

Research and Development at Shionogi

SHIONOGI & CO., LTD.

March 18, 2015

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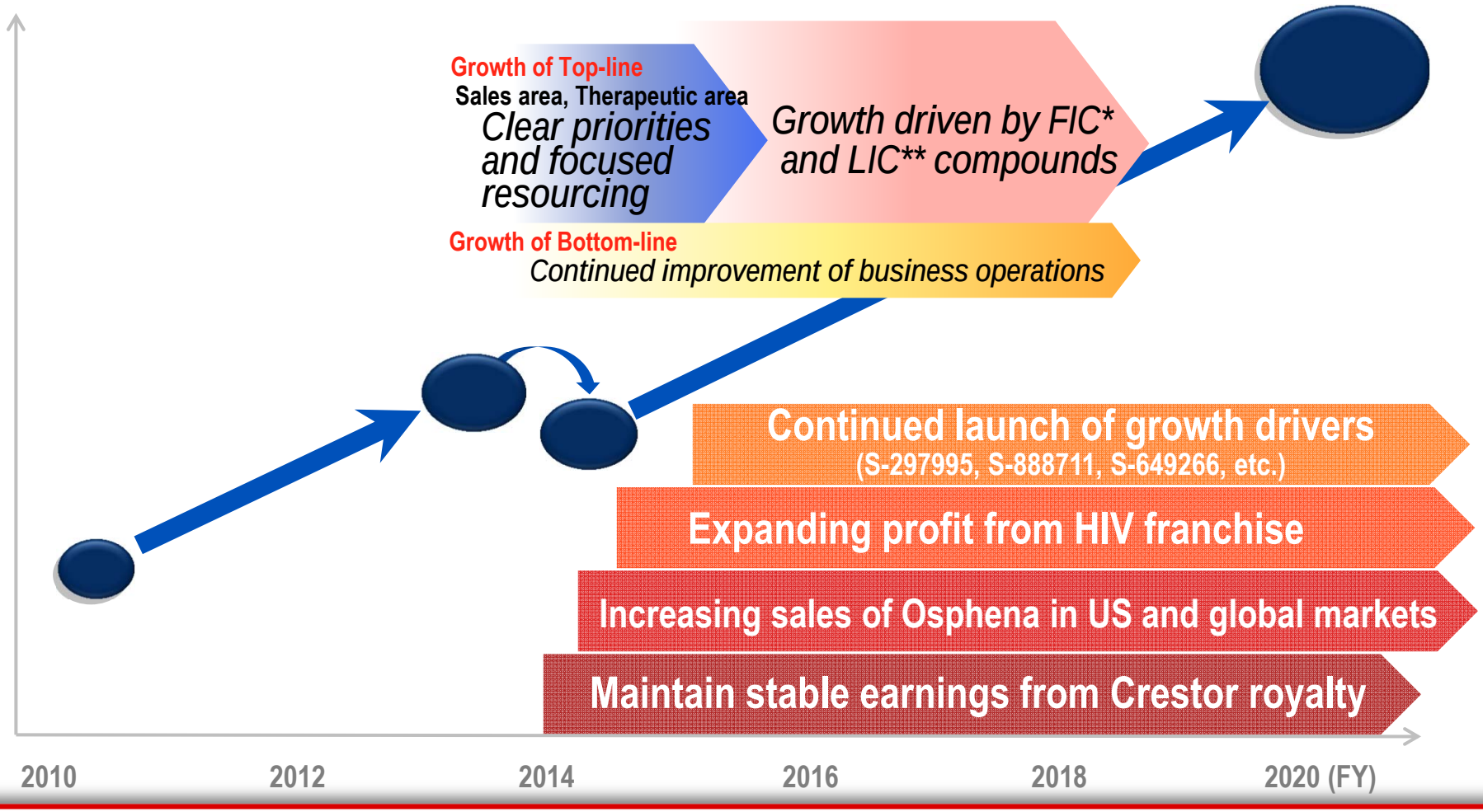
Agenda

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



New Medium-Term Business Plan: SGS2020

Grow as a drug discovery-based pharmaceutical company



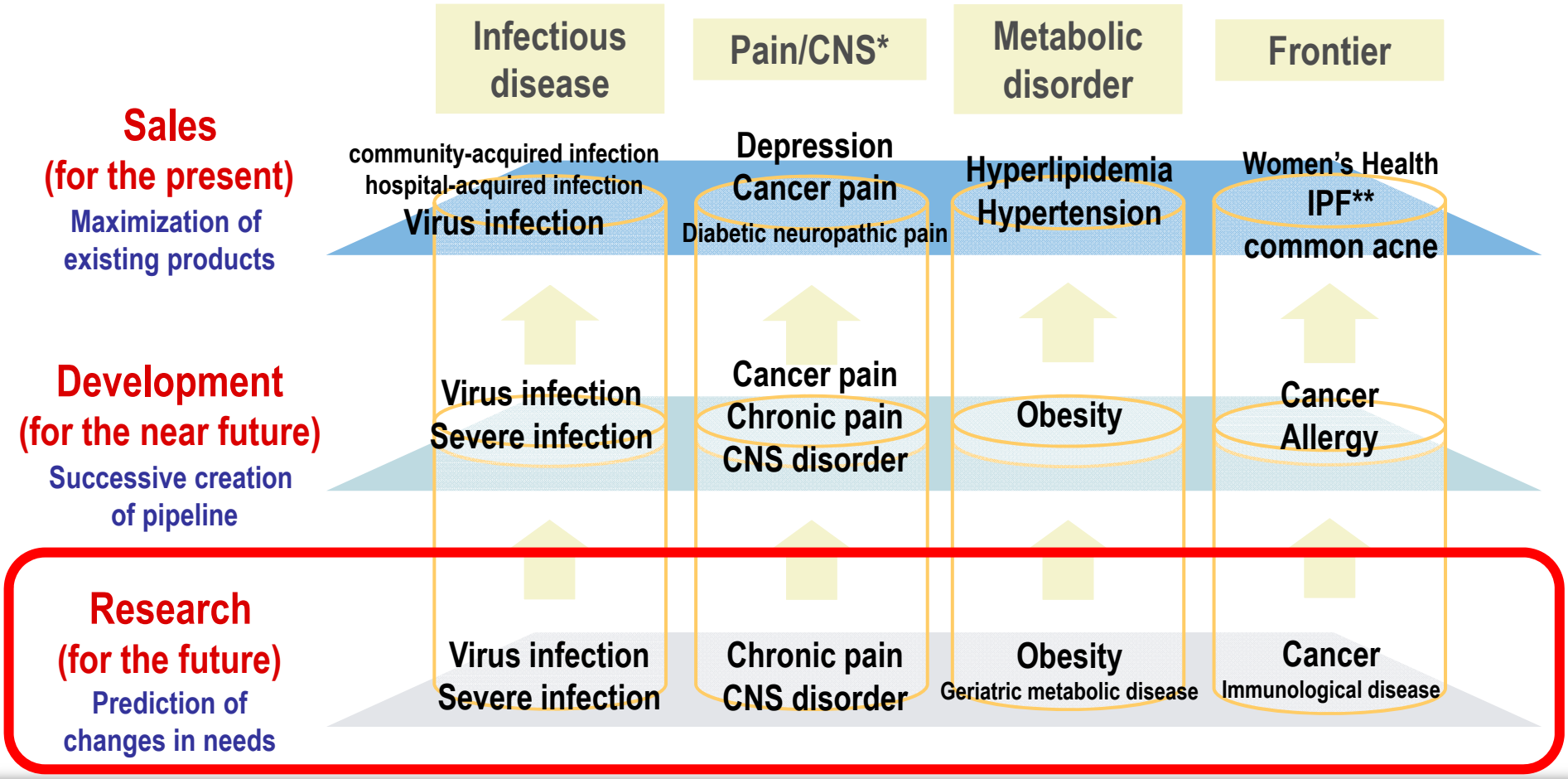
*: First in Class (Innovative medicines with particularly high novelty and therapeutic value that can significantly change the existing therapeutic paradigm)
**: Last in Class (Unrivaled medicines with clear superiority over others with the same mechanism of action)

Research

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

SGS2020: Target Research Therapeutic Areas

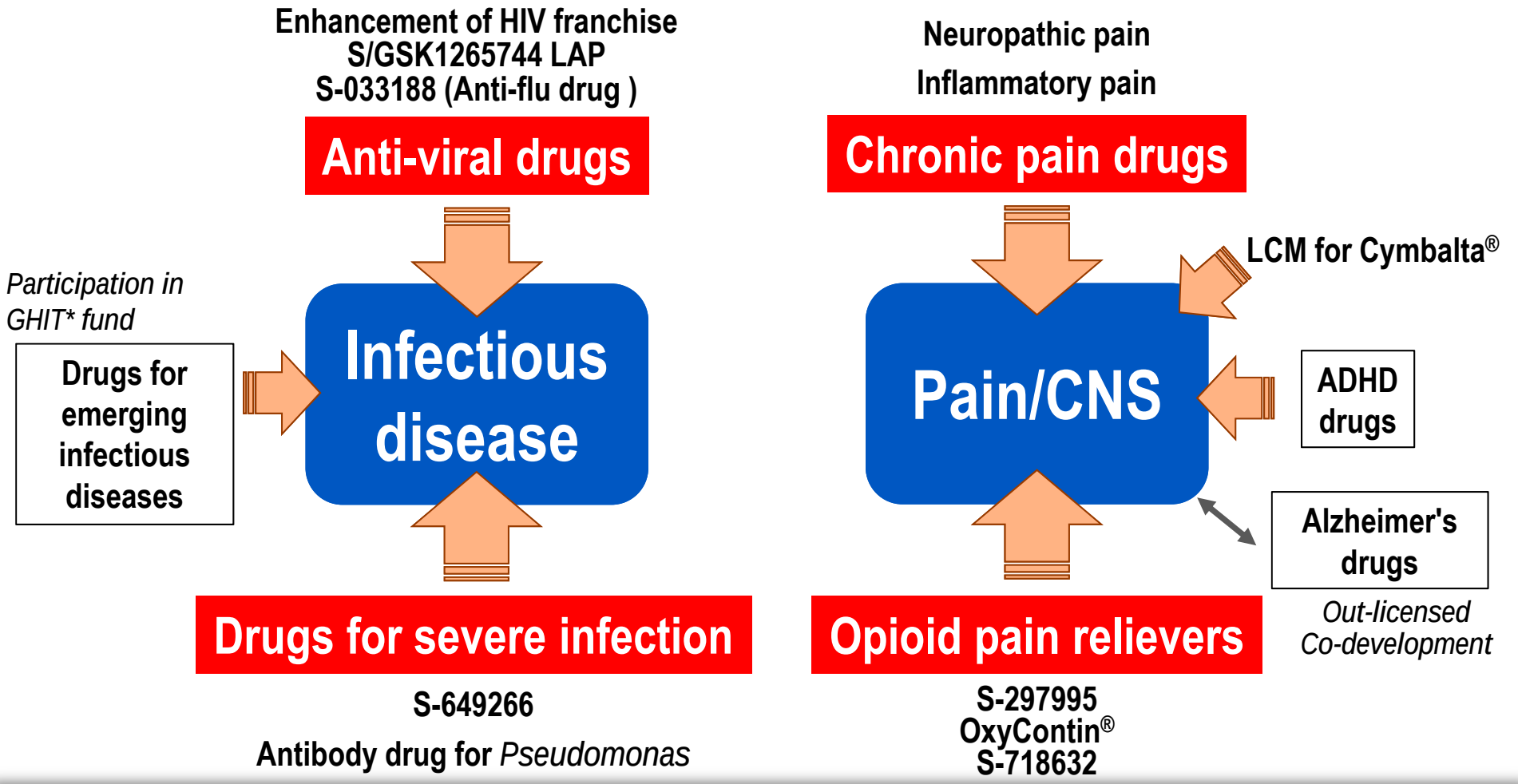
Clear priorities and focused resourcing to meet unmet medical needs



*: Central Nervous System **: Idiopathic Pulmonary Fibrosis

Clear Priorities and Focused Resourcing on our Core Therapeutic Areas

Maximize synergy with existing products



*: Global Health Innovative Technology Fund

Research

- **Approaches and Progress in Core Therapeutic Areas: (1) Infectious Diseases**
- Approaches and Progress in Core Therapeutic Areas: (2) Pain and CNS
- Approaches to Strengthen Next Generation Medicinal Research

Trends in Severe Bacterial Infections

- **Lack of effective antibiotics exposed by the global increase of multidrug-resistant bacteria**
  - "Antimicrobial Resistance: No Action Today, No Cure Tomorrow" (2011, 2014, WHO)
  - "Untreatable: Today's Drug-Resistant Health Threats" (2013, CDC*)
  - Obama Administration released "National Strategy on Combating Antibiotic-Resistant Bacteria" (2014)
- **Motivated recent US FDA approvals of novel antibiotics**
  - Dalvance® (dalbavancin), a glycopeptide by Actavis (formerly Durata)
  - Sivextro® (tedizolid), an oxazolidinone by Merck (formerly Cubist)
  - Orbactiv™ (oritavancin), a glycopeptide by The Medicines Company
  - Zerbaxa™ (ceftolozane/tazobactam), a cephem with a β-lactamase inhibitor by Merck (formerly Cubist)
  - Avycaz™ (ceftazidime/avibactam), a cephem with a β-lactamase inhibitor by Actavis (formerly Forest)

Tremendous unmet medical need remains for novel therapies against multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter spp.*

*: Centers for Disease Control and prevention

Our Research Strategies for Severe Infections

Continuously create novel drugs to treat severe infections with substantial unmet medical needs

- ## Severe bacterial infections

  Utilizing our experience in discovery of novel β-lactam antibiotics, such as Finibax®, create novel drugs against currently untreatable infections, such as those with multidrug-resistant *P. aeruginosa* and *Acinetobacter*, and enrich our pipeline of anti-infectives

- ## Invasive fungal infections

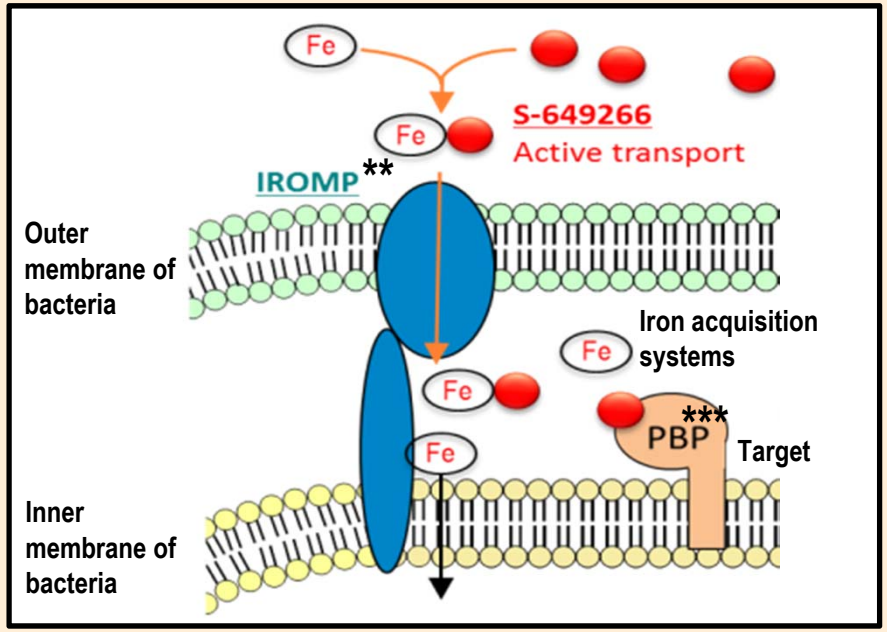
  Create novel antibiotics against invasive fungal infections with high mortality rates and where there is a need for drug with improved efficacy and safety

Bacterial Infections: Discovery of a Drug Candidate against Gram-Negative Bacteria

SONG for you!

