Research and Development at Shionogi

March 19, 2013
Agenda

1. **Research:**
   Kohji Hanasaki, Ph.D.
   *Executive General Manager*
   *Pharmaceutical Research Division*

2. **Development:**
   Takuko Sawada
   *Executive General Manager*
   *Global Development*

3. **Summary:**
   Isao Teshirogi, Ph.D.
   *President and Chief Executive Officer*

4. **Q&A**
The Business Plan and the Growth Strategy

- Steadily Advance the Global Development of Pipeline Compounds to Create Our New Growth Driver

Basic strategy 1
Steady growth mainly through enriched pipeline

Basic strategy 2
Investments in the new growth drivers

Basic Strategy 3
Therapeutic areas to be focused on
Back to growth era

Peptide vaccines/S-117957/S-649266 etc.
Drug candidate selections

Ospemifene (Osphena™)
Royalty income from dolutegravir franchise and dividends from Viiv

SHIONOGI & CO., LTD.

3rd Mid-Term Business Plan
4th Mid-Term Business Plan
5th Mid-Term Business Plan
Research

Kohji Hanasaki, Ph.D.
Executive General Manager
Pharmaceutical Research Division
Mission of the Research Division

**Sustainable growth path**

- **Launch Global Products and Maximize Value of In-line Products**
  - Research that supports development and sales
  - Submission of applications, differentiation, LCM

- **Sustainable DCS**
  - 4 or more DCS 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

**Milestone Timeline**

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

**Mission of the Research Division Company**

- Growth at home and abroad
- Crestor cliff

**Shionogi Pharmaceutical Research Center**

DCS: Drug Candidate Selection

**SHIONOGI & CO., LTD.**
Medicines that can save lives
Medicines that can improve quality of life
Medicines that cure 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.
Achievement in FY2012

- Continuous creation of compounds for Phase I and DCS

**Selected 2 compounds for DCS**
- Anti-*P. aeruginosa* antibody
- Cancer vaccine

**Advanced 3 compounds to Phase I**
- Anti-inflammatory pain: S-120083
- Anti-neuropathic pain: S-010887

Licensed-out a candidate compound for Alzheimer’s disease to Janssen Pharmaceuticals. Progressing into clinical phase.
<table>
<thead>
<tr>
<th>Three targeted R&amp;D areas</th>
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<tbody>
<tr>
<td>Infectious Disease</td>
<td>Metabolic Syndrome</td>
<td>Pain</td>
<td>Frontier areas</td>
<td>Peptide vaccines</td>
<td>Others</td>
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<td>DCS</td>
<td>Ph I</td>
<td>Ph IIa</td>
<td>Ph IIb</td>
<td>Ph III</td>
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<td>Anti-bacterial antibody</td>
<td>S-469266 (Bacterial Infection)</td>
<td>S/GSK1265744 LAP (HIV)</td>
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<td>Obesity</td>
<td>S-234462 (Obesity)</td>
<td>S-707106 (Type 2 Diabetes)</td>
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<td>S-556971 (Dislipidemia)</td>
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<td>S-2367 (Obesity)</td>
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<td>S-524101 (Allergic rhinitis)</td>
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<td>S-0373 (Spinocerebellar ataxia)</td>
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<td>Frontier areas</td>
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<td>S-646240 (AMD)</td>
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<tr>
<td>NF-kB decoy oligo</td>
<td>S-22611 (Cancer)</td>
<td>S-888711 (Thrombocytopenia)</td>
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</table>
Creation of Dolutegravir

- Optimization by using sophisticated compound design lead to a high genetic barrier to resistance

Research

Promote research to maximize the value of existing products under development

Medicines that can save lives

CROI 2010. The Discovery of S/GSK1349572

Elvitegravir
Raltegravir
Dolutegravir

Integrate Mutants
(shaded mutants observed in clinic with Elvitegravir or Raltegravir failure)

Creation of “Best in Class” Integrase Inhibitor
Sophisticated chemistry and ideas for other antiviral research
Aggressively fighting severe infectious disease
Expanding to antibody drug discovery

**New challenge against Gram-negative bacteria**

- **Anti-Pseudomonas aeruginosa** humanized monoclonal antibody
  - Drug for *P. aeruginosa* infection, next anti-microbial pipeline entry following S-649266 (anti-Gram-negative cephem)
  - Mechanism of action has potential for improved efficacy against *P. aeruginosa* infection, including multi-drug resistance

**Survival rate in pulmonary infected mice model**

![Graph showing survival rate in pulmonary infected mice model](image)

**Survival rate (%)**

- **Dose**
  - high
  - low

**Vehicle**

**Post- infection days**

0 1 2 3 4 5 6 7

SHIONOGI & CO., LTD.
Creation of Cancer Vaccine

- Vaccine produced using peptides derived from tumor-associated antigens can effectively induce cytotoxic lymphocytes which specifically destroy tumor cells and show anti-tumor effects.
- Created new clinical candidates, and accelerated global development by enhancing the range of human leukocyte antigen (HLA)-A-02:01 (20% of Japanese and 40-50% of Caucasian) restricted vaccine.
- New contract (March 2012) with OncoTherapy Science, Inc. (OTS, Japan) enables further expansion of the peptide vaccine lineup and target diseases.

Detection of cancer antigen by immunostaining (brownish-red)

Suppressing the growth of tumor cells by suppressing the target gene

Created new opportunities to overcome cancer
Enhanced peptide vaccine lineup
Created a Development candidate for Chronic Pain

The development candidate, which can be expected to show high efficacy against neuropathic pain, has passed safety tests, and preparations are currently ongoing for clinical studies.

