R&D Meeting

<New Fields>

March 5, 2014

Dainippon Sumitomo Pharma Co., Ltd.
Today’s Agenda

◆ Efforts in New Business Fields
◆ Regenerative and Cellular Medicine Business
  • Cell Therapy
    ➢ SB623
  • Regenerative Medicine
    ➢ Alliance with Healios K.K.
    ➢ Cooperation with iPS cell projects for practical use
◆ Vaccine Business
◆ Development of the in-licensed products in the field where no approved drugs exist
  • EPI-743 (Mitochondrial Disease)
  • DSP-1747 (NASH, PBC)
Efforts in New Business Fields

Toru Kimura, Ph.D., Director
Head of Regenerative & Cellular Medicine Office
Vision for the 3rd MTBP

First Phase
FY2007 to FY2009
Solid Fundamentals
- Strengthening and maintaining our business foundation towards globalization
  - Focus resources on four strategic products
  - Early maximization of new products

Second Phase
FY2010 to FY2014
Take off
- Creation and transformation toward a new stage of globalization
  - Transform domestic business foundation

Third Phase
FY2013 to FY2017
Sustained growth
- Quest for Further Innovation
  - Establish strong domestic business foundation

Japan Overseas
- Strengthen new drug discovery activities and in-licensing activities
- Expand North America business through our own sales organization
- Establish US marketing org.
- Expand US/EU clinical development organization
- Start-up US business in our own sales organization

Quest for Further Innovation
- Strengthen profitability in North America.
- Expansion into Europe and Asia

Expand new product pipeline
- Expand global pipeline
- Develop leading-edge science fields

R&D
- Aspire to be a globally active R&D-based company
- Contribute to medical care through leading-edge technologies
- New Vision
3rd MTBP: R&D Strategy (excerpt)

[Focus Therapeutic Areas]
- Psychiatry & Neurology
- Oncology

[Explore new business fields]
- Cell Therapy / Regenerative Medicine

Cell Therapy / Regenerative Medicine
- R&D for clinical application to intractable diseases
R&D Strategy

Explore New Business Fields

Commercialization Roadmap for New Business

2013 2017 2021 2025 2030

SanBio
Bone Marrow MSC

Cell Therapy/
Regenerative Medicine
New Project

Vaccine Project

US
50 Billion Yen~

global
100 Billion Yen~

global
50 Billion Yen~

Become a company that contributes to health outcomes by commercializing cell therapy/regenerative medicine and through full-scale initiatives in preventative care such as vaccines and diagnostics.
Regenerative and Cellular Medicine Business
Strengths and Activities of DSP

Regenerative medicine-related research started from investigation of neurite outgrowth inhibitor, Semaphorin

- Abundant know-how and experience in regenerative medicine-related research
- Consecutive collaboration with academia
  【Joint research with Prof. Okano (Keio University) etc.】

Knowledge acquired through applied research of ES cell & iPS cell
  【Joint research with CiRA* (Director: Prof. Yamanaka) etc.】
  *Center for iPS Cell Research and Application

Platform research using hES cell (Sumitomo Chemical)
Extensive research performance, know-how and patents in the fields of the eye

Partnership with a biotech company (SanBio)
- Technology and know-how of cell pharmaceutical products
- Preparation for the development and regulation

ES cell & iPS cell-related basic technology (DS Pharma Biomedical)
Sales and development of regenerative medicine-related products such as medium and culture vessel etc., and tissue culture educator

DSP is poised to become a leading company in regenerative and cellular medicine business in Japan with favorable environment

Act with speed, and take advantage of the knowledge/know-how of academia and biotech companies
Regenerative and cellular medicine business: The present situation and a future plan of the projects

- **Cell therapy**
  - SB623
    - Option Agreement with SanBio

- **Regenerative medicine**
  - HLS001
    - Alliance with Healios K.K.
  - Cooperation with iPS cell projects for practical use
SB623
Bone marrow-derived multipotent mesenchymal stromal cells (MSC) - Stroke Option Agreement with SanBio
Development status

SB623 (for disabilities caused by stroke) : SanBio (U.S.)