S-649266 and further compounds being created in collaboration with GSK based on the concept of "Trojan horse β-lactam, which use the bacteria's own transport system to enter and kill multidrug-resistant bacteria"

Utilize bacterial iron uptake system to drive active uptake into bacteria (As presented at international academic conferences*)



Created a novel drug candidate with strong antibacterial activity against multidrug-resistant gram-negative bacteria by utilizing our strength in medicinal chemistry to enrich our infectious disease pipeline

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*: Interscience Conference on Antimicrobial Agents and Chemotherapy (Poster summary). Infectious Disease Week. European Congress of Clinical Microbiology and Infectious Diseases. Japanese Society of Chemotherapy. The Japanese Association for Infectious Diseases. The pharmaceutical society of Japan. **: Iron regulated outer membrane protein ***: Penicillin-binding protein

Our Research Strategies for Viral Infections

Create novel antivirals for HIV/AIDS and respiratory virus infections, and enrich development pipeline following Tivicay® and Rapiacta®

- **HIV/AIDS infection**

  Create “First-in-Class” anti-HIV agents which can be important components of future combination therapies, to enrich development pipeline and maximize the value of Tivicay® franchise

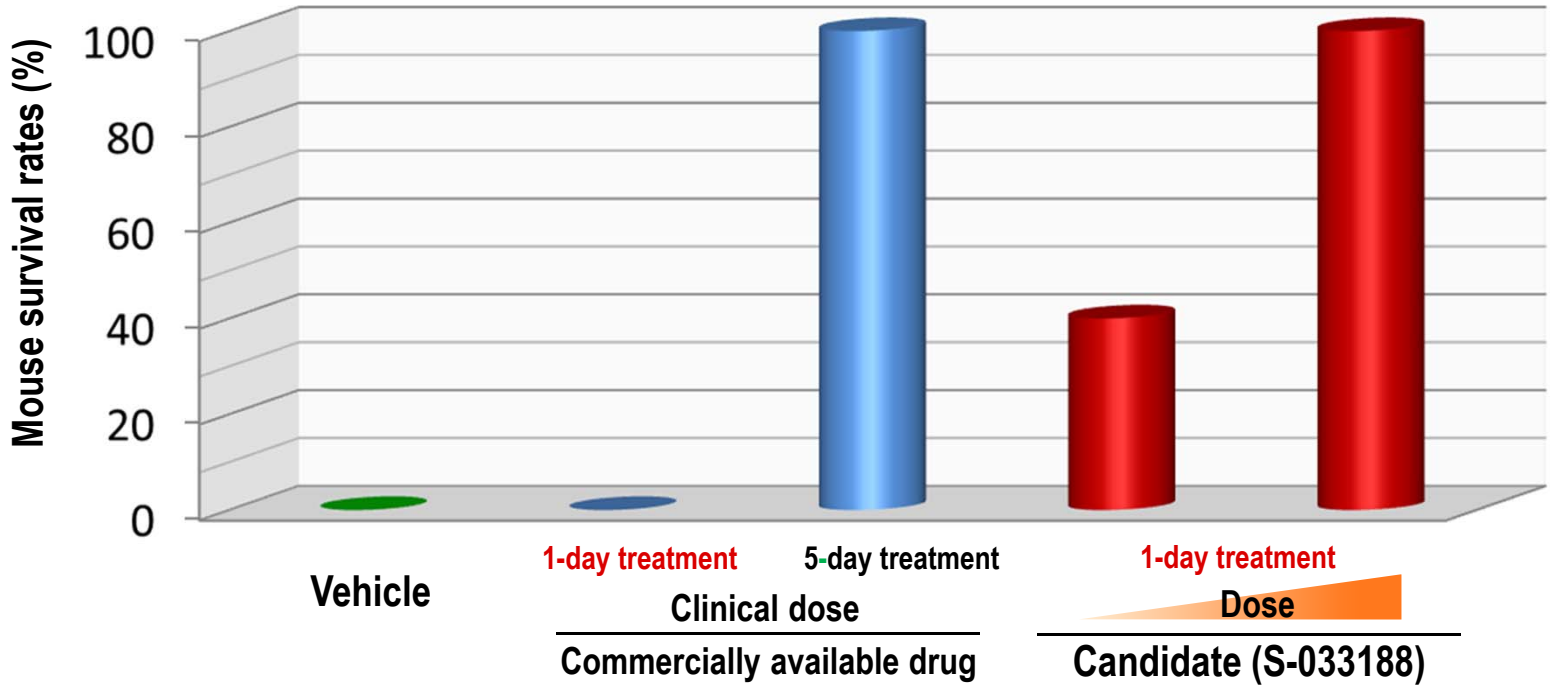
- **Respiratory virus infection**

  Utilizing capabilities built in HIV discovery research, create “First-in-Class” anti-flu agents and enrich development pipeline following Rapiacta®

Viral Infections: Discovery of an Anti-Influenza Drug Candidate

An anti-influenza drug candidate with a novel mechanism of action was progressed from non-clinical to clinical stage

Survival rates in the human influenza virus-infected mouse model



An innovative "First-in-Class" oral anti-influenza drug candidate, which may cure infection after a shorter treatment period than any other current treatments, was progressed into the clinic

Approaches to Emerging and Re-Emerging Infectious Diseases

Bacterial infection

Promote screening programs with the TB Alliance* through participation in the GHIT fund** to discover drugs against multidrug-resistant *M. tuberculosis*

Viral infection

Expand "The Matching Program for Innovations in Future Drug Discovery and Medical Care" at Hokkaido University, and promote drug discovery research for emerging and re-emerging infectious diseases (e.g. dengue virus infection) through collaboration with Hokkaido University Research Center for Zoonosis Control.

GHIT Fund
Global Health Innovative Technology Fund

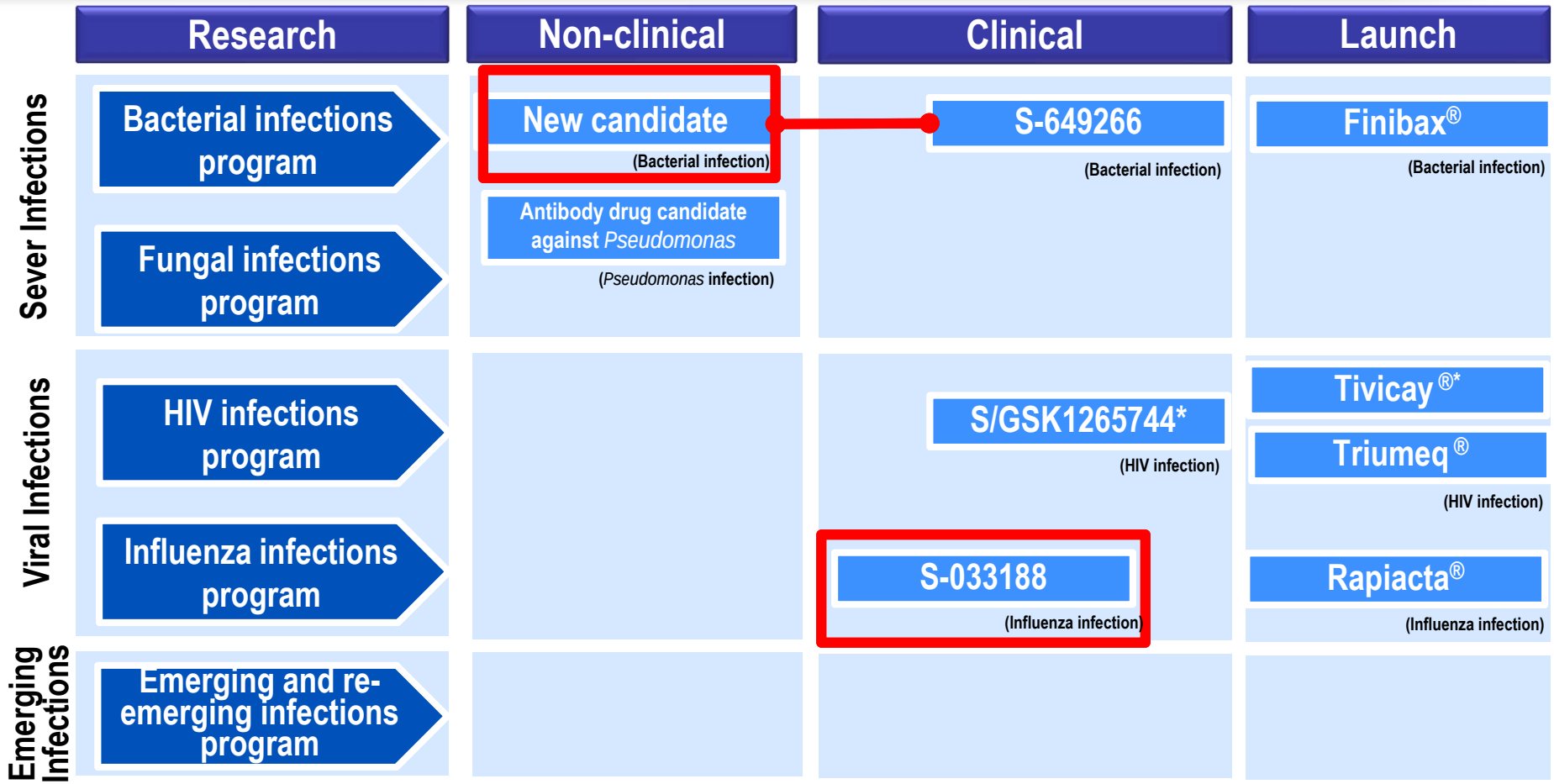
TB ALLIANCE
Putting science to work for a faster TB cure

Hokkaido University Research Center for Zoonosis Control

Promote research activities for emerging and re-emerging infectious diseases to increase our contributions to infectious disease therapy on a global basis

*: The Global Alliance for TB Drug Development **: Global Health Innovative Technology Fund

Our Pipeline in Infectious Diseases



Enrich development pipeline in infectious disease area through promoting "First-in-Class" and "Last-in-Class" research

Research

- Approaches and Progress in Core Therapeutic Areas (1) “Infectious Diseases”
- **Approaches and Progress in Core Therapeutic Areas: (2) Pain and CNS**
- Approaches to Strengthen Next Generation Medicinal Research

Trends in Chronic Pain

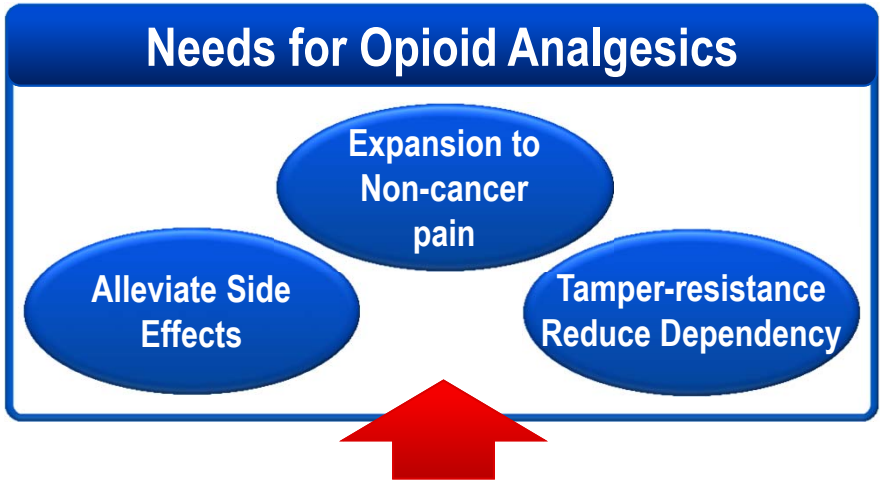
- **Opioid analgesics**
  - Efforts to expand opioid use to non-cancer pain treatment
  - Development of drugs to address side effects such as digestive system symptoms
  - Efforts to develop tamper-resistant opioids in global markets

To increase patient benefit from the strong analgesic effect of opioids, improved usability is required

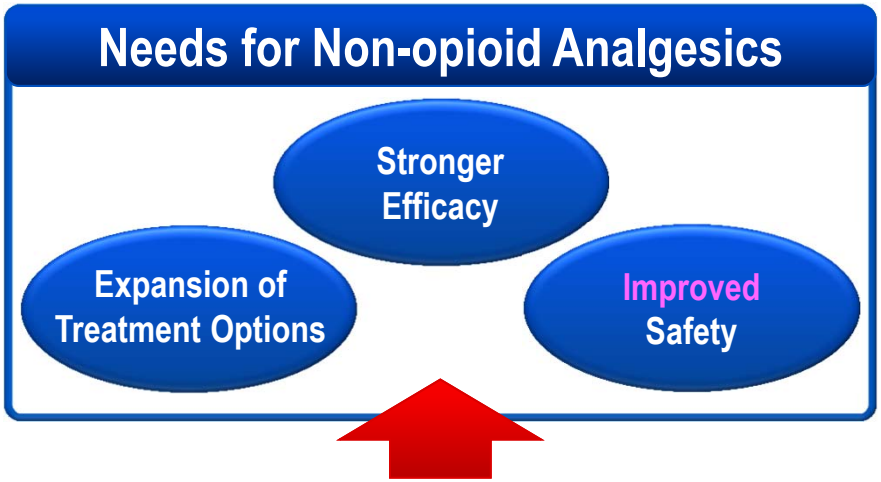
- **Non-opioid analgesics**
  - Therapeutic options to treat chronic pain are limited. Most drug s in clinical development are novel formulations of existing drugs and novel drugs with the same mechanism of action
  - However, some compounds with novel mechanisms of action have demonstrated analgesic effects in clinical trials in recent years

To obtain sufficient analgesic effect, drugs that affect different pathological mechanisms are required, because chronic pain conditions arise from multiple pathological mechanisms
⇒ New drugs with different mechanisms, offering expanded treatment options are required

Our Research Strategy in Chronic Pain



- Differentiates S-297995 from competitors by leveraging the mechanism of action
- Drug discovery research programs to create “Next-generation Opioids” aiming to reduce dependency



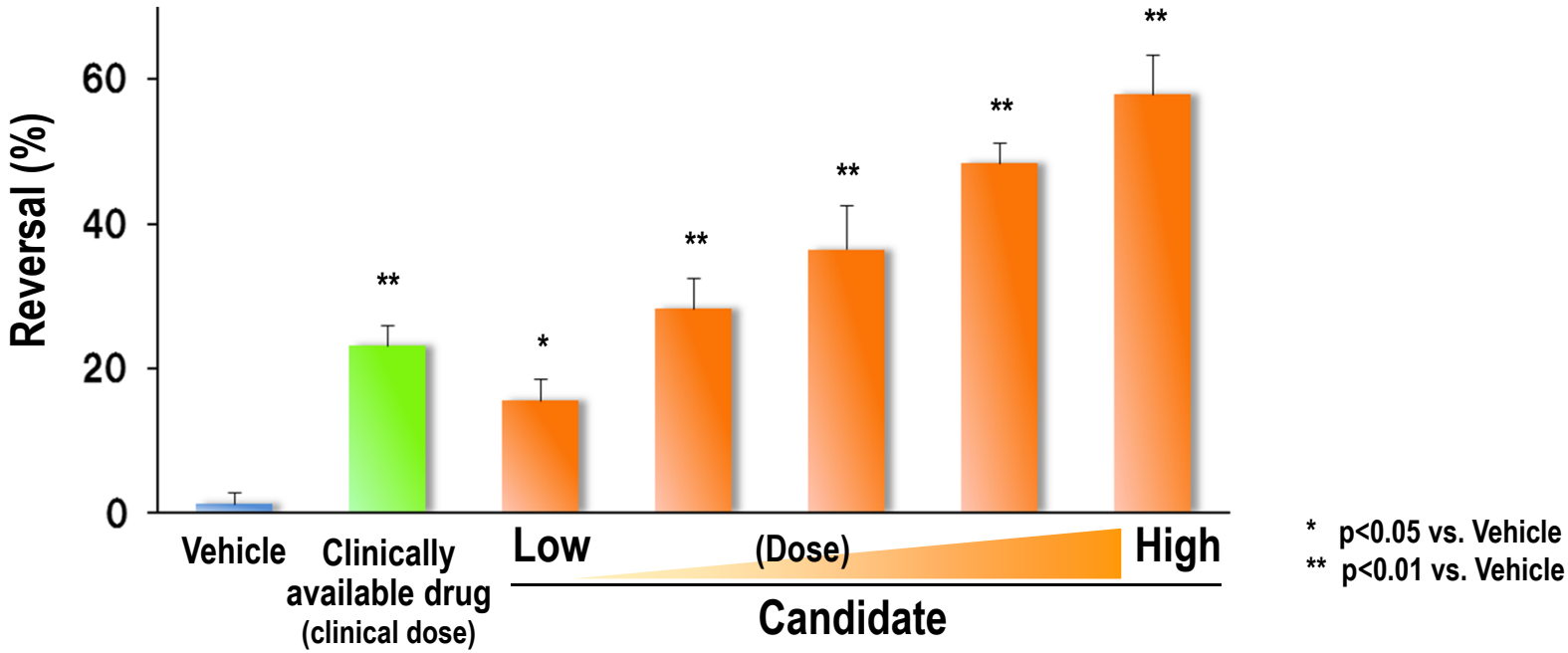
- Drug discovery research programs to create drugs against neuropathic pain
- Drug discovery research programs to create drugs against osteoarthritis or chronic low back pain

To meet unmet medical needs, progress drug discovery research of both opioid and non-opioid analgesics, and expand our pipeline

Non-Opioid Analgesics: Discovery of an Analgesic Drug Candidate

Identified a novel neuropathic pain drug candidate, follow-on from S-010887

Analgesic effect in an animal model of diabetic neuropathic pain



Progress multiple candidates for one target molecule to ensure the launch of "First-in-Class" drug

Our Research Strategy in CNS Diseases

Promote drug discovery research of CNS diseases, focusing on Alzheimer's disease and Attention deficit hyperactivity disorder (ADHD)

Alzheimer's disease research

- Anti-Aβ drug discovery: A clinical trial of the compound discovered by Shionogi is being conducted by Janssen, and collaborative research is being conducted to select a follow-up compound
- Novel mechanism of action drug discovery: Research is being conducted to identify a candidate with a novel mechanism of action

