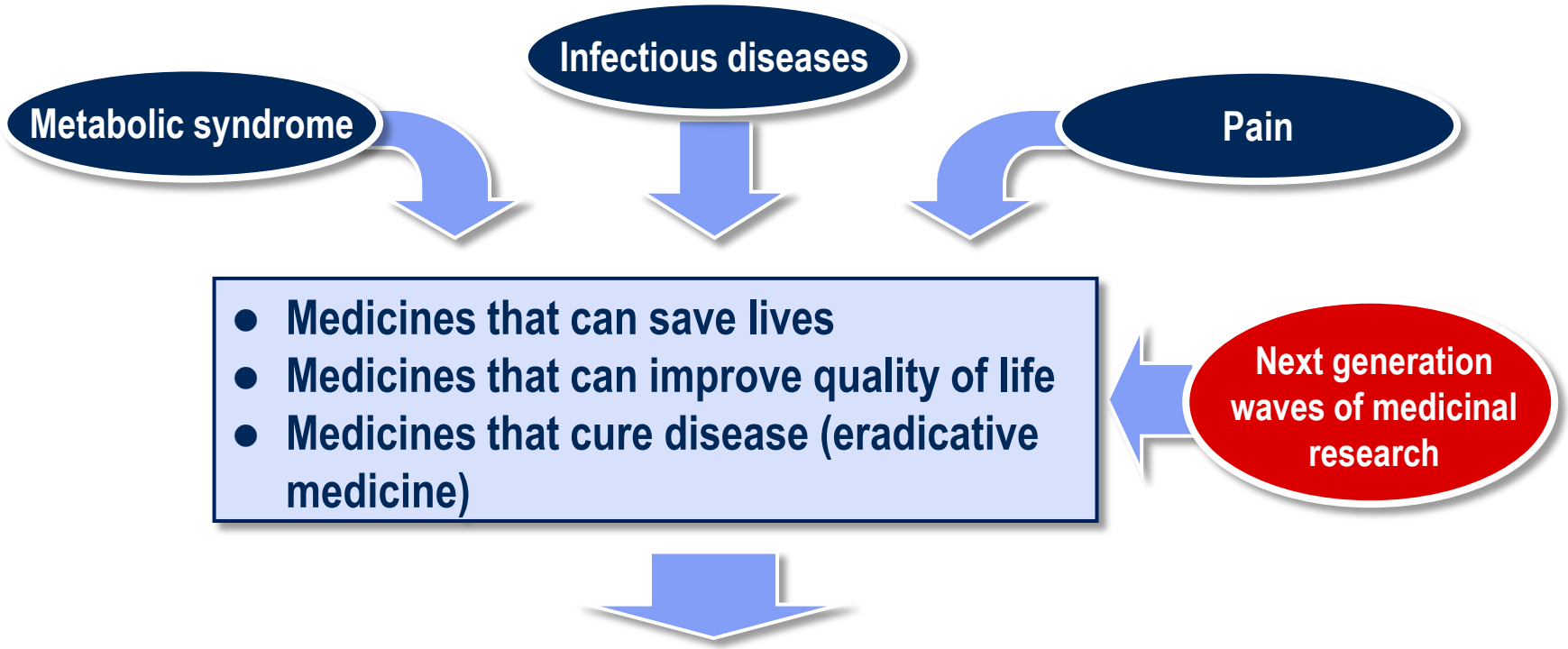
The Scope of Drug Discovery Research in Shionogi



Shionogi's purpose

"Shionogi strives constantly to supply the best possible medicine to protect the health and wellbeing of the patients we serve"

Goals for the 3rd Medium-Term Business Plan

Research productivity at a world-class level

- Discover new molecular entities with 50% or higher rate of successful progression from early to late clinical phases
- Discover 4 or more novel drug candidates (DCs) per year
  (Aim to establish a system that enables the discovery of 5 or more DCs/yr from 2015)

Strengthening early stage drug discovery portfolio

Improvement of success rate for clinical efficacy

Centralization of functions while increasing flexibility

Points emphasized during the 3rd Medium-term Business Plan

Strengths of Shionogi's drug discovery research capabilities built during the 2nd Medium-term Business Plan

"Highly efficient small-molecule drug discovery-engine"

Progress on the 3rd Medium-Term Business Plan

Discovered 12 innovative drug candidates (small and large molecules)
(including 1 compound currently under safety evaluation for candidate selection)

12 internally-discovered drug candidates progressed into clinical development
(including 1 compound in preparation for selection)
(Success rate in clinical phase progression: 80%)

Achieved greater than 50% success in moving from early to late clinical phases

- Continued strong commitment to internal drug discovery
- Increased rate of successful progression of drug candidates into clinical development, through optimization of candidate characteristics
- Established drug discovery platforms for large molecules in addition to small molecules - antibodies, vaccines, etc.

Approaches to Achieve
“Research Productivity at a World-Class Level”

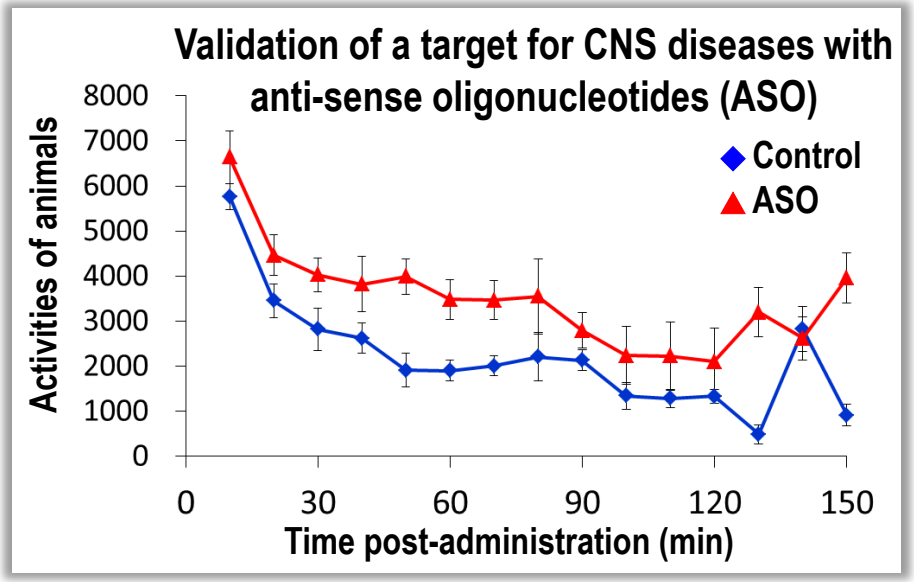
Activities in the 3rd Medium-Term Business Plan

- **Realizing the maximum potential from Shionogi's discovery research strengths**
  - Pursuit of research programs targeting "innovative First-in-Class" and "unrivaled Best-in-Class" candidates by utilizing Shionogi's established strengths in small-molecule drug discovery
- **Optimizing critical performance elements**
  - Strengthening the early drug discovery portfolio
    - Supplementing internal research through collaboration with academia and pharmaceutical and venture companies
  - Improving the success rate of Shionogi compounds in clinical trials
    - Enhance preclinical evaluation through adding new tests and technologies, including *in vitro* assays capable of predicting human performance, PET* imaging, iPS cells**, etc.
  - Integrating research functions while enhancing flexibility
    - Strengthening of cross-functional research collaboration in SPRC***
- **Establishing new drug discovery research platforms**
  - Added platforms for large molecules including antibodies and vaccines

*: Positron-Emission Tomography; **: induced pluripotent stem cells; ***: Shionogi Pharmaceutical Research Center

Reinforcement of Internal Research through Partnerships

Internal research



Collaboration with partners

Hokkaido University | University of Tokyo | Kyoto University | Osaka University | etc.

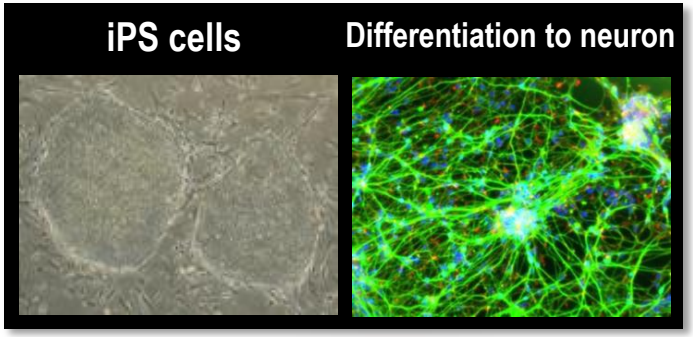
Purdue | GSK | Janssen | OTS | etc.

