

Research and Development at Shionogi

SHIONOGI & CO., LTD.
March 18, 2016

SHIONOGI

Agenda

1. Introduction ..... Isao Teshirogi, Ph.D.
   President and CEO



2. Research ..... Takeshi Shiota, Ph.D.
   Senior Vice President
   Pharmaceutical Research Division

   Miyuki Hiura
   Senior Vice President
   CMC Development Laboratories



3. Development ..... Kazuhiro Hatanaka
   Senior Vice President
   Global Development Division



4. Summary ..... Isao Teshirogi, Ph.D.
   President and CEO

5. Q&A

Introduction

Isao Teshirogi, Ph.D.
President and CEO

External Environment of Pharmaceutical Industry

Medical Insurance Systems	Technological Development	Challenges of Drug Discovery
Increased R&D Expenses	**SHIONOGI R&D**	Open Innovation
Pricing Pressures	Healthy Life Expectancy	Unmet Medical Needs

Direction of Shionogi R&D



Changing Circumstances

×

Global Development Division
Efficient and Consistent Development

CMC Development Laboratories
"Plus One" Product Development

Pharmaceutical Research Division
FIC*/LIC Drug Discovery**

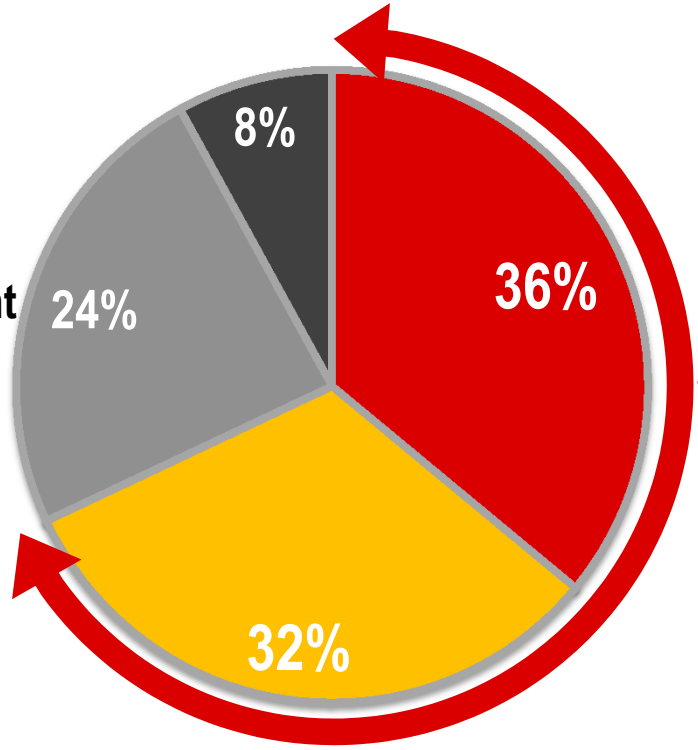
= **Best Possible Medicines**

*: 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)

◆More than half of our pipeline* was discovered within Shionogi

(Origin/Development)

- In-house/In-house
- Collaboration/Co-development
- In-license/In-house
- In-license/Co-development



Percent of pipeline products discovered in Shionogi research laboratories

68%

[As of Mar. 2016]

- Leveraging our capabilities in small molecule drug discovery
- Open innovation: Identify novel drug seeds and develop them

* Including collaboration products and internal selected drug candidates

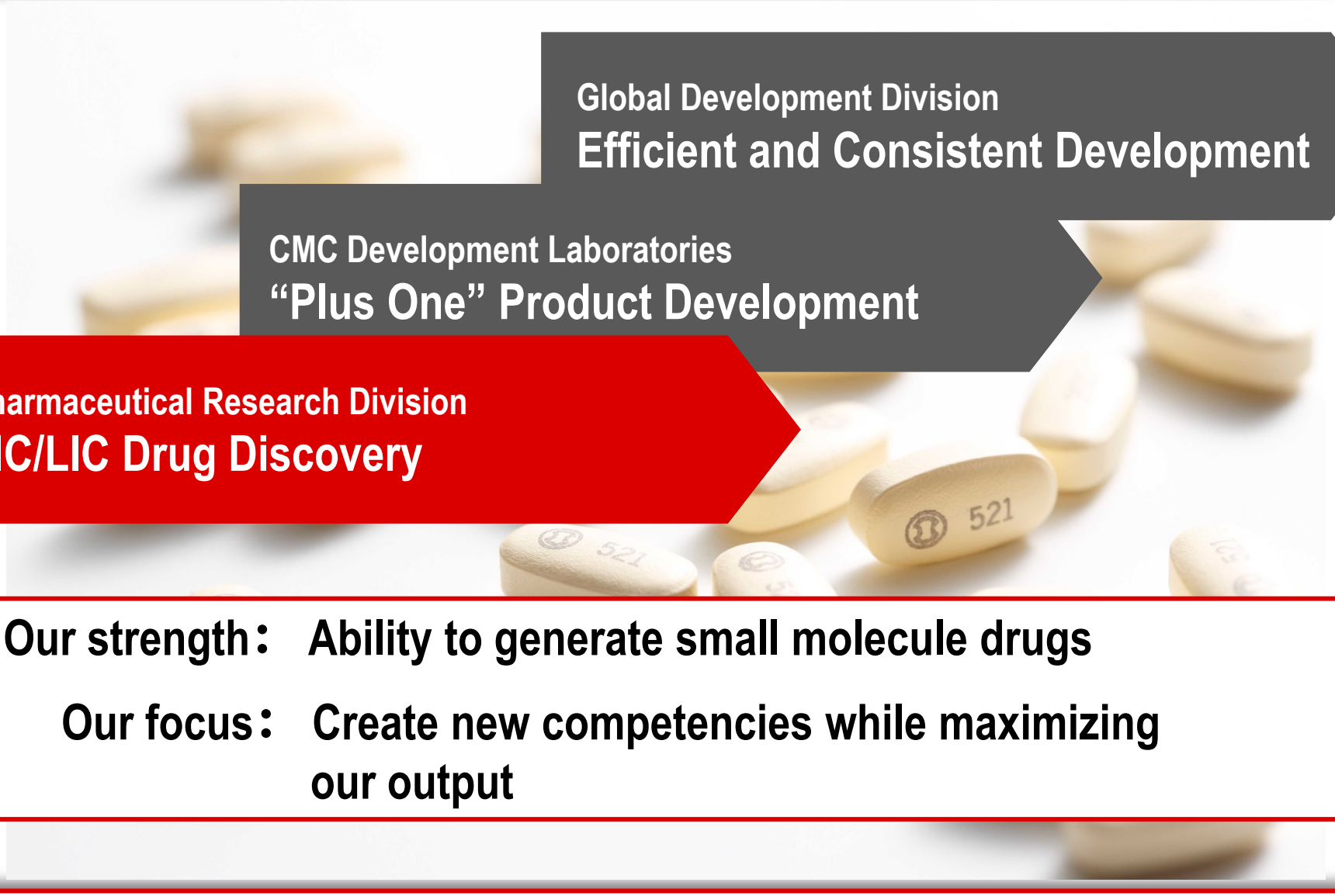


Research

Takeshi Shiota, Ph.D.
Senior Vice President
Pharmaceutical Research Division

SHIONOGI

Grow as a Drug Discovery-Based Pharmaceutical Company



Our strength： Ability to generate small molecule drugs

Our focus： Create new competencies while maximizing our output

Pharmaceutical Research Division: Agenda

- Focusing on:
  - Strengthening our capabilities in drug discovery
  - Leveraging external collaborations
- Expanding pipeline in core therapeutic areas
  - Infectious Diseases
  - Chronic Pain and CNS Diseases

CNS: Central Nervous System

Pharmaceutical Research Division: Agenda

- **Focusing on:**
  - **Strengthening our capabilities in drug discovery**
  - Leveraging external collaborations
- Expanding pipeline in core therapeutic areas
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  - Chronic Pain and CNS Diseases

Our Plans and Accomplishments in FY2015

Continue to conduct highly innovative drug discovery and enrich the drug discovery portfolio

Seek to improve research productivity and ability to predict clinical trial success

Maximize the value of our products and drug candidates

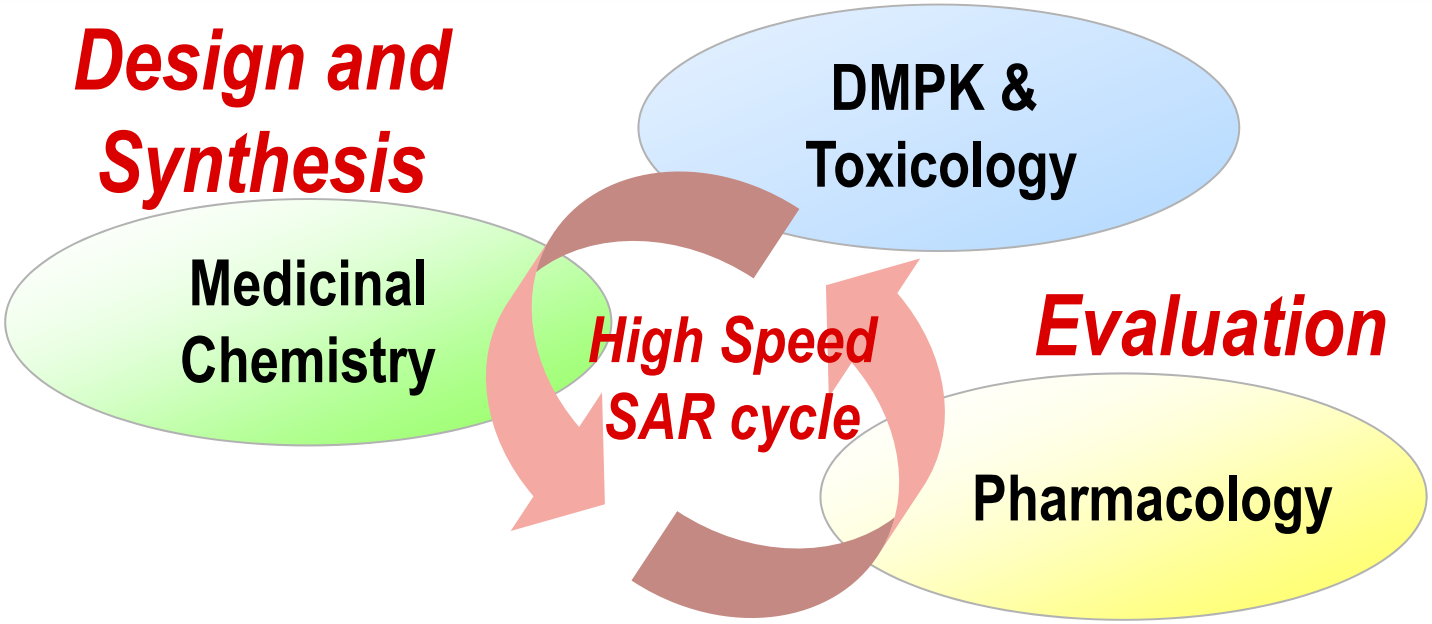
Licensed out an injectable cephalosporin compound

Created novel BACE inhibitors in collaborative research

Initiated new programs for drug discovery, utilizing product development funds

Initiated new industry-industry and industry-academia collaborations

Our Capabilities in Drug Discovery



High performance SAR engine for small molecule drug discovery

Our source of competitiveness;

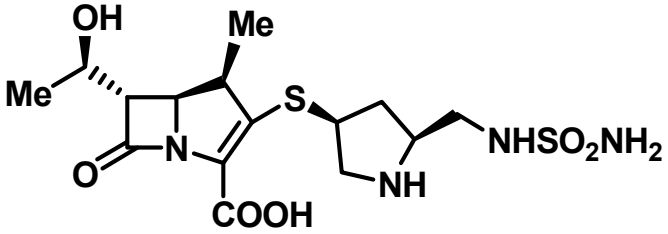
- High level of technological skill throughout SAR cycle
- Efficient and innovative problem solving through strong teamwork

Establishing new competencies to enhance our competitiveness

Products Arising from our Established Drug Discovery Platforms

Finibax® /Doribax®

- Carbapenem Antibiotics
- Potent antimicrobial activity against *P. aeruginosa*



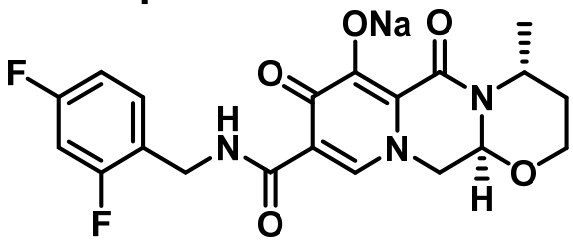
Antibiotics research
× β-lactam chemistry

S-649266

GSK3342830

Tivicay®

- HIV integrase inhibitor
- Potent activity and high barrier to development of the resistance