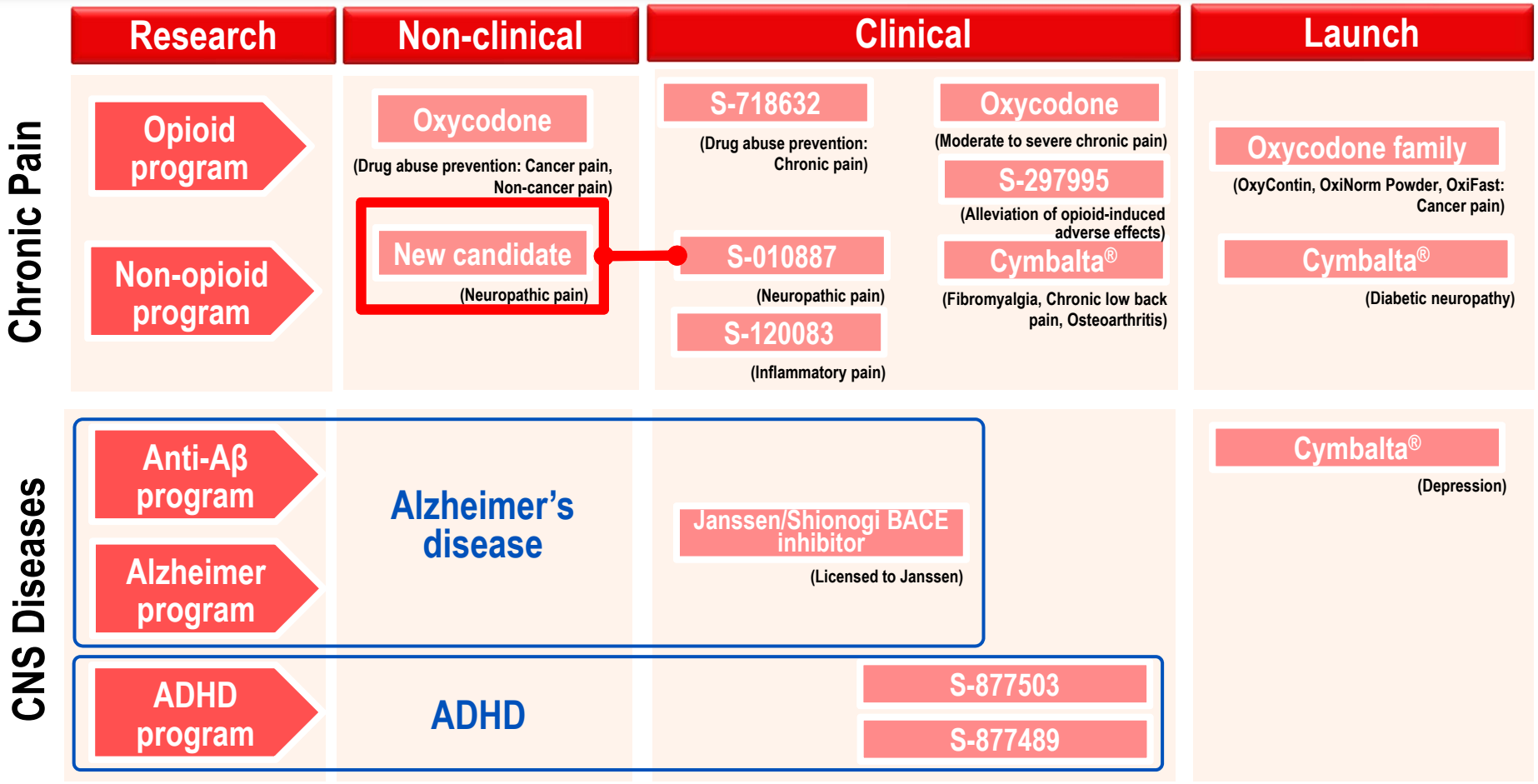
ADHD research

- Research strategy in place to create "Next generation drug against ADHD"
- Progressing research to create drugs with novel mechanisms of action which can meet unmet medical needs
- Improve predictability of clinical trial success using imaging technologies and primate studies

Basic research in CNS disease area

- Progress our internal neuroscience research as well as collaborative research, such as "Drug discovery and medical research for the regeneration of synapses and neuronal function" with Kyoto University to obtain novel target molecules for drug discovery research and new approaches for early evaluation efficacy
- Create innovative "First-in-Class" drugs and identify biomarkers for CNS diseases through collaborative research with academia

Our Pipeline in Pain/CNS



Enrich development pipeline in pain and CNS disease areas through promoting "First-in-Class" and "Last-in-Class" research

Research

- Approaches and Progress in Core Therapeutic Areas: (1) Infectious Diseases
- Approaches and Progress in Core Therapeutic Areas: (2) Pain and CNS
- **Approaches to Strengthen Next Generation Medicinal Research**

Oncology & Immunology: Collaborative Research in Tumor Immunology with Academia

Establishment of joint research at CoMIT* in Osaka University



- Discovery of PD-1** immune checkpoint inhibitors
- Collaboration to seek more effective drug targets for tumor immunology research, in addition to the research on cancer peptide vaccines

Research Themes

- Analysis of the immunological features of the tumor microenvironment
- Biology of immune suppressor cells

Seek new drug targets that control regulatory T cells and immunosuppressive factors

*: Center of Medical Innovation and Translational Research (CoMIT)
**: Programmed cell death 1

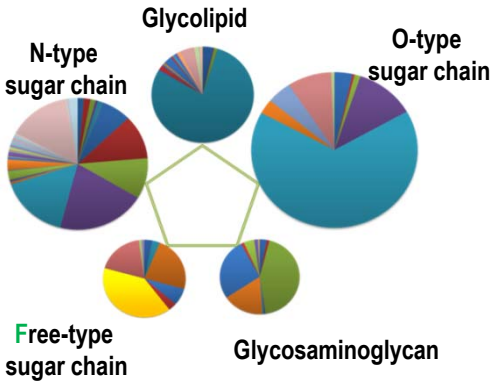
Approaches for Novel Biomarkers

SONG for you!

Application of the analysis techniques that were developed in collaboration with Hokkaido University in SIC*

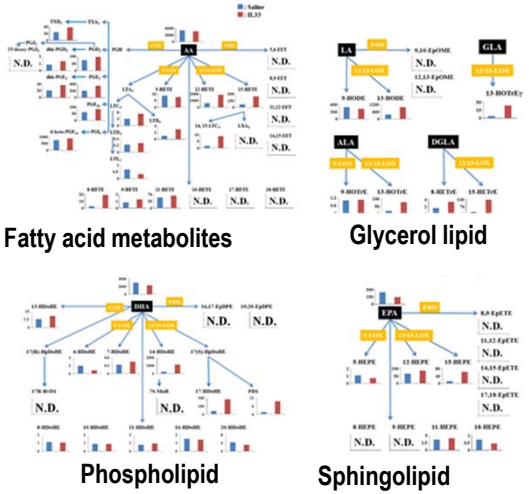
Comprehensive analysis of sugar chains

Characterization of cells based on the absolute quantitation of major glycoconjugates



Comprehensive analysis of lipids

Construction of lipid measurement system and mechanism analysis



Clinical specimens

Utilization of biobank at Hokkaido University Hospital



Identify novel biomarkers to support drug discovery research

*: Shionogi Innovation Center for Drug Discovery (Hokkaido University)

Accelerate Open Innovation

Acquire and cultivate unique ideas from academia, through the academic network built by our pioneering open innovation program FINDS* in Japan

Establishment of Global Innovation Office (GIO)

(April 2014)

Explore drug seeds in European academia in cooperation with Shionogi Ltd. (London)

SSP 2014** has successfully received a number of applications from 11 countries, including Japan

Collaborations with academia and bio-ventures for in-licensing early-stage clinical pipelines, as well as innovative seeds/technologies to strengthen our Research, CMC*, and Diagnostic divisions**

(Drug candidates entering clinical stage or GLP studies in FY2015)

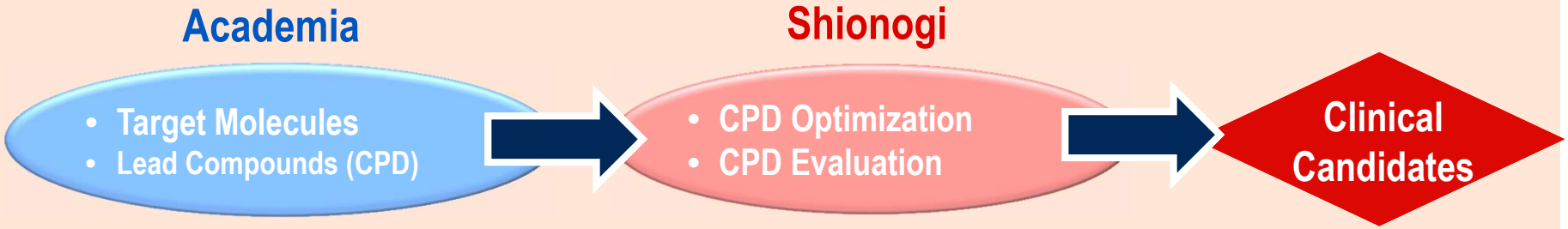
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*: PHarma-INnovation Discovery competition Shionogi, integrated into SSP in 2014

: Shionogi Science Program 2014 *: Chemistry, Manufacturing and Control

Identify Future Focus Areas for Discovery Research through Industry-Academia Collaboration

Application of academic innovation to drug discovery



- In-licensed a lead compound that could inhibit the activity of autotaxin, an enzyme related to tissue fibrosis, from the Open Innovation Center for Drug Discovery and School of Science at The University of Tokyo and Graduate School of Science and Faculty of Science, Tohoku University
- Developing a drug for CKD* by optimization of a lead discovered in academia

Accelerate drug discovery in new therapeutic areas by industry-academia collaboration

(Apply the achievements of academic research in NASH** including methods for evaluation of compounds for use as drugs)

*: Chronic Kidney Disease **: Non-Alcoholic Steatohepatitis

FY2015 Plan for Research

- **Continue to conduct highly innovative drug discovery and enrich the drug discovery portfolio**
  - Discover 3 or more drug candidates with a focus on infectious diseases and pain/neurology in FY2015
  - Enrich drug discovery portfolio utilizing external research collaboration
- **Seek to improve research productivity and ability to predict clinical trial success**
  - Promote efficient utilization of research budget by concentration in areas of core competence
  - Improve ability to predict of clinical trial success using iPS cells, imaging technologies, etc.
  - Actively apply BM/PGx* technology through collaboration with research, development and diagnostic departments
- **Maximize the value of our products and drug candidates**
  - Full support for LCM** of marketed products and NDA*** filings, including commitment to research in support of product differentiation and clarification of mechanism of action

*: Biomarkers/Pharmacogenomics **: Life Cycle Management ***: New Drug Application

Development

Takuko Sawada
Senior Vice President
Global Pharmaceutical Development Division

Development: Agenda

- SGS2020: Goals and Current Status of Development
- Achievements in FY2014
- Targeted Milestones for FY2015
- Core Development Products
  - Core Therapeutic Area
  - Frontier Therapeutic Area

Milestones Targeted by FY2020

Goals

More than 10 compounds, including out-licensed products and products currently approved in some countries, to be launched in a globally

Further improvement of productivity is critical to achieve our goals

1. **Further improvement and efficiency in strategic decision making**
2. **Establish solid framework for high quality, rapid, and efficient global development**

- **Some positive steps were taken toward the globalization of Shionogi's clinical development in the 3rd Medium-Term Business Plan**
- **However, we still have further to go to achieve full globalization**

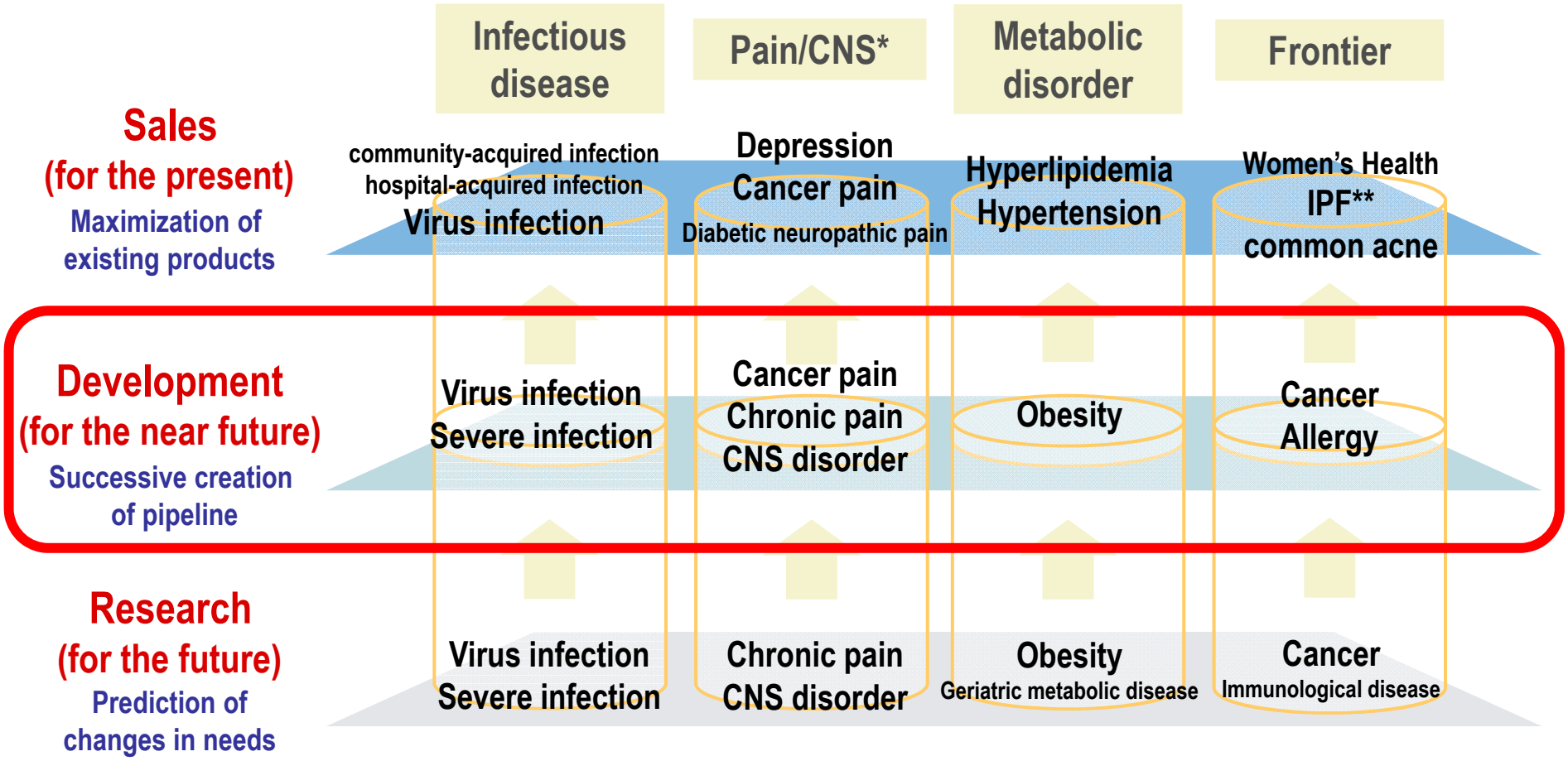
⇒ **Further improvement and enhancement in Shionogi's global development is an opportunity to breakthrough the low productivity of the pharmaceutical industry on average**

Enhancement of Strategic Decision Making, Efficient Development, and Framework Establishment

- **Decision-making regarding global development**
  - Project management and prioritization of compounds by the Global Portfolio Committee
    - Concentrate resources on core projects in infectious disease and pain/CNS areas and life cycle management of strategic marketed products
- **Efficient and rapid development**
  - Improve probability of success: identify and utilize biomarkers from the early stages of development to select appropriate patient populations; in collaboration with Research and Diagnostics Divisions
  - Reduce the total number of clinical subjects required by consulting with regulatory authorities to develop optimized clinical development program: S-297995, etc.
  - Reduce the number of clinical trials and refine clinical study designs by using epidemiological and observational studies and applying modeling and simulation
  - Form industrial-academic collaborations: including investigator-initiated clinical research, such as for cancer peptide vaccines, etc.
  - Increase efficiency of clinical studies through utilization of IT systems
- **Framework Establishment**
  - Establish worldwide collaborative framework; one example of success being the approval of ospemifene in EU
  - Accelerate of clinical trials in Japan: S-888711, etc.
  - Tightly link the project management system and the budget control system

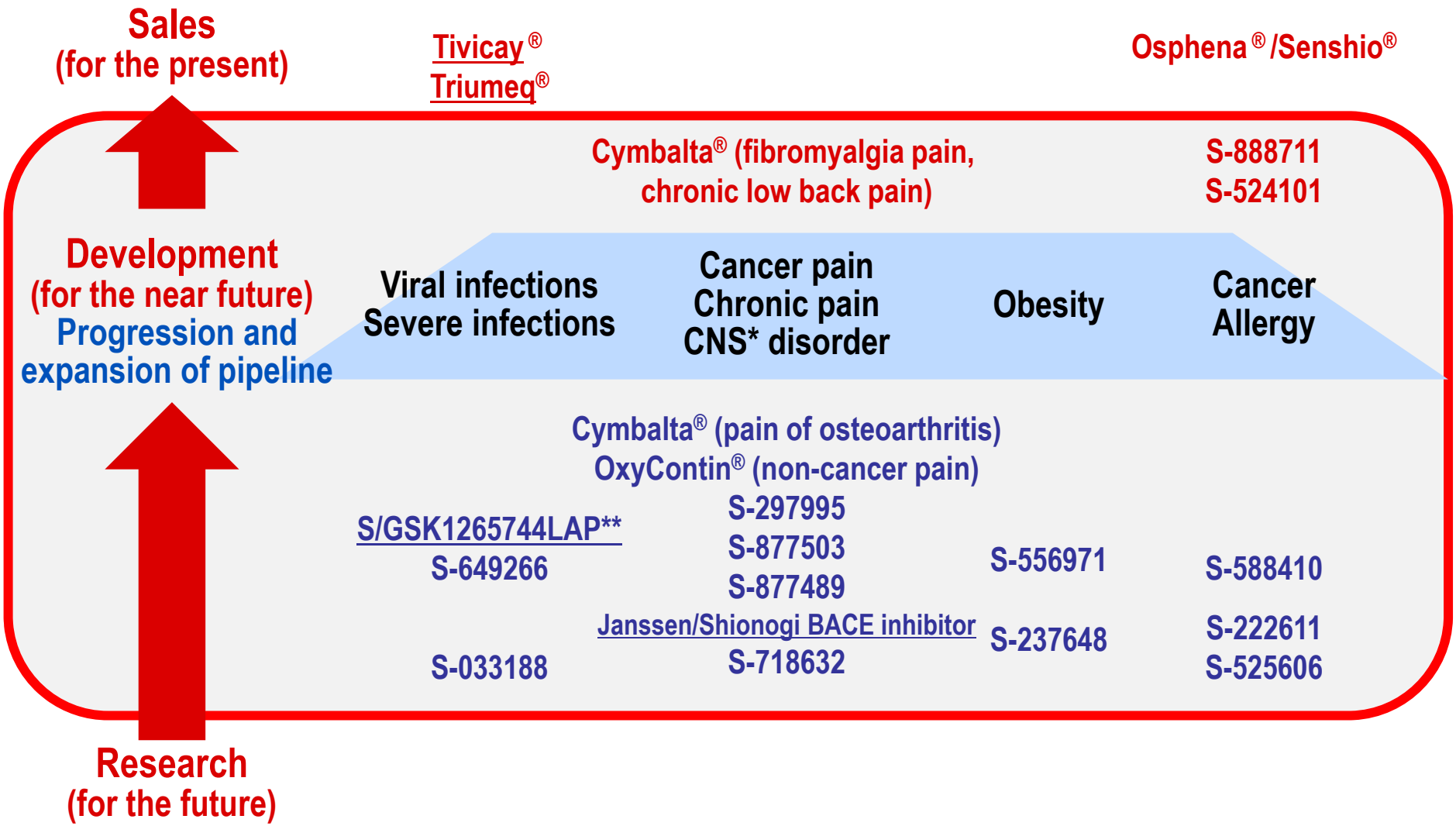
SGS2020: Target Development Therapeutic Areas

