Research and Development at Shionogi

SHIONOGI & CO., LTD.
March 18, 2015
Agenda

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

2. Development
   Takuko Sawada
   Senior Vice President
   Global Pharmaceutical Development Division

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

4. Q&A
Grow as a drug discovery-based pharmaceutical company

Clear priorities and focused resourcing

Continued launch of growth drivers
(S-297995, S-888711, S-649266, etc.)

Continued improvement of business operations

Expanding profit from HIV franchise

Increasing sales of Osphena in US and global markets

Maintain stable earnings from Crestor royalty

*: First in Class (Innovative medicines with particularly high novelty and therapeutic value that can significantly change the existing therapeutic paradigm)

**: Last in Class (Unrivaled medicines with clear superiority over others with the same mechanism of action)
Research

Kohji Hanasaki, Ph.D.
Senior Vice President
Pharmaceutical Research Division
SGS2020: Target Research Therapeutic Areas

Clear priorities and focused resourcing to meet unmet medical needs

Infectious disease
- Community-acquired infection
- Hospital-acquired infection
- Virus infection

Pain/CNS
- Depression
- Cancer pain
- Chronic pain
- CNS disorder

Metabolic disorder
- Hyperlipidemia
- Hypertension
- Obesity

Frontier
- Women’s Health
- IPF
- Common acne

Sales
(for the present)
Maximization of existing products

Development
(for the near future)
Successive creation of pipeline

Research
(for the future)
Prediction of changes in needs

*: Central Nervous System  **: Idiopathic Pulmonary Fibrosis
Maximize synergy with existing products

Enhancement of HIV franchise
S/GSK1265744 LAP
S-033188 (Anti-flu drug)

Neuropathic pain
Inflammatory pain

Anti-viral drugs

Infectious disease

Drugs for severe infection

S-649266
Antibody drug for *Pseudomonas*

Chronic pain drugs

Pain/CNS

Drugs for emerging infectious diseases

Participation in GHIT* fund

Drugs for severe infection

Out-licensed
Co-development

Opioid pain relievers

S-297995
OxyContin®
S-718632

LCM for Cymbalta®

ADHD drugs

Alzheimer’s drugs

*: Global Health Innovative Technology Fund
Research

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

- Lack of effective antibiotics exposed by the global increase of multidrug-resistant bacteria
  - “Untreatable: Today’s Drug-Resistant Health Threats” (2013, CDC*)
  - Obama Administration released “National Strategy on Combating Antibiotic-Resistant Bacteria” (2014)
- Motivated recent US FDA approvals of novel antibiotics
  - Dalvance® (dalbavancin), a glycopeptide by Actavis (formerly Durata)
  - Sivextro® (tedizolid), an oxazolidinone by Merck (formerly Cubist)
  - Orbactiv™ (oritavancin), a glycopeptide by The Medicines Company
  - Zerbaxa™ (ceftolozane/tazobactam), a cephem with a β-lactamase inhibitor by Merck (formerly Cubist)
  - Avycaz™ (ceftazidime/avibactam), a cephem with a β-lactamase inhibitor by Actavis (formerly Forest)

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

*: Centers for Disease Control and prevention
Our Research Strategies for Severe Infections

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

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

- **Invasive fungal infections**
  
  Create novel antibiotics against invasive fungal infections with high mortality rates and where there is a need for drug with improved efficacy and safety
Bacterial Infections: Discovery of a Drug Candidate against Gram-Negative Bacteria

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

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


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

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

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

- **Respiratory virus infection**
  
  Utilizing capabilities built in HIV discovery research, create “First-in-Class” anti-flu agents and enrich development pipeline following Rapiacta®
An anti-influenza drug candidate with a novel mechanism of action was progressed from non-clinical to clinical stage.

An innovative “First-in-Class” oral anti-influenza drug candidate, which may cure infection after a shorter treatment period than any other current treatments, was progressed into the clinic.
Approaches to Emerging and Re-Emerging Infectious Diseases

**Bacterial infection**

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

**Viral infection**

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

*: The Global Alliance for TB Drug Development

**: Global Health Innovative Technology Fund

Hokkaido University Research Center for Zoonosis Control

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

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

- **New candidate** (Bacterial infection)
- **S-649266** (Bacterial infection)
- **Finibax®** (Bacterial infection)
- **Tivicay®** (HIV infection)
- **Triumeq®** (HIV infection)
- **Rapiacta®** (Influenza infection)
- **S-033188** (Influenza infection)

- **Bacterial infections program**
- **Fungal infections program**
- **HIV infections program**
- **Influenza infections program**
- **Emerging and re-emerging infections program**

*: ViiV Healthcare
Research

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

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

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

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

To obtain sufficient analgesic effect, drugs that affect different pathological mechanisms are required, because chronic pain conditions arise from multiple pathological mechanisms

⇒ New drugs with different mechanisms, offering expanded treatment options are required
**Our Research Strategy in Chronic Pain**

### Needs for Opioid Analgesics
- **Expansion to Non-cancer pain**
- **Alleviate Side Effects**
- **Tamper-resistance Reduce Dependency**

### Needs for Non-opioid Analgesics
- **Stronger Efficacy**
- **Improved Safety**
- **Expansion of Treatment Options**

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

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

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To meet unmet medical needs, progress drug discovery research of both opioid and non-opioid analgesics, and expand our pipeline
Non-Opioid Analgesics: Discovery of an Analgesic Drug Candidate

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

Analgesic effect in an animal model of diabetic neuropathic pain

Progress multiple candidates for one target molecule to ensure the launch of “First-in-Class” drug
Our Research Strategy in CNS Diseases

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

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

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

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

**Chronic Pain**
- **Opioid program**
  - Oxycodone
    - (Drug abuse prevention: Cancer pain, Non-cancer pain)
  - New candidate
    - (Neuropathic pain)
- **Non-opioid program**
  - Cymbalta®
    - (Fibromyalgia, Chronic low back pain, Osteoarthritis)
    - S-877489
    - S-877503
    - S-297995
    - S-120083

