Research and Development at Shionogi

March 22, 2012

SHIONOGI & CO., LTD.

Agenda

1. **Research: Kohji Hanasaki, Ph.D.**

   Executive General Manager, Pharmaceutical Research Division

2. **Development: Takuko Sawada**

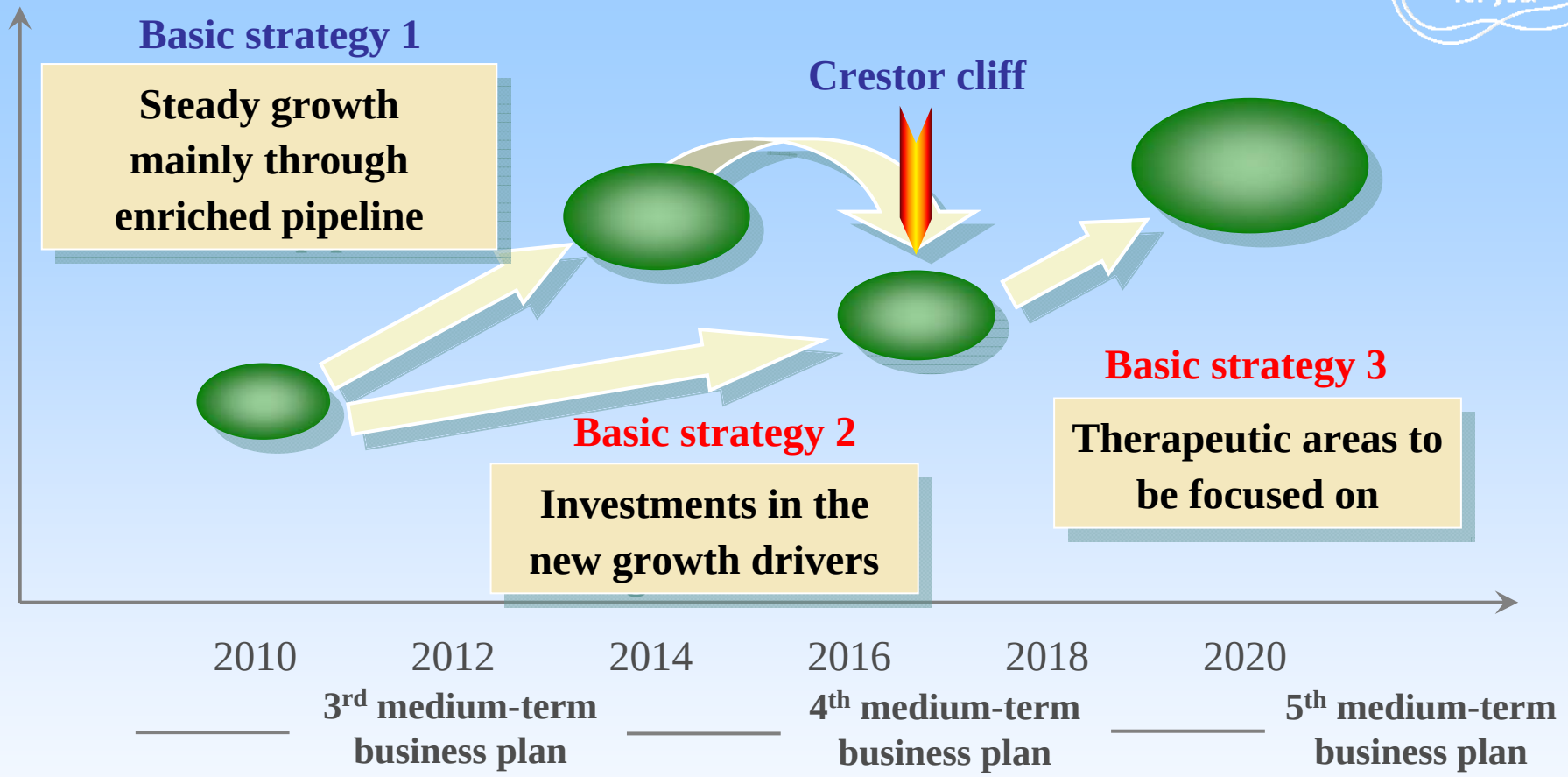
   Executive General Manager, Global Development

3. **Summary: Isao Teshirogi, Ph.D.**

   President and Chief Executive Officer

4. **Q&A**

Basic Strategy in the 3rd Medium-Term Business Plan



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

Global Strategy for the Mid to Long Term Growth

Goal in FY2020 Net sales: 600 B yen, Overseas net sales ratio: More than 50%

- **Establish footholds in EU, US and Asia for global development of new drugs**

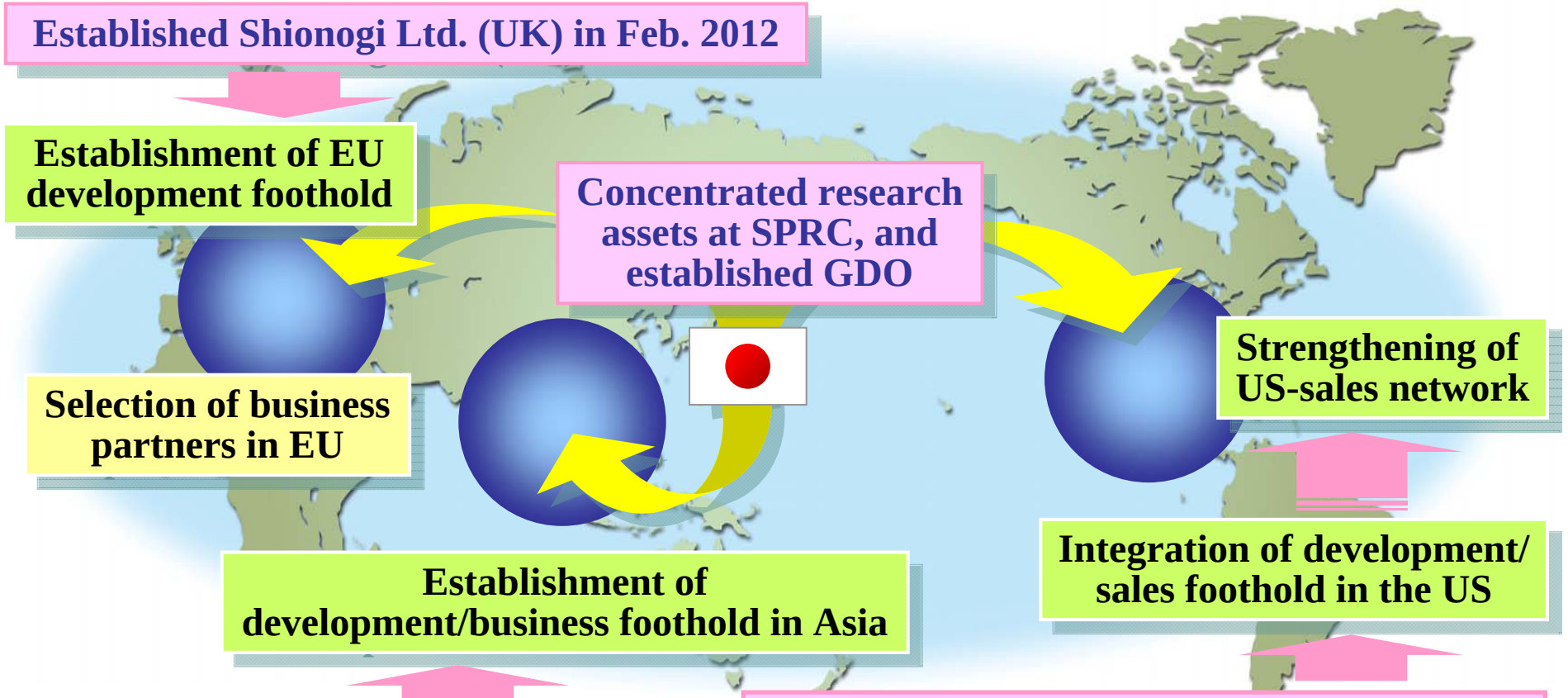
Established Shionogi Ltd. (UK) in Feb. 2012

Establishment of EU development foothold

Concentrated research assets at SPRC, and established GDO

Selection of business partners in EU

Strengthening of US-sales network



Establishment of development/business foothold in Asia

Integration of development/ sales foothold in the US

Acquired C&O Pharmaceutical Technology in Oct. 2011

Restarted Shionogi Inc. with new leadership (CEO and COO) from Apr. 2011

GDO: Global Development Office

Research

Kohji Hanasaki, Ph.D.

Executive General Manager
Pharmaceutical Research Division

Mission of the Research Division

2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020

Company

Growth at home and abroad

Crestor cliff

Sustainable growth path

Mission of the Research Division

Launch Global Products and Maximize Value of In-line Products

Research that supports development and sales

- **Submission of applications, differentiation, LCM**

Sources of Future Growth

4 or more DCSs per year with high potential for success

- **Improve clinical-stage predictions**
- **Improve productivity by enhancing early stage research and SPRC**

Sustainable DCSs

Acquire research assets that will bear fruit in the future

DCS: Drug candidate selection

Goals for the 3rd Medium-Term Business Plan

Our Goal: World Top-Level Research Productivity

- **Create NMEs with success rate of 50% or more in POC study***
- **Select 4 or more NMEs for DCS per year**
  (Aim to establish a system to realize 5 or more DCS in 2015)

Enhancement of early phase research-portfolio

Improvement of predictive performance for clinical efficacy

Centralization of functions and strengthening of flexibility

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

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

"Highly efficient low molecular SAR-engine"

NME: New molecular entity, POC: Proof of Concept, SAR: Structure-activity relationship
* Success rate in POC study: percentage of developing compounds with POC in ones in Phase IIa or POC studies

Concentrating Functions and Enhancing Flexibility to Improve Research Outcomes

- Hokkaido University
- *Shionogi Innovation Center*
- Academia
- External research institutes

SPRC2 Pharmacology

SPRC4
Drug Discovery, Chemistry
Pharmacology, Drug formulation

SPRC1 Toxicology
SPRC3 Drug metabolism and Pharmacokinetics

Speedy and Close Research Cycle

- Osaka University
- *PET Molecular Imaging Center*
- Pharmaceutical companies
- Bio-ventures

Toward Top Class Global Research Productivity

The Scope of Discovery Research of Shionogi

S-O-N-G for you!

Metabolic syndrome

Infectious diseases

Pain

- **Medicines enable to save lives**
- **Medicines enable to improve quality of life**
- **Medicines thoroughly fight against disease (eradicative medicine)**

Next generation waves of medicinal research

Shionogi's purpose:

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

Achievement in FY2011

- **Continuous creation of compounds for Phase I and DCS**

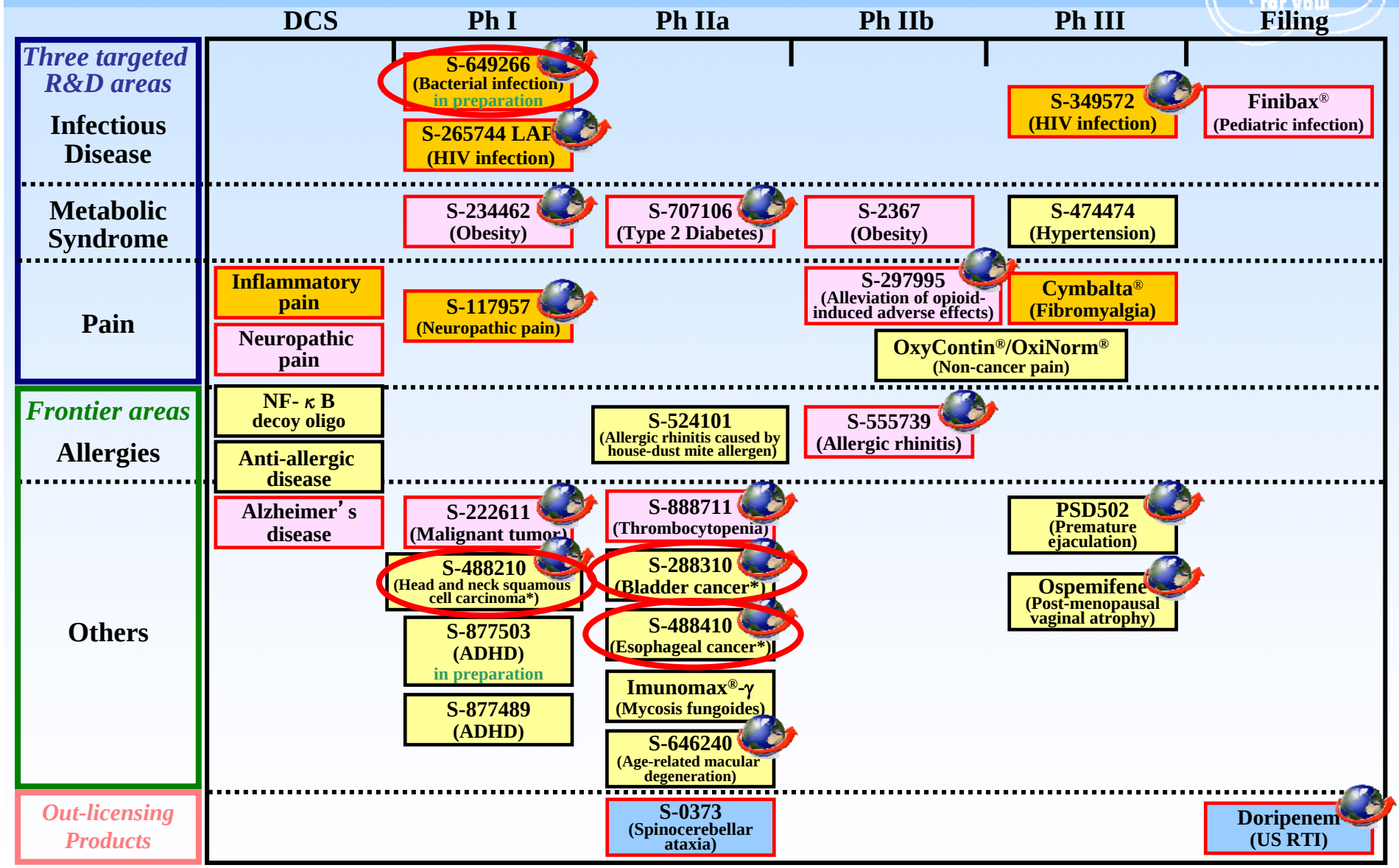
Selected 4 compounds for DCS

- Anti-allergic disease drug
- Anti-skin disorders drug (NF-κB decoy oligo)
- Anti-pain drug
- Final evaluation of anti-obesity drug