Basic research → Target discovery → Target validation → Drug discovery

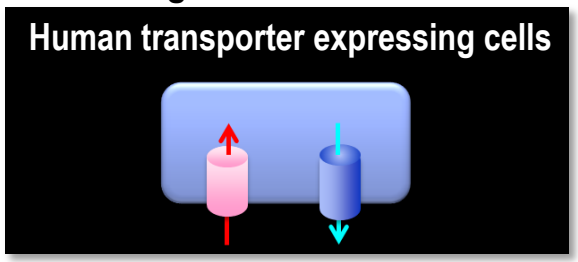
- **Internal**: Strengthened target discovery and validation platform, including use of ASO technology
- **Academia**: Funded and incubated innovative early research seeds
- **Pharmaceuticals and venture companies**: Licensed clinical candidates in our therapeutic areas of focus

Improvement of Ability to Predict Clinical Trial Success

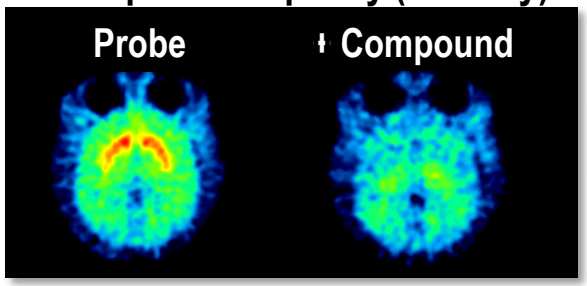
induced pluripotent stem (iPS) cells



Human gene transfected cells



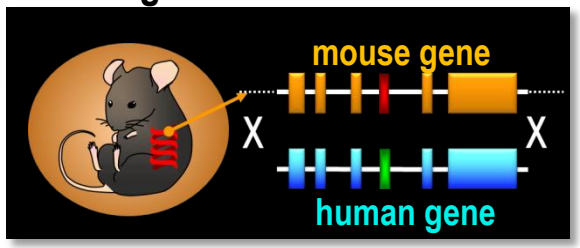
Receptor occupancy (monkey)



positron-emission tomography (PET) imaging

Improvement of predictive performance

Human gene transfected mouse



human gene transfected cells, animals

Introduced and applied useful technologies and techniques in our preclinical evaluation platform, including PET imaging, iPS cells, gene transfer, etc.

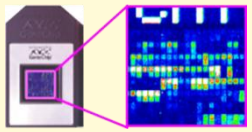
Discovery of High Quality Drug Candidates

Drug discovery → Candidate selection → Candidate → Long-term toxicity study → Clinical trial

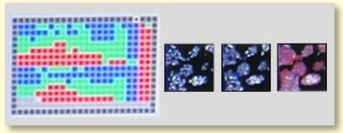
Feed back of information

Development and refinement of sophisticated evaluation process drawing upon information from prior long-term toxicology studies and clinical trials, and implementing this process in drug discovery

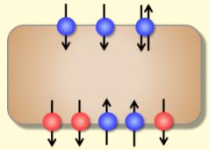
Toxicogenomics



High-content screening systems for safety evaluation



***In vitro* assay items reflected human pharmacokinetics**



Significantly increased success rate in candidate identification and long-term toxicity studies

High success rates achieved by enhancing the preclinical evaluation platform with the incorporation of new *in vitro* assays more closely reflecting effects in humans, and integration of this platform into the drug discovery process

Further Improvement of Research Productivity

Concentrating research functions in SPRC

Research Labs
(Fukushima-ku, Osaka)

CMC Development Labs
(Amagasaki, Hyogo)

Aburahi Labs
(Koka, Shiga)

Institute for Medical Science
(Settsu, Osaka)

Discovery | Chemistry
Pharmacology | Pharmacokinetics
Safety | CMC

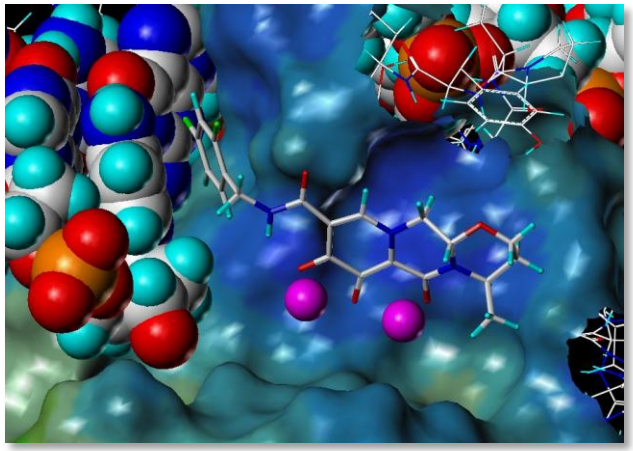
- Bringing together the expertise of researchers at SPRC
- Creating breakthrough ideas from closer and active discussion

Approaches and Progress in Our Therapeutic Areas of Focus

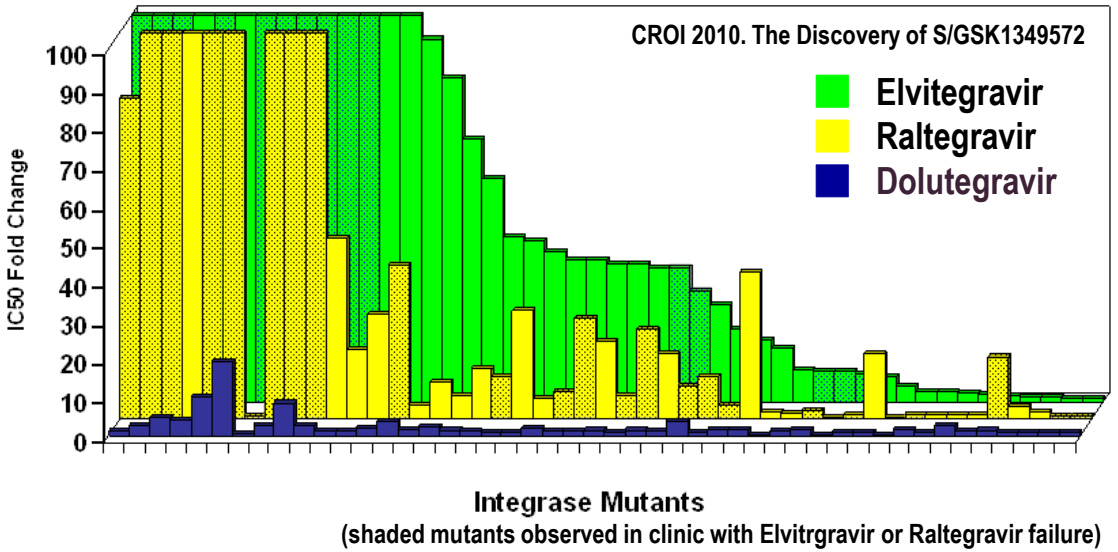
Infectious Diseases: Strength in Research for Anti-Viral Drugs

Created and launched "unrivaled Best-in-Class" anti-HIV drug; "Dolutegravir"

Concentrating research capabilities on small molecule drug discovery



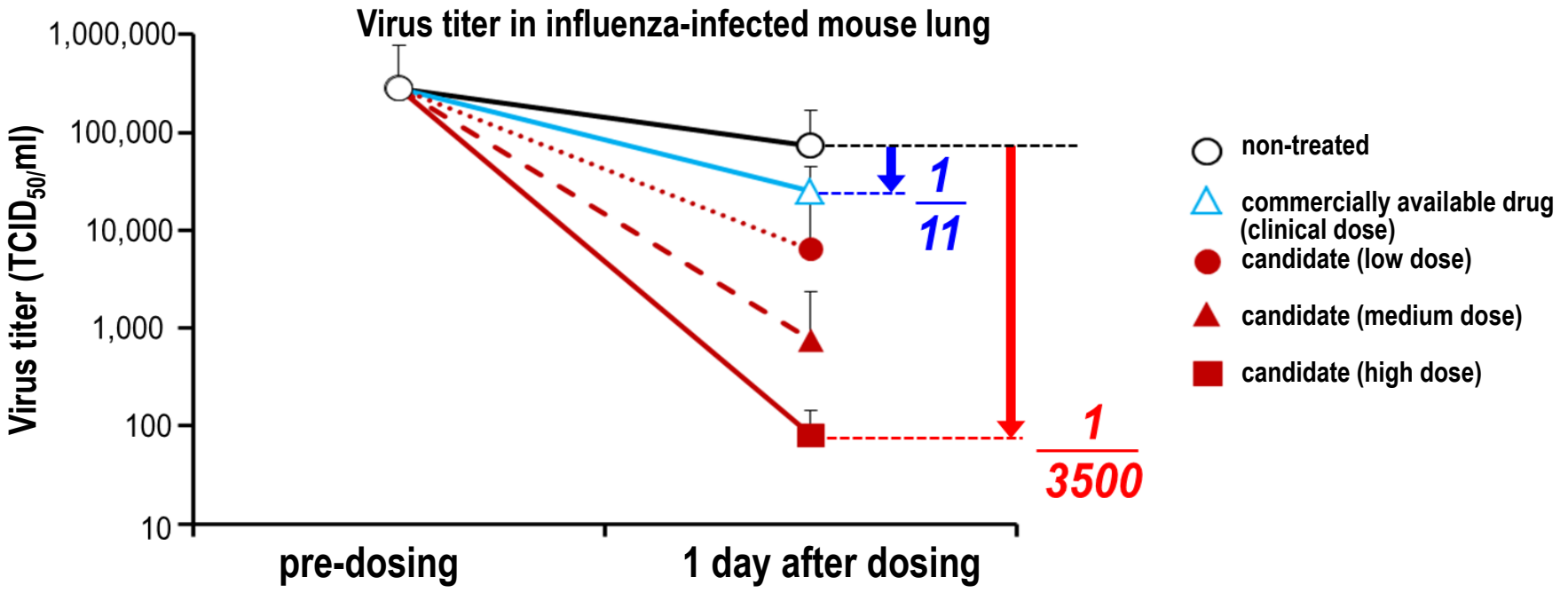
High genetic barriers



Expanding and applying our know-how in anti-HIV drug discovery to other anti-viral drug discovery