**CNS Diseases**
- **Anti-Aβ program**
  - Alzheimer’s disease
    - Janssen/Shionogi BACE inhibitor
      - (Licensed to Janssen)
- **Alzheimer program**
  - Cymbalta®
    - (Diabetic neuropathy)
- **ADHD program**
  - ADHD
    - S-877503
    - S-877489

**Enrich development pipeline in pain and CNS disease areas through promoting “First-in-Class” and “Last-in-Class” research**
Research

- Approaches and Progress in Core Therapeutic Areas: (1) Infectious Diseases
- Approaches and Progress in Core Therapeutic Areas: (2) Pain and CNS
- Approaches to Strengthen Next Generation Medicinal Research
Oncology & Immunology: Collaborative Research in Tumor Immunology with Academia

Establishment of joint research at CoMIT* in Osaka University

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

Research Themes

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

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

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

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

Comprehensive analysis of sugar chains

Characterization of cells based on the absolute quantitation of major glycoconjugates

Free-type sugar chain

Glycosaminoglycan

N-type sugar chain

O-type sugar chain

Glycolipid

Comprehensive analysis of lipids

Construction of lipid measurement system and mechanism analysis

Fatty acid metabolites

Glycerol lipid

Phospholipid

Sphingolipid

Clinical specimens

Utilization of biobank at Hokkaido University Hospital

Identify novel biomarkers to support drug discovery research

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

Establishment of Global Innovation Office (GIO) (April 2014)

- Acquire and cultivate unique ideas from academia, through the academic network built by our pioneering open innovation program FINDS in Japan
- SSP 2014** has successfully received a number of applications from 11 countries, including Japan
- Explore drug seeds in European academia in cooperation with Shionogi Ltd. (London)
- Collaborations with academia and bio-ventures for in-licensing early-stage clinical pipelines, as well as innovative seeds/technologies to strengthen our Research, CMC***, and Diagnostic divisions (Drug candidates entering clinical stage or GLP studies in FY2015)

*: PHarma-INnovation Discovery competition Shionogi, integrated into SSP in 2014
**: Shionogi Science Program 2014
***: Chemistry, Manufacturing and Control
Identify Future Focus Areas for Discovery Research through Industry-Academia Collaboration

Application of academic innovation to drug discovery

Academia
- Target Molecules
- Lead Compounds (CPD)

Shionogi
- CPD Optimization
- CPD Evaluation

Clinical Candidates

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

Accelerate drug discovery in new therapeutic areas by industry-academia collaboration
(Apply the achievements of academic research in NASH** including methods for evaluation of compounds for use as drugs)

*: Chronic Kidney Disease  **: Non-Alcoholic Steatohepatitis
FY2015 Plan for Research

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

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

Takuko Sawada
Senior Vice President
Global Pharmaceutical Development Division
Development: Agenda

- SGS2020: Goals and Current Status of Development
- Achievements in FY2014
- Targeted Milestones for FY2015
- Core Development Products
  - Core Therapeutic Area
  - Frontier Therapeutic Area
Milestones Targeted by FY2020

Goals

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

Further improvement of productivity is critical to achieve our goals
1. Further improvement and efficiency in strategic decision making
2. Establish solid framework for high quality, rapid, and efficient global development

- Some positive steps were taken toward the globalization of Shionogi’s clinical development in the 3rd Medium-Term Business Plan
- However, we still have further to go to achieve full globalization
  ⇒ Further improvement and enhancement in Shionogi’s global development is an opportunity to breakthrough the low productivity of the pharmaceutical industry on average
Enhancement of Strategic Decision Making, Efficient Development, and Framework Establishment

○ Decision-making regarding global development
  ● Project management and prioritization of compounds by the Global Portfolio Committee
    ○ Concentrate resources on core projects in infectious disease and pain/CNS areas and life cycle management of strategic marketed products

○ Efficient and rapid development
  ● Improve probability of success: identify and utilize biomarkers from the early stages of development to select appropriate patient populations; in collaboration with Research and Diagnostics Divisions
  ● Reduce the total number of clinical subjects required by consulting with regulatory authorities to develop optimized clinical development program: S-297995, etc.
  ● Reduce the number of clinical trials and refine clinical study designs by using epidemiological and observational studies and applying modeling and simulation
  ● Form industrial-academic collaborations: including investigator-initiated clinical research, such as for cancer peptide vaccines, etc.
  ● Increase efficiency of clinical studies through utilization of IT systems

○ Framework Establishment
  ● Establish worldwide collaborative framework; one example of success being the approval of ospemifene in EU
  ● Accelerate of clinical trials in Japan: S-888711, etc.
  ● Tightly link the project management system and the budget control system
Clear priorities and focused resourcing to meet unmet medical needs

SGS2020: Target Development Therapeutic Areas

**Sales** (for the present)
- Maximization of existing products

**Development** (for the near future)
- Successive creation of pipeline

**Research** (for the future)
- Prediction of changes in needs

- **Infectious disease**
  - community-acquired infection
  - hospital-acquired infection
  - Virus infection

- **Pain/CNS**
  - Depression
  - Cancer pain
  - Diabetic neuropathic pain

- **Metabolic disorder**
  - Hyperlipidemia
  - Hypertension

- **Frontier**
  - Women's Health
  - IPF
  - common acne

- **Virus infection**
- **Severe infection**

- **Cancer pain**
- **Chronic pain**
- **CNS disorder**

- **Obesity**

- **Cancer**
- **Allergy**

- **Depression**
- **Diabetic neuropathic pain**

- **Chronic pain**
- **CNS disorder**

- **Obesity**
- **Geriatric metabolic disease**

- **Cancer**
- **Immunological disease**

*: Central Nervous System  **: Idiopathic Pulmonary Fibrosis
Current Status of Development: Focused Pipeline

