Research and Development at Shionogi

March 22, 2012
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

Basic strategy 1
Steady growth mainly through enriched pipeline

Crestor cliff

3rd medium-term business plan


Basic strategy 2
Investments in the new growth drivers

4th medium-term business plan

Basic strategy 3
Therapeutic areas to be focused on

5th 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
- Establishment of development/business foothold in Asia
- Strengthening of US-sales network
- 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

**Launch Global Products and Maximize Value of In-line Products**
- Research that supports development and sales
  - Submission of applications, differentiation, LCM
- 4 or more DCSs per year with high potential for success
  - Improve clinical-stage predictions
  - Improve productivity by enhancing early stage research and SPRC

**Sources of Future Growth**
- Acquire research assets that will bear fruit in the future

**Sustainable DCSs**

**Company Growth at home and abroad**

**Crestor cliff**

**Sustainable growth path**

**Mission of the Research Division**

SHIONOGI & CO., LTD.
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)

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

- Enhancement of early phase research-portfolio
- Improvement of predictive performance for clinical efficacy
- Centralization of functions and strengthening of flexibility

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

“Highly efficient low molecular SAR-engine”


* 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

SPRC1 Toxicology
SPRC3 Drug metabolism and Pharmacokinetics

SPRC2 Pharmacology

SPRC4 Drug Discovery, Chemistry Pharmacology, Drug formulation

Speedy and Close Research Cycle

Toward Top Class Global Research Productivity

• Osaka University PET Molecular Imaging Center

• Hokkaido University Shionogi Innovation Center

• Academia
• External research institutes

• Pharmaceutical companies
• Bio-ventures
Medicines enable to save lives
Medicines enable to improve quality of life
Medicines thoroughly fight against disease (eradicative medicine)

Shionogi’s purpose:
Shionogi strives constantly to supply the best possible medicine to protect the health and wellbeing of the patients we serve.
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)

<table>
<thead>
<tr>
<th>Three targeted R&amp;D areas</th>
<th>In-house Developing products globally</th>
<th>Co-development</th>
<th>Out-licensed</th>
<th>In-licensed</th>
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<tr>
<td>Infectious Disease</td>
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<td>Metabolic Syndrome</td>
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<td>Pain</td>
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<td>Out-licensing Products</td>
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<tr>
<th>DCS</th>
<th>Ph I</th>
<th>Ph IIa</th>
<th>Ph IIb</th>
<th>Ph III</th>
<th>Filing</th>
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<tbody>
<tr>
<td>S-649266 (Bacterial infection) in preparation</td>
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<td>S-265744 LAF (HIV infection)</td>
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<td>S-234462 (Obesity)</td>
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<td>NF-κB decoy oligo</td>
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<td>Doripenem (US RTI)</td>
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LAP: Long-acting parenteral formulation, RTI: Respiratory tract infection, ADHD: Attention deficit/hyperactivity disorder, DCS: Drug candidate selection, *
Cancer peptide vaccine
Medicines Enable to Save Lives

- Injectable cepham 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 cepham 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**
### Three targeted R&D areas

#### Infectious Disease
- **Ph I**
  - S-265744 LAF (HIV infection)
  - S-649266 (Bacterial infection)

- **Ph IIa**
  - S-234462 (Obesity)

- **Ph IIb**
  - S-707106 (Type 2 Diabetes)

- **Ph III**
  - S-349572 (HIV infection)
  - Finibax® (Pediatric infection)

#### Metabolic Syndrome
- **Ph I**
  - S-234462 (Obesity)

- **Ph IIa**
  - S-117957 (Neuropathic pain)

- **Ph IIb**
  - S-2367 (Obesity)

- **Ph III**
  - S-474474 (Hypertension)

#### Pain
- **Inflammatory pain**
  - S-234462 (Obesity)
  - S-117957 (Neuropathic pain)

- **Neuropathic pain**
  - S-234462 (Obesity)

#### Frontier areas

#### Allergies
- **NF-κB decoy oligo**
  - S-524101 (Allergic rhinitis caused by house-dust mite allergen)

- **Anti-allergic disease**
  - S-222611 (Malignant tumor)
  - S-888711 (Thrombocytopenia)

- **Alzheimer’s disease**
  - S-488210 (Head and neck squamous cell carcinoma*)
  - S-877503 (ADHD)

