Research and Development at Shionogi

March 19, 2013

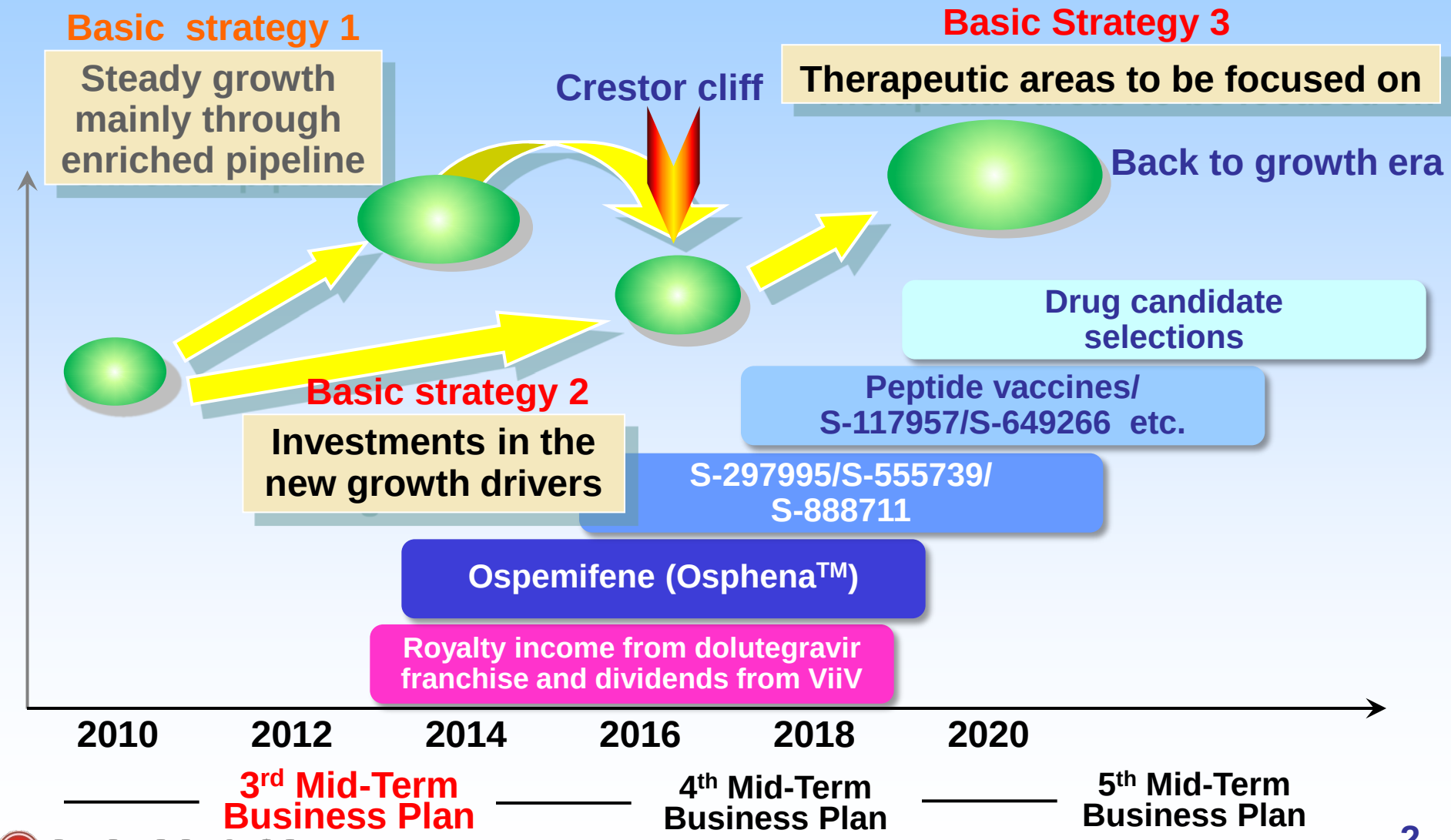
SHIONOGI & CO., LTD.

Agenda

1. **Research:**
   Kohji Hanasaki, Ph.D.
   Executive General Manager
   Pharmaceutical Research Division
2. **Development:**
   Takuko Sawada
   Executive General Manager
   Global Development
3. **Summary:**
   Isao Teshirogi, Ph.D.
   President and Chief Executive Officer
4. **Q&A**

The Business Plan and the Growth Strategy

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



Research

Kohji Hanasaki, Ph.D.

Executive General Manager

Pharmaceutical Research Division

Mission of the Research Division

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

Mission of the Research Division Company

Growth at home and abroad

Crestor cliff

Sustainable growth path

Launch Global Products and Maximize Value of In-line Products

Research that supports development and sales

- Submission of applications, differentiation, LCM

Sources of Future Growth

4 or more DCS per year with high potential for success

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

Sustainable DCS

Acquire research assets that will bear fruit in the future

SPRC: Shionogi Pharmaceutical Research Center
DCS: Drug Candidate Selection

The scope of Discovery Research of Shionogi

Metabolic syndrome

Infectious diseases

Pain

- Medicines that can save lives
- Medicines that can improve quality of life
- Medicines that cure disease (eradicative medicine)

Next generation waves of medicinal research

Shionogi's purpose:

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

Achievement in FY2012

- Continuous creation of compounds for Phase I and DCS

Selected 2 compounds for DCS

Anti-*P.aeruginosa* antibody

Cancer vaccine

Licensed-out a candidate compound for Alzheimer's disease to Janssen Pharmaceuticals. Progressing into clinical phase

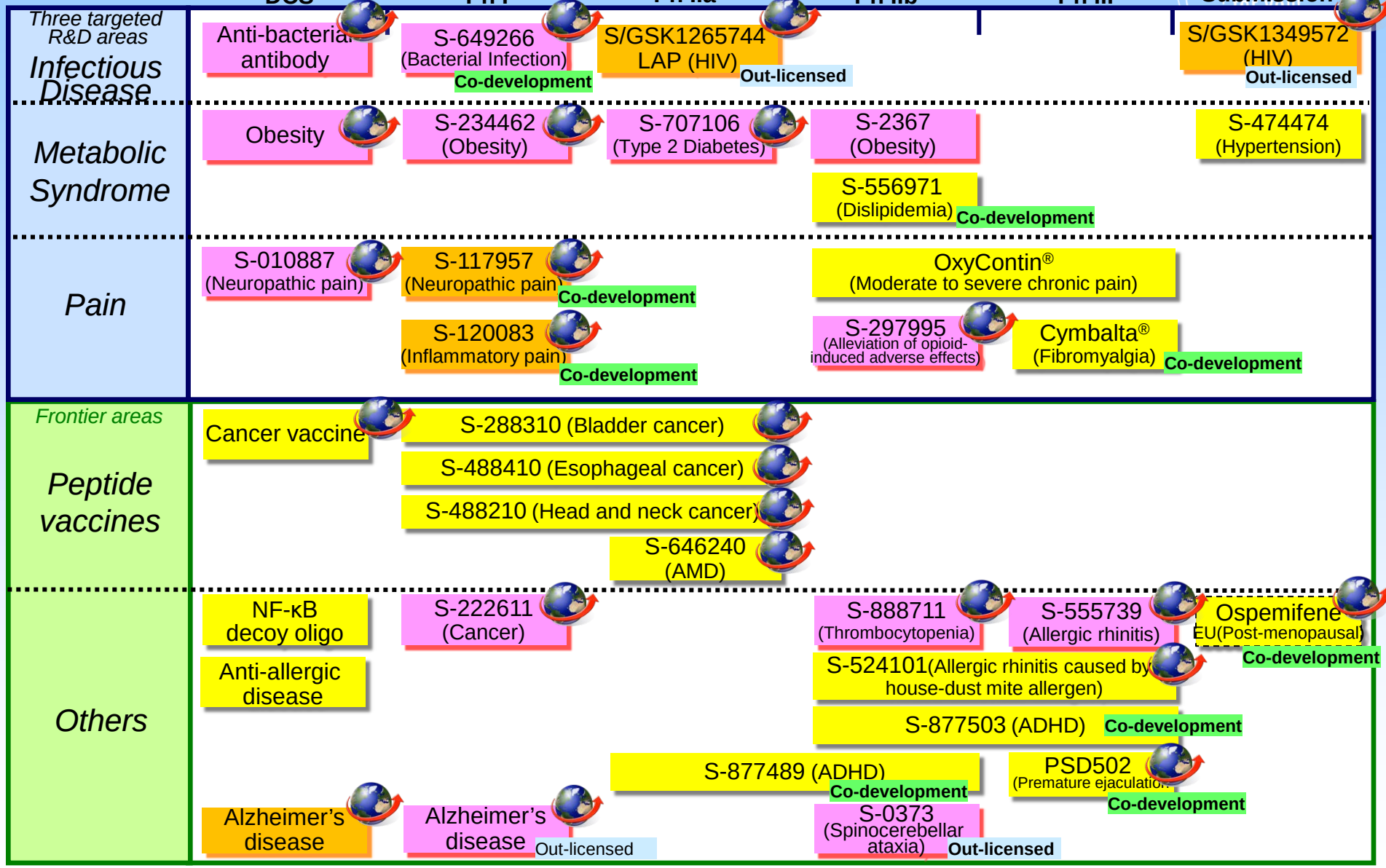
Advanced 3 compounds to Phase I

Anti-inflammatory pain: S-120083

Anti-neuropathic pain: S-010887

Research

Development Pipeline Enrichment (as of March 2013)



DCS: Drug candidate selection,
LAP: Long-acting parenteral formulation, ADHD: Attention Deficit Hyperactivity Disorder, AMD; Age-related Macular Degeneration