Sales (for the present)

Development (for the near future)
Progression and expansion of pipeline

Research (for the future)

- **Cymbalta® (fibromyalgia pain, chronic low back pain)**
  - S-888711
  - S-524101

- **Cymbalta® (pain of osteoarthritis)**
  - S/GSK1265744LAP**
    - S-649266

- **OxyContin® (non-cancer pain)**
  - S-297995
  - S-877503
  - S-877489

- **S/GSK1265744LAP**
  - S-649266

- **Janssen/Shionogi BACE inhibitor**
  - S-237648
  - S-033188

- **Osphena®/Senshio®**
  - S-556971
  - S-588410
  - S-525606

- **S-033188**
  - S-718632

Viral infections
Severe infections
Cancer pain
Chronic pain
CNS* disorder
Obesity
Cancer
Allergy

*: Central Nervous System  **: Long Acting Parenteral formulation
underlined: out-licensing to ViiV Healthcare or Janssen
Focused Targets for Development in FY2014

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

Consistently reached FY2014 development milestones worldwide

*: Opioid-Induced Constipation  **: Vulvar and Vaginal Atrophy in post-menopausal women
Maximization of the Value of High-Priority Compounds in Japan

Life cycle management of Cymbalta®
- Fibromyalgia pain: NDA submission (Jun. 2014)
- Chronic low back pain: NDA submission (Dec. 2014)
- Osteoarthritis pain: Phase III study continuing
- Diabetic peripheral neuropathic pain: in preparation

Expanding oxycodone pipeline
- OxyContin®: Phase III clinical study is continuing for the additional indication of non-cancer pain
- OxyContin® NEO: Clinical study of abuse-deterrent, tamper-resistant oxycodone tablets for the additional indication of non-cancer pain is in preparation
Achievements in FY2014: Approvals and NDA Submissions

<table>
<thead>
<tr>
<th>Approvals</th>
<th>NDA submissions</th>
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<tbody>
<tr>
<td><strong>Dolutegravir/abacavir/lamivudine</strong> [Triumeq®]</td>
<td><strong>Dolutegravir/abacavir/lamivudine</strong>*</td>
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<tr>
<td>HIV infection</td>
<td>HIV infection</td>
</tr>
<tr>
<td><strong>Ospemifene</strong> [Senshio®]</td>
<td><strong>S-524101</strong></td>
</tr>
<tr>
<td>Post-menopausal vaginal atrophy</td>
<td>Allergic rhinitis caused by house-dust mite allergen</td>
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<tr>
<td><strong>Cymbalta®</strong></td>
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</tr>
<tr>
<td>Fibromyalgia</td>
<td>Chronic low back pain</td>
</tr>
<tr>
<td><strong>S-888711 (Lusutrombopag)</strong></td>
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<tr>
<td>Thrombocytopenia</td>
<td></td>
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<tr>
<td>Japan: Dec. 2014</td>
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</table>

*: ViiV Healthcare
# Achievements in FY2014: Phase II - III

## Progress in development status

<table>
<thead>
<tr>
<th>Compound Number</th>
<th>Condition</th>
<th>Development Status</th>
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<tbody>
<tr>
<td>S-297995 (Naldeemedine)</td>
<td>Alleviation of opioid-induced adverse effects</td>
<td>Global: Phase III COMPOSE-1 code break</td>
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<tr>
<td>S-877503</td>
<td>ADHD*</td>
<td>Japan: Phase II/III completed</td>
</tr>
<tr>
<td>S-877489</td>
<td>ADHD</td>
<td>Japan: Phase III initiated</td>
</tr>
<tr>
<td>S-888711 (Lusutrombopag)</td>
<td>Thrombocytopenia</td>
<td>Global: Phase III initiated</td>
</tr>
<tr>
<td>S-588410</td>
<td>Esophageal cancer</td>
<td>Japan: Phase III initiated</td>
</tr>
<tr>
<td>S-556971</td>
<td>Dyslipidemia</td>
<td>Japan: Phase II completed</td>
</tr>
<tr>
<td>S-649266</td>
<td>Severe gram-negative infections</td>
<td>Global: Phase II initiated</td>
</tr>
</tbody>
</table>

*: Attention Deficit Hyperactivity Disorder
### Achievements in FY2014: Phase I

<table>
<thead>
<tr>
<th>Progress in development status</th>
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</thead>
<tbody>
<tr>
<td>S-237648 Obesity</td>
<td>Japan: Phase I completed</td>
</tr>
<tr>
<td>S-525606 Allergic rhinitis caused by Japanese cedar allergen</td>
<td>Japan: Phase I completed</td>
</tr>
<tr>
<td>S-033188 Influenza infection</td>
<td>Japan: Phase I initiated</td>
</tr>
<tr>
<td>S-718632 (Abuse deterrent) Chronic pain</td>
<td>US: Phase I initiated</td>
</tr>
</tbody>
</table>
## Expansion of indications: Status of progress

<table>
<thead>
<tr>
<th>Medication</th>
<th>Condition/Indication</th>
<th>Status</th>
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<tbody>
<tr>
<td>Vancomycin</td>
<td>Gram-positive bacteria-associated bloodstream infection</td>
<td>Approval: May 2014</td>
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<tr>
<td>Cymbalta®</td>
<td>Fibromyalgia</td>
<td>NDA submission: Jun. 2014</td>
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<tr>
<td>OxyContin®</td>
<td>For the treatment of moderate to severe chronic pain</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

### Requested for development by academia: Status of progress

<table>
<thead>
<tr>
<th>Medication</th>
<th>Condition/Indication</th>
<th>Status</th>
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<tbody>
<tr>
<td>Imunomax®-γ</td>
<td>Mycosis fungoides/Sezary syndrome</td>
<td>Approval: May 2014</td>
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</tbody>
</table>