- **Others**
  - S-877489 (ADHD)
  - S-488410 (Esophageal cancer*)

#### Out-licensing Products
- **In preparation**
  - Finibax® (Pediatric infection)

- **Others**
  - S-524101 (Allergic rhinitis)

- **Others**
  - S-555739 (Non-cancer pain)

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**Legend:**
- * Cancer peptide vaccine

**Developing products globally**

**In-house**

**Co-development**

**Out-licensed**

**In-licensed**
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

** p<0.01 vs. Vehicle.
+++ p<0.01 vs. marketed drug

Drug candidate for inflammatory pain

Analgesic effect in osteoarthritis pain model

** p<0.01 vs. Vehicle.
+++ p<0.01 vs. marketed drug

Towards the realization of “pain free” for patients around the world
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- **Out-licensing Products**
  - Doripenem (US RTI)
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  - PSD502 (Premature ejaculation)
  - Ospemifene (Post-menopausal vaginal atrophy)

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

**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))

**Graph:**
- Weight difference between KO and normal mice under High Fat Diet (HFD) condition
- WT/HFD: Normal
- SMS2 KO/HFD
- Liver TG: 80% reduction
- Weight of fat: 50% reduction
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
Research

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
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
## Development

### Achievements in FY2011: Approval and NDA Filing

<table>
<thead>
<tr>
<th>Approval</th>
<th>Description</th>
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</table>
| 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 |

<table>
<thead>
<tr>
<th>NDA filing</th>
<th>Description</th>
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</table>
| 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
### Development

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

<table>
<thead>
<tr>
<th>Progress in development status</th>
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<tbody>
<tr>
<td><strong>S-349572 (Dolutegravir)</strong> <em>(Developed by Shionogi-ViiV Healthcare LLC)</em></td>
<td>HIV infection</td>
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<tr>
<td><strong>S-474474</strong></td>
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<td><strong>S-707106</strong></td>
<td>Type 2 Diabetes</td>
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LPO: Last patient out

*Developed by Shionogi-ViiV Healthcare LLC*
### Development

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

<table>
<thead>
<tr>
<th>Progress in development status</th>
<th>Bladder cancer</th>
<th>Japan: Phase I/II registration completed</th>
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<tr>
<td>S-288310</td>
<td>Esophageal cancer</td>
<td>Japan: Phase I/II registration completed</td>
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<td>S-488410</td>
<td>Head and neck squamous cell carcinoma</td>
<td>EU: Phase I/II initiated</td>
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<td>S-488210</td>
<td>Age-related macular degeneration</td>
<td>Japan: Phase IIa initiated</td>
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<tr>
<td>S-646240</td>
<td>Allergic rhinitis caused by house-dust mite allergen</td>
<td>Japan: Phase I initiated, completed</td>
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<tr>
<td>S-524101</td>
<td>Neuropathic pain</td>
<td>US: Phase I initiated</td>
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<tr>
<td>S-117957</td>
<td>Bacterial infection</td>
<td>Japan: Phase I in preparation</td>
</tr>
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</table>
Achievements in FY2011: In-Licensing

Co-development and commercialization with Shire

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

Vyvanse® and Intuniv® are registered in the US.

CNS: Central nervous system
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

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<td>FINIBAX&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Additional indication for pediatric infection (Japan)</td>
</tr>
<tr>
<td>Ospemifene</td>
<td>Post-menopausal vaginal atrophy (US)</td>
</tr>
<tr>
<td>S-349572 (Dolutegravir)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>HIV infection (Global)</td>
</tr>
<tr>
<td>Irbetan&lt;sup&gt;®&lt;/sup&gt; (Irbesartan)</td>
<td>Hypertension: Additional dosage form of irbesartan 200mg tablet (Japan)</td>
</tr>
<tr>
<td>S-474474</td>
<td>Hypertension: Irbesartan/trichlormethiazide combination (Japan)</td>
</tr>
</tbody>
</table>