Advanced 3 compounds to clinical development

- Anti-neuropathic pain drug: S-117957
- Cancer peptide vaccine: S-488210
- Anti-severe infectious disease drug (Gram-negative): S-649266

Research Development Pipeline Enrichment (as of March 2012)



LAP: Long-acting parenteral formulation, RTI: Respiratory tract infection, ADHD: Attention deficit/ hyperactivity disorder, DCS: Drug candidate selection, * Cancer peptide vaccine

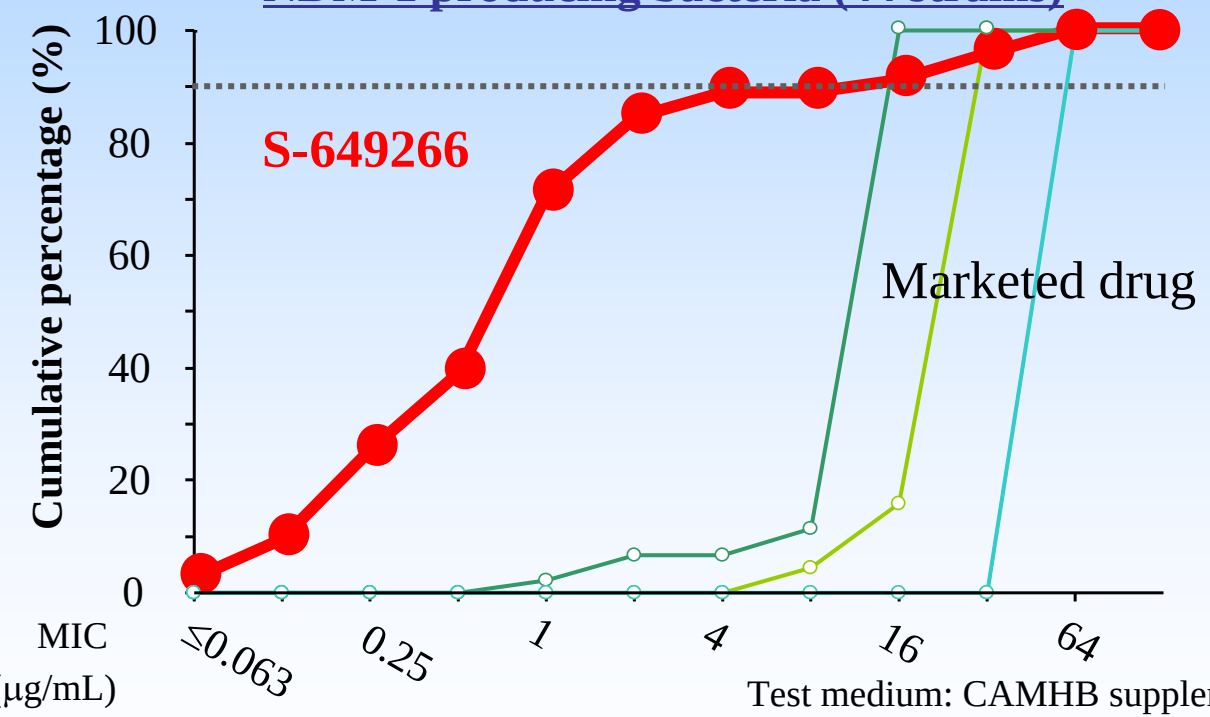
Developing products globally

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

Medicines Enable to Save Lives

- **Injectable cephem antibiotic drug: S-649266**
  (Collaboration with GSK, Phase I in preparation in Japan)
  - **S-649266 has the strongest anti-bacterial activity against New Delhi metallo-β-lactamase-1 (NDM-1) producing bacteria, which have developed resistance to many carbapenem and cephem antibiotics.**

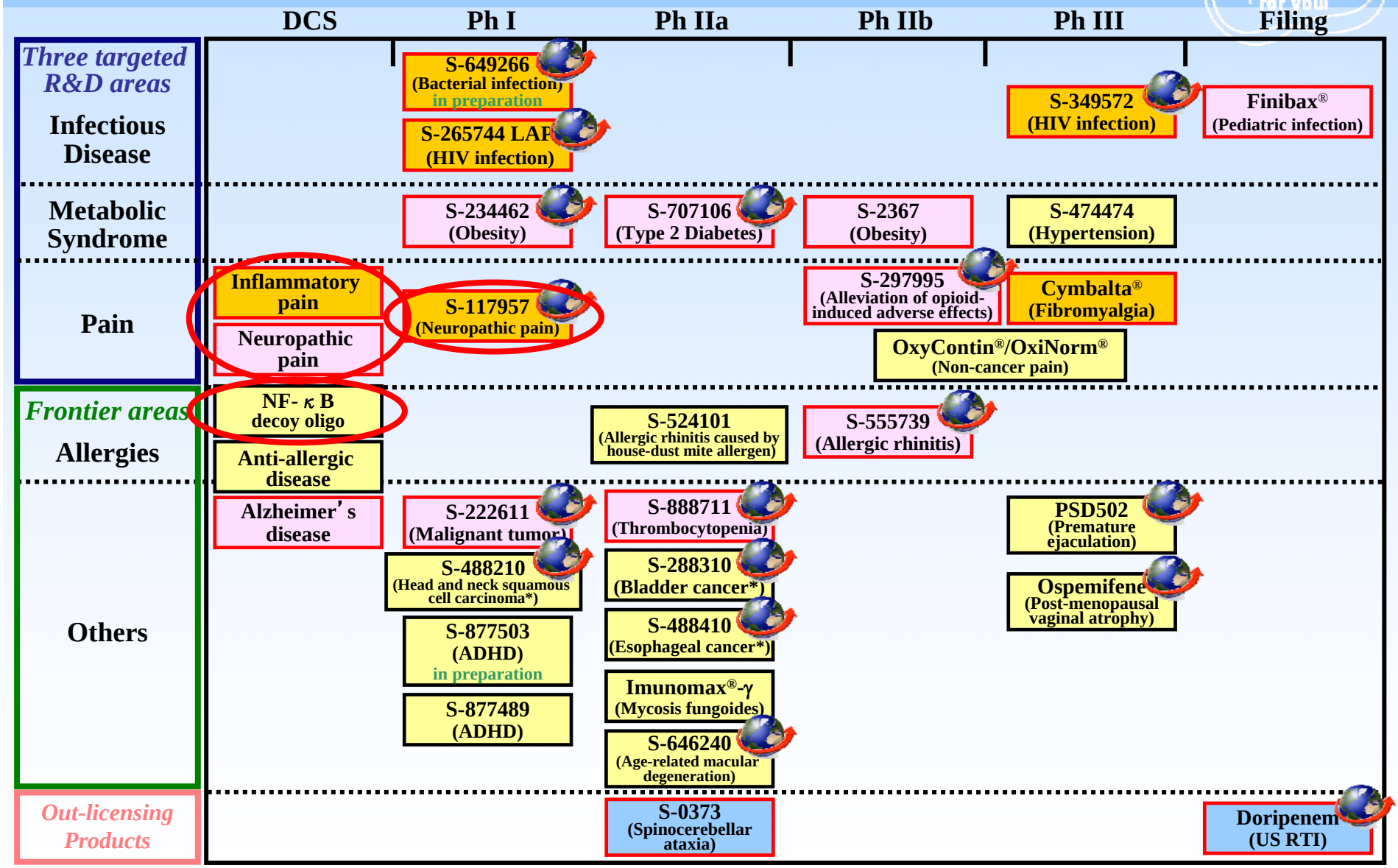
NDM-1 producing bacteria (44 strains)



Test medium: CAMHB supplemented with apo-transferrin

Provide drugs to rescue many patients suffering from multidrug-resistant bacterial infections

Research Development Pipeline Enrichment (as of March 2012)



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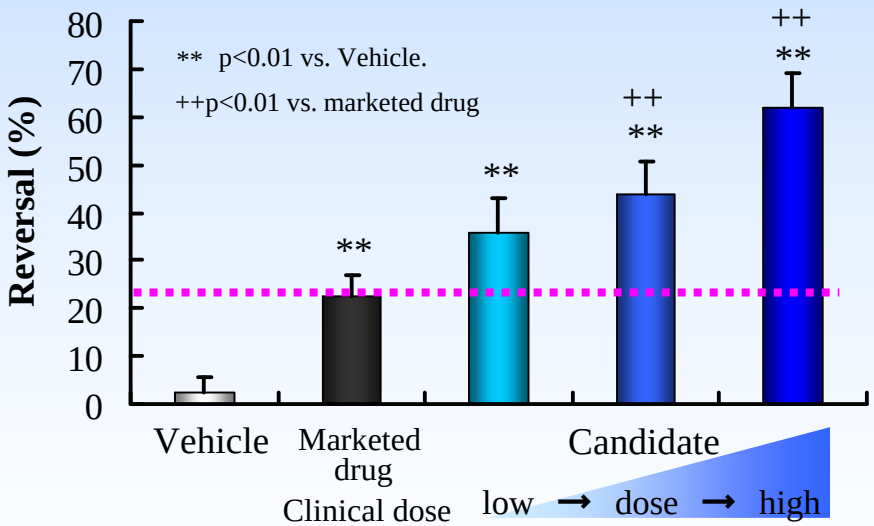
Medicines Enable to Improve Quality of Life

- **Creation of drug candidates against pain**
  - **Created two drug candidates against chronic pain, which have different mechanisms, to beat neuropathic pain and inflammatory pain**

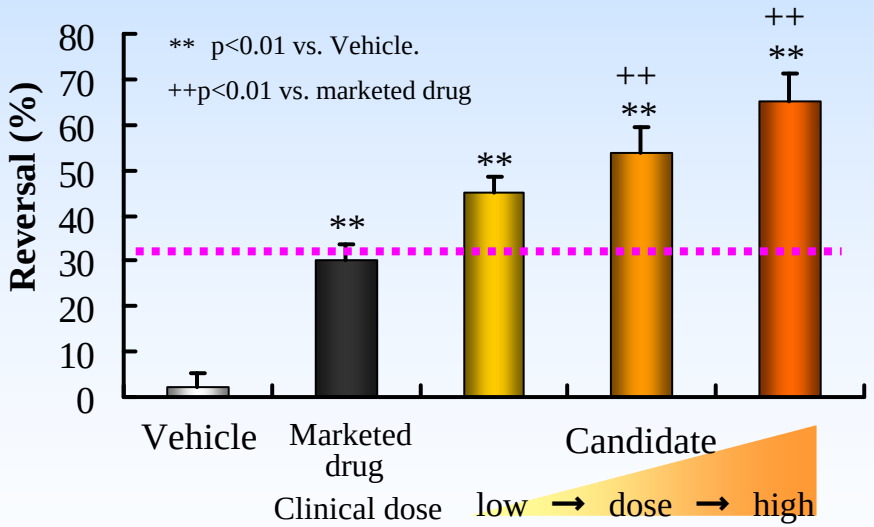
Drug candidate for neuropathic pain

Antihyperalgesic effect in neuropathic pain model



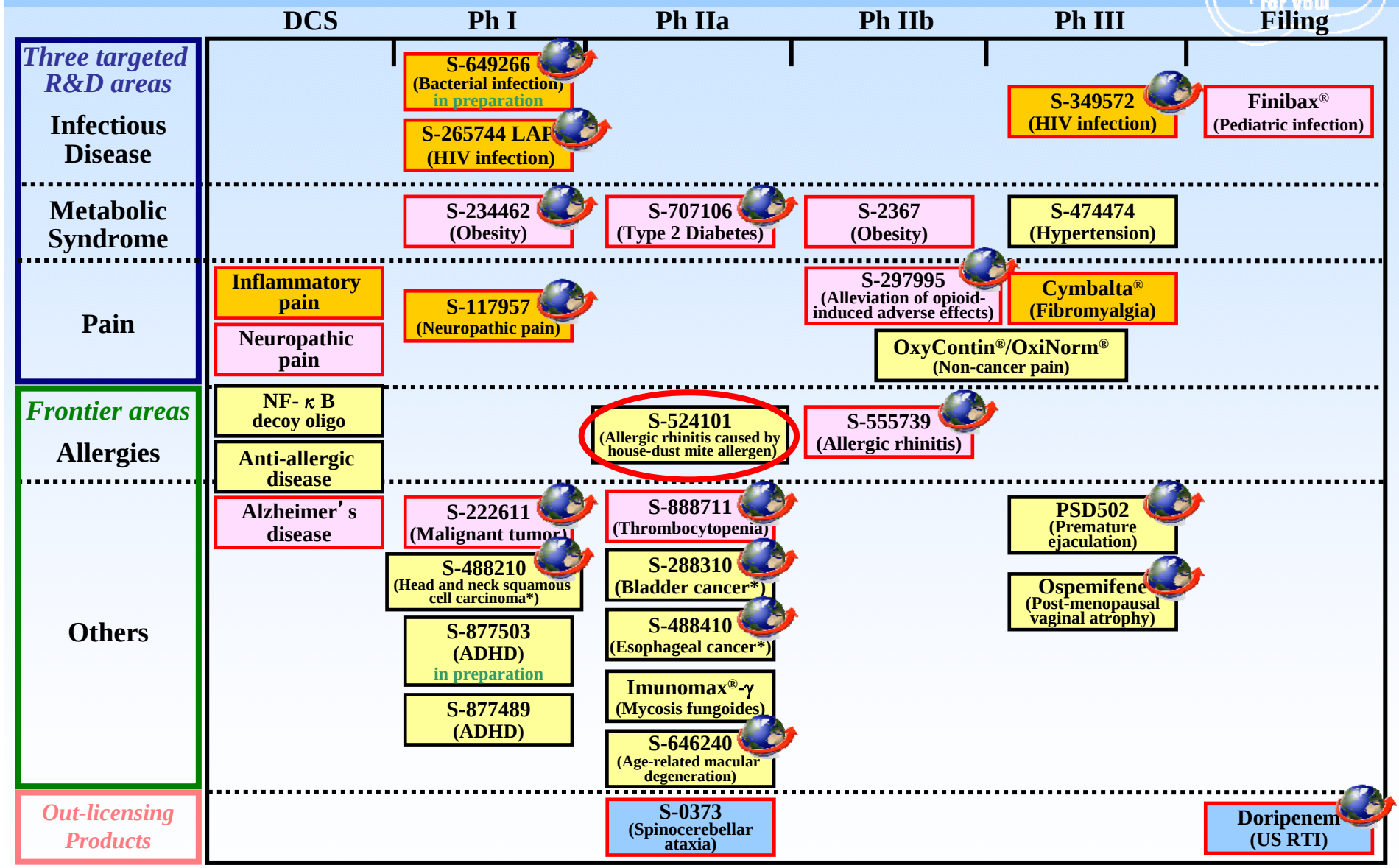
Drug candidate for inflammatory pain

Analgesic effect in osteoarthritis pain model



Toward the realization of "pain free" for patients around the world

Research Development Pipeline Enrichment (as of March 2012)



