Research and Development at Shionogi

March 16, 2017

Shionogi & Co., Ltd.

SHIONOGI

Agenda

1. **Introduction**
   - **Isao Teshirogi**, Ph.D., President and CEO
2. **Research**
   - **Takeshi Shiota**, Ph.D., Senior Vice President
     Pharmaceutical Research Division
3. **CMC**
   - **Miyuki Hiura**, Senior Vice President, CMC R&D Division
4. **Development**
   - **Kazuhiro Hatanaka**, Senior Vice President
     Global Development Division
5. **Summary**
   - **Isao Teshirogi**, Ph.D., President and CEO
6. **Q&A**

Introduction

Isao Teshirogi, Ph.D.
President and CEO

Research

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

Vision for R&D

R&D Vision

Research: Innovation in Drug Discovery to Serve Society

CMC: Product Development Bringing "Benefit for All"

Development: Efficient and Consistent Development

Action:
Improve research productivity based on our core strengths

- Create a sustained pipeline of development products in core area
- Establish new drug discovery platforms generating innovative products in frontier areas
- Maximize drug discovery output through open innovation
- Improve ability to predict clinical trial success using biomarker
- Strengthen capability of research organization by optimizing research personnel system

Agenda: Pharmaceutical Research Division

- **To Achieve SGS2020**
  - Innovation in Drug Discovery to Serve Society
- **Accomplishments in FY2016**
  - Discovered Development Products/Drug Candidates
  - External Collaboration with Partners
  - Biomarker Research
- **Targets for FY2017**
  - Review of Our Drug Discovery Research
    - > Infectious Disease Area
    - > Pain/CNS Area
    - > Frontier Area

Agenda: Pharmaceutical Research Division

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Innovation in Drug Discovery to Serve Society

As a drug discovery-based pharmaceutical company

We demonstrated our excellent scientific capabilities through our drug discovery innovations

2016's Heroes of Chemistry Award (an award given by the American Chemical Society for innovation in chemistry) for the discovery of Tivicay®

Naldemedine

Lusutrombopag

Dolutegravir

Rosuvastatin

Doripenem

Cefcapene pivoxil

Serve the needs of society

Focused on infectious disease, pain and CNS* areas where society has high medical need

Focused on the small molecule drug discovery, allowing our innovative drugs to be affordable as well

Continue to grow

Cefiderocol: Saving lives by fighting multi-drug-resistant bacteria

S-033188: Relieving flu symptoms with the simplicity of a single oral dose

* CNS: Central nervous system

Research Targets for FY2020

Goals

10 or more development products from our internal research as well as collaborative research, to be created from 2017 to 2020

Achieving our goal will require an even greater increase research productivity building on our core strengths:

- Drug discovery research capabilities: Strengthening SAR* engine for small molecule drug discovery, expansion of platforms for drug discovery
- Promotion of open innovation: Contribution to the continuous growth of the pipeline with new products
- Improve probability of clinical trial success using biomarkers: Successful progression from early to late clinical trials
- Maximization of the value of our compounds: Expand drug pipeline through LCM** strategy
- Human resource development in research: Fostering "spirit of challenge" to create competitive strength

More than half of our pipeline is discovered within Shionogi

* SAR: Structure activity relationship ** LCM: Life cycle management

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Our Plans and Accomplishments in FY2016

- **Plans in FY2016**
  - To promote a program on drug discovery research to continue conducting FIC/LIC* drug discovery
    - > Discover 2 or more drug candidates in our core therapeutic areas
    - > Discover 3 or more development products
    - > Proceed our drug discovery research program by new approaches
- **Accomplishments in FY2016**
  - **Discovered 3 drug candidates: in-house anti-pain and anti-obesity drug candidates, and in-licensed product (Botulinum toxin)**
  - **One development product: S-600918 (neuropathic pain)**
  - **GSK3342830 discovered in a collaboration with GSK has moved into a Phase I clinical study**
  - **A cardiovascular program licensed to MedImmune has moved into a Phase I clinical study as of Feb. 2017**
  - **Licensed out a drug discovery program in diabetes area to a global pharma**
  - **Commencement of drug discovery programs utilizing peptide drug discovery platform technologies**

* FIC: First-in-Class/LIC: Last-in-Class

External Collaborations/Biomarker Research in FY2016

- **Plans in FY2016**
  - Expansion of core drug discovery platform
    - > Strengthen our drug discovery capability by initiating new external collaborations with partners globally
    - > Improve biomarker research capability for biomarkers and promote translational research through new units focused on these areas

- **Accomplishments in FY2016**
  - **Initiated a collaboration with NB Health Laboratory Co. Ltd. to accelerate infectious disease research at Hokkaido University**
  - **Discovered a clinical PET imaging compound for a new drug candidate in the pain area**

License Agreement with Tokushima University for a Botulinum Toxin Candidate

SHIONOGI ← DSANJ * (Drug Seeds Alliance Network Japan) ← 徳島大学 TOKUSHIMA UNIVERSITY

- **License for novel type A Botulinum toxin candidate "A2NTX"**
- **High level of expertise in Botulinum toxin therapy**

Novel type A Botulinum toxin candidate "A2NTX"

- Potential treatment for post-stroke spasticity of upper and lower limbs
- Less likely to spread from target organ or to induce production of neutralizing antibodies

To support rehabilitation, and to encourage patients and their families to return to active lives

* DSANJ: Drug Seeds Alliance Network Japan

External Collaborations

SONG for you!

Value chain in drug discovery

Obtain novel drug seeds
Build new platforms for drug discovery

- Launched collaboration with NB* for anti-infective drugs
- Pursuing active collaboration with MTC**

Strengthen small molecule SAR platform and maximize outputs

- Progress drug discovery in core areas as planned, including through collaborations with Janssen, Pionnier, Nissan Chemical Industries, Ltd.
- Pursue drug discovery for emerging and re-emerging infectious diseases with GHIT Fund

Pursue macrocyclic/constrained peptides as a novel class of small molecule products, leveraging and expanding our small molecular drug discovery skills

- To launch drug discovery programs for difficult targets, utilizing PEPTIDREAM's peptide hit discovery technology

We will diversify our approaches, develop new expertise, and maximize output from small molecule drug discovery

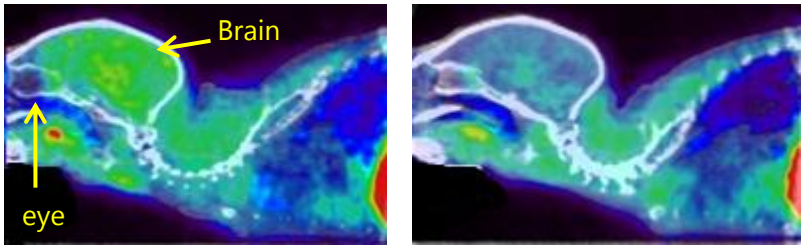
* NB: NB Health Laboratories Co. Ltd.
** MTC: Milner Therapeutics Consortium

Biomarker Research

Novel PET probe as valuable tool for improving clinical research

Drug candidate: First-in class CNS compound for neuropathic pain

(-) compound　(+) compound



Evaluate target receptor binding of the candidate compound by competitive inhibition of binding of novel PET probe

- **Confirmed the relationship between efficacy and receptor occupancy in non-clinical study**
- **Use for optimization of dose and regimen in clinical study**

Use to improve decision making, accelerate drug development, and reduce development costs

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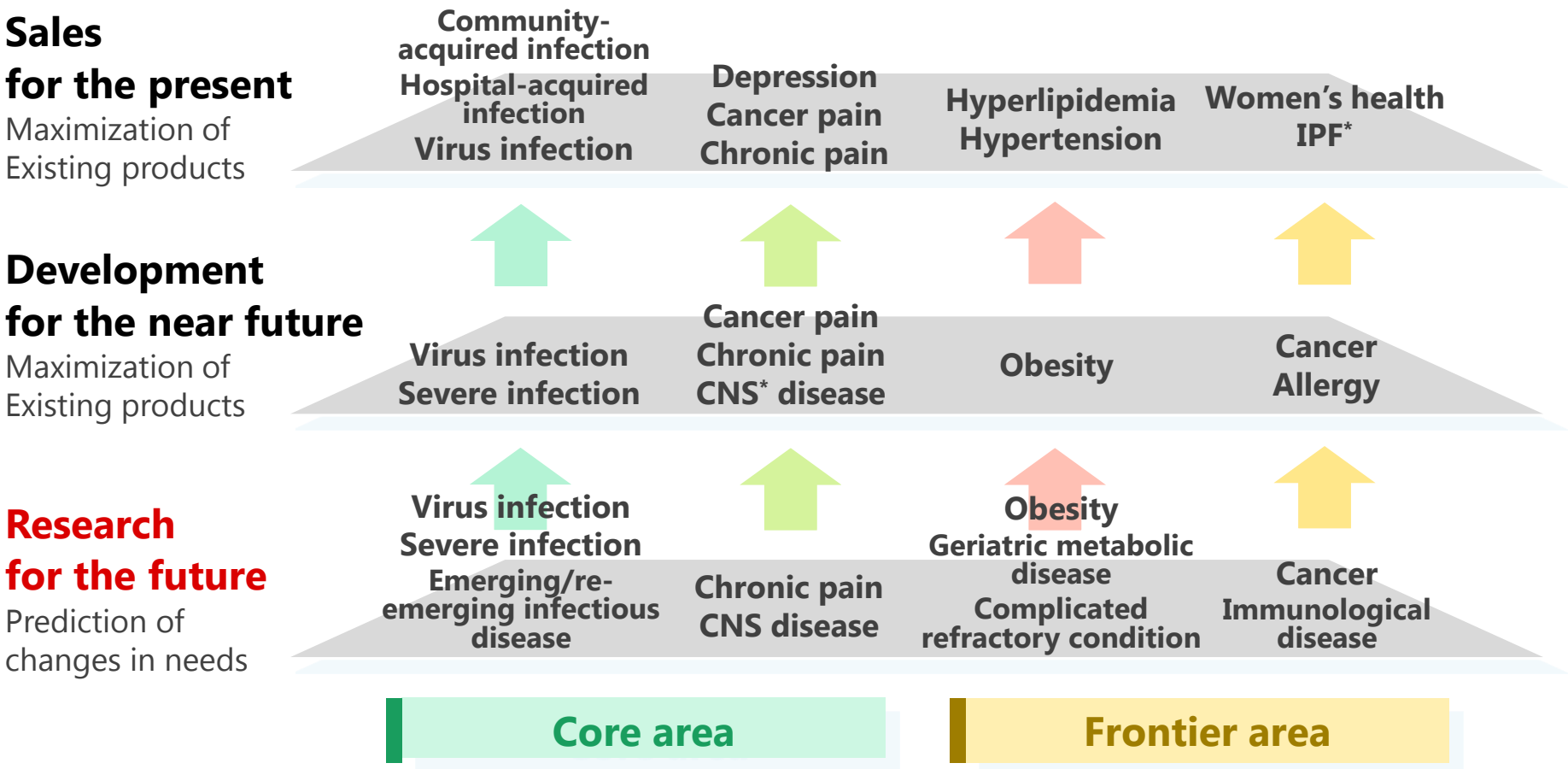
SGS2020: Target Therapeutic Areas for Research

Clear priorities and focused resourcing to meet unmet medical needs



* IPF: Idiopathic pulmonary fibrosis

Infectious Diseases

Virus infection

Expand HIV franchise with further FIC/LIC compounds

Establish drug discovery program pipeline for viral respiratory infections, including flu

HIV

- Supporting development progress for DTG*/CAB**
- In last stages of nomination assessment for a candidate compound in a late stage drug discovery program
- Progressing further drug discovery programs to continue pipeline

Respiratory virus

- Supporting development progress and conference presentations for S-033188
- Progressing further drug discovery programs to continue pipeline

Severe infection

New drugs for antibiotics-resistance/fatal systemic fungal infections

- Supporting development progress and conference presentations for Cefiderocol
- Progressing drug discovery programs focused on antibiotic resistance
- Linking biomarker discovery research to diagnosis of severe infection

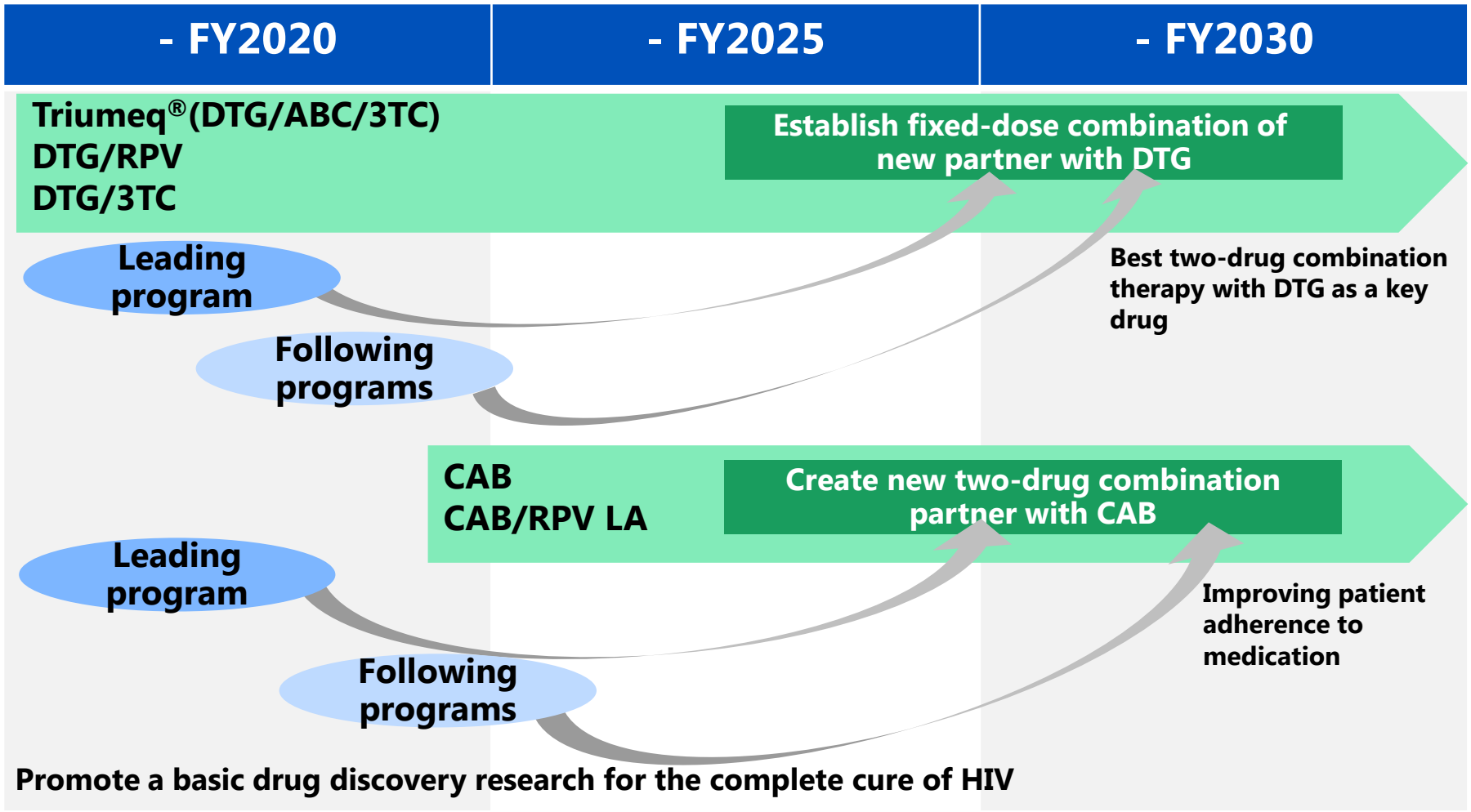
Emerging/re-emerging infectious diseases

Create new opportunities through participation in the GHIT fund

- Screening of a lead compound against tuberculosis
- Screening of hit compounds against Chagas' disease/leishmaniasis