* Developed by Shionogi-ViiV Healthcare LLC
## Development

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

<table>
<thead>
<tr>
<th>Milestone Code</th>
<th>Condition/Condition Details</th>
<th>Development Status/Decision Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-297995</td>
<td>Alleviation of opioid-induced adverse effects</td>
<td>US/Japan: Phase IIb LPO, key-opening Meeting with each regulatory agency</td>
</tr>
<tr>
<td>S-555739</td>
<td>Allergic rhinitis</td>
<td>Japan: Phase IIb LPO, key-opening US: Phase IIa FPI</td>
</tr>
<tr>
<td>S-888711</td>
<td>Thrombocytopenia</td>
<td>Japan: Phase IIb initiation</td>
</tr>
<tr>
<td>S-707106</td>
<td>Type 2 Diabetes</td>
<td>Go/No-go decision</td>
</tr>
<tr>
<td>S-524101</td>
<td>Allergic rhinitis caused by house-dust mite allergen</td>
<td>Japan: Phase II initiation</td>
</tr>
<tr>
<td>S-2367</td>
<td>Obesity</td>
<td>Japan: Phase IIb registration completion</td>
</tr>
<tr>
<td>S-288310</td>
<td>Bladder cancer</td>
<td>Japan: Go/No-go decision based on Phase I/II results</td>
</tr>
<tr>
<td>S-488410</td>
<td>Esophageal cancer</td>
<td>Japan: Go/No-go decision based on Phase I/II results</td>
</tr>
</tbody>
</table>

LPO: Last patient out, FPI: First patient in
### Target Milestones for FY2012: Phase I–III (2/2)

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Disease Area</th>
<th>Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-488210</td>
<td>Head and neck squamous cell carcinoma</td>
<td>EU: Phase I/II FPI</td>
</tr>
<tr>
<td>S-646240</td>
<td>Age-related macular degeneration</td>
<td>Japan: Phase IIa FPI</td>
</tr>
<tr>
<td>S-222611</td>
<td>Malignant tumor</td>
<td>EU: Phase Ib LPO</td>
</tr>
<tr>
<td>S-265744 LAP*</td>
<td>HIV infection</td>
<td>US: Phase I completion, Phase II initiation</td>
</tr>
<tr>
<td>S-117957</td>
<td>Neuropathic pain</td>
<td>US: Phase I completion</td>
</tr>
<tr>
<td>S-877489</td>
<td>ADHD</td>
<td>US: Phase I completion</td>
</tr>
<tr>
<td>S-877503</td>
<td>ADHD</td>
<td>Japan: Phase I initiation</td>
</tr>
<tr>
<td>S-649266</td>
<td>Bacterial infection</td>
<td>Japan: Phase I completion, US: Phase I initiation</td>
</tr>
</tbody>
</table>

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

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

- Phase II initiation: Additional indication for mycosis fungoides and Sezary's syndrome
### Development Pipeline Enrichment (as of March 2012)

<table>
<thead>
<tr>
<th>Three targeted R&amp;D areas</th>
<th>Infectious Disease</th>
<th>Metabolic Syndrome</th>
<th>Pain</th>
<th>Frontier areas</th>
<th>Others</th>
<th>Out-licensing Products</th>
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<tr>
<td>S-649266 (Bacterial infection) in preparation</td>
<td>S-265744 LAP (HIV infection)</td>
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**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)
Number of people living with HIV: Approx. 34 million

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)

Actual sales and forecast by treatment class

* 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)

Diagram:
- HIV-1 RNA >1000c/mL, 1:1:1:1 Randomization
- DTG 10mg + 2NRTIs*
- DTG 25mg + 2NRTIs*
- DTG 50mg + 2NRTIs*
- EFV 600mg + 2NRTIs*
- Wk 96 (Interim analysis)
- DTG Selected Dose + 2NRTIs* from 96W

*Investigator choice of TDF/FTC or ABC/3TC

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.

50 mg QD of DTG maintained about 90% efficacy through 96 weeks, while EFV showed 72% efficacy.

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)

Allocated to one of two groups based on genotype at screening to ensure broad sensitivity range

- **Functional Monotherapy Phase**
  - Replace RAL with DTG or add, if RAL already stopped

- **Continuation Phase**
  - DTG + OBR

- **Q148H/K/R + one or more secondary resistance mutations***
  - N~ 10 (cohort II)

- **All other mutations (including codon 148 single mutation)***
  - N~ 10 (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
DTG was well tolerated in both Cohorts I and II.
DTG was efficacious for INI-resistant virus (Particularly, 50mg BID).
## Dolutegravir: Phase III Current Status