Infectious Diseases: Discovery of an Anti-Flu Drug Candidate

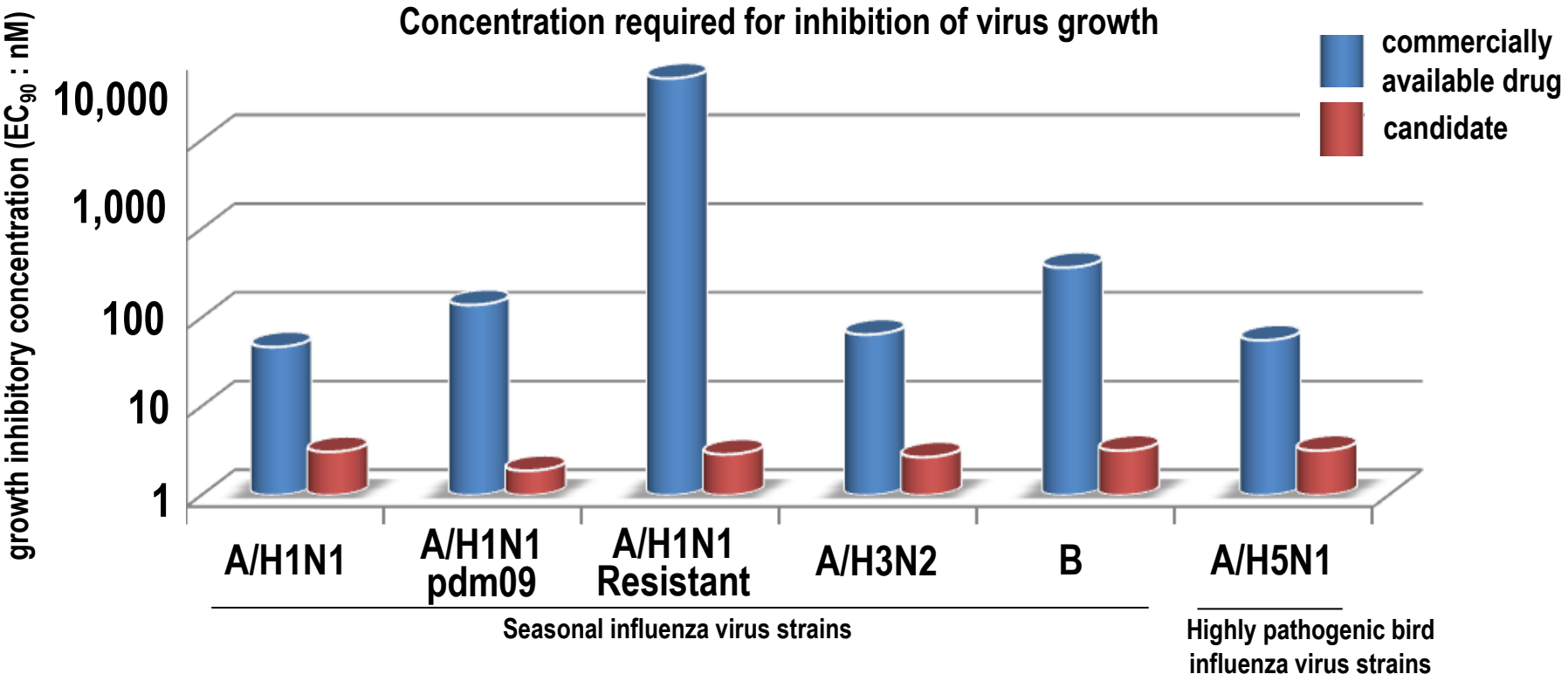
Discovered an oral anti-flu drug candidate, aiming at "innovative First-in-Class"



- Discovered a candidate with strong anti-flu activity with a novel mechanism of action
- Much greater decline in viral load in mouse model compared to that achieved with a commercially available comparator

Infectious Diseases: Discovery of an Anti-Flu Drug Candidate

Antiviral activity against various influenza virus strains

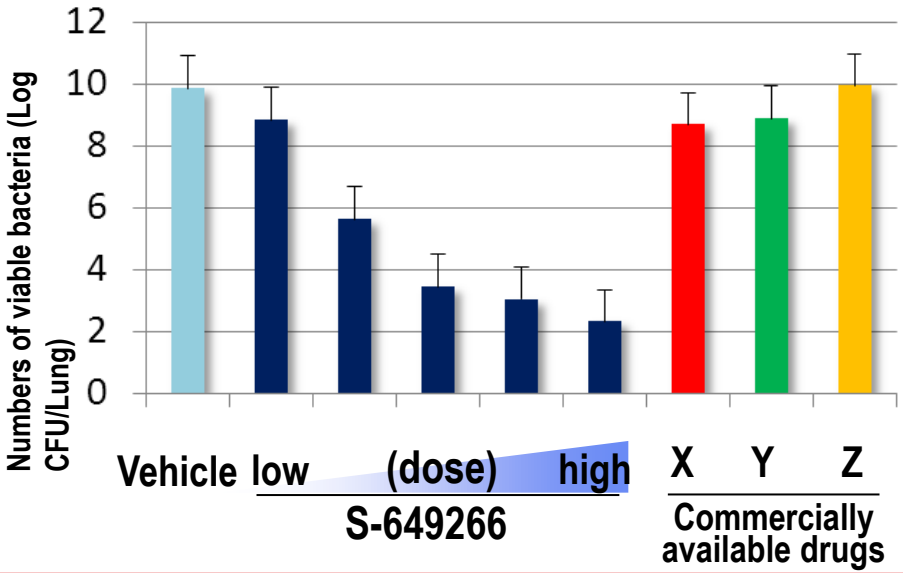


Showed potent *in vitro* inhibitory activity against both seasonal and highly pathogenic bird influenza strains resistant to a commercially available comparator

Infectious Diseases: Discovery of Anti-Bacterial Drugs

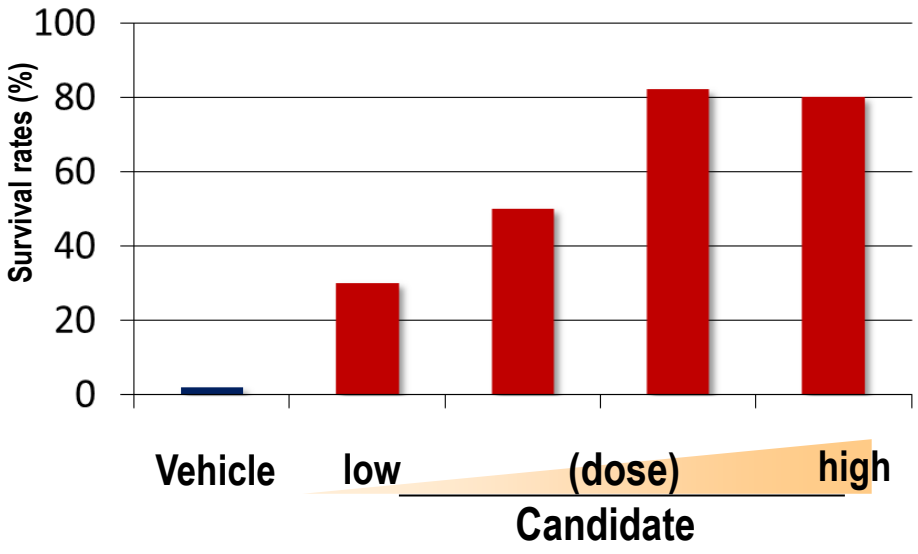
Progressing S-649266, an anti-gram-negative-bacteria candidate, into the clinical stage

Number of multi-drug-resistant *Acinetobacter* in the lung



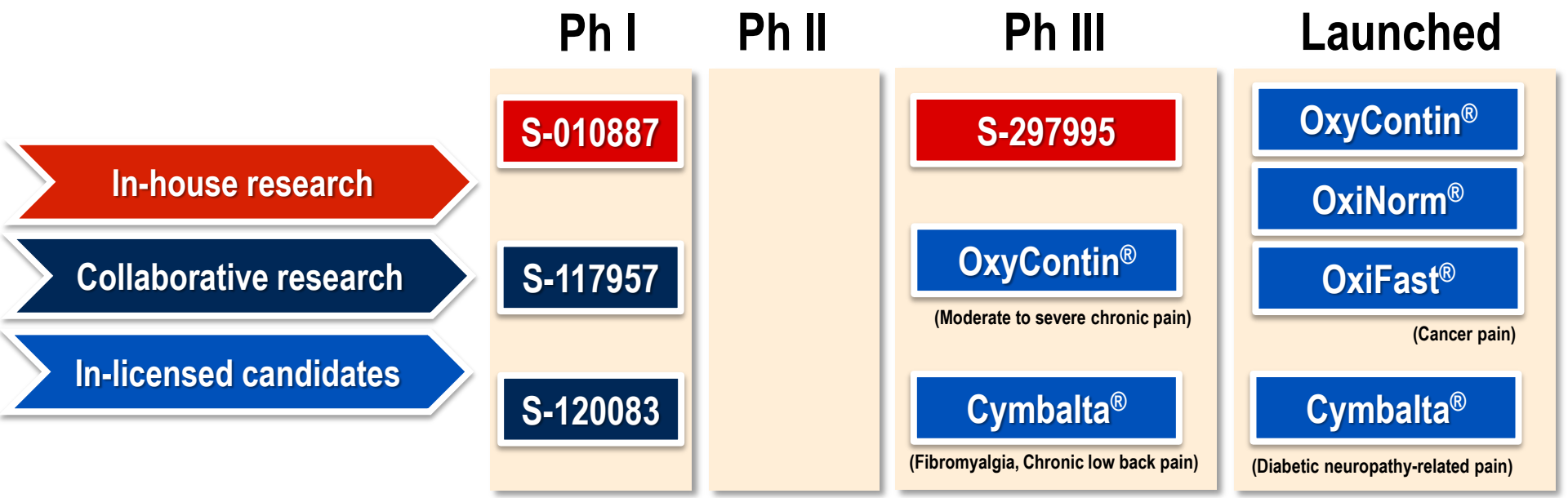
Discovery of an antibody drug candidate against *Pseudomonas*