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Medicines Thoroughly Fight Against Disease

- **Allergic diseases: Allergen-specific sublingual immunotherapy**
  - **Allergen-specific immunotherapies**
    - **Weaken body's immune response by repeating causative allergen administration**
    - **Result in long-term remission and lead to permanent cure**
    - **Traditional subcutaneous immunotherapies**
      - ✓ **Duration of treatment: about 3 years, require hospital visit every 2 to 4 weeks**
      - ✓ **Rarely develop serious adverse effects, anaphylaxis**
    - **Sublingual immunotherapies (SLIT)**
      - ✓ **Significantly reduce systemic adverse effects**
      - ✓ **Possible to take drugs at home**
  - **Cooperative research and development agreement with Stallergenes**
    - **A leading company specialized in allergen-specific immunotherapy**
    - **Has know-how and experience in allergen extraction, formulation, development, and sales**
    - **Contracts for collaborative development of house dust mite allergen SLIT agents in Japan and collaborative research and development of Japanese Cedar allergen SLIT agents in Japan**

Provide a paradigm shift to "permanent cure" in allergic disease therapy

Research

Point of Reinforcement: Strengthening Drug Discovery Portfolio for Continuous Output and Acceleration of External Collaboration to Continuously Improve Outcomes

FINDS: PHarma-Innovation Discovery competition Shionogi)

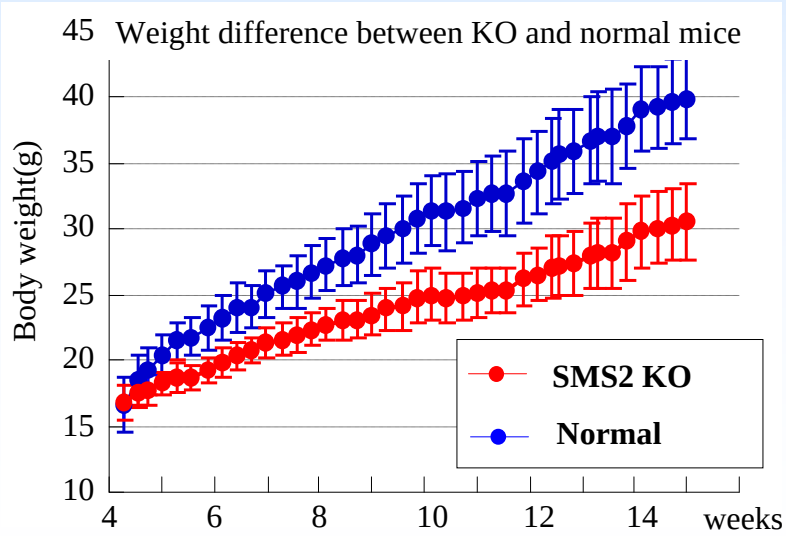
- **Open innovation by industry-academia: Academic researchers have submitted seeds and ideas for drug discovery needs as called for by Shionogi, and work together in commercialization.**
- **Recruiting started in FY2007, and 19 collaborative studies have started from 140-250 submissions/year.**
- **Experience in developing drug discovery programs** **http://www.shionogi.co.jp/finds/index.html**

- **Started overseas operations for academia in UK: SHIONOGI Science Program**

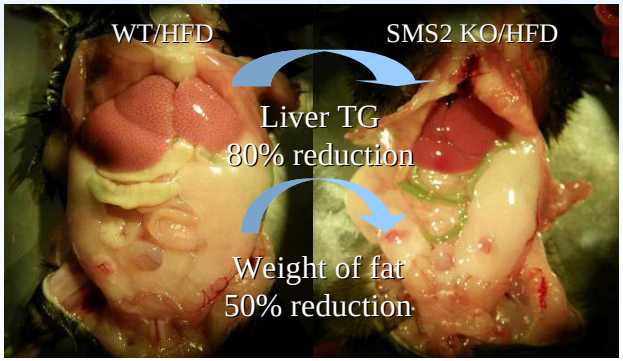
Continuous exploration of original seeds through fundamental research collaboration

Point of Reinforcement: Strengthening Drug Discovery Portfolio for Continuous Output and Acceleration of External Collaboration to Continuously Improve Outcomes

- **Shionogi Innovation Center**
  - **Industry-academia collaboration research center was established in Hokkaido University in May 2008**
  - **Participating in "The Matching Program for Innovations in Future Drug Discovery and Medical Care" (2006-2016)**
  - **Cultivating drug discovery seeds in Hokkaido University and development of human resources of great originality**
- **Starting a new program of antibiotic drugs, based on new uniquely-found site of action.**
- **Discovery of original target for obesity, Sphingomyelin Synthase 2 (SMS2)**
  - **Patent application and publication in collaboration with Hokkaido University** J. Biol. Chem. 286, 28544-28555 (2011)

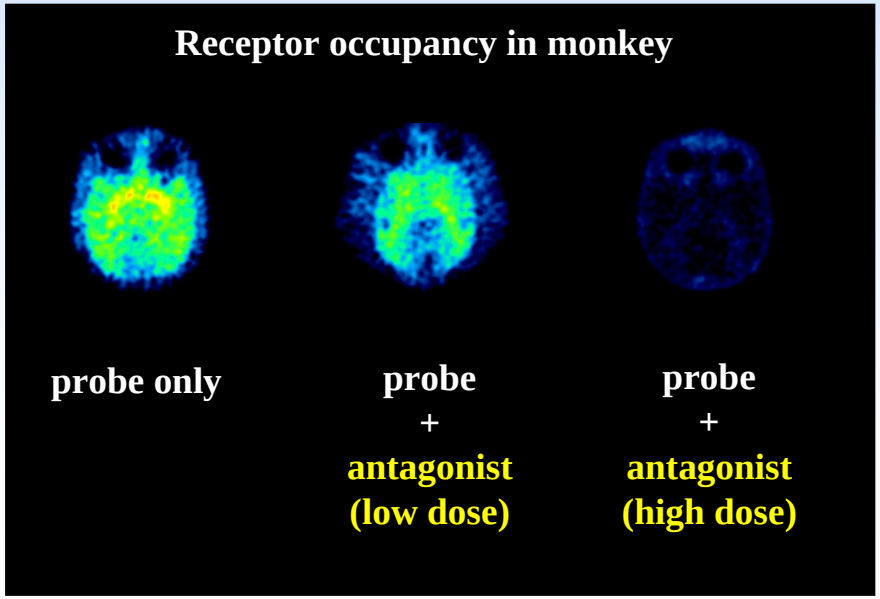


Difference between KO and normal mice under High Fat Diet (HFD) condition



Point of Reinforcement: Improvement of Clinical-Stage Predictions

- **Creating a new PET imaging probe for evaluation of development products**
  - **Developed a new probe candidate for the target receptor**
  - **Established a method of synthesis of positron PET probe at Osaka University PET molecular imaging center**
  - **Conducted PET imaging analysis in rodents, and confirmed the correlation between efficacy and receptor occupancy in disease model animals**
  - **Conducted PET imaging analysis in monkeys, and confirmed specific binding to the target receptor**



Constructing a framework to conduct a microdosing clinical study of the new PET probe at Osaka University hospital

Targets and Measures for FY2012

- **Promote research to maximize value of existing products and development products**
  - **Support research for LCM of existing products**
  - **Promote new drug applications and differentiation studies**
- **Again turn out 4 or more DCSs over the course of the year**
  - **Prioritize core programs in Shionogi's therapeutic areas of focus**
  - **Expand external research collaboration and fulfillment of creative drug discovery programs**
  - **Accelerate development of large molecule drugs and develop new core therapeutic area studies for the future**
- **Establish drug discovery technologies to improve clinical POC ratio**
  - **Drug technologies that close the gap between clinical and non-clinical**
    - **Utilize imaging technology, at Osaka University PET molecular imaging center, in clinical and non-clinical fields and build the implementation system of Exploratory IND Studies**
    - **Strengthen safety and efficacy evaluation system that benefits from clinical results feedback**

Development

Takuko Sawada

Executive General Manager
Global Development

Agenda

- **Development Division Actions under the 3rd Medium-Term Business Plan**
- **Achievements in FY2011**
- **Target Milestones for FY2012**
- **Core Development Products**

Goals under the 3rd Medium-Term Business Plan

Speed Up Global Clinical Development

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

- **Enhance Strategic Decision-Making Function**
- **Establish Development Footholds Worldwide**

Our Current Actions

- **Build global R&D systems**
  - **Unify development function in the US: completed**
  - **Establish a Global Development Office: completed**
  - **Establish development foothold in the EU: completed (London, UK)**
  - **Establish development foothold in China: acquisition of C&O**
- **The Front-line global compounds**
  - **Submit overseas NDA by the end of FY2012**
    S-349572, Ospemifene
  - **Initiate Phase IIb by the end of FY2012**
    S-297995, S-555739, S-888711, Cancer peptide vaccines

Our Future Actions

- **Expansion of GDO function and promotion of clinical development for global compounds**
  - **Cultivation of human resources with global standpoint and expansion of personnel recruitment in each host country**
  - **Enhancement of research function of epidemiology and marketability**
  - **Management of portfolio of global compounds**
- **Development foothold in the EU**
  - **Established in the UK in February 2012**
  - **Efficient and speedy clinical development by selection of appropriate region for each stage**
- **Expansion of activities in Asia**
  - **Application of development strategies in Japan to other areas of Asia**
  - **Expansion of R&D activities for global compounds or others in China**

Maximization of the Value of High-Priority Compounds

- **Lifecycle management of HIV integrase inhibitors**
  - **Development of oral FDC in parallel with monotherapy**
  - **Development of injectable long-acting parenteral formulation**
- **Lifecycle management of Cymbalta®**
  - **Additional indication for diabetic peripheral neuropathic pain: approved**
  - **Additional indication for Fibromyalgia: Phase III initiated**
- **Lifecycle management of Irbetan®**
  - **New dosage form of irbesartan 200mg tablet*: NDA filling in 1Q FY2012**
  - **Development of FDC with Fluitran®: NDA filing in 2Q FY2012**
- **Lifecycle management of doripenem**
  - **Addition of high dosage regimen: approved**
  - **Additional indication for pediatric infection: NDA filed**
- **Buildup of oxicodone pipeline**
  - **Line-up of OxyContin®, OxiNorm®, and OxiFast®**
  - **Additional indication for non-cancer pain: initiated**

*** Co-developed with Dainippon Sumitomo Pharma**
FDC: Fixed dose combination

Achievements in FY2011: Approval and NDA Filing

Approval	
FINIBAX®	**Approved in April 2011 (Japan)** **Addition of new dosage regimen for infection**
OxiFast®	**Approved in January 2012 (Japan)** **For the treatment of moderate to severe pain in patients with cancer pain**
Cymbalta®	**Approved in February 2012 (Japan)** **Additional indication for diabetic peripheral neuropathic pain**
NDA filing	
FINIBAX®	**NDA filed in August 2011 (Japan)** **Additional indication for pediatric infection**
Ospemifene	**BE confirmed, NDA in preparation (US)** **Post-menopausal vaginal atrophy**

BE: Bioequivalence

Achievements in FY2011: Phase I–III (1/2)

Progress in development status		
S-349572 (Dolutegravir)*	HIV infection	Global: Phase III registration completed
S-474474	Hypertension	Japan: Phase III (LPO), key-opening
S-555739	Allergic rhinitis	Japan: Phase IIb initiated US: Phase I initiated
S-2367	Obesity	Japan: Phase IIb initiated
S-297995	Alleviation of opioid-induced adverse effects	US/Japan: Phase IIb initiated
S-707106	Type 2 Diabetes	US: Phase IIa (LPO), key-opening

LPO: Last patient out

* Developed by Shionogi-ViiV Healthcare LLC

Achievements in FY2011: Phase I–III (2/2)

Progress in development status		
S-288310	Bladder cancer	Asia: Phase I/II registration completed
S-488410	Esophageal cancer	Japan: Phase I /II registration completed
S-488210	Head and neck squamous cell carcinoma	EU: Phase I /II initiated
S-646240	Age-related macular degeneration	Japan: Phase IIa initiated
S-524101	Allergic rhinitis caused by house-dust mite allergen	Japan: Phase I initiated, completed
S-117957	Neuropathic pain	US: Phase I initiated
S-649266	Bacterial infection	Japan: Phase I in preparation

Achievements in FY2011: In-Licensing

Co-development and commercialization with Shire

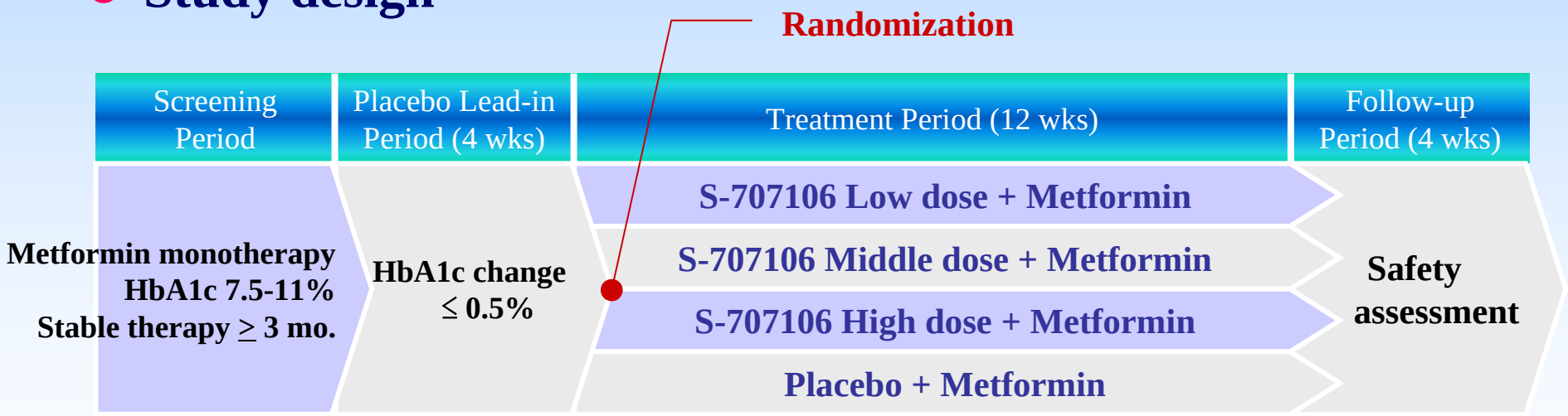
Details of In-Licensing Products	
S-877489 [Vyvanse®]	CNS stimulant, oral Attention deficit hyperactivity disorder (ADHD) Phase I initiated
S-877503 [Intuniv®]	Non-CNS stimulant, oral Attention deficit hyperactivity disorder (ADHD)

Vyvanse® and Intuniv® are registered in the US.