- SB623 cells are modified bone marrow derived cells collected from healthy adult donors.
- Expect to function by producing proteins that aid the regenerative process.
- In preclinical studies to date, SB623 has dramatically improved function in animal models of stroke disability with no significant adverse effects.
- SB623 is an allogeneic product that production can be scaled, enabling a more cost effective therapy for stroke patients.
- **Ph1/2 clinical Study is ongoing (dosing finished).**

→ DSP has received an option for co-development and exclusive marketing rights for U.S. and Canada (Announced on Oct. 4, 2010).
SanBio SB623  Phase 1/2a Clinical Study

- Overall Design
  - Open-label safety study
  - 18 pts (3 dose levels, 6 pts each)—Stanford and Univ Pittsburgh
    - Standard, staggered escalation paradigm (2.5M, 5M, 10M)
  - 6-month efficacy, 2-year follow-up

Stereotactic Frame Positioning

Needle tracks for cell implantation and implant sites
Preliminary Unaudited Clinical Results

National Institutes of Health Stroke Scale (0 = no symptoms; 21 – 42 = severe symptoms)
HLS001
iPS cell-derived RPE cells, Eye diseases including age-related macular degeneration
Joint development with Healios K.K.
Wet AMD (Age-related macular degeneration)

- Denaturation atrophy detachment RPE cell
  => Nutrition to retina, digestion of waste, depression of barrier ability
- Accumulation of waste
- Occurrence of choroidal neovascular

Japan: No.4 cause of blindness. Affects about 1% of people aged 50 and over.
  Increase with advancing age
  (Estimated number of patients (2011): 540,000; source: Decision Resource)

U.S. and Europe: No.1 cause of blindness
  (Estimated number of patients: 1,910,000/US, 3,020,000/EU Five countries; source: Decision Resource)

From Japanese Ophthalmological Society web site
http://www.nichigan.or.jp/public/disease/momaku_karei.jsp
Manufacture of iPS cell-derived retinal pigment epithelial cells

Human induced pluripotent stem cells (iPS cells) → Retinal Pigment Epithelium (RPE) cells derived from human iPS cells → RPE cell sheet

Provided by RIKEN
http://www.riken.jp/pr/topics/2013/
Joint development agreement

[Scope]
- Products: iPS cell-derived RPE cells products (sheet or suspension)
- Indications: Eye diseases / Wet AMD, Dry AMD, others
  To be determined by Joint-development committee
- Territory: Japan

[Sharing roles]

<table>
<thead>
<tr>
<th>Healios</th>
<th>DSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Joint development committee:</td>
<td>➢ Review of documents before submitting to authorities</td>
</tr>
<tr>
<td>joint development policy, assigning tasks, decision making</td>
<td>➢ Evaluation of study findings</td>
</tr>
<tr>
<td>➢ Examination of the quality and the stability of RPE</td>
<td></td>
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<tr>
<td>➢ Non-clinical and clinical studies</td>
<td></td>
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<tr>
<td>➢ Manufacturing products for studies</td>
<td></td>
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<tr>
<td>➢ Post-marketing clinical studies</td>
<td></td>
</tr>
<tr>
<td>➢ Obtain and maintain manufacturing and marketing approval</td>
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</tbody>
</table>

[Development costs] DSP cover maximum 5.2 billion yen

[Manufacturing, sales promotion] Contracted exclusively to the joint venture company

[Post-marketing clinical study required for approval] Contracted to DSP from Healios

[Tentative Schedule]
- (Physician-led) Clinical study: Scheduled to start in 2016
- Conditional Approval: 2018 (Fastest)
Joint venture

[Purpose]
- Healios and DSP jointly establish a company
- The joint venture company acts as a contract manufacturing and sales organization for pharmaceuticals, medical equipment, regenerative medicine products in the field of eye diseases

[Company name] SIGHREGEN Co., Ltd.