Developing globally

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

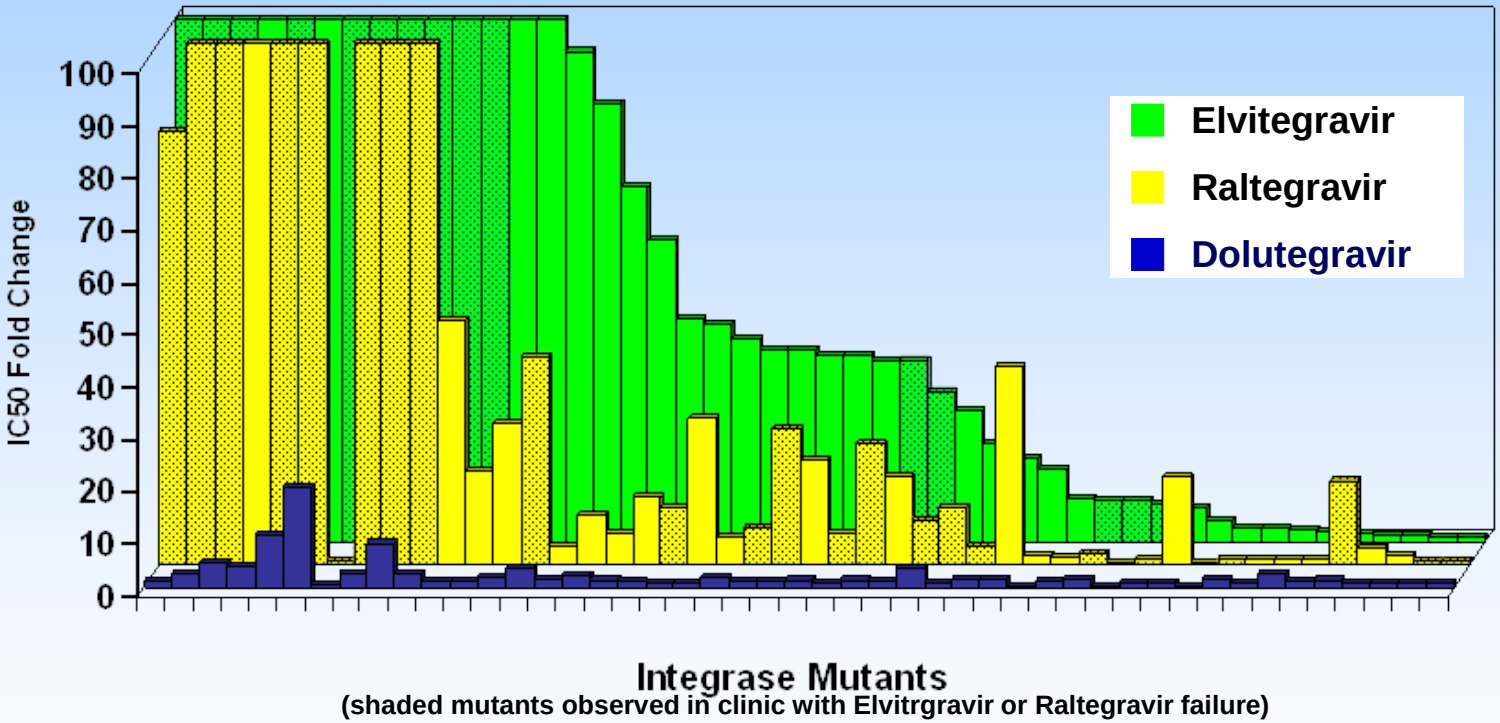
Promote research to maximize the value of existing products under development

Medicines that can save lives

Creation of Dolutegravir

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

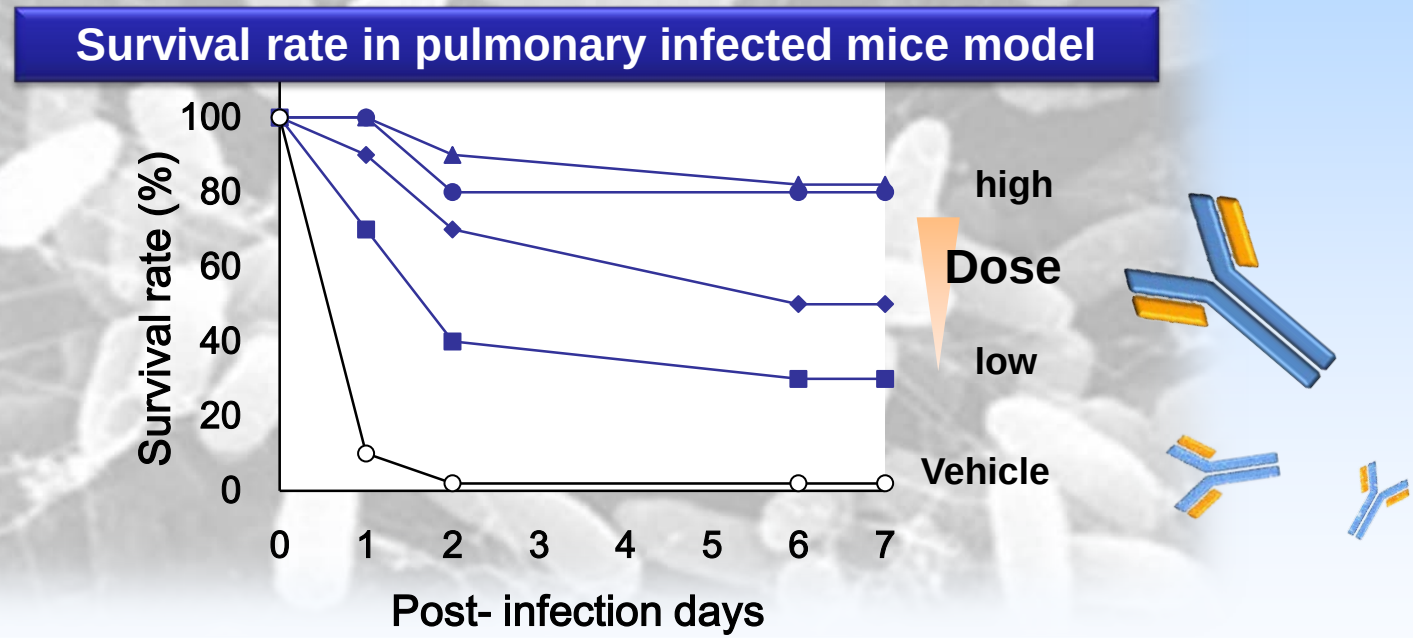
CROI 2010. The Discovery of S/GSK1349572



Creation of "Best in Class" Integrase Inhibitor
Sophisticated chemistry and ideas for other antiviral research

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

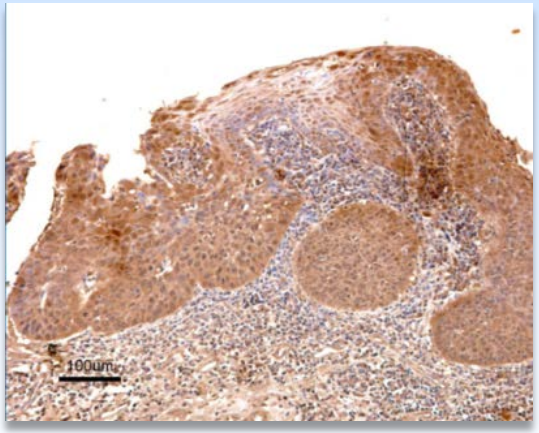


Aggressively fighting severe infectious disease
Expanding to antibody drug discovery