CNS: Central nervous system

S-707106: Outline of Phase IIa Study

- **Objectives**
  - **To evaluate the safety and efficacy of 3 doses of S-707106 co-administered with metformin**
  - **To assess the pharmacokinetics of S-707106**
- **Treatment Duration: 12 weeks**
- **Study design**



- **Preliminary report: 0.8% or more decrease in HbA1c value from baseline (criterion of go decision) was not observed**
  - **Conducting an additional analysis**

Development

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

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

S-349572 (Dolutegravir)
Ospemifene

S-297995
S-555739
S-888711

S-265744 LAP
S-288310
S-488410
S-488210
S-222611
S-117957
S-649266
S-707106
S-646240

NF-κB decoy oligo
DCS

Constructing a strategic pipeline that incorporates in-licensing products

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

Target Milestones for FY2012: Approval and NDA Filing

Approval	
FINIBAX®	**Additional indication for pediatric infection (Japan)**
NDA filing	
Ospemifene	**Post-menopausal vaginal atrophy (US)**
S-349572 (Dolutegravir)*	**HIV infection (Global)**
Irbetan® (Irbesartan)	**Hypertension: Additional dosage form of irbesartan 200mg tablet (Japan)**
S-474474	**Hypertension: Irbesartan/trichlormethiazide combination (Japan)**

* Developed by Shionogi-ViiV Healthcare LLC

Target Milestones for FY2012: Phase I–III (1/2)

Progress in development status		
S-297995	Alleviation of opioid-induced adverse effects	US/Japan: Phase IIb LPO, key-opening Meeting with each regulatory agency
S-555739	Allergic rhinitis	Japan: Phase IIb LPO, key-opening US: Phase IIa FPI
S-888711	Thrombocytopenia	Japan: Phase IIb initiation
S-707106	Type 2 Diabetes	Go/No-go decision
S-524101	Allergic rhinitis caused by house-dust mite allergen	Japan: Phase II initiation
S-2367	Obesity	Japan: Phase IIb registration completion
S-288310	Bladder cancer	Japan: Go/No-go decision based on Phase I/II results
S-488410	Esophageal cancer	Japan: Go/No-go decision based on Phase I/II results

LPO: Last patient out, FPI: First patient in

Target Milestones for FY2012: Phase I–III (2/2)

Progress in development status		
S-488210	Head and neck squamous cell carcinoma	EU: Phase I/II FPI
S-646240	Age-related macular degeneration	Japan: Phase IIa FPI
S-222611	Malignant tumor	EU: Phase Ib LPO
S-265744 LAP*	HIV infection	US: Phase I completion, Phase II initiation
S-117957	Neuropathic pain	US: Phase I completion
S-877489	ADHD	US: Phase I completion
S-877503	ADHD	Japan: Phase I initiation
S-649266	Bacterial infection	Japan: Phase I completion US: Phase I initiation
FTIH: 3 or more compounds		

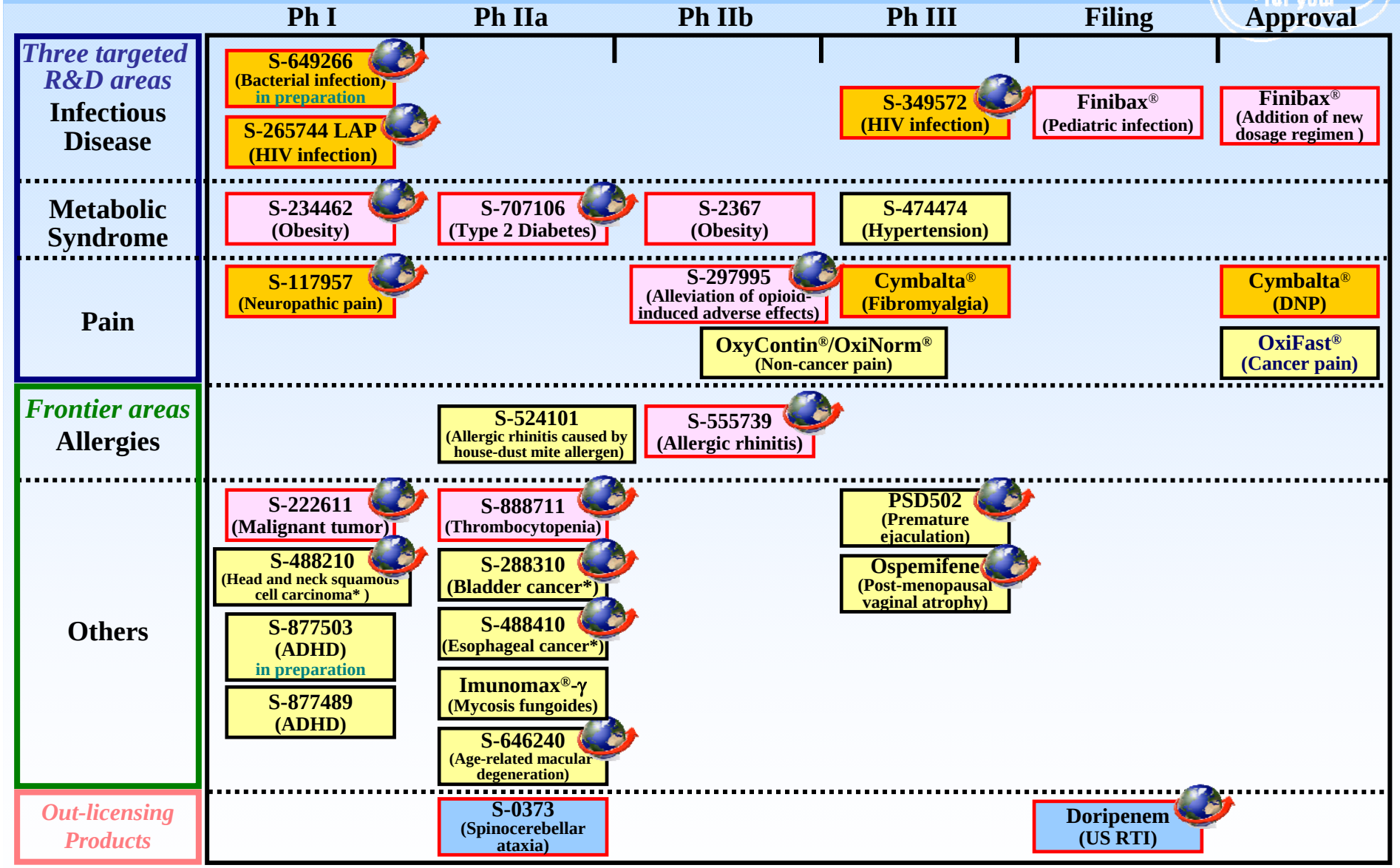
FPI: First patient in, LPO: Last patient out, LAP: Long-acting parenteral formulation, ADHD: Attention deficit hyperactivity disorder, FTIH: First trial in humans

* Developed by Shionogi-ViiV Healthcare LLC

Development of Unapproved and Off-label Drugs, and a Drug Requested for Development by Academy

Unapproved and off-label: Status of progress	
Endoxan®	Approved in September 2011: Nephrotic syndrome
Flagyl®	Approved in March 2012: Bacterial vaginosis
Ifomide	Approved in March 2012: Malignant lymphoma
Longes®	NDA filing: Childhood hypertension
Flagyl®	NDA filing: Infections caused by anaerobic bacteria, and amebiasis giardiasis
Baktar®	NDA filing: Pneumocystis carinii
OxyContin®, OxiNorm®	Clinical trial in preparation: Moderate to severe chronic pain (non-cancer pain)
Cymbalta®	Phase III: Fibromyalgia
Vancomycin	Under consideration: Gram-positive bacteria-associated bloodstream infection
Requested for development by academy: Status of progress	
Imunomax®-γ	Phase II initiation: Additional indication for mycosis fungoides and Sezary's syndrome

Development Development Pipeline Enrichment (as of March 2012)



LAP: Long-acting parenteral formulation, RTI: Respiratory tract infection,
DNP: Diabetic peripheral neuropathic pain,
ADHD: Attention deficit hyperactivity disorder, * Cancer peptide vaccine

Developing products globally

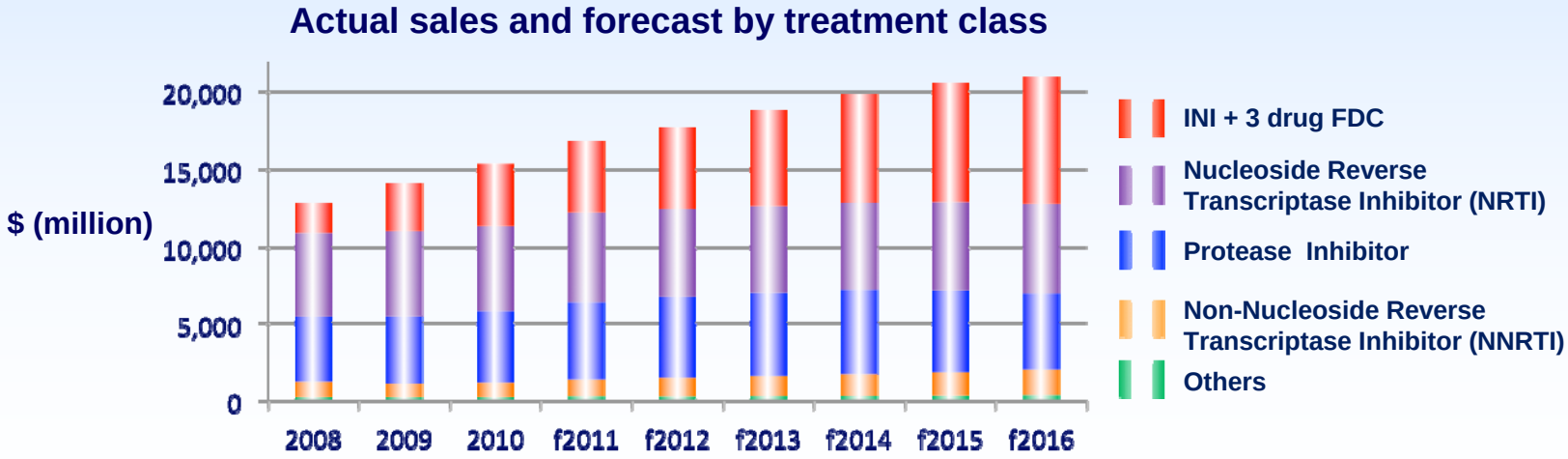
In-house | Co-development | Out-licensed | In-licensed

Core Global Development Products

(Dolutegravir, S-649266, S-888711)

Dolutegravir: Market Information

- **Number of people living with HIV: Approx. 34 million**
  (WHO, UNICEF, UNAIDS, Progressive report 2011)
- **Anti-HIV agent sales in global market***
  - **Approx. $15,300 million (2010, +9% from 2009): 48% of this from US market, 28% from EU, and the balance of 23% from the rest of the world**
  - **Integrase inhibitors (INI) and 3-drug fixed-dose combinations (FDC, e.g., EFV/TDF/FTC * *) drive the market growth.**
  - **INI: $1,360 million (+25% from 2010, launched in 2007)**
    FDC: $3,259 million (+11%, from 2010, first market entrant in 2006)



(f: forecast)

* EvaluatePharma and Web-based Annual Report
** Efavirenz/ Tenofovir/ Emtricitabine

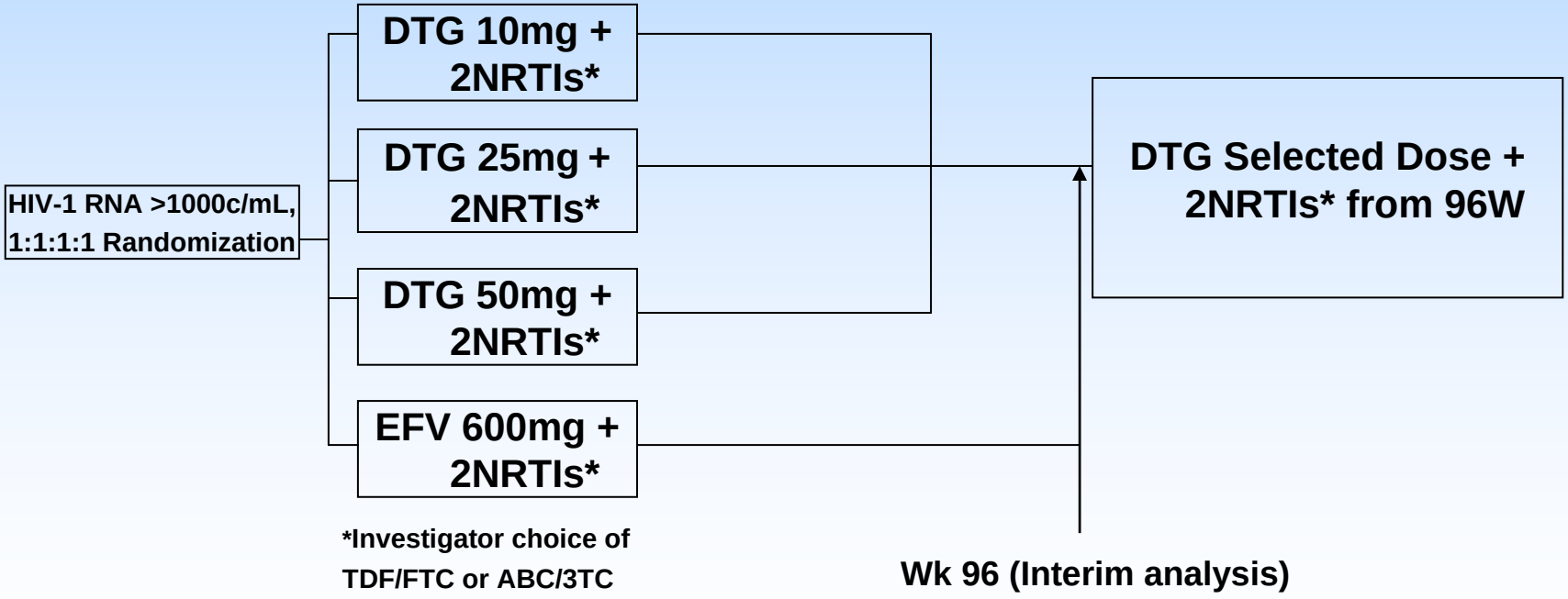
Dolutegravir: Profile

- **Developed by Shionogi-ViiV Healthcare LLC**
- **HIV integrase inhibitor (oral)**
- **Characteristics of DTG**
  - **50 mg QD maintained HIV RNA <50 c/mL for 88% of subjects through 96 weeks in Phase IIb SPRING-1 study**
  - **No DTG-resistant mutants emerged in SPRING-1 through 96 weeks (High genetic barrier to resistance)**
  - **Active against patients with RAL resistance mutations (VIKING)**
  - **Clear PK/PD relationship**
  - **Can administer with most of anti-HIV drugs without dose adjustment**
- **Phase III studies are ongoing mainly in the US and the EU**