Anti-hyperalgesic effects in diabetic neuropathic pain model

- ** p<0.01 vs. Vehicle.
- ++ p<0.01 vs. Marketed drug
- * p<0.05 vs. Vehicle.
- + p<0.05 vs. Marketed drug

Vehicle Marketed drug Developing compound

Low → Dose → High

Working to free patients from pain around the world
**Collaborative Research on Alzheimer’s Disease (BACE inhibitor) with Janssen Pharmaceuticals, Inc.**

- Out-licensed the clinical candidate created in Shionogi to Janssen
- Selected follow-up clinical candidate (preclinical stage)
- Began collaborative research for further discovery

**Effect of the out-licensed clinical candidate in reducing amyloid β42 levels in the spinal fluid of dogs**

<table>
<thead>
<tr>
<th>Compound Dose</th>
<th>Aβ42 in the spinal fluid (% of pre-dosing)</th>
</tr>
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<tbody>
<tr>
<td>Vehicle</td>
<td>0</td>
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<tr>
<td>Low</td>
<td>10</td>
</tr>
<tr>
<td>High</td>
<td>100</td>
</tr>
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</table>

12 h after administration:

- 12 h after administration
- 24 h after administration

**Strengthening Drug Discovery Portfolio through Increased Productivity and Expanding External Collaboration Opportunities**

**BACE:** β-site Amyloid Precursor Protein Cleaving Enzyme
Kyoto University Medical Innovation Center

- Drug discovery and medical research project based on regeneration of synapses and neural function
  - Kyoto University and Shionogi will collaborate for 5 years to identify new targets for drug discovery and create novel drugs by studying the underlying pathology of Alzheimer’s and other CNS diseases, which particularly focus on regenerating synapses and neural function.
  - The collaboration structure involves a joint steering committee established by Kyoto University and Shionogi. The project efforts are conducted mainly in the research center of Kyoto University.
  - The collaboration will encompass both basic and clinical medicine. In addition, it will promote the training and development of academic and industrial scientists in medicine and drug discovery research.

Our aim is to develop drugs for CNS diseases utilizing Shionogi’s know-how in the identification of small molecule drugs that can penetrate the blood-brain barrier, including the BACE inhibitor research.

BACE: β-site Amyloid Precursor Protein Cleaving Enzyme
Establish drug discovery technologies to improve clinical POC rate

Application of Imaging Technology to Research and Clinical Studies

PET Molecular Imaging Center, Osaka University
- Created novel imaging probe, and confirmed the non-clinical efficacy of a CNS compound under development.
- Preparing for microdosing clinical study
- Preparing framework to manufacture PET imaging formulations under GMP

Evaluation of receptor occupancy brains with PET (monkey)

MRI equipment for use with experimental animals at SPRC
- Evaluated the efficacy of anti-allergic agents in guinea pig rhinitis models

Evaluation of efficacy against rhinitis with MRI (guinea pig)

Enabling the application of molecular imaging technology to in non-clinical to clinical translational research
Utilizing iPS Cells in Drug Discovery Research

Collaborative Research with Hokkaido University
- Began screening for non-differentiation or differentiation tropic markers of human iPS cells
- Mature basic research to allow its reliable application in drug discovery research

Utilize iPS cells for research in the field of CNS diseases
- Established methods to enable differentiation of human iPS cells into various kinds of neural cells
- Succeeded in induction of cerebral neurons and constructed an efficacy evaluation system

Utilize human iPS cells in drug discovery research to improve predictability of clinical results
Oligonucleotide Drugs

- Accelerate research and development of oligonucleotide drugs, including antisense and decoy
  ⇒ Establish drug discovery platform for novel oligonucleotide drugs.
- Create novel oligonucleotide drugs, on the basis of our drug design technology
- Accelerate research collaborations with academia
  ➢ R&D of unique modified oligonucleotide drugs and new DDS technology are ongoing.
Explore research seeds from strong relationship with academia

**Strengthening Drug Discovery Portfolio and Expanding External Collaboration Network**

**SHIONOGI Science Program**
- Global open innovation by industry and academia: Academic researchers propose seeds and ideas to address drug discovery needs identified by Shionogi, followed by collaborative efforts to implement them.
- Overseas efforts began in the UK in FY2011; 2 proposals were adopted.
- In FY2012, the program expanded to Australia, Belgium, Denmark, Luxembourg, and the Netherlands, in addition to the UK. Three proposals were adopted.

**FINDS** (FINDS: PHarma-Innovation Discovery competition Shionogi)
- Open innovation by industry and academia in Japan
- Program started in FY2007. A total of 31 proposals have been adopted, 8 of them in FY2012.
- New drug discovery programs have resulted.

http://www.shionogi.co.jp/finds/index.html

Continuous exploration of original seeds ideas through global research collaboration
Toward Top Level Global Research Productivity

SPRC as a Hub of Research Network

- Hokkaido University
- Shionogi Innovation Center
- Osaka University PET Molecular Imaging Center
- Pharmaceutical companies
- Bio-ventures
- Academia
- External research institutes

Brand-new Research Hub
Tight-knit organization

Free and Fluid Discussions
Innovative Ideas

Speedy and Close Research Cycle

Self-organized workshop

Started innovative research programs
Targets and Measures for FY2013

- Develop 4 or more DCS over the course of the year
  - Prioritize core programs in Shionogi’s therapeutic areas of focus
  - Expand external research collaborations and progress creative drug discovery programs
  - Accelerate development of large molecule drugs and develop new core therapeutic area studies for future studies

- Establish drug discovery technologies to improve clinical POC rate
  - Drug technologies that bridge 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 for exploratory IND Studies
    - Strengthen safety and efficacy evaluation system that efficiently incorporates feedback from clinical results
  - Identify and mature research seeds from strong relationship with academia