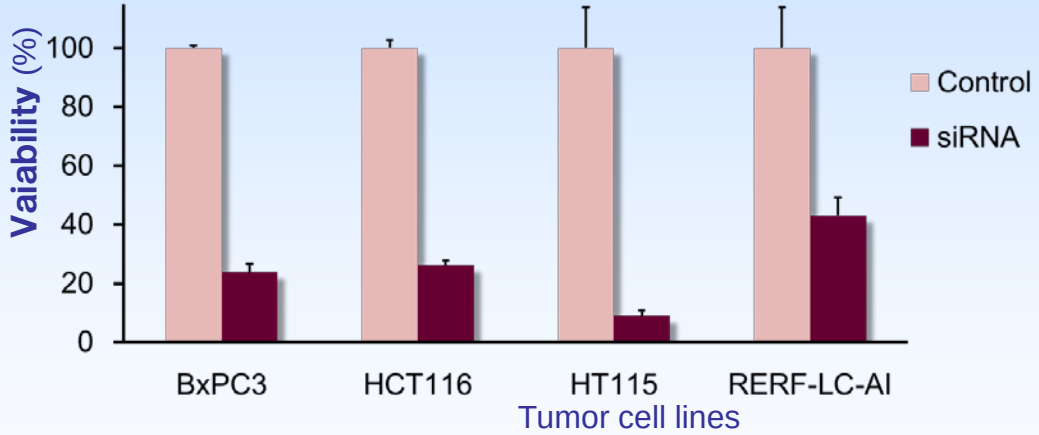
Creation of Cancer Vaccine

- 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

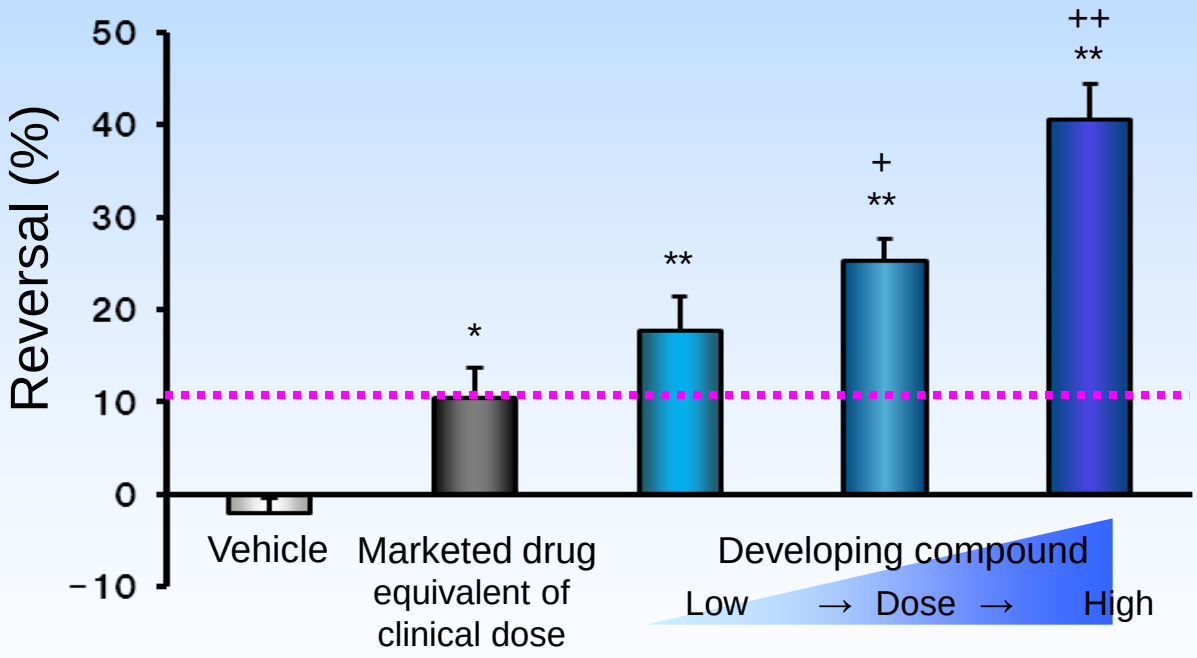


Created new opportunities to overcome cancer
Enhanced peptide vaccine lineup

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**

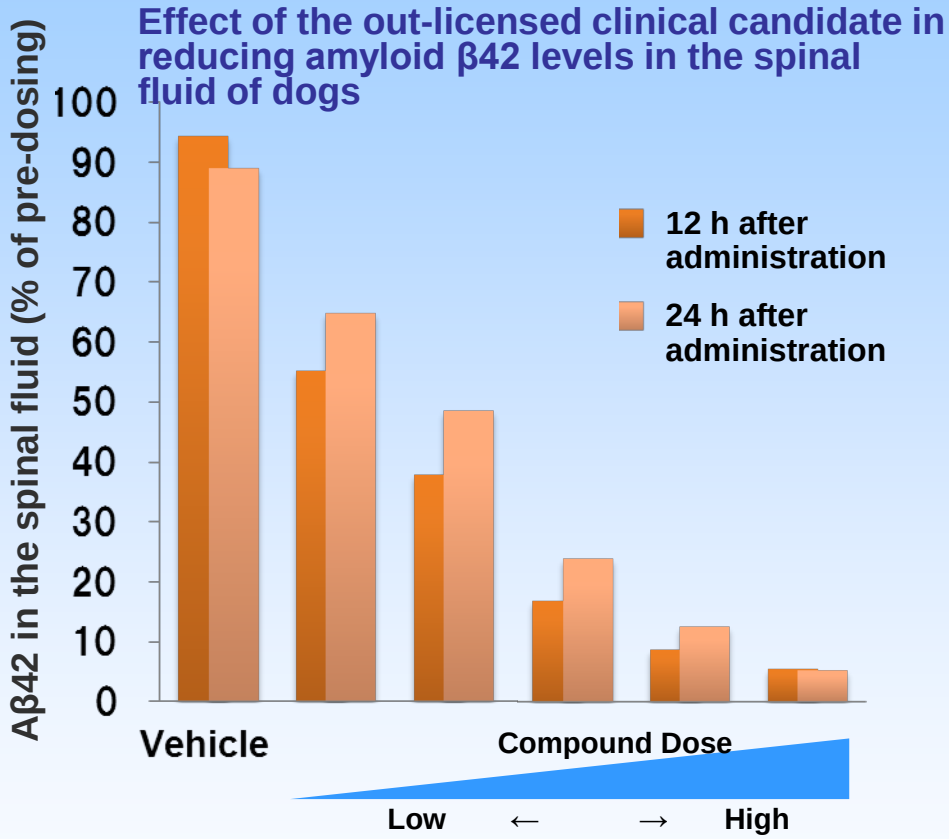
Anti-hyperalgesic effects in diabetic neuropathic pain model



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



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

BACE: β-site Amyloid Precursor Protein Cleaving Enzyme

Expand external research collaboration to nucleate creative drug discovery programs

Medicines that can improve the quality of life

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

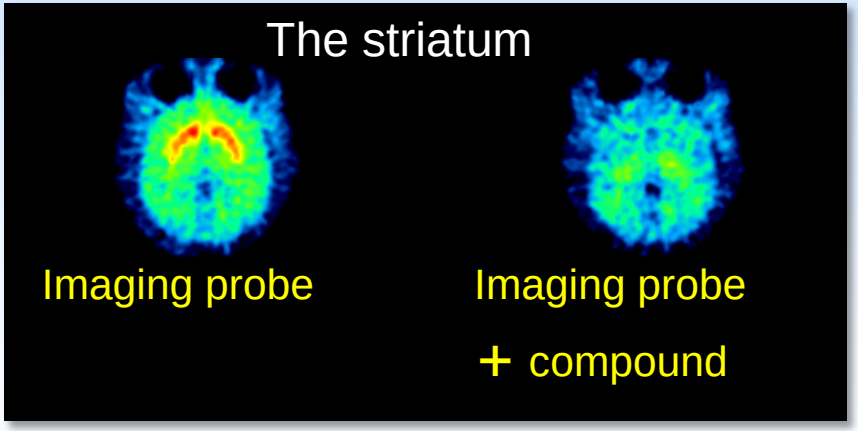
S-O-N-G for you!

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

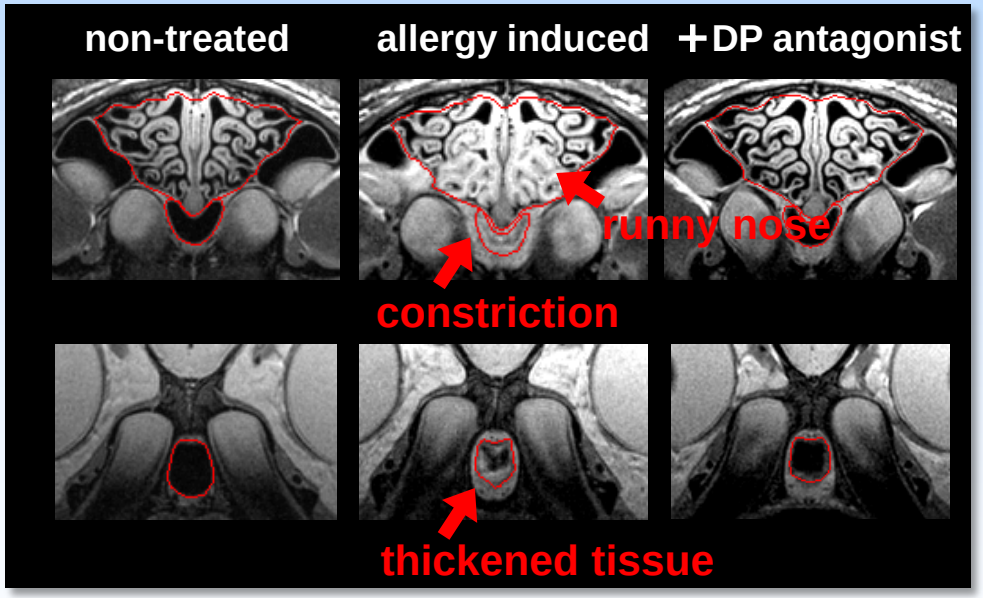
Evaluation of receptor occupancy brains with PET (monkey)



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

Establish drug discovery technologies to improve clinical POC rate

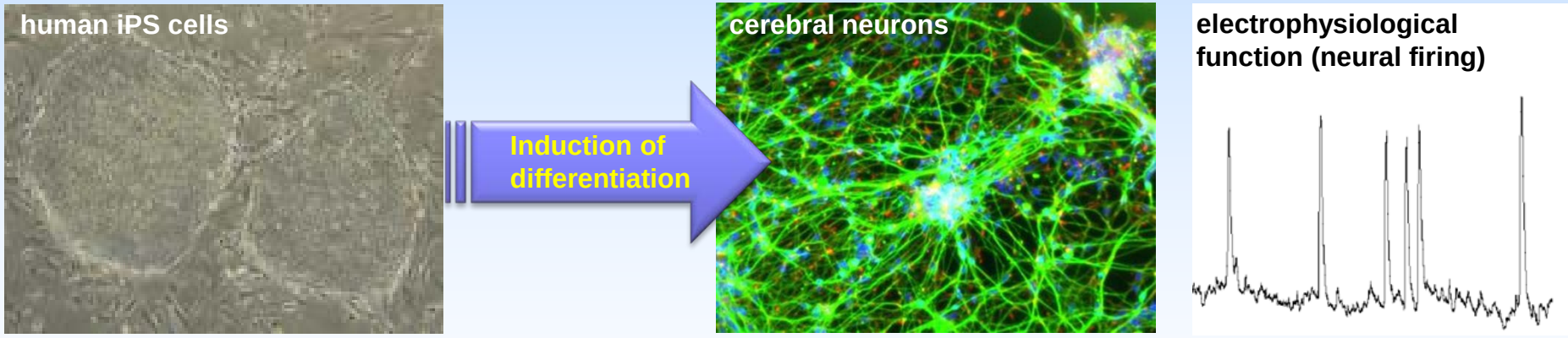
Utilizing iPS Cells in Drug Discovery Research

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

Accelerate development of large molecule drugs and develop new core therapeutic area studies for future studies

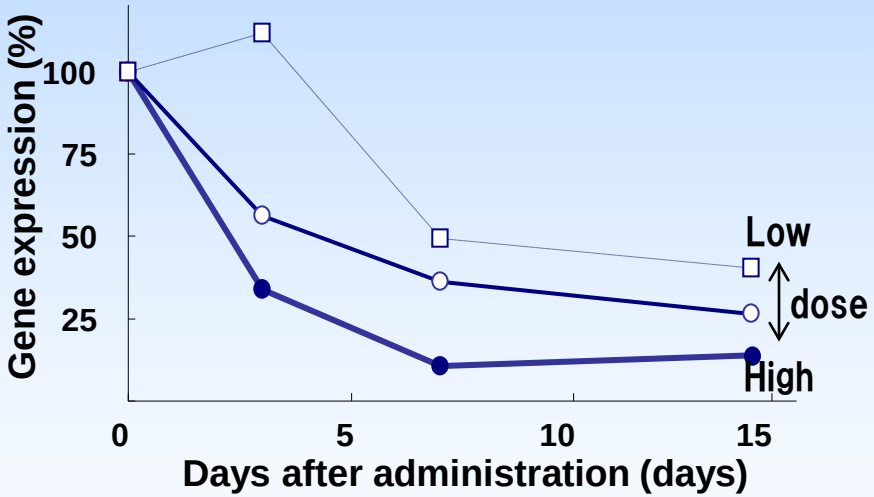
Oligonucleotide Drugs

- 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.

The repression of drug target gene expression by novel antisense oligonucleotide



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

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

Research SPRC as a Hub of Research Network

Speedy and Close Research Cycle

- Hokkaido University
- *Shionogi Innovation Center*

- Academia
- External research institutes

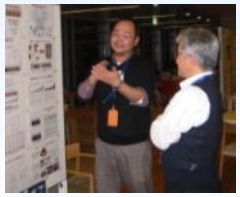
- Osaka University *PET Molecular Imaging Center*

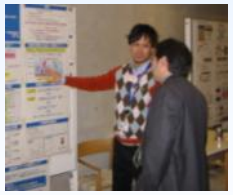
- Pharmaceutical companies
- Bio-ventures

Brand-new Research Hub
Tight-knit organization

Free and Fluid Discussions
Innovative Ideas

Self-organized workshop





Started innovative research programs

Toward Top Level Global Research Productivity

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

Agenda

- 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.**

MAA: Marketing Authorization Application
DTG: Dolutegravir, FDC: Fixed dose combination

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

Approval		
FINIBAX®	Additional indication for pediatric infection	Japan: May 2012
Ospemifene (Osphena™)	Post-menopausal vaginal atrophy	US: Feb. 2013
NDA submission		
Irbetan® 200mg tablet	Hypertension	Japan: Apr. 2012
S-474474	Hypertension	Japan: Jul. 2012
Metreleptin	Lipodystrophy	Japan: Jul. 2012
S/GSK-349572* (Dolutegravir)	HIV infection	Global: Dec. 2012
Ospemifene	Post-menopausal vaginal atrophy	EU: Mar. 2013

* ViiV Healthcare Ltd.