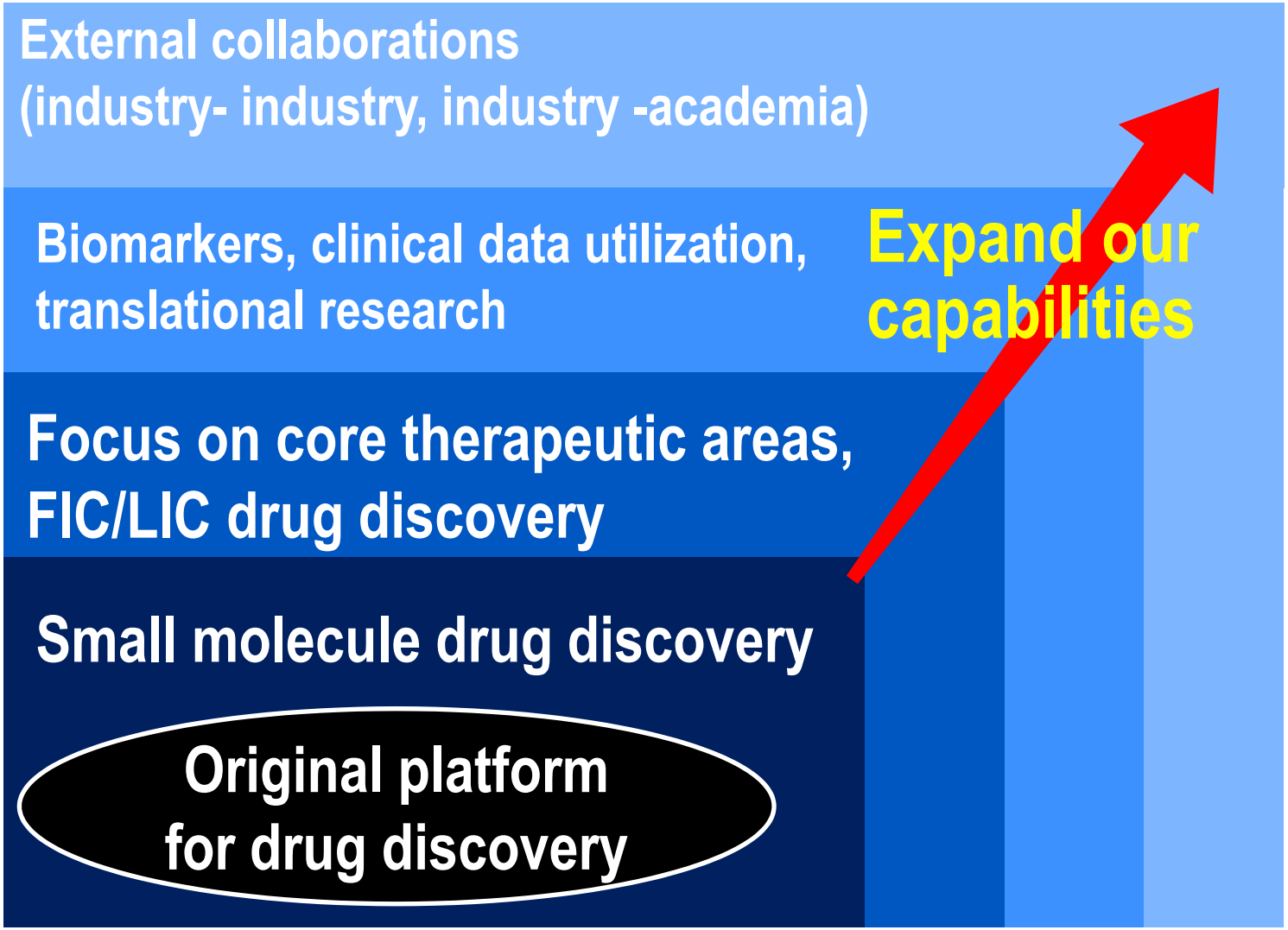


Antiviral drug research
× original compound design

S-033188

Our original 'Platforms for drug discovery' still continuously enable us to create new drugs

Expanding our Capabilities in Drug Discovery



Reorganization to Build and Strengthen Our Capabilities



Pharmaceutical Research Division: Agenda

- **Focusing on:**
  - Strengthening our capabilities in drug discovery
  - **Leveraging external collaborations**
- Expanding pipeline in core therapeutic areas
  - Infectious Diseases
  - Chronic Pain and CNS Diseases

Our Goals in External Collaborations

Value chain in drug discovery



Enhance our capability to obtain novel drug seeds

Build new platforms for drug discovery

- Open innovation with academia

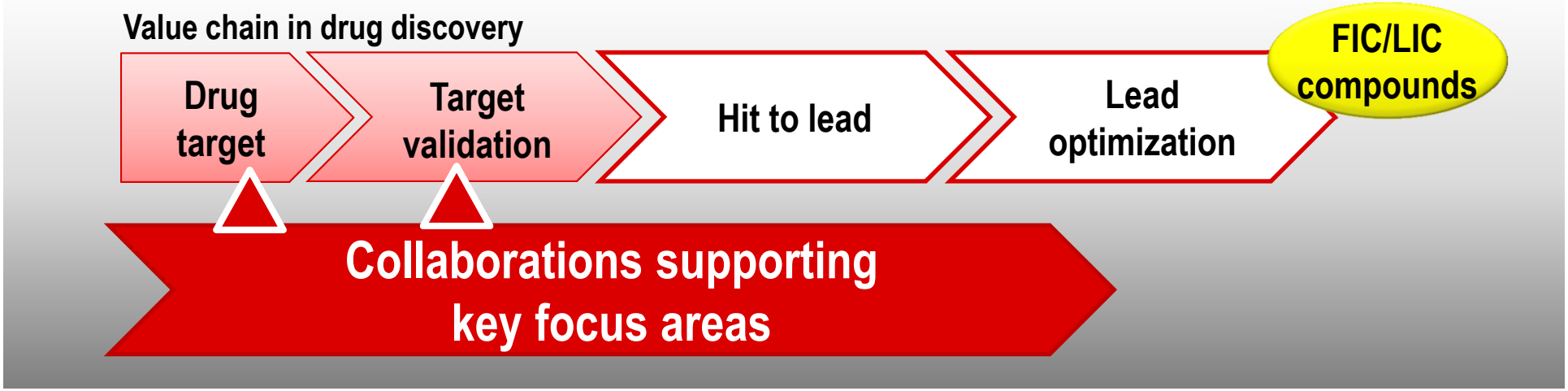
Strengthen small molecule SAR platform and maximize outputs

- Expand compound library
- Collaborate with external partners
- Judicious investment

- Successfully identify drugs from highly difficult targets
- Discover innovative drugs through utilization of peptide drug discovery platform technologies

Build new platforms for drug discovery, expanding our competencies
Maximize output from small molecule drug discovery

Open Innovation with Academia

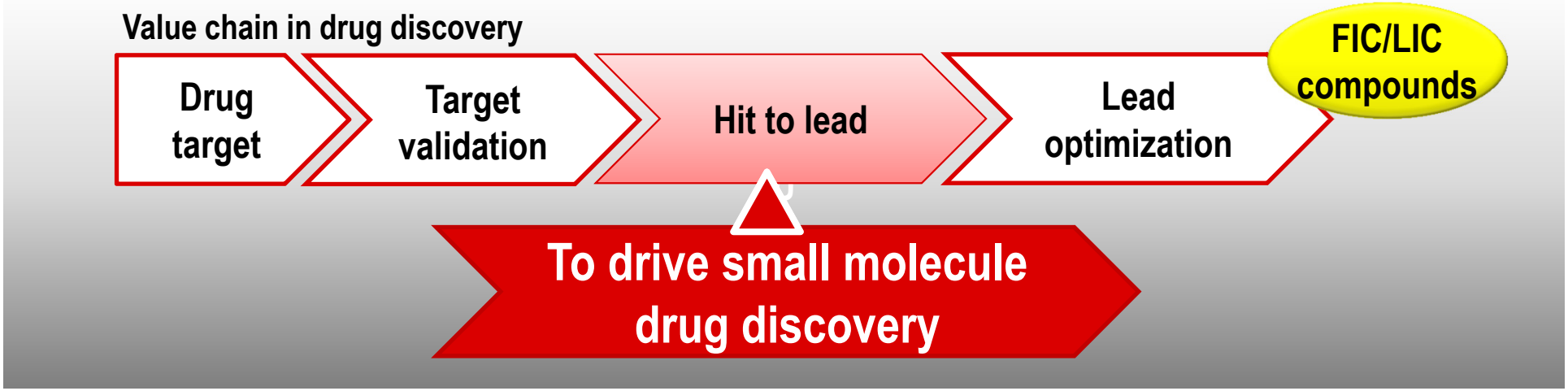


- Joint researches based at CoMIT (Osaka Univ.), MIC (Kyoto Univ.) and SIC (Hokkaido Univ.)
- Continue and expand collaboration with Hokkaido Univ.
- Participate in Cambridge Therapeutic Consortium (industry-academia collaboration in UK)
- Acquire and cultivate unique ideas from academia by FINDS/SSP

Establish drug discovery program pipeline based on seeds from academia
Accelerate development of new drug discovery platforms via collaborations with domestic and international academia

MIC: Medical Innovation Center CoMIT : Center of Medical Innovation and Translational Research
FINDS:: PHarma-INnovation Discovery competition Shionogi, SSP: Shionogi Science Program

Strengthening Our Capabilities in Drug Discovery



Pre-competitive research:
- Joint purchasing of compound libraries, led by JPMA
- Compound library exchange among pharma companies
- Drug-Discovery Innovation and Screening Consortium (DISC)

→ **Expand compound library**

Collaboration with PEPTIDREAM → **FIC drug discovery**

Discover FIC/LIC compounds steadily leveraging synergies between external collaboration and our SAR engine

Pre-competitive research: research at previous stage of product development competition
JPMA: Japan Pharmaceutical Manufacturers Association

Promotion of Research Programs



- Janssen (Alzheimer's disease)
- Pionnier (Opioid, Chronic pain)

→ Pain/CNS

- GHIT Fund (Emerging/reemerging infectious diseases)
- Nissan Chemical Industries, Ltd. (Fungal infection)

→ Infectious diseases

Build mid- to long-term pipeline through synergistic collaborations

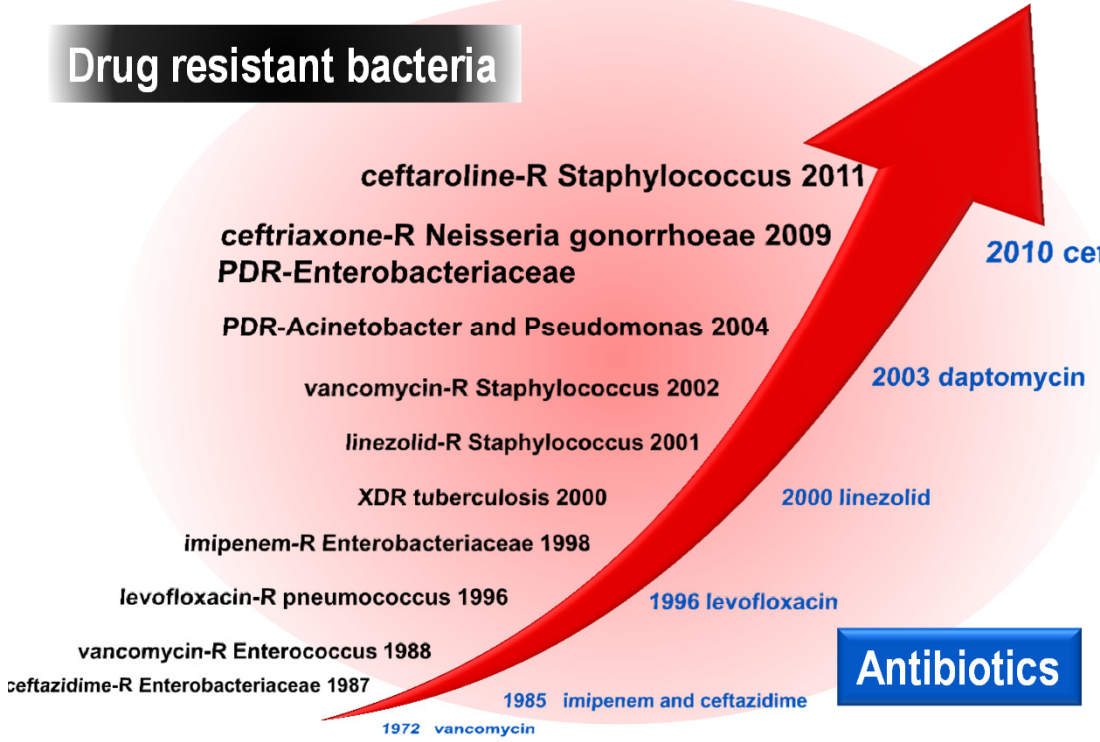
Pharmaceutical Research Division: Agenda

- Focusing on:
  - Strengthening our capabilities in drug discovery
  - Leveraging external collaborations
- **Expanding pipeline in core therapeutic areas**
  - **Infectious Diseases**
  - Chronic Pain and CNS Diseases

Increasing threat from Infectious Diseases

Address mounting threats from infectious disease using our capabilities in small molecule drug discovery

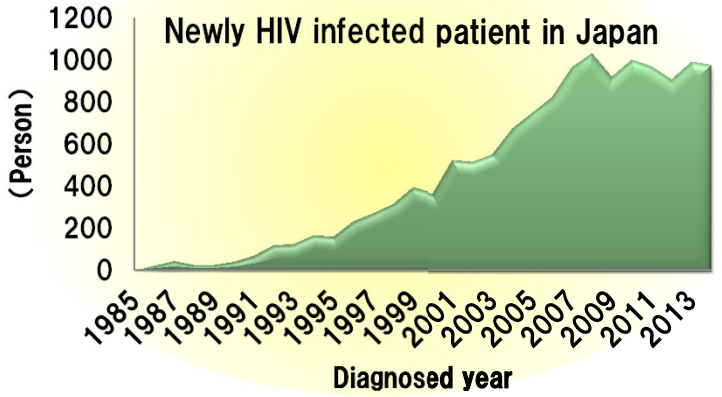
Drug resistant bacteria



Based on CDC, ANTIBIOTIC RESISTANCE THREATS in the United States, 2013

Outbreaks of Emerging/ Re-emerging infectious diseases

Increasing exposure to infection
due to globalization and changing lifestyle



Based on data in the annual report from Japanese Ministry of Health, Labor and Welfare in 2013

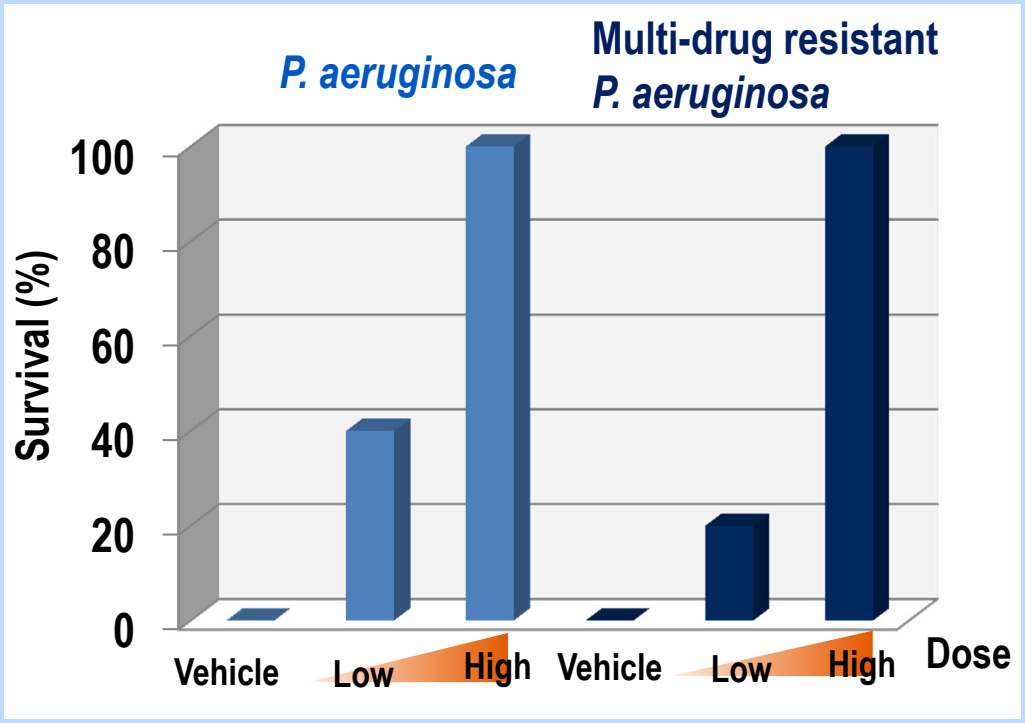
Core Therapeutic Area: Infectious Diseases