[Capital etc.]
- Co-founded by DSP and Healios
- Paid-in capital: 50 million yen (+ capital reserve of 50 million yen)
- Shareholding : 50:50

[Directors]
- Representative director: Hardy T S Kagimoto, MD
- Directors: 4 persons (2 persons each from Healios and DSP)

[Others]
- Date of establishment: February 28, 2014 (under application for registration of establishment)
- Head Office: Chuo-ku, Kobe
- Business planning: to make, including the additional investment by the end of 1 year
Outline of alliance with Healios K.K.

December 2, 2013
Signed an Alliance Agreement to put iPS cell technology into practical use for the treatment of eye diseases in Japanese market.

Joint development agreement for the treatment of eye diseases using iPS cell-derived RPE cells (Age-related macular degeneration etc.)
NDA will be submitted by Healios

Entrust sales promotion and production of the product
Purpose of Alliance

◆ Start world’s first regenerative medicine business based on iPS cells
  – Launch regenerative medicine business based on iPS cells
  – Build business base in a field of eye diseases
  – Establish business base in-house to develop, manufacture and set standards of regenerative and cellular medicine products
  – Expand regenerative medicine business globally utilizing patents and know-how which are licensed from Healios

◆ First step to becoming a leading company in regenerative medicine and cellular therapy based on iPS cells etc.
iPS cell-derived neural retina tissue

For retinal pigmentary disease etc.
Collaborate with RIKEN CDB
Base technology: 3D culture of neural retina

Self-formation of neural retina from iPS/ES cell

SFEBq culture
(Serum-free Floating culture of Embryoid Body-like aggregates with quick reaggregation)

Eye of mouse embryo

World’s first!

Succeeded in 3D formation of neural retina containing retina-like layers and many photoreceptor cells by 3D culturing technology
Number of vision disorders in Japan is about 1.64 million.

Retinal pigmentary degeneration (RP) → Photoreceptor cells are degenerated and lost

Need the transplantation of retina

Data from Nakae K, 2005
Number of vision disorder patients in Japan is about 1.64 million.
iPS cell-derived Neural Precursor Cells
iPS cell – Spinal Cord Injury/Stroke

Joint Project with
Keio University
National Hospital Organization Osaka National Hospital
Objective / Implementation Structure

- Establishment of stocks of clinical-grade Neural Precursor Cells of iPS cell origin
- Implementation of first-in-man studies within four years on sub-acute spinal cord injury

Keio University
Director of the center: Prof. Hideyuki Okano

Clinical research for Sub-acute Spinal Cord Injury

Preclinical study for Spinal Cord Injury
Design clinical research protocol
Safety confirmation
Rehabilitation

Clinical research for Stroke

Clinical research for Sub-acute Spinal Cord Injury

Preclinical study for Stroke

Induction and Amplification protocol establishment / Design SOP

GMP-compliant Neural Precursor Cells of iPS cell origin

QC Validation
GMP-compliant test validation

Sema3A inhibitors

DSP

Osaka National Hospital
Stage-dependent Progression of Spinal Cord Injury and Optimal Timing for Cell Transplantation

Acute Phase
- Inflammation

Sub-Acute Phase
- Significant Axon Degeneration
- Glial Scar/Cavity Formation
- Cell Transplantation

Chronic Phase
- Functional recovery in animal models
- Permanent Functional Loss of Spinal Cord
<table>
<thead>
<tr>
<th>Partnering</th>
<th>Region</th>
<th>cell type</th>
<th>Schedule for practical use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td>SanBio</td>
<td>North America</td>
<td>Allo MSC</td>
</tr>
<tr>
<td><strong>AMD</strong></td>
<td>Healios RIKEN</td>
<td>Japan</td>
<td>Investigator initiated clinical trial</td>
</tr>
<tr>
<td>(age-related macular degeneration)</td>
<td></td>
<td>Allo iPS cell</td>
<td></td>
</tr>
<tr>
<td><strong>Retinitis pigmentosa</strong></td>
<td>RIKEN</td>
<td>global</td>
<td>Allo iPS cell</td>
</tr>
<tr>
<td>Keio Uni, Osaka National Hospital</td>
<td>global</td>
<td>Allo iPS cell</td>
<td></td>
</tr>
<tr>
<td><strong>Spinal Cord Injury</strong></td>
<td></td>
<td>global</td>
<td></td>
</tr>
</tbody>
</table>
DSP’s Efforts in Regenerative Medicine and Cell Therapy