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

Progress in development status (at the end of March 2013)		
S-555739	Allergic rhinitis	Japan: Phase III initiated US: Phase IIa LPO
S-297995	Alleviation of opioid-induced adverse effects	Japan/US: Phase IIb completed Global: Phase III in preparation
S-2367	Obesity	Japan: Phase IIb registration completed
S-556971	Dyslipidemia	Japan: Phase IIb initiated, registration completed
S-524101	Allergic rhinitis caused by house-dust mite allergen	Japan: Phase II/III initiated, registration completed
S-888711	Thrombocytopenia	Japan: Phase IIb initiated, registration completed
S-877489	ADHD	Japan: Phase II initiated
S-877503	ADHD	Japan: Phase II/III initiated

ADHD: Attention deficit hyperactivity disorder
LPO: Last patient out

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

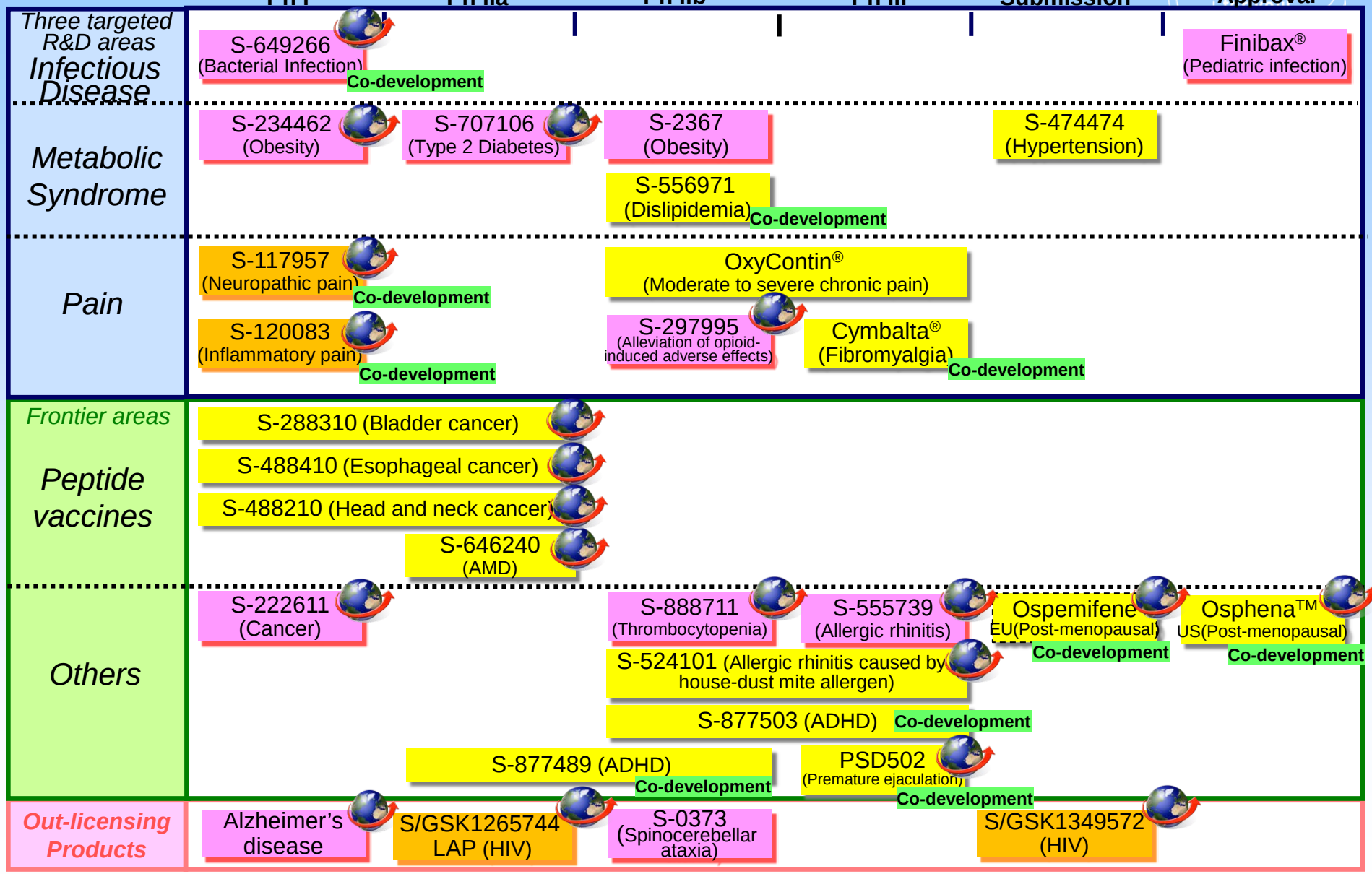
Progress in development status (at the end of March 2013)		
S-288310	Bladder cancer	Asia: Phase I/II continued
S-488410	Esophageal cancer	Japan: Phase I/II continued
S-488210	Head and neck squamous cell carcinoma	EU: Phase I/II continued
S-646240	Age-related macular degeneration	Japan: Phase IIa continued
S-222611	Malignant tumor	EU: Phase Ib continued
S-649266	Bacterial infection	Japan: Phase I single/ multiple dose completed
S-120083	Inflammatory pain	Japan: Phase I initiated

Development for as yet Unapproved Indications, and Drugs Requested for Development by Academy

Unapproved and off-label: Status of progress		
Cymbalta®	Fibromyalgia	Phase III
OxyContin®	Moderate to severe chronic pain (non-cancer pain)	Phase II/III initiated
Longes®	Childhood hypertension	Approved in Jun. 2012
Flagyl®	Infections caused by anaerobic bacteria, and amebiasis giardiasis	Approved in Aug. 2012
Baktar®	Pneumocystis carinii	Approved in Aug. 2012
Endoxan®	Pheochromocytoma	NDA submission
Predonine®	Duchenne muscular dystrophy	NDA submission
Vancomycin	Gram-positive bacteria-associated bloodstream infection	Under consideration
Requested for development by academy: Status of progress		
Metreleptin	Lipodystrophy	NDA filing*
Imunomax®-γ	Additional indication for mycosis fungoides and Sezary's syndrome	Phase II
Flagyl®	Helicobacter pylori infection, stomach inflammation	Approved in Feb. 2013
Predonine®	Kawasaki disease (acute phase)	NDA submission

* Passed Drug Committee Meeting on March 8, 2013

Development Development Pipeline Enrichment (as of March 2013)



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

Developing products globally

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

Target Milestones for FY2013: Approval and NDA Submission

Approval		
S/GSK-349572* (Dolutegravir)	HIV infection	Global (US: PDUFA, Aug. 2013)
S-474474	Hypertension	Japan
Metreleptin	Lipodystrophy	Japan
NDA submission		
Imunomax®-γ	Mycosis fungoides and Sezary's syndrome	Japan

* ViiV Healthcare Ltd.

PDUFA: Prescription Drug User Fee Act

Target Milestones for FY2013: Phase I-III (1/2)

Progress in development status		
Cymbalta®	Chronic low back pain	Japan: Phase III initiation
S-297995	Alleviation of opioid-induced adverse effects	Global: Phase III initiation
S-555739	Allergic rhinitis	Japan: Phase III (SAR) code-break US/EU: Phase II completion
S-888711	Thrombocytopenia	Japan: Phase IIb code-break, go/no-go decision
S-2367	Obesity	Japan: Phase IIb code-break, go/no-go decision
S-556971	Dyslipidemia	Japan: Phase IIb code-break, go/no-go decision
S-524101	Allergic rhinitis caused by house-dust mite allergen	Japan: Phase II/III code-break
S-646240	Age-related macular degeneration	Japan: Phase IIa code-break, go/no-go decision

SAR: Seasonal allergic rhinitis

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

Progress in development status		
S-588410*	Bladder cancer	Japan/EU: POC initiation
S-222611	Malignant tumor	EU: Phase II initiation
S-649266	Bacterial infection	US: Phase II initiation
S-120083	Inflammatory pain	Japan/US: Phase II initiation
S-117957	Neuropathic pain	US: POM initiation
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

Dolutegravir: Developed by ViiV Healthcare (from November, 2012) Market Information

- **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.**

* EvaluatePharma and Web-based Annual Report

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

Dolutegravir: Ongoing Phase III studies

Study No.	Population	Study design	Efficacy
ING113086 (SPRING-2)	Treatment-naïve patients	ART-naive patients (n=788) DTG 50QD vs. RAL (+ NRTIs of choice) non-inferiority design	Week 48 Non-inferior
ING114467 (SINGLE)		ART-naive patients (n=788) ABC/3TC/DTG 50QD vs. Atripla non-inferiority design	Week 48 Superior
ING111762 (SAILING)	Treatment-experienced but INI-naïve patients	ART-experienced, INI-naïve patients (n=688) DTG 50QD vs. RAL (+ BR) non-inferiority design	Week 24 Superior
ING112574 (VIKING-3)	INI-resistant patients	INI-resistant patients (n=~200) Single cohort, DTG 50BID + OBR*	Week 24 63% patients HIV RNA <50c/mL

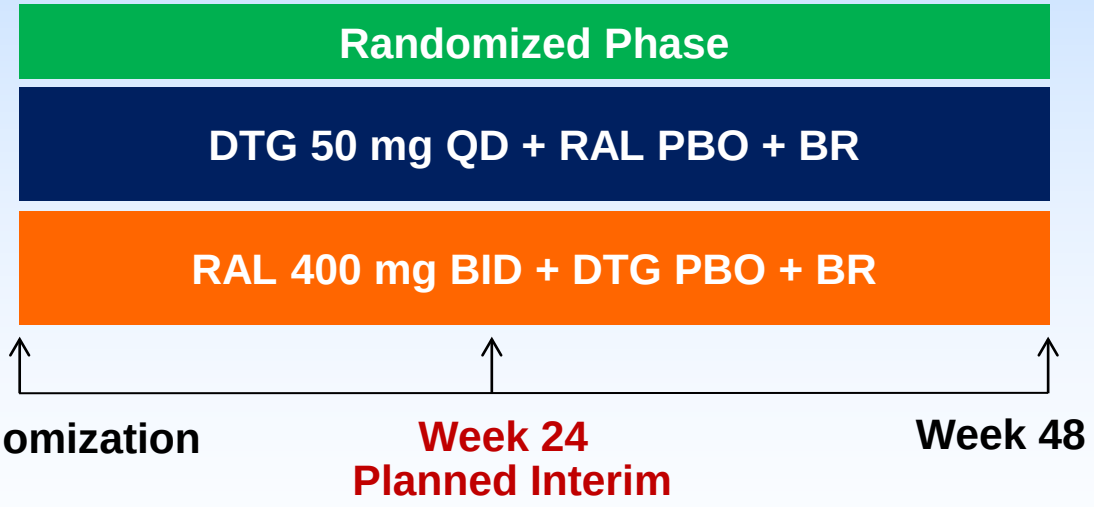
* Optimised background regimen

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-naive
HIV-1 RNA >400 copies/mL[a]
1:1 Randomization
Stratified by HIV-1 RNA
(≤ or >50,000), DRV/r use
and # of fully active drugs