Survival rates of mice infected with *Pseudomonas* in the lung



- Discovered a candidate with excellent activity against multi-drug-resistant bacteria through our established drug discovery platform for beta-lactam antibiotics, aiming at “unrivaled Best-in-Class”
- Discovered an antibody drug candidate against *Pseudomonas*, which was difficult to treat with beta-lactams, with greater activity in mouse lung models compared to commercially available comparators

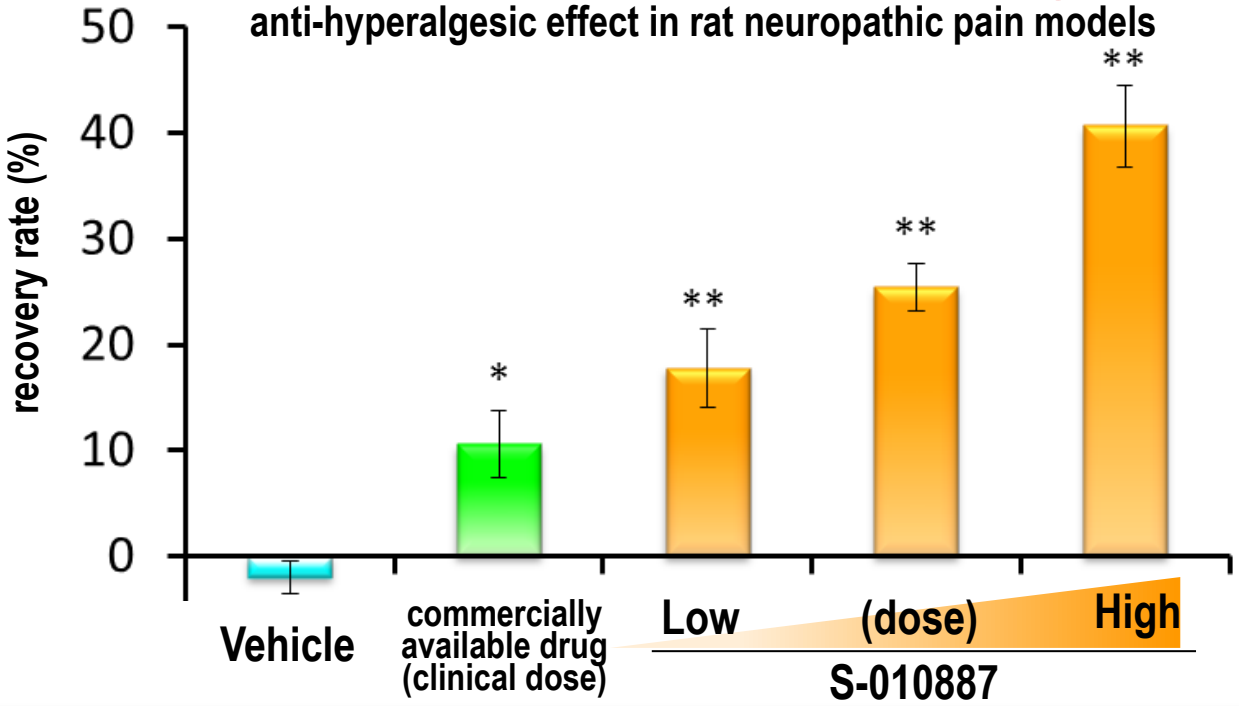
Pain: Strengthening and Enriching of Pipeline in Pain Research



- Discovered three “next generation-analgesics” entities through in-house and collaborative research
- Enriched development pipeline in pain area, including clinical candidates licensed from other pharmaceutical companies

Pain: Discovery of a Neuropathic Pain Drug Candidate

Progressing S-010887, an "innovative First–in-Class" drug candidate, into the clinical stage

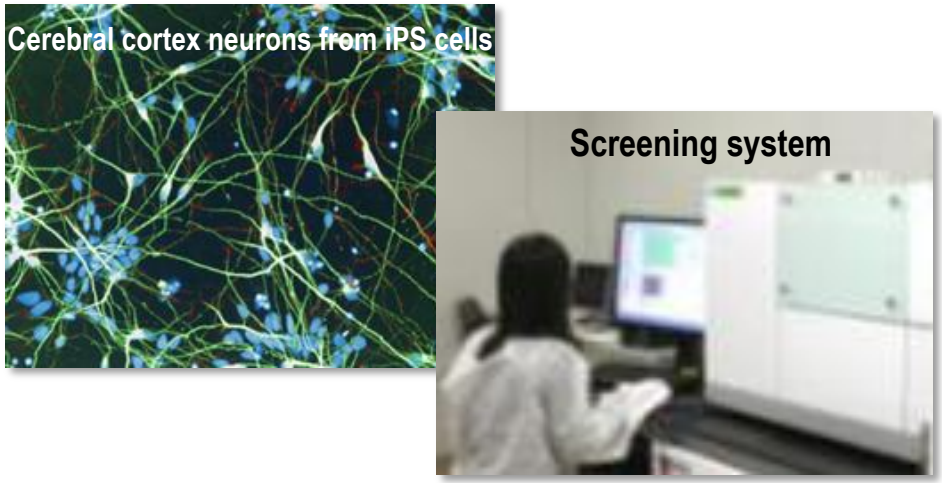


*:p<0.05 vs. Vehicle
**:p<0.01 vs. Vehicle

Discovered a candidate with a novel mechanism and better efficacy in neuropathic pain models than a commercially available comparator, and advanced it into clinical development

Neurology: Expanding CNS Drug Discovery Through External Research Collaborations

Started full-scale operation of the Kyoto University Medical Innovation Center to discover innovative drugs for improving synapse function



Established the methods for differentiation of iPS cells into neurons, and applied these methods to neuroregeneration drug discovery

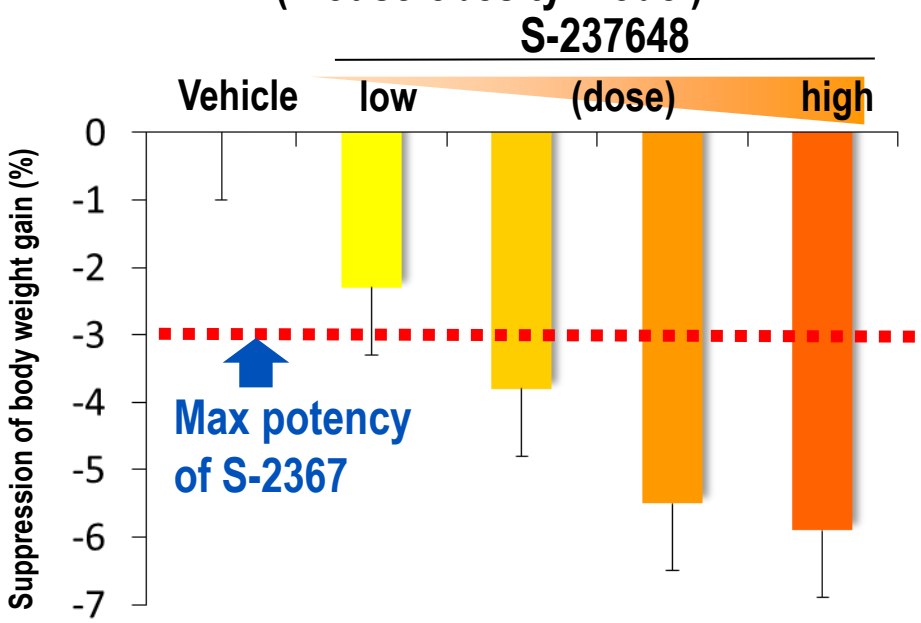
- Discovered a BACE inhibitor for treatment above Alzheimer's disease through in-house research, and established a collaboration with Janssen for further progression of this compound and program in pursuit of an "unrivaled Best-in-Class" BACE inhibitor
- Pursuing discovery of "innovative First-in-Class" drugs for CNS diseases with a novel mechanisms of action through both in-house and collaborative research

CNS: Central nervous system BACE: Beta-site amyloid precursor protein cleaving enzyme

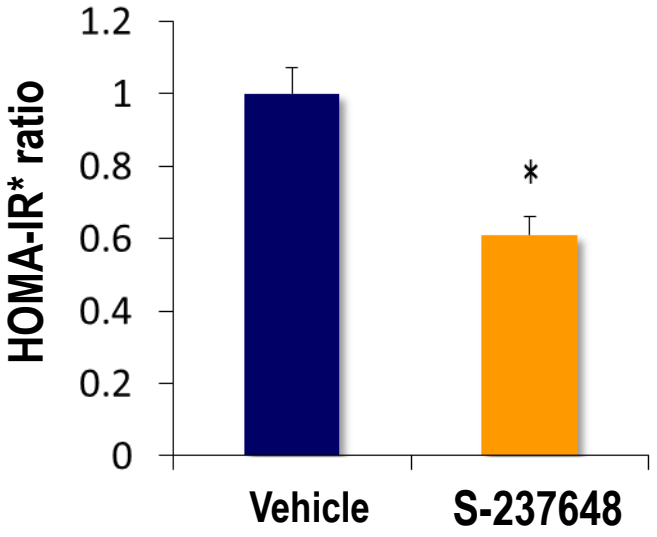
Metabolic Diseases: Discovery of an Anti-Obesity Drug Candidate

Discovery of an anti-obesity drug candidate, targeting an "innovative First-in-Class" profile

Suppression of body weight gain
(mouse obesity model)



Improvement of insulin resistance
(mouse obesity model)