DTG: Dolutegravir, RAL: Raltegravir

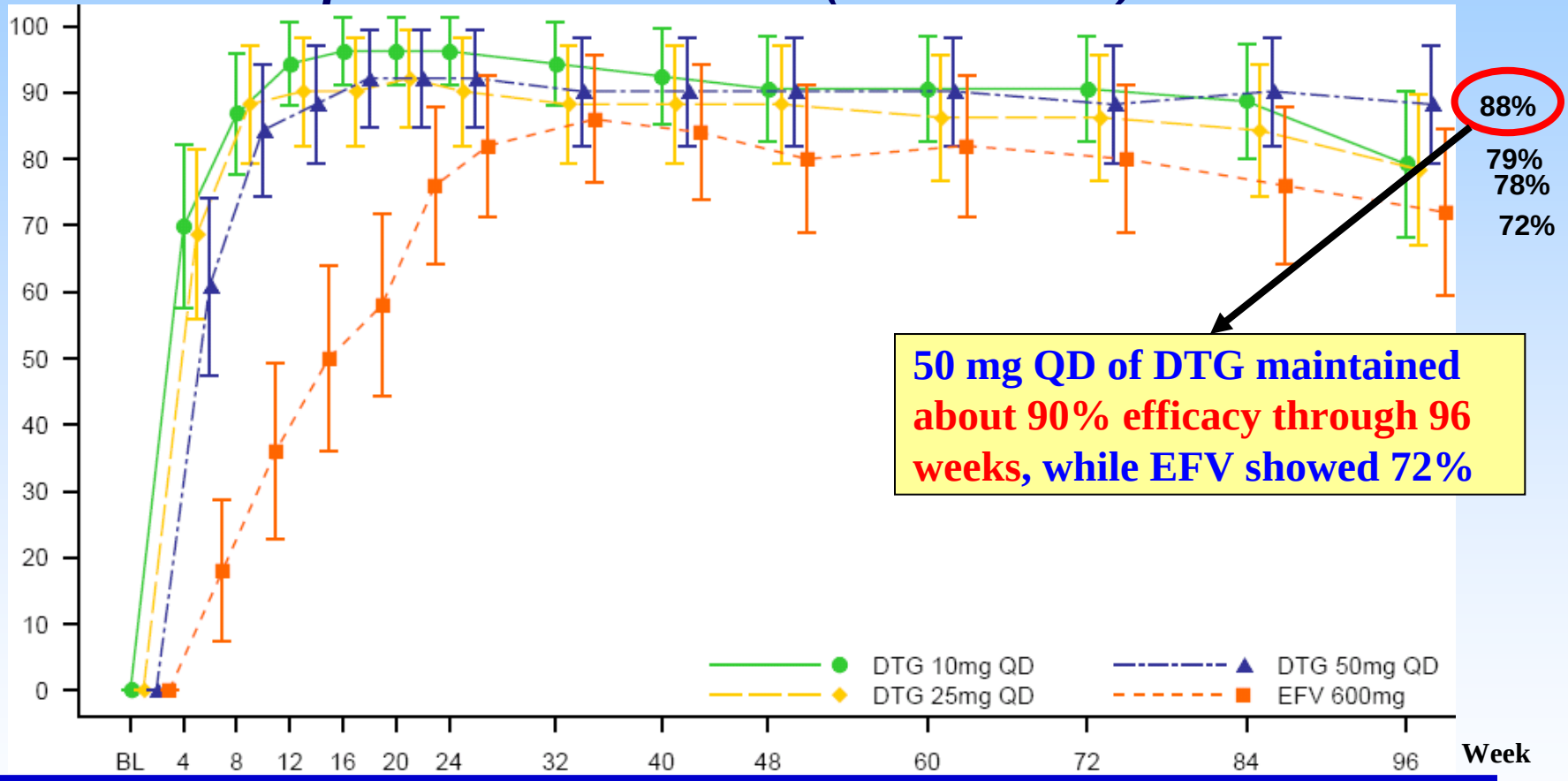
Dolutegravir: ING112276 (Phase IIb Naive Patients Study)

- **Phase IIb dose-ranging, partially-blinded trial**
- **N=200 therapy-naive patients (actual: n=208)**
- **Comparator: Efavirenz (EFV)**



DTG: Dolutegravir, EFV: Efavirenz
NRTI: Nucleoside reverse transcriptase inhibitor

Dolutegravir: Once-Daily DTG Combination Therapy in Antiretroviral-Naive Adults: Rapid and Potent 96-Week Antiviral Responses in SPRING-1 (ING112276)

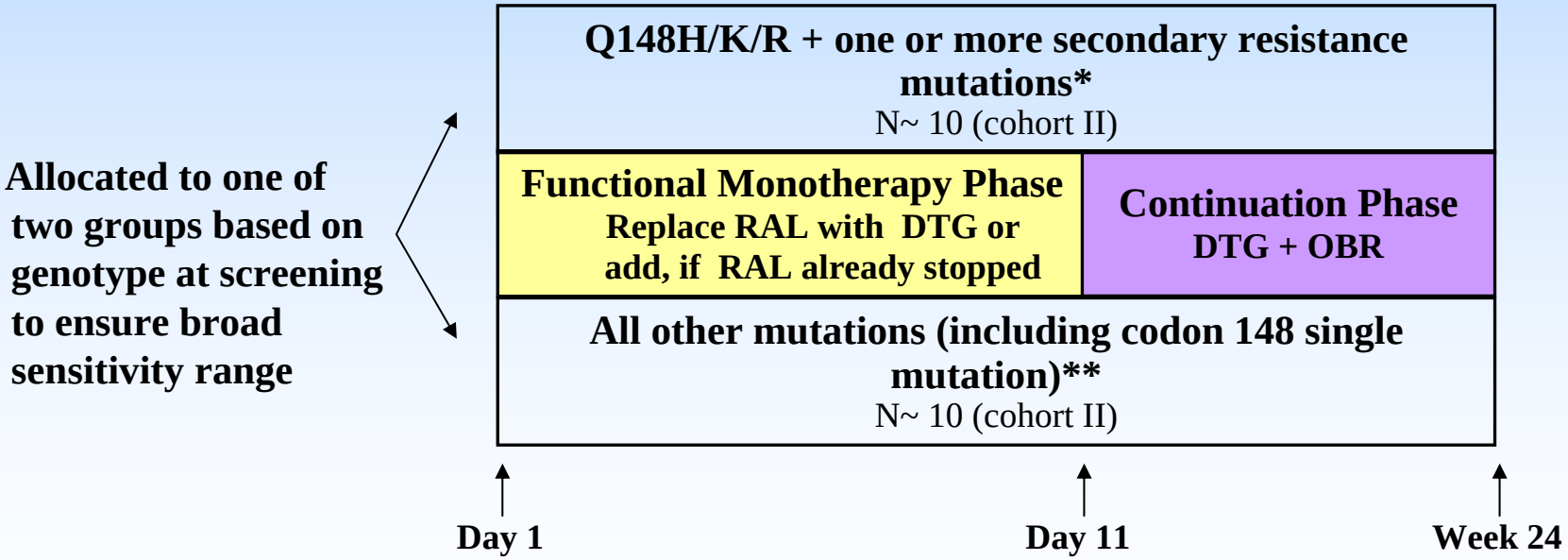


- DTG was well tolerated with less impact on lipid parameters than EFV.
- No DTG-resistant mutants emerged in SPRING-1 through 96 weeks.
- DTG is a new drug that can strongly reduce the amount of virus.

DTG: Dolutegravir, EFV: Efavirenz

Dolutegravir: ING112961 (RAL Rescue Pilot Study)

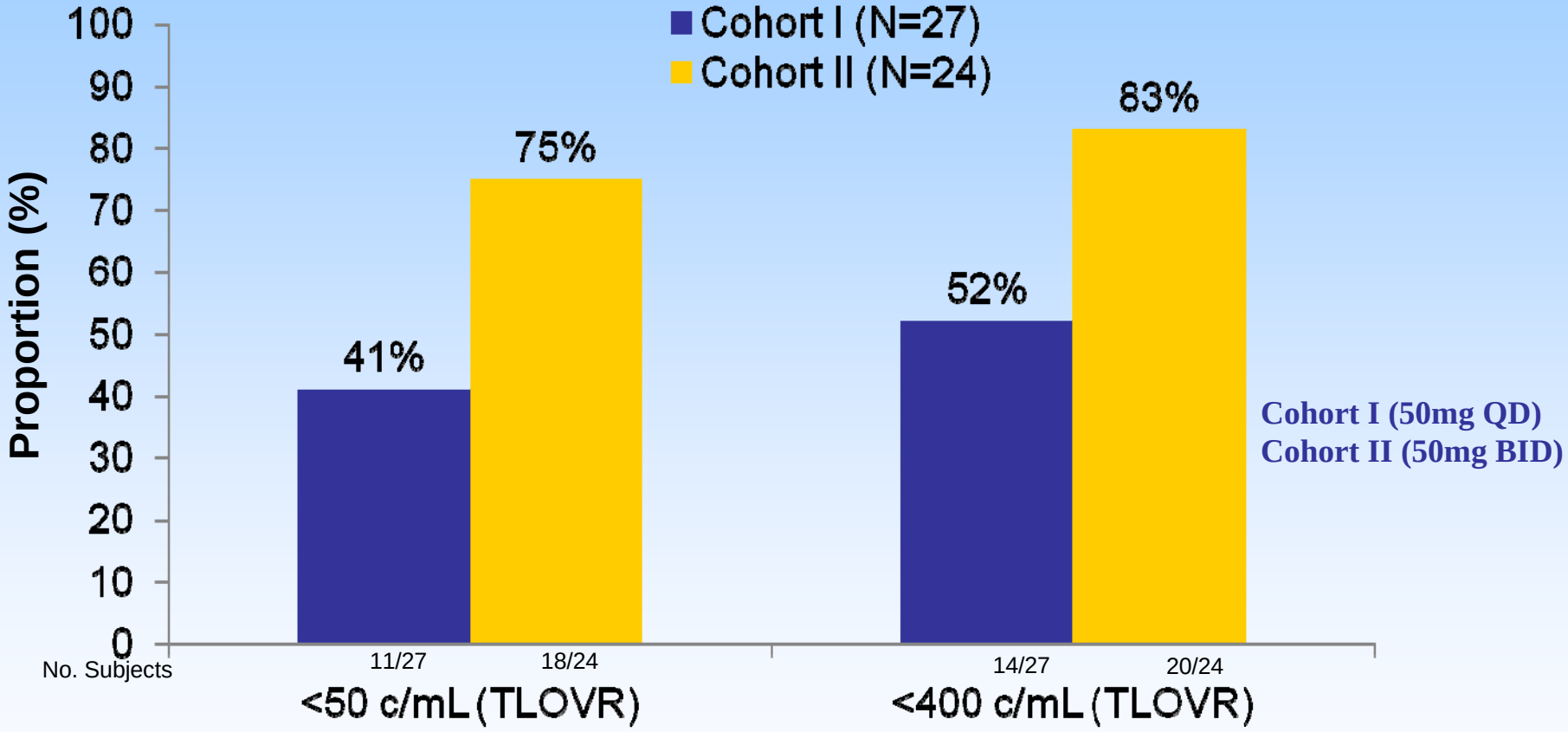
- **Current or historic RAL-failures with evidence of RAL resistance**
  - **At least 3 ART-class resistant (including INI)**
  - **Subjects received DTG 50mg QD (Cohort I) and 50mg BID (Cohort II)**



*Q148H/K/R plus changes in L74 and/or E138 and/or G140
**N155H and Y143H pathways or Q148H/K/R single mutants

DTG: Dolutegravir, RAL: Raltegravir,
OBR: Optimized Background Regimen

Dolutegravir: Response to DTG at Week 24 in Subjects with RAL-Resistant Virus at Screening



Cohort I (50mg QD)
Cohort II (50mg BID)

- **DTG was well tolerated in both Cohorts I and II.**
- **DTG was efficacious for INI-resistant virus (Particularly, 50mg BID).**

DTG: Dolutegravir, RAL: Raltegravir, INI: Integrase inhibitor

Dolutegravir: Phase III Current Status

Study No.	Patient Population	Study Design	Status
ING113086 SPRING-2	**Treatment-naive**	ART-naive pts (n=788) DTG 50QD vs. RAL (+ NRTIs of choice) non-inferiority design	**Active** fully recruited
ING114467 SINGLE		ART-naive pts (n=788) ABC/3TC/DTG 50QD vs. Atripla non-inferiority design	**Active** fully recruited
ING111762 SAILING	**Treatment-experienced but INI-naive**	ART-experienced, INI-naïve pts (n=688) DTG 50QD vs. RAL (+ OBR) non-inferiority design	**Active** fully recruited
ING112574 VIKING-3	**INI-resistance patients**	INI-resistant pts (n=~200) Single cohort, DTG 50BID + OBR	**Recruiting**

DTG: Dolutegravir, RAL: Raltegravir, Atripla: EFV/TDF/FTC,
OBR: Optimized Background Regimen, INI: Integrase inhibitor

Dolutegravir: Positioning

Target population 1: Treatment-naive patients

1) No DTG-resistant mutants emerged in SPRING-1 through 96 weeks (High genetic barrier to resistance)
2) 50mg QD maintained HIV RNA <50 c/mL for 88% of subjects through 96 weeks in Phase IIb SPRING-1 study
3) Once daily FDC (fixed-dose combination) development ongoing

Target population 2: Treatment-experienced but INI-naive

1) Can expect higher efficacy rate for experienced patients from SPRING-1 and VIKING-1 study results
2) Can administer with most of anti-HIV drugs without dose adjustment

Target population 3: INI-failure

Can expect high efficacy in RAL- or ELV-resistant patients

Pediatric study is also ongoing.