	Research areas	UN and disease background	Research Strategy
Sever Infections	Bacterial infections Fungal infections	Requirement for • Drugs for antibiotic-resistant bacteria • Improvement in compliance (early hospital discharge, high barrier to the development of resistance) • Safe and efficacious anti-fungal drug	Develop drugs for antibiotic-resistant bacteria by β-lactam chemistry Develop drugs for fatal systemic fungal infections
Viral Infections	HIV Respiratory virus	• Increased risk of HIV infection with lifestyle changes • Requirement for ➢ Improvement in QOL of HIV patients (long term use, long administration interval, high barrier to the development of resistance) ➢ Efficacious drugs for respiratory virus infection	Expand HIV Pipeline by FIC/LIC drug discovery Develop anti-respiratory virus drugs by original compound design
Emerging Infections	Emerging/ re-emerging infectious disease	• Outbreak of emerging/re-emerging infectious diseases • Requirement for efficacious drugs	Drug discovery through external collaborations

Infectious Diseases: Anti-*Pseudomonas* Antibody

- Humanized monoclonal antibody against *Pseudomonas aeruginosa*

Survival rate in a mouse model of *P. aeruginosa* lung infection



- Investigated genetic variance among the antigens from clinical strains including multi-drug resistant (MDR) strains and confirmed excellent binding profile of this antibody, which covers ≥ 99% of these strains
- Confirmed potent efficacy against *P. aeruginosa* including MDR strains

External Collaboration to Develop Drugs for Emerging/Re-emerging Infectious Diseases

SONG for you!

The GHIT Fund is the world's first product development fund for global health R&D. It is built on the strength of contributions from partners in the public, private, and civil sectors.

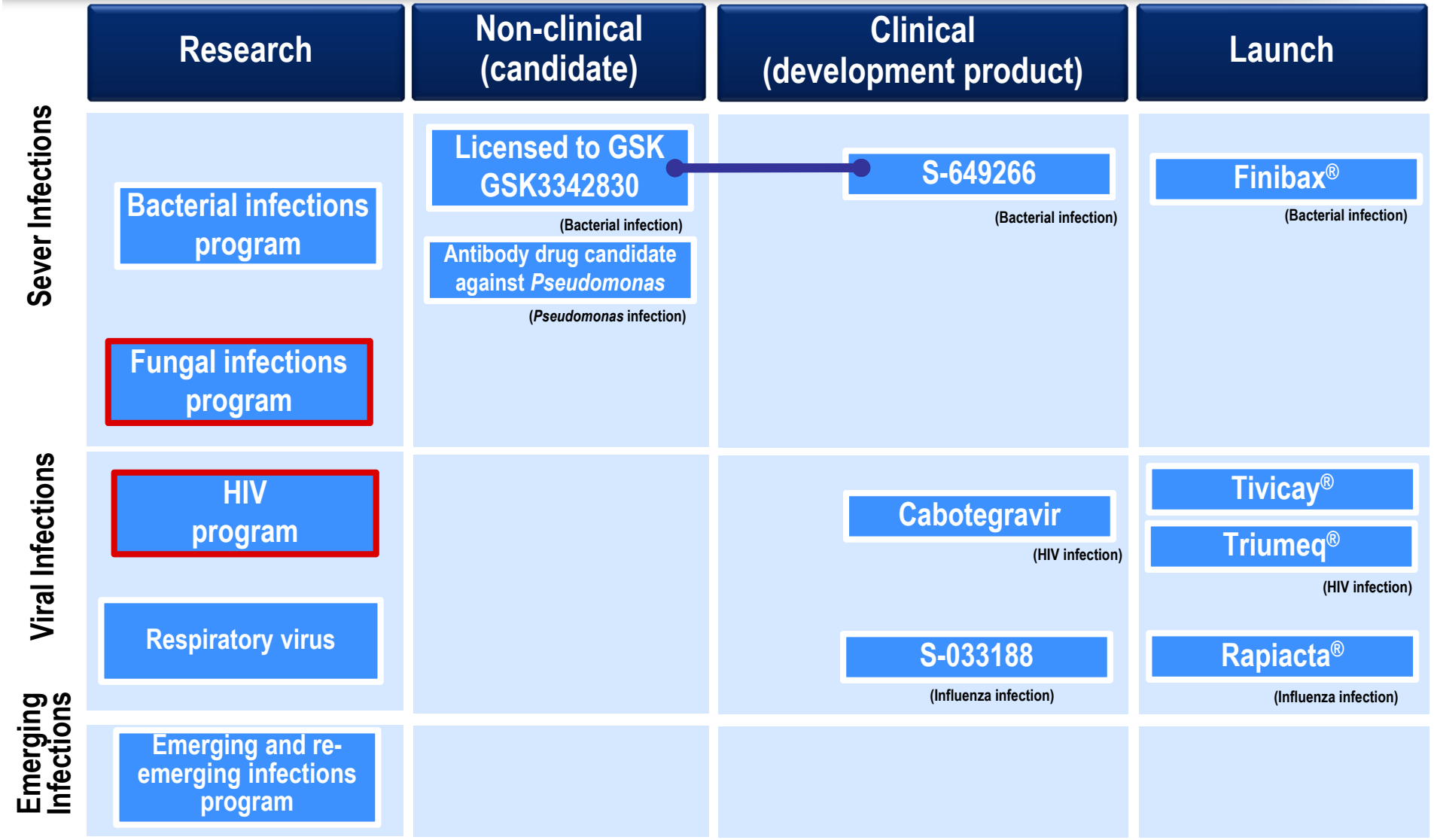


- Successfully found hit compounds from Shionogi's compound library
- Promote collaborative research to create lead compounds from the hits through investment by GHIT Fund

- Participate in consortium of DNDi and pharmaceutical companies
- Started screening process to find active compounds

TB ALLIANCE: The Global Alliance for TB Drug Development, GHIT Fund: Global Health Innovative Technology Fund
RIT: Research Institute of Tuberculosis, DNDi: Drugs for Neglected Diseases initiative

Our Pipeline in Infectious Diseases



Red frame: Program in which candidate compound will be discovered in FY2016

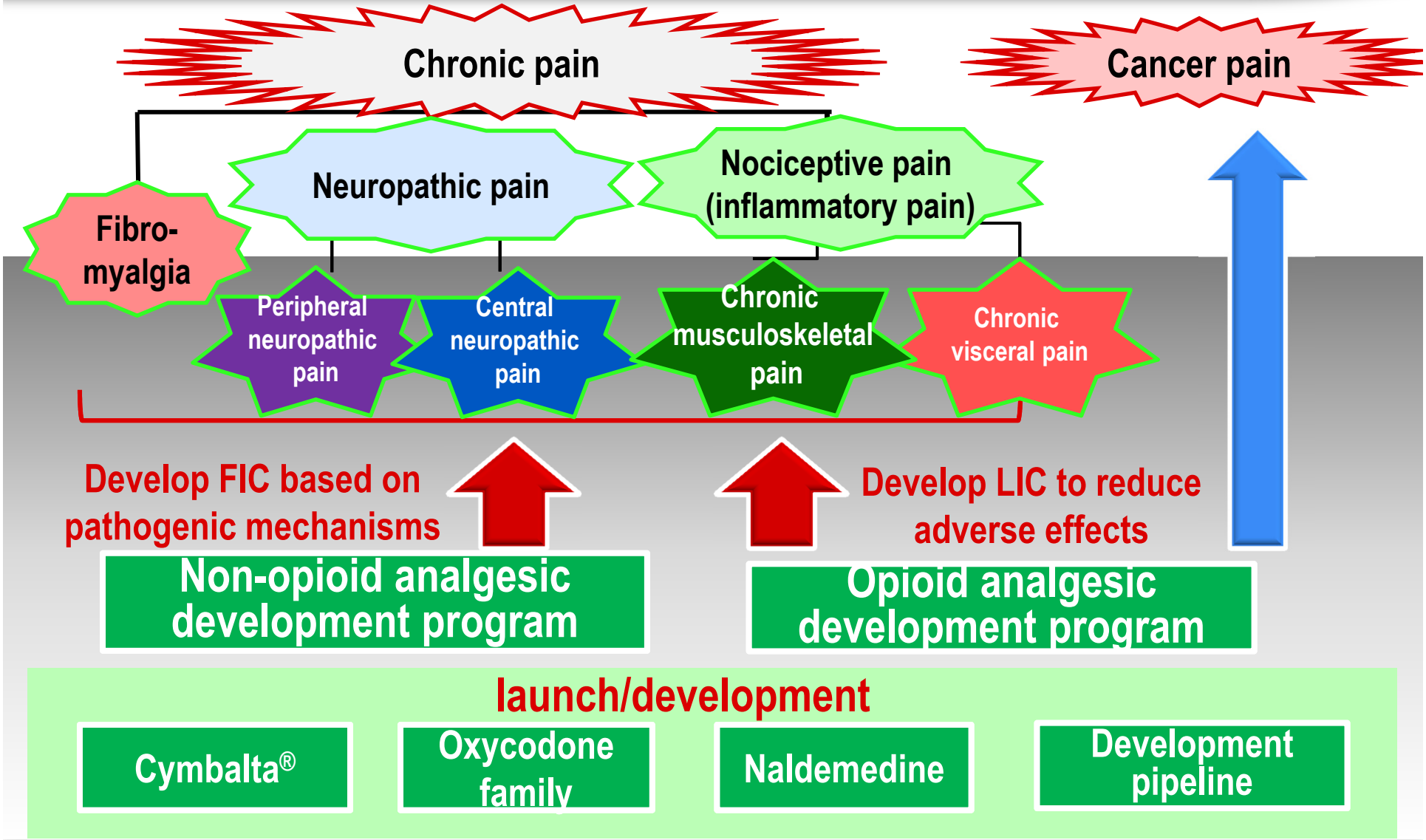
Pharmaceutical Research Division: Agenda

- Focusing on:
  - Strengthening our capabilities in drug discovery
  - Leveraging external collaborations
- **Expanding pipeline in core therapeutic areas**
  - Infectious Diseases
  - **Chronic Pain and CNS Diseases**

Core Therapeutic Area: Pain and CNS

	Research area	UN and disease background	Research strategies
Chronic pain	Opioids	• Low satisfaction with safety and efficacy of drugs placed on the market • Alleviation of side effects and reduced drug dependence • Requirement for new drugs against pain, offering expanded treatment options	Develop LIC to reduce adverse effects
Chronic pain	Non-opioids		Develop FIC based on pathogenic mechanisms
CNS	Alzheimer's Disease	• Increase in number of patients due to aging population and development of diagnostic methods • Increase in medical care expenses • Needs for novel safe and efficacious drugs	Develop anti-AD drugs through collaboration with Janssen
CNS	ADHD		Develop LIC to reduce adverse effects