- Promote research to maximize value of marketed and pipeline products
  - Support research for Life Cycle Management of marketed products
  - Promote evaluation of new indications and differentiation studies for pipeline products
Development

Takuko Sawada

Executive General Manager
Global Development
The 3rd Medium-Term Business Plan: Goals and Current Status of Development Division

Achievements in FY2012 and Target Milestones for FY2013

Core Development Products
The 3rd Medium-Term Business Plan: Goals and Current Status of Development Division

**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**
- Establishment of a Global Development Office (GDO)
- Portfolio management

**Establish Development Footholds Worldwide: completed**
- Unification of development function in the US
- Establishment of development footholds in the EU
- Establishment of development footholds in China
Enhance Strategic Decision Making Function and Efficient Development

- Establishment of cross-organizational function in GDO
  - Global Project Management (FY2011)
  - New Product Planning (FY2011)
  - Global Regulatory Affairs (FY2012)
  - Portfolio Management (FY2011)
  - Market Access (FY2012)

- Strategic decision making for global compounds
  - Global Development Committee / Global Commercial Committee / Global Portfolio Management Committee

- Information sharing through new IT systems connecting the US, the EU and Japan, and improved response time through use of a transparent process (FY2011 - FY2013)

- Best selection of target patient population and improved prediction of clinical study outcomes through intensive collaboration between epidemiology and statistics (FY2012 -)

- Development of companion diagnostics through industrial-academic collaborations (FY2012 -)
Two Compounds are in the Final Phase toward Full-Scale Globalization

- **Ospemifene:** Post-menopausal vaginal atrophy
  - NDA filed in April 2012; approved on February 26, 2013 in the US
  - First drug, containing a new active ingredient, developed by Shionogi to gain approval in the US
  - MAA submission was completed in the EU; development in Asia is under consideration

- **S/GSK1349572 (Dolutegravir): HIV infection**
  - Shionogi transferred the exclusive global rights for DTG to ViiV Healthcare in October 2012.
    - Shionogi will receive a royalty averaging in the high teens on net sales of the integrase inhibitor portfolio, including an FDC.
    - Shionogi became a 10% shareholder in ViiV Healthcare and received a proportional share of dividends paid on net sales of all the ViiV's drugs for HIV.
    - Shionogi will be entitled to representation on the ViiV Healthcare Board, which contributes to maximization of the complete potential of DTG.
    - Shionogi will assign releasing financial, operational, and R&D resources to support its other pipeline products.
  - NDA filed in December 2012 globally; FDA granted a priority review designation to the product.
Selection of Development Compounds and Concentration of Investment

- Increased the number of late-phase compounds domestically and abroad in FY2013, which increased potential development costs significantly.
- Investment will be made intensively in 2 global late-phase compounds followed by that for high-priority domestic compounds.
  - S-297995 (Alleviation of opioid-induced adverse effects)
    - End-of-Phase II meeting held with FDA.
    - Global Phase III trials in preparation.
  - S-555739 (Allergic rhinitis)
    - Phase III trial for seasonal allergic rhinitis is being conducted in Japan in advance of other countries.
    - Another dose-finding study will be started outside Japan.
- Some projects will be temporarily suspended, and budget allocations will be reviewed periodically.
Successive Maximization of the Value of High-Priority Compounds

- Lifecycle management of Cymbalta®
  - Additional indication for fibromyalgia: clinical trial continued.
  - Additional indication for chronic low back pain: clinical trial planned.

- Lifecycle management of Irbetan®
  - Development of an FDC with Fluitran®: NDA filed in July 2012
  - License agreement for the co-marketing of a combination product of anti-hypertension drugs irbesartan and amlodipine besilate with Dainippon Sumitomo Pharma: signed in June 2012 (launched in December 2012)
  - New dosage form of Irbetan® 200mg tablet: NDA filed in April 2012

- Lifecycle management of Finibax®
  - Additional indication for pediatric infection: approved in May 2012

- Buildup of oxycodone pipeline
  - Additional indication for non-cancer pain: clinical trial initiated

FDC: Fixed dose combination
### Achievements in FY2012: Approval and NDA Submission

<table>
<thead>
<tr>
<th>Approval</th>
<th>Additional indication for pediatric infection</th>
<th>Japan: May 2012</th>
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<tbody>
<tr>
<td>FINIBAX®</td>
<td></td>
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<tr>
<td>NDA submission</td>
<td>Hypertension</td>
<td>Japan: Apr. 2012</td>
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<tr>
<td>Irbetan® 200mg tablet</td>
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<tr>
<td>S-474474</td>
<td>Hypertension</td>
<td>Japan: Jul. 2012</td>
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<tr>
<td>Metreleptin</td>
<td>Lipodystrophy</td>
<td>Japan: Jul. 2012</td>
</tr>
<tr>
<td>Ospemifene</td>
<td>Post-menopausal vaginal atrophy</td>
<td>EU: Mar. 2013</td>
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</table>

*S ViiV Healthcare Ltd.*
### Development

**Achievements in FY2012: Phase I-III (1/2)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Condition</th>
<th>Development Status</th>
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</thead>
<tbody>
<tr>
<td>S-555739</td>
<td>Allergic rhinitis</td>
<td>Japan: Phase III initiated US: Phase IIa LPO</td>
</tr>
<tr>
<td>S-2367</td>
<td>Obesity</td>
<td>Japan: Phase IIb registration completed</td>
</tr>
<tr>
<td>S-556971</td>
<td>Dyslipidemia</td>
<td>Japan: Phase IIb initiated, registration completed</td>
</tr>
<tr>
<td>S-524101</td>
<td>Allergic rhinitis caused by house-dust mite allergen</td>
<td>Japan: Phase II/III initiated, registration completed</td>
</tr>
<tr>
<td>S-888711</td>
<td>Thrombocytopenia</td>
<td>Japan: Phase IIb initiated, registration completed</td>
</tr>
<tr>
<td>S-877489</td>
<td>ADHD</td>
<td>Japan: Phase II initiated</td>
</tr>
<tr>
<td>S-877503</td>
<td>ADHD</td>
<td>Japan: Phase II/III initiated</td>
</tr>
</tbody>
</table>