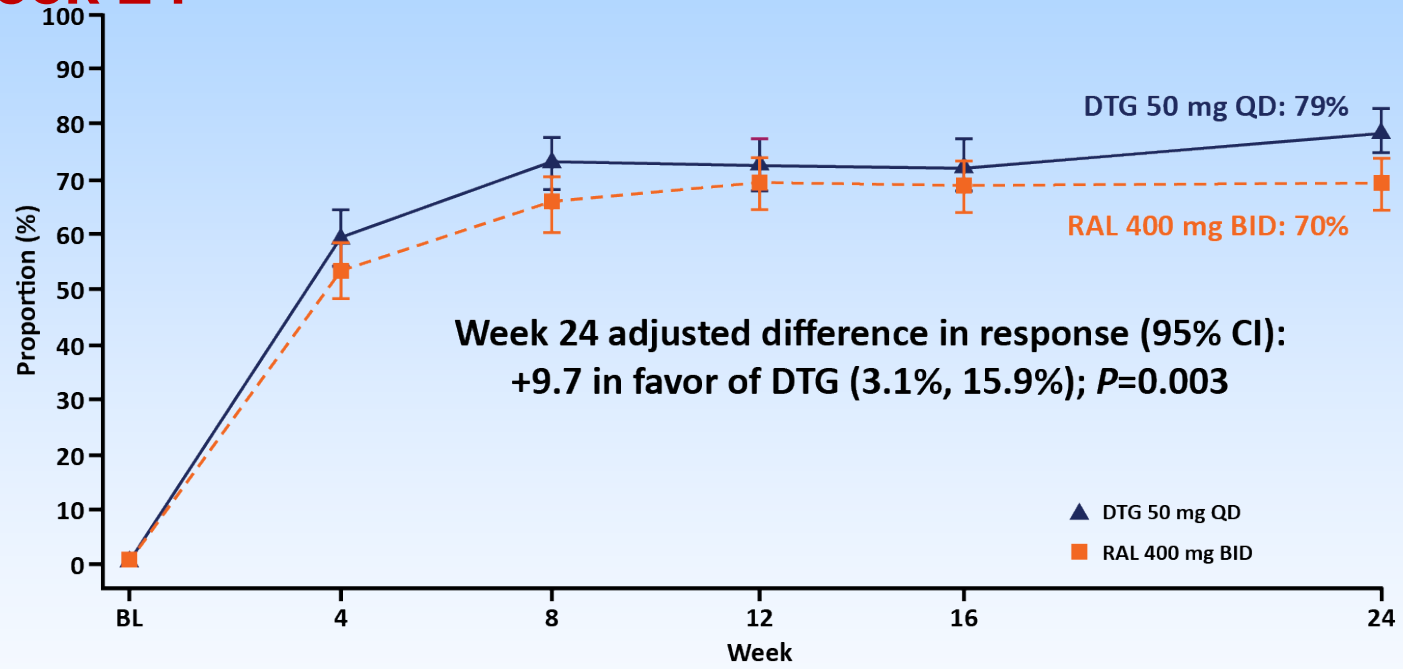
At Screening and a second consecutive test >400 c/mL within 4 months prior to Screening (if Screening HIV-1 RNA >1000 c/mL, no additional HIV-1 RNA assessment was needed)

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



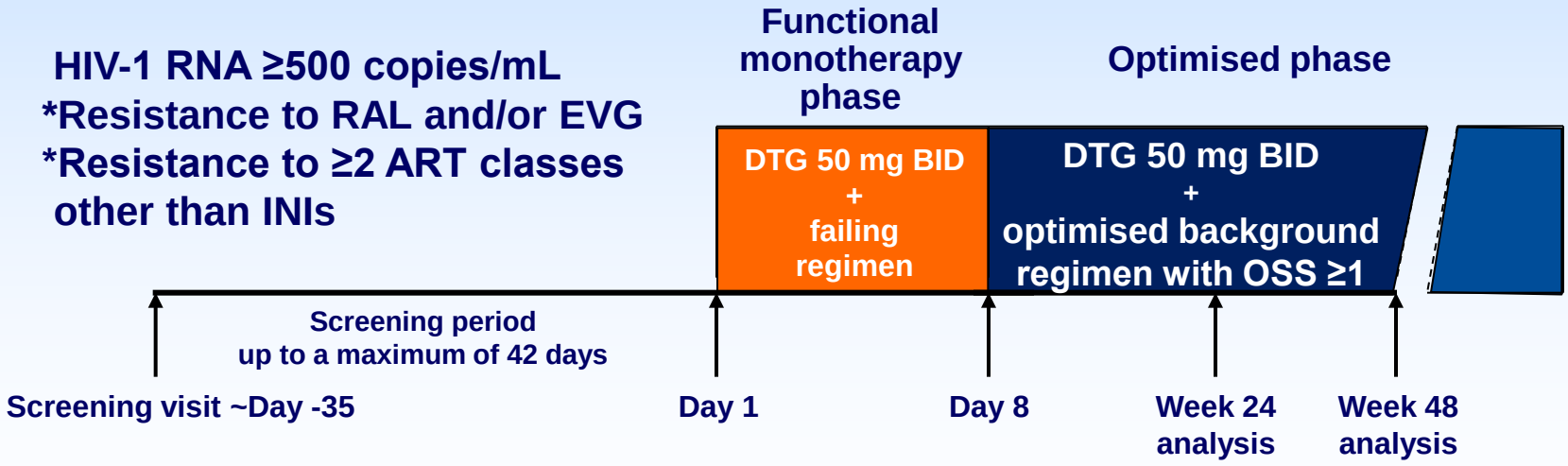
* Adjusted difference based on stratified analysis adjusting for Baseline HIV-1 RNA (≤50,000 copies/mL vs. >50,000 copies/mL), DRV/r use without primary PI mutations and Baseline PSS (2 vs. <2)

- 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.

Phase III study with treatment-experienced and INI-resistant patients (VIKING-3)

- Study objective: To assess the anti-viral activity of DTG in patients with failure of raltegravir (RAL) or elvitegravir (EVG) patients
- Subjects failed with at least 3 classes of anti-retrovirals including INI
- Number of evaluable subjects on Day 8, 183 adults; Number of evaluable subjects on Week 24, 114
- DTG 50mg twice daily (BID)

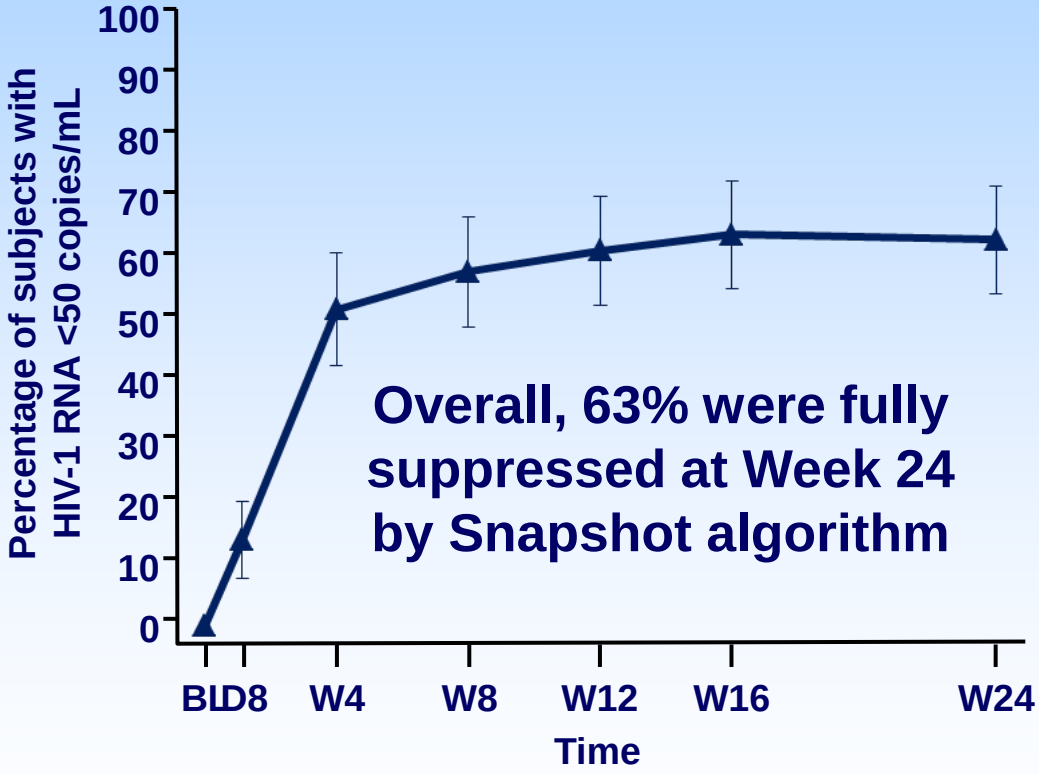


*Screening or documented historical evidence
OSS (overall susceptibility score) determined by Monogram Biosciences net assessment

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

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



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 elicit 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

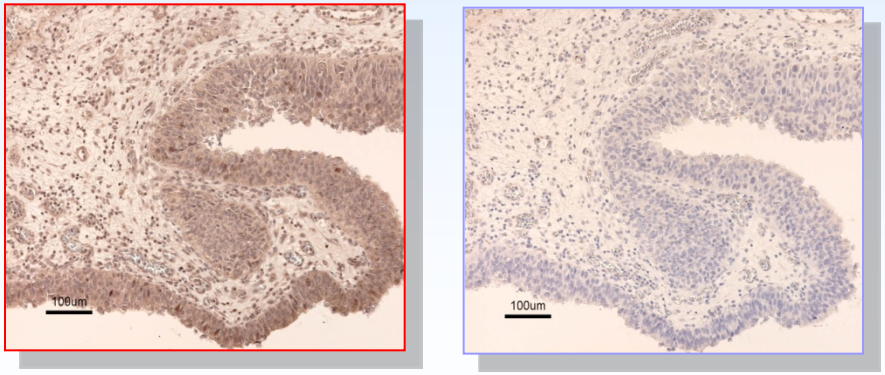
- **Phase I/II (Japan)**
  - Target patients
    - ✓ Patients with advanced metastatic bladder cancer
  - Objectives
    - ✓ To evaluate the safety, tolerability, and immunologic response
  - Status
    - ✓ Interim analysis for safety and efficacy has been completed
    - ✓ Extension study is ongoing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

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

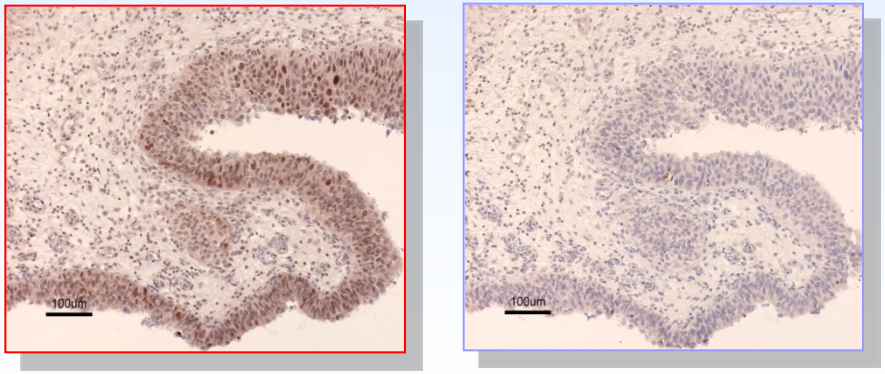
Oncoantigen expression rate		CTL induction rate by S-288310	
Oncoantigen A	36/38 (95%)	Oncoantigen A peptide	22/33 (67%)
Oncoantigen B	35/38 (92%)	Oncoantigen B peptide	24/33 (73%)
Either A/B	37/38 (97%)	Either A/B peptide	29/33 (88%)