Clear priorities and focused resourcing to meet unmet medical needs



*: Central Nervous System **: Idiopathic Pulmonary Fibrosis

Current Status of Development: Focused Pipeline



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*: Central Nervous System **: Long Acting Parenteral formulation
underlined: out-licensing to ViiV Healthcare or Janssen

Focused Targets for Development in FY2014

- Acceleration of development of high-priority compounds in Japan
  - Cymbalta® (fibromyalgia pain, chronic low back pain): NDA submission in FY2014
  - S-888711 (lusutrombopag for thrombocytopenia): NDA submission in FY2014
  - S-524101 (sublingual tablets of house dust mite allergen extracts for immunotherapy): NDA submission at the beginning of FY2014
    - S-525606 (sublingual tablets of Japanese cedar allergen extracts) with larger market: clinical study initiation
- Advancing global development compounds
  - S-297995 (OIC*): Acceleration of Phase III studies and agreements of revised submission plan after FDA advisory committee
  - S-888711: Initiated of global studies after meeting with regulatory authorities
  - S-649266 (severe gram-negative infections): Global Phase II initiation after meetings with regulatory authorities
  - S-222611 (malignant tumor): Phase I/II acceleration based on results from Phase I
  - Senshio® (ospemifene for VVA**): Managed issues identified by regulatory authorities and obtained approval in EU
- Selected of promising compounds and pursued and established creative alliances activity

Consistently reached FY2014 development milestones worldwide

*: Opioid-Induced Constipation **: Vulvar and Vaginal Atrophy in post-menopausal women

Maximization of the Value of High-Priority Compounds in Japan

- **Life cycle management of Cymbalta®**
  - Fibromyalgia pain: NDA submission (Jun. 2014)
  - Chronic low back pain: NDA submission (Dec. 2014)
  - Osteoarthritis pain: Phase III study continuing
  - Diabetic peripheral neuropathic pain: in preparation
- **Expanding oxycodone pipeline**
  - OxyContin®: Phase III clinical study is continuing for the additional indication of non-cancer pain
  - OxyContin® NEO: Clinical study of abuse-deterrent, tamper-resistant oxycodone tablets for the additional indication of non-cancer pain is in preparation

Achievements in FY2014: Approvals and NDA Submissions

Approvals		
Dolutegravir/abacavir/ lamivudine* [Triumeq®]	HIV infection	US: Aug. 2014 EU: Sep. 2014 Japan: Mar. 2015
Ospemifene [Senshio®]	Post-menopausal vaginal atrophy	EU: Jan. 2015
NDA submissions		
Dolutegravir/abacavir/ lamivudine*	HIV infection	Japan: Dec. 2014
S-524101	Allergic rhinitis caused by house-dust mite allergen	Japan: Apr. 2014 (Passed Drug Committee Meeting in Jan. 2015)
Cymbalta®	Fibromyalgia	Japan: Jun. 2014
Cymbalta®	Chronic low back pain	Japan: Dec. 2014
S-888711 (Lusutrombopag)	Thrombocytopenia	Japan: Dec. 2014

*: ViiV Healthcare

Achievements in FY2014: Phase II - III

Progress in development status		
S-297995 (Naldemedine)	Alleviation of opioid-induced adverse effects	Global: Phase III COMPOSE-1 code break
S-877503	ADHD*	Japan: Phase II/III completed
S-877489	ADHD	Japan: Phase III initiated
S-888711 (Lusutrombopag)	Thrombocytopenia	Global: Phase III initiated
S-588410	Esophageal cancer	Japan: Phase III initiated
S-556971	Dyslipidemia	Japan: Phase II completed
S-649266	Severe gram-negative infections	Global: Phase II initiated

*: Attention Deficit Hyperactivity Disorder

Achievements in FY2014: Phase I

Progress in development status		
S-237648	Obesity	Japan: Phase I completed
S-525606	Allergic rhinitis caused by Japanese cedar allergen	Japan: Phase I completed
S-033188	Influenza infection	Japan: Phase I initiated
S-718632 (Abuse deterrent)	Chronic pain	US: Phase I initiated

Studies to Expand Indications and Respond to Academia Requests

Expansion of indications: Status of progress		
Vancomycin	Gram-positive bacteria-associated bloodstream infection	Approval : May 2014
Cymbalta®	Fibromyalgia	NDA submission : Jun. 2014
OxyContin®	For the treatment of moderate to severe chronic pain	Phase III
Requested for development by academia : Status of progress		
Imunomax®-γ	Mycosis fungoides/Sezary syndrome	Approval : May 2014

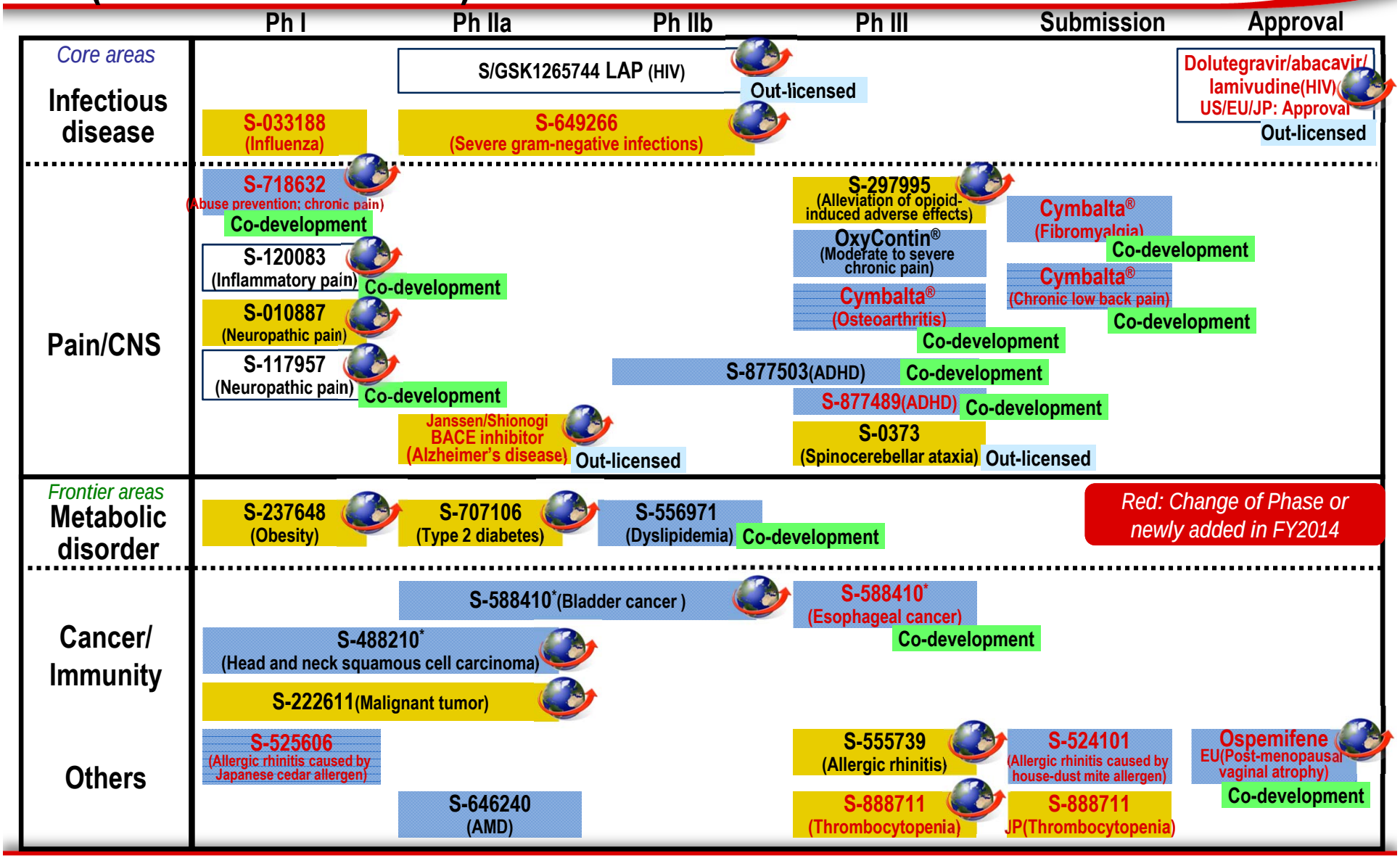
[Achievements since 2010]

Development for expanded indications: 14 (Approvals: 12)

Development requests from academia:

- Publication-based application: 3
- Clinical trial implementation: 2 (all approved)

Development Pipeline Progression and Expansion (as of March 2015)



LAP: Long-Acting Parenteral formulation
ADHD: Attention Deficit Hyperactivity Disorder
AMD: Age-related Macular Degeneration

Developing products globally

*: Cancer peptide vaccine

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

Target Milestones for FY2015: Approvals and NDA Submissions

Approvals		
S-524101	Allergic rhinitis caused by house-dust mite allergen	Japan
Cymbalta®	Fibromyalgia	Japan
Cymbalta®	Chronic low back pain	Japan
S-888711 (Lusutrombopag)	Thrombocytopenia	Japan
NDA submissions		
S-877503	ADHD	Japan
S-297995 (Naldemedine)	Alleviation of opioid-induced adverse effects	US/Japan

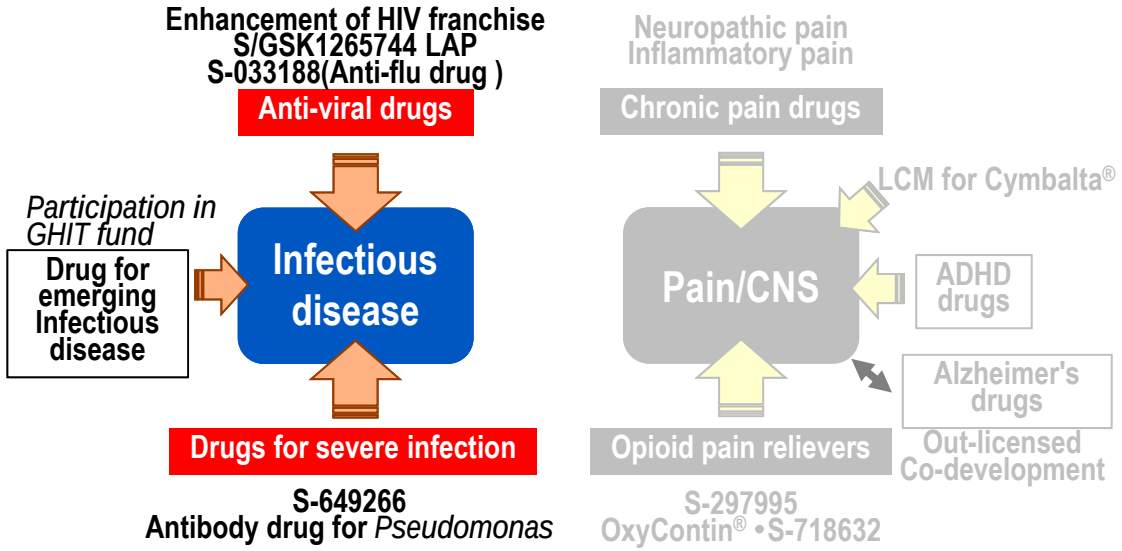
Target Milestones for FY2015: Phase I - III

Progress in development status		
Cymbalta®	Osteoarthritis	Japan: Phase III completed
S-649266	Severe gram-negative infections	Global: Phase III initiated
OxyContin® (Abuse deterrent)	Cancer/Non-cancer pain	Japan: Phase I initiated
S-718632 (Abuse deterrent)	Chronic pain	US: Decision on final formulation
S-033188	Influenza infection	Japan: Phase I completed Go / No Go decision

Core Development Products

- Core Areas -

Infectious Diseases



Infectious Diseases: Maximize HIV Integrase Inhibitor Franchise

- **Ongoing efforts to maximize HIV franchise with ViiV Healthcare**
  - **Triumeq® (dolutegravir/abacavir/lamivudine single-pill regimen)**
    - **Approval: Aug. 2014 (US), Sep. 2014 (EU) and Mar. 2015 (Japan)**
  - **Development of a single pill combining dolutegravir and Janssen's NNRTI rilpivirine**
    - **Phase III study will be initiated in 2015 (calendar)**
  - **S/GSK1265744 LAP***
    - **Phase II study (LATTE II study) is on-going**

*: Long Acting Parenteral formulation

Infectious Diseases: HIV Integrase Inhibitor

- **Development status by ViiV Healthcare**
  - Development of oral fixed dose combination tablet of dolutegravir (DTG) and rilpivirine (RPV)
    - Phase I study in healthy subjects for various test formulations of DTG+RPV fixed dose tablet to select the best formulation
  - DTG resistance outcomes at the scheduled study end of treatment naïve Phase III/IV studies
    - SPRING-2: 96-week, No DTG resistance emerged (*Lancet Infect Dis* 2013;13: 927-35)
    - SINGLE: 144-week, No DTG resistance emerged (ICAAC, Sep, 2014)
    - FLAMINGO: 96-week, No DTG resistance emerged (HIV Drug Therapy Glasgow, Nov. 2014)
  - Development of cabotegravir (S/GSK1265744) long-acting (LA) injectable
    - A Phase IIb study to evaluate a long-acting intramuscular regimen for maintenance of virologic suppression (following induction with an oral regimen of GSK1265744 and abacavir/lamivudine) in HIV-1 infected, antiretroviral therapy naïve subjects
    - ÉCLAIR study to evaluate the safety, tolerability, and acceptability of long acting injections of the HIV integrase inhibitor, GSK1265744, in HIV uninfected men (Phase IIa study for pre-exposure prophylaxis)

Infectious Diseases: S-649266

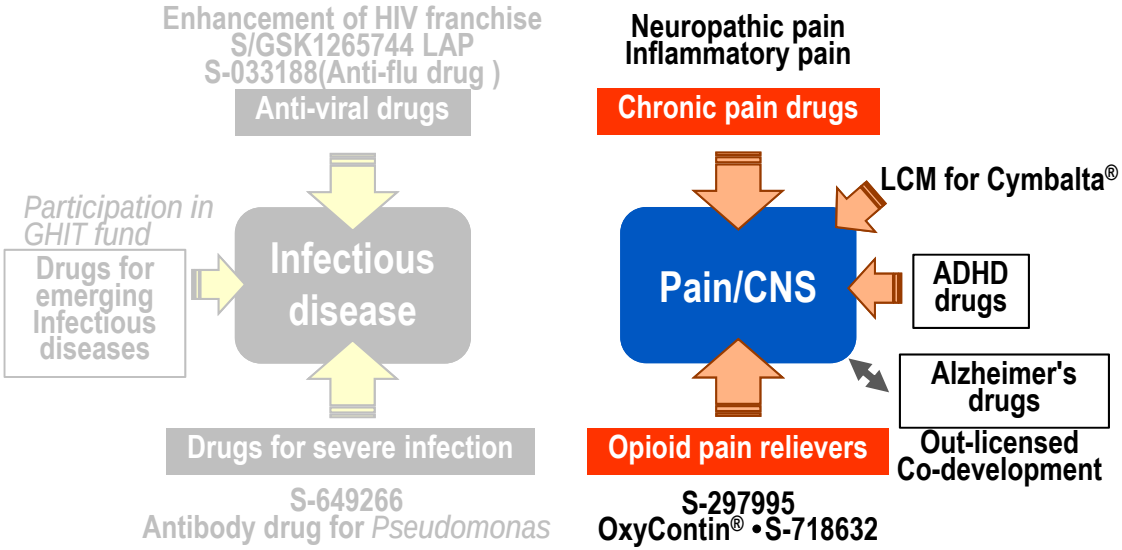
- **Indication**
  - Severe Gram-negative infections
- **Mechanism of action**
  - Cell wall synthesis inhibitor
- **Product characteristic**
  - An injectable cephalosporin with potent activity against gram-negative pathogens
  - Showing potent activity against multidrug (e.g., carbapenem and cephalosporin)-resistant strains such as metallo-β-lactamase (e.g., NDM-1*)-producing strains, multi-drug resistant *P. aeruginosa* (MDRP), *A. baumannii* and Enterobacteriaceae (*K. pneumoniae,* etc.)
- **Development status**
  - Phase II cUTI** study (global) in progress
  - Phase III study (global) scheduled in FY2015

*: New Delhi Metallo-beta-lactamase-1 **: Complicated Urinary Tract Infection

Infectious Diseases: S-033188

- **Indication**
  - Influenza virus infection
- **Mechanism of action**
  - Novel mechanism of action
- **Product characteristic**
  - Broad and strong antiviral activity against influenza A and B viruses including highly pathogenic avian influenza virus
  - No cross resistance to marketed neuraminidase inhibitors
  - Rapid and potent virus reduction in virus-infected animals
- **Development status**
  - Phase I single and multiple dose study ongoing
  - Go/No Go decision in FY2015
  - NDA submission in Japan in FY2017 at the earliest