* P<0.05 vs Vehicle

Discovered the best NPY Y5 receptor antagonist S-237648 following S-2367 and S-234462, and progressed it into clinical development

*: Homeostasis model assessment-Insulin Resistance

Our Action Plan for FY2014:

Meeting Society's Healthcare Needs by Applying Our Strong Drug Discovery Research Capabilities

Waves of Next Generation Medicinal Research Guided by Society's Needs

Facing a rapidly-aging society in developed countries

- Reduction in working age population
- Increase in economic burden of healthcare
- Increase in requirements for healthcare

Rapidly-aging society*	2010		2030
	Japan	→	Japan, Canada, France, Germany (US: 19.9%)

Addressing the needs of a rapidly-aging society (i.e., extension of healthy life expectancy, support for patients in the desire to return to productive activities etc.) by capitalizing on our strengths in drug discovery research

- Geriatric Metabolic Disease
- Oncology and novel immuno-modulating therapies

*: more than 21% of its population aged 65 or over from Population Statistics (2013) - National Institute of Population and Social Security Research

Reorganization of Research Laboratories

- **Discovery Research Laboratory for Core Therapeutic Areas**: Capitalize on our strength

Infectious Diseases

- Expand anti-HIV drug discovery platform into other anti-viral discovery areas
- Accelerate research and development for multi-drug-resistant bacteria
- Pursue drug discovery for emerging and re-emerging infectious disease

Pain/CNS

- Strengthen R&D for treatment of pain
- Enter neurology/psychiatric areas, starting with Alzheimer's disease and ADHD*
- Pursue discovery of neuro-regeneration drugs that may improve synapse and neural function

- **Discovery Research Laboratory for Innovative Frontier Medicines**: Establish our next core therapeutic areas

Obesity/Geriatric Metabolic Disease

- Progress R&D for anti-obesity drugs
- Pursue research for complicated/refractory/geriatric condition

Oncology/Immunological Disease

- Progress cancer peptide vaccines
- Pursue research into novel immuno-modulating therapies

- **Research Laboratory for Development**: Provides supply for drug discovery, development, and the post-launch period

Evaluation of drug safety, drug metabolism and pharmacokinetics, physical properties of compounds, and methods for small to medium scale synthesis

*: Attention deficit hyperactivity disorder

Expanding our External Collaborative Network

Establishment of Global Innovation Office (GIO)

Pioneer in cultivating drug seeds from Japanese academia

10 discovery programs in 4 years through FINDS*, SSP** and research collaborations with venture companies

Alliances with highly-innovative venture companies

5 drug candidates in 4 years

GIO Mission

"Co-creation"

Promote in-licensing of early clinical opportunities

Acquire seeds and technologies for research, CMC, diagnostics and development

*: PHarma-Innovation Discovery competition Shionogi; **: Shionogi Science Program

FY2014 Plan for Research

- **Continuing to conduct highly-innovative drug discovery and to enrich the drug discovery portfolio**
  - Discover drug candidates through the progression of drug discovery research programs
    - Particular emphasis on the areas of infectious diseases and pain/CNS
  - Enrichment of innovative drug discovery portfolio
    - Research strategies to meet the needs of rapidly-aging societies
    - Creating the platform for "next generation open-innovation" through the Global Innovation Office
- **Improving success rates in clinical development**
  - Effective use of biomarkers and pharmacogenomics from non-clinical through clinical stages
  - Further application of differentiated cells generated from iPS cells
  - Clinical application of PET imaging technology
  - Utilizing information from clinical studies, improve non-clinical evaluation platform to increase ability to predict efficacy, pharmacokinetics and safety
- **Maximizing the value of our products and drug candidates**
  - Full support for LCM* of marketed products and NDA** filings, including commitment to research to support product differentiation and clarification of mechanism of action

*: Life cycle management; **: New Drug Application

Development

Takuko Sawada
Senior Vice President
Global Development, Pharmaceutical Development Division

SHIONOGI

Development

- The 3rd Medium-Term Business Plan: Goals and Current Status of Development Division
- Achievements in FY2013
- Targeted Milestones for FY2014
- Core Development Products

The 3rd Medium-Term Business Plan: Goals and Current Status of Development Division

Accelerate Global Clinical Development

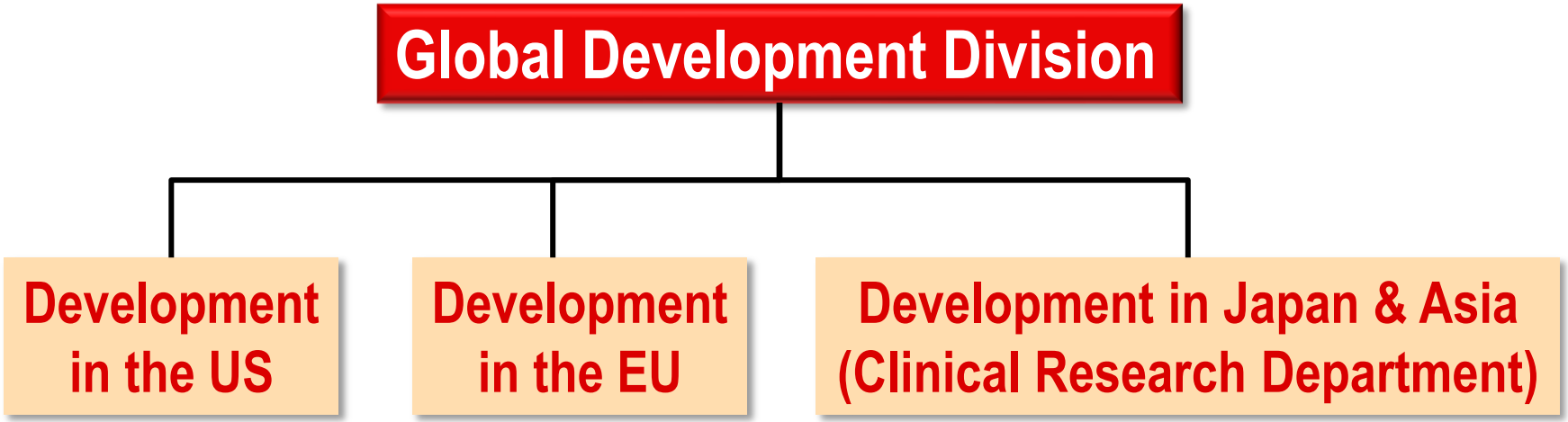
- **Globally develop at least 5 late stage products (Phase IIb and beyond)**
- **Submit NDAs overseas for 4 products (originating from Shionogi or Japanese research institutes) and launch at least one product by FY2014**

- **Enhance Strategic Decision-Making Function**
  - Establishment of a Global Development Office (GDO)
  - Portfolio management

- **Establish Development Footholds Worldwide: completed**
  - Unification of development function in the US
  - Establishment of development foothold in the EU
  - Establishment of development foothold in China

Enhance Strategic Decision Making Function

- **Establishment of Global Business Committee**, in addition to Global Portfolio Management Committee, to define global strategy in a timely and flexible manner with a strong business perspective
- **Integration of the Global Development and the Pharmaceutical Development Divisions**, effective on April 1, 2014, and renaming the combined entity the Global Development Division



Efficient and Rapid Development

- **Systems to support fully integrated global development**
  - Activation of global project management system and other systems for development operations to integrate development in Japan, US and Europe
  - Unification of the development process via global policies, standards, and SOP*s
- **Application of cutting-edge technology**
  - Utilization of internal and external “big data” and implementation of biomedical informatics, including PGx**
  - Selection of appropriate patient populations for treatment and search for biomarkers, in collaboration with academia and the Diagnostics Division
  - Utilization of modeling and simulation

*: Standard operating procedure; **: Pharmacogenomics

Progress of Three Late-Stage Global Pipeline Compounds

- **Ospemifene: Post-menopausal vaginal atrophy**
  - Approved in Feb. 2013, and launched in Jun. 2013 (Osphena™) in the US
  - NDA submitted in Mar. 2013 in the EU
  - Expansion into Asia under consideration
- **Dolutegravir: HIV infection**
  - Approved in Aug. 2013 in the US, in Oct. 2013 in Canada, and in Jan. 2014 in the EU
  - NDA submitted in Dec. 2013 for the treatment of HIV (rare disease) in Japan
- **Combination tablet of dolutegravir with abacavir and lamivudine: HIV infection**
  - NDA submitted in Oct. 2013 in the US and the EU
  - Single-tablet containing dolutegravir plus abacavir and lamivudine (nucleoside reverse transcriptase inhibitors), which provides one-tablet, once-daily, convenient treatment for patients with HIV

Selection of Global Pipeline Compounds

- **Focus allocation of resources onto late-phase global compounds**
  - S-297995 (Naldemedine, alleviation of opioid-induced adverse effects)
    - Phase III trial for opioid-induced constipation is being conducted globally, including Japan
  - S-888711 (Lusutrombopag, thrombocytopenia)
    - Phase III trial is being conducted in Japan, in advance of other countries, for a novel, oral, and low-molecular TPO*-mimetic with good pharmacokinetic profile (minimal effects of food, race, and hepatic impairment). NDA submission is planned in FY2014 in Japan, and overseas development is under consideration
- **Next candidates following S-297995 and S-888711**
  - S-649266 (Bacterial infections)
    - A cephem antibiotic with potent activity against gram-negative pathogens, including multidrug-resistant strains
    - Phase I trial has been initiated in the US (global phase II trial is in preparation)
  - S-222611 (Malignant tumor)
    - Phase I/II trial for HER2-positive breast cancer patients has been initiated