ADHD: Attention deficit hyperactivity disorder

LPO: Last patient out
### Development

**Achievements in FY2012: Phase I-III (2/2)**

<table>
<thead>
<tr>
<th>Project Code</th>
<th>Disease/Condition</th>
<th>Status</th>
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<tbody>
<tr>
<td>S-288310</td>
<td>Bladder cancer</td>
<td>Asia: Phase I/II continued</td>
</tr>
<tr>
<td>S-488410</td>
<td>Esophageal cancer</td>
<td>Japan: Phase I/II continued</td>
</tr>
<tr>
<td>S-488210</td>
<td>Head and neck squamous cell carcinoma</td>
<td>EU: Phase I/II continued</td>
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<tr>
<td>S-646240</td>
<td>Age-related macular degeneration</td>
<td>Japan: Phase IIa continued</td>
</tr>
<tr>
<td>S-222611</td>
<td>Malignant tumor</td>
<td>EU: Phase Ib continued</td>
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<tr>
<td>S-649266</td>
<td>Bacterial infection</td>
<td>Japan: Phase I single/multiple dose completed</td>
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<tr>
<td>S-120083</td>
<td>Inflammatory pain</td>
<td>Japan: Phase I initiated</td>
</tr>
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### Development for as yet Unapproved Indications, and Drugs Requested for Development by Academy

#### Unapproved and off-label: Status of progress

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Status</th>
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<tbody>
<tr>
<td>Cymbalta®</td>
<td>Fibromyalgia</td>
<td>Phase III</td>
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<tr>
<td>OxyContin®</td>
<td>Moderate to severe chronic pain (non-cancer pain)</td>
<td>Phase II/III initiated</td>
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<tr>
<td>Longes®</td>
<td>Childhood hypertension</td>
<td>Approved in Jun. 2012</td>
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<tr>
<td>Flagyl®</td>
<td>Infections caused by anaerobic bacteria, and amebiasis giardiasis</td>
<td>Approved in Aug. 2012</td>
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<tr>
<td>Baktar®</td>
<td>Pneumocystis carinii</td>
<td>Approved in Aug. 2012</td>
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<tr>
<td>Endoxan®</td>
<td>Pheochromocytoma</td>
<td>NDA submission</td>
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<tr>
<td>Predonine®</td>
<td>Duchenne muscular dystrophy</td>
<td>NDA submission</td>
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<tr>
<td>Vancomycin</td>
<td>Gram-positive bacteria-associated bloodstream infection</td>
<td>Under consideration</td>
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#### Requested for development by academy: Status of progress

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<th>Indication</th>
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<tr>
<td>Metreleptin</td>
<td>Lipodystrophy</td>
<td>NDA filing*</td>
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<tr>
<td>Imunomax®-γ</td>
<td>Additional indication for mycosis fungoides and Sezary's syndrome</td>
<td>Phase II</td>
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<tr>
<td>Flagyl®</td>
<td>Helicobacter pylori infection, stomach inflammation</td>
<td>Approved in Feb. 2013</td>
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<tr>
<td>Predonine®</td>
<td>Kawasaki disease (acute phase)</td>
<td>NDA submission</td>
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* Passed Drug Committee Meeting on March 8, 2013
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<td>S/GSK1265744 (LAP (HIV))</td>
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</table>

**Out-licensing Products**

- Alzheimer's disease
- S/GSK1265744 (LAP (HIV))
- S-0373 (Spinocerebellar ataxia)
- S/GSK1349572 (HIV)

**Origin:**

- In-house
- Co-development
- In-licensed

LAP: Long-acting parenteral formulation
ADHD: Attention Deficit Hyperactivity Disorder
AMD: Age-related Macular Degeneration

Developing products globally
## Target Milestones for FY2013: Approval and NDA Submission

### Approval

<table>
<thead>
<tr>
<th>Product</th>
<th>Disease</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/GSK-349572* (Dolutegravir)</td>
<td>HIV infection</td>
<td>Global (US: PDUFA, Aug. 2013)</td>
</tr>
<tr>
<td>S-474474</td>
<td>Hypertension</td>
<td>Japan</td>
</tr>
<tr>
<td>Metreleptin</td>
<td>Lipodystrophy</td>
<td>Japan</td>
</tr>
</tbody>
</table>

### NDA submission

<table>
<thead>
<tr>
<th>Product</th>
<th>Disease</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imunomax®-γ</td>
<td>Mycosis fungoides and Sezary’s syndrome</td>
<td>Japan</td>
</tr>
</tbody>
</table>

* ViiV Healthcare Ltd.