Pain/CNS


Enhancement of HIV franchise
S/GSK1265744 LAP
S-033188(Anti-flu drug)
Anti-viral drugs
Participation in GHIT fund
Drugs for emerging Infectious diseases
Infectious disease
Drugs for severe infection
S-649266
Antibody drug for Pseudomonas
Neuropathic pain
Inflammatory pain
Chronic pain drugs
LCM for Cymbalta®
Pain/CNS
ADHD drugs
Alzheimer's drugs
Opioid pain relievers
Out-licensed
Co-development
S-297995
OxyContin® •S-718632

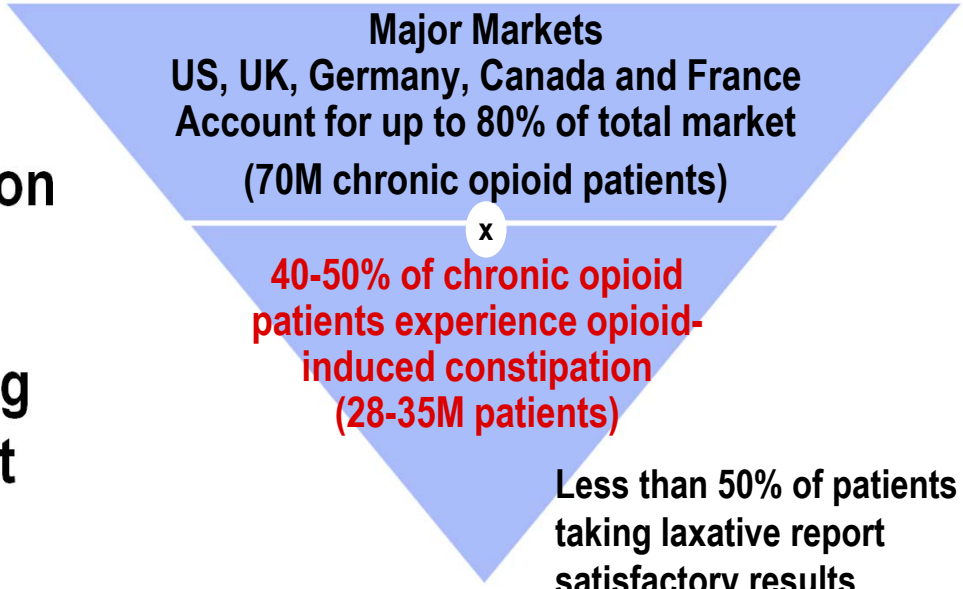
Pain/CNS: S-297995 (Naldemedine)

Compound Profile

- **Indication**
  - Treatment of opioid-induced constipation
- **Mechanism of action**
  - An oral, peripherally acting opioid receptor antagonist
- **Development status**
  - COMPOSE Program on-going (Global phase III studies in chronic noncancer pain patients and cancer patients)

Global Opioid Market*

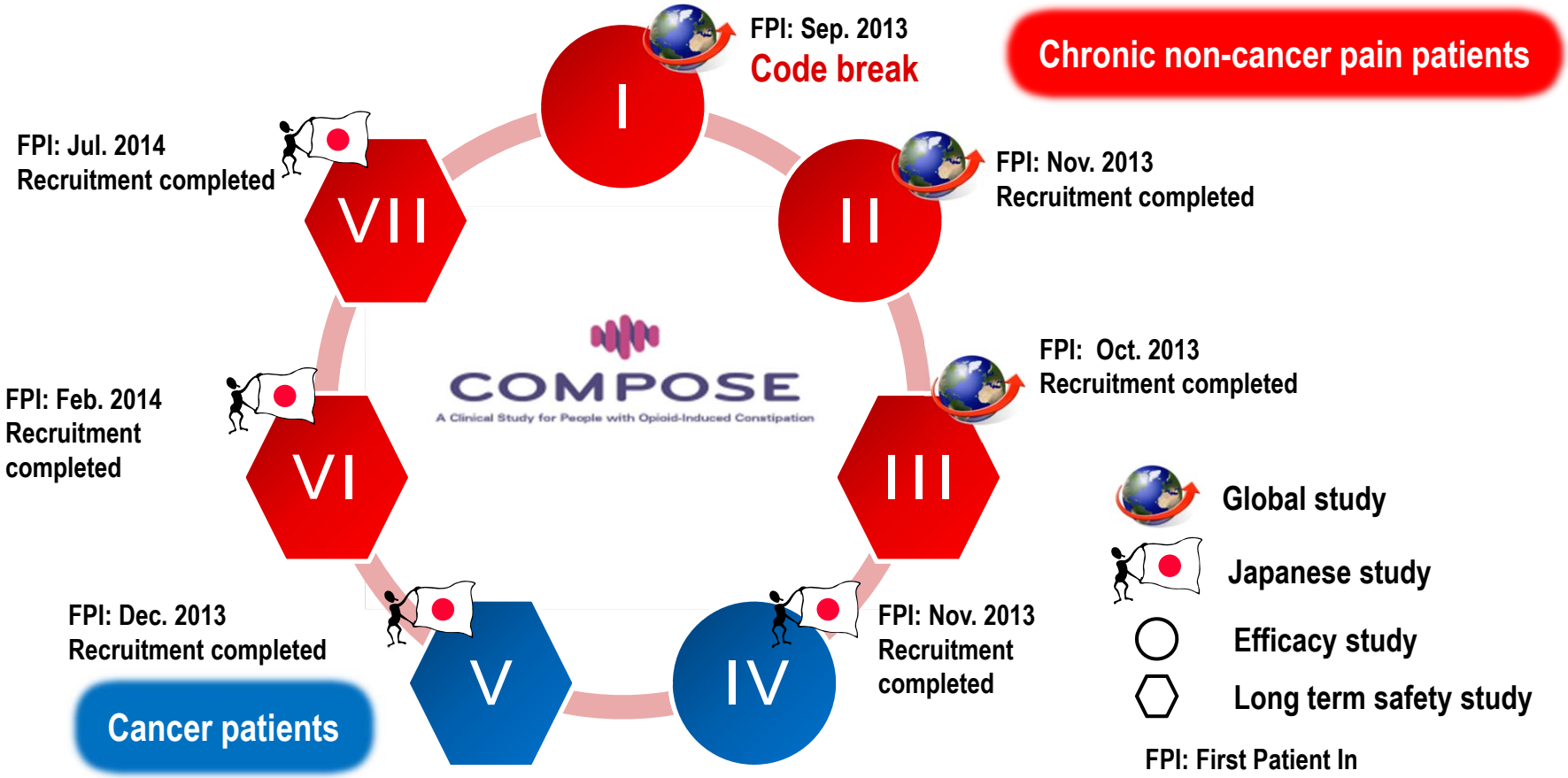
US$14.8 B



* Source: Calculated based on IMS Health MIDAS MAT-2Q12, etc.

Phase III Studies (COMPOSE Program)

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



COMPOSE-1 Study Design

The study was designed as a multicenter, randomized, double-blind, placebo-controlled, parallel-group study

Screening Period → **12-week Treatment Period** → **4-week Follow-up Period**

Study Population

- Must have non-malignant chronic pain treated with opioids and must have OIC
- Must not be currently using laxatives or must be willing to discontinue laxative use
- Must meet no more than 3 SBMs* in a given week of the qualifying period
- Must meet experience one or more of bowel symptoms in 25% or more of BMs

Placebo (n=270)

Naldemedine 0.2 mg QD (n=270)

Rescue laxative therapy is optional and may be initiated if a subject has not had a BM for any period of 72 hours

Efficacy Assessments

Primary Endpoint
- Proportion of responders**

Secondary Endpoints
- Frequency of SBMs, CSBMs, SBMs without straining

Safety Assessments

- GI-related AEs

PK Assessments

COMPOSE
A Clinical Study for People with Opioid-Induced Constipation

SHIONOGI

*: Spontaneous bowel movement (SBM) is defined as a BM that occurs without the use of a rescue laxative medication during the 24 hours prior to the BM.
**: A responder is defined as having 9 positive response weeks or more out of the 12-week Treatment Period and 3 positive response weeks out of the last 4 weeks of the 12-week Treatment Period. A positive response week will be defined as ≥ 3 SBMs per week and an increase from baseline of ≥ 1 SBM per week for that week.

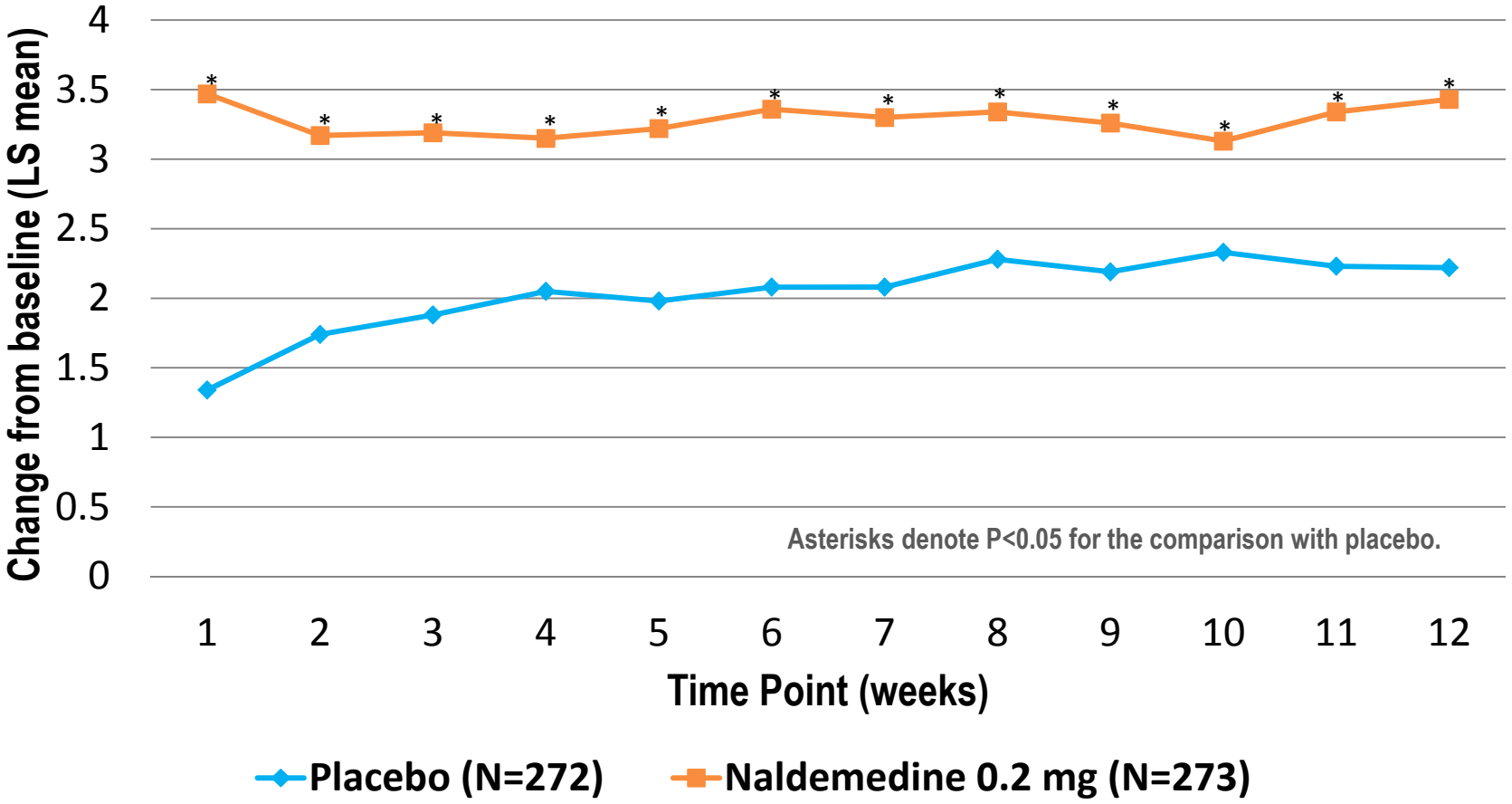
COMPOSE-1 Study Top Line Results

- **Efficacy profile**
  - The treatment difference in Responder Rate (the primary endpoint) between naldemedine and placebo were statistically significant
  - The treatment difference in all secondary endpoints (frequency of SBM, SBMs without straining and CSBM) between naldemedine and placebo were statistically significant
- **Safety profile**
  - Naldemedine was generally well tolerated
  - The most commonly reported (>= 5%) TEAEs with naldemedine were gastrointestinal disorders (Abdominal pain and Diarrhea)
  - No significant changes over the 12-week treatment period were seen in the pain intensity Numerical Rating Scale (NRS) scores and COWS** scores

*: Clinical Opiate Withdrawal Scale

Frequency of SBMs from Baseline to Each Week

Change in the frequency of SBMs per week from baseline to each week of the treatment period (ITT)



SHIONOGI

The MMRM model has terms for treatment group, time, treatment-by-time as a fixed effect and the opioid dose strata as a covariate

Pain/CNS: Cymbalta®

Cymbalta® (duloxetine, LY248686)

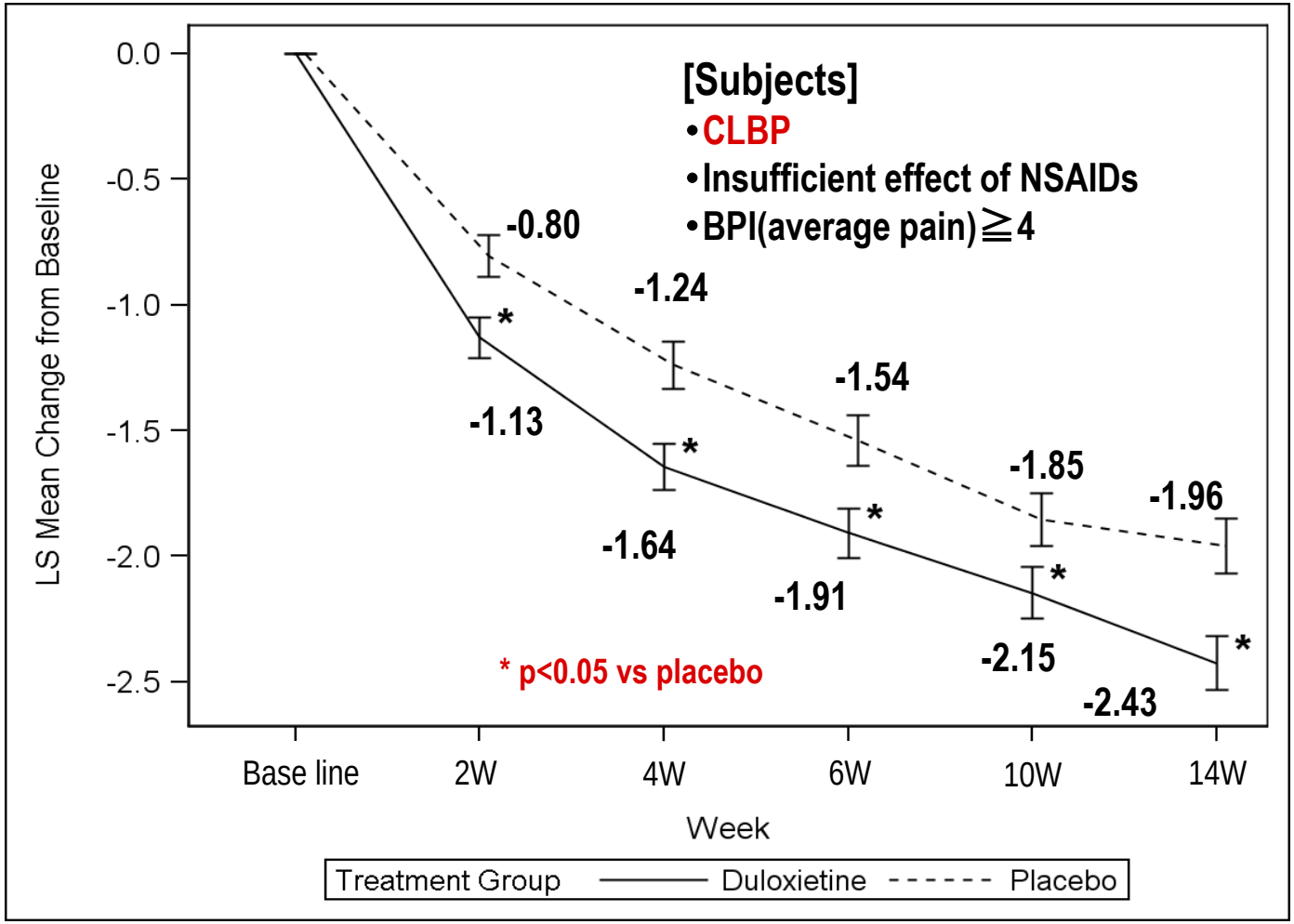
- **Product characteristic**
  - Serotonin noradrenaline reuptake inhibitor
  - Licensed from Eli Lilly
- **Indications**
  - Global (approved as of April 2014)

    Major depressive disorder in 105 countries, DPNP* in 100 countries,
    Generalized anxiety disorder in 88 countries, Fibromyalgia in 35 countries,
    Abdominal pressure - induced incontinence in 48 countries and
    Chronic musculoskeletal pain in 31 countries
  - Japan

    Depression and depressive symptoms: Launched in Apr. 2010
    DPNP: Approved in Feb. 2011