NDA/MAA by the end of fiscal year 2012 for all HIV patients

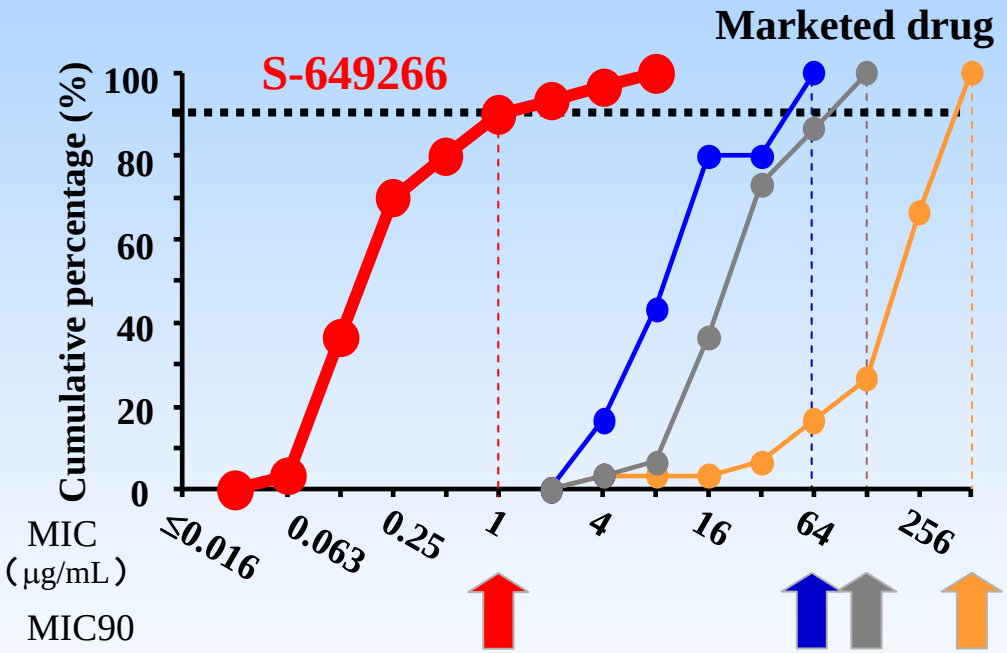
DTG: Dolutegravir, RAL: Raltegravir, ELV: Elvitegravir

S-649266: Profile

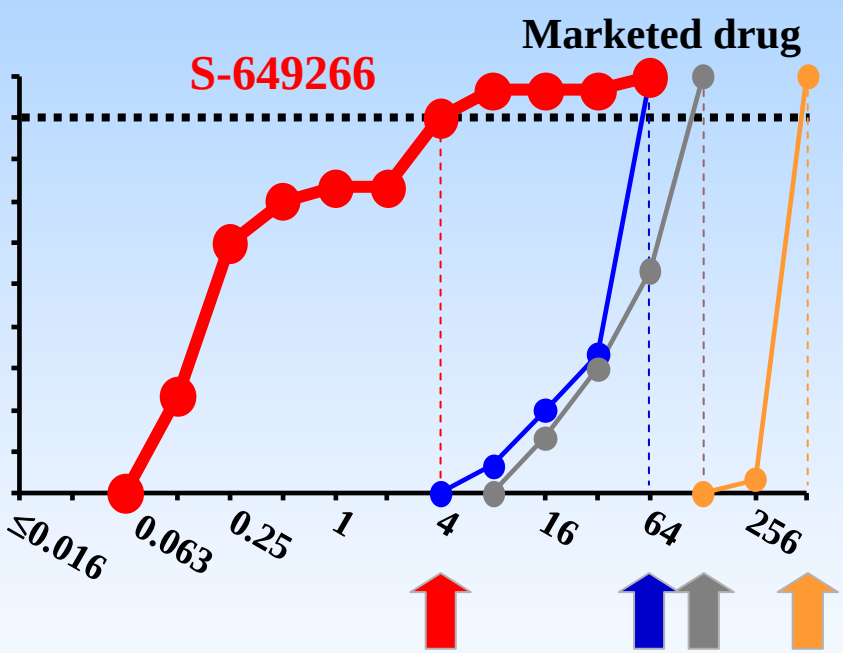
- **Co-developed with GSK**
- **Development concept: Novel cephalosporin with potent activity against gram-negative pathogens, including multidrug (e.g., carbapenem and cephalosporin)-resistant strains such as:**
  - **Metallo-β-lactamase (e.g., NDM-1)-producing strains**
  - **Multidrug resistant *P. aeruginosa***
  - ***A. baumannii*, *S. maltophilia*, or *B. cepacia***
- **Indication: Gram-negative infections, including multidrug-resistant pathogens**
  - **Respiratory tract infection**
  - **Complicated urinary tract infection**
  - **Others**
- **Mechanism of action: Cell wall synthesis inhibitor**
- **Stage: Phase I in preparation**

S-649266: Antibacterial Activity Against Multidrug-Resistant Strains

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



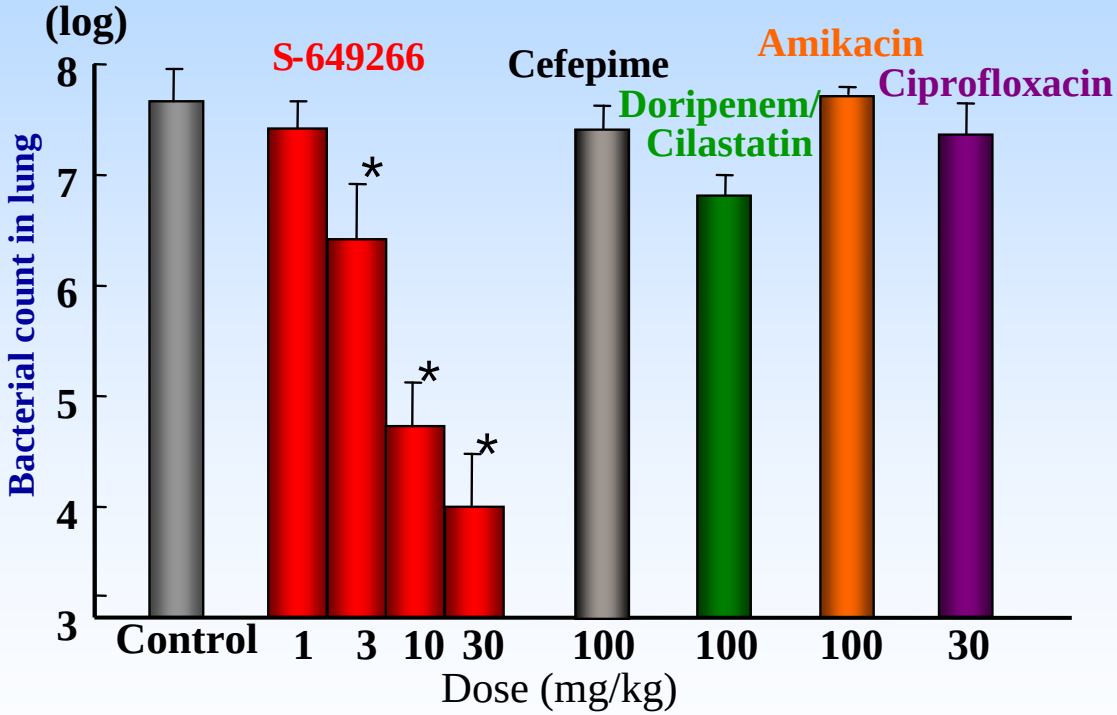
Antibacterial Activity Against Multidrug-resistant *A. baumannii* (number of strains; 29)



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

S-649266: Therapeutic Effect of S-649266 in Model of Mouse Lung Infection with Multidrug-Resistant P. aeruginosa

- **Animal: ICR mouse, male, n=3-4/group**
- **Infection: intranasal infection of *P. aeruginosa* SR24888 (multidrug-resistant *P. aeruginosa* producing metallo-β-lactamase) after treatment with cyclophosphamide**
- **Administration: Subcutaneous injection at 2, 5, and 8 hr. after infection**



MIC (μg/mL)	
S-649266	0.5
Cefepime	>64
Doripenem	>64
Amikacin	>64
Ciprofloxacin	64

**** p<0.05 vs. control: Dunnett's test***

Antibacterial activity of S-649266 against MDRP in mouse lung infectious model was more potent than Cefepime, Dripenem/Cliastatin, Amikacin Ciprofloxacin, and S-649266 also showed similar potency in systemic, urinary tract, and skin infection models.

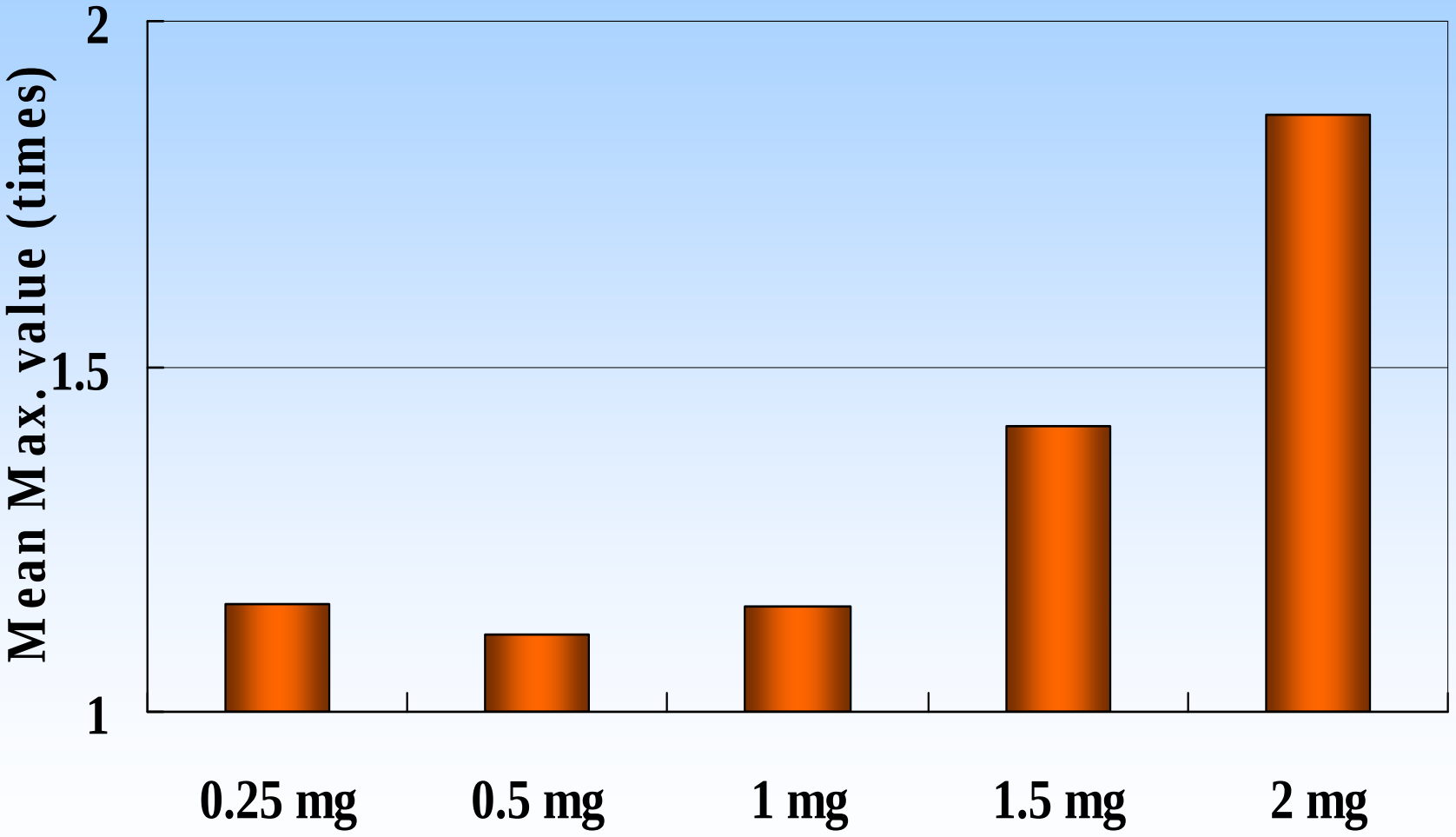
S-888711: Profile

- **Indications: Various diseases with thrombocytopenia**
- **Thrombopoietin receptor agonist (oral)**
- **Developmental stage**
  - **Japan: Phase IIa**
    - **(1) Exploratory dose-finding study in thrombocytopenic patients with chronic liver diseases (POC achieved)**
    - **(2) Study with higher dose in the same patient population (in progress)**
  - **Global: Phase II**
    - **Dose-finding study/open label study in patients with immune thrombocytopenia (completed)**
- **Pharmacological properties from clinical studies**
  - **Good pharmacokinetic profiles**
    - **Increases Cmax and AUC dose-dependency**
    - **Minimal food effect on PK profiles**
    - **Minimal race effect on PK profiles (Japanese vs. Caucasian)**
    - **Minimal risk of drug-drug interaction (CYP3A4 substrate)**
    - **Small impact of hepatic impairment on PK profiles**
  - **Fast onset of platelet increase with QD dosing schedule**
  - **Good tolerability and safety profiles**

S-888711: Exploratory Dose-Finding Study in Thrombocytopenic Patients with Chronic Liver Diseases