PDUFA: Prescription Drug User Fee Act
### Progress in development status

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease Area</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cymbalta®</td>
<td>Chronic low back pain</td>
<td>Japan: Phase III initiation</td>
</tr>
<tr>
<td>S-297995</td>
<td>Alleviation of opioid-induced adverse effects</td>
<td>Global: Phase III initiation</td>
</tr>
<tr>
<td>S-555739</td>
<td>Allergic rhinitis</td>
<td>Japan: Phase III (SAR) code-break</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US/EU: Phase II completion</td>
</tr>
<tr>
<td>S-888711</td>
<td>Thrombocytopenia</td>
<td>Japan: Phase IIb code-break, go/no-go decision</td>
</tr>
<tr>
<td>S-2367</td>
<td>Obesity</td>
<td>Japan: Phase IIb code-break, go/no-go decision</td>
</tr>
<tr>
<td>S-556971</td>
<td>Dyslipidemia</td>
<td>Japan: Phase IIb code-break, 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/III code-break</td>
</tr>
<tr>
<td>S-646240</td>
<td>Age-related macular degeneration</td>
<td>Japan: Phase IIa code-break, go/no-go decision</td>
</tr>
</tbody>
</table>

SAR: Seasonal allergic rhinitis
**Development**

Target Milestones for FY2013: Phase I-III (2/2)

<table>
<thead>
<tr>
<th>Progress in development status</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-588410</strong>*</td>
<td>Bladder cancer</td>
<td>Japan/EU: POC initiation</td>
</tr>
<tr>
<td>S-222611</td>
<td>Malignant tumor</td>
<td>EU: Phase II initiation</td>
</tr>
<tr>
<td>S-649266</td>
<td>Bacterial infection</td>
<td>US: Phase II initiation</td>
</tr>
<tr>
<td>S-120083</td>
<td>Inflammatory pain</td>
<td>Japan/US: Phase II initiation</td>
</tr>
<tr>
<td>S-117957</td>
<td>Neuropathic pain</td>
<td>US: POM initiation</td>
</tr>
</tbody>
</table>

FTIH: 3 or more compounds

* 5-peptide cocktail vaccine
  POC: Proof of concept
  POM: Proof of mechanism
  FTIH: First trial in humans
Core Development Products
S/GSK1349572 (Dolutegravir): HIV infection
Number of people infected with the human immunodeficiency virus (HIV): Approximately 34 million (WHO, UNICEF, UNAIDS, Progressive report 2011)

Sales of anti-HIV agents in global market*:
- Approximately $16,800 million (2011, +10% from 2011): 47% of these sales are from the US market and 53% from EU and the rest of the world.
- Integrase inhibitors (INI) and 3-drug fixed-dose combinations (FDC, e.g., EFV/TDF/FTC) drive the market growth.
- Annual sales of raltegravir in 2012 were $1,515 million.

*Dolutegravir: Developed by ViiV Healthcare (from November, 2012) Market Information
**Development (Infectious Diseases)**

**Dolutegravir: Filed NDA/MAA to US, EU and Canada from ViiV on December 17, 2012. Granted priority review status from FDA**

### Target Indication 1: Treatment naive patients; 50mg once daily
1) Once daily DTG non-inferior to twice-daily RAL. Comparable tolerability
2) No treatment emergent resistance mutations in the DTG treatment arm vs. 5 in the RAL arm
3) DTG + ABC/3TC was superior to Atripla (differences in efficacy were primarily driven by a higher rate of discontinuation due to adverse events in the Atripla arm)

### Target Indication 2: Treatment experienced but INI naive patients; 50mg once daily
1) Superior to RAL in this patient population. Fewer subjects failed therapy with INI resistance mutations on DTG (n=2) than on RAL (n=10, p=0.016)
2) Low potential of drug interactions, less restrictions to co-administered drugs

### Target Indication 3: INI failure patients; 50mg twice daily
63% of patients with limited treatment options achieved plasma HIV RNA <50 c/mL at Week 24

### Target Initial indication to children: age 12 – 18 (study ongoing)
50mg once daily has similar DTG plasma concentration, safety and efficacy to adults

DTG: dolutegravir, RAL: raltegravir, ABC/3TC: abacavir/lamivudine
Atripla: EFV/TDF/FTC
## Development (Infectious Diseases)

### Dolutegravir: Ongoing Phase III studies

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Population</th>
<th>Study design</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING113086</td>
<td>Treatment-naïve patients</td>
<td>ART-naïve patients (n=788) DTG 50QD vs. RAL (+ NRTIs of choice) non-inferiority design</td>
<td>Week 48 Non-inferior</td>
</tr>
<tr>
<td>ING114467</td>
<td>Treatment-experienced but INI-naïve patients</td>
<td>ART-naive patients (n=788) ABC/3TC/DTG 50QD vs. Atripla non-inferiority design</td>
<td>Week 48 Superior</td>
</tr>
<tr>
<td>ING111762</td>
<td>ART-experienced, INI-naïve patients (n=688) DTG 50QD vs. RAL (+ BR) non-inferiority design</td>
<td>Week 24 Superior</td>
<td></td>
</tr>
<tr>
<td>ING112574</td>
<td>INI-resistant patients (n~200) Single cohort, DTG 50BID + OBR*</td>
<td>Week 24 63% patients HIV RNA &lt;50c/mL</td>
<td></td>
</tr>
</tbody>
</table>

* Optimised background regimen

DTG: dolutegravir, RAL: raltegravir, Atripla: EFV/TDF/FTC
Phase III study with treatment-experienced and INI-naïve patients (SAILING)

- Double blind trial
- Evaluable subjects: 719 adults
- Comparator: RAL
- Endpoint: Proportion of subjects with HIV RNA level <50 copies/mL at Week 24 and 48
- DTG 50 mg once daily vs. RAL 400 mg twice daily

HIV-1 ART-experienced, INI-naïve
HIV-1 RNA >400 copies/mL
1:1 Randomization
Stratified by HIV-1 RNA
(≤ or >50,000), DRV/r use
and # of fully active drugs

Randomized Phase

DTG 50 mg QD + RAL PBO + BR
RAL 400 mg BID + DTG PBO + BR

At Screening and a second consecutive test >400 c/mL within 4 months prior to Screening (if Screening HIV-1 RNA >1000 c/mL, no additional HIV-1 RNA assessment was needed)
DTG: dolutegravir, RAL: raltegravir, PBO: placebo, BR: background regimen