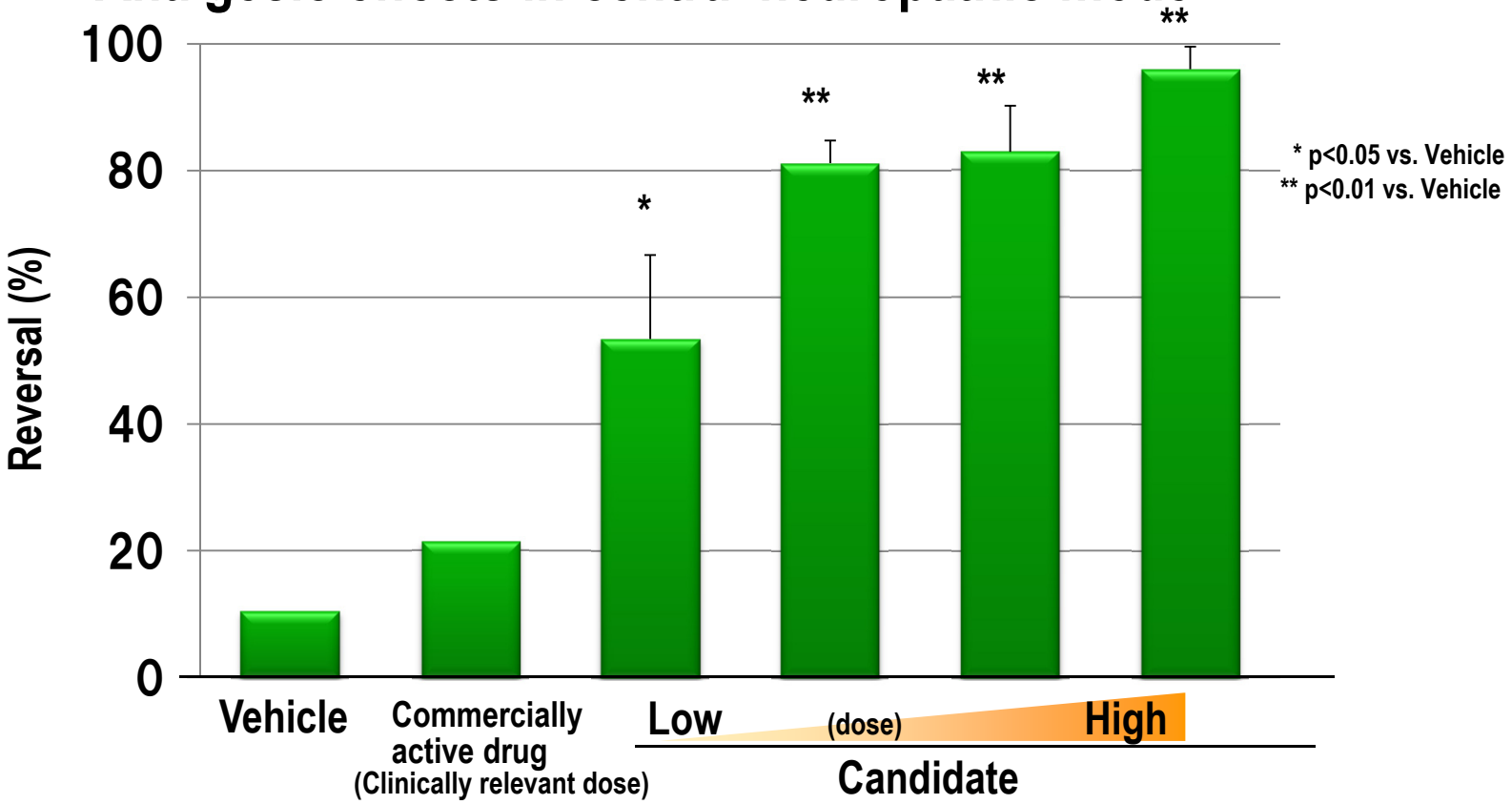
Our Research Strategy in Chronic Pain



Chronic Pain: Novel Analgesic Candidate

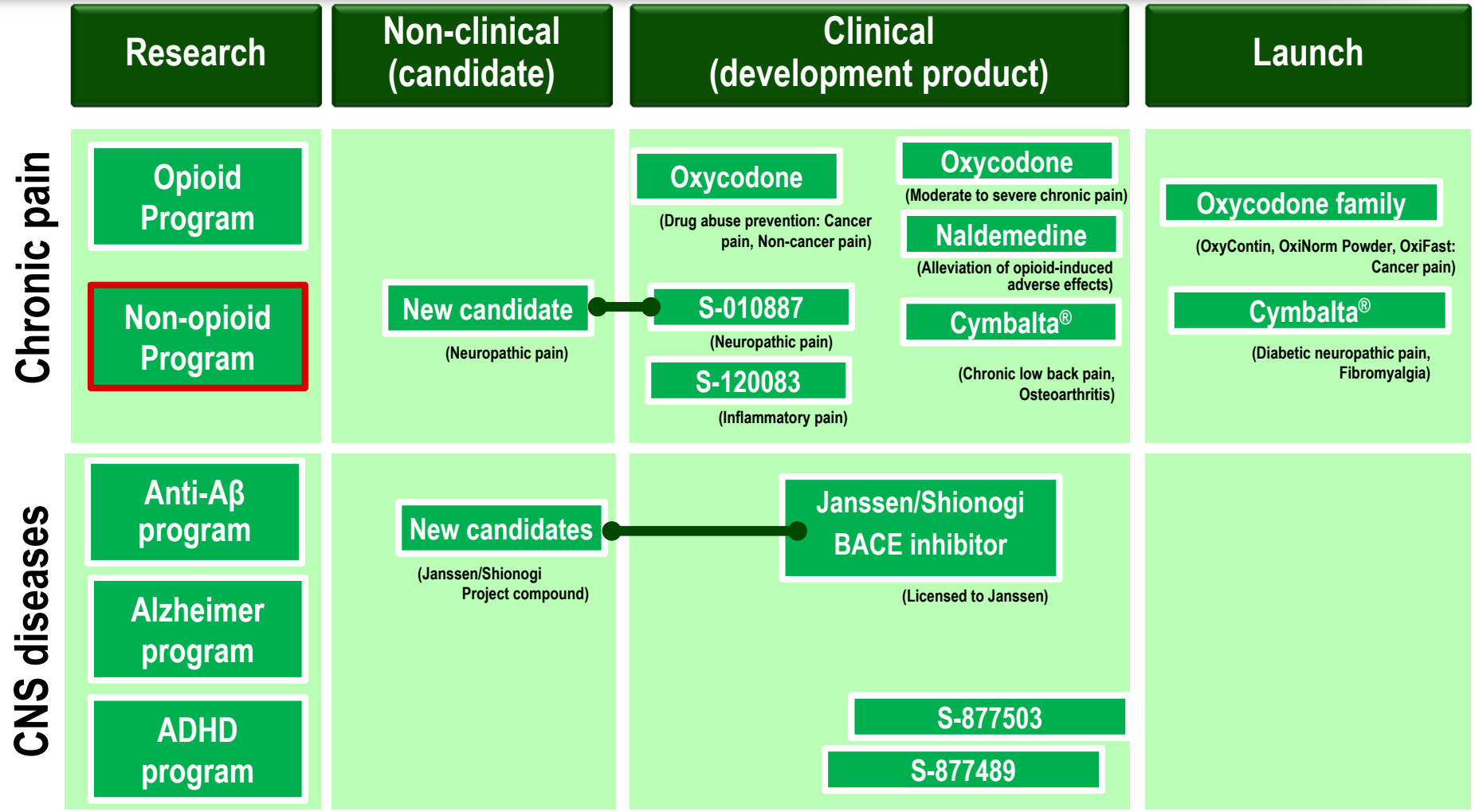
Created new drug candidate for central neuropathic pain

Analgesic effects in central neuropathic model



The new non-opioid candidate showed more potent analgesic effect than current commercially-available drug

Our Pipeline in Pain/CNS



Targets for FY2016

- **Progress research programs to continue discovering FIC/LIC compounds**
  - Discover 2 or more drug candidates in our core therapeutic areas
  - Discover 3 or more development products
  - Progress drug discovery research programs utilizing new approaches
- **Expansion of core drug discovery platform**
  - Strengthen our drug discovery capabilities by initiating new external collaborations with partners around the world
  - Improve capabilities in biomarkers and translational research through our new specialized units

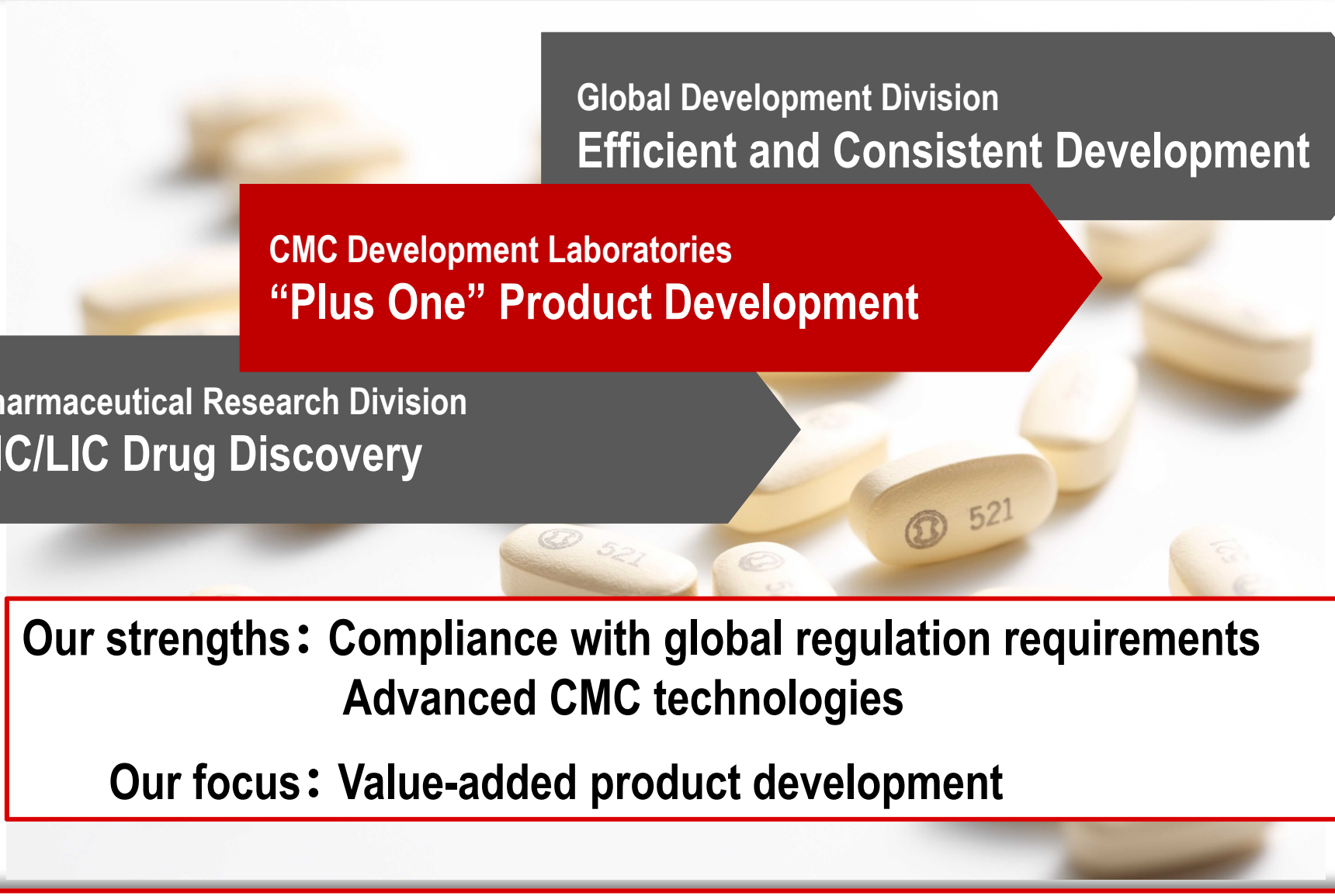


Research

Miyuki Hiura
Senior Vice President
CMC Development Laboratories

SHIONOGI

Grow as a Drug Discovery-Based Pharmaceutical Company



Our strengths：Compliance with global regulation requirements
Advanced CMC technologies

Our focus：Value-added product development

CMC Development Laboratories: Agenda

- Activities in CMC Development Laboratories
  - Reorganization reflecting Shionogi's vision of a drug discovery-based pharmaceutical company
  - "Plus one" product development
    - Contribute to new product launches through CMC technologies
    - Develop new therapeutic entities (NTE)
  - Targets for FY2016

Reorganization Reflecting our Vision as a Drug Discovery-Based Pharmaceutical Company (Apr, 2013)

Organization chart as of Mar, 2013

- Pharmaceutical Research Division
- Pharmaceutical Development Division
- Manufacturing & Technology Division
  - CMC Technology Laboratories
  - Settsu Plant
  - Kanegasaki Plant
  - etc.
- etc.

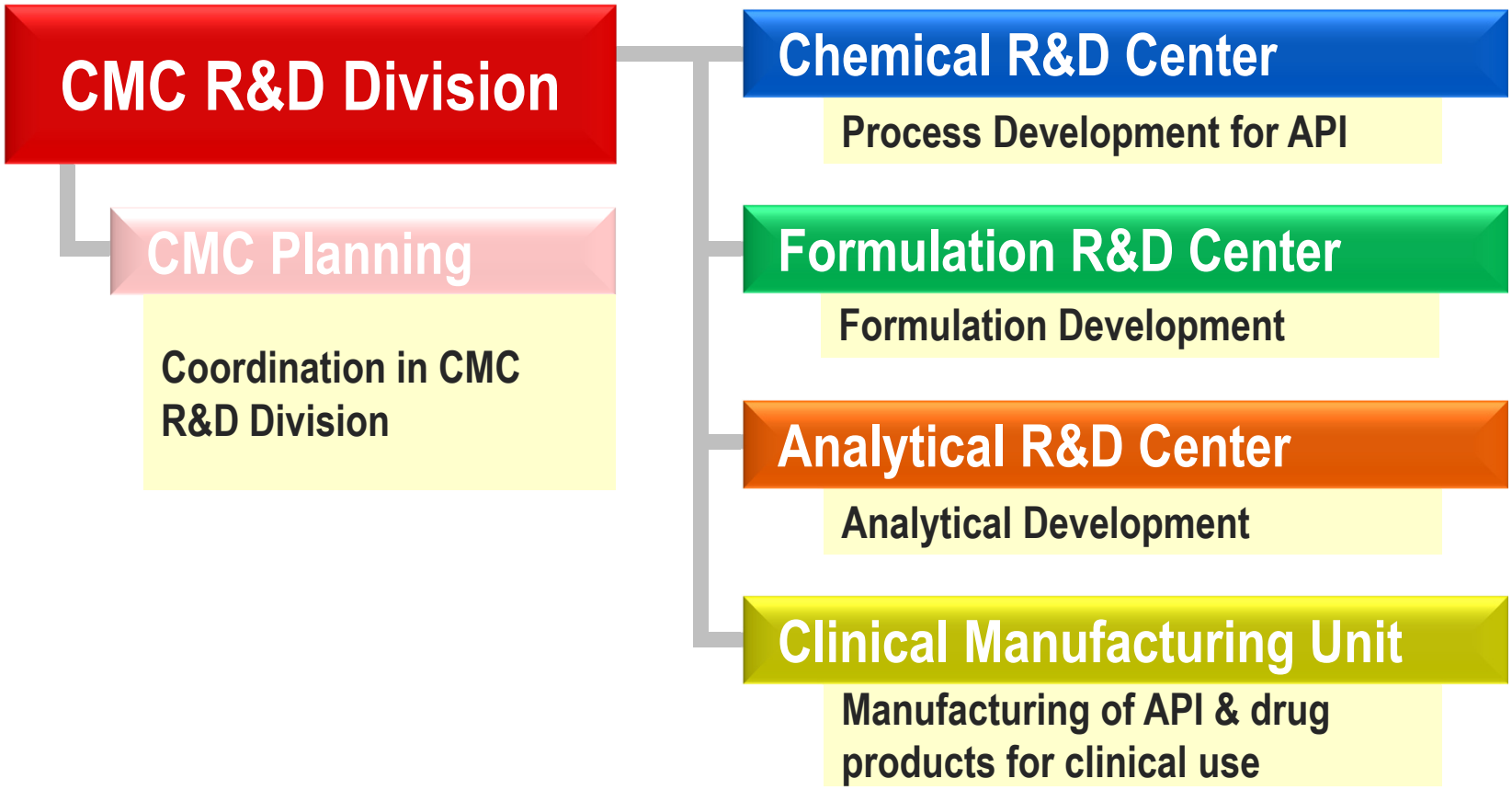
Organization chart after Apr, 2016

- Pharmaceutical Research Division
- Global Pharmaceutical Development Division
- **CMC R&D Division**
- Manufacturing Division
- etc.

CMC; Chemistry, Manufacturing and Controls

CMC Division clearly defined as an R&D organization

Organization of CMC R&D Division* *After Apr. 2016



API: Active pharmaceutical ingredient
Formulation: Final medicinal form in which API can show its efficacy in the human body.

“Plus One” Product Development

Our Focus

Value-added product development using advanced CMC technologies



Create new products to meet market needs and maximize their value

- **Absorption enhancement technologies**
- **sustained release technology**
- **improvement of yield, COGS reduction**

etc.