*: Diabetic Peripheral Neuropathic Pain

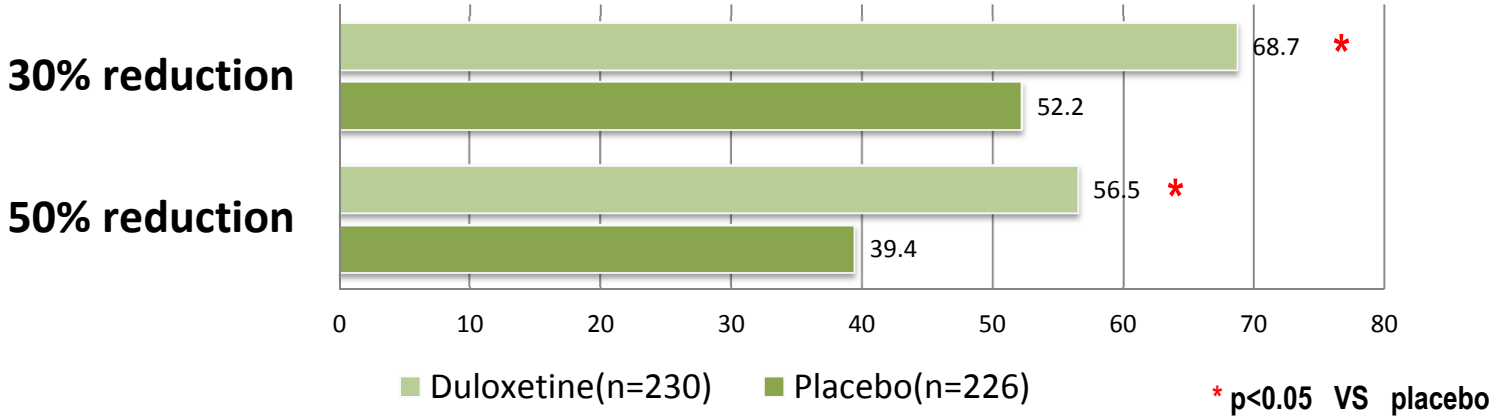
Cymbalta® (CLBP*) Phase III: Primary Endpoint



BPI: Brief Pain Inventory, FAS: Full Analysis Set

Cymbalta® (CLBP*) Phase III: Secondary Endpoint

- **Response Rate for the BPI Average Pain Score**



- **RDQ-24 (Roland-Morris Disability Questionnaire): CLBP specific QOL score patient evaluation (24 QOL scale for CLBP)**

	Baseline mean±SD	(n)	Change mean±SE	Difference [95% CI]	P value
Placebo	7.77±4.77	(226)	-3.23±0.22		
Duloxetine	7.59±4.38	(230)	-3.86±0.22	-0.64 [-1.25, -0.02]	0.0439

Life Cycle Management for Cymbalta®

- **Current Status of development**
  - Fibromyalgia(development of new indications with high medical need, requested by Review Committee): NDA submission
  - Chronic low back pain(additional indication): NDA submission
  - Osteoarthritis(additional indication): Phase III study
  - Diabetic peripheral neuropathic pain (Phase IV, Non-Inferiority study comparing with Pregabalin): in preparation

Maximize Cymbalta's value as a growth driver for the medium-term business in Japan by securing approval for the same pain indications as are approved globally

Pain/CNS: OxyContin®

OxyContin® tablets (S-8117)

- **Product characteristics**
  - Orally available sustained release tablets of oxycodone
  - Strong opioid analgesic
  - Developed by Purdue/Mundipharma and launched at US in1995 (now launched in 59 countries)
  - In-licensed from Mundipharma
- **Domestic sales**
  - OxyContin® Tablets: 5mg, 10mg, 20mg, 40mg
  - Indication: For the treatment of moderate to severe chronic pain
  - Launched in 2003

Effective Abuse Deterrence by OxyContin® NEO

- Abuse deterrent formulation of OxyContin® (OxyContin® NEO) was launched in Apr. 2010 in US and ordinary OxyContin® was abandoned in Apr. 2013
- In the same month, US FDA decided that oxycodone products not containing abuse-deterrent feature would not be approved through the ANDA** system
- Due to introduction of the abuse-deterrent formulation, the number of reported deaths by abuse was reduced

pharmacoepidemiology and drug safety 2014; 23: 1238–1246

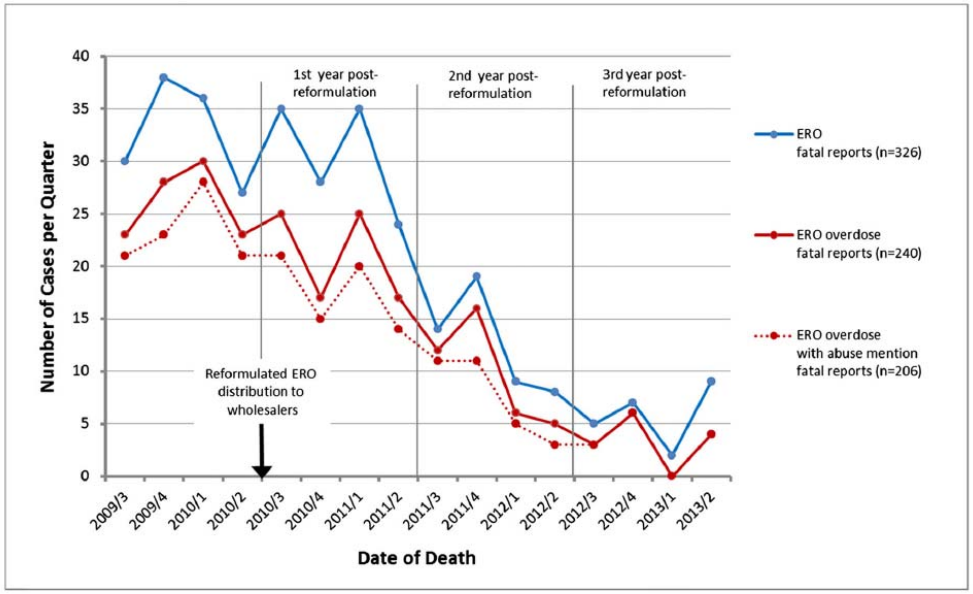


Figure 1. Number of extended-release oxycodone (ERO) fatality reports per quarter. Categories entitled overdose and overdose with mention of abuse-related behavior are defined in methods. Distribution of reformulated ERO to wholesalers was initiated 9 August 2010 (indicated by the arrow).

By switching to abuse deterrent formulation, the number of abuse-related deaths was reduced in US

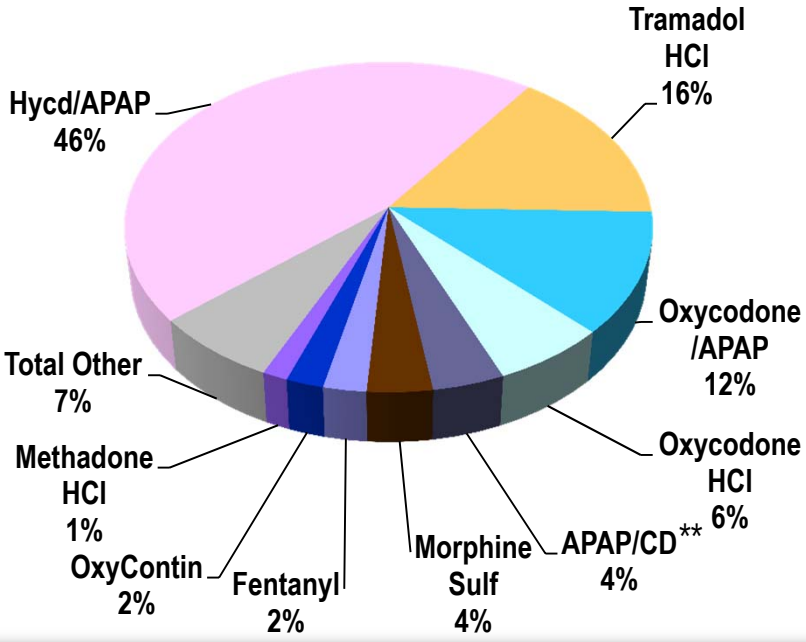
Planning to switch to abuse-deterrent formulation in Japan with development of non-cancer pain indication

*: Abbreviated New Drug Application

Opioid Analgesics: Market Environment

- OxyContin® is the largest selling product in sales (29% of sales), however, Hydrocodone/APAP* is, by far, the most commonly prescribed opioid with 46% of all opioid prescriptions
- Approximately 25% of short-acting hydrocodone is prescribed for >30 days (IMS, 2011), thereby creating the need for long acting formulations
- The market environment might change because hydrocodone combination products were rescheduled from Class III to Class II (Jun. 10, 2014)

Share of TRxs by Product
MAT Mar/14



Competitor Landscape

- Hydrocodone
  - Zohydro® ER (Zogenix): First approved in Oct. 2013. Abuse deterrent product was approved in Jan. 2015 (abuse-deterrent claims not yet approved)
  - Hysingla™ ER (Purdue): Approved in Nov. 2014 with abuse-deterrent properties and claims
  - CEP-33237 (Teva): NDA submission in Oct. 2014
- Hydrocodone + Acetaminophen
  - MNK-155 (Mallinckrodt): NDA submission in May 2014

*: Acetaminophen **: Codeine

Source: IMS NSP MAT May 2014 and IMS NPA MAT May 2014

Opioid Analgesics: Development Status and Future Direction

- **Development of OxyContin® tablets (S-8117)**
  - Request from MHLW* (Dec. 2010)
    For treatment of moderate to severe chronic pain: Phase III study

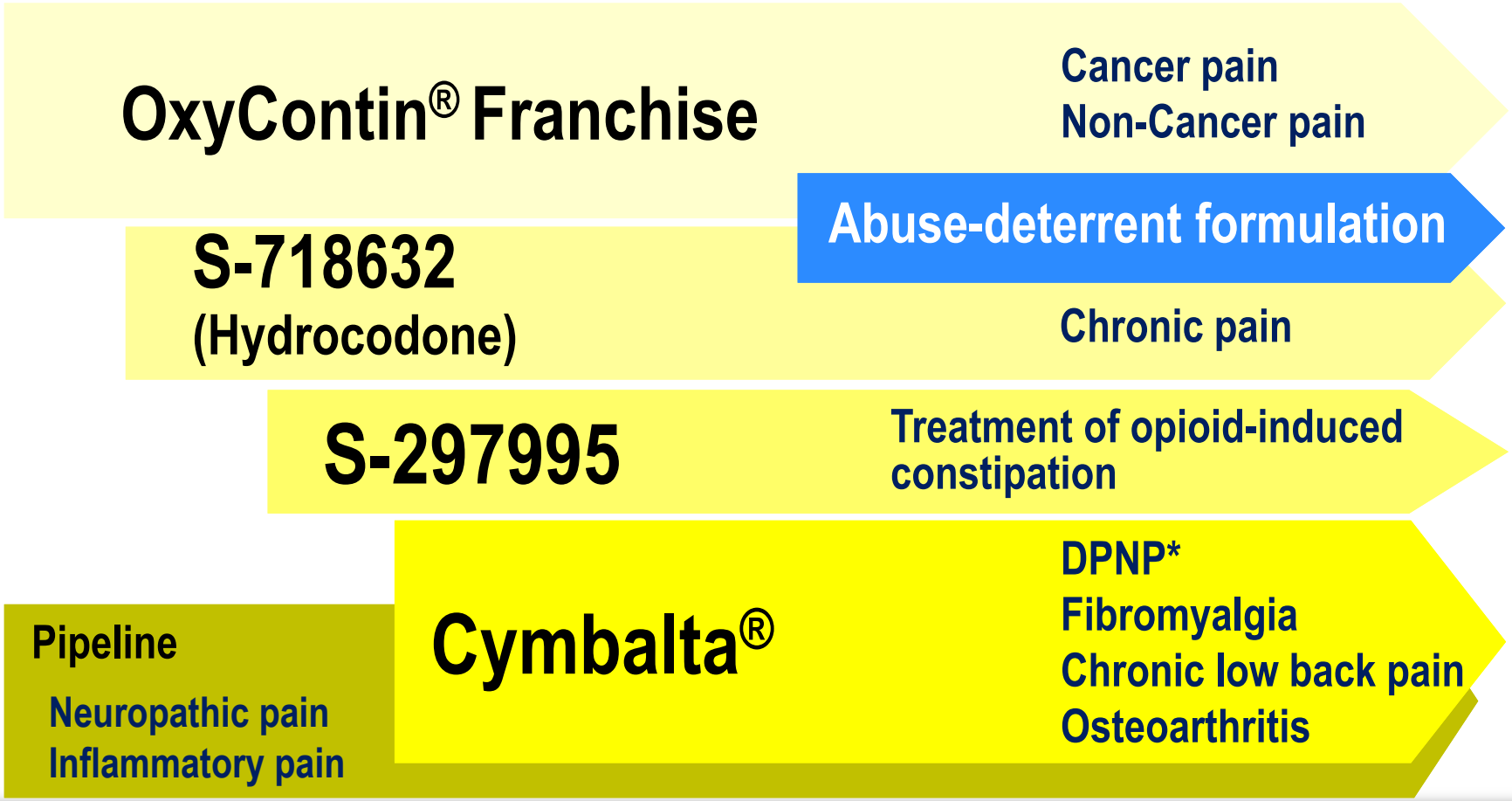
- **Development of abuse-deterrent formulation in Japan**
  - Abuse-deterrent via tamper resistance
  - In-licensed from Mundipharma (Nov. 2013)
  - NDA data package already accepted by PMDA**

- **Entered into a global alliance for abuse-deterrent hydrocodone with Egalet**

*: Ministry of Health, Labour and Welfare **: Pharmaceuticals and Medical Devices Agency

Pain: Improve Patients' Quality of Life (QOL)

Promote comprehensive research and development of proper use of medical narcotics and pain relief



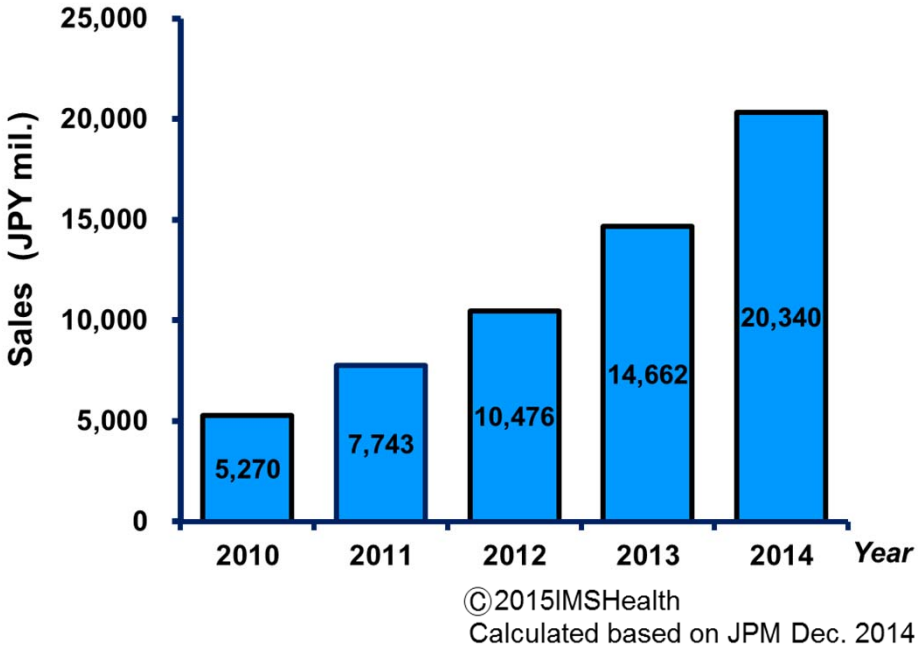
*: Diabetic Peripheral Neuropathic Pain

Pain/CNS: S-877489 and S-877503

Attention-Deficit/Hyperactivity Disorder (ADHD)

- **Description of disorder**
  - Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous neurobehavioral disorder characterized by a persistent pattern of developmentally inappropriate inattentiveness, impulsivity, and hyperactivity (diagnostic criteria: DSM-5)
- **Prevalence of ADHD in Japan**
  - Children: 2.5% (research by the Education Ministry), Adults: 1 - 7%
- **Competitive landscape in Japan**
  - Concerta® (Stimulant, indicated for children, adolescents and adults)
  - Strattera® (Non-stimulant, indicated for children, adolescents and adults)
- **Current unmet medical needs**
  - Improvement of efficacy for non-responding patients
  - Reduction of adverse events such as insomnia or anorexia

ADHD Market Situation in Japan and Expected Role of New Treatment Options



©2015IMSHealth
Calculated based on JPM Dec. 2014

Japanese ADHD market

- The size of the ADHD market is rapidly increasing due to the expansion of awareness of ADHD (2010-2014 Compound Average Growth Rate: 31.01%)
- Recently, the adult ADHD market is significantly expanding

Value of offering new treatment options for ADHD

- By offering both stimulant and non-stimulant treatment options, we can better assist in tailoring therapy to the needs of the patient (symptoms, ADRs*, etc.) and can provide more comprehensive information

*: Adverse Drug Reactions

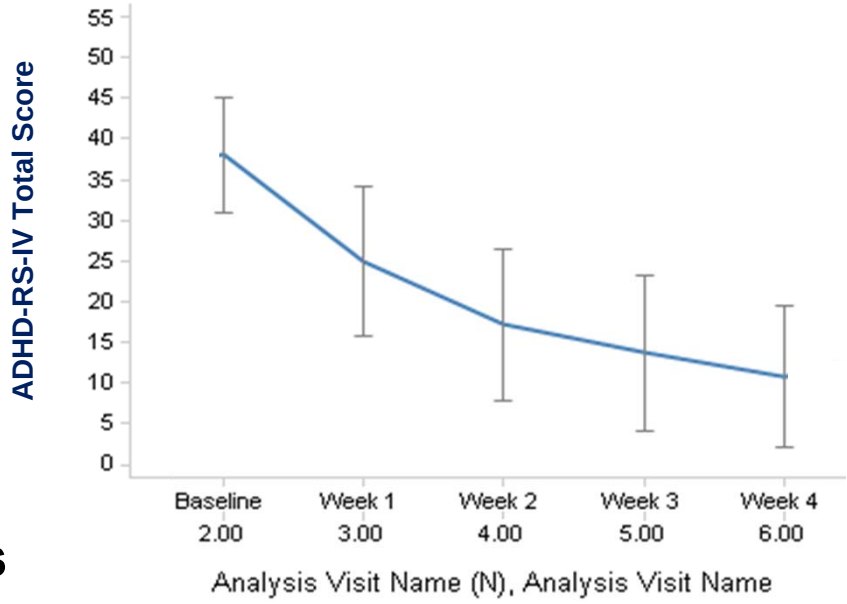
S-877489 [Vyvanse®]: Compound Profile

- **Development concept**
  - S-877489 is classified as a central nervous system (CNS) stimulant indicated for the treatment of ADHD in children and adolescents
- **Mechanism of action**
  - Pharmacologically inactive prodrug stimulant for ADHD which is enzymatically hydrolysed primarily to the active molecule
  - To block the reuptake of norepinephrine and dopamine and increase the release of these monoamines
- **Development status**
  - Phase II/III and extension studies are on-going in Japan
  - Marketed in US (since 2007), Canada, Brazil and EU by Shire
- **Future plan in Japan**
  - Phase II/III study will be completed in 2016