*: Thrombopoietin

Toward Sustained and Accelerating Growth

- **Acceleration of development of high-priority Japanese domestic compounds**
  - Treatment for ADHD*: S-877503, S-877489
  - Sublingual allergen immunotherapy tablets (allergic rhinitis caused by house-dust mite allergen): S-524101
- **Selection of next-generation compounds**
  - Anti-obesity drug: Switching from S-2367 and S-234462 to the follow-up compound S-237648, utilizing the knowledge gained from the development of the earlier compounds
  - Other development compounds: Sublingual allergen immunotherapy tablets (allergic rhinitis caused by cedar pollen), cancer peptide vaccines, pain therapies, anti-infective drugs, etc.
  - Maximization of the potential of our assets in development, using a combination of partnering, licensing-in, and licensing-out

*: Attention deficit hyperactivity disorder

Maximization of the Value of High-Priority Japanese Domestic Compounds

- **Life cycle management of Cymbalta®**
  - Phase III clinical trials continuing in the additional indications of fibromyalgia and chronic low back pain
  - Additional indication of diabetic neuropathic pain; planning of post-marketing clinical trial
- **Life cycle management of doripenem**
  - Addition of a high-dosage regimen
  - Additional indications of pediatric infection and septic meningitis
- **Life cycle management of Irbetan®**
  - Launch of a combination product of amlodipine besilate, followed by that of Fluitran®, and Irbetan® 200 mg tablet
- **Expanding oxycodone pipeline**
  - Phase III clinical trial is continuing for the additional indication of non-cancer pain
  - Licensing-in an abuse-deterrent oxycodone formulation: OxyContin® NEO and oxycodone/naloxone combination tablet (brand name overseas; TARGIN® or TARGINACT® tablet)

Enhancement of Life Cycle Management: Creation and Maximization of the Value of Compounds by "CMC Souyaku"

- **What is "CMC Souyaku"?**

  CMC-directed Innovative Drug Design and Development (CMC DIDD)

  - To produce medically valuable products from drug candidates with inadequate characteristics or to add new value to marketed drug products through strong CMC capability and experience in marketing products

- **Mission of CMC Development Laboratories**

Present Business Model	Shift	New Business Model
New drugs (NME*)	→	New drugs (NME+NTE**)

  - Complement current strengths in NME development
  - Accelerate CMC DIDD which requires advanced CMC technologies
  - Improve probability of launch success and maximize product value through a hybrid model, pursuing both NMEs with high risk - high return and NTEs with medium risk - medium return

*: New Molecular Entity;
**: New Therapeutic Entity: known molecule that is formulated, delivered, or used in a novel way

Achievements in FY2013: Approvals and NDA Submissions

Approvals		
Irtra® Combination Tablets	Hypertension	Japan: Jun. 2013
Dolutegravir*	HIV infection	US: Aug. 2013 Canada: Oct. 2013 EU: Jan. 2014
NDA submissions		
Dolutegravir/Abacavir/ Lamivudine*	HIV infection	US/EU: Oct. 2013
Dolutegravir*	HIV infection	Japan: Dec. 2013 (Passed Drug Committee Meeting in Feb. 2014)

*: ViiV Healthcare

Achievements in FY2013: Phase I-III (1/2)

Progress in development status		
Cymbalta®	Chronic low back pain	Japan: Phase III initiated
S-297995	Alleviation of opioid-induced adverse effects	Global: Phase III initiated
S-888711	Thrombocytopenia	Japan: Phase III initiated
S-555739	Allergic rhinitis	Japan: SAR*/PAR** Phase III completed
S-524101	Allergic rhinitis caused by house-dust mite allergen	Japan: Phase II/III completed
S-877503	ADHD***	Japan: Phase II/III initiated
S-877489	ADHD***	Japan: Phase II initiated
S-646240	Age-related macular degeneration	Japan: Phase IIa LPO****

*: Seasonal allergic rhinitis; **: Perennial allergic rhinitis;
: Attention deficit hyperactivity disorder; *: Last patient out

Achievements in FY2013: Phase I-III (2/2)

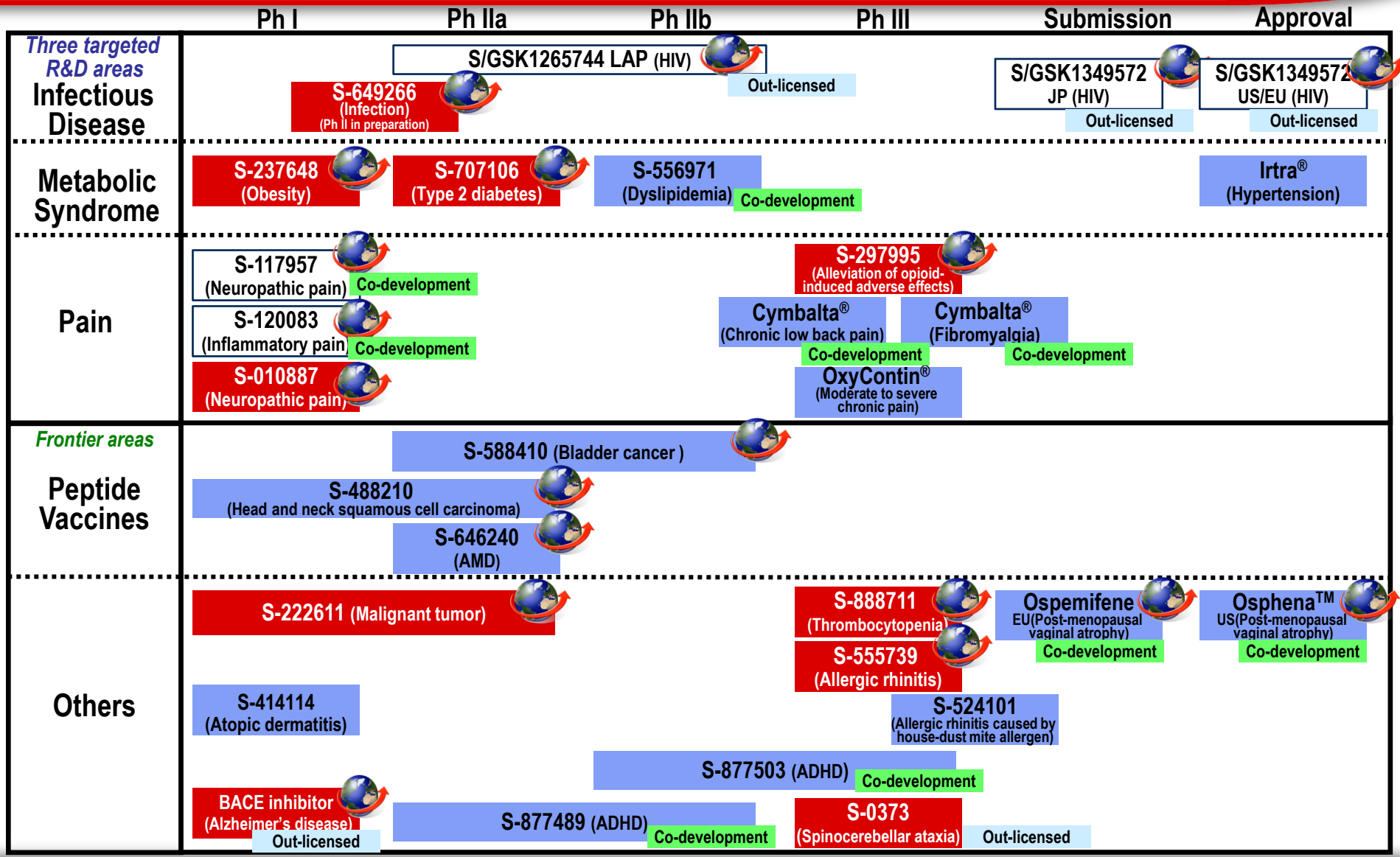
Progress in development status		
S-588410	Bladder cancer	Japan/EU: Phase II initiated
S-222611	Malignant tumor	EU: Phase I/II initiated
S-649266	Infection	US: Phase I initiated
S-556971	Dyslipidemia	Japan: Phase IIb completed, go/no go decision, Phase I initiated (usage change)
S-120083	Inflammatory pain	Japan: Phase I completed
S-414114	Atopic dermatitis	Japan: Phase I initiated
S-117957	Neuropathic pain	US: POM* initiated
S-010887	Neuropathic pain	Japan: Phase I initiated
S-237648	Obesity	Japan: Phase I initiated

*: Proof of mechanism

Development for as yet Unapproved Indications, and Drug Requested for Development by Academia

Unapproved and off-label: Status of progress		
Cymbalta®	Fibromyalgia	NDA submission in preparation
OxyContin®	For the treatment of moderate to severe chronic pain	Phase III
Endoxan®	Pheochromocytoma	Approval (Mar. 2013)
Predonine®	Synthetic corticosteroid	Approval (Sep. 2013)
Vancomycin	Gram-positive bacteria-associated bloodstream infection	NDA submission (Nov. 2013)
Requested for development by academia. Status of progress		
Metreleptin	Lipodystrophy	Approval (Mar. 2013)
Predonine®	Kawasaki disease (Acute stage)	Approval (Sep. 2013)
Imunomax®-γ	Mycosis fungoides/Sezary syndrome	NDA submission (Aug. 2013)

Development Pipeline Enrichment (as of March 2014)



LAP: Long-acting parenteral formulation
AMD: Age-related macular degeneration
ADHD: Attention deficit hyperactivity disorder