◆ Establishment of Regenerative & Cellular Medicine Office
◆ Operation of research facilities in the Kobe Biomedical Innovation Cluster

◆ Execution of option agreement for therapeutic agents of stroke with SanBio (in North America area)
◆ Alliance with Healios K.K., aiming for the world's first regenerative and cellular medicine business (AMD etc.) using iPS cell
◆ Aggressive alliance and collaboration with academia and biotech companies
Vaccine Business
- New Tuberculosis (TB) Vaccines -

Koichi Kozuki
Director, Global Strategy
A new partnership formed to facilitate international partnerships that enable Japanese technology, innovations, and insights to play a more direct role in reducing disparities in health between the rich and the poor of the world.

*GHIT Fund: The Global Health Innovative Technology Fund

Collaboration agreement was entered into on December 26, 2013.
Significance of the Participation

Medical needs

- TB is one of the world’s Big Three infectious diseases. It is widespread, particularly in Asia and Africa.
  - World: Some 8.6 million people become infected every year, while some 1.3 million patients are fatally victimized.
  - Japan: More than 20,000 people contract TB and more than 2,000 die from it.

- It exacts its greatest toll on individuals during their most productive years, from ages 15 to 44 and causes serious social losses.

- The global emergence and spread of multidrug-resistant TB are imposing enormous personal costs and a significant economic burden on national health systems.

- Although the currently available BCG vaccine provides some protection in infants, it is ineffective against adolescent and adult pulmonary TB.

Contribution to global health with a central focus on emerging and developing countries
Significance of the Participation

Technology

✓ NIBIO’s human parainfluenza type-2 (rhPIV2) vector technology – The first TB vaccine using this technology in the world.

rhPIV2 vector technology

• A human respiratory virus of extremely low pathogenicity.
• Infects respiratory tract including upper airway and expresses inserted genes efficiently.

✓ The vaccine is designed to target mucous membranes to keep TB from entering the lungs.

✓ Intranasal Vaccine – easy to apply, safer medical waste without needles

✓ Global collaboration formed by Aeras’s expertise, NIBIO’s technology, JBL’s know-how in TB vaccine fields

Establishment of vaccine business base with original and leading-edge technologies
rhPIV2-Ag85B vaccine prevents *M. tuberculosis* infection

Vaccinated or control mice were challenged by Mtb infection.

Eight weeks later, the numbers of Mtb in the lung were determined.

![Bar graph showing the number of M. Tuberculosis (Log 10) in lung](image)

Reference: NIBIO's data

- **Control**
- PIV2 vaccine
- BCG vaccine
Future Plan for New TB Vaccines

- Advance vaccine candidates based on the rhPIV2 technology through preclinical stages with a goal to advance to safety and immunogenicity testing in clinical studies

- Characterization of new vaccine constructs with a variety of antigens, the conduct of immunology studies to identify the most promising novel vaccines and the establishment of manufacturing process complying with cGMP
Development of the in-licensed products in the field where no approved drugs exist

Hideo Tomiya
Deputy Executive Director, Drug Development Division; Director, Project Management
EPI-743 (Mitochondrial Disease)
EPI-743

- Licensor: Edison Pharmaceuticals, Inc
- Licensed Territory: Japan
- Mode of Action: Synchronize energy generation in the mitochondria with the counterbalancing of redox stress
- Development stage (Japan): Phase 2b/3 clinical study for Leigh syndrome ongoing
- Development stage (outside Japan; conducted by Edison): Phase 2b clinical study for Leigh syndrome and clinical studies for various diseases ongoing
- Advantages
  - Expected to be a first-in-market efficacious agent against mitochondrial diseases such as Leigh Syndrome, which currently has no treatments
  - Expected to contribute to the treatment of neuropsychiatric indications that share as a common etiology disorders of redox biochemistry

Extension of the target diseases

- Neuropsychiatric diseases associated with oxidative stress
- Mitochondrial Disease
- Leigh Syndrome
Mitochondrial diseases

- Mitochondria are organelles with functions such as producing energy for cells. Diseases caused by mitochondrial dysfunction are collectively referred to as “Mitochondrial disease.”