* DTG: Dolutegravir ** CAB: Cabotegravir

Drug Discovery Strategy for HIV Area

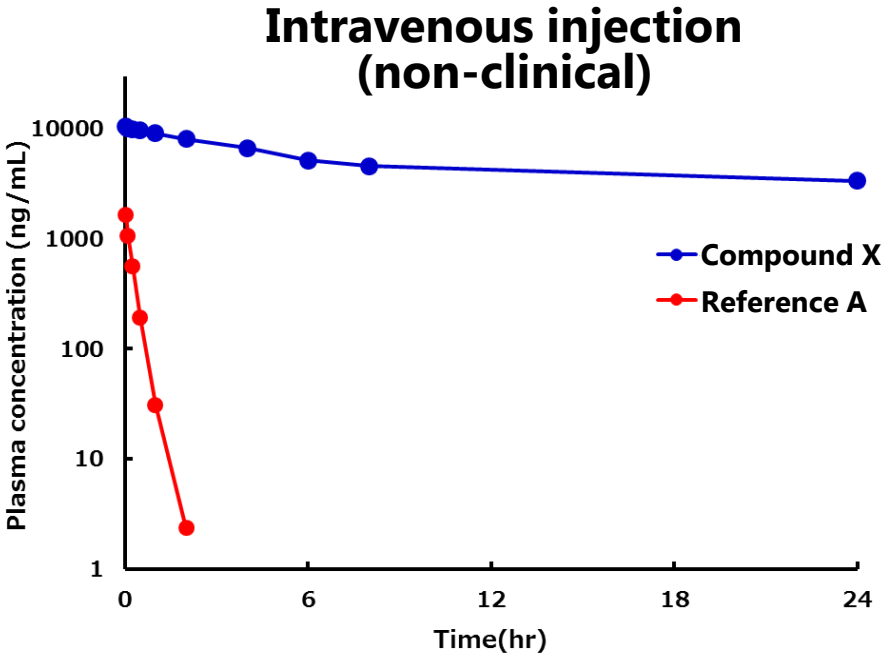


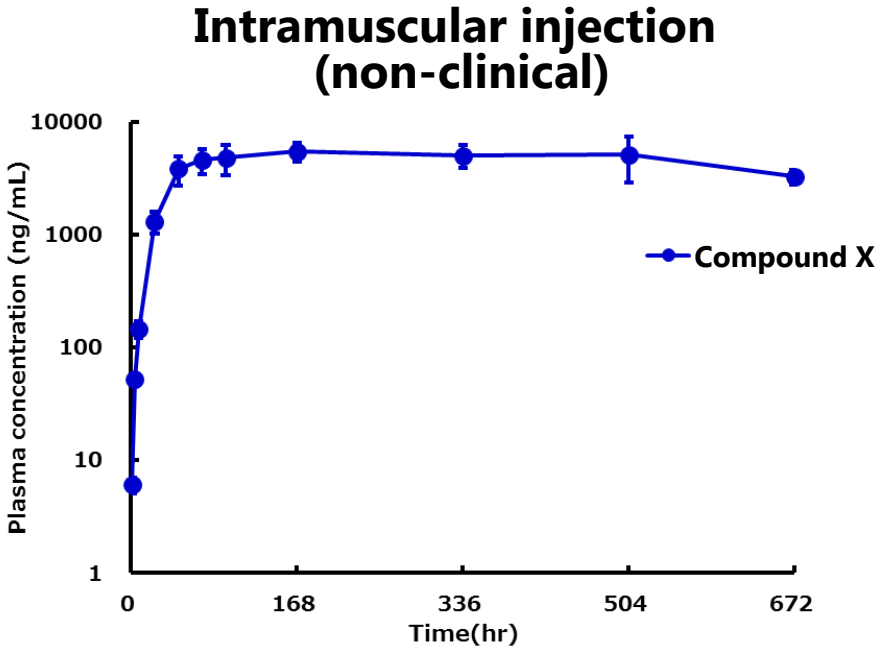
Create novel anti-HIV drugs continuously to improve QOL with recovery and maintenance of patient health

ABC: Abacavir 3TC: Lamivudiner RPV: Rilpivirine LA: Long acting

Drug Discovery Program: HIV

Create a new two-drug combination partner with Cabotegravir



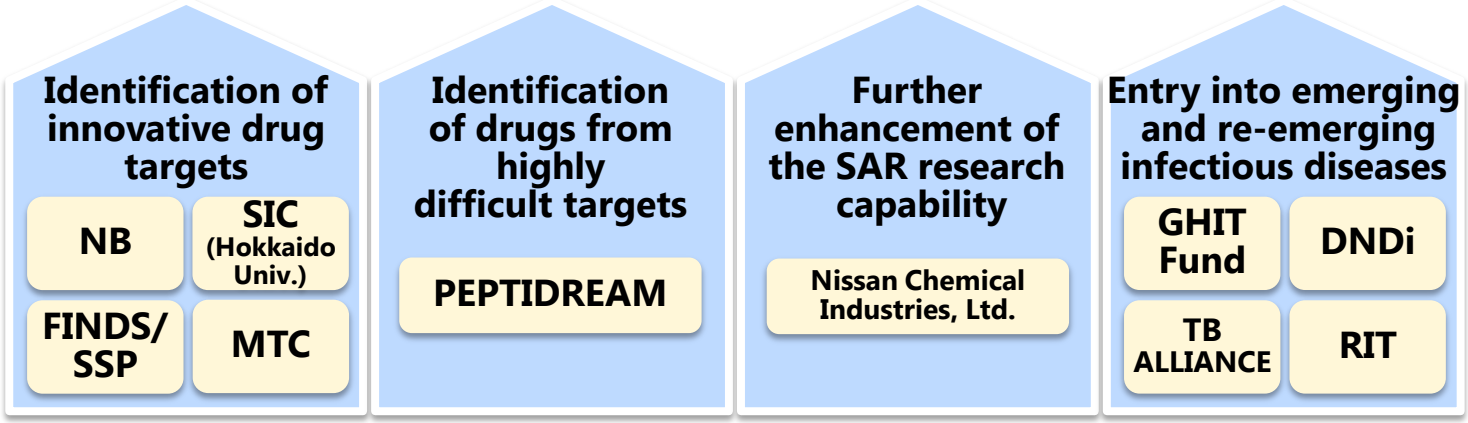


- Maintains a high plasma concentration for an extended period without a PK booster
- Therapeutic exposure levels maintained for more than one month after local administration

Based on good PK results, final assessment to nominate a candidate compound will be carried out

Infectious Disease: Research Strategy

Establish the presence of Shionogi's infectious disease drugs in the global market



Overcoming challenges and strengthening capabilities through external collaborations

Strengths in infectious disease area

SAR* engine for small molecule drug discovery

Established drug discovery platforms for antibacterial and antiviral drugs

FINDS/SSP: PHarma-INnovation Discovery competition Shionogi/Shionogi Science Program
SIC: Shionogi Innovation Center MTC: Milner Therapeutics Consortium DNDi: Drug for Neglected Diseases initiative
RIT: Research Institute of Tuberculosis * SAR: Structure activity relationship

Pain and CNS

Chronic pain

Develop LIC opioids

Develop FIC non-opioids

Opioid

- Progress drug discovery programs with new mechanism to reduce adverse effects

Non-opioid

- Created novel development product and a candidate compound
- Created a novel PET probe
- Progressed drug discovery programs targeting pathogenic mechanisms

CNS disorders

Anti-Aβ drug discovery/novel mechanism of action drug discovery

Develop FIC anti-ADHD drugs with better adverse event profiles

AD*

- Develop Anti-Aβ drugs in collaboration with Janssen
- Progress drug discovery programs with novel mechanisms of action

ADHD**

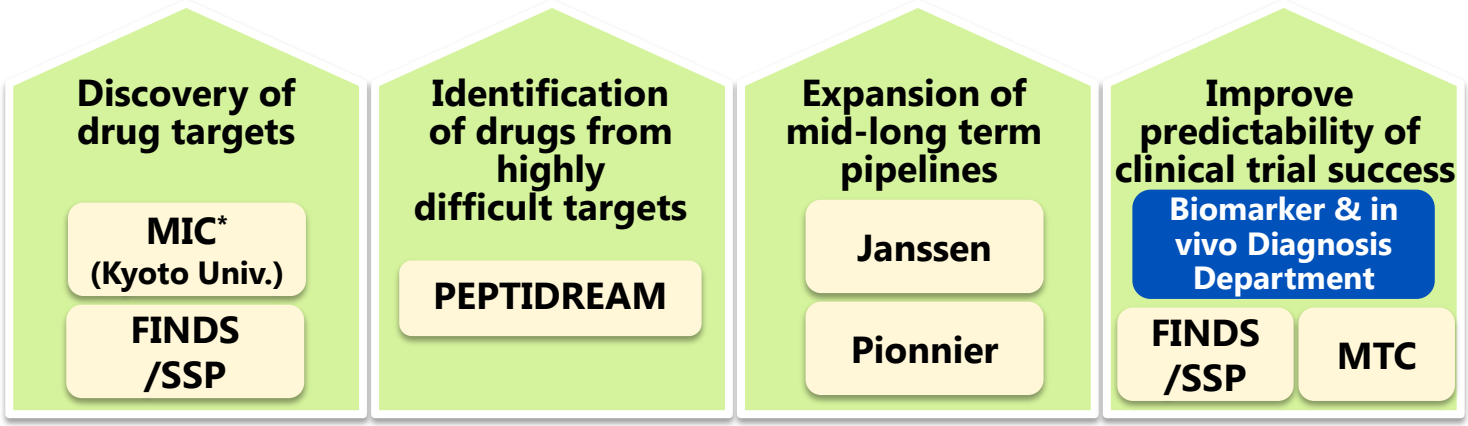
- Support launch of our products
- Advance drug discovery programs to create sustainable pipeline

* AD: Alzheimer's disease

** ADHD: Attention-deficit/hyperactivity disorder

Pain and CNS: Research Strategy

Improve probability of POC success in a high difficult area



Overcoming challenges and strengthening capabilities through external collaborations

Strengths in pain and CNS area

SAR engine for small molecule drug discovery
Research capabilities that produce 3 FIC drug candidates

* MIC: Medical Innovation Center

Frontier

Obesity/geriatric metabolic disease

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

Obesity

- Systematically progress drug discovery programs to establish sustainable pipelines

Complicated/refractory/geriatric conditions

- Drive drug discovery programs for CKD* and NASH**
- Progress drug discovery research in Sarcopenia

Oncology/immunological disease

Continue progression of cancer peptide vaccines
Pursue novel immunomodulating therapies

Cancer peptide vaccines

- Support ongoing development activities

Novel immunomodulating therapies

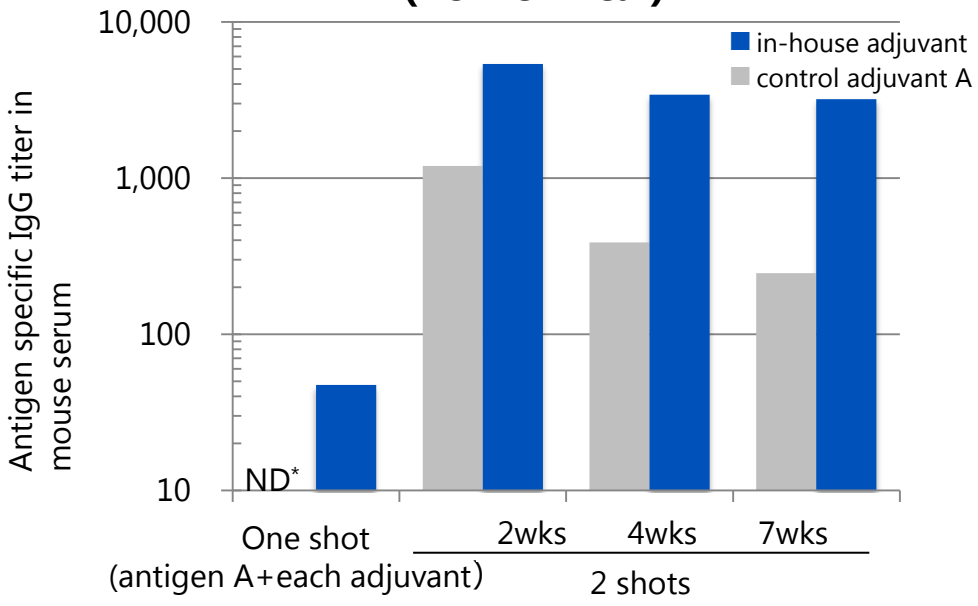
- Exploration of target molecules for novel cancer immunotherapy through joint research with CoMIT*** in Osaka University
- Create new adjuvant (immunostimulating product)

* CKD: Chronic kidney disease ** NASH: Non-alcoholic steatoheptitis
*** CoMIT: Center of Medical Innovation and Translational Research

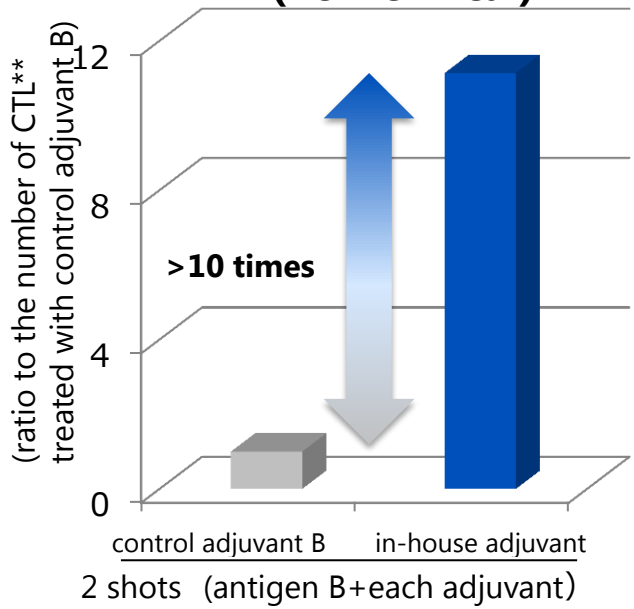
Frontier: Original Adjuvant

Create a novel adjuvant with superior enhancement of immunological response

Production of IgG (non-clinical)



Enhancement of cellular immunity (non-clinical)



- Antigen specific antibody detectable after a single dose and sustainable high IgG production confirmed after boosting
- Increase in number of CTL after local injection of antigen with our adjuvant
- Does not cause local irritation and lacks systemic toxicity concerns in non-clinical studies

Applicable to a range of diseases/vaccines

* ND: Not detected ** CTL: Cytotoxic T Lymphocyte

FY2017 Plans for Research

Innovation in Drug Discovery to Serve Society

10 or more development products to be created by FY2020

- **Continuous creation of drug candidates and development products**
  - New drug candidates for HIV
  - Two or more additional development products
- **Maximization of drug discovery productivity through external collaborations**
  - Initiation of new innovative drug discovery program
  - Initiation of new external collaborations in support of drug discovery programs
  - Achievement of key milestones in collaboration studies
  - Generate research tools/output that can improve predictability of clinical trial success
- **Verify clinical applicability of newly created PET imaging compound**

Human Resource Development in the Pharmaceutical Research Division

Globally competitive drug discovery-based pharmaceutical company

Excellent Science

A researcher (leader) who can propose a new drug discovery program and implement it

A research manager who has deep scientific insight and can lead the organization

Create a high productive research environment by combining a diversity of skills and roles

A research professional who has a focused scientific expertise and can solve challenges in drug discovery

A research technician who is highly skilled and can create high quality data and useful tools to promote drug discovery

Encourage a spirit of challenge and development of world-class talent by supporting and maturing management, leadership, and research capabilities

CMC

Miyuki Hiura
Senior Vice President
CMC R&D Division

Vision for R&D

R&D Vision

Research: Innovation in Drug Discovery to Serve Society

CMC: Product Development Bringing "Benefit for All"

Development: Efficient and Consistent Development

Action:
Create New Product Value Realizing Social Expectation by Innovative CMC Technologies

- **Providing reliable & effective medicines**
- **Improving medical economics**
- **Increasing the success rate of drug development**

Agenda: CMC R&D Division

- **To Achieve SGS2020**
  - Responding to the Changing Needs of Society for New Drugs
- **Achievements in FY2016**
  - NDA Submissions and Market Launches of Pipeline Products
  - Breakthroughs by CMC Technologies
    - > Synthesis Technology for Preparation of Mid-Molecular Weight API*s
    - > Uniformity Technology for Formulations with Low API Content
    - > Formulation Technology for Inhalation DDS**
    - > Analytical Technology for Residual Metals in Pharmaceutical Products
- **Targets for FY2017**
  - To Grow for the Future by Meeting Society's Needs