Developing products globally

Origin: In-house | Co-development | In-licensed

Target Milestones for FY2014: Approvals and NDA Submissions

Approvals		
Dolutegravir*	HIV infection	Japan
Dolutegravir/Abacavir/ Lamivudine*	HIV infection	US/EU
NDA submissions		
Cymbalta®	Fibromyalgia	Japan
Cymbalta®	Chronic low back pain	Japan
S-888711	Thrombocytopenia	Japan
S-524101	Allergic rhinitis caused by house-dust mite allergen	Japan

*: ViiV Healthcare

Target Milestones for FY2014: Phase I-III

Progress in development status		
S-877503	ADHD*	Japan: Phase II/III completed
S-877489	ADHD*	Japan: Phase II/III initiated
S-556971	Dyslipidemia	Japan: Phase IIb initiated
S-888711	Thrombocytopenia	Global: Phase II initiated
S-649266	Infection	Global: Phase II FPI**
S-646240	Age-related macular degeneration	Japan: Go/no-go decision
S-117957	Neuropathic pain	US: Go/no-go decision
S-010887	Neuropathic pain	Japan: Phase I completed, go/no-go decision
S-237648	Obesity	Japan: Phase I completed, go/no-go decision
FTIH***: 2 or more compounds		

*: Attention deficit hyperactivity disorder; **: First patient in; ***: First trial in humans

Core Development Products

Naldemedine (S-297995)

Treatment of opioid-induced constipation

Compound Profile

- **Indication**
  - Treatment of opioid-induced constipation
- **Mechanism of action**
  - A oral, peripherally acting opioid receptor antagonist
- **Development status**
  - End of Phase II meeting
    - FDA*: 19 February, 2013
    - PMDA** : 24 June, 2013
  - COMPOSE*** program (global phase III studies in chronic non-malignant pain patients and cancer patients) is being conducted

*: Food and Drug Administration; **: Pharmaceuticals and Medical Devices Agency;
***: A Clinical Study for People with Opioid Induced Constipation

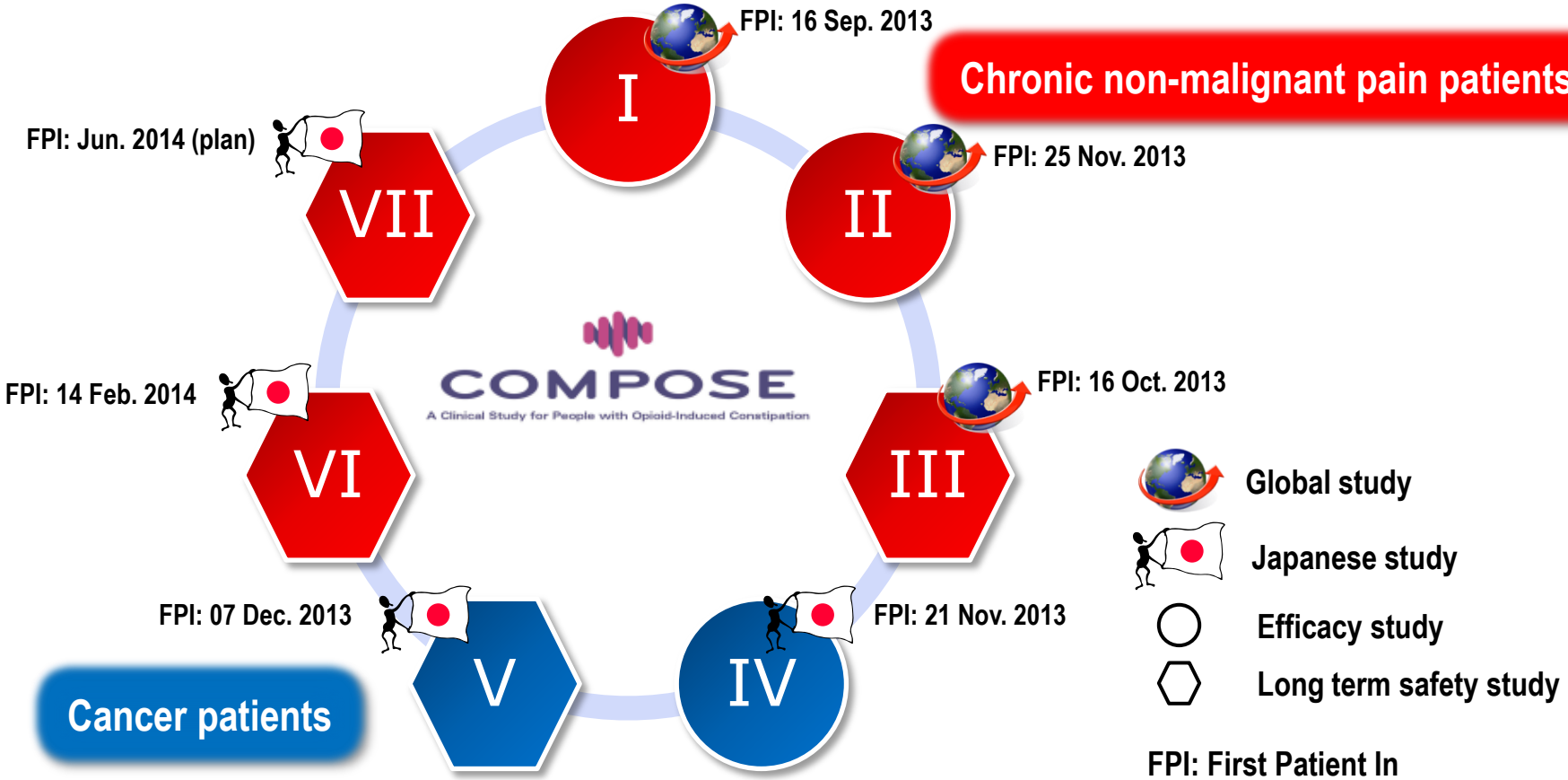
Market Opportunity

- US$14.8 billion global opioid market[1]
  - Top 5 markets (US, UK, Germany, Canada and France) account for ~80% of units[1]
  - 70 million chronic opioid patients in the top 5 markets[2]
- 40%-50% of chronic opioid patients (28-35 million in the top 5 markets) experience opioid-induced constipation[1-5]
- <50% of patients taking laxatives report a satisfactory result[5]
- Opioid is used mainly for cancer patients in Japan
  - Estimated >300,000 cancer patients take opioids

Source: [1] Calculated based on IMS Health MIDAS MAT-2Q12, [2] Calculated based on IMS patient level data MAT-2Q09, [3] Reimer, K et al. Meeting the Challenges of Opioid-Induced Constipation in Chronic Pain Management – A Novel Approach. Pharmacology. 2009;83:10-17, [4] Review Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Kalso E, Edwards JE, Moore RA, McQuay HJ; Pain 2004 Dec; 112(3):372-80. [5]Ford et al, Efficacy of Pharmacological Therapies for the Treatment of Opioid-Induced Constipation: Systematic Review and Meta-Analysis, The American Journal of Gastroenterology, 11 June, 2013 doi:10.1038/ajg.2013.169. Calculated based on MIDAS 2012 June MAT, and Patient Level Data 2009 Q2 MAT etc.

Phase III Studies (COMPOSE Program)

- **Target patients**
  - US: Chronic non-malignant pain patients
  - JP: Cancer patients and chronic non-malignant pain patients



S-649266

Severe Gram-negative bacterial infections

Compound Profile

- **Indication**
  - Severe Gram-negative bacterial infections
- **Mechanism of action**
  - Cell wall synthesis inhibitor
- **Product characteristic**
  - An injectable cephalosporin with potent activity against gram-negative pathogens
  - Showing potent activity against multidrug (e.g., carbapenem and cephalosporin)-resistant strains such as metallo-β-lactamase (e.g., NDM-1*)-producing strains, multi-drug resistance *P. aeruginosa* (MDRP), *A. baumannii* and Enterobacteriaceae (*K. pneumoniae* etc.)
- **Development status**
  - Phase I single/multiple-dose study completed
  - Phase I renal impairment PK study (US) is being conducted, Phase II cUTI** study (global) is in preparation

*: New Delhi metallo-beta-lactamase-1; **: Complicated urinary tract infection

Market Opportunity (Severe Infections)

- **Healthcare-associated infections (hospital-acquired infections)**
  - The total annual incidence in the US, Europe and Japan is estimated at 6 million and has been increasing at 1.7% per year
  - The additional healthcare cost related to healthcare-associated infections is estimated to be about US$154,000 in the US (PHC4[*1])
  - Global sales of carbapenem is US$1.9 billion (2013, EvaluatePharma)
- **Prevalence of carbapenem resistance (NHSN[*2], ECDC[*3])**

	E. coli	*P. aeruginosa*	*A. baumannii*	*K. pneumoniae*
US	2%	23%	61%	12%
France	<1%	18%	81% (29 European countries)	<1%
Germany	<1%	11%		<1%
Italy	<1%	25%		29%
Spain	<1%	21%		<1%
UK	<1%	6%		<1%

- **Severe infections**
  - Each year in the US, about 2 million people acquire serious infections with "resistant bacteria" and about 20,000 people die each year (CDC[*4])
  - The increase of resistant bacteria is a serious problem in Eastern Europe, Latin-America and Asia