- Mitochondrial dysfunction can cause decrease in ATP (adenosine triphosphate) and increase in ROS (reactive oxygen species). As a result, organs that require a lot of energy such as nerves, muscles, the heart, etc. are affected most often. This is associated with a decrease in GSH (reduced glutathione) and can eventually cause degeneration of mitochondria and cell death.

- 1,087 mitochondrial disease patients were registered in the Specified Disease Treatment Research Program (“Tokutei Shikkan Chiryo Kenkyu Jigyo”) in Japan in 2012.
Leigh syndrome

- Leigh syndrome is a rare inherited neurometabolic disorder that affects the CNS.
  - Mutations in mitochondrial DNA or nuclear DNA account for the majority of Leigh disease.

- Signs and symptoms
  - Psychomotor regression
  - Muscular hypotonia
  - Feeding disorder
  - Eye movement abnormality, etc

- Prognosis
  - Leigh syndrome is poor-prognosis refractory chronic progressive disease.
    - Most of patients with Leigh syndrome die during childhood.

- Treatment
  - There is no approved treatment for now.
EPI-743 features

- Antioxidant treatments have been tried over the years, but great effectiveness has not been demonstrated.
- Principal factor responsible for the failure of antioxidant treatment is their inability to enter the mitochondria.
- EPI-743 acts as a cofactor of NQO1 (NAD(P)H quinone oxidase 1) and promotes GSH production. GSH improves cellular function and prevents cell death by eliminating ROS.
① EPI-743 acts as a cofactor of and promotes GSH production

② GSH enters the mitochondria through the intermediary of the transporter.

③ GSH eliminates ROS. GSSG reduced to GSH by GR and GSH is reutilized.

- GR: glutathione reductase
- GPx: glutathione peroxidase
- GSSG: glutathione disulfide (oxidized glutathione)
The clinical results obtained in this study were compared to an historical cohort obtained from the published natural history of Leigh syndrome. In contrast to the frequency of the combined disease progression and mortality (179/180=99.4%), 100% (10/10) of the EPI-743 treated subjects reversed disease progression and improved.
# Phase 2b/3 study of EPI-743 in Patients with Leigh Syndrome

<table>
<thead>
<tr>
<th>Study objectives</th>
<th>To evaluate the effects and safety of EPI-743 in patients with Leigh syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study patients</td>
<td>Patients with Leigh syndrome (up to 17 Years)</td>
</tr>
<tr>
<td>Study design</td>
<td>Multicenter, Open-label (non-comparative and non-blinded)</td>
</tr>
<tr>
<td>Target enrollment</td>
<td>5 and more</td>
</tr>
<tr>
<td>Dosage</td>
<td>15 mg/kg up to 200 mg three times daily</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Amount of change in NPMDS (PediatricNewcastle Pediatric Mitochondrial Disease Scale) (Sections 1-3)</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>Glutathione cycle biomarkers, etc</td>
</tr>
</tbody>
</table>

Aim to submit application for approval in Japan: Fiscal 2015
## Clinical development status of EPI-743

<table>
<thead>
<tr>
<th>Clinical indication</th>
<th>Phase</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leigh syndrome</td>
<td>2b</td>
<td>U.S.</td>
</tr>
<tr>
<td>Leigh syndrome</td>
<td>2b/3</td>
<td>Japan (DSP)</td>
</tr>
<tr>
<td>MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, Stroke-like episodes)</td>
<td>2a</td>
<td>Japan (NCNP)</td>
</tr>
<tr>
<td>Friedreich's ataxia</td>
<td>2b</td>
<td>U.S.</td>
</tr>
<tr>
<td>Friedreich's ataxia point mutation</td>
<td>2b</td>
<td>U.S.</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>2a</td>
<td>Italy</td>
</tr>
<tr>
<td>Cobalamin C Defect</td>
<td>2a</td>
<td>Italy</td>
</tr>
<tr>
<td>NIH undiagnosed disease of redox and metabolism</td>
<td>2a</td>
<td>U.S.</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>2a</td>
<td>U.S.</td>
</tr>
<tr>
<td>Tourette syndrome</td>
<td>2a</td>
<td>U.S.</td>
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Clinicaltrials.gov, JAPIC clinicaltrials information, UMIN Clinical Trials Registry