* API: Active pharmaceutical ingredient ** DDS: Drug delivery system

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Social Needs for New Drugs

- **New Expectation from Society**
  - "**Improving medical economics**" as well as "**creation of innovative new drugs**" is becoming more important, given society's expectation of value-based medicines
- **To Grow for the Future Meeting Society's Needs**

Providing **reliable & effective medicines**	Improving **medical economics**	Increasing **success rate** of our drug development
Creation of **High-Value Products** of good quality and meeting medical needs Delivering relief reliably to all	Achievement of **Cost Reduction** and **Insightful Development** Demonstrating cost-effectiveness	Application of CMC technology at **Early R&D Stage** Providing new solutions for drug discovery research

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* API: Active pharmaceutical ingredient ** DDS: Drug delivery system

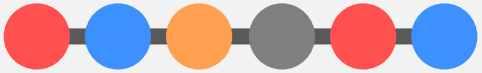
Achievements in FY2016

Plus One for Product Development

- **NDA submissions and product launches**
  - Naldemedine: Complete launch preparations
  - Cefiderocol (S-649266): Phase III study, ready for NDA
  - Oxycodone Tamper Resistant Formulation: Complete NDA and prepare for commercial manufacturing
  - S-033188: Phase III study, ready for NDA
- **Breakthroughs in CMC technology**
  - Synthesis Technology for Mid-Molecular Weight API
  - Uniformity Technology for Formulation with Low API Content
  - Formulation Technology for Inhalation DDS
  - Analytical Technology for Residual Metals in Pharmaceutical Products

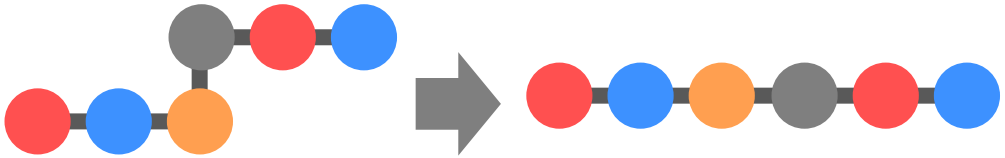
Synthesis Technology for Mid-Molecular Weight API

Sparingly Soluble Peptide

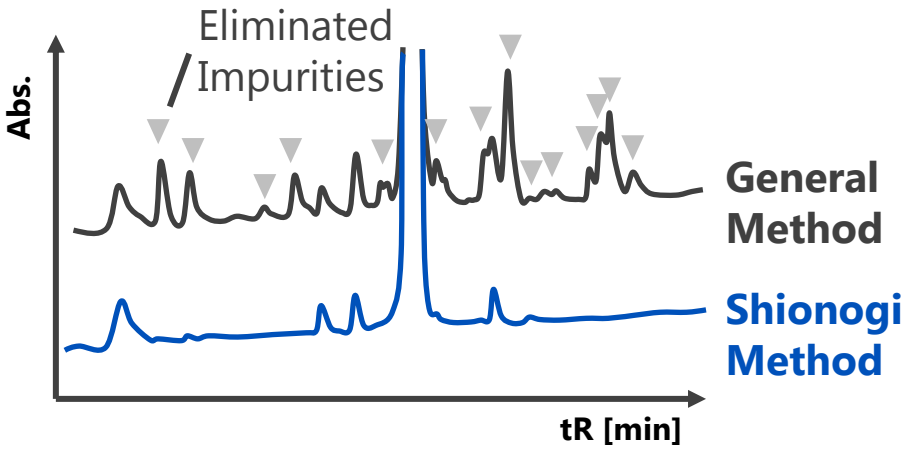


Peptide with certain sequences have very low solubility, which leads to difficulties in synthesis and purification

Overcoming Poor Solubility



- Synthesizing and purifying with modified more soluble structure first
- Converting to the desired peptide at the final step

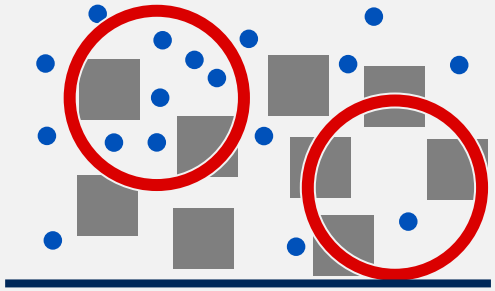


Impurity: Less than **1/5**
Yield: More than **Double**

API produced in this manner has enabled cancer peptide vaccine development

Uniformity Technology for Formulation with Low API Content

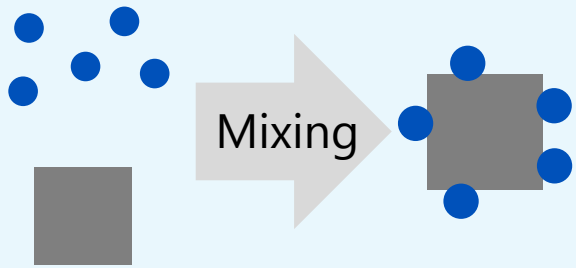
Conventional Method

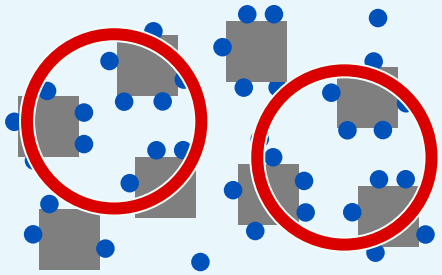


● API ■ Excipient

Uniformity is difficult to achieve with low API content

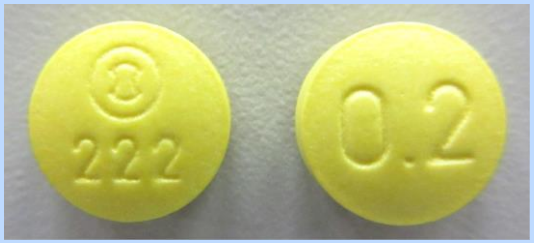
Shionogi Method





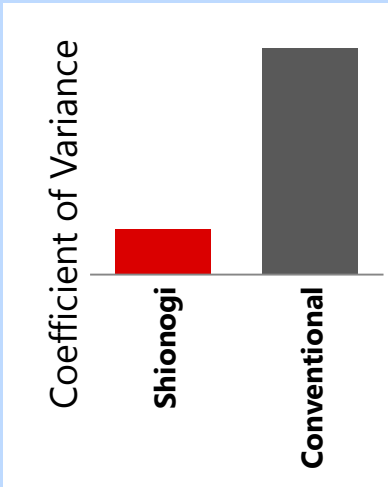
An API/excipient complex is formed before formulation

Tableting



Patent Pending

High Quality Formulation with evenly dispersed API content



Contributed to the development of naldemedine 0.2 mg tablets

Formulation Technology for Inhalation DDS

SONG for you!

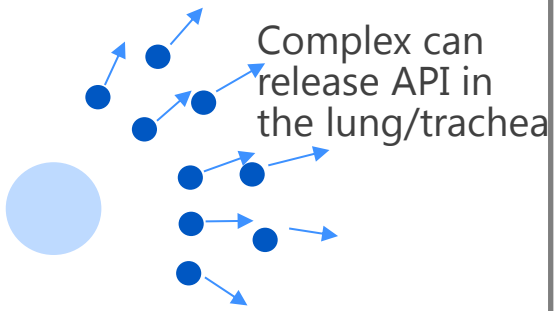
Efficient DDS for the Lung/Trachea

API Micronization	Established technology for micronization
Complex Formation	Formation of optimal complex for inhalation
Device Development	Development of a device with high functionality and ease-of-use

Dilemma of Micro-nization	Micronization is necessary to reach the target	⇔	Micronized API aggregates easily, reducing absorption

Transfer by complex

Release at the target



Created a foundation for a widely applicable formulation technology for inhalation

Highly efficient delivery of API to the lung/trachea was demonstrated

Delivery ratio: **1.4**% ➡ **55**%
(in vitro)

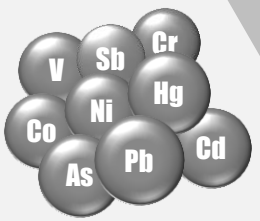
Inhalation efficiency improved **40**-fold

Analytical Technology for Residual Metals in Pharmaceutical Products

Conventional Standard

Analyses of Residual Metals

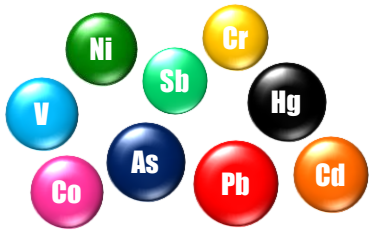
- Guaranteed only NMT **10-20** ppm
- Individual metals are **not distinguished**



More resolution

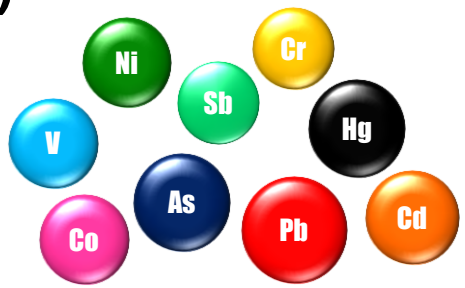
ICP-MS Analysis**

- Guaranteed NMT **0.1-1** ppm
- **Individual** analysis of metal species



More quality/speed

New Global Standard (ICH*-Q3D)



Technical Development

- Higher resolution of NMT **0.01-0.1** ppm
- Establishing analytical method in the **short term**

Developed a key technology for residual metal analysis in compliance ICH, with high efficiency

* ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

** ICP-MS: inductively coupled plasma mass spectrometry

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For Continuous Growth with Society

New slogan of the CMC R&D Division in FY2017

Benefit for ALL

- Create new product value by meeting the expectations of all stakeholders
  - Patients, healthcare professionals, healthcare cost sponsors, Shionogi shareholders and employees, etc.

Targets for FY2017 (1)

Rapid/high quality NDA and launch

Cefiderocol (S-649266)	Completion of NDA submission in the US
S-033188	Establishment of commercial manufacturing completion of NDA in Japan Trial for new LCM* formulation
Pediatric ADHD (Guanfacine, Lisdexamfetamine)	Completion of market-launch preparation

Development approach that reliably meets the requirements of global regulatory authorities

- Drug development with predictive risk assessment and proactive resolution
- No delays in approval of NDA submissions due to quality of filing package and excellent communication with authorities

Consistent reduction of COGs in all stages through improvement of CMC technology**

* LCM: Life cycle management
** CoGs: Cost of goods sold

Targets for FY2017 (2)

Maximize the value of the compound

Conventional NTE*: Targeting a wide range of therapeutic areas

⬇ As technologies are refined and developed

Strategic LCM: Focusing on our original drugs or candidates using advanced CMC technologies in NME trial**

NME Moving projects forward to RSC/S stage by innovative and advanced CMC technologies

➡ **Advance ≧ 4 projects to RSC/S by 2020**

Developing revolutionary CMC technologies for the next generation NME

➡ **Develop ≧ 3 technologies by 2020**

LCM Developing new LCMs utilizing improved technology created for NTEs

➡ **Advance ≧ 2 projects to RSC/S by 2020**

Collaborate to apply CMC core competencies across the value chain, beyond the traditional role of CMC

* NTE: New therapeutic entity ** NME: New molecular entity

Development

Kazuhiro Hatanaka
Senior Vice President
Global Development Division

Vision for R&D

R&D Vision

Research: Innovation in Drug Discovery to Serve Society

CMC: Product Development Bringing "Benefit for All"

Development: Efficient and Consistent Development

Actions:

- **Moving from cost control to intelligent cost management**
- **Enhancement of global operations**

Agenda: Global Development Division

- **To Achieve SGS2020**
  - Development Targets for FY2020
  - Current Status and Actions
- **Achievements in FY2016**
  - Pipeline
  - Core Development Products
    - > S-033188
    - > Cefiderocol
    - > Guanfacine, Lisdexamfetamine
    - > S-237648
- **Targeted Milestones for FY2017**
  - Pipeline

Agenda: Global Development Division

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Development Targets for FY2020

Goals

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

Currently 3 compounds

Further improvement of productivity is essential to achieve our goals

- Further improvement in the efficiency of strategic decision making
- Establish a solid framework for high quality, rapid, and efficient global development

Current Status of Global Development

External environment

- **On average, low productivity of the pharmaceutical industry on average**
- **Unpredictable market and policy**

FY2016 in Shionogi

- **Implementation of the first full-fledged global phase III study**
- **Increased cost of development and some study delays**

Pharmaceutical cost pressures

Rise of populism

Requirements for approval ⇧

Simple target for drug ⇩

Number of subjects ⇧

Number of IND data package ⇧

Number of countries ⇧

Enhancements in cost management and global clinical trial operations are necessary

Actions in FY2016

Moving from cost control to intelligent cost management

- Global Portfolio Committee
  - Prioritization of development assets and major clinical trials
- **R&D Budget Implementation Meeting**
  - Investment decision based on prioritization of clinical trials
- Monthly Project Update Meeting
  - Timely management of trial progress
- Monthly Budget Monitoring Meeting
  - Detailed budget management for each project

Enhancement of global operations

- **Global Development Planning Meeting**
  - Sharing and coordination of clinical trial plans
- **Global Clinical Operations Meeting**
  - Consensus and information sharing about clinical trial approach and execution
- Consolidation of Global Development Policy

We are still only halfway to achieving SGS2020

⇒ It is necessary to further demonstrate our ability to consistently bring our products into the global market

Agenda: Global Development Division

- **To Achieve SGS2020**
  - Development Targets for FY2020
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  - Core Development Products
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    - > Cefiderocol
    - > Guanfacine, Lisdexamfetamine
    - > S-237648
- **Targeted Milestones for FY2017**
  - Pipeline

Achievements in FY2016: Approvals and NDA Submissions

Product (indication)	Phase I	Phase II	Phase III	NDA submission	Approval
Cymbalta® (Pain associated with chronic low back pain)				Japan (Dec. 2014)	Japan (Mar. 2016)
Cymbalta® (Pain associated with osteoarthritis)				Japan (Feb. 2016)	Japan (Dec. 2016)
Guanfacine (Pediatric ADHD)				Japan (Jan. 2016)	Japan** (Mar. 2017)
Naldemedine (Opioid-induced constipation)				US/Japan (Mar. 2016)	Japan** (Mar. 2017)
					US (Mar. 2017)
				EU (Mar. 2017)	
Oxycodone (Treatment of moderate to severe chronic pain*/Abuse-deterrent tablets)			Japan Phase III	Japan (Nov. 2016)	
Actair® (Pediatric allergic rhinitis caused by house-dust mite allergen)			Japan Phase III	Japan (Mar. 2017)	

* Development for expansion of indications
** Passed Drug Committee Meeting

Achievements in FY2016: Phase III Study

Product (indication)	Phase I	Phase II	Phase III	NDA submission	Approval
S-033188 (Influenza virus infection)	US: completed	Japan: completed	Global: initiated		
S-033188 (Influenza virus infection (pediatric))			Japan: initiated		
Cefiderocol (Multidrug-resistant Gram-negative bacteria infection)		Global: completed	Global: ongoing		
Lusutrombopag (Thrombocytopenia)			Global: ongoing*		
Lisdexamfetamine (Pediatric ADHD)			Japan: completed		
Guanfacine (Adult ADHD)			Japan: ongoing		
S-588410 (Esophageal cancer)			Japan: ongoing		
Osphena® (Vaginal dryness associated with postmenopausal VVA)			US: ongoing		

* Designated Fast Track in the US (Mar. 2017)

Achievements in FY2016: Phase I - II Study

Product (indication)	Phase I	Phase II	Phase III	NDA submission	Approval
S-237648 (Obesity)	US: completed	Japan: completed			
S-588410 (Bladder cancer)		Japan/EU: ongoing			
S-222611 (Malignant tumor)	EU: ongoing				
S-120083 (Inflammatory pain)	US: completed	US: initiated			
S-600918 (Neuropathic pain)	Japan: initiated				