**[Achievements since 2010]**

Development for expanded indications: 14 (Approvals: 12)

Development requests from academia:
- Publication-based application: 3
- Clinical trial implementation: 2 (all approved)
## Development Pipeline Progression and Expansion (as of March 2015)

### Core areas

<table>
<thead>
<tr>
<th>Phase</th>
<th>Product</th>
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</tr>
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<tbody>
<tr>
<td>Ph I</td>
<td>S-033188 (Influenza)</td>
<td>Out-licensed</td>
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<tr>
<td>Ph IIa</td>
<td>S-718632 (Severe gram-negative infections)</td>
<td>Ph Iia</td>
</tr>
<tr>
<td>Ph IIb</td>
<td>S-649266 (Severe gram-negative infections)</td>
<td>Ph IIb</td>
</tr>
<tr>
<td>Ph III</td>
<td>S-297995 (Allergen induced adverse effects)</td>
<td>Ph III</td>
</tr>
<tr>
<td>Submission</td>
<td>Ospemifene</td>
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### Infectious disease

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### Pain/CNS

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### Metabolic disorder

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<th>Status</th>
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<tbody>
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<tr>
<td>Ph IIa</td>
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<td>Ph Iia</td>
</tr>
<tr>
<td>Ph IIb</td>
<td>S-649266 (Severe gram-negative infections)</td>
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<tr>
<td>Ph III</td>
<td>S-297995 (Allergen induced adverse effects)</td>
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</tr>
<tr>
<td>Submission</td>
<td>Ospemifene</td>
<td>Approval</td>
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### Cancer/Immunity

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### Others

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</table>

### Development Pipeline Progression and Expansion

- **Ph I**: Phase I clinical trials.
- **Ph IIa**: Phase IIa clinical trials.
- **Ph IIb**: Phase IIb clinical trials.
- **Ph III**: Phase III clinical trials.
- **Submission**: Regulatory submission.
- **Approval**: Regulatory approval.

### Products

- **S-033188**: Influenza.
- **S-718632**: Severe gram-negative infections.
- **S-649266**: Severe gram-negative infections.
- **S-297995**: Allergen induced adverse effects.
- **Ospemifene**: EU Post-menopausal vaginal atrophy.

### Origin

- **In-house**: Products developed in-house.
- **Co-development**: Products developed with other companies.
- **In-licensed**: Products licensed from other companies.

### Notes

- **LAP**: Long-Acting Parenteral formulation.
- **ADHD**: Attention Deficit Hyperactivity Disorder.
- **AMD**: Age-related Macular Degeneration.
- ***: Cancer peptide vaccine.

### Legend

- **Red**: Change of Phase or newly added in FY2014.

### Additional Information

- **Ospemifene**: EU Post-menopausal vaginal atrophy.
- **Cymbalta**: Fibromyalgia.
- **Cymbalta**: Chronic low back pain.
- **OxyContin**: Moderate to severe chronic pain.

**Developing products globally**

**Origin:** In-house, Co-development, In-licensed
## Target Milestones for FY2015: Approvals and NDA Submissions

<table>
<thead>
<tr>
<th>Approvals</th>
<th>Description</th>
<th>Location</th>
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<tbody>
<tr>
<td>S-524101</td>
<td>Allergic rhinitis caused by house-dust mite allergen</td>
<td>Japan</td>
</tr>
<tr>
<td>Cymbalta®</td>
<td>Fibromyalgia</td>
<td>Japan</td>
</tr>
<tr>
<td>Cymbalta®</td>
<td>Chronic low back pain</td>
<td>Japan</td>
</tr>
<tr>
<td>S-888711 (Lusutrombopag)</td>
<td>Thrombocytopenia</td>
<td>Japan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NDA submissions</th>
<th>Description</th>
<th>Location</th>
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</thead>
<tbody>
<tr>
<td>S-877503</td>
<td>ADHD</td>
<td>Japan</td>
</tr>
<tr>
<td>S-297995 (Naldemedine)</td>
<td>Alleviation of opioid-induced adverse effects</td>
<td>US/Japan</td>
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</tbody>
</table>
### Target Milestones for FY2015: Phase I - III

**Progress in development status**

<table>
<thead>
<tr>
<th>Product</th>
<th>Disease/Condition</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Cymbalta®</td>
<td>Osteoarthritis</td>
<td>Japan: Phase III completed</td>
</tr>
<tr>
<td>S-649266</td>
<td>Severe gram-negative infections</td>
<td>Global: Phase III initiated</td>
</tr>
<tr>
<td>OxyContin® (Abuse deterrent)</td>
<td>Cancer/Non-cancer pain</td>
<td>Japan: Phase I initiated</td>
</tr>
<tr>
<td>S-718632 (Abuse deterrent)</td>
<td>Chronic pain</td>
<td>US: Decision on final formulation</td>
</tr>
<tr>
<td>S-033188</td>
<td>Influenza infection</td>
<td>Japan: Phase I completed Go / No Go decision</td>
</tr>
</tbody>
</table>
Core Development Products
- Core Areas -
Infectious Diseases

Enhancement of HIV franchise
S/GSK1265744 LAP
S-033188 (Anti-flu drug)

Anti-viral drugs

Participation in GHIT fund

Drug for emerging Infectious disease
S-649266
Antibody drug for Pseudomonas

Infectious disease

Neuropathic pain
Inflammatory pain

Chronic pain drugs

Pain/CNS

Out-licensed Co-development

ADHD drugs

Alzheimer's drugs

S-297995
OxyContin® • S-718632

Opioid pain relievers
Ongoing efforts to maximize HIV franchise with ViiV Healthcare

- Triumeq® (dolutegravir/abacavir/lamivudine single-pill regimen)
  - Approval: Aug. 2014 (US), Sep. 2014 (EU) and Mar. 2015 (Japan)

- Development of a single pill combining dolutegravir and Janssen’s NNRTI rilpivirine
  - Phase III study will be initiated in 2015 (calendar)

- S/GSK1265744 LAP*
  - Phase II study (LATTE II study) is on-going

*: Long Acting Parenteral formulation
Development status by ViiV Healthcare

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

Mechanism of action
- Cell wall synthesis inhibitor

Product characteristic
- An injectable cephalosporin with potent activity against gram-negative pathogens
- Showing potent activity against multidrug (e.g., carbapenem and cephalosporin)-resistant strains such as metallo-β-lactamase (e.g., NDM-1*)-producing strains, multi-drug resistant *P. aeruginosa* (MDRP), *A. baumannii* and Enterobacteriaceae (*K. pneumoniae*, etc.)