Immunohistochemistry: Oncoantigen A



Specific Ab　　Control Ab

Immunohistochemistry: Oncoantigen B



Specific Ab　　Control Ab

S-288310: Phase I/II

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

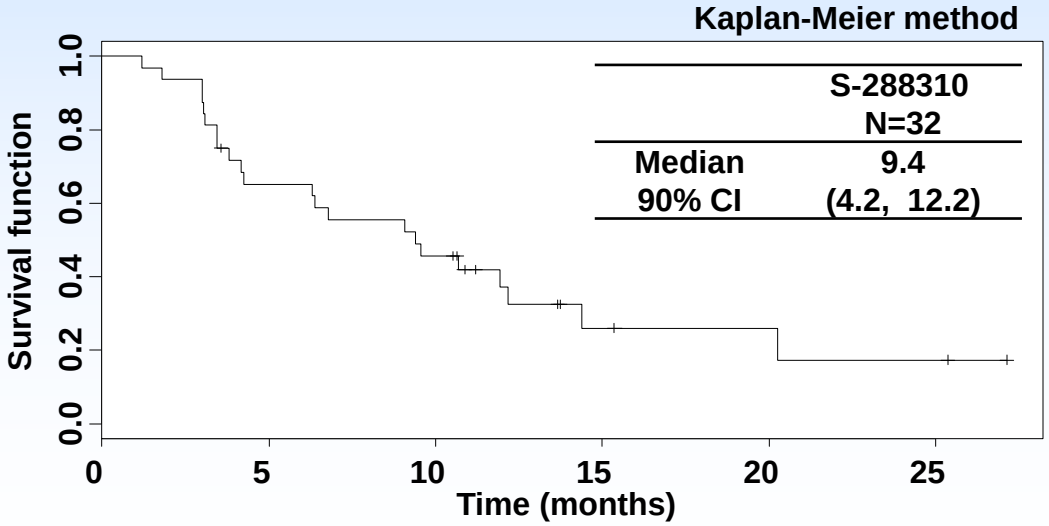
Response rate (irCR+irPR)	**2/32 (6.3%)**
Disease control rate (irCR+irPR+irSD)	**18/32 (56.3%)**

*immune-related response criteria

Criteria for evaluation of immune therapy activity in solid tumors

irCR	: complete response Disappearance of all lesions in two consecutive observations not less than 4 wk apart
irPR	: partial response ≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
irSD	: Stable Disease 50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir

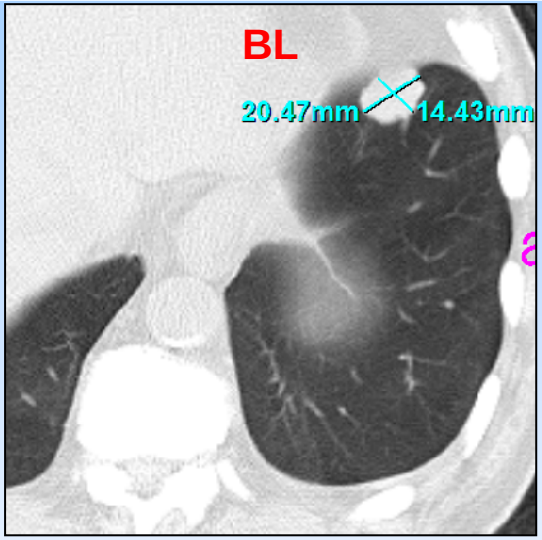
- **Overall survival (OS)**

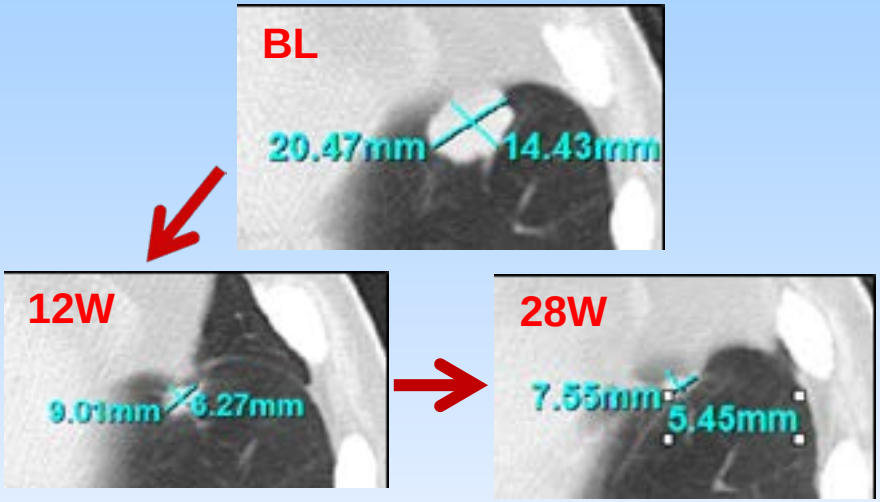


S-288310: a patient with good response (1)

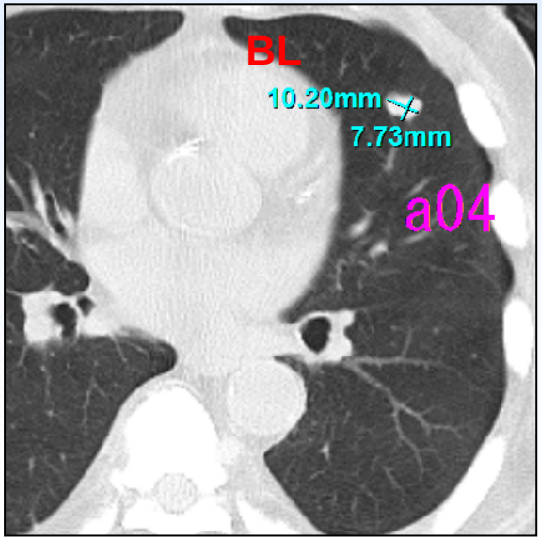
73-year-old man, best overall response: irPR (Partial Response)

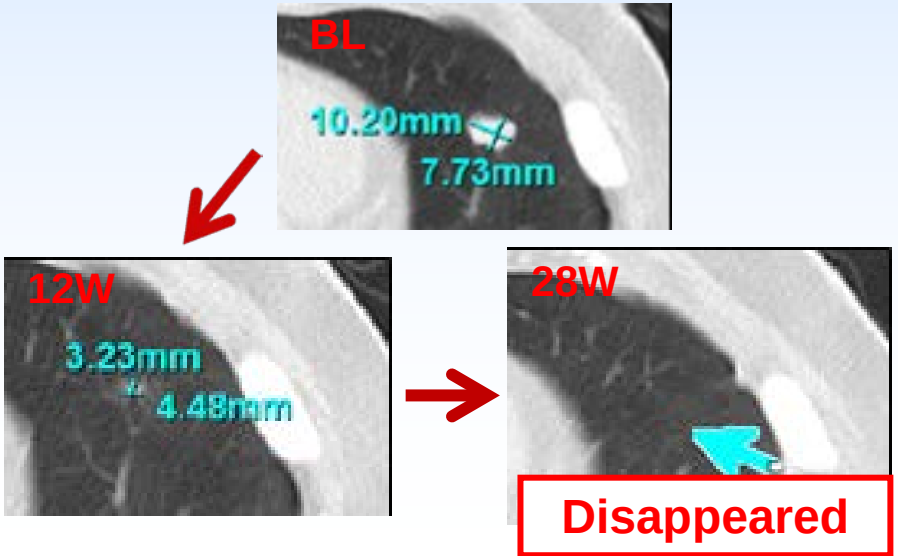
Lower lobe of the left lung





Superior lingular segment of the left lung

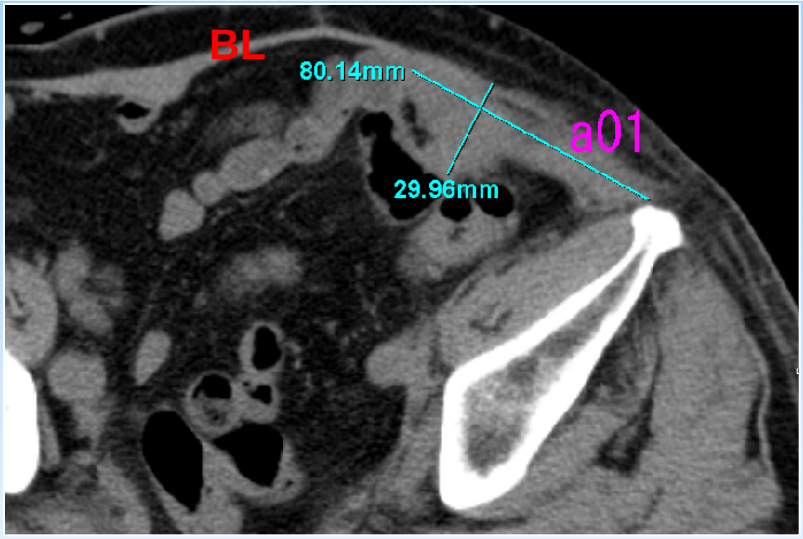


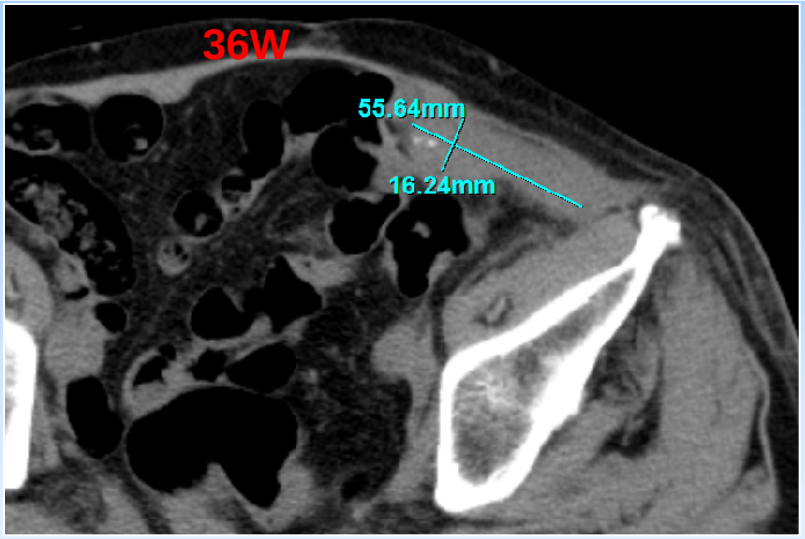


S-288310: A Patient with Good Response (2)