Pozniak et al. CROI 2013; Atlanta, GA. Poster #179LB.
Proportion of Subjects With HIV-1 RNA level <50 copies/mL (Snapshot, mITT-E)

DTG 50 mg QD was statistically superior to RAL 400 mg BID at Week 24

Week 24 adjusted difference in response (95% CI):
+9.7 in favor of DTG (3.1%, 15.9%); \(P=0.003\)

* Adjusted difference based on stratified analysis adjusting for Baseline HIV-1 RNA (\(\leq50,000\) copies/mL vs. >50,000 copies/mL), DRV/r use without primary PI mutations and Baseline PSS (2 vs. <2)

- Median CD4+ (interquartile range [IQR]) change from Baseline (observed case) was similar between arms: DTG: +99 cells/mm\(^3\) (n=325; IQR: 34, 184); RAL: +93 cells/mm\(^3\) (n=326; IQR: 46, 166).

Pozniak et al. CROI 2013; Atlanta, GA. Poster #179LB.
*Screening or documented historical evidence
OSS (overall susceptibility score) determined by Monogram Biosciences net assessment
Day 8 and Week 24 Efficacy Endpoints

- Day 8 change from BL: \(-1.43 \log_{10} \) copies/mL HIV-1 RNA, \( P<0.001 \)
  - 95% CI, -1.52 to -1.34 (ITT-E, N=183)

- Week 24 by Snapshot (MSDF): 72/114 (63%) <50 copies/mL HIV-1 RNA
  - 37/114 (32%) were virologic non-responders
    - 6/114 (5%) changed OBR
  - Only 5/114 (4%) were non-responders for discontinuation due to AEs

Overall, 63% were fully suppressed at Week 24 by Snapshot algorithm

Week 24 population (N=114) was those subjects who had opportunity to reach Week 24 at time of data cut-off

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012; Oral #O232.
S-288310, S-488410:

Cancer Peptide Vaccine
Cancer Peptide Vaccines: Profile

- In-licensed from OncoTherapy Science, Inc. (OTS, Japan)
- Worldwide rights to develop and market cancer peptide vaccines
- Mechanism of action:
  - Vaccination with peptides derived from tumor-associated antigen selectively expressed in tumor cells can effectively induce cytotoxic T-lymphocytes (CTLs), which elicite the antitumor effect.
- Indications:
  - Clinical trials for bladder cancer, esophageal cancer and head and neck cancer are ongoing
  - Acquire worldwide rights to all indications from OTS last May
- Characteristics:
  - S-288310 and S-488410
    - Contain 2 or 3 human leukocyte antigen (HLA)-A*24:02-restricted peptides
      (positive in 60% of the Japanese population and 15 to 20% of the Caucasian population)
  - S-488210:
    - Contains 3 HLA-A*02:01-restricted peptides
      (positive in 20% of the Japanese population and 40 to 50% of the Caucasian population)
S-288310 (bladder cancer): Development Status

● Phase I/II (Japan)
  ➢ Target patients
    ✓ Patients with advanced metastatic bladder cancer
  ➢ Objectives
    ✓ To evaluate the safety, tolerability, and immunologic response
  ➢ Status
    ✓ Interim analysis for safety and efficacy has been completed
    ✓ Extension study is ongoing

● Phase I (Asia)
  ➢ Target patients
    ✓ Patients with resected non-muscle invasive bladder cancer after transurethral resection of the bladder tumor (TURBT)
  ➢ Objectives
    ✓ To evaluate the safety, tolerability, and immunologic response
  ➢ Status
    ✓ Ongoing
**Development (Peptide Vaccines)**

**S-288310: Phase I/II**

- Oncoantigen A and B are highly expressed in bladder cancer tissues
- S-288310 showed a high rate of induction of CTL

<table>
<thead>
<tr>
<th>Oncoantigen expression rate</th>
<th>CTL induction rate by S-288310</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncoantigen A</td>
<td>36/38 (95%)</td>
</tr>
<tr>
<td>Oncoantigen B</td>
<td>35/38 (92%)</td>
</tr>
<tr>
<td>Either A/B</td>
<td>37/38 (97%)</td>
</tr>
<tr>
<td>Oncoantigen A peptide</td>
<td>22/33 (67%)</td>
</tr>
<tr>
<td>Oncoantigen B peptide</td>
<td>24/33 (73%)</td>
</tr>
<tr>
<td>Either A/B peptide</td>
<td>29/33 (88%)</td>
</tr>
</tbody>
</table>

**Immunohistochemistry: Oncoantigen A**

- Specific Ab
- Control Ab

**Immunohistochemistry: Oncoantigen B**

- Specific Ab
- Control Ab
S-288310: Phase I/II

- **Antitumor response (Evaluation criteria: irRC*)**

<table>
<thead>
<tr>
<th>Response rate (irCR+irPR)</th>
<th>2/32 (6.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease control rate (irCR+irPR+irSD)</td>
<td>18/32 (56.3%)</td>
</tr>
</tbody>
</table>

*immune-related response criteria

Criteria for evaluation of immune therapy activity in solid tumors

<table>
<thead>
<tr>
<th>irCR</th>
<th>complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disappearance of all lesions in two consecutive observations not less than 4 wk apart</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>irPR</th>
<th>partial response</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>irSD</th>
<th>Stable Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir</td>
<td></td>
</tr>
</tbody>
</table>

**Overall survival (OS)**

Kaplan-Meier method

- **Survival function**
- **Time (months)**
- **S-288310**
  - N=32
  - Median: 9.4
  - 90% CI: (4.2, 12.2)
Development (Peptide Vaccines)

S-288310: a patient with good response (1)

73-year-old man, best overall response: irPR (Partial Response)

Lower lobe of the left lung

![Images of CT scans showing size changes over time.]