Development status
- Phase II cUTI** study (global) in progress
- Phase III study (global) scheduled in FY2015

*: New Delhi Metallo-beta-lactamase-1  **: Complicated Urinary Tract Infection
**Indication**
- Influenza virus infection

**Mechanism of action**
- Novel mechanism of action

**Product characteristic**
- Broad and strong antiviral activity against influenza A and B viruses including highly pathogenic avian influenza virus
- No cross resistance to marketed neuraminidase inhibitors
- Rapid and potent virus reduction in virus-infected animals

**Development status**
- Phase I single and multiple dose study ongoing
- Go/No Go decision in FY2015
- NDA submission in Japan in FY2017 at the earliest
Pain/CNS

Enhancement of HIV franchise
S/GSK1265744 LAP
S-033188 (Anti-flu drug)

Anti-viral drugs

Participation in GHIT fund

Drugs for emerging infectious diseases

S-649266
Antibody drug for *Pseudomonas*

Infectious disease

Neuropathic pain
Inflammatory pain

Chronic pain drugs

LCM for Cymbalta®

ADHD drugs

Alzheimer’s drugs

Out-licensed Co-development

Opioid pain relievers

S-297995
OxyContin® • S-718632

Participation in GHIT fund

Drugs for severe infection

SHIONOGI
Pain/CNS: S-297995 (Naldemedine)

Compound Profile

- **Indication**
  - Treatment of opioid-induced constipation

- **Mechanism of action**
  - An oral, peripherally acting opioid receptor antagonist

- **Development status**
  - COMPOSE Program on-going (Global phase III studies in chronic noncancer pain patients and cancer patients)

---

Global Opioid Market*

US$14.8 B

Major Markets
US, UK, Germany, Canada and France
Account for up to 80% of total market
(70M chronic opioid patients)

40-50% of chronic opioid patients experience opioid-induced constipation
(28-35M patients)

Less than 50% of patients taking laxative report satisfactory results

---

* Source: Calculated based on IMS Health MIDAS MAT-2Q12, etc.
Phase III Studies (COMPOSE Program)

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

**II**
- FPI: Sep. 2013
- Code break
- Recruitment completed

**I**
- FPI: Nov. 2013
- Recruitment completed

**V**
- FPI: Dec. 2013
- Recruitment completed

**VI**
- FPI: Feb. 2014
- Recruitment completed

**VII**
- FPI: Jul. 2014
- Recruitment completed

**V**
- FPI: First Patient In

**IV**
- Global study
- Japanese study
- Efficacy study
- Long term safety study

**III**
- FPI: Oct. 2013
- Recruitment completed
COMPOSE-1 Study Design

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

**Screening Period**

12-week

**Treatment Period**

4-week

**Follow-up Period**

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

**Study Population**

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

**Placebo**

(n=270)

**Naldemedine 0.2 mg QD**

(n=270)

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

**Efficacy Assessments**

- Primary Endpoint
  - Proportion of responders**
- Secondary Endpoints
  - Frequency of SBMs, CSBMs, SBMs without straining

**Safety Assessments**

- GI-related AEs

**PK Assessments**

*Spontaneous bowel movement (SBM) is defined as a BM that occurs without the use of a rescue laxative medication during the 24 hours prior to the BM.

**A responder is defined as having 9 positive response weeks or more out of the 12-week Treatment Period and 3 positive response weeks out of the last 4 weeks of the 12-week Treatment Period. A positive response week will be defined as ≥ 3 SBMs per week and an increase from baseline of ≥ 1 SBM per week for that week.
COMPOSE-1 Study Top Line Results

● Efficacy profile
  ● The treatment difference in Responder Rate (the primary endpoint) between naldemedine and placebo were statistically significant.
  ● The treatment difference in all secondary endpoints (frequency of SBM, SBMs without straining and CSBM) between naldemedine and placebo were statistically significant.

● Safety profile
  ● Naldemedine was generally well tolerated.
  ● The most commonly reported (>= 5%) TEAEs with naldemedine were gastrointestinal disorders (Abdominal pain and Diarrhea).
  ● No significant changes over the 12-week treatment period were seen in the pain intensity Numerical Rating Scale (NRS) scores and COWS** scores.

*: Clinical Opiate Withdrawal Scale
Change in the frequency of SBMs per week from baseline to each week of the treatment period (ITT)

The MMRM model has terms for treatment group, time, treatment-by-time as a fixed effect and the opioid dose strata as a covariate.
Pain/CNS: Cymbalta®

Cymbalta® (duloxetine, LY248686)

- **Product characteristic**
  - Serotonin noradrenaline reuptake inhibitor
  - Licensed from Eli Lilly

- **Indications**
  - Global (approved as of April 2014)
    
    Major depressive disorder in 105 countries, DPNP* in 100 countries,
    Generalized anxiety disorder in 88 countries, Fibromyalgia in 35 countries,
    Abdominal pressure - induced incontinence in 48 countries and
    Chronic musculoskeletal pain in 31 countries

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

*: Diabetic Peripheral Neuropathic Pain
Cymbalta® (CLBP*) Phase III: Primary Endpoint