- **NME projects**
- **LCM***
- **NTE programs****

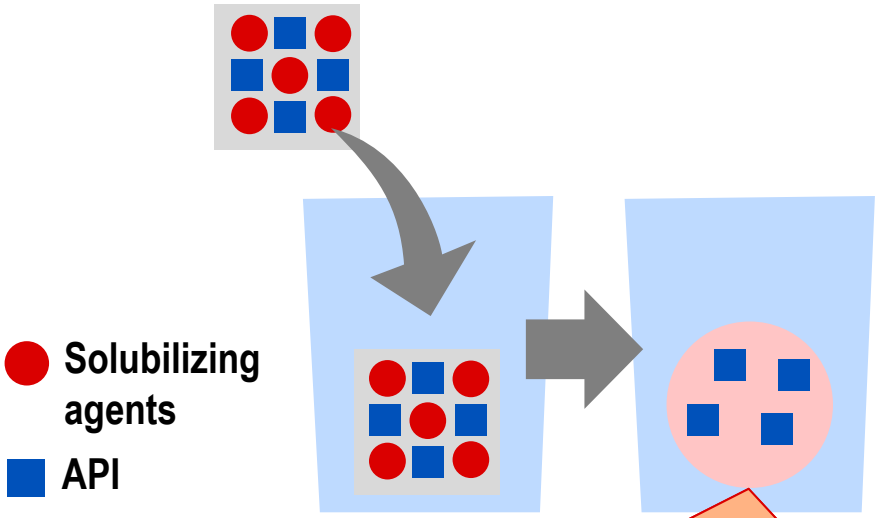
Plus One

* LCM: Life Cycle Management, ** NTE (New Therapeutic Entities) : Drug development for new dosage form, new administration route and new indication with known compound

Absorption Enhancement Technology Applied to Mulpleta®

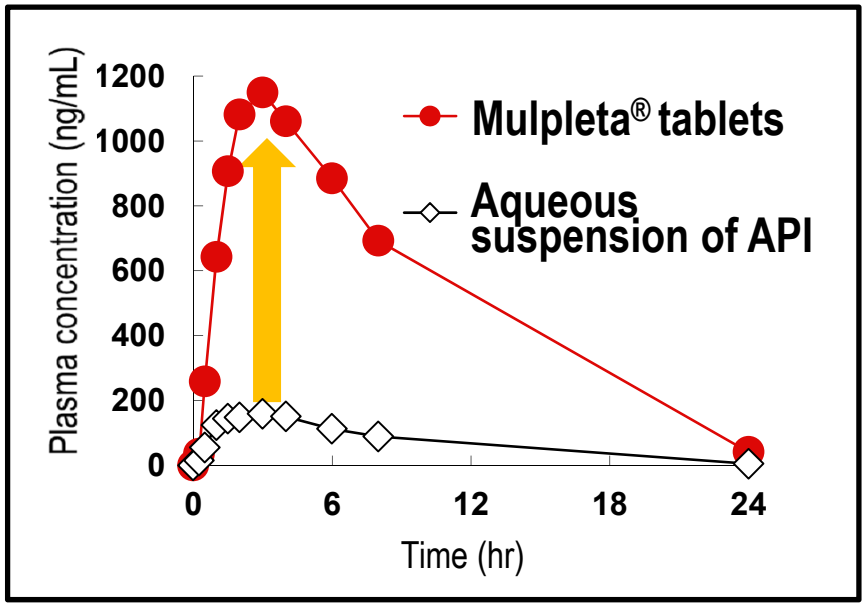
Characteristics of API: practically insoluble at physiological pH

Schematic diagram of dissolution process of the formulation in stomach



Created innovative formulation in which the micro environment surrounding API helps to solubilize it

Result of dog PK study



Cmax and AUC enhanced 7 times and 8 times, respectively.

Contributed to launch of Mulpleta® through its successful formulation development

OxyContin® Tamper Resistant Formulation



Current formulation
Can be easily crushed



Tamper resistant formulation*
Difficult to manipulate for misuse and abuse

- Sustained release matrix tablet using polyethylene oxide as a release controlling agent*
- Under development for expansion of indication to non-cancer pain

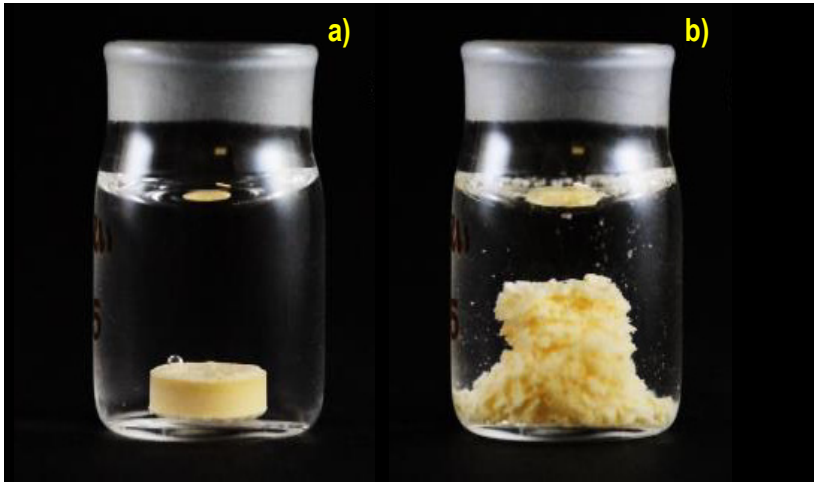
Will contribute towards proper use of opioids for medical use in Japan

* in-licensed from Mundipharma ®: *OXYCONTIN* is a Registered Trademark.

Orally Disintegrating Tablet Technology in Crestor® OD* Tablets

Rapid disintegration

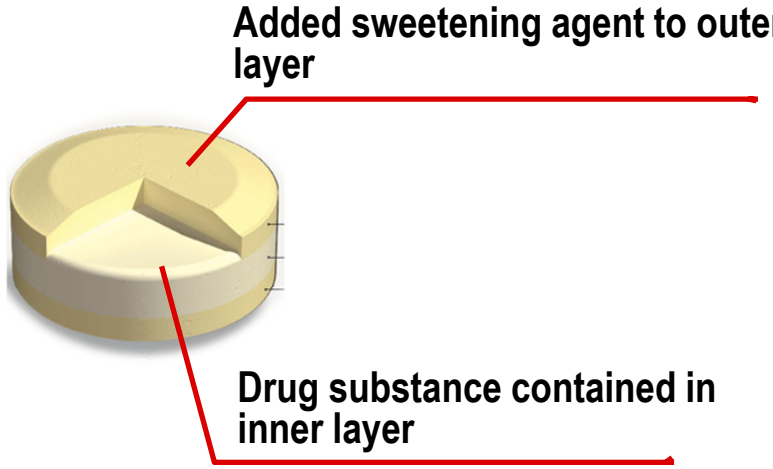
- Formulation has both high degree of hardness and rapid disintegration
- Can be taken with or without water



a) just after putting the tablet into water, b) 10 seconds later

First trilayer OD tablet in the world

- Improved ease of swallowing



Approved in Feb, 2016 and will be launched in Jun, 2016.

Expected to help improve patient compliance

* OD: Orally Disintegrating

Next stage of “Plus One” : NTE concept

NTE: New Therapeutic Entities

Increase both the benefit to patients and the commercial value of our compounds

New dosage form

New administration route

New indication

- Increase efficacy
- Reduce of side effects
- Improve dosing compliance
- Contribute to home healthcare
- Meet regulatory requirements

Move from「Only NME*」to「NME + NTE」 for the next stage of new product development

* NME: New Molecular Entities, new active ingredients

NTE Research Programs

Inhalation	Injection 1	Injection 2
Pre-clinical stage	Research stage	Research stage
Shionogi product LCM	Original compound came from another company	Original compound came from another company
Changed administration route Expected to reduce side effects	Long acting Expected to improve convenience for patients	New route of administration Expected to improve dosing compliance

Several programs are ongoing

Targets for FY2016

- **Contributions to rapid submission and launch of late stage development projects**
  - Naldemedine: Complete launch preparations
  - S-649266: Complete the NDA submission
  - *OxyContin*® Tamper Resistance: Complete NDA submission and prepare for commercial manufacture
  - S-033188: Prepare for Phase III and NDA submission
- **Drive new product development with CMC technologies**
  - NME: Utilize CMC technologies to accelerate program progress
  - NTE: Bring more than one program to clinical stage and initiate several new programs



Development

Kazuhiro Hatanaka
Senior Vice President
Global Development Division

Grow as a Drug Discovery-Based Pharmaceutical Company



Global Development Division
Efficient and Consistent Development

CMC Development Laboratories
“Plus One” Product Development

Pharmaceutical Research Division
FIC/LIC Drug Discovery

Our strength：Development in Japan (Quality and Speed)

Our focus：Global development
Moving from cost control to intelligent cost management

Development in Japan (Quality and Speed)

First launches worldwide in Japan

Pirespa®

- Licensed from Marnac (US) and KDL (Japan)
- First approved in 2008 in Japan; first approval worldwide for idiopathic pulmonary fibrosis
- Clinical data from Japan were used for approval in other countries
- Product launch
  - Europe and US: since 2011 (Roche)
  - South Korea: 2012 (providing product to IL DONG)

Rapiacta®

- Japan: launched in 2010 (first launch worldwide)
- South Korea: launched in 2010 (Green Cross)
- US: launched in 2015 (CSL)

Mulpleta®

- Japan: launched in 2015 (first launch worldwide)
- Developing globally

Naldemedine

- Japan and US: NDA submissions in Mar. 2016 in preparation

Global Development Division: Agenda

- Progress toward achieving SGS2020 goals
- Achievements in FY2015
- Core development products
- Targeted milestones for FY2016

SGS2020: FY2020 targets

Goals

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

Further improvement of productivity is essential to achieve our goals

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

Globalization of Shionogi has just started

⇒ Further improvement and enhancement in Shionogi's global development is necessary

Key competitive area given the low productivity of the pharmaceutical industry on average

Efficient and Rapid Development

Establish framework for global development

- Global development policy
- Global Study Operation Guidelines (G-SONG)
- Globalization of operating team

Enhancement of strategic decision making functions

- Global Portfolio Committee
  - Prioritization of compounds
  - Effective investment
- Monthly Project Update Meeting, Monthly Budget Meeting
  - Progress and budget management

Efficient development

- Utilization of IT systems
- Utilization of clinical data
  - Epidemiological studies
  - Modeling and simulation
- Selection of appropriate patient populations
  - Biomarker research
- Utilization of investigator initiated clinical research

Utilization of Investigator Initiated Clinical Research

Metreleptin

- Licensed from Amylin
- Conducted investigator initiated clinical research at Kyoto University
- The world's first human leptin preparation for lipodystrophy
- Product launch
  - Japan: 2013
  - US: 2014 (Aegerion)

SR-0379

- From research conducted at Osaka University Hospital, and other centers (FunPep Co., Ltd.)
- For refractory skin ulcer
- Functional peptide composed of 20 amino acids

hANP

- From research conducted at National Cerebral and Cardio-vascular Center, Osaka University Hospital and other centers
- Cancer metastasis inhibitor
- Human atrial natriuretic peptide

S-588210

- Studies being conducted at The University of Chicago
- For malignant pleural mesothelioma
- Cancer peptide vaccine

S-588410

- Studies being conducted at The Institute of Medical Science, The University of Tokyo and other centers
- For lung cancer
- Cancer peptide vaccine

Achievements in FY2015: Approvals and NDA Submissions

Product (Indication)	Phase II - III	NDA Submission	Approval
Actair® (Allergic rhinitis caused by house-dust mite allergen)		Japan (Apr. 2014)	Japan (Mar. 2015)
Cymbalta® (Pain associated with fibromyalgia)		Japan (Jun. 2014)	Japan (May 2015)
Mulpleta® [Lusutrombopag] (Thrombocytopenia associated with chronic liver disease)		Japan (Dec. 2014)	Japan (Sep. 2015)
Crestor® OD tablet (Hypercholesterolemia)		Japan (Feb. 2015)	Japan (Feb. 2016)
Cymbalta® (Pain associated with chronic low back pain)		Japan (Dec. 2014)	Passed Drug Committee Meeting (Feb. 2016)
S-877503[Guanfacine hydrochloride] (Pediatric ADHD*)	Japan Phase II/III	Japan (Jan. 2016)	
Cymbalta® (Pain associated with osteoarthritis)	Japan Phase III	Japan (Feb. 2016)	
Naldemedine (Opioid-induced constipation)	Global Phase III	US, Japan (Mar. 2016)	

*ADHD: Attention deficit hyperactivity disorder

Achievements in FY2015: Phase I - II

Product (Indication)	Phase I	Phase II	Phase III
S-033188 (Influenza virus infection)	Japan: initiated US: initiated	Japan: initiated	
S-237648 (Obesity)	Japan: completed	Japan: initiated	
S-525606 (Allergic rhinitis caused by Japanese cedar allergen)	Japan: completed	Japan: completed	

Achievements in FY2015: Phase III

Product (Indication)	Phase I	Phase II	Phase III
S-649266 (Multidrug-resistant Gram-negative bacteria infection)		Global: ongoing	Global: initiated
S-877489 [Lisdexamfetamine] (Pediatric ADHD)			Japan: ongoing
S-877503 [Guanfacine hydrochloride] (Adult ADHD)			Japan: initiated
Lusutrombopag (Thrombocytopenia)			Global: ongoing
S-588410 (Esophageal cancer)			Japan: ongoing
Actair® (Pediatric allergic rhinitis caused by house-dust mite allergen)			Japan: initiated
Osphena® (Vaginal dryness associated with postmenopausal VVA)			US: initiated

Studies to Expand Indications and Respond to Academic Requests

Development for expansion of indications

Cymbalta® (Pain associated with fibromyalgia)	Japan: Approval (May 2015)
OxyContin® (For the treatment of moderate to severe chronic pain (non-cancer pain))	Japan: Phase III ongoing

Development requested by academia

Endoxan® (Malignant lymphoma)	Japan: Approval (Jun. 2015)
Prednisolone® (Malignant lymphoma)	Japan: Approval (Jun. 2015)

<Achievements since 2010>

Development for expansion of indications: 13 (approvals: 11)

Development requests from academia: 6 (all approved)