Additional indication for EPI-743 in Japan to be considered based on the result of these clinical studies.
Strategic Alliance with Edison Pharmaceuticals

Deepen cooperation with a biotech company who leads the world in the research on therapeutics for mitochondrial diseases

1. Amendment of the License Agreement for EPI-743 and EPI-589

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Licensed Rights</th>
<th>Territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPI-743</td>
<td>Exclusive research, development and commercial</td>
<td>Japan</td>
</tr>
<tr>
<td>EPI-589</td>
<td>Exclusive research, development and commercial</td>
<td>Japan/ North America</td>
</tr>
</tbody>
</table>

Added exclusive rights for EPI-589 in North America for indications in adults

2. Joint Research Agreement

Development of the novel candidate pharmaceutical compounds on mitochondrial and other cellular energy metabolism
Aiming to discover 10 candidates over the next five years

DSP will have exclusive development and commercial rights in Japan and in North America on three novel compounds of DSP’s choice from among those resulting from the joint research.

Neuropsychiatric diseases associated with oxidative stress
Mitochondrial Disease
Leigh Syndrome

Extension of the target diseases of EPI-743/EPI-589
DSP-1747 (NASH, PBC)
## DSP-1747

<table>
<thead>
<tr>
<th>Licensor</th>
<th>In-licensed from Intercept Pharmaceuticals, Inc.</th>
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<tbody>
<tr>
<td><strong>Compound Name</strong></td>
<td>Obeticholic acid</td>
</tr>
<tr>
<td><strong>Territories</strong></td>
<td>Japan and China</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>• NASH (Non-Alcoholic Steatohepatitis)</td>
</tr>
<tr>
<td></td>
<td>• PBC (Primary Biliary Cirrhosis)</td>
</tr>
<tr>
<td><strong>Mode of Action</strong></td>
<td>FXR agonist (FXR is a nuclear receptor activated by bile acid)</td>
</tr>
<tr>
<td><strong>Development Stage</strong></td>
<td>• NASH: Ongoing Ph2 study in Japan, Ph2 in the US (FLINT study, sponsored by NIDDK*)</td>
</tr>
<tr>
<td></td>
<td>• PBC: Under consideration in Japan (Ongoing Ph3 study in US/EU, conducted by Intercept)</td>
</tr>
</tbody>
</table>

*NIDDK: National Institute of Diabetes & Digestive & Kidney Diseases, a part of the National Institutes of Health (NIH)*

*FLINT study, sponsored by NIDDK*
Non-Alcoholic Steatohepatitis (NASH)

<Disease condition>
- NASH is the most extreme form of NAFLD*, and shows inflammation, hepatocellular ballooning, and fibrosis by liver biopsy.
- Typical cases of NASH show fibrosis and have the potential to progress to hepatocellular carcinoma, eventually.

<Definitive diagnosis>
- Tissue examination of liver biopsy sample is required.

<Treatment>
- There is no approved drug for NASH treatment; primary therapy is mainly diet therapy and exercise.
- To treat the complications, drugs, for instance, insulin sensitizer, fibrates, statins, and vitamin E, are prescribed to NASH patients.

<Number of patients>
- Morbidity of NASH is projected at least 1% of adults in Japan (i.e., one to two million).