Vyvanse®: Product brand name in the US and Canada

S-877489 [Vyvanse®]: Phase II Study Results

- **Target**
  - Pediatric patients aged 6-17 years old with ADHD
- **Study Design**
  - The safety of S-877489 was assessed in an open-label study . Dose was increased or decreased following the up- and down-titration criteria
- **Safety**
  - Most AEs* were mild in severity. There were no serious AEs. The profile is similar to that observed in overseas clinical studies
- **Efficacy**
  - The mean change of ADHD-RS-IV total score from baseline was -26.4±8.2 at the last visit (week 4). The change is similar to overseas clinical studies



*: Adverse Events

S-877503 [Intuniv®]: Compound Profile

Development concept

- S-877503 is classified as a non-stimulant with no known potential for dependence/abuse indicated for the treatment of ADHD
- In the US, indicated for treatment of ADHD in children and adolescents as monotherapy and adjunctive therapy to stimulants
- Expected total care of ADHD patients with S-877489

Mechanism of action

- Selective alpha 2 adrenergic receptor agonist

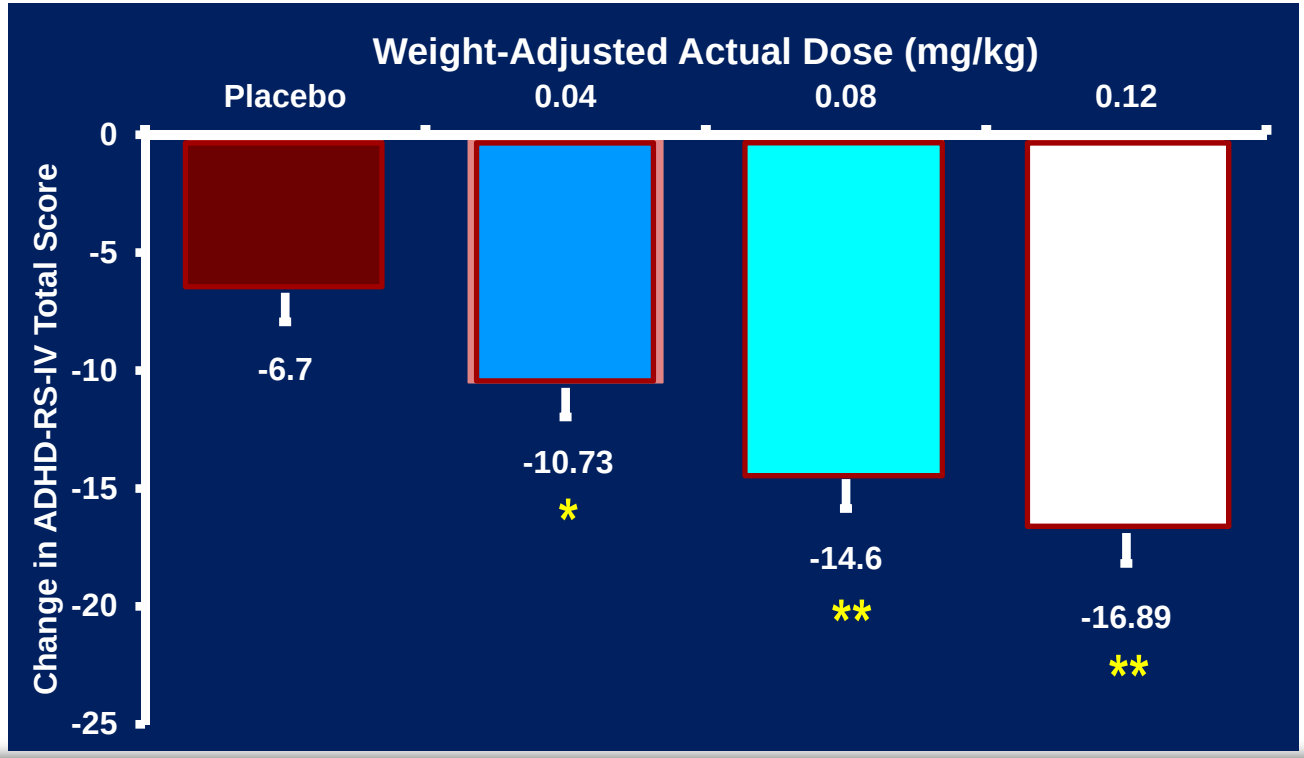
Development status

- Phase II/III was completed and NDA submission is in preparation in Japan
- Marketed in US (since 2009) by Shire
- MAA submission in EU by Shire

Intuniv®: Product brand name in the US

S-877503 [Intuniv®]: Phase II/III Study Top Line Results

- **Efficacy profile:** The mean change of ADHD-RS-IV total score from baseline was significantly greater than placebo for all S-877503 weight adjusted dosing groups (m-ITT population)
- **Safety profile:** Most AEs were mild in severity. There were no serious AEs. The safety profile is similar to that observed in overseas clinical studies



*P<.05; **P<.01 Primary endpoint: The change of ADHD-RS-IV total score from baseline at the treatment endpoint (Week 7). (MMRM analysis)

Pain/CNS: Progress of Janssen/Shionogi BACE* Inhibitor

- **Phase I data to be announced by Janssen at AD/PD™ 2015**

Symposium 26: AMYLOID-REDUCING THERAPIES IN ALZHEIMER'S DISEASE (March 20, 2015)
PROFILING THE DYNAMICS OF CSF AND PLASMA ABETA REDUCTION WITH JNJ-54861911, AN ORAL BACE INHIBITOR

Study design

- Healthy participants, aged 55 to 85, were randomized (Janssen/Shionogi BACE inhibitor / placebo)
- Assessed safety, tolerability, plasma and CSF pharmacokinetics (PK) and pharmacodynamics (PD) including Aβ**, sAPP***α, sAPPβ after a single dose and subsequent multiple ascending 14-day dose

Summary

- Janssen/Shionogi BACE inhibitor is a potent, brain-penetrant BACE inhibitor, achieving up to 95% Aβ reduction with once-daily oral dosing
- Aβ reduction outlasted plasma/CSF PK, leading to sustained PD activity

- **Progressed into Phase II following the favorable results in Phase I**

*: Beta-secretase Cleaving Enzyme
: Amyloid Beta Protein *: Soluble Amyloid Precursor Protein

CNS: Addressing Society's Unmet Medical Needs

Strengthen our product portfolio in the CNS area through partnerships, driving our mid-to-long-term growth

Depression / depressive condition

Cymbalta®

(Japan, in-licensed from Eli Lilly)

Promotion scheme:

Joint promotion with Shire

Attention deficit hyperactivity disorder

S-877489 S-877503

(Japan, in-licensed from Shire)

Promotion scheme :

Janssen has the global right to promote exclusively

Shionogi holds joint promotion rights in some territories including Japan and the US

Alzheimer's disease

Janssen/Shionogi BACE inhibitor

(Global, out-licensed to Janssen)

Core Development Products
- Frontier Areas -

Oncology/Immunological Disease: Cancer Peptide Vaccines

Compound Profile

- In-licensed from OncoTherapy Science, Inc. (OTS, Japan)
  - Shionogi possesses worldwide rights to develop and market cancer peptide vaccines
- Mechanism of action
  - Vaccination with peptides derived from antigens selectively and highly expressed in tumor cells which can effectively induce cytotoxic T-lymphocytes (CTLs), which elicit the antitumor effect.
- Indications
  - In addition to bladder cancer, esophageal cancer and head and neck cancer in the ongoing clinical studies, Shionogi retains worldwide rights to all indications
- Product characteristics: 5-peptide cocktail vaccine
  - Single formulation of cocktail vaccine with potential for efficacy against many types of cancers
    ⇒ Expansion of indications and maximization of value
  - Five oncoantigens are highly expressed in a range of tumor types (immunohistochemistry)

Code name	HLA restriction		Characteristics	Status
S-588410	A*24:02	Japanese: about 60% Caucasian: about 15-20%	Combination vaccine of S-288310 and S-488410	Clinical trials ongoing
-	A*02:01	Japanese: about 20% Caucasian: about 50%	Combination vaccine of A*02:01 restricted peptides derived from the same oncoantigens of S-588410	Clinical trials in preparation

S-588410 (Cancer Peptide Vaccine)

Status of clinical trials

- S-588410 (A*24:02, a 5-peptide cocktail vaccine)

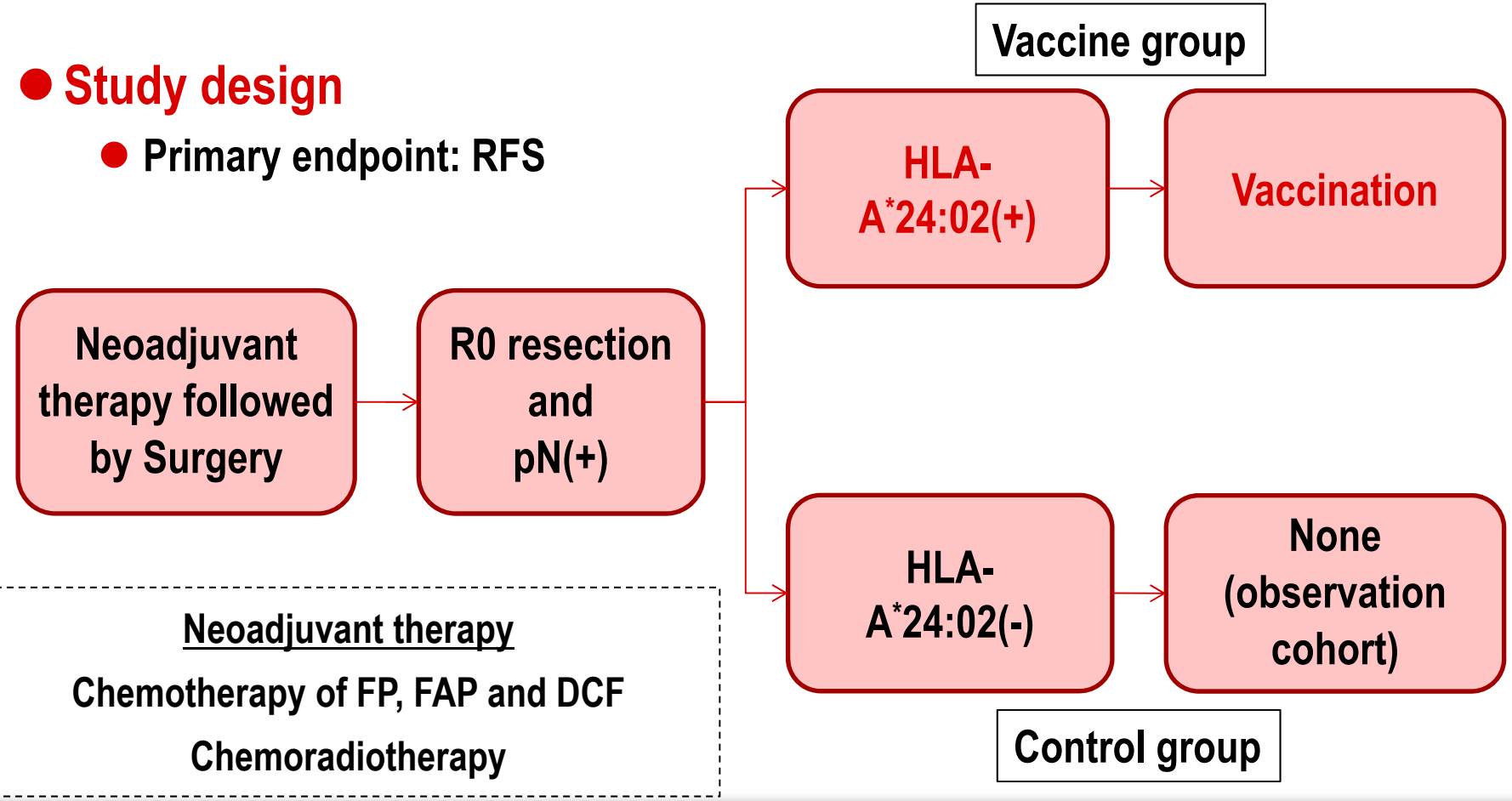
  Shift target segments from STF(standard therapy failure) to the earlier-stage segment in which cancer peptide vaccines are expected to achieve more efficacy

  - Bladder cancer: Phase II study (Japan, EU)
    - Target indication: Bladder cancer in maintenance setting after 1st-line chemotherapy
  - Esophageal cancer: Phase III study (Japan)
    - Target indication: Esophageal SCC in adjuvant setting after surgery
    - Initiated Phase III based on the results of translational research of 3-peptide cocktail vaccine in adjuvant setting after surgery at Kinki Univ. (co-development with OncoTherapy Science, Inc.)

Translational Research of 3-Peptide Cocktail Vaccine for Esophageal Cancer (Kinki Univ.)

Adjuvant therapy for ESCC patients after neoadjuvant therapy followed by curative resection

- **Study design**
  - Primary endpoint: RFS

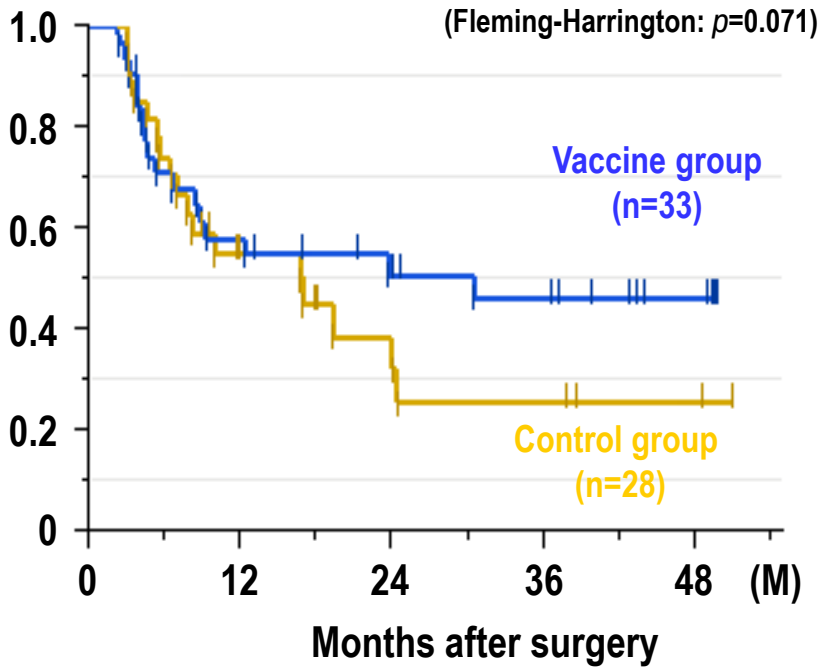


(Reference: Takushi Yasuda et. al., The 73rd Annual Meeting of the Japanese Cancer Association, 2014)

Translational Research of 3-Peptide Cocktail Vaccine for Esophageal Cancer (Kinki Univ.)