Subjects
- CLBP
- Insufficient effect of NSAIDs
  - BPI(average pain) ≥ 4

BPI: Brief Pain Inventory, FAS: Full Analysis Set

* p<0.05 vs placebo

*: Chronic Low Back Pain
Cymbalta® (CLBP*) Phase III: Secondary Endpoint

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

  - 30% reduction
  - 50% reduction

<table>
<thead>
<tr>
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<th>Duloxetine (n=230)</th>
<th>Placebo (n=226)</th>
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<tbody>
<tr>
<td>Baseline Mean±SD</td>
<td>7.59±4.38</td>
<td>7.77±4.77</td>
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<tr>
<td>Baseline (n)</td>
<td>230</td>
<td>226</td>
</tr>
<tr>
<td>Change Mean±SE</td>
<td>-3.86±0.22</td>
<td>-3.23±0.22</td>
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<tr>
<td>Difference [95% CI]</td>
<td>-0.64 [-1.25,-0.02]</td>
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<tr>
<td>P value</td>
<td>0.0439</td>
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</table>

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

  * * p<0.05 VS placebo

*: Chronic Low Back Pain
Life Cycle Management for Cymbalta®

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

Maximize Cymbalta’s value as a growth driver for the medium-term business in Japan by securing approval for the same pain indications as are approved globally
Pain/CNS: OxyContin®

OxyContin® tablets (S-8117)

- **Product characteristics**
  - Orally available sustained release tablets of oxycodone
  - Strong opioid analgesic
  - Developed by Purdue/Mundipharma and launched at US in 1995 (now launched in 59 countries)
  - In-licensed from Mundipharma

- **Domestic sales**
  - OxyContin® Tablets: 5mg, 10mg, 20mg, 40mg
  - Indication: For the treatment of moderate to severe chronic pain
  - Launched in 2003
Effective Abuse Deterrence by OxyContin® NEO

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

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

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

Planning to switch to abuse-deterrent formulation in Japan with development of non-cancer pain indication.
Opioid Analgesics: Market Environment

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

### Share of TRxs by Product
**MAT Mar/14**

- **Hycd/APAP** 46%
- **Tramadol HCl** 16%
- **Oxycodone/APAP** 12%
- **Oxycodone HCl** 6%
- **Morphine Sulf APAP/CD** 4%
- **OxyContin** 2%
- **Methadone HCl** 1%
- **Fentanyl** 2%
- **Total Other** 7%

---

**Competitor Landscape**

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

- **Hydrocodone + Acetaminophen**
  - **MNK-155** (Mallinckrodt): NDA submission in May 2014.

---

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

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

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

Entered into a global alliance for abuse-deterrent hydrocodone with Egalet
Promote comprehensive research and development of proper use of medical narcotics and pain relief

**OxyContin® Franchise**
- S-718632 (Hydrocodone)
- S-297995
- **Cymbalta®**

- **Cancer pain**
  - Non-Cancer pain
- **Abuse-deterrent formulation**
- **Chronic pain**
- **Treatment of opioid-induced constipation**
- **DPNP*:** Diabetic Peripheral Neuropathic Pain

**Pipeline**
- Neuropathic pain
- Inflammatory pain
- **Neuropathic pain**
- **Fibromyalgia**
- **Chronic low back pain**
- **Osteoarthritis**
Attention-Deficit/Hyperactivity Disorder (ADHD)

- **Description of disorder**
  - Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous neurobehavioral disorder characterized by a persistent pattern of developmentally inappropriate inattentiveness, impulsivity, and hyperactivity (diagnostic criteria: DSM-5)

- **Prevalence of ADHD in Japan**
  - Children: 2.5% (research by the Education Ministry), Adults: 1 - 7%

- **Competitive landscape in Japan**
  - Concerta® (Stimulant, indicated for children, adolescents and adults)
  - Strattera® (Non-stimulant, indicated for children, adolescents and adults)

- **Current unmet medical needs**
  - Improvement of efficacy for non-responding patients
  - Reduction of adverse events such as insomnia or anorexia
ADHD Market Situation in Japan and Expected Role of New Treatment Options

Japanese ADHD market

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

Value of offering new treatment options for ADHD

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

*: Adverse Drug Reactions
S-877489 [Vyvanse®]: Compound Profile

- **Development concept**
  - S-877489 is classified as a central nervous system (CNS) stimulant indicated for the treatment of ADHD in children and adolescents

- **Mechanism of action**
  - Pharmacologically inactive prodrug stimulant for ADHD which is enzymatically hydrolysed primarily to the active molecule
  - To block the reuptake of norepinephrine and dopamine and increase the release of these monoamines

- **Development status**
  - Phase II/III and extension studies are on-going in Japan
  - Marketed in US (since 2007), Canada, Brazil and EU by Shire

- **Future plan in Japan**
  - Phase II/III study will be completed in 2016
S-877489 [Vyvanse®]: Phase II Study Results

- **Target**
  - Pediatric patients aged 6-17 years old with ADHD

- **Study Design**
  - The safety of S-877489 was assessed in an open-label study. Dose was increased or decreased following the up- and down-titration criteria

- **Safety**
  - Most AEs* were mild in severity. There were no serious AEs. The profile is similar to that observed in overseas clinical studies

- **Efficacy**
  - The mean change of ADHD-RS-IV total score from baseline was \(-26.4 \pm 8.2\) at the last visit (week 4). The change is similar to overseas clinical studies

---

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

**Mechanism of action**
- Selective alpha 2 adrenergic receptor agonist

**Development status**
- Phase II/III was completed and NDA submission is in preparation in Japan
- Marketed in US (since 2009) by Shire
- MAA submission in EU by Shire
**Efficacy profile:** The mean change of ADHD-RS-IV total score from baseline was significantly greater than placebo for all S-877503 weight adjusted dosing groups (m-ITT population)