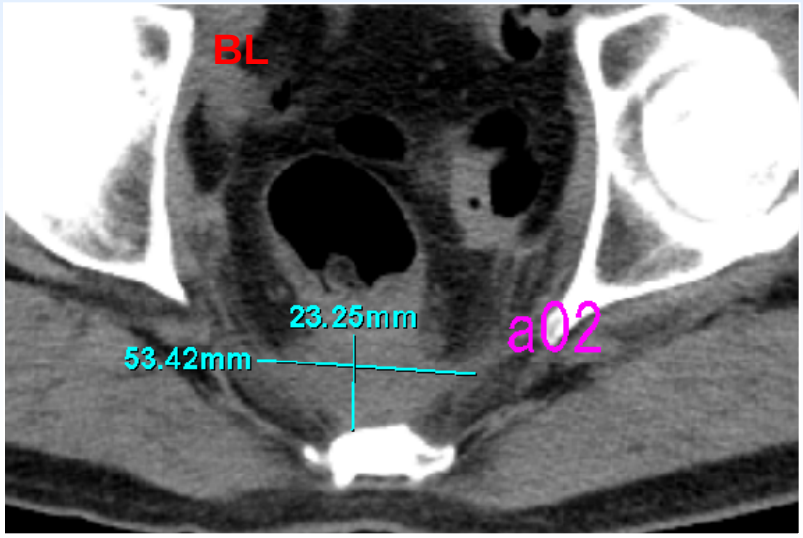
79-year-old man, best overall response: irPR (Partial Response)

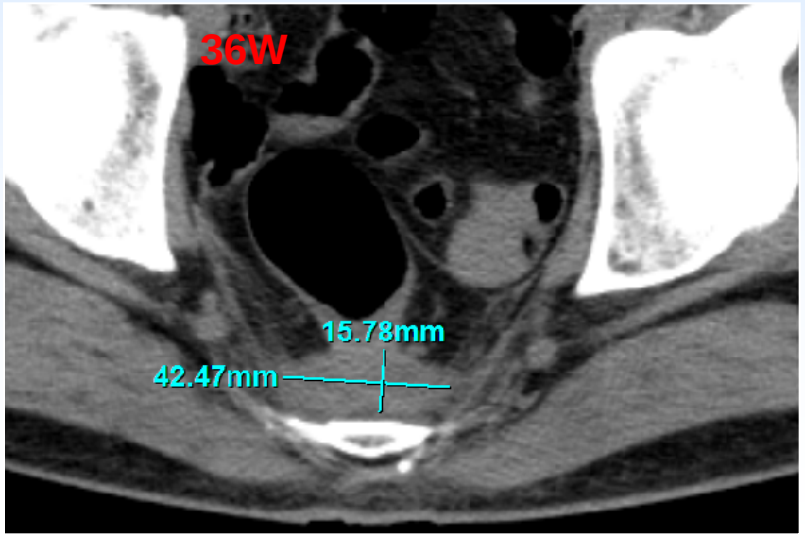
The left musculus rectus abdominis





Presacral region

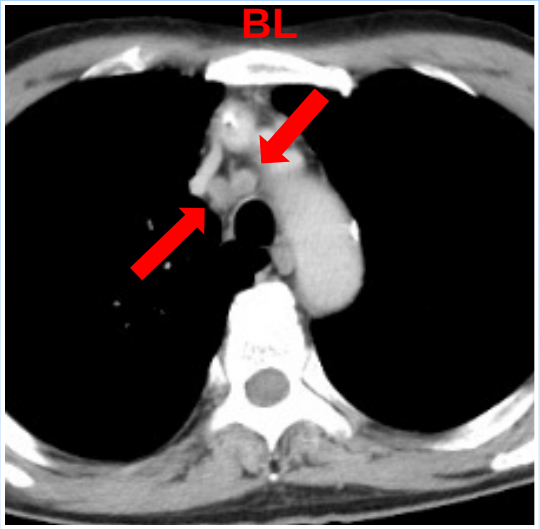


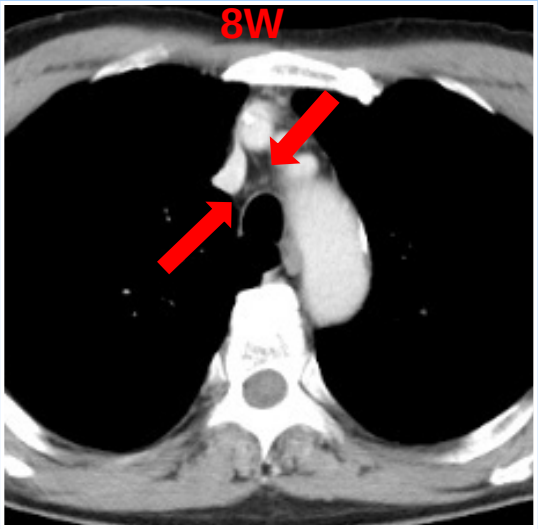


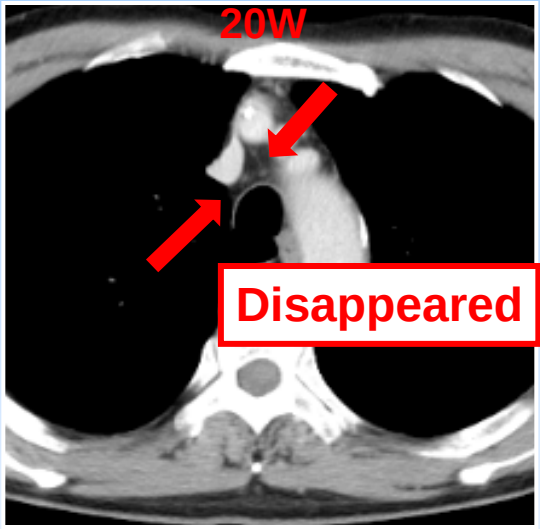
S-288310: A Patient with Good Response (3*)

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

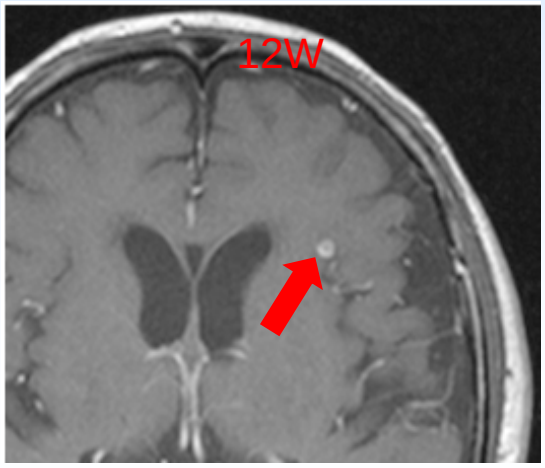
Mediastinal lymph node

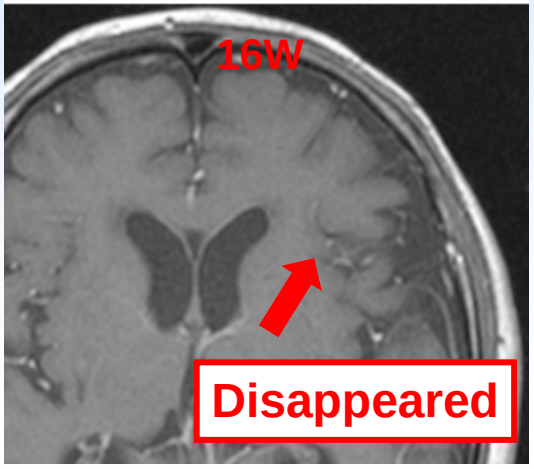


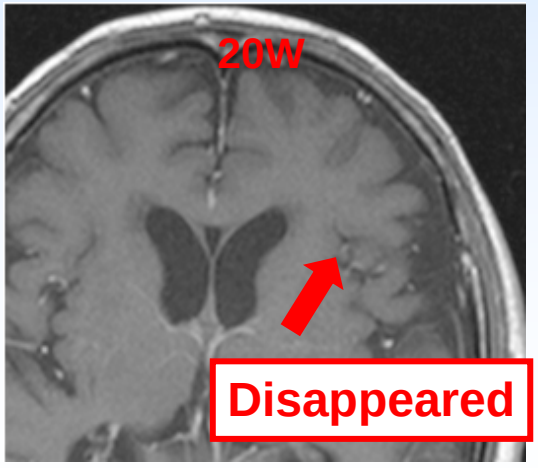




Brain metastasis near the left lateral fissure



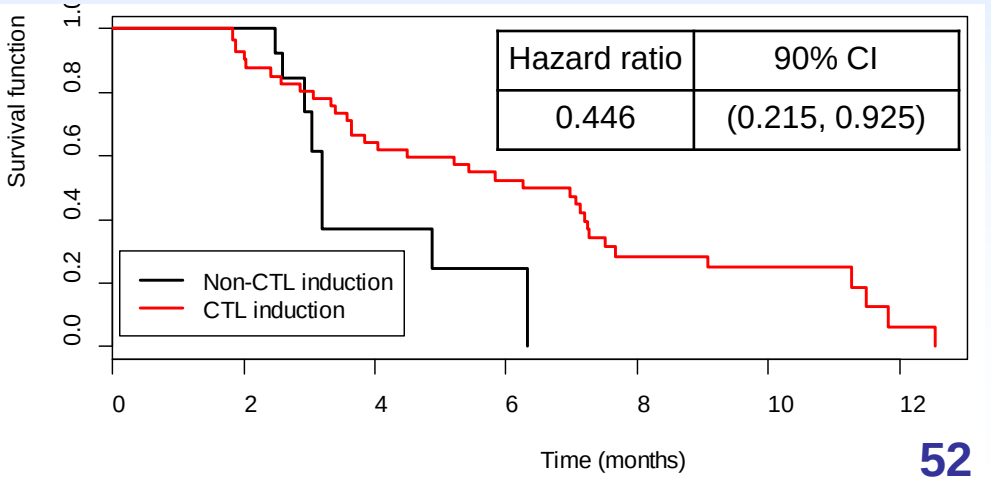




* The primary lesion (bladder) was not responsive.