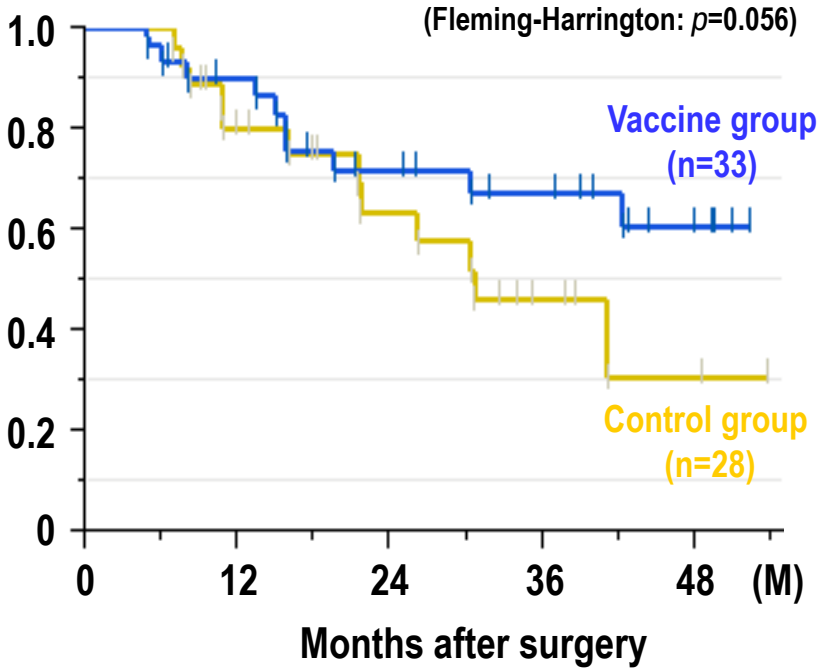
RFS(Relapse-Free Survival)

	1-year	2-year	3-year	4-year
Vaccine group	58.2%	51.1%	46.5%	46.5%
Control group	55.2%	32.3%	25.8%	25.8%



OS(Overall survival)

	1-year	2-year	3-year	4-year
Vaccine group	90.2%	72.1%	67.6%	60.8%
Control group	80.4%	63.8%	46.4%	30.9%



SHIONOGI

Fleming-Harrington test: The weighted log-rank test with the Fleming-Harrington class of weights
(Reference: Takushi Yasuda et. al., The 73rd Annual Meeting of the Japanese Cancer Association, 2014)

Prevention of Tumor Metastasis: Human Atrial Natriuretic Peptide (hANP)

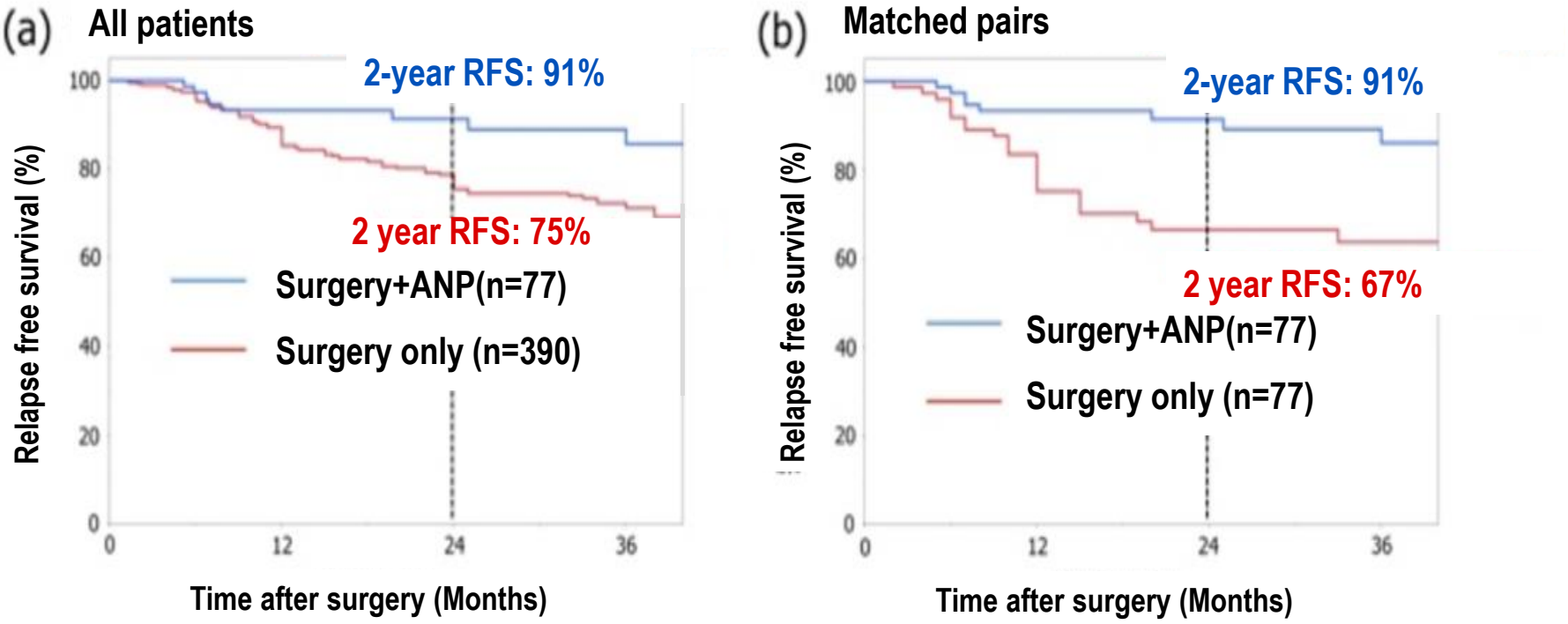
Compound Profile

- **Indication**
  - Prevention of tumor metastasis
- **Mechanism of action**
  - hANP is expected to prevent recurrence and/or metastasis after surgery by inhibiting adhesion of cancer cells to artery endothelial cells by suppressing E-selectin expression which is prompted by inflammation associated with surgery
- **Collaboration**
  - Shionogi will support the clinical research, in part by providing research funds, under a collaborative research agreement with the National Cerebral and Cardiovascular Center (NCVC) and Osaka University
- **Clinical research**
  - Based on the outcome of a retrospective study, improvement in relapse-free survival (RFS) after surgery in patients with non-small cell lung cancer (NSCLC) is confirmed (next slide).
  - A multicenter, randomized, Phase 2 study of hANP during the perioperative period in completely resected NSCLC (JANP study) is planned as a prospective investigator-initiated study under an advanced medical care system B grant
- **Development plan**
  - As an NTE program, Shionogi will develop a new formulation of hANP with improved pharmacokinetics and initiate an oncology clinical study.

Inhibitor of Tumor Metastasis: Human Atrial Natriuretic Peptide (hANP)

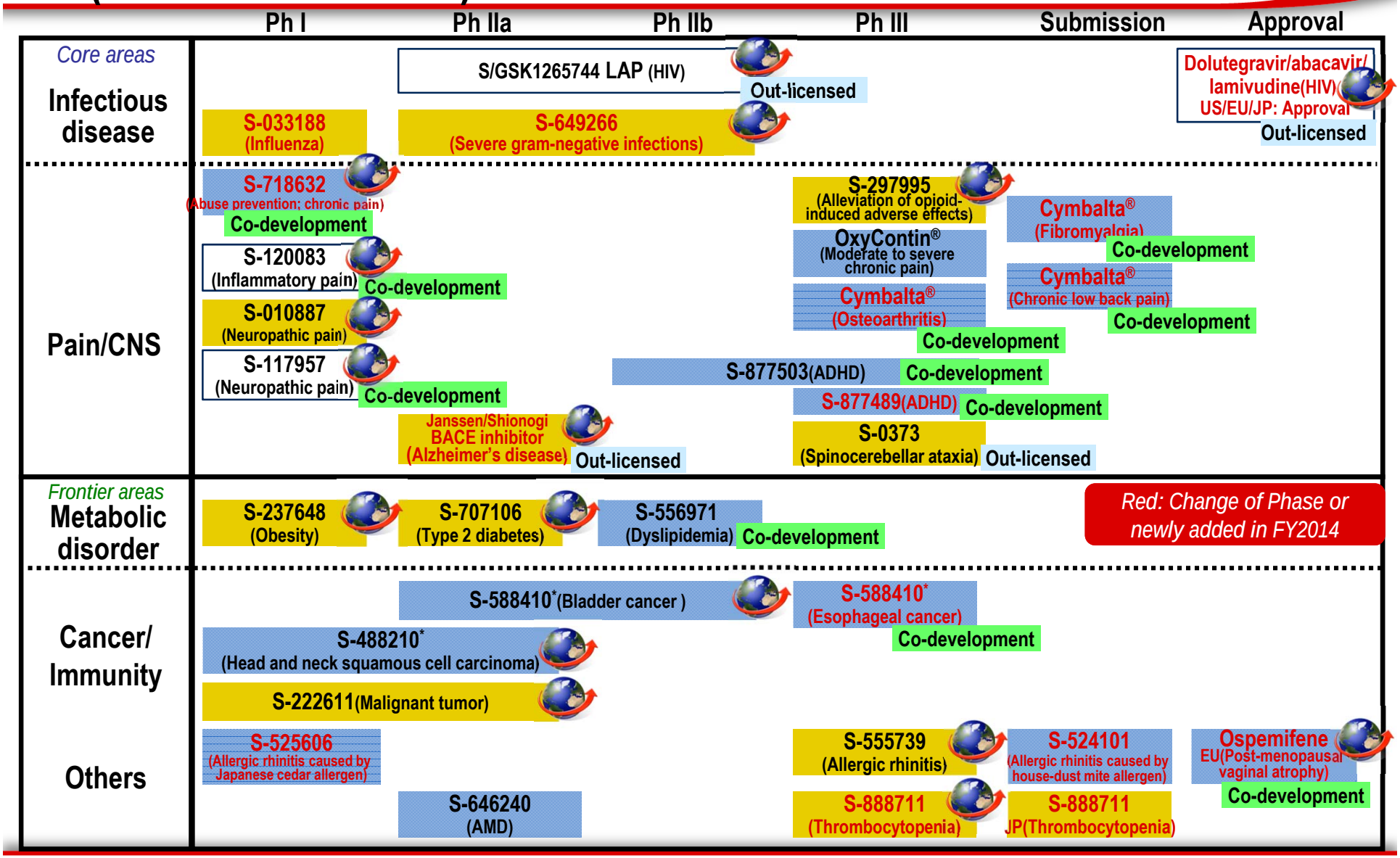
Results of retrospective study

- Improvement in RFS after surgery in patients with NSCLC who had received perioperative hANP (continuous infusion for 3 days from the time of surgery) was confirmed in a retrospective, non-randomized study



NCVC HP: (http://www.ncvc.go.jp/pr/release/007403.html)

Development Pipeline Progression and Expansion (as of March 2015)



LAP: Long-Acting Parenteral formulation
ADHD: Attention Deficit Hyperactivity Disorder
AMD: Age-related Macular Degeneration

Developing products globally

*: Cancer peptide vaccine

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

Summary

Isao Teshirogi, Ph.D.
President and CEO

Q&A

Appendix

Disclosed data in FY2014

S-888711

S-649266

S-888711 (Lusutrombopag): Phase III Code-break in Japan

◆ Phase III code-break

[Summary of results]

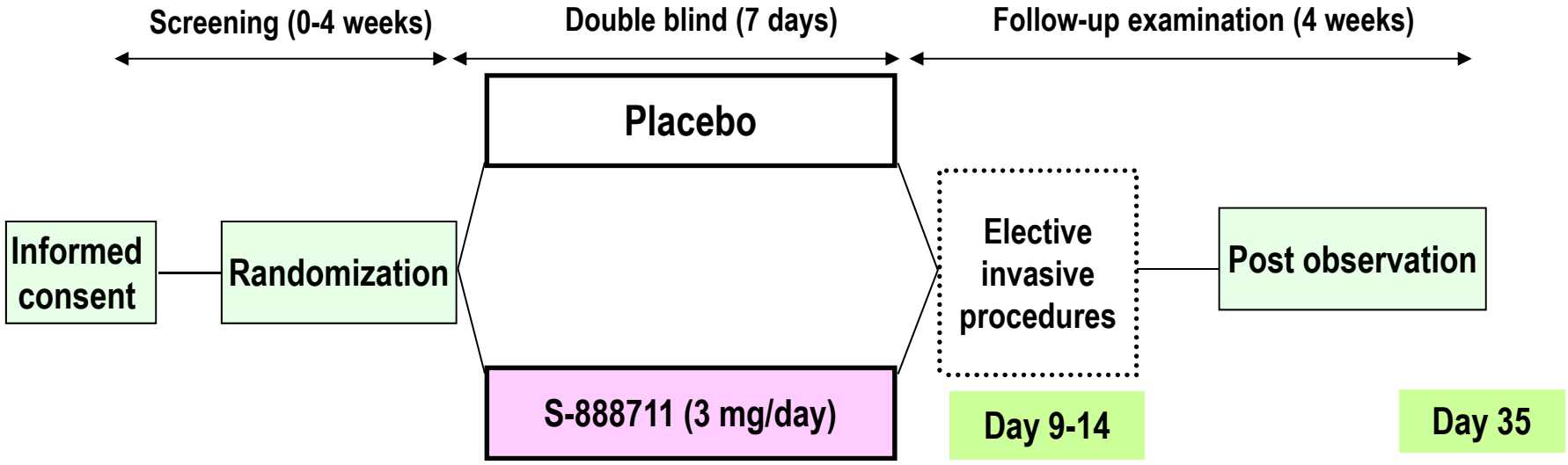
- Proportion of patients not requiring platelet transfusion: the S-888711 group showed statistically higher percentage than the placebo group

- One subject in each of the S-888711 group and the placebo group experienced portal thrombosis

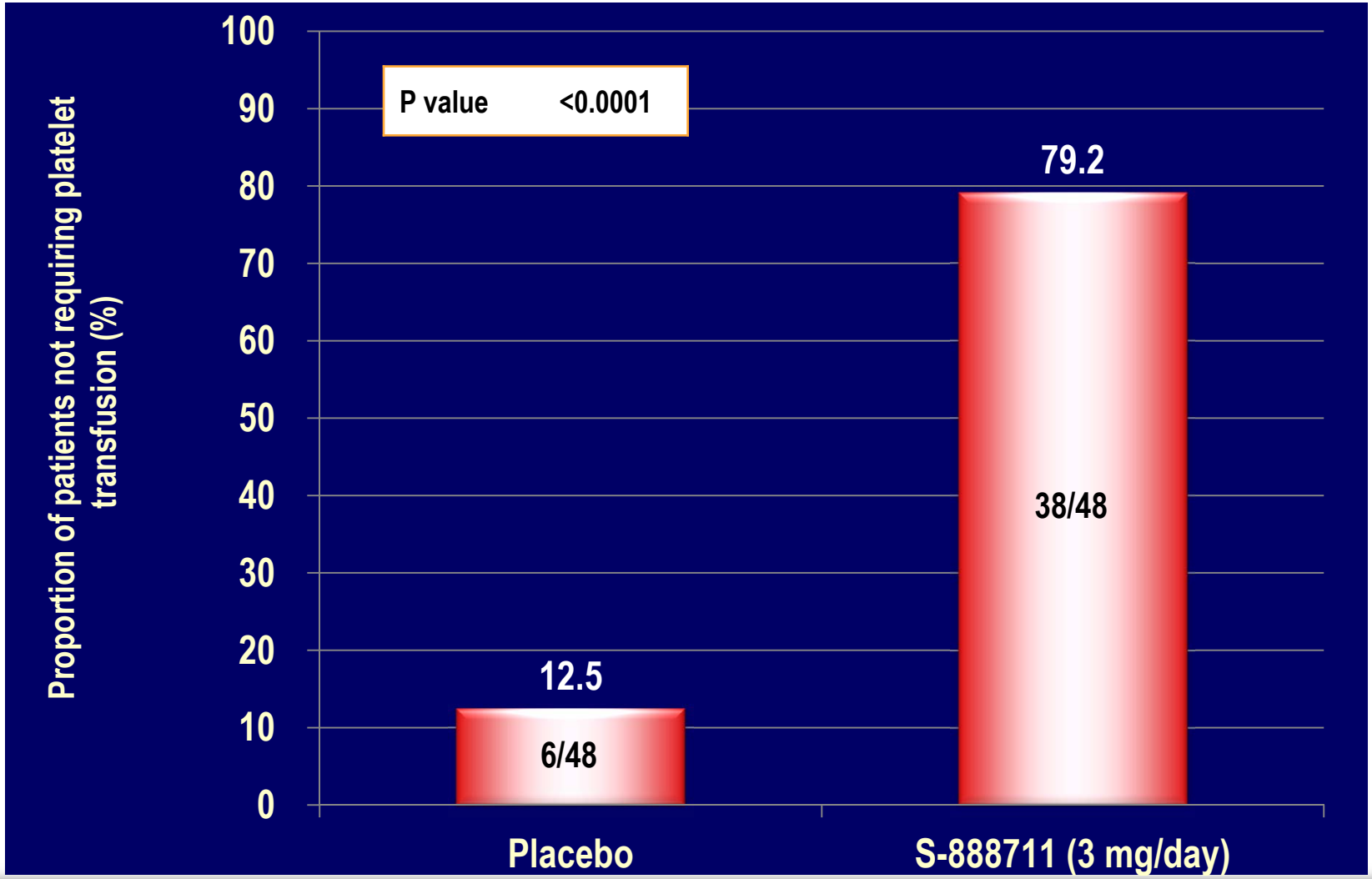
⇒ In FY2014, plan to submit the NDA in Japan, and to proceed to regulatory consultations with Western authorities

S-888711 (Lusutrombopag): Summary of Phase III Design

Purpose	Evaluate superiority to placebo after 7-day multiple dose administration of S-888711 in subjects for thrombocytopenia with chronic liver diseases prior to elective invasive procedures
Primary endpoint	Proportion of patients who did not require platelet transfusion before elective invasive procedures



S-888711 (Lusutrombopag): Primary Endpoint (FAS)



FAS: Full analysis set

S-888711 (Lusutrombopag): Safety

	Placebo	S-888711 (3 mg/day)
Number of patients	48	48
Patients with adverse events (AEs)	48	45
Patients with AEs related to study drug	1	4
Patients with significant AEs	20	20
Patients with serious AEs	4	1
Patients with thromboembolic AEs	1	1
Patients with bleeding-related AEs	13	7

S-649266: Potent Antibacterial Activity Against Multidrug-resistant Bacteria

- *In vitro* antibacterial activity of S-649266 against clinical isolates of β-lactamase-producing gram-negative bacteria

Phenotype. Genotype (number of isolates)	Test Compound (MIC：μg/mL)							
	S-649266		Meropenem		Cefepime		Piperacillin/ Tazobactam	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Carbapenemase producers(193)	0.25	4	≧32	≧32	≧64	≧64	N.D.	>256
KPC producers(47)	≦0.063	0.5	8	≧32	32	≧64	>256	>256
NDM-1 producers (50)	1	4	≧32	≧32	≧64	≧64	N.D.	N.D.
VIM producers (28)	0.25	4	16	≧32	≧64	≧64	256	>256
Metallo beta-lactamase producing *Pseudomonae aeruginosa*(33)	0.5	4	≧32	>32	>64	>64	128	>256
Multidrug-resistant *Pseudomonas aeruginosa*(30)	0.25	1	16	>32	32	>64	256	>256
Multidrug-resistant *Acinetobacter baumannii*(30)	0.25	4	≧32	>32	64	>64	>256	>256

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

DATA: IDWeek 2014, Poster No. 252 (Partial modification)
MIC: Minimum inhibitory concentration N.D.: Not determined

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.

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