Superior lingular segment of the left lung

![Images of CT scans showing size changes over time.]

Disappeared
Development (Peptide Vaccines)

S-288310: A Patient with Good Response (2)

79-year-old man, best overall response: irPR (Partial Response)

The left muscularis rectus abdominis

Presacral region
Development (Peptide Vaccines)

S-288310: A Patient with Good Response (3*)

73-year-old man, best overall response: irSD (Stable Disease)

* The primary lesion (bladder) was not responsive.
**Development (Peptide Vaccines)**

**S-488410 (esophageal cancer): Development Status**

- **Phase I/II (Japan)**
  - **Target patients**
    - Patients with unresectable advanced or recurrent esophageal squamous cell carcinoma
  - **Objectives**
    - To evaluate the safety, tolerability, and immunologic response (CTL induction)
  - **Status**
    - Patients enrollment was completed on schedule in March 2012
    - CTL induction rate in HLA-A*24-positive patients was 82% Sufficient level of CTL was induced in all dosage groups
    - OS period of CTL-induced patients prolonged with statistical significance compared to CTL-non-induced patients in HLA-A*24:02-positive subjects

![Survival function graph](chart.png)

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.446</td>
<td>(0.215, 0.925)</td>
</tr>
</tbody>
</table>
Summary of Japan Phase I/II Results (Bladder and Esophageal Cancer)

- **Safety**
  - Good safety and tolerability were confirmed; however, a high incidence of injection site reactions was observed

- **Expression of oncoantigens**
  - Each antigen was highly expressed in tumor tissues

- **Induction of cytotoxic T lymphocytes (CTLs)**
  - Each peptide induced CTL with a high frequency
    - Bladder cancer, 88%; esophageal cancer, 82% (human leukocyte antigen [HLA]-matched patients)

- **Antitumor response**
  - Two patients with bladder cancer achieved partial response (PR), but none of the patients with esophageal cancer had PR

- **Overall survival (OS)**
  - Patients with induction of CTLs showed a trend of increase in OS

*Development (Peptide Vaccines)*
Development (Peptide Vaccines)

Development of a 5-peptide Cocktail Vaccine

• Five oncoantigens are highly expressed in the tissues of patients with bladder cancer and esophageal cancer (immunohistochemistry)

<table>
<thead>
<tr>
<th>Oncoantigens</th>
<th>Antigen A</th>
<th>Antigen B</th>
<th>Antigen C</th>
<th>Antigen D</th>
<th>Antigen E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder cancer (n=20)</td>
<td>100%</td>
<td>100%</td>
<td>80%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Esophageal cancer (n=20)</td>
<td>100%</td>
<td>100%</td>
<td>90%</td>
<td>90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

• Distribution and intensity of oncoantigen expression are heterogeneous even in tissues of one patient
• The patients showed different intensities of oncoantigen expression.
• Induction of multiple cytotoxic T lymphocytes (CTLs) against oncoantigen-derived peptides may increases the overall survival (OS)
  - Prolongation of OS in patients with multiple CTL induction was observed in Phase I/II studies both of both S-288310 and S-488410.
Importance of Development of a 5-peptide Cocktail Vaccine

- **Improvement of efficacy**
  - For individual difference in CTL inducibility by each peptide
  - For heterogeneity of antigen expression in one patient
  - For diversity of antigen expression among patients
  - Improvement of CTL induction rate
  - Enhancement of efficacy in one patient
  - Improvement of efficacy rate in the target patient population

- **Expansion of indications and maximization of value**
  - Single formulation of cocktail vaccine will exert efficacy against many types of cancers

- **Development plan**
  - Regarding 5-peptide cocktail vaccine, a POC study in patients with advanced metastatic bladder cancer in Japan and the EU will be started with a priority for bladder cancer
  - A global Phase III study will be prepared in parallel with conducting a POC study
Ospemifene:
Vulvar and Vaginal Atrophy
About Dyspareunia (Painful Intercourse) and Vulvar and Vaginal Atrophy (VVA)

- Dyspareunia is one of the most common symptoms of VVA, a chronic and progressive condition due to menopause.
- Declining estrogen levels during menopause can cause tissues of the vaginal lining to grow thinner and to lose elasticity, a condition known as vaginal atrophy.
- Menopause also causes increases in vaginal pH which may increase the likelihood of developing urinary tract infection or vaginitis.
- These changes can lead to dyspareunia.
- While approximately 32 million postmenopausal women in the U.S. experience symptoms of VVA, 93 percent are not being treated with a prescription medication.

Pre menopause

- Superficial cells: 15%
- Intermediate cells: 80%
- Parabasal cells: 5%

Post menopause

- Superficial cells: 1%
- Intermediate cells: 60%
- Parabasal cells: 39%

Vaginal epithelium

Development (Others)
Osphena™ (Ospemifene): Approved by the FDA in the US for the Treatment of Moderate to Severe Dyspareunia (Painful Intercourse), a Symptom of Vulvar and Vaginal Atrophy (VVA), due to Menopause

● Profile
  - As an estrogen agonist/antagonist with tissue selective effects, is the first and only oral treatment alternative to vaginal or oral steroidal estrogens for women with dyspareunia due to menopause.
  - Its biological actions are mediated through binding to estrogen receptors, which results in activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism).
  - Efficacy and safety was demonstrated in three clinical trials with demonstrated significant improvements in dyspareunia and increased superficial cells and decreased parabasal cells and vaginal pH.