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



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 of a 5-peptide Cocktail Vaccine

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

Oncoantigens	Antigen A	Antigen B	Antigen C	Antigen D	Antigen E
Bladder cancer (n=20)	100%	100%	80%	100%	90%
Esophageal cancer (n=20)	100%	100%	90%	90%	100%

- **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	Improvement of CTL induction rate
For heterogeneity of antigen expression in one patient	Enhancement of efficacy in one patient
For diversity of antigen expression among patients	Improvement of efficacy rate in the target patient population

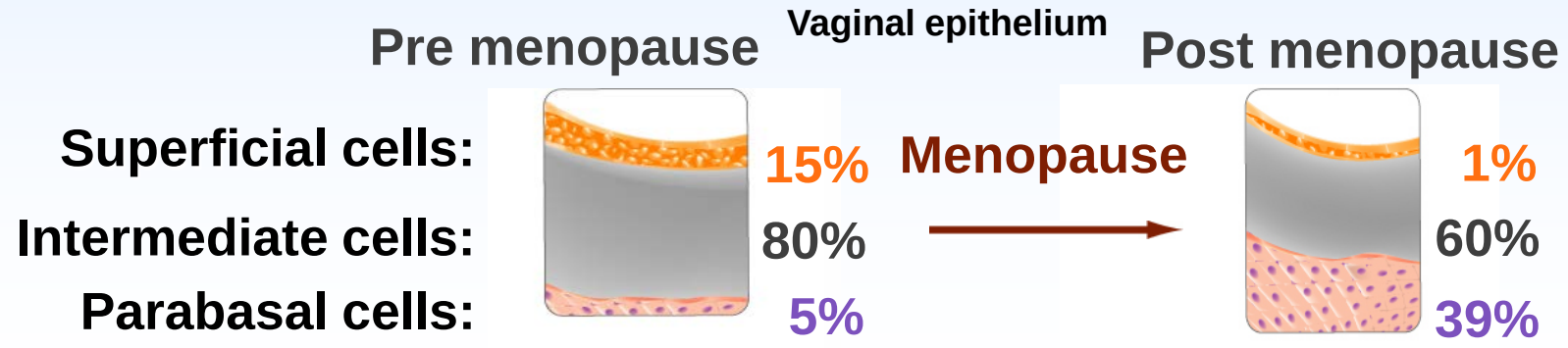
- **Expansion of indications and maximization of value**
  - Single formulation of cocktail vaccine will exert efficacy against many types of cancers
- **Development plan**
  - Regarding 5-peptide cocktail vaccine, a POC study in patients with advanced metastatic bladder cancer in Japan and the EU will 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



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

MAA: Marketing Authorization Application

Week 12 Effects on Dyspareunia (the Woman's Self-Identified Most Bothersome Moderate to Severe Symptom of VVA at Baseline)

Mean Change in Severity at Week 12 with Last Observation Carried Forward (LOCF), Modified Intent-to-Treat Population

1st Clinical Trial Results		
Most Bothersome Moderate to Severe Symptom at Baseline	OSPHENA™ 60 mg (N=110)	Placebo (N=113)
Dyspareunia		
Baseline Mean (SD)	2.7 (0.44)	2.7 (0.45)
LS Mean Change from Baseline (SE)	-1.39 (0.11)	-0.89 (0.11)
p-value vs. placebo	0.0012	---
2nd Clinical Trial Results		
Most Bothersome Moderate to Severe Symptom at Baseline	OSPHENA™ 60 mg (N=301)	Placebo (N=297)
Dyspareunia		
Baseline Mean (SD)	2.7 (0.47)	2.7 (0.47)
LS Mean Change from Baseline (SE)	-1.55 (0.06)	-1.29 (0.07)
p-value vs. placebo	<0.0001	---

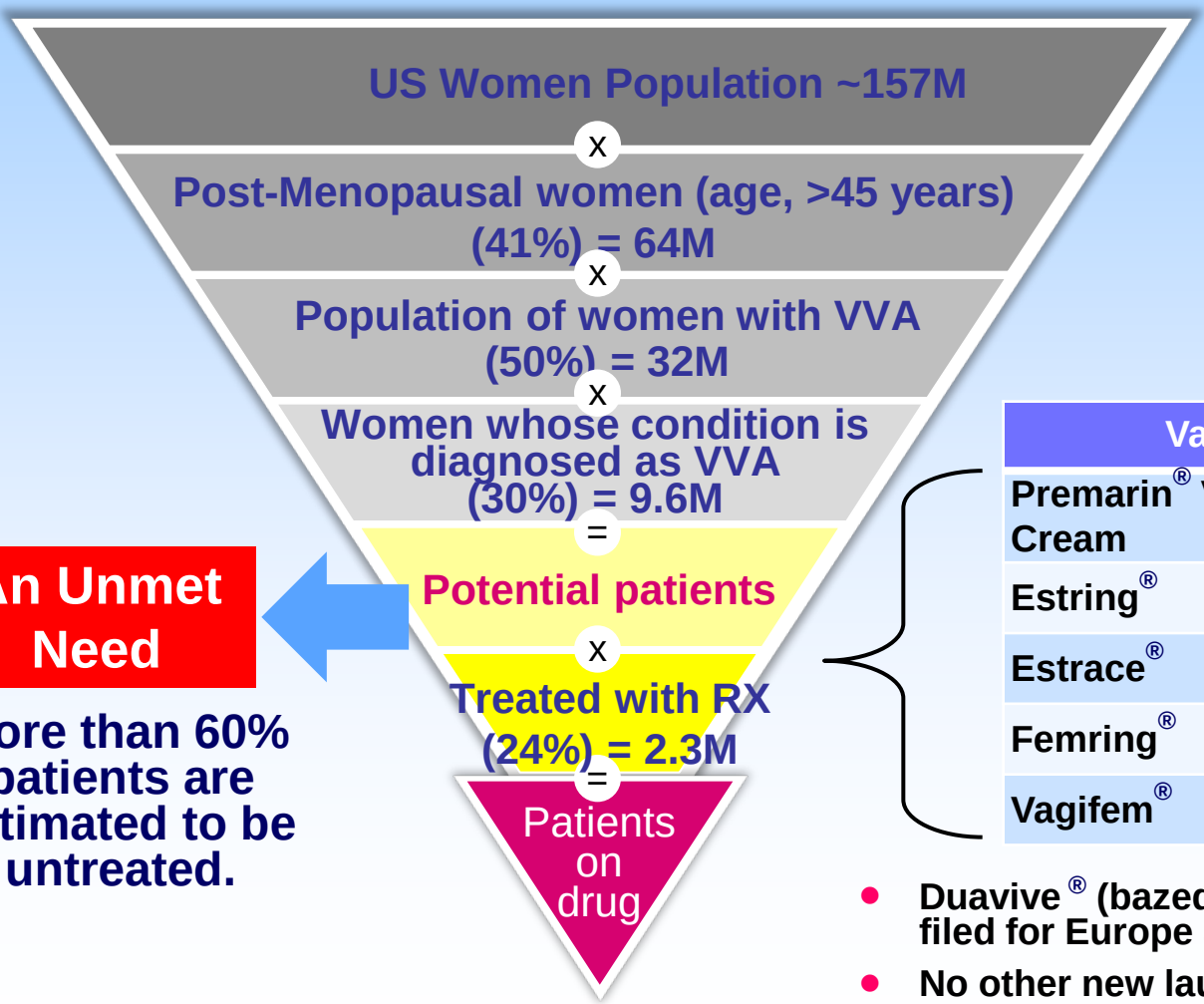
SD: Standard deviation, LS: Least Squares, SE: Standard error

Change from Baseline to Week 12 in Superficial and Parabasal Cells and Vaginal pH

- 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.

Vaginal Estrogen Products	
Premarin® Vaginal Cream	(Conjugated estrogens)
Estring®	(Estradiol vaginal ring)
Estrace®	(Estradiol vaginal tablet)
Femring®	(Estradiol acetate ring)
Vagifem®	(Estradiol vaginal tablet)

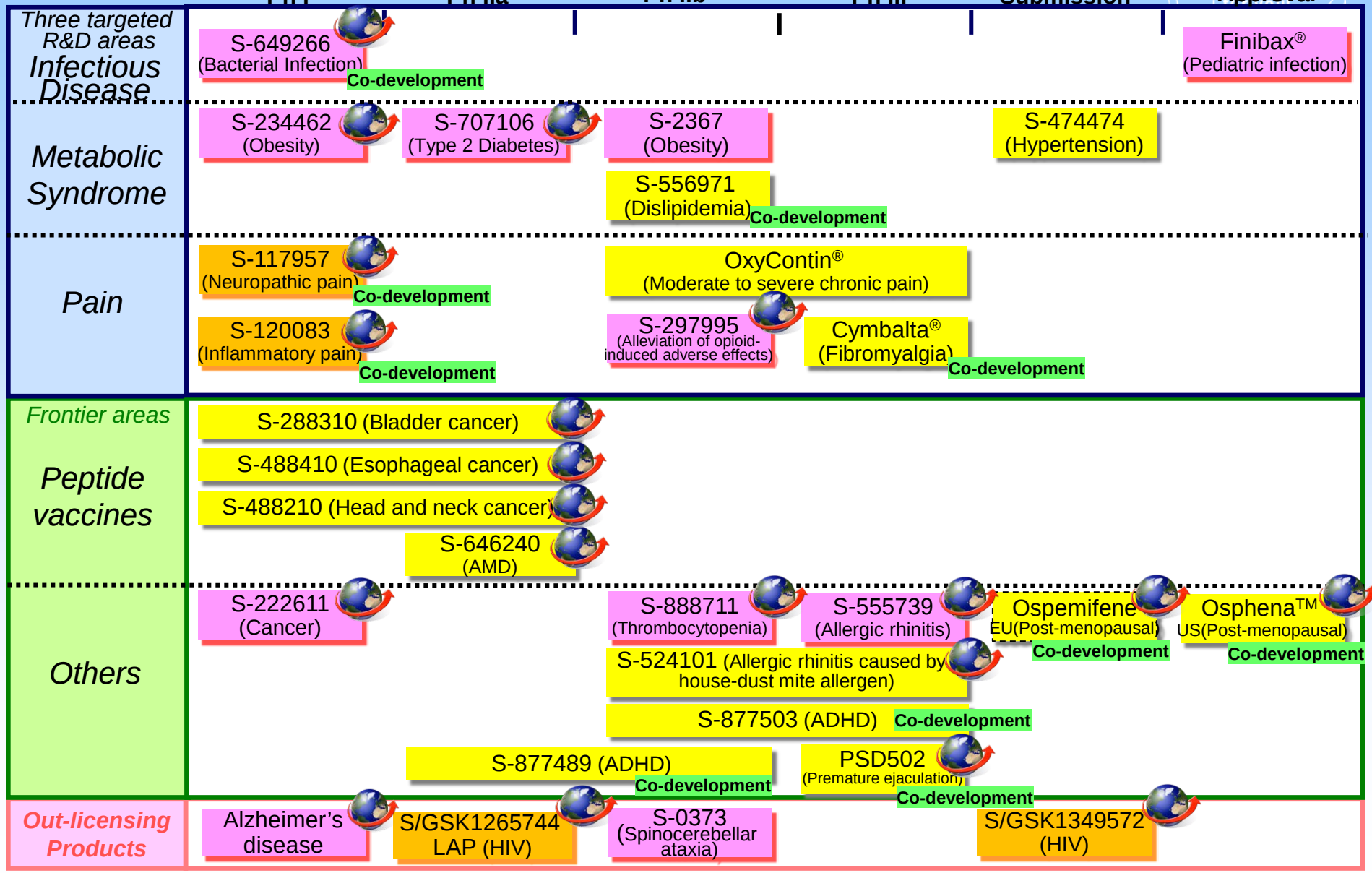
- Duavive® (bazedoxifene-conjugated estrogens) filed for Europe and for US
- No other new launches expected in the prescription cream market

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 Development Pipeline Enrichment (as of March 2013)



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

Developing products globally

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

Summary

Isao Teshirogi, Ph.D.

President and Chief Executive Officer

Q&A

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.

- The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.

- This material contains information on pharmaceuticals (including compounds under development), but this information is not intended to make any representations or advertisements regarding the efficacy or effectiveness of these preparations nor provide medical advice of any kinds.

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