**Safety profile:** Most AEs were mild in severity. There were no serious AEs. The safety profile is similar to that observed in overseas clinical studies

*P<.05;  **P<.01  
Primary endpoint: The change of ADHD-RS-IV total score from baseline at the treatment endpoint (Week 7). (MMRM analysis)
Pain/CNS: Progress of Janssen/Shionogi BACE* Inhibitor

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

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

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

Summary
- Janssen/Shionogi BACE inhibitor is a potent, brain-penetrant BACE inhibitor, achieving up to 95% Aβ reduction with once-daily oral dosing
- Aβ reduction outlasted plasma/CSF PK, leading to sustained PD activity
- Progressed into Phase II following the favorable results in Phase I

*: Beta-secretase Cleaving Enzyme  **: Amyloid Beta Protein  ***: Soluble Amyloid Precursor Protein
CNS: Addressing Society’s Unmet Medical Needs

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

Depression / depressive condition
Cymbalta®
(Japan, in-licensed from Eli Lilly)

Promotion scheme:
Joint promotion with Shire

Attention deficit hyperactivity disorder
S-877489 S-877503
(Japan, in-licensed from Shire)

Promotion scheme:
Janssen has the global right to promote exclusively
Shionogi holds joint promotion rights in some territories including Japan and the US

Alzheimer’s disease
Janssen/Shionogi BACE inhibitor
(Global, out-licensed to Janssen)
Core Development Products
- Frontier Areas -
Oncology/Immunological Disease: Cancer Peptide Vaccines

**Compound Profile**

- **In-licensed from OncoTherapy Science, Inc. (OTS, Japan)**
  - Shionogi possesses worldwide rights to develop and market cancer peptide vaccines

- **Mechanism of action**
  - Vaccination with peptides derived from antigens selectively and highly expressed in tumor cells which can effectively induce cytotoxic T-lymphocytes (CTLs), which elicit the antitumor effect.

- **Indications**
  - In addition to bladder cancer, esophageal cancer and head and neck cancer in the ongoing clinical studies, Shionogi retains worldwide rights to all indications

- **Product characteristics: 5-peptide cocktail vaccine**
  - Single formulation of cocktail vaccine with potential for efficacy against many types of cancers
  - Expansion of indications and maximization of value
  - Five oncoantigens are highly expressed in a range of tumor types (immunohistochemistry)

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

- **S-588410 (A*24:02, a 5-peptide cocktail vaccine)**
  Shift target segments from STF (standard therapy failure) to the earlier-stage segment in which cancer peptide vaccines are expected to achieve more efficacy

- **Bladder cancer: Phase II study (Japan, EU)**
  - Target indication: Bladder cancer in maintenance setting after 1st-line chemotherapy

- **Esophageal cancer: Phase III study (Japan)**
  - Target indication: Esophageal SCC in adjuvant setting after surgery
  - Initiated Phase III based on the results of translational research of 3-peptide cocktail vaccine in adjuvant setting after surgery at Kinki Univ. (co-development with OncoTherapy Science, Inc.)
Adjuvant therapy for ESCC patients after neoadjuvant therapy followed by curative resection

**Study design**
- Primary endpoint: RFS

**Neoadjuvant therapy followed by Surgery**

**R0 resection and pN(+)**

**Neoadjuvant therapy**
- Chemotherapy of FP, FAP and DCF
- Chemoradiotherapy

**Vaccine group**
- HLA-A*24:02(+)
- Vaccination

**Control group**
- HLA-A*24:02(-)
- None (observation cohort)

(Reference: Takushi Yasuda et. al., The 73rd Annual Meeting of the Japanese Cancer Association, 2014)
Translational Research of 3-Peptide Cocktail Vaccine for Esophageal Cancer (Kinki Univ.)

RFS (Relapse-Free Survival) vs. OS (Overall survival)

<table>
<thead>
<tr>
<th></th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>4-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>58.2%</td>
<td>51.1%</td>
<td>46.5%</td>
<td>46.5%</td>
</tr>
<tr>
<td>Control</td>
<td>55.2%</td>
<td>32.3%</td>
<td>25.8%</td>
<td>25.8%</td>
</tr>
</tbody>
</table>

1.0 0.8 0.6 0.4 0.2 0.0
0 12 24 36 48 (M) Months after surgery

(Fleming-Harrington: $p=0.071$)

Vaccine group (n=33)

Control group (n=28)

OS (Overall survival)

<table>
<thead>
<tr>
<th></th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>4-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>90.2%</td>
<td>72.1%</td>
<td>67.6%</td>
<td>60.8%</td>
</tr>
<tr>
<td>Control</td>
<td>80.4%</td>
<td>63.8%</td>
<td>46.4%</td>
<td>30.9%</td>
</tr>
</tbody>
</table>

1.0 0.8 0.6 0.4 0.2 0.0
0 12 24 36 48 (M) Months after surgery

(Fleming-Harrington: $p=0.056$)

Vaccine group (n=33)

Control group (n=28)

Fleming-Harrington test: The weighted log-rank test with the Fleming-Harrington class of weights

(Reference: Takushi Yasuda et. al., The 73rd Annual Meeting of the Japanese Cancer Association, 2014)
Prevention of Tumor Metastasis: Human Atrial Natriuretic Peptide (hANP)

Compound Profile

- **Indication**
  - Prevention of tumor metastasis

- **Mechanism of action**
  - hANP is expected to prevent recurrence and/or metastasis after surgery by inhibiting adhesion of cancer cells to artery endothelial cells by suppressing E-selectin expression which is prompted by inflammation associated with surgery

- **Collaboration**
  - Shionogi will support the clinical research, in part by providing research funds, under a collaborative research agreement with the National Cerebral and Cardiovascular Center (NCVC) and Osaka University