Agenda: Global Development Division

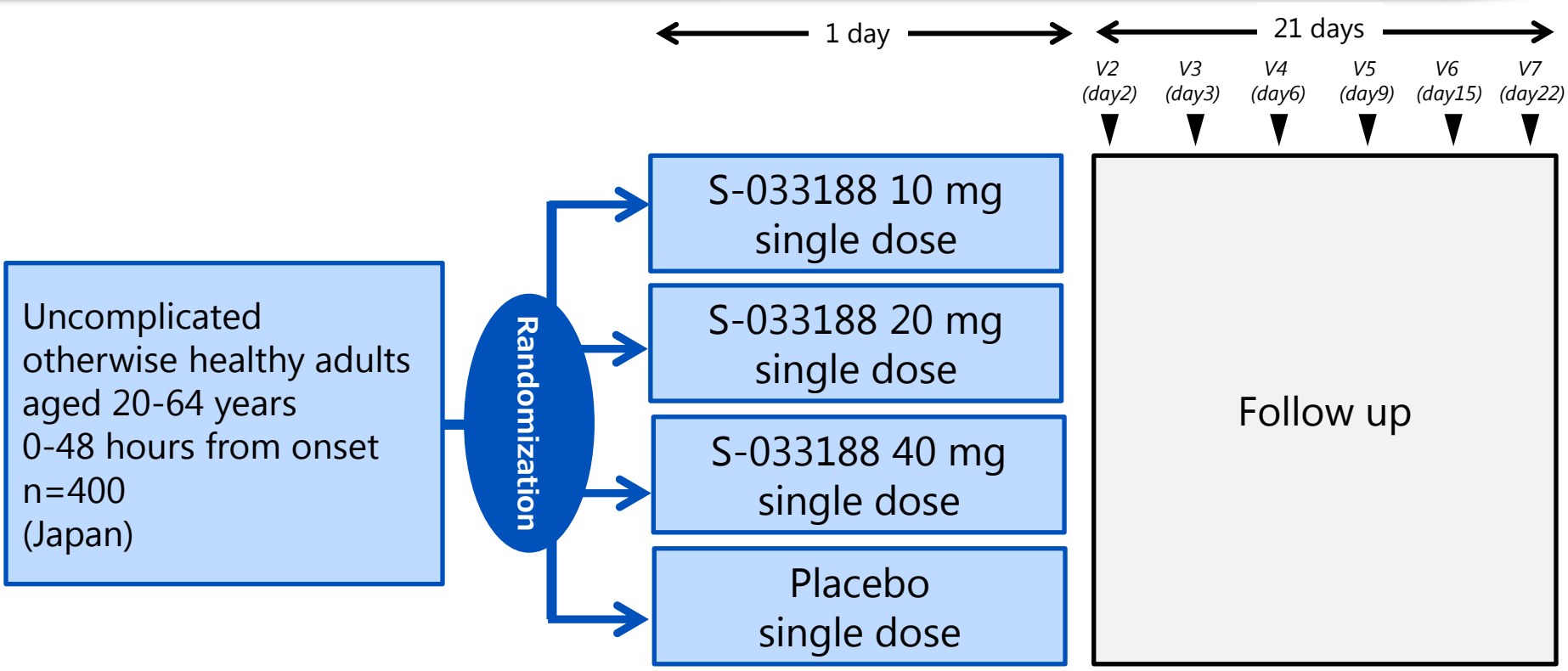
- **To Achieve SGS2020**
  - Development Targets for FY2020
  - Current Status and Actions
- **Achievements in FY2016**
  - Pipeline
  - Core Development Products
    - > S-033188
    - > Cefiderocol
    - > Guanfacine, Lisdexamfetamine
    - > S-237648
- **Targeted Milestones for FY2017**
  - Pipeline

S-033188
Influenza Virus Infection

Profile

Indication	Influenza virus infection
Mechanism of action	Cap-dependent endonuclease inhibition (novel mechanism of action)
Special characteristics	Influenza type A/B viruses Highly pathogenic avian influenza viruses Single oral dose
Stage	Japan/Global: Phase III study
Future plan	Japan: NDA submission in FY2017
Note	Designated for “priority review system” by Ministry of Health, Labour and Welfare (MHLW)

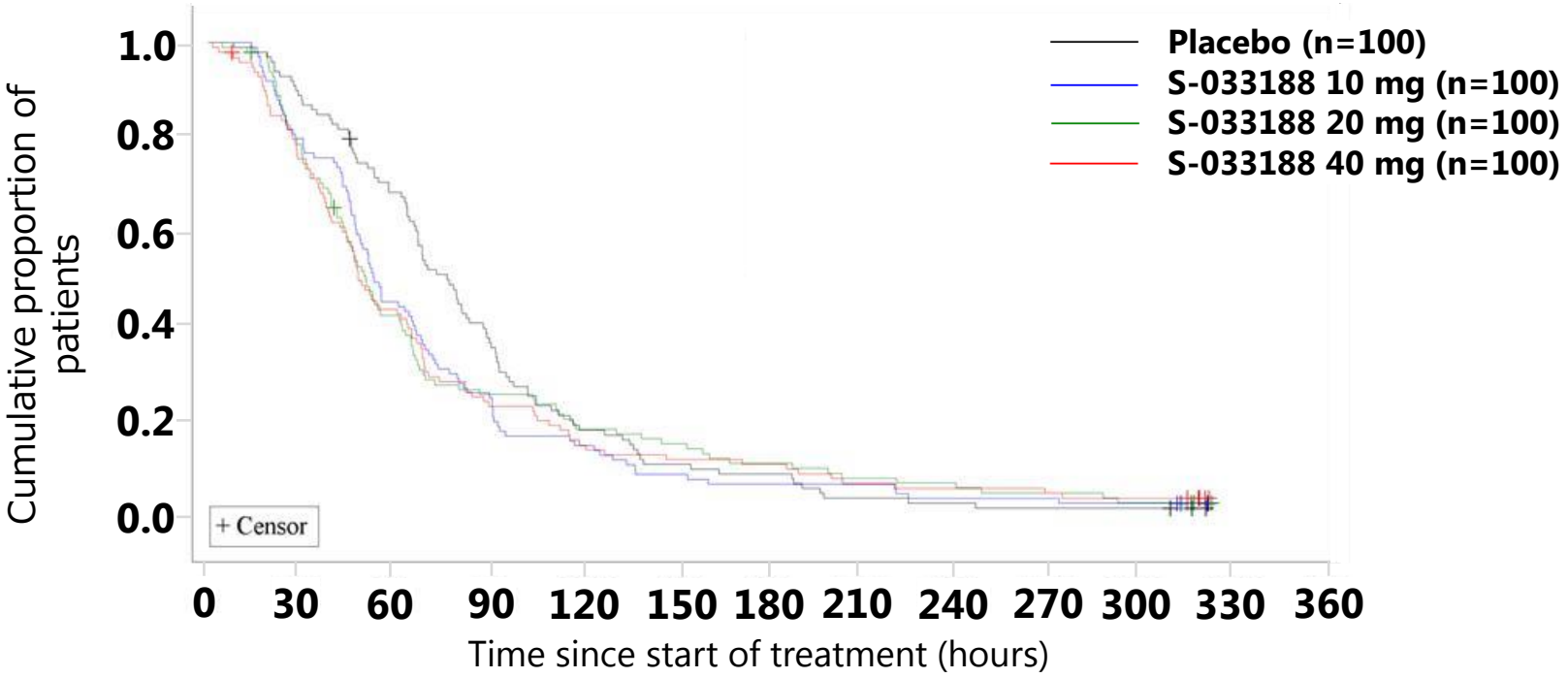
Phase II Study Design



- **Primary Objective: Time to improvement of 7 major flu symptoms compared to placebo**
- **Primary Endpoint: Time to improvement of 7 major flu symptoms**

Summary Results of Phase II Study (Efficacy)

Time to improvement of 7 major flu symptoms

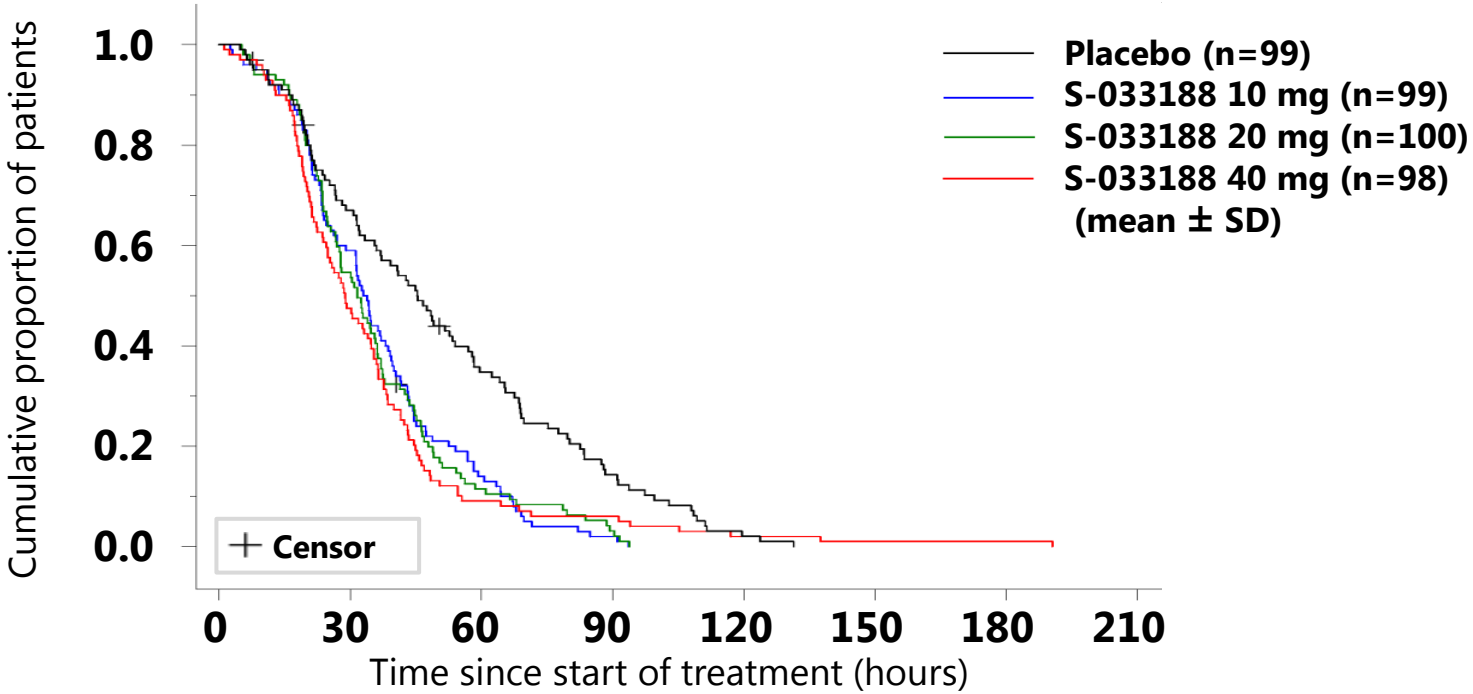


	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Median time [95% CI] (hrs)	54.2 [47.7, 66.8]	51.0 [44.5, 62.4]	49.5 [44.5, 64.4]	77.7 [67.6, 88.7]
Difference (vs placebo) (hrs)	-23.4	-26.6	-28.2	---
P-value*	**0.0085**	**0.0182**	**0.0046**	---

* Stratified Generalized Wilcoxon test
Stratified and covariate factors: smoking habit, composite symptom scores at baseline

Summary Results of Phase II Study (Efficacy)

Time to resolution of fever

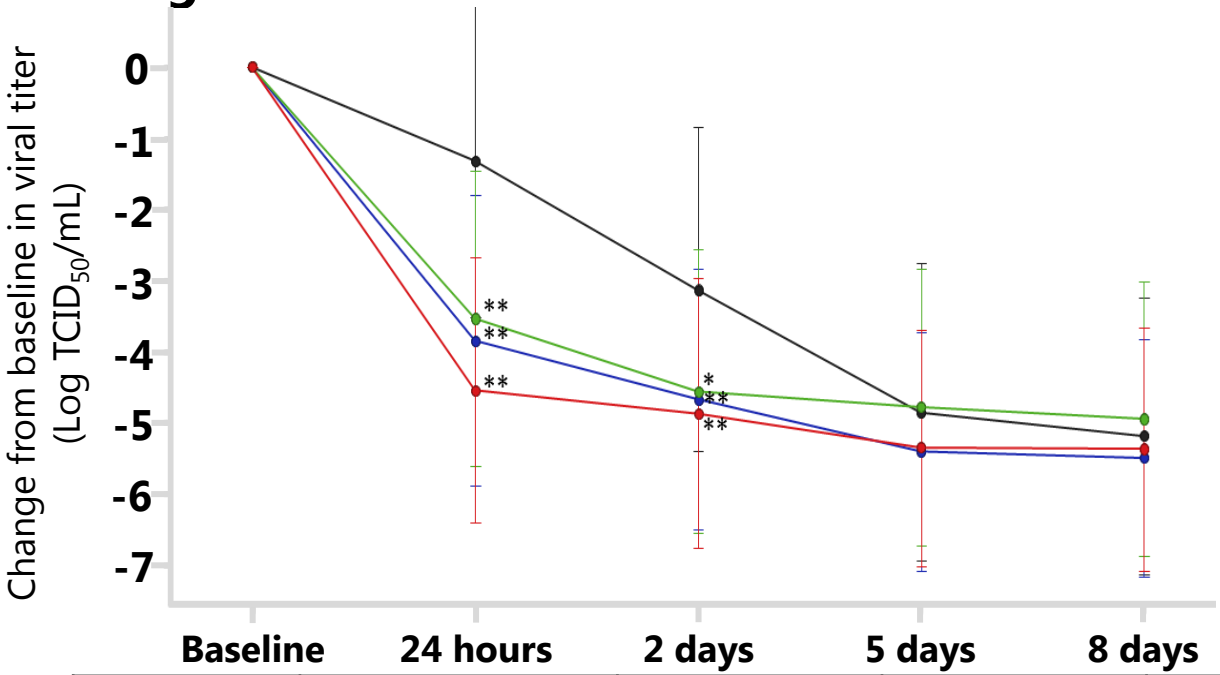


	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Median time [95% CI] (hrs)	33.4 [26.9, 38.1]	31.6 [26.9, 35.8]	28.9 [24.5, 34.7]	45.3 [35.6, 54.0]
Difference (vs placebo) (hrs)	-11.9	-13.7	-16.5	---
Hazard ratio*	0.538	0.546	0.554	---
P-value*	**<.0001**	**<.0001**	**<.0001**	---

* Cox proportional hazards model vs placebo (Covariates: smoking habit, composite symptom scores at baseline, body temperature at baseline)

Summary Results of Phase II Study (Efficacy)

Change from baseline in viral titer



*p < 0.001 and **p < 0.0001 vs placebo (van Elteren test, two-sided, covariates: smoking habit, composite symptom scores at baseline)

		S-033188 10mg	S-033188 20mg	S-033188 40mg	Placebo
24hr after treatment	n[1)]	99	100	95	98
	mean	**-3.83**	**-3.53**	**-4.54**	**-1.32**
	SD	2.05	2.07	1.87	2.19
	P-value (vs Placebo)	**<.0001**	**<.0001**	**<.0001**	---
2 days after treatment	n	67	70	69	65
	mean	**-4.67**	**-4.55**	**-4.87**	**-3.12**
	SD	1.82	2.00	1.89	2.28
	P-value (vs Placebo)	**<.0001**	**0.0004**	**<.0001**	---

[1)] Subset of patients who were positive for influenza virus titer at baseline

Summary Results of Phase II Study (Safety)