Current Status in Core Disease Areas

Infectious disease area

- S-033188 (Influenza virus infection)
  - Designated for "priority review system" by the MHLW*
  - Out-licensed to Roche
- Multidrug-resistant Gram-negative bacteria infections
  - Shionogi and GSK** decided to independently develop and commercialize novel cephalosporin antibiotics
    - S-649266 will be separately progressed by Shionogi
    - GSK3342830 will be separately progressed by GSK

Pain/CNS area

- Global development of naldemedine
  - Completion of COMPOSE Program
  - NDA submissions in Japan and US are planned in FY2015
- Life cycle management of Cymbalta®
  - Pain associated with fibromyalgia: approval
  - Pain associated with chronic low back pain: passed Drug Committee Meeting
  - Pain associated with osteoarthritis: NDA submission
  - Pain associated with DPNP***: post-marketing clinical study
- Expanding oxycodone pipeline
  - Non-cancer pain: Phase III study
  - Abuse-deterrent, tamper-resistant oxycodone tablet

*MHLW: Ministry of Health, Labour and Welfare, **GSK: GlaxoSmithKline plc.,
***DPNP: Diabetic peripheral neuropathic pain

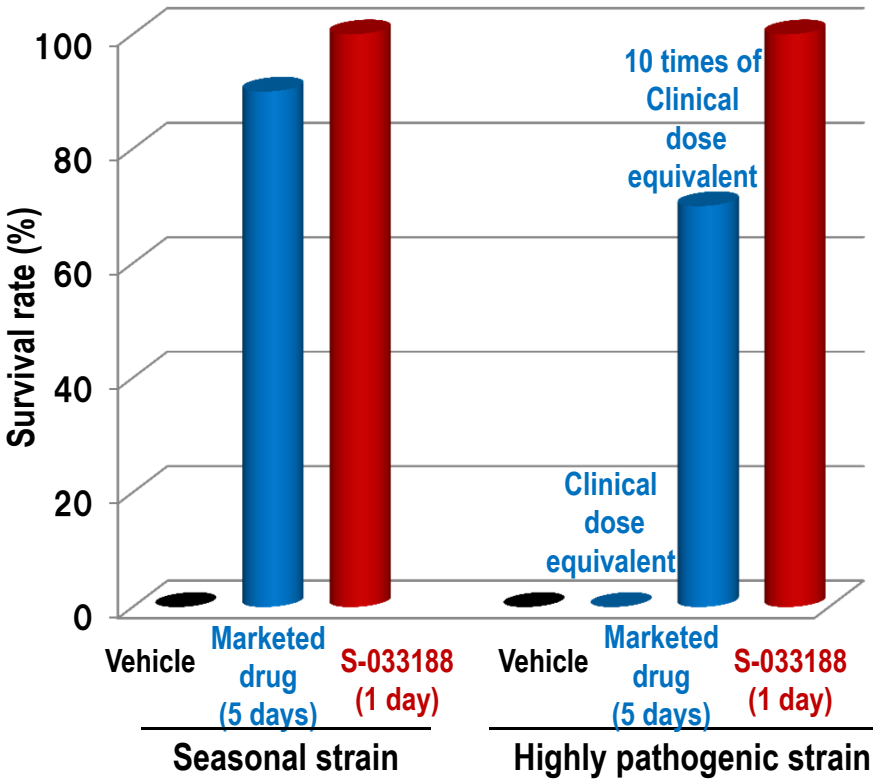
Core Development Products
- Infectious Diseases-

S-033188: Profile

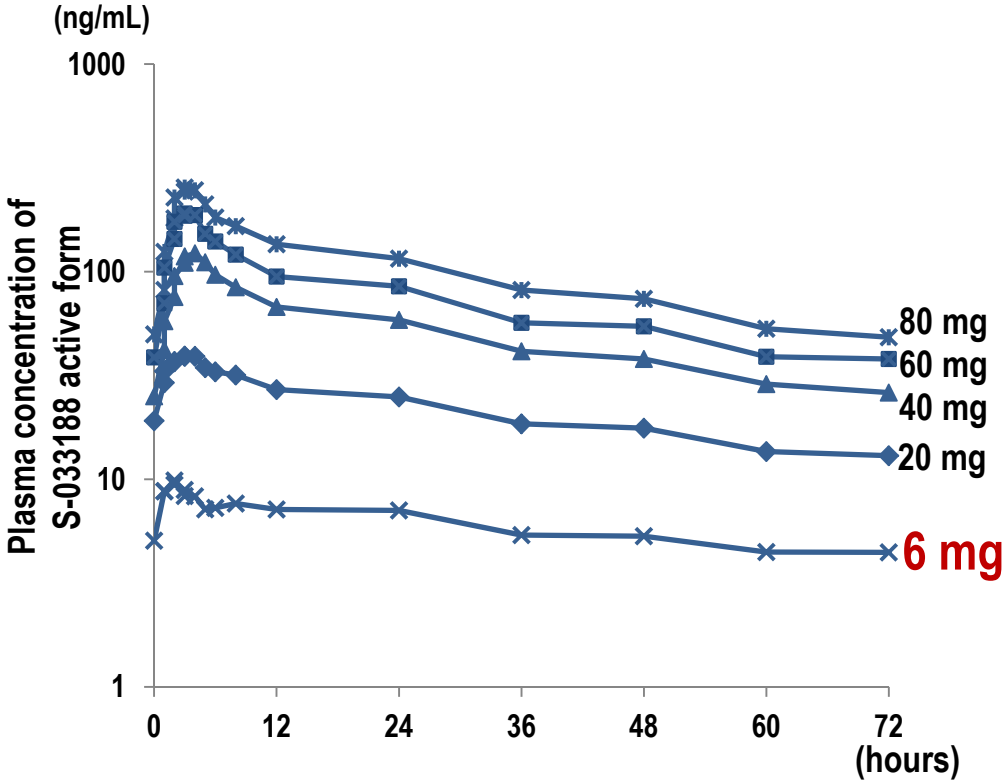
S-033188	
Indication	Influenza virus infection
Mechanism of action	Cap-dependent endonuclease inhibition (Novel mechanism of action)
Special characteristics	Broad and potent antiviral activity against seasonal influenza A and B viruses as well as highly pathogenic avian influenza virus Single oral dose treatment
Stage	Japan: Phase II, US: Phase I
Plan	Japan: Phase III, Global: Phase III Planned NDA submission in Japan: FY2017
Notes	Designated for “Priority review system” by the MHLW Out-licensed to Roche except for Japan and Taiwan

S-033188: Non-Clinical & Phase I (Single Dose) Study Results

Survival rate in mice infection model (14 days after dosing)



Plasma concentration in Phase I Study



Single dose (6 mg) administration achieved plasma exposures that are expected result in efficacy surpassing currently marketed drugs

S-649266: Profile

S-649266

Indication	Multidrug-resistant Gram-negative bacterial infections
Mechanism of action	Cell-wall synthesis inhibition
Special characteristics	Injectable cephalosporin antibiotics Highly active against Gram-negative pathogens including MDR
Stage	Phase II study in complicated urinary tract infections (Global) Phase III CREDIBLE Study (Global) A multicenter, randomized, open-label clinical study of S-649266 or best available therapy for the treatment of severe infections caused by carbapenem-resistant Gram-negative pathogens
Plan	US NDA filing by the end of FY2016 (QIDP designated drug)

MDR: Multidrug resistant, QIDP: Qualified Infectious Disease Product

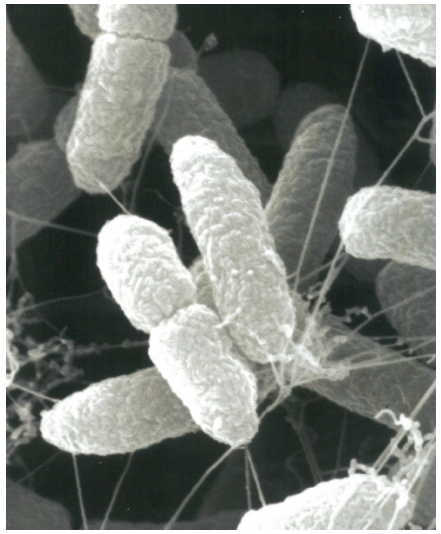
Changing the Environment for Development of Anti-Microbial Drugs

◆Changes of external environment

- Global sense of urgency to make new antimicrobial agents available
- High unmet medical need for treatment infections caused by MDR *P. aeruginosa* and MDR *A. baumannii*

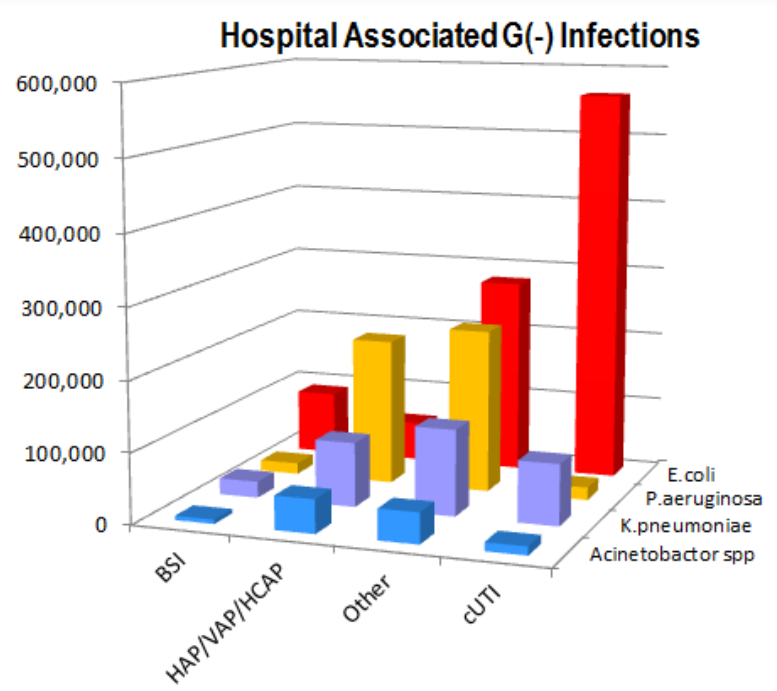
◆Shionogi's focus on development of antimicrobial agents

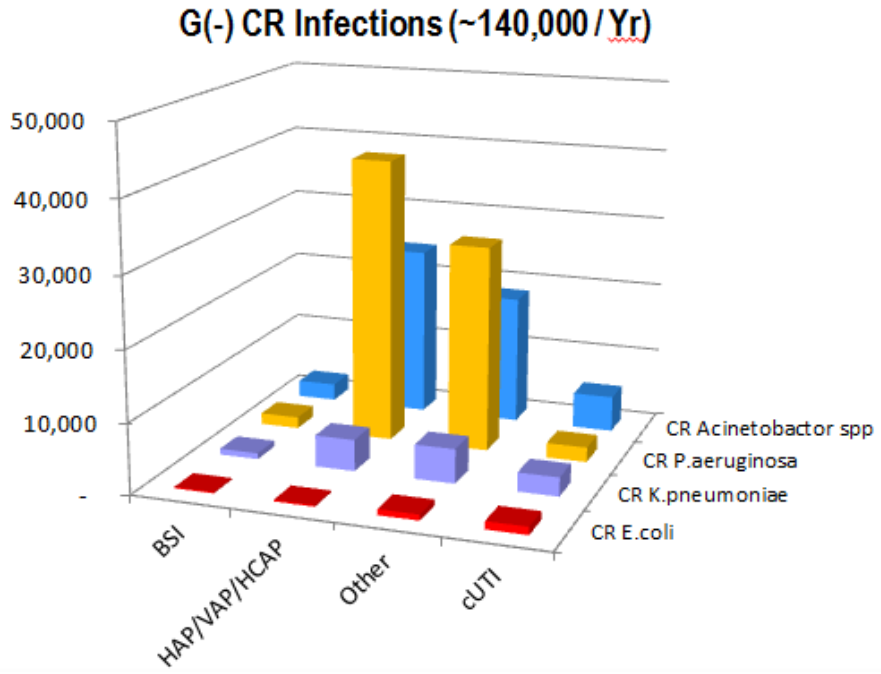
- Working toward acceptance of pathogen-focused indications, not solely site of infection such as pneumonia
- Clinical data collection for appropriate use aligned with the antimicrobial stewardship



Unmet Medical Need for Carbapenem Resistant Pathogens (1)

US, 2009-13, Premier database*





CR *P. aeruginosa* and *Acinetobacter baumannii* account for majority of CR in US

*B Cai, et al, 2016 "Geographic Distribution of Carbapenem-resistant Gram-negative Infections in Adult Patients in US Hospitals" – to be published

Unmet Medical Need for Carbapenem Resistant Pathogens (2)

US, 2009-13, Premier database*

Pathogens	Infected site	Carbapenem-resistant		Carbapenem-sensitive		Odds Ratio
		Death /Patient	Mortality (%)	Death /Patient	Mortality (%)	
A.boumannii	Blood	103 / 270	38.2	55 / 404	13.6	2.46
	Respiratory	305 / 1175	26.0	230 / 1155	19.9	1.27
	Urine	35 / 365	9.6	31 / 504	6.2	0.62
	Other	173 / 1106	15.6	117 / 1529	7.7	1.19
P.aeruginosa	Blood	112 / 336	33.3	590 / 2931	20.1	1.19
	Respiratory	661 / 3209	20.6	1977 / 13372	14.8	1.11
	Urine	208 / 2134	9.8	1031 / 16142	6.3	1.05
	Other	389 / 2315	16.8	1139 / 16038	7.1	1.20
K.pneumoniae	Blood	63 / 231	27.3	819 / 6193	13.2	1.10
	Respiratory	98 / 386	25.4	1547 / 7526	20.6	0.97
	Urine	90 / 987	9.1	1616 / 30832	5.2	1.07
	Other	76 / 421	18.1	863 / 9976	8.7	1.02

* Logistic regression adjusting for age, gender, race, comorbidities in Charlson comorbidity index, mechanical ventilation use, admission source, and admission type

*E Ogura et al, 2015 "Impact of Carbapenem-resistant Pathogens on Mortality among Hospitalized Adult Patients