● Schedule
  - MAA submission in EU: March 2013
  - Under consideration for development in Asia
### 1st Clinical Trial Results

<table>
<thead>
<tr>
<th>Most Bothersome Moderate to Severe Symptom at Baseline</th>
<th>OSPHENA™ 60 mg (N=110)</th>
<th>Placebo (N=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspareunia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean (SD)</td>
<td>2.7 (0.44)</td>
<td>2.7 (0.45)</td>
</tr>
<tr>
<td>LS Mean Change from Baseline (SE)</td>
<td>-1.39 (0.11)</td>
<td>-0.89 (0.11)</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>0.0012</td>
<td>---</td>
</tr>
</tbody>
</table>

### 2nd Clinical Trial Results

<table>
<thead>
<tr>
<th>Most Bothersome Moderate to Severe Symptom at Baseline</th>
<th>OSPHENA™ 60 mg (N=301)</th>
<th>Placebo (N=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspareunia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean (SD)</td>
<td>2.7 (0.47)</td>
<td>2.7 (0.47)</td>
</tr>
<tr>
<td>LS Mean Change from Baseline (SE)</td>
<td>-1.55 (0.06)</td>
<td>-1.29 (0.07)</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>&lt;0.0001</td>
<td>---</td>
</tr>
</tbody>
</table>

SD: Standard deviation, LS: Least Squares, SE: Standard error
In both clinical trials, there was a statistically significant:

- Increase in the proportion of superficial cells (p<0.0001)
- Decrease in the proportion of parabasal cells (p<0.0001)
- Decrease in vaginal pH (p<0.0001)
**Osphena™ - Market Opportunity**

- Vulvar and vaginal atrophy (VVA) market in the US as of 2012

**An Unmet Need**

More than 60% patients are estimated to be untreated.

**Development (Others)**

- Duavive® (bazedoxifene-conjugated estrogens) filed for Europe and for US
- No other new launches expected in the prescription cream market

**US Women Population ~157M**

- Post-Menopausal women (age, >45 years) (41%) = 64M
- Population of women with VVA (50%) = 32M
- Women whose condition is diagnosed as VVA (30%) = 9.6M

**Potential patients**

- Treated with RX (24%) = 2.3M

**Patients on drug**

**Vaginal Estrogen Products**

- Premarin® Vaginal Cream (Conjugated estrogens)
- Estring® (Estradiol vaginal ring)
- Estrace® (Estradiol vaginal tablet)
- Femring® (Estradiol acetate ring)
- Vagifem® (Estradiol vaginal tablet)
Osphena™ - Preparation for Commercial Launch in the US

- Progress to launch Shionogi Inc.’s first NCE
  - Trade name: Osphena™
  - Approved by the FDA on February 26, 2013
  - Indication: For the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
  - Targeted launch date: June 2013

- Osphena™ offers an important treatment alternative to women who are living with dyspareunia
  - Oral, 60 mg once daily tablet

NCE: New Chemical Entity
### Development Pipeline Enrichment (as of March 2013)

#### Three targeted R&D areas

<table>
<thead>
<tr>
<th>Infectious Disease</th>
<th>Ph I</th>
<th>Ph IIa</th>
<th>Ph IIb</th>
<th>Ph III</th>
<th>Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-649266 (Bacterial Infection)</td>
<td>Co-development</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-234462 (Obesity)</td>
<td>Co-development</td>
<td>S-707106 (Type 2 Diabetes)</td>
<td></td>
<td></td>
<td>S-474474 (Hypertension)</td>
</tr>
<tr>
<td>S-117957 (Neuropathic pain)</td>
<td>Co-development</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-120083 (Inflammatory pain)</td>
<td>Co-development</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-297995 (All alleviation of opioid-induced adverse effects)</td>
<td>Co-development</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

#### Metabolic Syndrome

<table>
<thead>
<tr>
<th>Ph IIb</th>
<th>Ph III</th>
<th>Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-2367 (Obesity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-556971 (Dislipidemia)</td>
<td></td>
<td></td>
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<tr>
<td>S-524101 (Allergic rhinitis caused by house-dust mite allergen)</td>
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#### Pain

<table>
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<tr>
<th>Ph I</th>
<th>Ph IIa</th>
<th>Ph IIb</th>
<th>Ph III</th>
<th>Submission</th>
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<tr>
<td>S-288310 (Bladder cancer)</td>
<td>Co-development</td>
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<tr>
<td>S-488410 (Esophageal cancer)</td>
<td>Co-development</td>
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<td>S-488210 (Head and neck cancer)</td>
<td>Co-development</td>
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<td>S-646240 (AMD)</td>
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</tbody>
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#### Frontier areas

- **Peptide vaccines**
  - S-222611 (Cancer)
  - S-888711 (Thrombocytopenia)
  - S-555739 (Allergic rhinitis)
  - S-524101 (Allergic rhinitis caused by house-dust mite allergen)
  - S-8777503 (ADHD) Co-development
  - S-877489 (ADHD) Co-development
  - PSD502 (Premature ejaculation) Co-development

- **Others**
  - S-297995 (All alleviation of opioid-induced adverse effects) Co-development
  - S-887711 (Thrombocytopenia)
  - S-555739 (Allergic rhinitis)
  - S-524101 (Allergic rhinitis caused by house-dust mite allergen)
  - S-8777503 (ADHD) Co-development
  - S-877489 (ADHD) Co-development
  - PSD502 (Premature ejaculation) Co-development

#### Out-licensing Products

- S/GSK1265744 LAP (HIV) Co-development
- S/GSK1349572 (HIV) Co-development

#### Origin

- In-house
- Co-development
- In-licensed

LAP: Long-acting parenteral formulation
ADHD: Attention Deficit Hyperactivity Disorder
AMD: Age-related Macular Degeneration

*Developing products globally*
Summary

Isao Teshirogi, Ph.D.

President and Chief Executive Officer
Q&A
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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