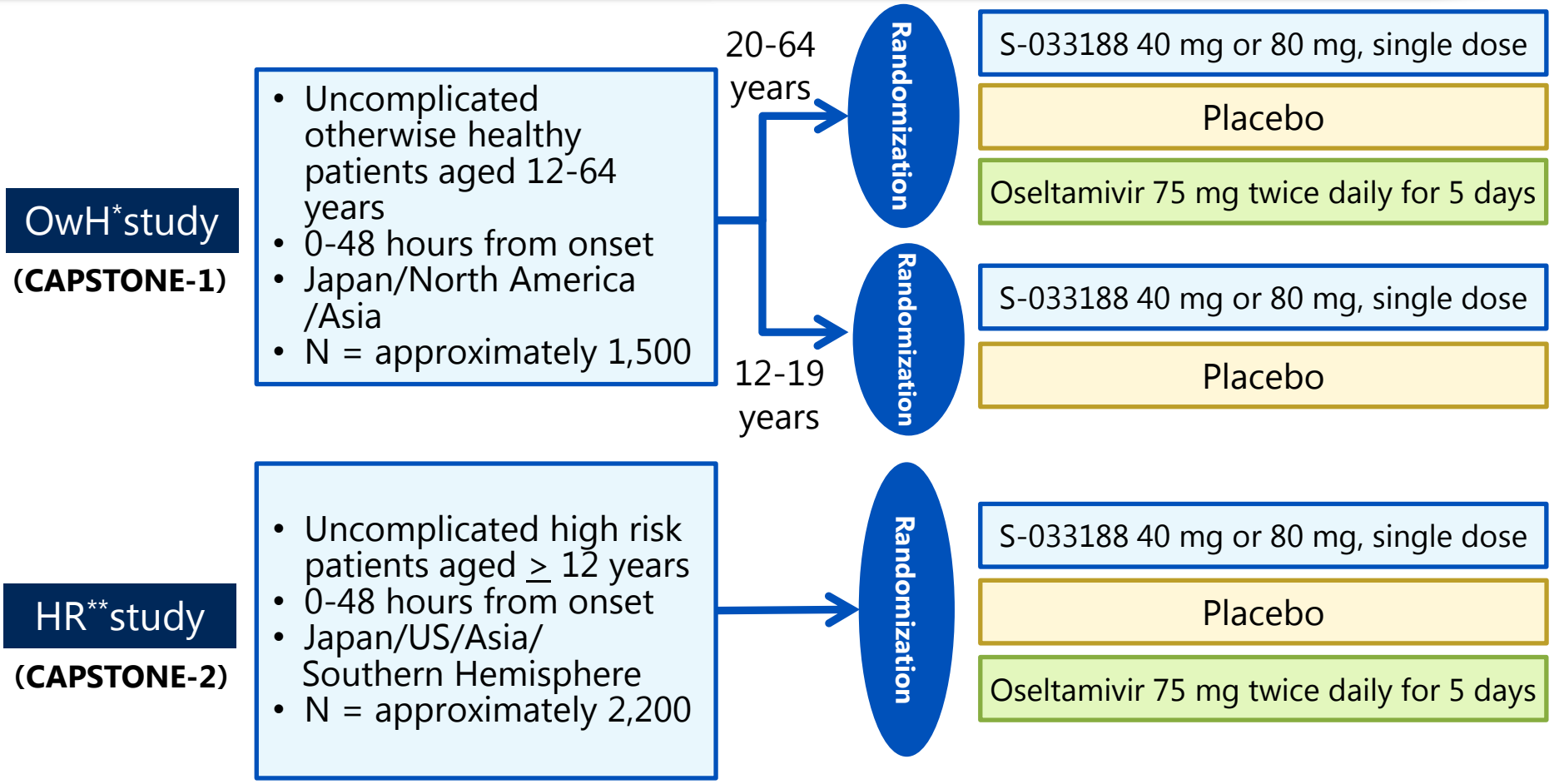
Incidence of adverse events/drug reactions

	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Adverse events	27 (27.0)	23 (23.0)	26 (26.0)	29 (29.0)
Adverse drug reactions	9 (9.0)	7 (7.0)	6 (6.0)	10 (10.0)

Adverse events occurring at an incidence of 3% or higher in any treatment groups

Adverse events, n (%)	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Headache	3 (3.0)	1 (1.0)	4 (4.0)	3 (3.0)
Diarrhoea	0	3 (3.0)	2 (2.0)	5 (5.0)
ALT increased	3 (3.0)	0	2 (2.0)	3 (3.0)
AST increased	3 (3.0)	0	1 (1.0)	1 (1.0)
WBC count decreased	3 (3.0)	1 (1.0)	0	0

Global Phase III Studies (CAPSTONE Studies) Design

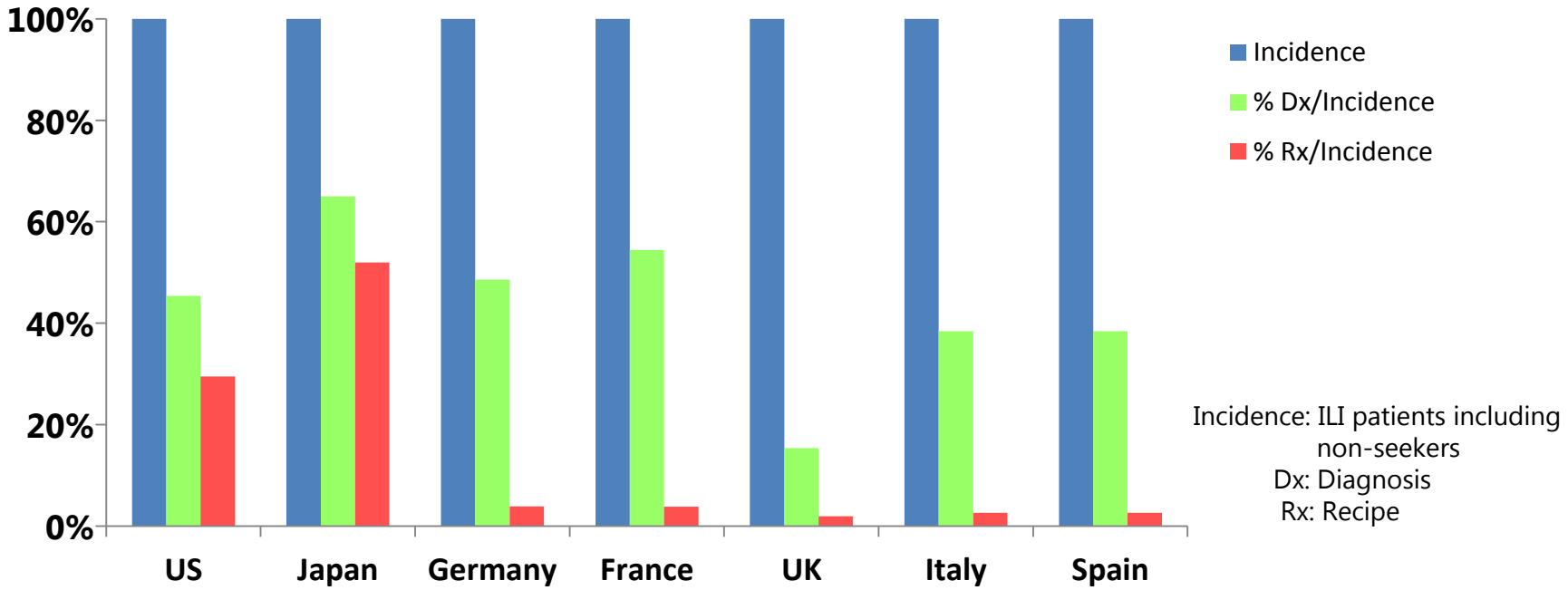


- **Primary Objective: Time to improvement of 7 major flu symptoms compared to placebo**
- **Major Secondary Objective: Time to improvement of 7 major flu symptoms compared to oseltamivir** (using stratified generalized Wilcoxon test which is suitable for proving a rapid symptom improvement by S-033188)

* OwH: Otherwise healthy ** HR: High risk

Market Potential

- **Patient number per year (Japan/US/EU)**
  - Japan: 14-16 million[1)]
  - US: 15 million, EU5: 13 million[2)]
- **Diagnosis/prescription rate[2)]**



Incidence: ILI patients including non-seekers
Dx: Diagnosis
Rx: Recipe

Large latent market in US/EU

Pursuing product value maximization globally coupled with HTA

1) Press release from MHLW (2010-2016)
2) Decision Resources Biopharma (2014)

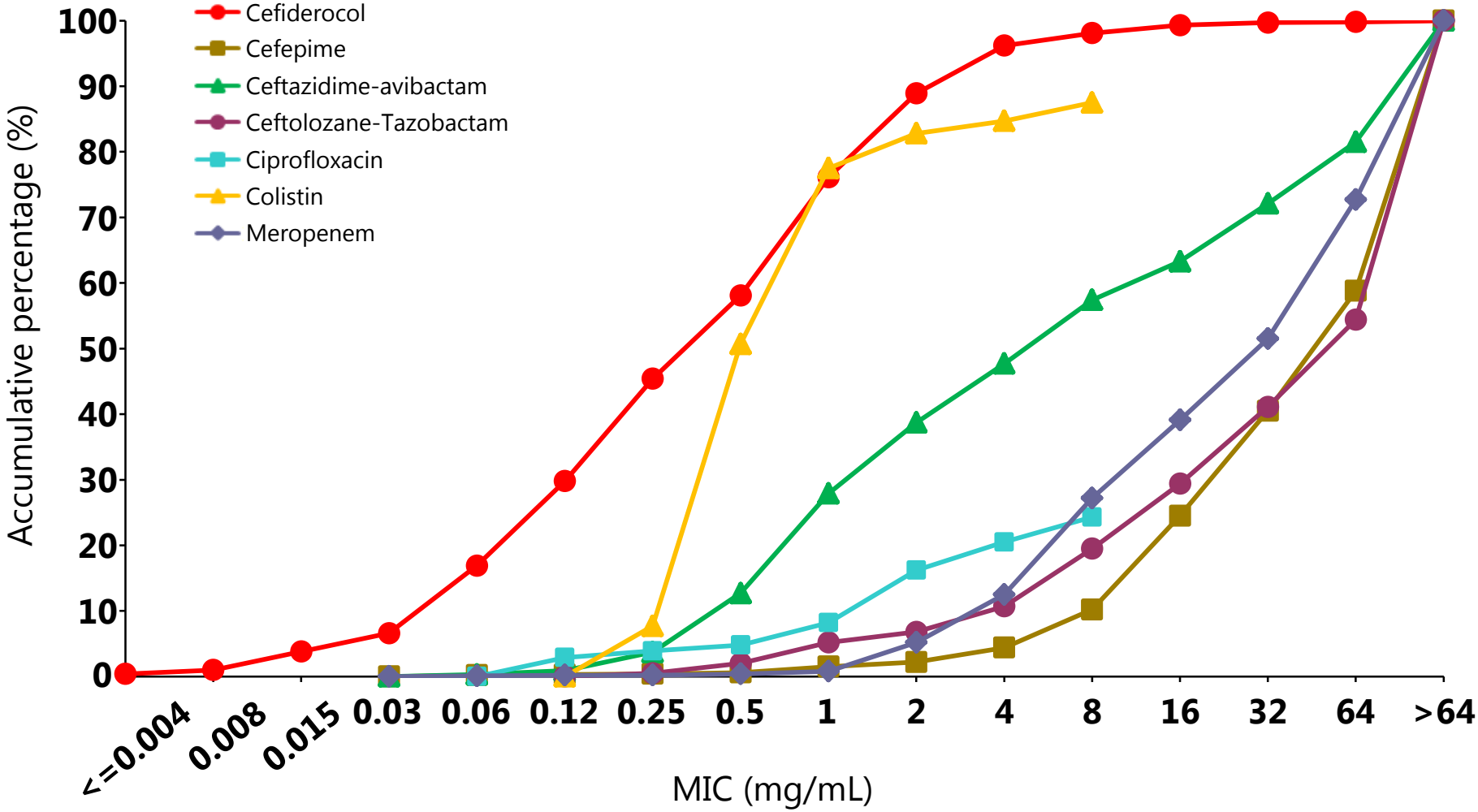
Cefiderocol
Multidrug-resistant Gram-negative bacterial infection

Profile

Indication	Multidrug-resistant Gram-negative bacterial infection
Mechanism of action	Cell wall synthesis inhibition
Special characteristics	Injectable siderophore cephalosporin Wide range of Gram-negative pathogens
Stage	Phase II complicated urinary tract infection study (global, complete) Phase III Gram-negative carbapenem-resistant study (global) Phase III hospital-acquired pneumonia/ventilated-associated pneumonia study (global)
Future plan	US: NDA submission in 1H FY2017 (QIDP* designated compound)

* QIDP: Qualified infectious disease product

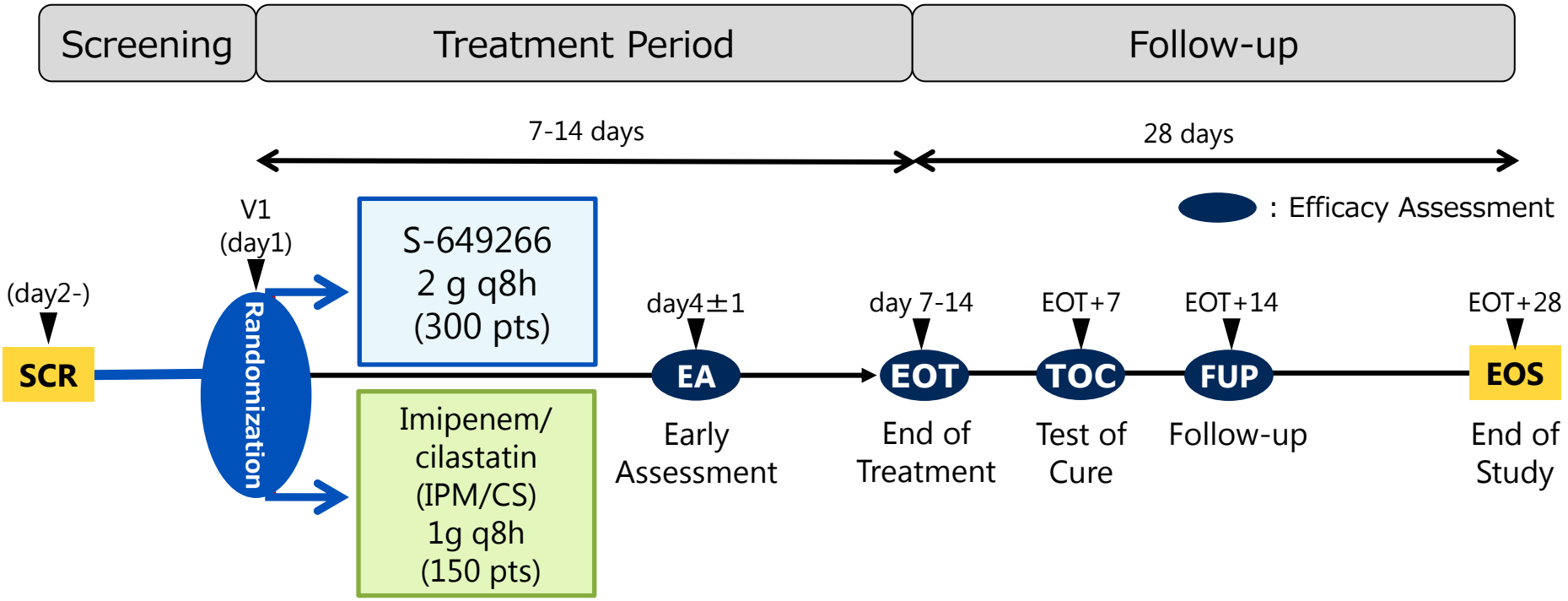
CRE and MDR Non-fermenters Collected Globally in 2014-2016



CRE* and MDR** non-fermenters collected from global countries in 2014-2016 (SIDERO-CR-2014/2016, 1873 isolates)