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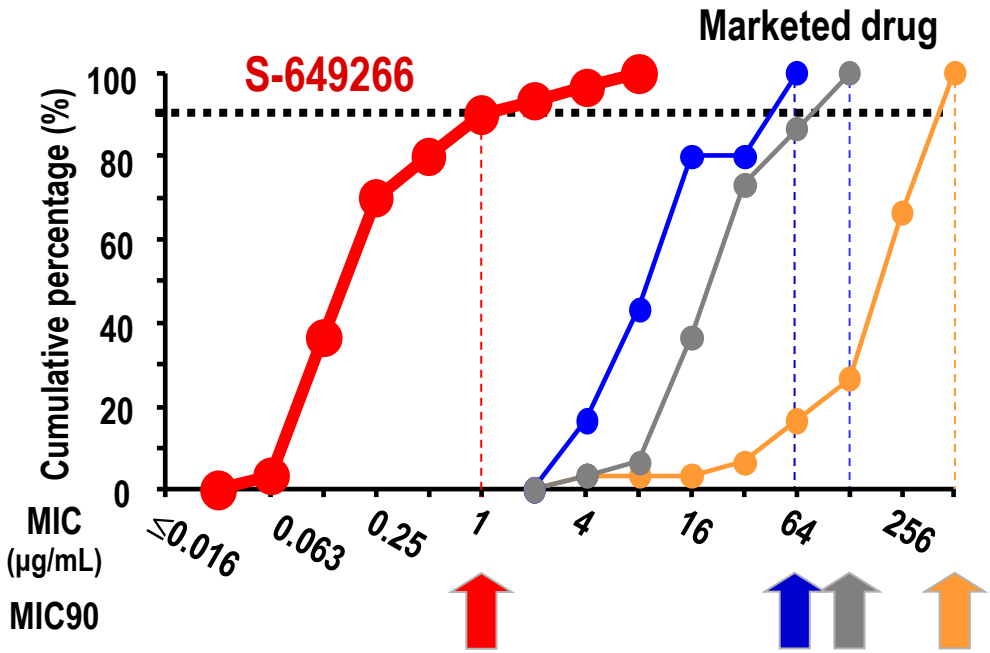
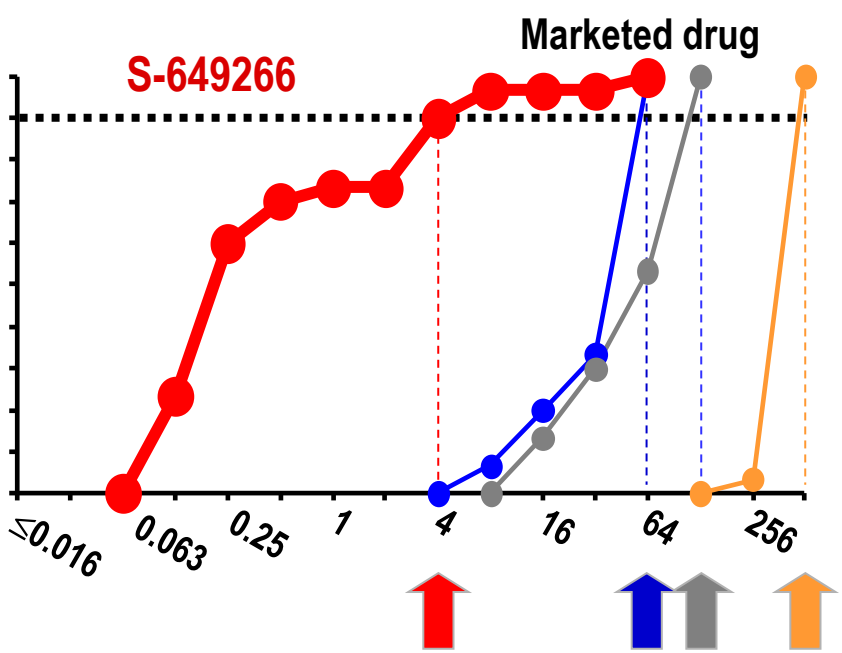
*1: Pennsylvania Health Care Cost Containment Council; *2: National Healthcare Safety Network;
*3: European Centre for Disease Prevention and Control; *4: Centers for Disease Control and Prevention

Antibacterial Activity Against Multidrug-Resistant Strains

Antibacterial Activity Against Multidrug resistant *P. aeruginosa* (number of strains; 33)



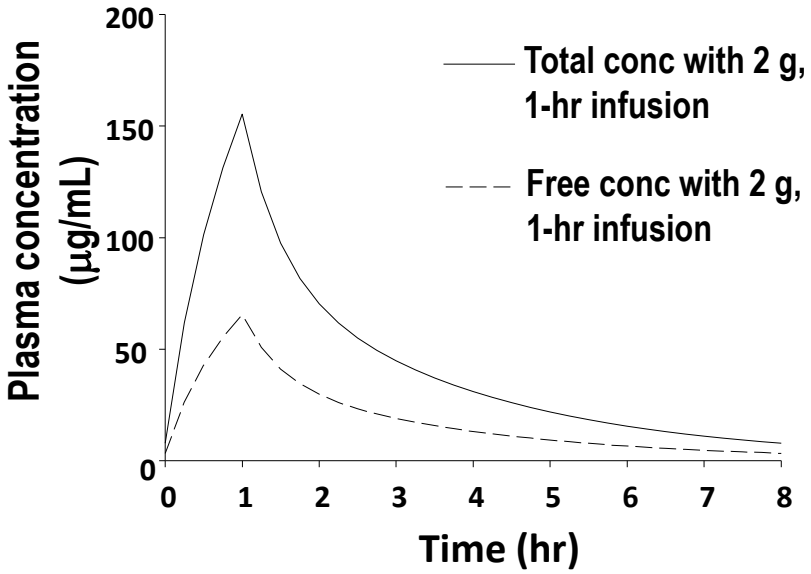
Antibacterial Activity Against Multidrug-resistant *A. baumannii* (number of strains; 29)



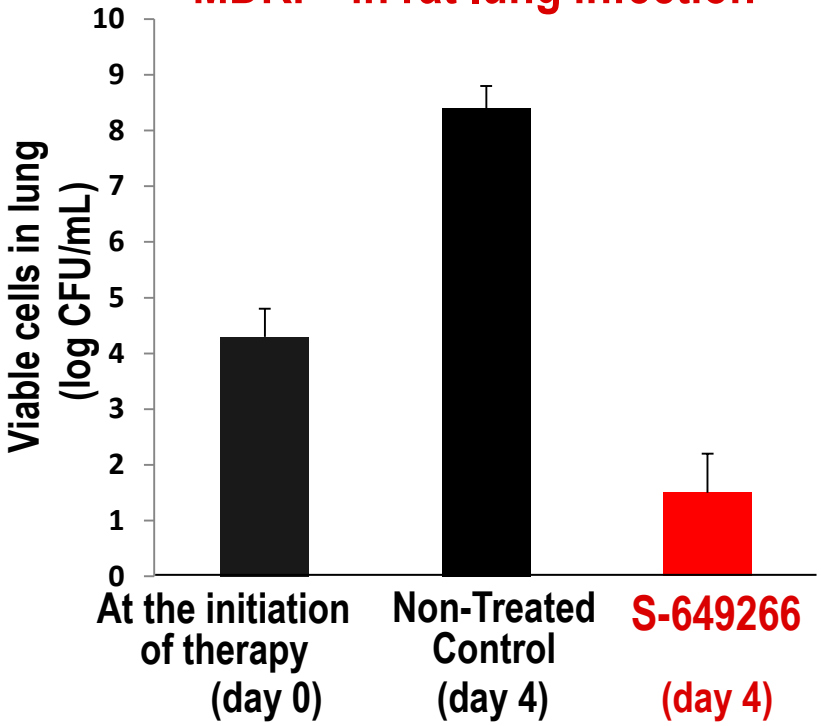
Antibacterial activity shown against multidrug-resistant *P. aeruginosa* and multidrug-resistant *A. baumannii*, which are problematic in clinical settings

Therapeutic Efficacy against MDR Strain

Plasma concentration in healthy volunteers



Efficacy of S-649266 (human PK by 2g IV infusion tid) against MDRP* in rat lung infection



The human intravenous infusion profile of S-649266 showed potent therapeutic efficacy in rat lung infection model caused by MDR

*: Multidrug-resistant *Pseudomonas aeruginosa*

S-222611

Tumors with over-expression of HER2/EGFR

Compound Profile

- **Indication**
  - Solid tumors with over-expression of HER2*/EGFR**
- **Mechanism of action**
  - Reversible HER2/EGFR tyrosine kinase inhibitor
- **Efficacy profiles (non-clinical)**
  - Selective and strong inhibitory effects against HER2 and EGFR
  - Superior anti-tumor activities in several cancer models with once-daily dosing in comparison with other approved drugs with the same mechanism of action
  - Superior anti-tumor activity in intra-femur and intra-cranial implantation models in comparison to other approved drugs with the same mechanism of action
- **Development status**
  - Phase I/II study in HER2 positive breast cancer patients
- **Future plan**
  - Phase II study to be conducted after the optimal dose of S-222611 in combination with other anti-cancer drug(s) is determined in the phase I/II study

*: Human epidermal growth factor receptor 2; **: Epidermal growth factor receptor

Results of Phase I study

- **Phase I repeated dose study in cancer patients (EU)**
  - **Dose-Escalation Phase:**
    To determine maximum tolerated dose (MTD), and assess pharmacokinetics (PK) and anti-tumor activities of S-222611 administered repeatedly, once daily in patients with solid tumors expressing HER2/EGFR who have failed standard therapy
  - **Expansion Phase:**
    To assess safety, PK, and anti-tumor activities of S-222611 at maximum well-tolerated dose administered repeatedly once daily

- **Good safety profiles confirmed in humans at doses far exceeding those at which anti-tumor activities were observed in animal models**
- **Tumor shrinkage and stable disease observed in various type of tumors**
- **Poster presentation at ESMO* 2013 and SABCS** 2013**

*: European Society for Medical Oncology; **: San Antonio Breast Cancer Symposium

Summary

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