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Patient Population</th>
<th>Study Design</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING113086</td>
<td>Treatment-naive</td>
<td>ART-naive pts (n=788) DTG 50QD vs. RAL (+ NRTIs of choice) non-inferiority design</td>
<td>Active fully recruited</td>
</tr>
<tr>
<td>ING114467</td>
<td>Treatment-experienced but INI-naive</td>
<td>ART-naive pts (n=788) ABC/3TC/DTG 50QD vs. Atripla non-inferiority design</td>
<td>Active fully recruited</td>
</tr>
<tr>
<td>ING111762</td>
<td>INI-resistance patients</td>
<td>ART-experienced, INI-naive pts (n=688) DTG 50QD vs. RAL (+ OBR) non-inferiority design</td>
<td>Active fully recruited</td>
</tr>
<tr>
<td>ING112574</td>
<td>INI-resistance patients</td>
<td>INI-resistant pts (n=~200) Single cohort, DTG 50BID + OBR</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

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
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

Antibacterial activity of S-649266 against MDRP in mouse lung infectious model was more potent than Cefepime, Doripenem/Cilastatin, 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
**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
Development (Core Global Development Products)

S-888711: Maximum Value-Change from Baseline

Mean Max. value (times)

Data after platelet transfusion excluded

SHIONOGI & CO., LTD.
Development (Core Global Development Products)

S-888711: Rate of Platelet Transfusion

Rate of platelet transfusion (%)

- 0.25 mg
- 0.5 mg
- 1 mg
- 1.5 mg
- 2 mg
**Development (Core Global Development Products)**

**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)

Irbesartan 200mg monotherapy
Irbesartan 100mg Trichlormethiazide 1mg FDC
Irbesartan 200mg Trichlormethiazide 1mg FDC

Reduction of BP (mmHg)

-25
-15
-5

-18.1
-21.6
-23.5

p=0.0018 Primary endpoint was achieved.

Double-blind test, 8 weeks treatment

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® (Atomoxetine 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 in Japan
  - Marketed in the US, Canada, and Brazil
  - File under review in the EU

- Future plan
  - Phase I study initiation: 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 $\alpha_{2A}$ adrenoceptor agonist

Development Stage
- Phase I in Japan
- On market in the US since 2009

Future Plan
- Phase I study initiation: May 2012

CNS: Central nervous system
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

GXR = guanfacine extended release (S-877503)


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

a: p<0.05 vs. Placebo

GXR AM + psychostimulant
GXR PM + psychostimulant
### Development Pipeline Enrichment (as of March 2012)

#### Three targeted R&D areas

**Infectious Disease**
- S-649266: (Bacterial infection), in preparation
- S-265744 LAP: (HIV infection)

**Metabolic Syndrome**
- S-234462: (Obesity)
- S-707106: (Type 2 Diabetes)
- S-2367: (Obesity)
- S-474474: (Hypertension)

**Pain**
- S-117957: (Neuropathic pain)
- S-297995: (All alleviation of opioid-induced adverse effects)
- S-524101: (Non-cancer pain)
- S-555739: (Allergic rhinitis)

#### Frontier areas

**Allergies**
- S-222611: (Malignant tumor)
- S-488210: (Head and neck squamous cell carcinoma*)
- S-888711: (Thrombocytopenia)
- S-288310: (Bladder cancer*)
- S-488410: (Esophageal cancer*)
- S-646240: (Age-related macular degeneration)
- S-488410: (Age-related macular degeneration)
- S-877503: (ADHD)
- S-877489: (ADHD)
- S-0373: (Spinocerebellar ataxia)
- PSD502: (Premature ejaculation)
- Ospemifene: (Post-menopausal vaginal atrophy)

**Others**
- S-877503: (ADHD)
- S-877489: (ADHD)
- S-646240: (Age-related macular degeneration)
- Imunomax®-γ: (Mycosis fungoides)

#### Out-licensing Products

- Finibax®: (Pediatric infection)
- Finibax®: (Addition of new dosage regimen)
- Cymbalta®: (Fibromyalgia)
- Cymbalta®: (DNP)
- OxyContin®/OxiNorm®: (Non-cancer pain)
- OxiFast®: (Cancer pain)
- Doripenem: (US RTI)

#### 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 | 64
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Risks and uncertainties include general domestic and international economic conditions such as general industry and market conditions, and changes of interest rate and currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials and entry of competitive products.

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