* CRE: Carbapenem-resistant enterobacteriaceae ** MDR: Multidrug-resistant

Global Phase II Study Design



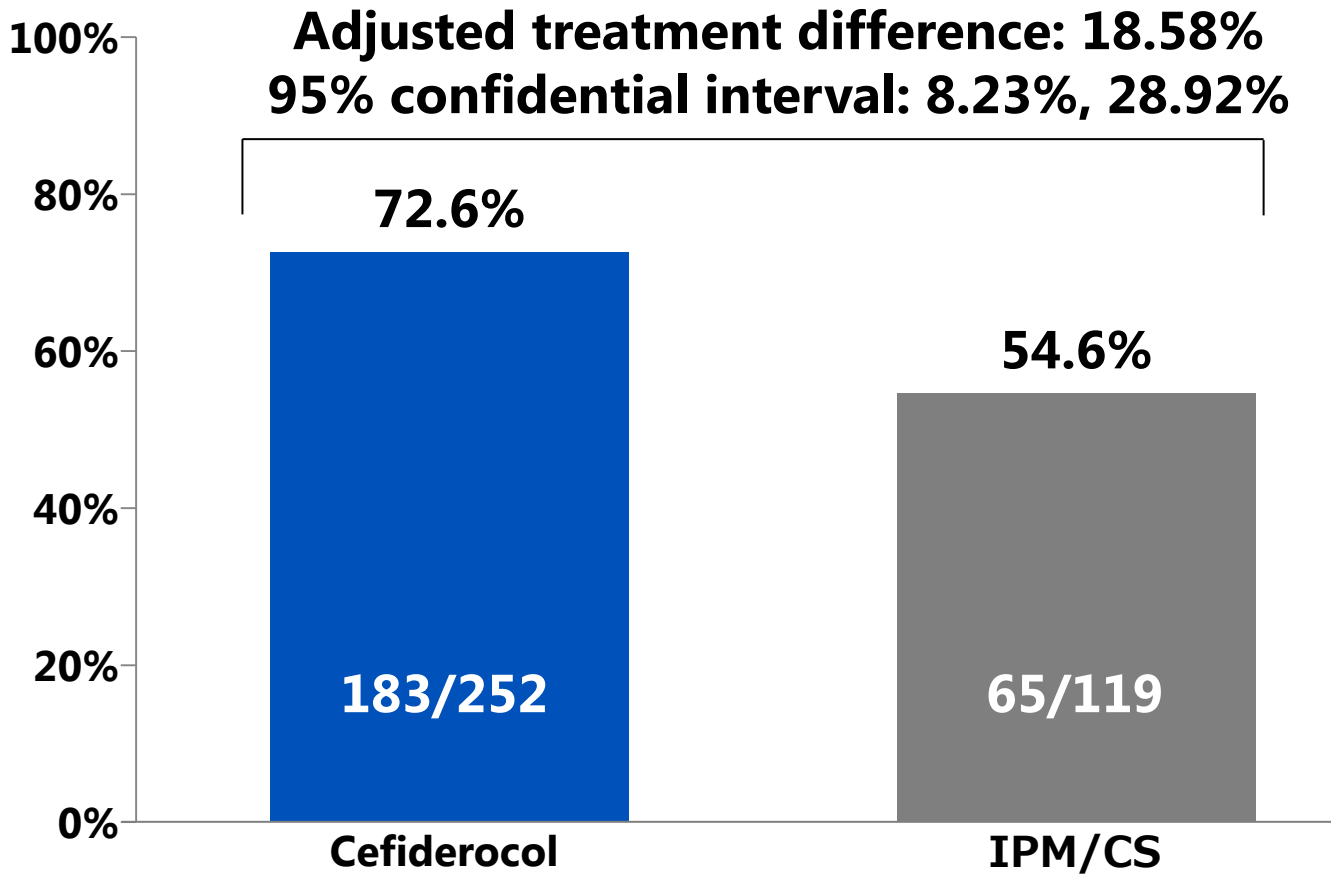
- **Primary Objective: To assess the efficacy and safety of S-649266 in complicated urinary tract infections (cUTI)*, versus imipenem/cilastatin (IPM/CS)**
  *: cUTI caused by Gram-negative bacteria including Enterobacteriaceae and non-fermenters such as *Pseudomonas aeruginosa*
  - **Enrolled patients who needed treatment for 7 to 14 days in hospital**
- **Primary Efficacy Endpoint: Composite outcome (clinical response and microbiologic response) at the test of cure (TOC)**

SCR: Screening EA: Early assessment EOT: End of treatment TOC: Test of cure
FUP: Follow up EOS: End of study

Global Phase II Study: Efficacy

Non-inferiority Study in Patients with cUTI

Composite Outcome (Clinical Response and Microbiologic Response) at TOC (approx. 7 days after EOT)



*Treatment difference (Cefiderocol minus IPM/CS) is the adjusted estimate of the difference in the responder rate between the 2 treatment arms. The adjusted difference estimates and the 95% CIs (2-sided) are calculated using a stratified analysis with Cochran-Mantel-Haenszel weights based on the stratified factor at baseline (cUTI with or without pyelonephritis vs. acute uncomplicated pyelonephritis).

Global Phase II Study: Safety

Incidence of adverse events/drug reactions

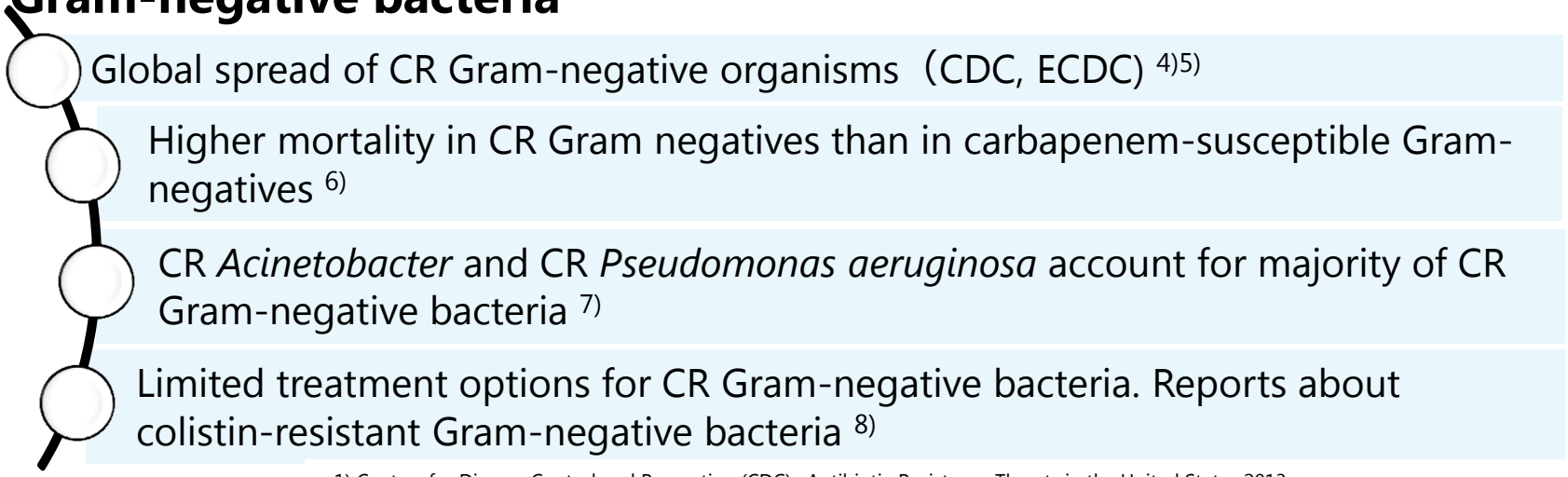
Adverse events/drug reactions, n (%)	Cefiderocol 2g, q8h N=300	Imipenem/cilastatin 1g, q8h N=148
Adverse events	120 (40.0)	74 (50.0)
Adverse drug reactions	26 (8.7)	17 (11.5)

Adverse events occurring at an incidence of 3% or higher in either treatment group

Adverse events, n (%)	Cefiderocol 2g, q8h N=300	Imipenem/cilastatin 1g, q8h N=148
Diarrhoea	13 (4.3)	9 (6.1)
Hypertension	13 (4.3)	7 (4.7)
Constipation	10 (3.3)	6 (4.1)
Infusion site pain	7 (2.3)	8 (5.4)
Headache	9 (3.0)	5 (3.4)
Nausea	7 (2.3)	6 (4.1)
Renal cyst	3 (1.0)	5 (3.4)
Abdominal pain upper	2 (0.7)	5 (3.4)

AMR (Antimicrobial Resistance): Current Situation

- **Threat by AMR**
  - **US:** More than 2 million are infected every year with antibiotic-resistant bacteria, resulting in at least 23,000 deaths (CDC [1)2)], 2013)
  - **Europe:** About 25,000 patients died in the Europe from an infection every year, and two thirds of these deaths were caused by infections due to Gram-negative bacteria (ECDC [3)], 2009)
- **Carbapenem-resistant (CR): Most difficult to treat among AMR Gram-negative bacteria**



1) Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States 2013.
2) President's Council of Advisors on Science and Technology. Report to the President on combating antibiotic resistance. September 2014.
3) European Centre for Disease Prevention and Control (ECDC). Technical Report: the bacterial challenge: time to react. 2009
4) Infection Control Hosp Epidemiology 2016: 1-14
5) Summary of the latest data on antibiotic resistance in the European Union. EARS-Net surveillance data November 2016 data.
6) B. Cai, et al., abstract #268, ASM-Microbe 2016
7) B. Cai, et al., poster #362, ID Week 2016
8) ECDC Press release, 18 November 2016

Guanfacine
Lisdexamfetamine
ADHD (Attention-deficit/hyperactivity disorder)

Profile: Guanfacine

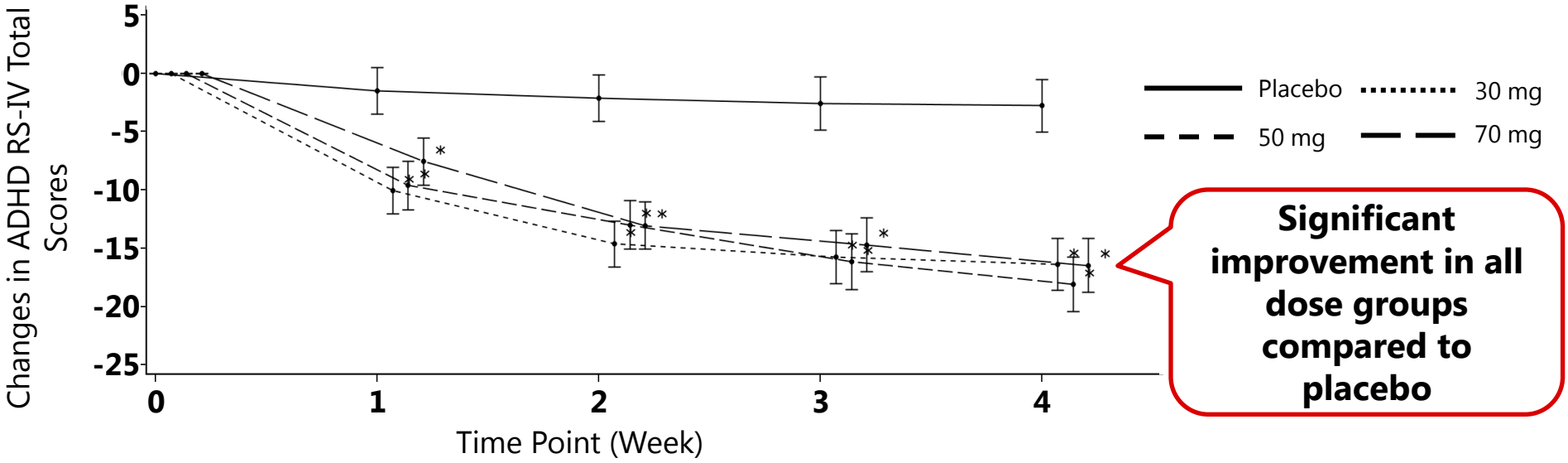
Indication	ADHD (Attention-deficit/hyperactivity disorder)
Mechanism of action	Selective alpha 2 adrenergic receptor agonist
Product profile	Taken once-daily (AM/PM), S-877503 controls ADHD core symptoms (hyperactivity-impulsivity and inattention) significantly compared to the placebo Safety of clinical dose established by abundant overseas Approved as monotherapy and adjunctive therapy to stimulants in the US and Canada. Approved as monotherapy in the EU
Stage	Japan: Pediatric ADHD: regulatory review, Adult ADHD: Phase III study US, Canada, EU: on the market (Shire)
Future plan in Japan	Pediatric ADHD indication approved Completion of adult Phase III study in FY2017

Profile: Lisdexamfetamine

Indication	ADHD (Attention-deficit/hyperactivity disorder)
Mechanism of action	To block the reuptake of norepinephrine and dopamine and increase their release
Product profile	Taken once-daily, S-877489 controls ADHD core symptoms significantly compared to placebo Comparable safety profile to CR methylphenidate One of the first line drugs in the US and Canada. Second-line drug for the uncontrolled patients by other drugs in the EU
Stage	Japan: Pediatric ADHD: Phase III long term study US, Canada, Brazil, EU and Israel: on the market (Shire)
Future plan in Japan	Pediatric ADHD indication NDA submission in FY2017

Lisdexamfetamine: Phase II/III Study in Japan (Efficacy)

LS mean change from baseline in ADHD-RS IV total score



	Baseline		Week4				
	Observed Value		Observed Value		Change from Baseline	vs Placebo	
	n	Mean (SD)	n	Mean (SD)	LS Mean (SE)	Difference of LS Mean [95% CI]	p-value
Placebo	19	37.95 (7.40)	19	34.68 (10.73)	-2.78 (2.25)		
30 mg	19	38.05 (6.74)	18	19.78 (9.74)	-16.38 (2.24)	-13.61 [-19.80, -7.42]	**<.0001**
50 mg	18	37.06 (6.94)	17	17.41 (9.04)	-18.10 (2.35)	-15.32 [-21.65, -9.00]	**<.0001**
70 mg	20	37.15 (7.80)	17	20.47 (13.15)	-16.47 (2.29)	-13.69 [-19.98, -7.40]	**<.0001**

Lisdexamfetamine: Phase II/III Study in Japan (Safety)

SONG for you!

TEAEs* occurring in 3 patients or more in any active dose group

TEAEs, n, (%)	Placebo N=19	30 mg N=19	50 mg N=18	70 mg N=20
Nasopharyngitis	4 (21.1)	2 (10.5)	4 (22.2)	1 (5.0)
Decreased appetite	0	9 (47.4)	14 (77.8)	11 (55.0)
Initial insomnia	0	2 (10.5)	5 (27.8)	5 (25.0)
Insomnia	0	0	3 (16.7)	1 (5.0)
Headache	0	2 (10.5)	7 (38.9)	1 (5.0)

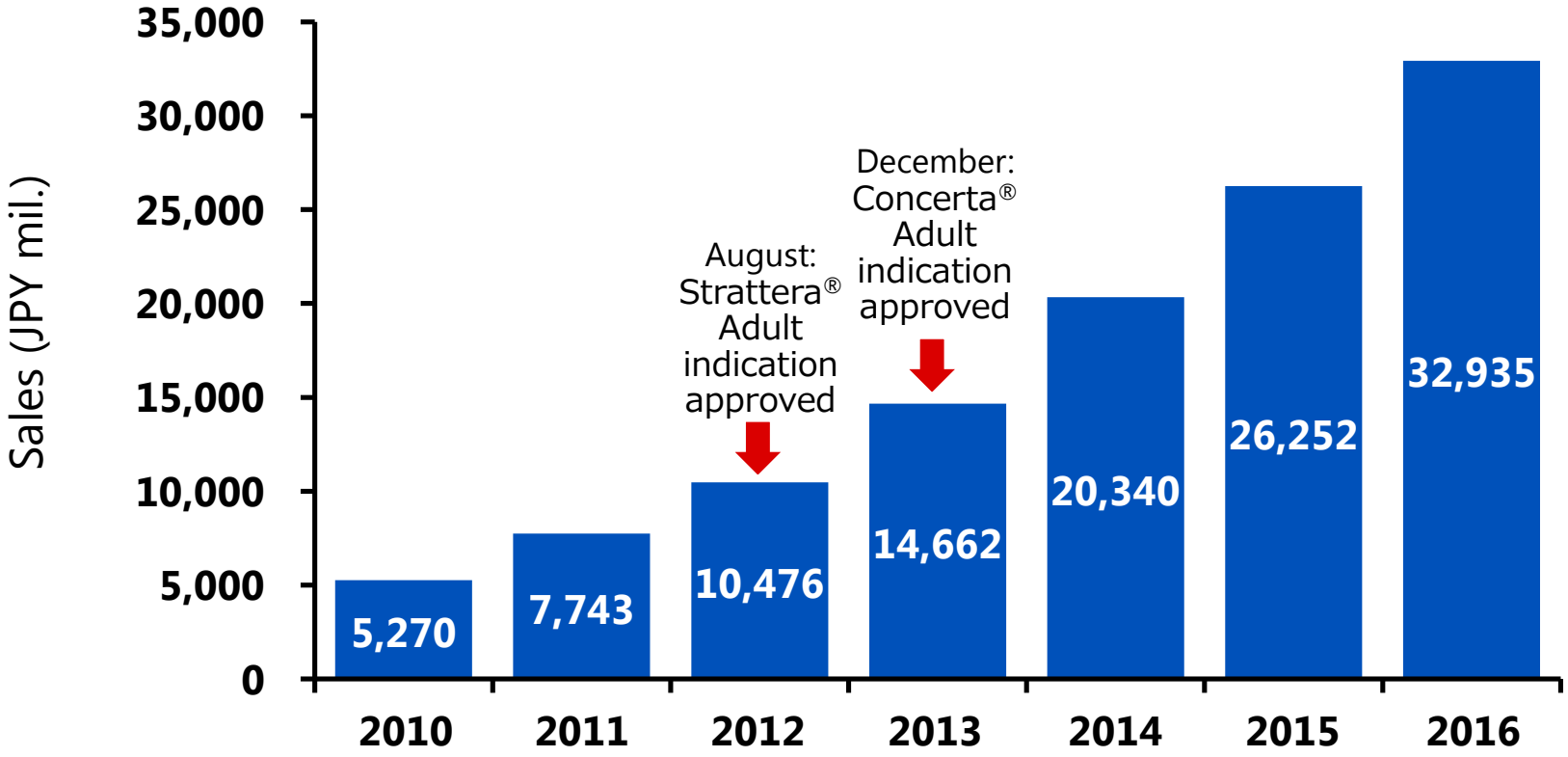
⇒ Most of the onset timing was during 30 mg treatment