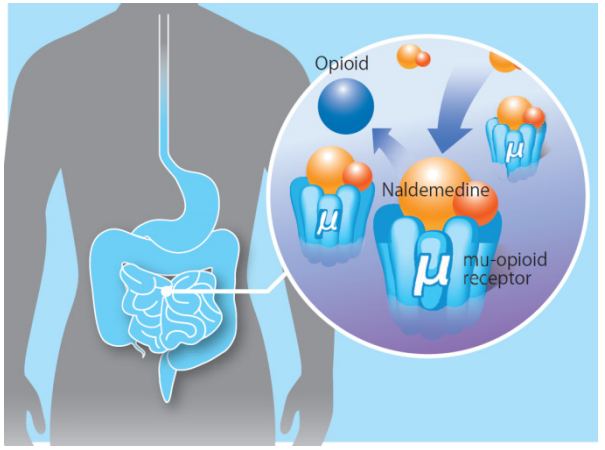
Core Development Products
-Pain/CNS-

Naldemedine: Profile

Naldemedine

Indication	Treatment of opioid-induced constipation (OIC)
Mechanism of action	An oral, peripherally-acting mu-opioid receptor antagonist
Target Milestones	Japan and US: NDA submissions in Mar. 2016
Global opioid market	Major Markets US, UK, Germany, Canada and France Account for up to 80% of total market (70M chronic opioid patients) x 40-50% of chronic opioid patients experience opioid-induced constipation (28-35M patients)

US$14.8 B*



Less than 50% of patients taking laxative report satisfactory results

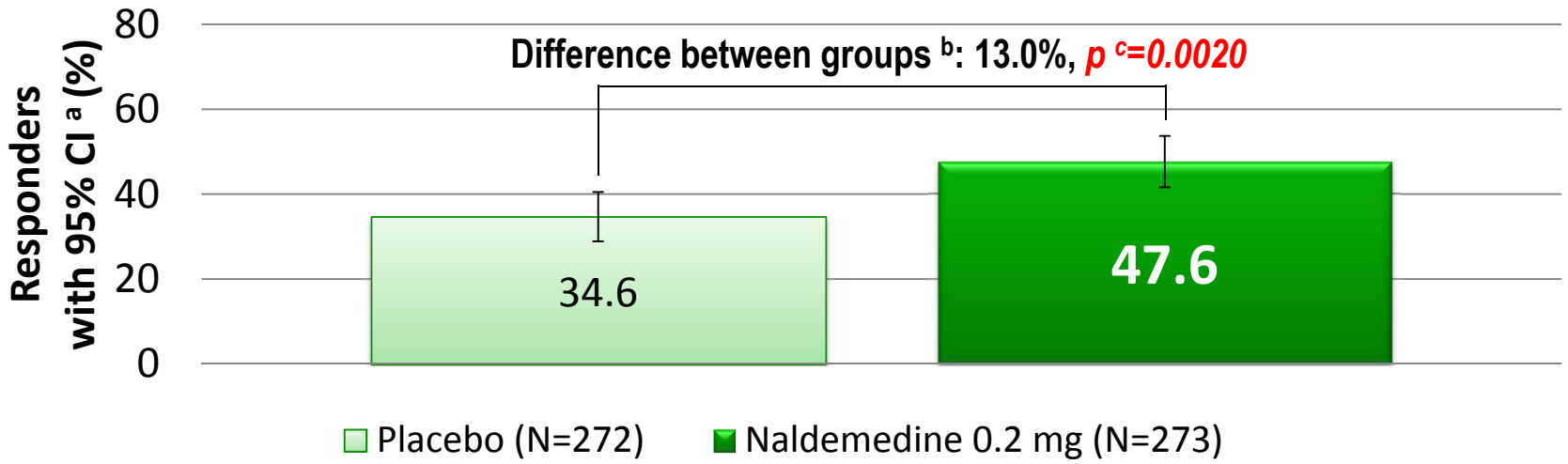
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* Source: Calculated based on IMS Health MIDAS MAT-2Q12, etc.

Naldemedine: Global Phase III Study - Efficacy

The treatment difference between naldemedine 0.2 mg once daily and placebo in the proportion of SBM responders* was statistically significant in patients with OIC and chronic non-cancer pain (COMPOSE I)

Proportion of SBM responders



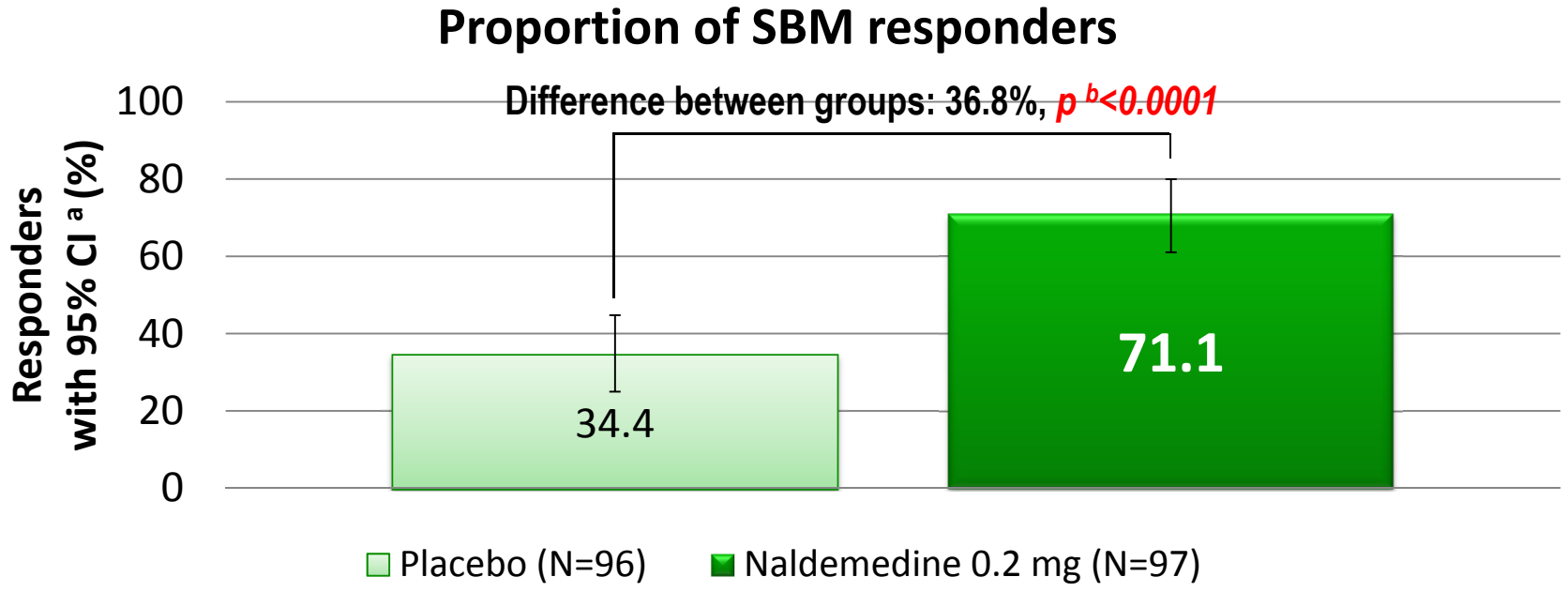
* A responder was defined as a subject with at least 9 positive-response weeks (PRWs) out of the 12-week treatment period and ≥ 3 PRWs out of the last 4 weeks of the treatment period. A PRW was defined as a week with ≥ 3 spontaneous bowel movements (SBMs) and an increase from baseline of ≥ 1 SBM. A BM occurring in the 24 hours following rescue laxative therapy was not considered a SBM.

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[a] Clopper-Pearson method, [b] Difference of Proportion was calculated by using the estimator given by Koch et al., [c] P-value was calculated by Cochran-Mantel-Haenszel test adjusted by the opioid dose strata.

Naldemedine: Phase III Study in Japan - Efficacy

The treatment difference between naldemedine 0.2 mg once daily and placebo in the proportion of SBM responders* was statistically significant in Japanese patients with OIC and cancer (COMPOSE IV)



* Proportion of patients with ≥ 3 SBMs/week and an increase from baseline of ≥ 1 SBM/week during 2-week treatment period

a Clopper-Pearson method, b P-value is from the chi-square test.

Naldemedine: Safety and Tolerability

Treatment-emergent adverse events for ≥ 5% of patients

	Pivotal Phase III study in patients with OIC and chronic non-cancer pain (COMPOSE I)		Pivotal Phase III study in patients with OIC and cancer (COMPOSE IV)	
	Naldemedine 0.2 mg (N=271) n (%)	Placebo (N=272) n (%)	Naldemedine 0.2 mg (N=97) n (%)	Placebo (N=96) n (%)
Abdominal Pain	17 (6.3%)	5 (1.8%)	2 (2.1%)	1 (1.0%)
Diarrhoea	18 (6.6%)	8 (2.9%)	19 (19.6%)	7 (7.3%)

- Naldemedine 0.2 mg once daily was generally well tolerated.
  - The most common AEs were gastrointestinal disorders.
  - Treatment with naldemedine was not associated with signs and symptoms of opioid withdrawal and did not affect the analgesic effect of opioids.

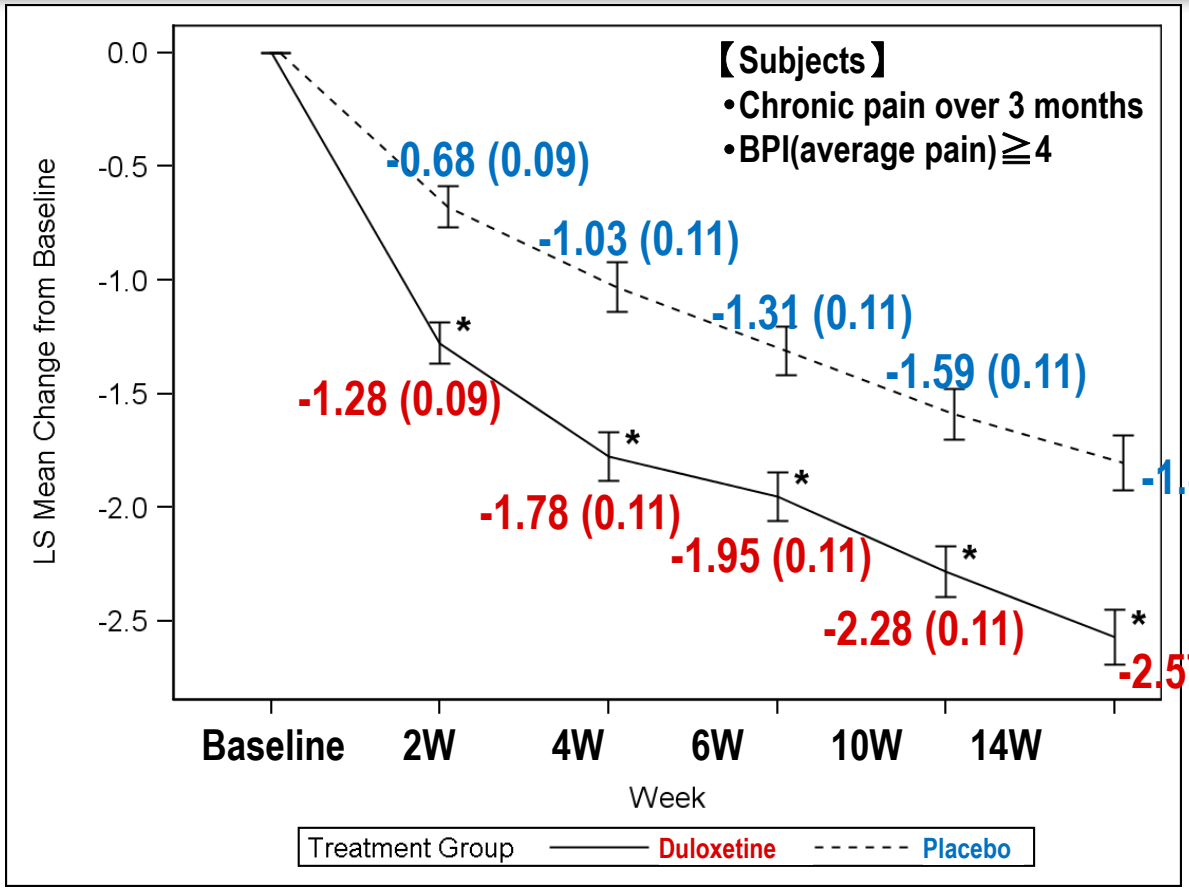
Cymbalta®: Profile

Cymbalta®

Indication	● Depression and depressive symptoms ● Pain associated with DPNP ● Pain associated with fibromyalgia
Product features	Serotonin and norepinephrine reuptake inhibitor Licensed from Eli Lilly and Company
Stage of clinical development	● Pain associated with CLBP: Passed the Drug Committee Meeting ● Pain associated with osteoarthritis: Under review ● Pain associated with DPNP: Post marketing clinical trial (ongoing)

CLBP: Chronic low back pain

Cymbalta® (OA): Phase III Primary Endpoint



LS Mean Change (SE)

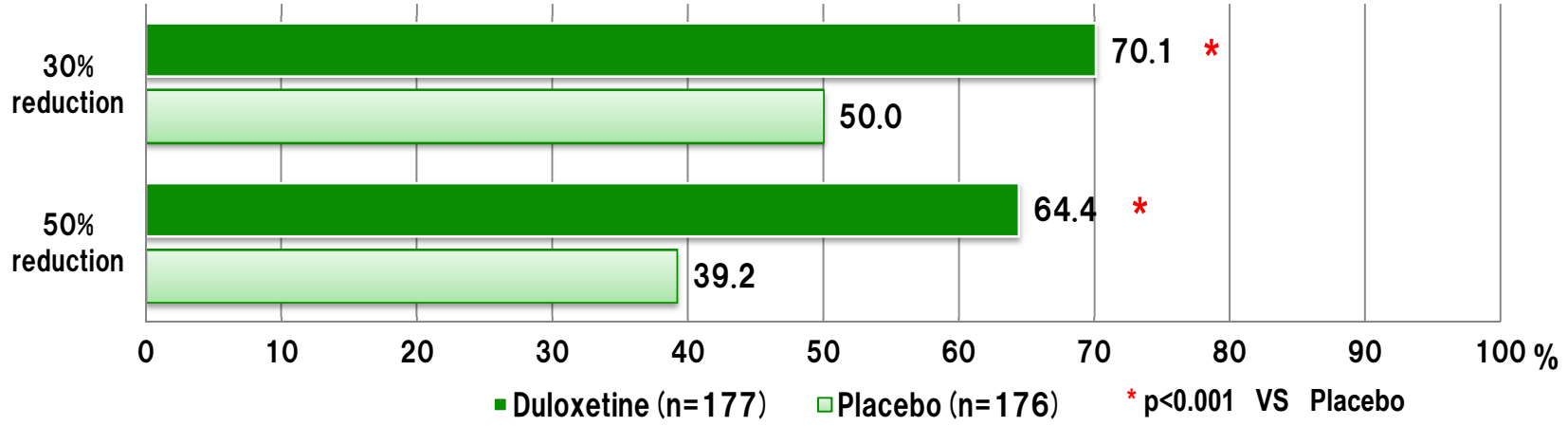
* p<0.0001 vs Placebo

- Duloxetine showed significantly superior efficacy comparing the change from baseline to week14 in the BPI compared to Placebo.
- Safety profile in patients with osteoarthritis was similar to that seen in other approved indications; no new safety events were observed in the study.