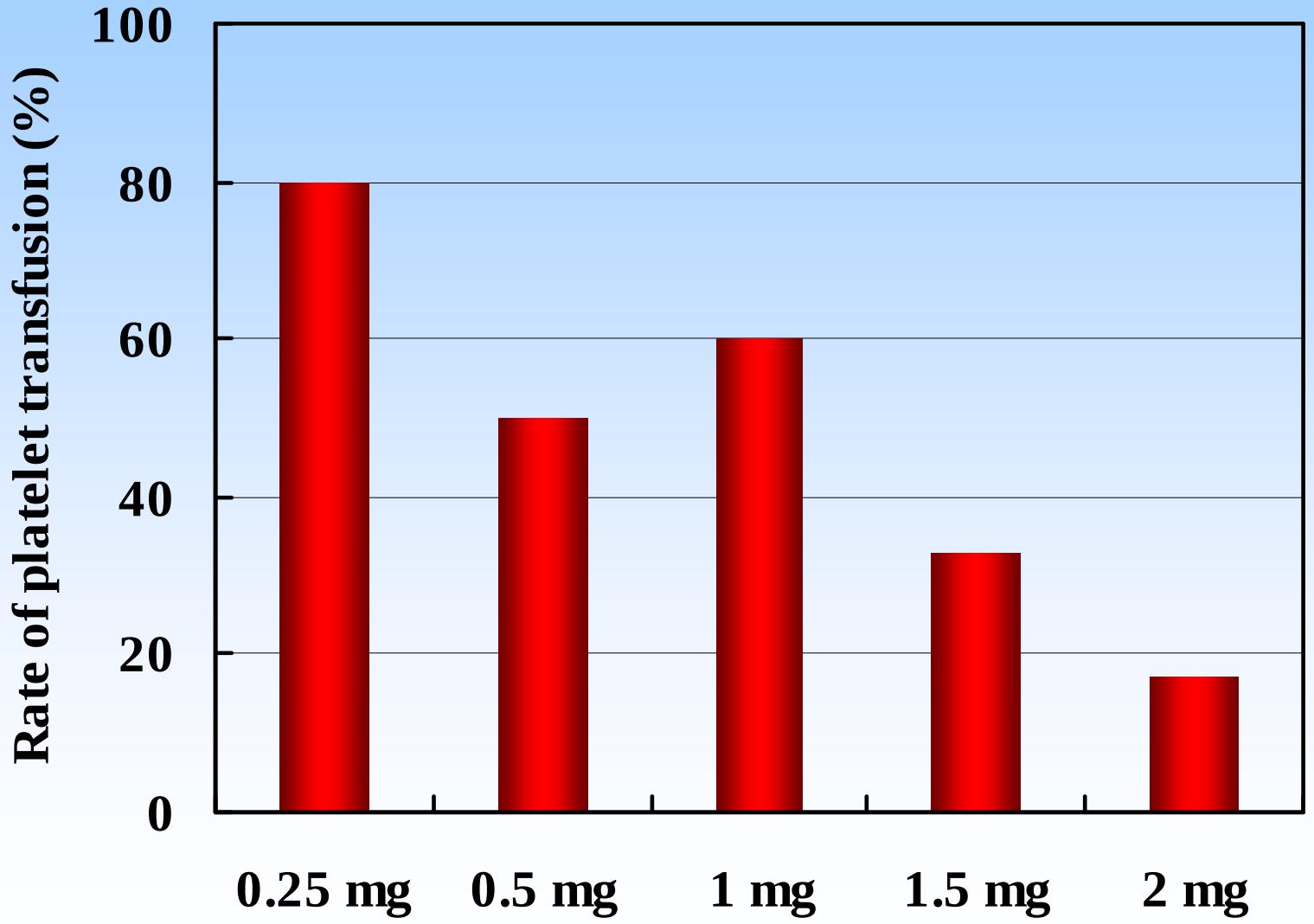
- **Synopsis**
  - Evaluate the efficacy, safety, and pharmacokinetics after 7-day multiple administration, and explore an optimal dose of S-888711
  - Doses
    - 0.25 - 2.0 mg QD, PO
  - Endpoints
    - Platelet count and number of platelet transfusions
    - Adverse events and side effects
- **Results**
  - 1.5 mg/day or more resulted in increase of platelet count and decrease of patients who required platelet transfusion
  - Increases in systemic exposure (Cmax and AUC) appeared to be dose-proportional
  - No issues on safety, including evaluation of thrombotic events
- **Upcoming events**
  - Initiate Ph IIb dose-finding study in FY2012 after investigating the potential of the higher doses

S-888711: Maximum Value-Change from Baseline



Data after platelet transfusion excluded

S-888711: Rate of Platelet Transfusion



S-888711: Clinical Implication in Chronic Liver Diseases

- **Can be an alternative to platelet transfusion in thrombocytopenic patients who are undergoing elective invasive procedures.**
  - **Avoids risk of infection associated with platelet transfusion**
  - **Does not evoke platelet immunologic refractory state**
    - **Can limit platelet transfusion to medically emergent use**
    - **Expect clinical efficacy in patients who are refractory to platelet transfusion**
  - **Saves medical resources related to platelet administration**
    - **Time-consuming ordering, complicated pre-transfusion preparations, etc**

New alternative to platelet transfusion and first-line therapy, for the treatment of patients with thrombocytopenia due to chronic liver diseases

Core Domestic Development Products

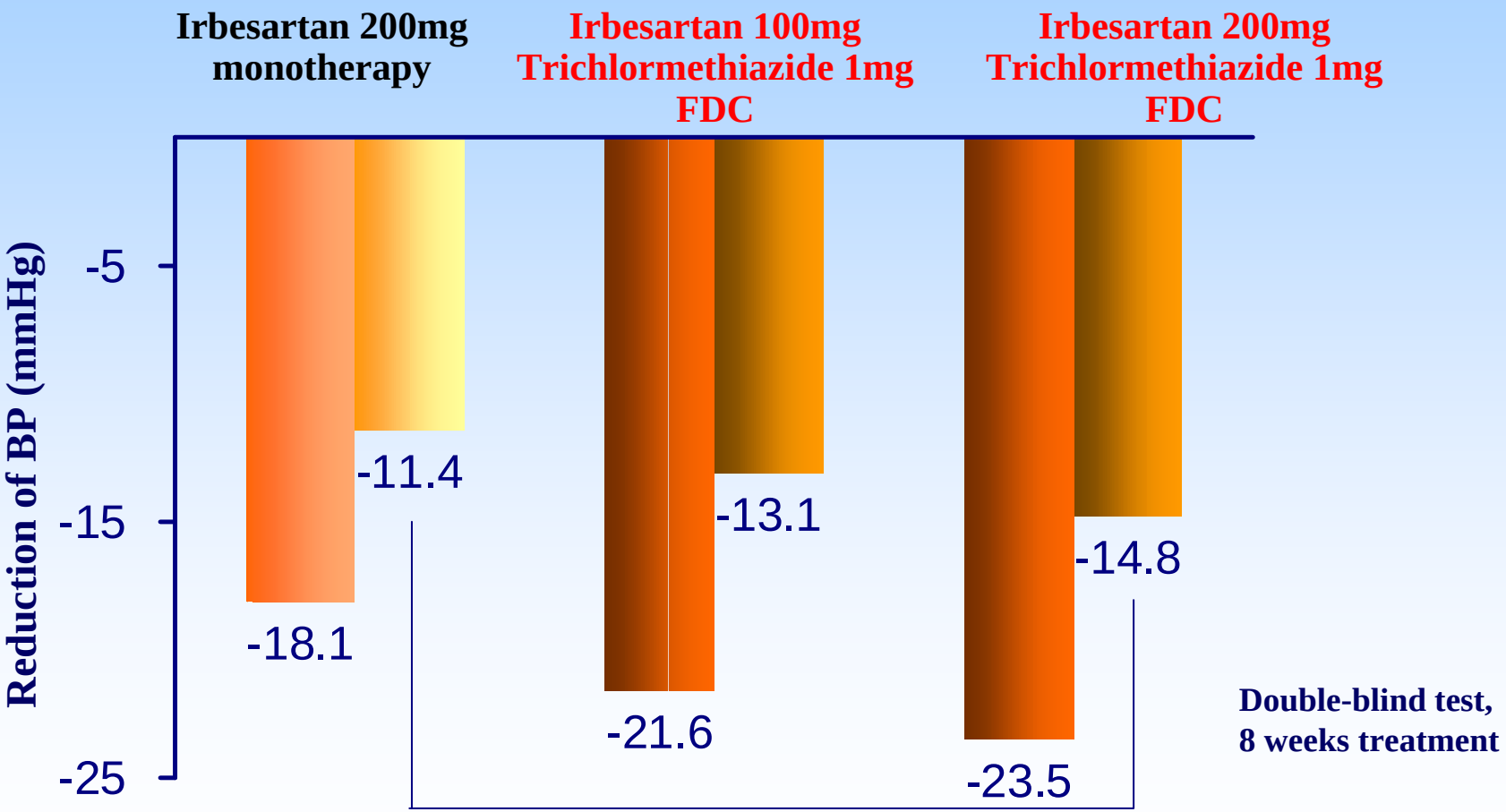
(S-474474, S-877489, S-877503)

S-474474: Profile

- **Target indication: Hypertension**
- **Category: Combination with angiotensin receptor blocker (ARB) and thiazide diuretics**
- **Characteristics: Demonstrates synergistic effect on lowering blood pressure, and safety in combination with irbesartan and low-dose trichlormethiazide**
- **Future Plan: NDA preparation in 2Q FY2012**

S-474474: Results of 200mg FDC Superiority Study

Reduction of blood pressure from baseline (SBP/DBP)



p=0.0018 **Primary endpoint was achieved.**

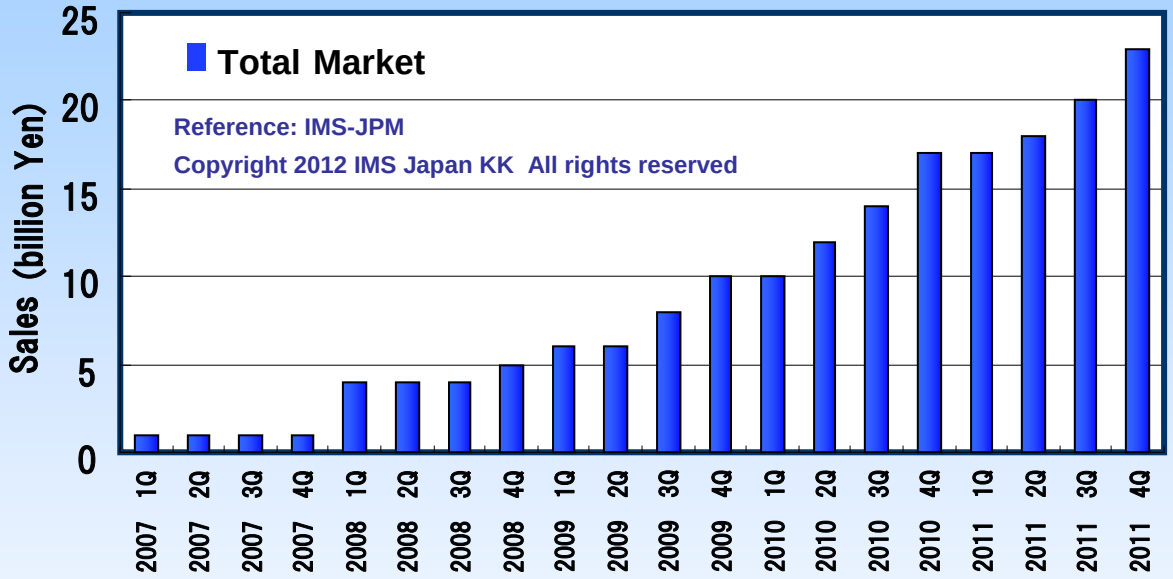
SBP: Systolic blood pressure, DBP: Diastolic blood pressure,
FDC: Fixed dose combination

ADHD (Attention Deficit Hyperactivity Disorder)

- **Symptoms: ADHD is a neurobehavioral disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity and is more frequent and severe than is typically observed in individuals at a comparable level of development.**
- **Etiology: The specific etiology is unknown, but the following are thought to be related.**
  - **Dysfunction in the frontosubcortical pathways that control attention and motor behavior**
  - **Catecholamine dysregulation as at least one source of ADHD brain dysfunction, e.g., insufficient dopamine and noradrenalin levels**
- **Prevalence (Japan): 1-7% of school-aged children**
- **Competitive compounds (Japan)**
  - **Concerta® (stimulant) and Strattera® (Non-stimulant) are on the market.**
  - **There is no compound under development except liquid formulation of Strattera®.**
- **Unmet needs for current pharmacotherapy**
  - **Improved efficacy compared with currently available treatment options**
  - **Reduction of the side effects such as insomnia and loss of appetite**

ADHD Market in Japan

ADHD market in Japan is growing rapidly after launches of Concerta® and Strattera®.



Competitors in Japan

Concerta® (Methylphenidate hydrochloride)
- Active ingredient is methylphenidate hydrochloride, a standard therapeutic agent in the world.
- Controlled release tablet (Once daily)

Strattera® (Atomoxetin hydrochloride)
- First-in-class of non-stimulant (Twice daily)
- Low risk of dependency and abuse
- Coadministration of Methylphenidate hydrochloride is described as precaution in PI.

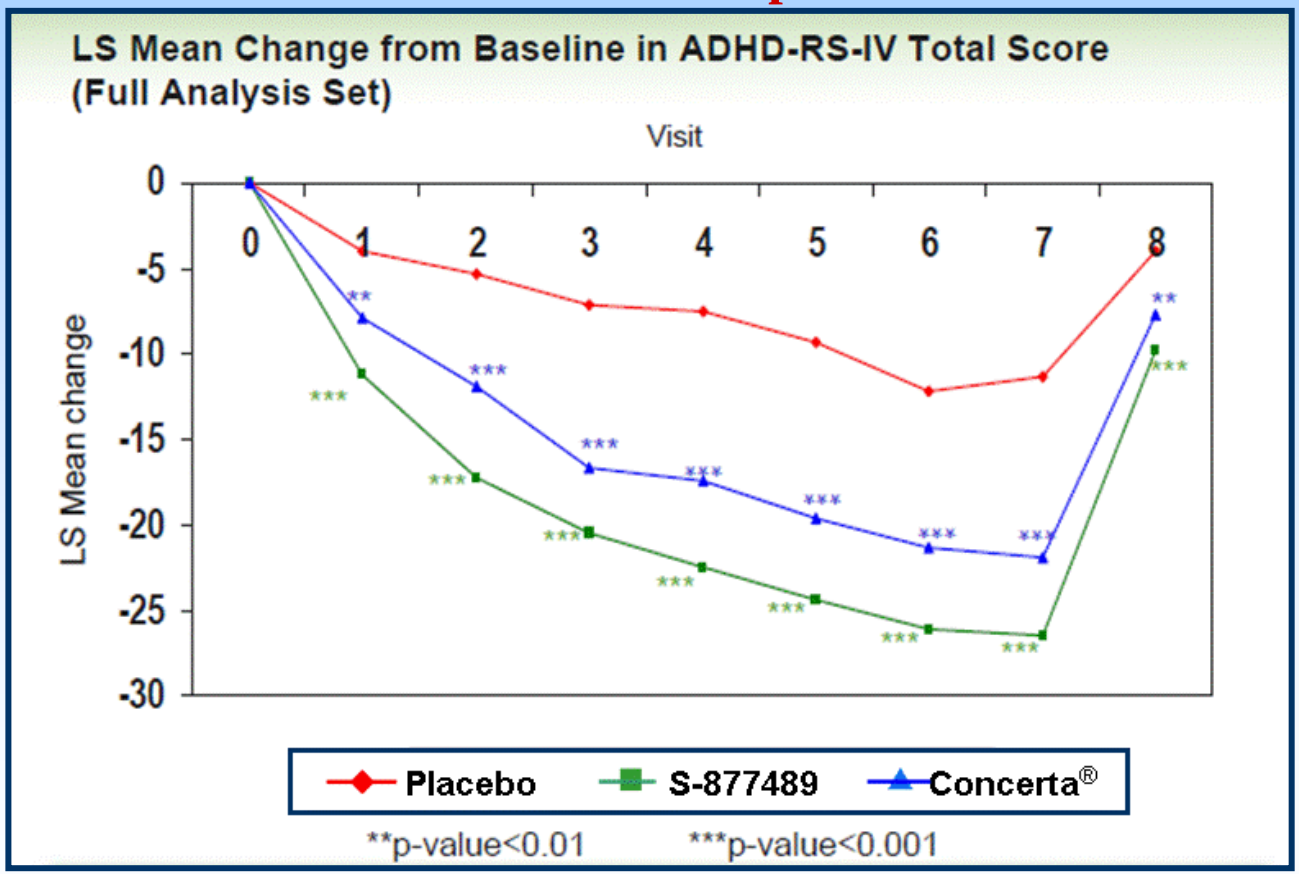
S-877489 [Vyvanse®]: Profile

- **Development concept**
  - **Classified as a CNS stimulant indicated for the treatment of ADHD in countries where currently approved**
- **Mechanism of action**
  - **DA/NE release enhancer/reuptake inhibitor**
- **Development stage**
  - **Phase I study in the US for a clinical trial in Japan**
  - **Marketed in the US, Canada, and Brazil**
  - **File under review in the EU**
- **Future plan**
  - **Phase I study initiation in the US: April 2012**

CNS: Central nervous system, DA: Dopamine, NE: Norepinephrine (noradrenaline)

S-877489 [Vyvanse®]: Efficacy

S-877489 provided significant improvement in ADHD scores at all time points evaluated.