Safety profiles are same as those abroad with no severe TEAEs, and only mild adverse events in most cases

* Treatment-emergent adverse events

ADHD Market in Japan

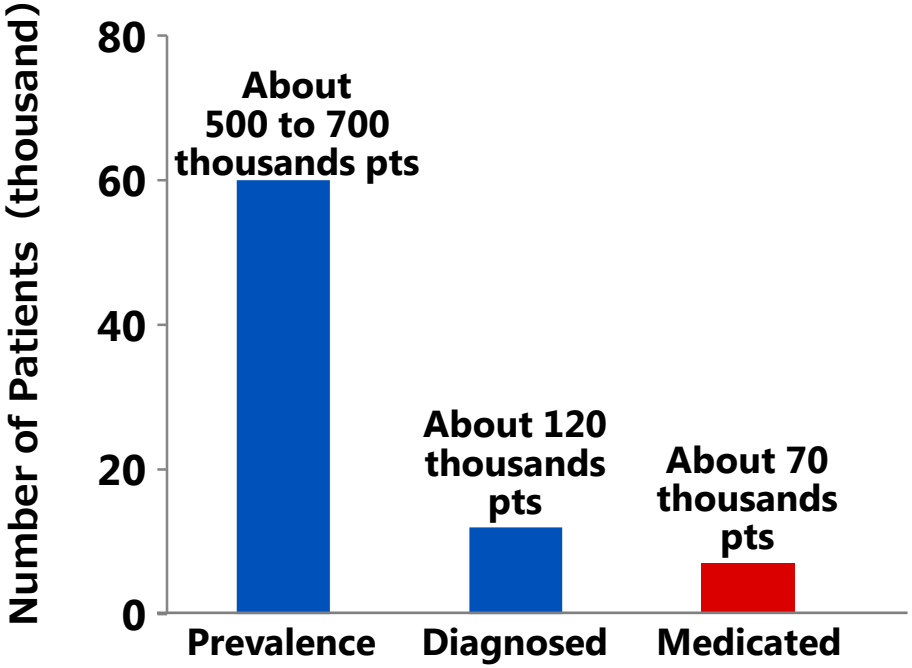
Sales are expanding 30% or more* annually



* $\left(\frac{Sales\ for\ fiscal\ n\ year}{Sales\ for\ fiscal\ 2010}\right)^{\frac{1}{n-1}} - 1$

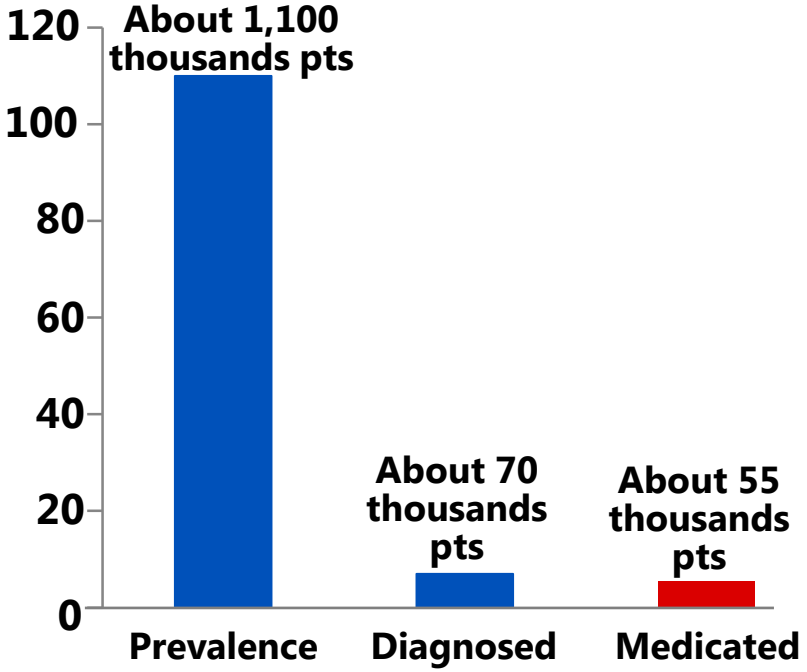
Current Situation of ADHD Treatment in Japan

Pediatric ADHD patients who had a medical examination



Reference:
- The survey carried out by MEXT, 2012
- Polanczyk G. et al., Am J Psychiatry; 164 (6): 942-8, 2007
- JAMMNET 2015

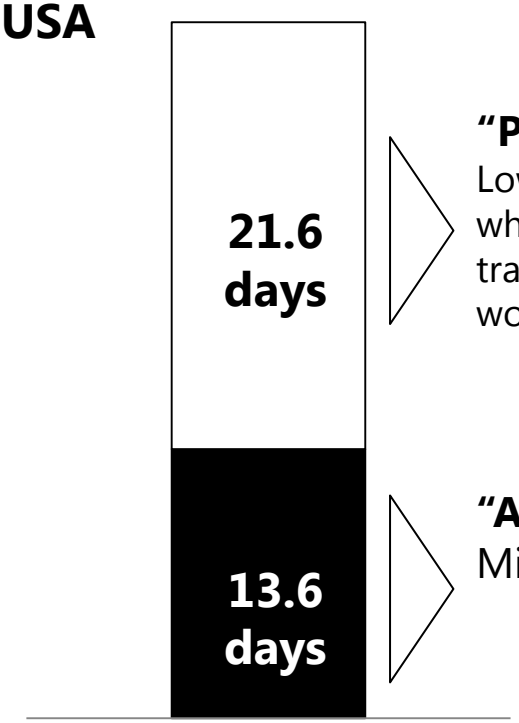
Adult ADHD patients who had a medical examination



Reference:
- Uchiyama et. al., The Journal of Child and Brain Development; 3(1): 34-42, 2012
- JAMMNET 2014

Contribution to Society through ADHD Patient Support

USA



"Presenteeism"
Low performance while at work transformed to lost work day equivalents

"Absenteeism"
Missed work days

Lost work performance[1)]

Estimated lost work performance is equivalent to about 35 lost days of work per worker with ADHD per year

Japan

GDP	**529 trillion Yen[2)]**
	×
Prevalence	**1.65%[3)]**
	×
Work loss	**35/250[4)]**

Untapped Resources

About 1.2 trillion Yen

(Estimated with US Data)

Shionogi intends to provide support to patients with developmental disorders, in various forms. More broadly, Shionogi aspires to support the goal of all individuals to achieve their maximum potential through our capability to develop new drugs that meet their medical needs

SHIONOGI

[1)] Kessler RC., JOEM. 2005; 47(6): 565-572, [2)] Nominal GDP of 2015 calendar year, Cabinet Office
[3)] Uchiyama et. al., The Journal of Child and Brain Development; 3(1): 34-42, 2012,
[4)] Estimate from General Survey on Working Conditions by MHLW 2015

S-237648
Obesity

Phase II Study in Japan

Mechanism of action	Neuropeptide Y Y5 receptor antagonist (Oral)
Subjects	Obese patients diagnosed with type 2 diabetes and hyperlipidemia, aged 20-64 years, body mass index (BMI) ≥ 25, visceral fat area ≥ 100 cm^2
Study design	Multicenter, randomized, double-blind, placebo-controlled trial N = 216 (54 subjects × 4 groups) 24 weeks on-drug treatment regimen of once-daily or once-weekly Dose setting from results of NPY Y5 receptor occupancy using PET
Summary	Safety: Extremely well tolerated at all doses with no clinically significant safety issues. The only reported adverse drug reaction was one incidence of nausea in a single subject. There were no other adverse effects related to cardiovascular or psychoneurotic systems, and no concerns about erythrocyte reductions or liver disorders, which were observed in studies of previous compounds Efficacy: Statistically significant reduction in body weight at all doses compared to the placebo group at Week 24 (primary endpoint), but not clinically meaningful (< 3 % of JASSO* benchmark for approval)
Future plan	Based on further analysis of study results, the future development plan, including injectable, formulation will be reconsidered

* JASSO: Japan Society for the Study of Obesity

Agenda: Global Development Division

- **To Achieve SGS2020**
  - Development Targets for FY2020
  - Current Status and Actions
- **Achievements in FY2016**
  - Pipeline
  - Core Development Products
    - > S-033188
    - > Cefiderocol
    - > Guanfacine, Lisdexamfetamine
    - > S-237648
- **Targeted Milestones for FY2017**
  - Pipeline

Targeted Milestones for FY2017

Efficient and Consistent Development

For consistently bring our new products to the global market

- **Global operations framework**
  - Review of implementation and management system for global studies at the portfolio level and at various clinical trial phases
  - Efficient study management through use of new IT systems
- **Cost management**
  - Endure realistic and predictable cost projections by thoroughly checking the feasibility of each clinical trial
- **Utilization of investigator-initiated clinical research**

Approvals: 2

NDA submissions: 5 (6 indications)

Target Milestones for FY2017: Approvals and NDA Submissions

Product (indication)	Phase I	Phase II	Phase III	NDA submission	Approval
Oxycodone (Treatment of moderate to severe chronic pain*/Abuse-deterrent tablets)				Japan (Nov. 2016)	Japan
Actair® (Pediatric allergic rhinitis caused by house-dust mite allergen)				Japan (Mar. 2017)	Japan
Lusutrombopag (Thrombocytopenia)			Global**	US/EU	
S-033188 (Influenza virus infection)			Global	Japan	
S-033188 (Influenza virus infection (pediatric))			Japan	Japan	
Cefiderocol (Multidrug-resistant Gram-negative bacteria infection)			Global: ongoing	US	
Lisdexamfetamine (Pediatric ADHD)			Japan	Japan	
Osphena® (Vaginal dryness associated with postmenopausal VVA)			US	US	

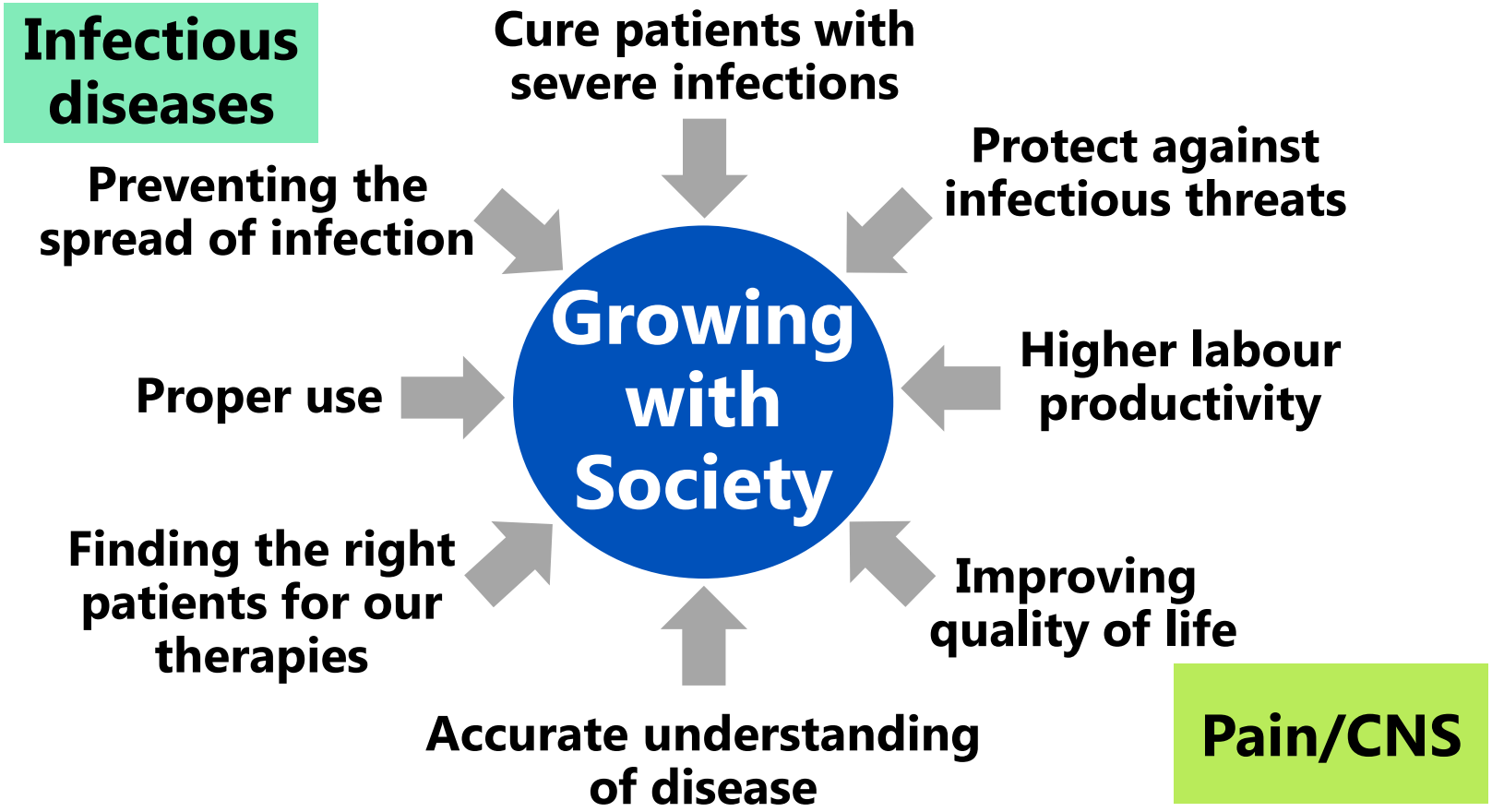
* Development for expansion of indications ** Designated Fast Track in the US (Mar. 2017)

Target Milestones for FY2017: Phase I - III Study

Product (indication)	Phase I	Phase II	Phase III	NDA submission	Approval
S-120083 (Inflammatory pain)		US: ongoing			
S-600918 (Neuropathic pain)	Japan: completion	Initiation (regions to be determined)			
S-588410 (Bladder cancer)		Japan/EU: ongoing			
S-222611 (Malignant tumor)	EU: ongoing				
S-588410 (Esophageal cancer)			Japan: ongoing		
Guanfacine (Adult ADHD)			Japan: completion		

Progress Toward SGS2020

Showing Shionogi's contribution to society by consistently bringing our products to the global market