OA: Osteoarthritis, BPI: Brief pain inventory

Cymbalta® (OA): Phase III Secondary Endpoint

- **Efficacy Rate (BPI average pain intensity)**



- **WOMAC(Western Ontario and McMaster Universities Osteoarthritis Index) Total score**

	Baseline mean±SD	(n)	Change mean(SE)	Difference [95% CI]	P value
Placebo	32.70±13.71	(176)	-10.45(0.91)		
Duloxetine	32.67±13.18	(177)	-17.41(0.91)	-6.96 [-9.50, -4.41]	<0.0001

MMRM(Mixed-Effects Model Repeated Measures)

FAS：Full Analysis Set

Cymbalta® (OA): Phase III Safety profile

Adverse event and adverse reaction

	Duloxetine	Placebo	p-value
Adverse event	67.4 (120/178)	55.70% (98/176)	0.0287
Adverse reaction	43.3 (77/178)	14.80% (26/176)	<.0001

Adverse events with ≧5% incidence in any groups in all randomized patients

	Duloxetine (n=178)	Placebo (n=176)	p-value
Nasopharyngitis	27 (15.2%)	28 (15.9%)	0.8841
Somnolence	24 (13.5%)	6 (3.4%)	0.0009
Constipation	19 (10.7%)	3 (1.7%)	0.0006
Thirst	19 (10.7%)	3 (1.7%)	0.0006
Nausea	18 (10.1%)	1 (0.6%)	<.0001
Confusion	9 (5.1%)	7 (4.0%)	0.7991
Fatigue	12 (6.7%)	2 (1.1%)	0.0113
Decreased appetite	9 (5.1%)	1 (0.6%)	0.0198

Most adverse events were mild in severity and resolved or resolving

Attention-Deficit/Hyperactivity Disorder (ADHD): Profile

S-877489 (Lisdexamfetamine)[a]	S-877503 (Guanfacine hydrochloride)[b]
Mechanism of Action	
◆ Dual mode of action blocks norepinephrine and dopamine reuptake and increases monoamine neurotransmitter release into the synapse	◆ Selective alpha 2A adrenergic receptor agonist
Product Profile	
◆ Once daily S-877489 significantly improves core ADHD symptom control vs placebo [1] ◆ Adverse reactions to S-877489 reflect side effects seen with other stimulant medications [1-7] ◆ Licensed for first line therapy in US / Canada, second line therapy in the EU and in patients who have failed other therapies	◆ Once-daily S-877503 provides significantly improved ADHD core symptom control vs placebo, reducing symptoms of hyperactivity/impulsivity & inattention [8,9] ◆ Well documented safety profile across the dose range [10-12] ◆ Licensed for mono / adjunctive therapy with stimulant drugs in the US/Canada and as monotherapy in the EU
Development Stage	
◆ JAPAN ● Phase II / III study ● Phase III long-term study ◆ US, Canada, Brazil, EU*, Israel: marketed (Shire)	◆ JAPAN ● Pediatric ADHD : regulatory review ● Adult ADHD: Phase III study ◆ US, Canada, EU: marketed (Shire)
Future Plans in Japan	
◆ 2016: Completion of Phase II / III study	◆ 2017: Completion of adult Phase III study

* EU markets include: UK, DE, DK, SE, ES, FI, IE, NO, CH

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a) Vyvanse®
b) Intuniv® (brand names in US)

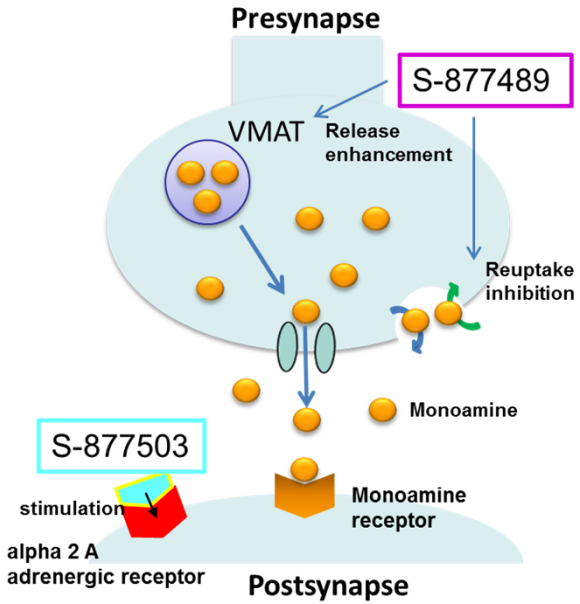
Required References: 1. Coghill et al. 2013. 2. Biederman et al. 2007. 3. Wigal et al. 2009. 4-7. Findling RL et al. 2008, 2009, 2011, 2013. 8. Hervas et al. 2014. 9. INTUNIV SPC, SPIL. 10. Newcorn et al. 2013. 11, 12. Biederman J et al. 2008a, 2008b.

Attention-Deficit/Hyperactivity Disorder (ADHD): Profile

S-877489 (Lisdexamfetamine)	S-877503 (Guanfacine hydrochloride)
Overseas Sales (Shire Press Release)	
◆ 2014: USD 1,449 mm ◆ 2015: USD 1,722 mm	◆ 2014: USD 327 mm ◆ 2015: USD 65 mm*

Development Concept

To offer a portfolio of two drugs with unique mechanisms of action that make an important contribution to all ADHD patients who need pharmacological treatment



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* Patent expired in 2015

Target Milestones for FY2016: Approvals and NDA Submissions

Product (Indication)	Phase II - III	NDA Submission	Approval
S-877503 [Guanfacine hydrochloride] (Pediatric ADHD)		Japan (Jan. 2016)	Japan
Cymbalta® (Pain associated with osteoarthritis)		Japan (Feb. 2016)	Japan
Naldemedine (Opioid-induced constipation)		US, Japan (Mar. 2016)	US, Japan
Lusutrombopag (Thrombocytopenia)	Global: Phase III	US, EU	
Oxycodone (Treatment of moderate to severe chronic pain)	Japan: Phase III	Japan	
Oxycodone (Abuse-deterrent tablets)		Japan	
S-649266 (Multidrug-resistant Gram-negative bacteria infection)	Global: Phase II & III	US	

Target Milestones for FY2016: Phase I - II

Product (Indication)	Phase I	Phase II	Phase III
S-237648 (Obesity)	US: initiated	Japan: completed Go/No Go decision	
S-222611 (Malignant tumor)	EU: Phase I/II completed		

Target Milestones for FY2016: Phase III

Product (Indication)	Phase I	Phase II	Phase III
S-033188 (Influenza virus infection)	US: completed	Japan: completed	Japan: initiated Global: initiated
S-877489 [Lisdexamfetamine] (Pediatric ADHD)			Japan: completed
Actair® (Pediatric allergic rhinitis caused by house-dust mite allergen)			Japan: completed

Summary

Isao Teshirogi, Ph.D.
President and CEO

Pipeline (as of Mar. 2016)

Non-clinical	Phase I	Phase II		Phase III		NDA submission
	【Global】		S-649266 MDR Gram-negative infections			
	S-033188 Influenza virus Infection	S-707106 Type2 diabetes	S-488210 Head and neck squamous cell carcinoma	S-649266 MDR Gram-negative infections		
	S-117957 Insomnia	S-222611 Malignant tumor	S-588410 Bladder cancer	Osphena® Vaginal dryness associated with postmenopausal VVA	S-888711 Thrombocytopenia	Naldemedine Opioid-induced constipation
	【In Japan】			S-649266 MDR Gram-negative infections		Naldemedine Opioid-induced constipation
Antibody drug candidate against Pseudomonas	Oxycodone Tamper resistant formulation	S-649266 MDR Gram-negative infections		S-877489 Pediatric ADHD	S-877503 Adult ADHD	Cymbalta® Pain associated with chronic low back pain
central neuropathic pain	S-120083 Inflammatory pain	S-033188 Influenza virus Infection	S-237648 Obesity	S-524101 Pediatric patients with perennial allergic rhinitis	Oxycodone Moderate to severe chronic pain	Cymbalta® Pain associated with osteoarthritis
NTE Inhalation	S-010887 Neuropathic pain	S-525606 Allergic rhinitis caused by Japanese cedar allergen	S-588410 Bladder cancer	S-555739 Allergic rhinitis	S-588410 Esophageal cancer	S-877503 Pediatric ADHD

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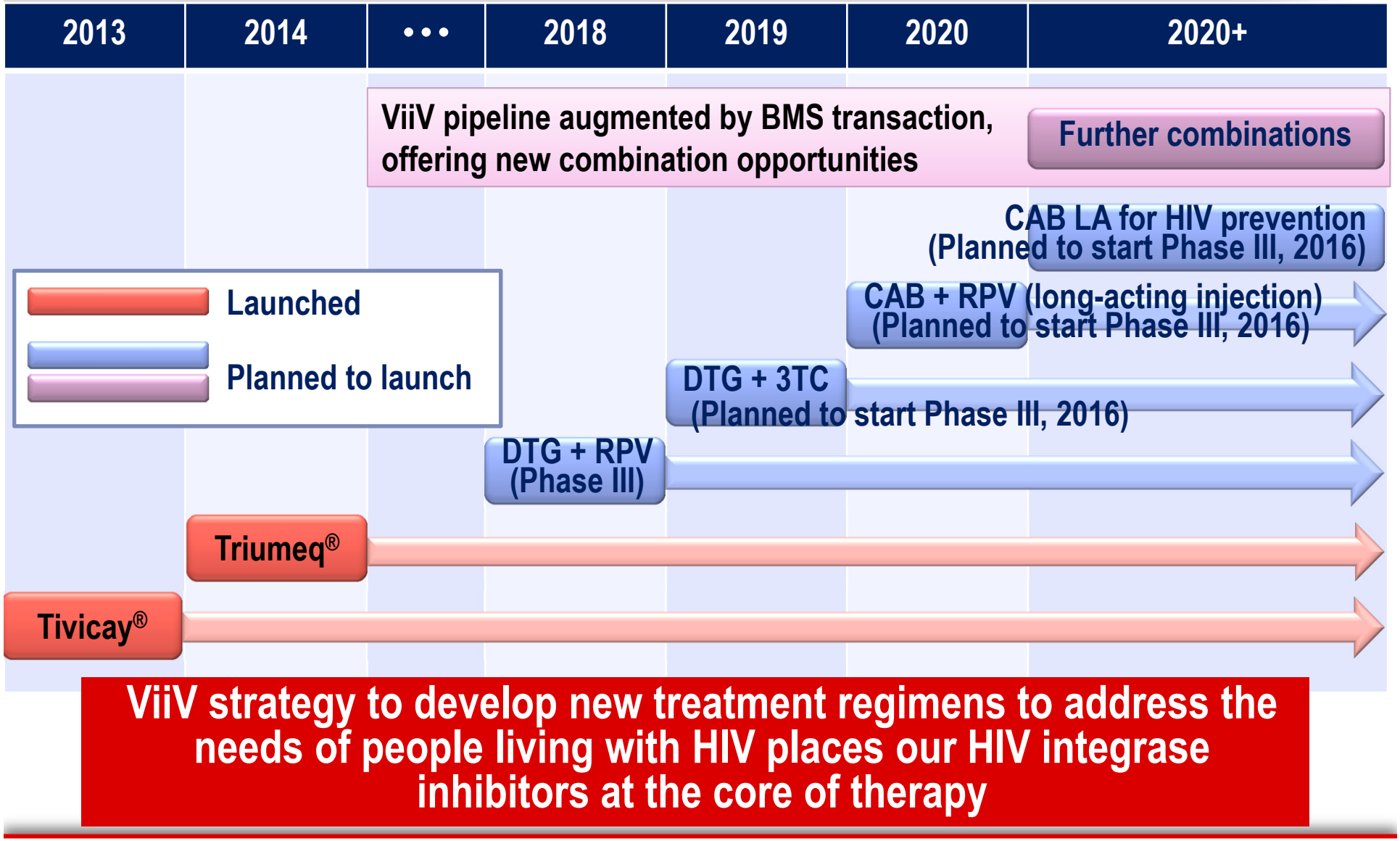
Infectious diseases | Pain/CNS | Metabolic disorder | Frontier

MDR: Multidrug resistant

Pipeline (as of Mar. 2016)

Non-clinical	Phase I	Phase II	Phase III	NDA submission
【Out-licensed】		Cabotegravir+rilpivirine LAP Treatment for HIV infection		
GSK3342830 MDR Gram-negative infections		Cabotegravir LAP Prevention for HIV infection	Dolutegravir+rilpivirine Treatment for HIV infection	
Janssen/Shionogi Project compound Alzheimer's disease			Janssen/Shionogi BACE inhibitor Alzheimer's disease	

HIV Integrase Inhibitor Franchise



Source: GSK disclosure (R&D Day on Nov. 2, 2015 and press release on Dec.18, 2015)
DTG: doluteguravir, RPV: rilpivirine, CAB: cabotegravir, LA: log-acting, BMS: Bristol-Myers Squibb

FY2015(result)	FY2016	FY2017		FY2018
【Global】		S-649266 MDR Gram-negative infections		
Senshio® postmenopausal VVA		Naldemedine Opioid-induced constipation	S-888711 Thrombocytopenia	Osphena® Vaginal dryness associated with postmenopausal VVA
【In Japan】				
Triumeq® Treatment for HIV infection	*ISODINE*® *for medical use* disinfectant			
Cymbalta® Pain associated with fibromyalgia	Cymbalta® Pain associated with chronic low back pain			S-033188 Influenza virus Infection
Mulpleta® Thrombocytopenia	Cymbalta® Pain associated with osteoarthritis	Naldemedine Opioid-induced constipation	S-877503 Pediatric ADHD	S-877489 Pediatric ADHD
Actair® Allergic rhinitis caused by house-dust mite	Crestor®OD tablets Hyper ripidemia	Oxycodone Moderate to severe chronic pain	Oxycodone Tamper resistant formulation	Actair® Pediatric patients with perennial allergic rhinitis

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Q&A

Forward-Looking Statements

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

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

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