- **Clinical research**
  - Based on the outcome of a retrospective study, improvement in relapse-free survival (RFS) after surgery in patients with non-small cell lung cancer (NSCLC) is confirmed (next slide).
  - A multicenter, randomized, Phase 2 study of hANP during the perioperative period in completely resected NSCLC (JANP study) is planned as a prospective investigator-initiated study under an advanced medical care system B grant

- **Development plan**
  - As an NTE program, Shionogi will develop a new formulation of hANP with improved pharmacokinetics and initiate an oncology clinical study.
Results of retrospective study

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

\[
\begin{align*}
\text{All patients} & & \text{Matched pairs} \\
\text{Time after surgery (Months)} & & \text{Time after surgery (Months)} \\
\text{Relapse free survival (%)} & & \text{Relapse free survival (%)} \\
\text{2-year RFS: 91%} & & \text{2-year RFS: 91%} \\
\text{2-year RFS: 75%} & & \text{2-year RFS: 67%} \\
\end{align*}
\]

Surgery+ANP (n=77)  
Surgery only (n=390)  
Surgery+ANP (n=77)  
Surgery only (n=77)
### Development Pipeline Progression and Expansion (as of March 2015)

<table>
<thead>
<tr>
<th>Core areas</th>
<th>Ph I</th>
<th>Ph IIa</th>
<th>Ph IIb</th>
<th>Ph III</th>
<th>Submission</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious disease</strong></td>
<td></td>
<td>S/GSK1265744 LAP (HIV)</td>
<td></td>
<td></td>
<td></td>
<td>Out-licensed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S-649266 (Severe gram-negative infections)</td>
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<td>Out-licensed</td>
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<tr>
<td></td>
<td>S-033188 (Influenza)</td>
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<tr>
<td></td>
<td>S-718632 (Abuse prevention; chronic pain)</td>
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</tr>
<tr>
<td></td>
<td>S-120083 (Inflammatory pain)</td>
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<tr>
<td></td>
<td>S-010887 (Neuropathic pain)</td>
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<tr>
<td></td>
<td>S-117957 (Neuropathic pain)</td>
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<tr>
<td><strong>Pain/CNS</strong></td>
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<tr>
<td></td>
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<td>S-010887 (Neuropathic pain)</td>
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<tr>
<td></td>
<td>S-117957 (Neuropathic pain)</td>
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<tr>
<td><strong>Frontier areas</strong></td>
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<tr>
<td><strong>Metabolic disorder</strong></td>
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<td></td>
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<tr>
<td></td>
<td>S-237648 (Obesity)</td>
<td>S-707106 (Type 2 diabetes)</td>
<td>S-556971 (Dyslipidemia)</td>
<td></td>
<td></td>
<td>Co-development</td>
</tr>
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<td></td>
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<tr>
<td><strong>Cancer/ Immunity</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>S-488210* (Head and neck squamous cell carcinoma)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>S-525606 (Allergic rhinitis caused by Japanese cedar allergen)</td>
<td></td>
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</tr>
<tr>
<td><strong>Others</strong></td>
<td>S-646240 (AMD)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Red:** Change of Phase or newly added in FY2014

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

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

Developing products globally

Dolutegravir/abacavir/ lamivudine (HIV), US/EU/JP: Approval

Out-licensed

In-licensed
Summary

Isao Teshirogi, Ph.D.
President and CEO
Q&A
Appendix

Disclosed data in FY2014
S-888711
S-649266
Phase III code-break

[Summary of results]

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

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

⇒ In FY2014, plan to submit the NDA in Japan, and to proceed to regulatory consultations with Western authorities
**Purpose**
Evaluate superiority to placebo after 7-day multiple dose administration of S-888711 in subjects for thrombocytopenia with chronic liver diseases prior to elective invasive procedures

**Primary endpoint**
Proportion of patients who did not require platelet transfusion before elective invasive procedures

---

**Diagram**

- **Screening (0-4 weeks)**
- **Double blind (7 days)**
- **Follow-up examination (4 weeks)**

**Informed consent** → **Randomization** → **Placebo** → **Elective invasive procedures** → **Post observation**

**S-888711 (3 mg/day)**

- **Day 9-14**
- **Day 35**
S-888711 (Lusutrombopag): Primary Endpoint (FAS)

Proportion of patients not requiring platelet transfusion (%)

- Placebo: 12.5% (6/48)
- S-888711 (3 mg/day): 79.2% (38/48)

P value <0.0001

FAS: Full analysis set
### S-888711 (Lusutrombopag): Safety

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>S-888711 (3 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td><strong>Patients with adverse events (AEs)</strong></td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td><strong>Patients with AEs related to study drug</strong></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Patients with significant AEs</strong></td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td><strong>Patients with serious AEs</strong></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Patients with thromboembolic AEs</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Patients with bleeding-related AEs</strong></td>
<td>13</td>
<td>7</td>
</tr>
</tbody>
</table>
In vitro antibacterial activity of S-649266 against clinical isolates of β-lactamase-producing gram-negative bacteria

<table>
<thead>
<tr>
<th>Phenotype. Genotype (number of isolates)</th>
<th>Test Compound (MIC: μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S-649266</td>
</tr>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>Carbapenemase producers (193)</td>
<td>0.25</td>
</tr>
<tr>
<td>KPC producers (47)</td>
<td>≤0.063</td>
</tr>
<tr>
<td>NDM-1 producers (50)</td>
<td>1</td>
</tr>
<tr>
<td>VIM producers (28)</td>
<td>0.25</td>
</tr>
<tr>
<td>Metallo beta-lactamase producing</td>
<td>0.5</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (33)</td>
<td></td>
</tr>
<tr>
<td>Multidrug-resistant</td>
<td>0.25</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (30)</td>
<td></td>
</tr>
<tr>
<td>Multidrug-resistant</td>
<td>0.25</td>
</tr>
<tr>
<td>Acinetobacter baumannii (30)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

- 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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