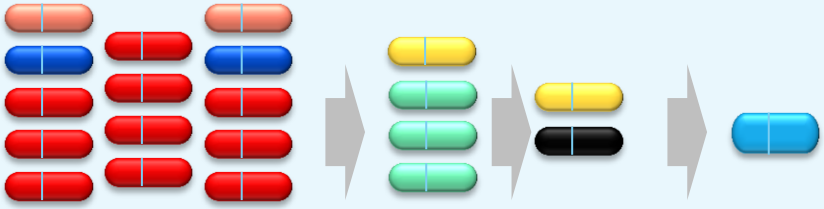
Summary

Isao Teshirogi, Ph.D.
President and CEO

Therapeutic Strategy for HIV

1996	2000	2010	2020
Deadly illness	Treatable disease	Restore and maintain their health	

ART



Three HIV medicines from at least two different drug classes

Improve dosage and administration by improving therapeutic agents

STR

2-drug treatment regimens
2-drug regimens

1-drug treatment

cure

Unmet patient needs

- Same quality of life as uninfected individuals
- Prevention
- Cure

HIV Discovery at Shionogi

Created Tivicay® (DTG)

STRT Triumeq® (DTG/ABC/3TC)

Created long-acting injectable Cabotegravir (CAB) Phase III study

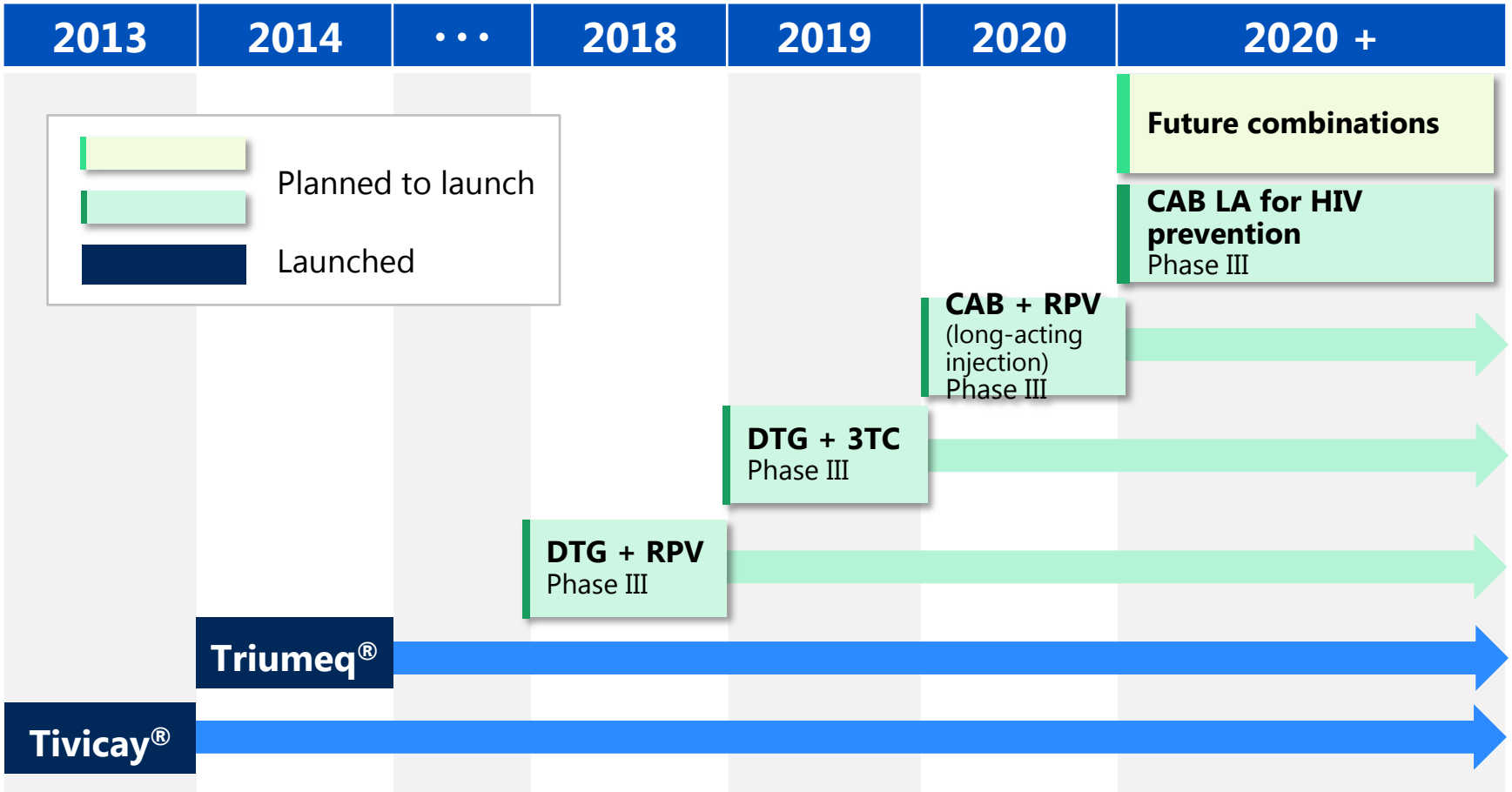
Drug discovery strategy to advance HIV Therapy

- Create compounds for STR with DTG
- Create compounds suited for injectable combination therapy
- Establish our agents in prevention

SHIONOGI

STR: Single tablet regimen
DTG: Dolutegravir ABC: Abacavir 3TC: Lamivudine

HIV Integrase Inhibitor Franchise



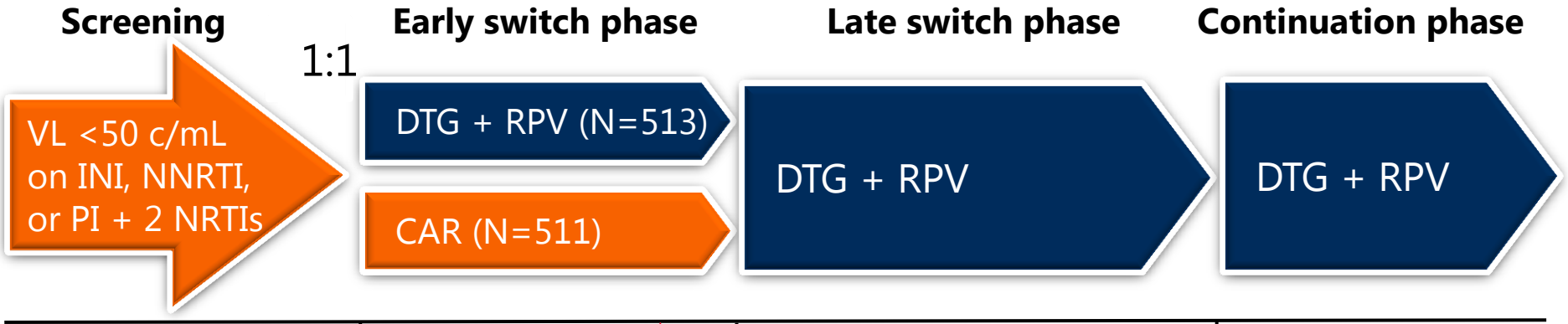
ViiV's strategy to develop new treatment regimens to address the needs of people living with HIV places our HIV integrase inhibitors at the core of therapy

RPV: Rilpivirine

SWORD-1 and SWORD-2 Phase III Study Design

The SWORD-1&2 studies evaluated whether a 2DR of DTG + RPV once daily was as effective as a 3- or 4DR for the maintenance of virologic suppression

Identically designed, randomized, multicenter, open-label, parallel-group, non-inferiority studies



Inclusion criteria
- On stable CAR ≥6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA < 50 c/mL during the 12 months before screening
- HBV negative

Primary endpoint at 48 weeks: subjects with VL <50 c/mL (ITT-E snapshot)[a]

Countries
Argentina, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Russia, Spain, Taiwan, United Kingdom, United States

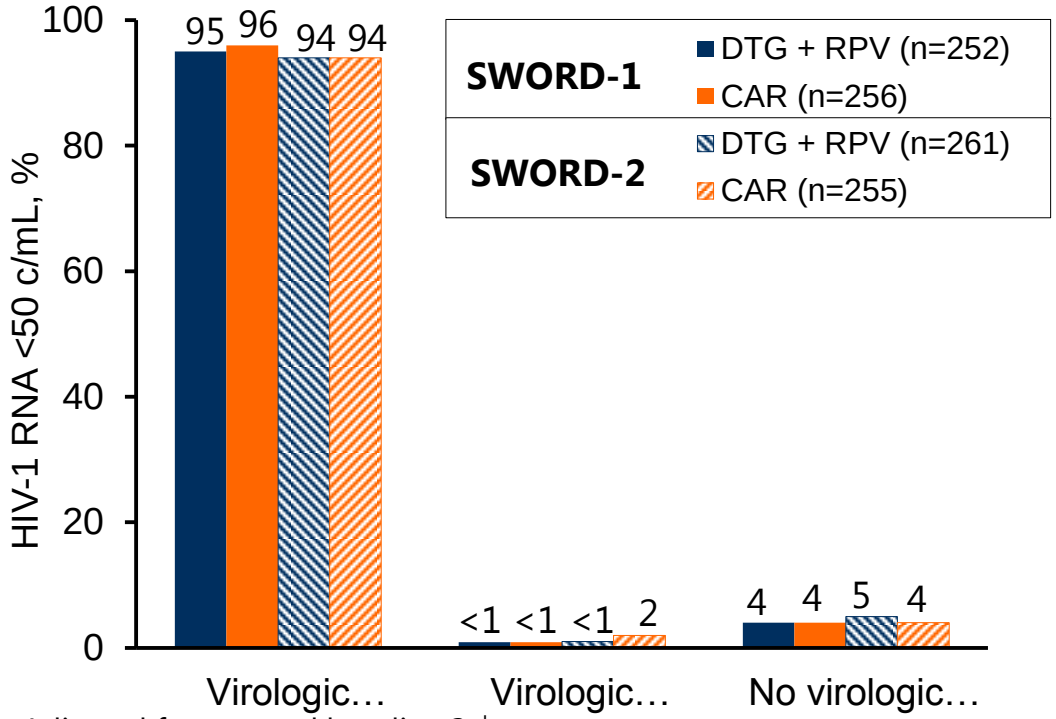
[a]-8% non-inferiority margin for pooled data. -10% non-inferiority margin for individual studies

NRTI: Nucleoside analogue reverse transcriptase inhibitor NNRTI: Non-nucleoside reverse transcriptase inhibitor
INI: Integrase inhibitor PI: Protease inhibitor CAR: Current antiretroviral regimen DTG: Dolutegravir
CAB: Cabotegravir ABC: Abacavir 3TC: Lamivudine

Presented at CROI 2017; Seattle, WA. Abstract 2421

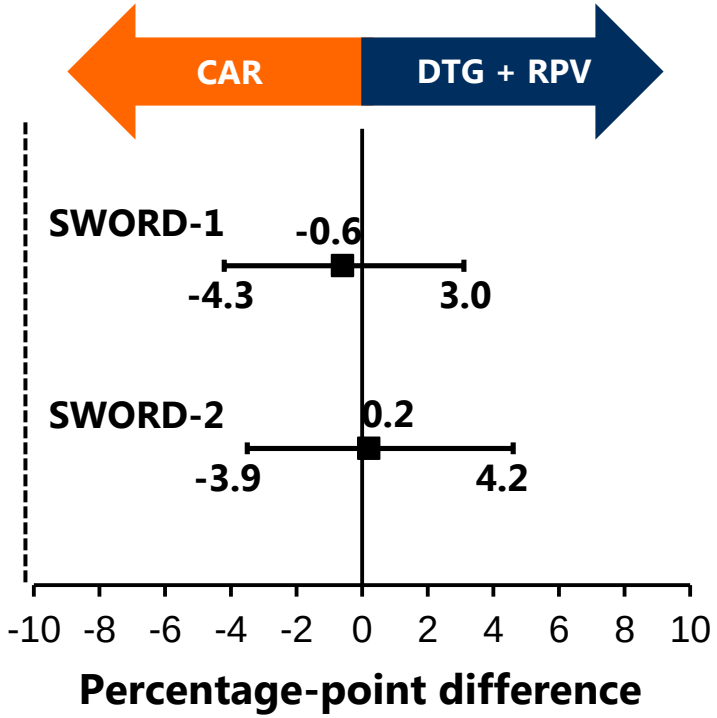
Snapshot Outcomes at Week 48 (SWORD-1&2)

Virologic outcomes



[a] Adjusted for age and baseline 3rd agent

Adjusted treatment differences (95% CI)[a]



- **A switch to a novel, once-daily 2DR of DTG + RPV demonstrated high efficacy and was non-inferior to the continuation of a 3- or 4DR in virologically suppressed HIV-1–infected adults**
  - The safety profiles of both DTG and RPV were consistent with their respective labels
  - Switching to DTG+RPV had a neutral effect on lipids, while significantly improving bone turnover biomarkers
  - These data support the use of DTG+RPV as a 2DR for streamlining therapy for maintenance of suppression

Pipeline (as of Mar. 2017)

SONG for you!

Preclinical	Phase I	Phase II	Phase III	NDA submission
Global		**Cefiderocol** Multidrug-resistant Gram-negative bacterial infections	**S-033188** Influenza virus infection	**Naldemedine** Opioid-induced constipation
		S-120083 Inflammatory pain	**Cefiderocol** Multidrug-resistant Gram-negative bacterial infections	
Antibody drug candidate against pseudomonas	**S-117957** Insomnia	**S-707106** Type2 diabetes	**Lusutrombopag** Thrombocytopenia	
Central neuropathic pain	**S-237648** Obesity	**S-488210** Head and neck squamous cell carcinoma	**Osphena®** Vaginal dryness associated with postmenopausal VVA	
Obesity		**S-222611** Malignant tumor		
LCM inhalation		**S-588410** Bladder cancer		
In Japan		**Cefiderocol** Multidrug-resistant Gram-negative bacterial infections	**S-033188** Influenza virus infection	**Naldemedine** Opioid-induced constipation
		S-237648 Obesity	**S-033188** Influenza virus Infection (pediatric)	**Guanfacine** ADHD (pediatric)
	S-010887 Neuropathic pain	**S-525606** Allergic rhinitis caused by Japanese cedar allergen	**Cefiderocol** Multidrug-resistant Gram-negative bacterial infections	**Oxycodone** Moderate to severe chronic pain
	S-600918 Neuropathic pain	**S-588410** Bladder cancer	**Lisdexamfetamine** ADHD (pediatric)	**Oxycodone** Tamper resistant formulation
			Guanfacine ADHD (adult)	**Actair®** Pediatric patients with perennial allergic rhinitis
			S-588410 Esophageal cancer	
Out-licensed	**GSK3342830** Multidrug-resistant Gram-negative bacterial infections		**DTG+RPV** Treatment for HIV infection	
			DTG+3TC Treatment for HIV infection	
Janssen/Shionogi Project compound Alzheimer's disease			**CAB LAP** Prevention for HIV infection	
			CAB + RPV LAP Treatment for HIV infection	
			Janssen/Shionogi BACE inhibitor Alzheimer's disease	

Infectious diseases

Pain/CNS

Metabolic disorder

Frontier

Target Milestones for Launch of New Products

FY2016 (results)	FY2017	FY2018	FY2019
Japanese business			
Crestor® OD tablet **Cymbalta®** Pain associated with chronic low back pain Pain associated with osteoarthritis **ISODINE® brand ethical products**	**Naldemedine** **Guanfacine** ADHD (adult) **Oxycodone** Tamper resistant formulation Moderate to severe chronic pain **Actair®** Pediatric patients with perennial allergic rhinitis	**S-033188** **Lisdexamfetamine**	**Guanfacine** ADHD (adult)
Global business			
	Naldemedine	**Cefiderocol** **Osphena®** Vaginal dryness associated with postmenopausal VVA **Lusutrombopag** **Naldemedine** (EU)	
Global out-licensed products			
		DTG + RPV	**DTG + 3TC**

Q&A

Forward-Looking Statements

- Forecast or target figures in this material are neither official forecasts of earnings and dividends nor guarantee of target, achievement and forecasts, but present the midterm strategies, goals and visions. Official earnings guidance should be referred to in the disclosure of the annual financial report (*kessan tanshin*) in accordance with the rules set by Tokyo Stock Exchange.
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