*NAFLD: Non-alcoholic Fatty Liver Disease
Prognosis of NASH/NAFLD

NAFLD

• Most simple steatosis does not progress

NASH

• Five to 20% of NASH progress to cirrhosis in 5 to 10 years.
• The 5-year survival rates of NASH cirrhosis is comparable to that of Hepatitis C

1) Japan Society of Hepatology: NASH/NAFLD practice guideline 2010
2) The Journal of the Japan Medical Association: 2010; 139(9); 1880
DSP-1747: First-in-Class FXR Agonist

- **DSP-1747**
  - Obeticholic acid (OCA)
  - 6-α ethyl substitution
  - 100x more potent than CDCA on FXR
  - First-in-class with novel mechanism of action

- **CDCA**
  - Chenodeoxycholic acid
  - Endogenous FXR agonist

- **UDCA (Ursodiol)**
  - Ursodeoxycholic acid
  - No FXR activity
  - Only product approved for PBC

FXR EC$_{50}$ 0.09 µM 8.6 µM No activity

~100x increased potency

Intercept Pharmaceuticals, Inc.; Company presentation Jan. 2014
Mode of Action: FXR agonist

◆ NASH:
  ➢ Improvement of fatty liver mediated by lipid metabolism regulation
  ➢ Improvement of liver function mediated by potent anti-fibrosis effect
  ➢ Anti-inflammatory effect

◆ PBC:
  ➢ Bile acid synthesis↓, Bile acid secretion↑, Bile acid absorption↓
  ➢ Bile acid pool in the liver↓; improvement of liver function
FLINT trial: The Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment Trial

- **Sponsor:** NIDDK
  - NIDDK selected OCA for next CRN trial (FLINT) based on data from preclinical animal models and Phase 2 trial in diabetic NAFLD patients (NCT00501592, sponsored by Intercept).

- **Interim analysis** has been done when approximately 50% of the patients of the 283 enrolled had completed end of treatment 72 week biopsies.

- **Primary endpoint** met the stopping criteria of efficacy -&gt; treatment phase stopped early for efficacy (Jan. 2014)
  - Primary endpoint: improvement in NAFLD Activity Score (NAS)* by ≥2 points with no worsening of fibrosis in comparison with placebo after 72 weeks administration
  - ITT interim analysis result: p=0.0024 vs. stopping threshold of p<0.0031

- **FLINT interim results** also found disproportionate lipid abnormalities in patients on OCA.
  - Increased total cholesterol with increased LDL, and decreased HDL cholesterol (no detailed information available yet)

*Total NAS score represents the sum of scores for steatosis, ballooning, and lobular inflammation in liver biopsy samples (Kleiner DE., et al.: Hepatography 2005; 41: 1313-1321)
# NASH Phase 2 study in Japan

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To investigate dose-relationship of efficacy and safety of DSP-1747 in NASH patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Multi-center, Placebo-controlled, Randomized, Double Blind, Parallel group, exploratory Study</td>
</tr>
<tr>
<td><strong>Target patients' #</strong></td>
<td>200</td>
</tr>
</tbody>
</table>
| **Inclusion criteria** | - Patients who are diagnosed with NASH in the pathological evaluation  
- Male and female of 20 - 64 years of age |
| **Endpoint**  | Primary: Improvement of histology  
Secondary: Liver enzymes, markers related to NASH |
| **Progress** | Jan. 2014: Completion of enrollment (Target: 200 patients) |
| **Topline result** | Expected by the end of 2015 |
Future Plan

◆ NASH
  ➢ Detailed FLINT results: expected to be available 4Q 2014
  ➢ Discussions on NASH between Intercept and FDA expected to start in 2014
  ➢ Topline results of NASH Phase 2 study in Japan: to be available by the end of 2015
  ➢ DSP continues pursuing early NDA for NASH in Japan, while watching the outcome of the discussion between FDA and Intercept

◆ PBC
  ➢ Intercept POISE Phase 3 results: expected to be available 2Q 2014
  ➢ DSP considers clinical development plan in Japan after reviewing the result of POISE study
  ➢ File NDA and MAA for PBC by Intercept: 4Q 2014
### 3rd MTBP: Product Launch Plan (Updated March 2014)