Study population: Children and adolescents aged 6 - 17 with ADHD

Study design: A randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled, double-optimization safety and efficacy study of Lysdexamphetamin (S-877489)

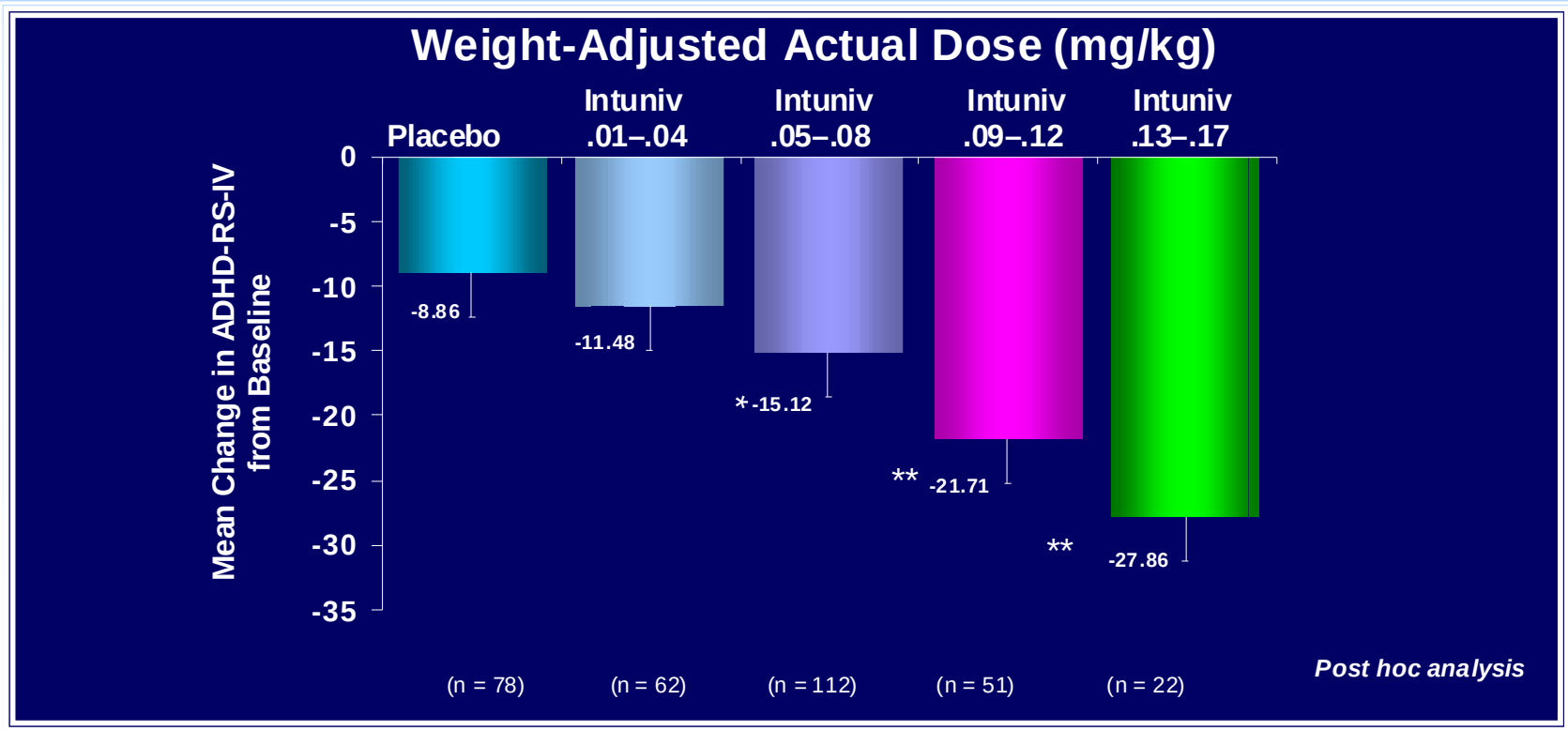
S-877503 [Intuniv®]: Profile

- **Development concept**
  - **Therapeutic agent for ADHD**
  - **Approved as monotherapy and adjunctive therapy to stimulants in the US**
  - **Classified as "non-CNS stimulant," as there is no known potential for abuse**
- **Mechanism of Action**
  - **Selective α_{2A} adrenoceptor agonist**
- **Development Stage**
  - **Phase I study in preparation in Japan**
  - **On market in the US since 2009**
- **Future Plan**
  - **Phase I study initiation: May 2012**

CNS: Central nervous system

S-877503 [Intuniv®]: Monotherapy Study

Mean Change in ADHD-RS-IV from Baseline to Endpoint by Weight-Adjusted Actual Dose (ITT Population)

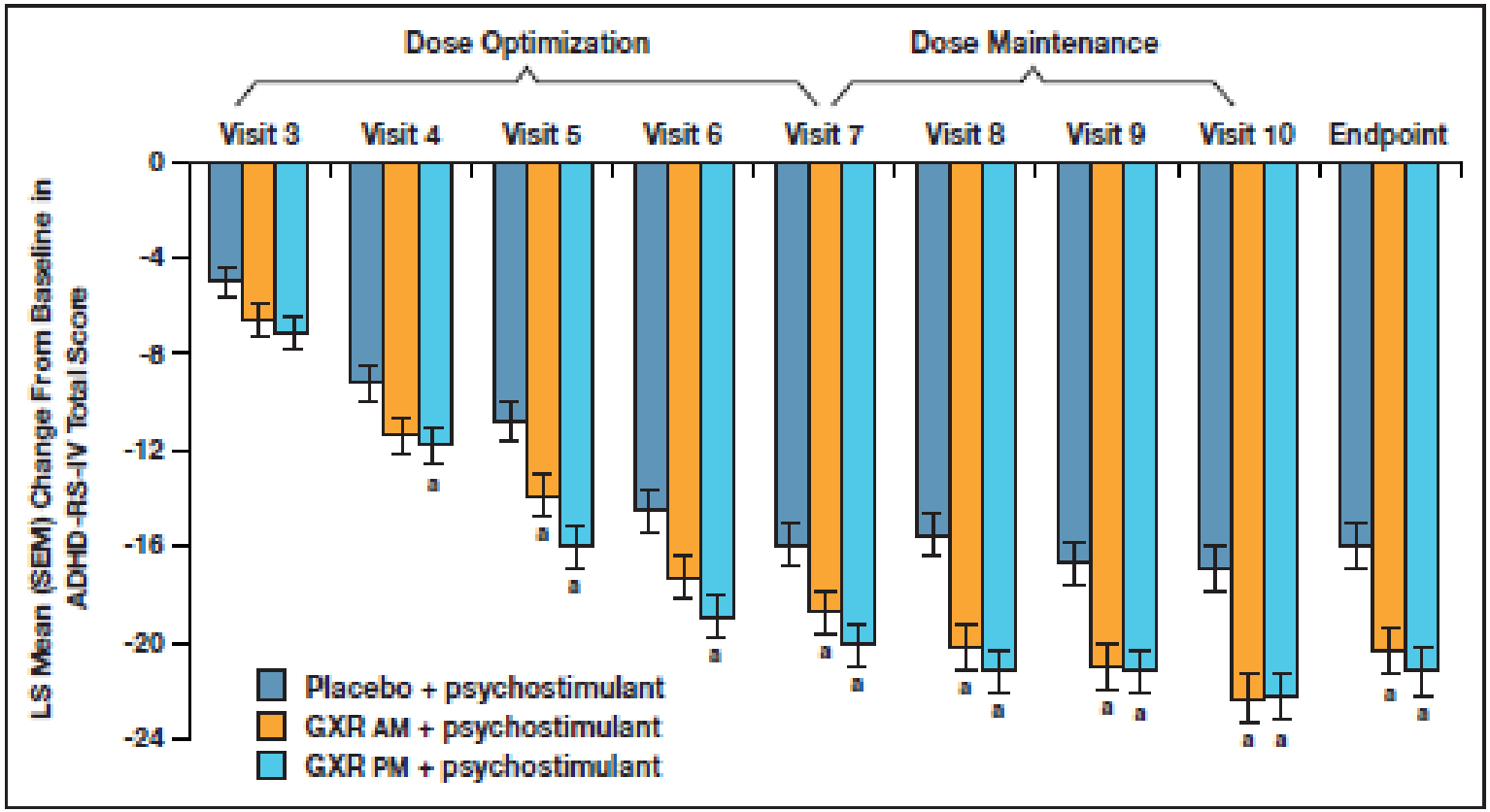


*P<0.01; **P<0.0001

Endpoint is the last valid measurement after randomization (last observation carried forward) prior to dose tapering.

Data on File, Clinical Study Report SPD503-301(75), Shire US Inc.

S-877503 [Intuniv®]: Adjunctive Study



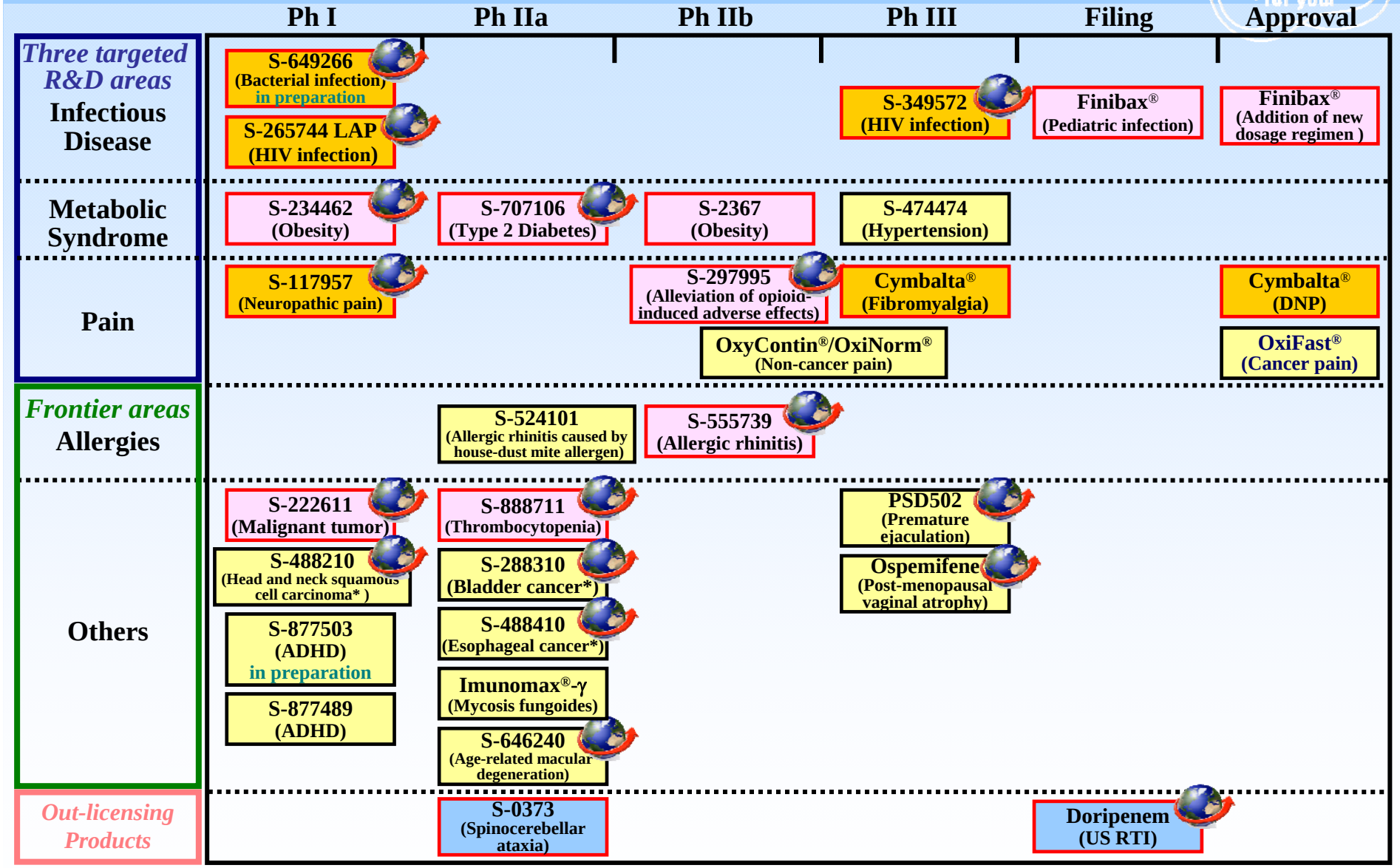
a: $p<0.05$ vs. Placebo

GXR = guanfacine extended release (S-877503)

Reference: Timothy EW, Oscar B, et al. A controlled trial of extended-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adoloesc Pshchiatry 2012; 51(1): 74-85

- **GXR + psychostimulant treatment groups showed significantly greater improvement compared to placebo + psychostimulant treatment groups at endpoint.**

Development Development Pipeline Enrichment (as of March 2012)



LAP: Long-acting parenteral formulation, RTI: Respiratory tract infection,
DNP: Diabetic peripheral neuropathic pain,
ADHD: Attention deficit hyperactivity disorder, * Cancer peptide vaccine

Developing products globally

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

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

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