#### Japan

<table>
<thead>
<tr>
<th>FY2013～FY2015</th>
<th>FY2016～FY2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUREPOST®</strong> &lt;repaglinide&gt; (Type 2 diabetes/ Combination therapies with DPP-4 inhibitors)</td>
<td><strong>SM-13496</strong> &lt;lurasidone hydorchloride&gt; (Schizophrenia)</td>
</tr>
<tr>
<td><strong>METGLUCO®</strong> &lt;metformin hydrochloride&gt; (Type 2 diabetes/ Pediatric usage)</td>
<td><strong>SM-13496</strong> &lt;lurasidone hydorchloride&gt; (Bipolar disorder)</td>
</tr>
<tr>
<td><strong>MEROPEN®</strong> &lt;meropenem hydrate&gt; (Bacterial meningitis/ 6g daily)</td>
<td><strong>AS-3201</strong> &lt;ranirestat&gt; (Diabetic neuropathy/ neuropathy)</td>
</tr>
</tbody>
</table>

#### US

<table>
<thead>
<tr>
<th>FY2013～FY2015</th>
<th>FY2016～FY2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LATUDA®</strong> &lt;lurasidone hydorchloride&gt; (Bipolar I Depression)</td>
<td><strong>SB623</strong> (Stroke)</td>
</tr>
<tr>
<td><strong>LATUDA®</strong> &lt;lurasidone hydorchloride&gt; (Bipolar Maintenance)</td>
<td><strong>SUN-101</strong> (COPD)</td>
</tr>
<tr>
<td><strong>APTIOM®</strong> &lt;eslicarbazepine acetate&gt; (Epilepsy-Adjunct)</td>
<td><strong>BBI608</strong> (Colorectal cancer)</td>
</tr>
<tr>
<td><strong>APTIOM®</strong> &lt;eslicarbazepine acetate&gt; (Epilepsy-monotherapy)</td>
<td><strong>BBI503</strong> (Solid cancer)</td>
</tr>
<tr>
<td><strong>BBI608</strong> (Colorectal cancer)</td>
<td><strong>BBI503</strong> (Solid cancer)</td>
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#### China

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<tr>
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<tbody>
<tr>
<td><strong>LONASEN®</strong> &lt;blonanserin&gt; (Schizophrenia)</td>
<td><strong>SM-13496</strong> &lt;lurasidone hydorchloride&gt; (Schizophrenia)</td>
</tr>
<tr>
<td><strong>CALSED®</strong> &lt;amurubicin hydrochloride&gt; (Small cell lung cancer)</td>
<td><strong>SM-13496</strong> &lt;lurasidone hydorchloride&gt; (Bipolar disorder)</td>
</tr>
</tbody>
</table>

#### UK

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<tbody>
<tr>
<td><strong>SM-13496</strong> &lt;lurasidone hydorchloride&gt; (Schizophrenia)</td>
<td><strong>SM-13496</strong> &lt;lurasidone hydorchloride&gt; (Bipolar disorder)</td>
</tr>
</tbody>
</table>

#### After FY2018 (not all)

**Japan**

- **LONASEN®** <blonanserin> (Schizophrenia/ Patch, Pediatric usage)
- **WT4869** (Hematologic cancer/ Solid cancer)
- **DSP-5990** <ceftaroline fosamil> (MRSA Infection)
- **DSP-1747** (NASH)
- **DSP-6952** (IBS with constipation, Chronic idiopathic constipation)
- **DSP-3025** (Asthma/ Allergic rhinitis)
- **IPS cell-derived RPE cells HLS001** (Age-related macular degeneration)

**Global**

- **DSP-2230** (Neuropathic pain)
- **SEP-225289** (ADHD)
- **DSP-1053** (Depression)
- **SEP-363856** (Schizophrenia)
- **WT2725** (Solid cancer/ Hematologic cancer)

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- **Approved**
- **Newly added**

New Chemical Entities

- **New Indication etc.**
Disclaimer Regarding Forward-looking Statements

The statements made in this presentation material are forward-looking statements based on management’s assumptions and beliefs in light of information available up to the day of announcement, and involve both known and unknown risks and uncertainties.

Actual financial results may differ materially from those presented in this document, being dependent on a number of factors.

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