Research and Development at Shionogi

March 14, 2019
Shionogi & Co., Ltd.
Agenda

1. Introduction
   – **Isao Teshirogi**, Ph.D., President and CEO

2. Research
   – **Takeshi Shiota**, Ph.D., Senior Vice President Pharmaceutical Research Division

3. CMC
   – **Ryuichi Kume**, Ph.D., Senior Executive Officer, Senior Vice President, CMC R&D Division

4. Development
   – **Toshinobu Iwasaki**, Ph.D., Corporate Officer, Senior Vice President, Global Development Division

5. Summary
   – **Isao Teshirogi**, Ph.D., President and CEO

6. Q&A
### Eight High-Priority Projects We Concentrate on During FY2019

<table>
<thead>
<tr>
<th>Stage</th>
<th>Disease Area</th>
<th>Project</th>
<th>Indication</th>
<th>Pages in the slide</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>Infectious disease</td>
<td>S-004992</td>
<td>Tuberculosis</td>
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<td></td>
<td>Pain/CNS</td>
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<td>Refractory/unexplained chronic cough</td>
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<td>S-637880</td>
<td>Neuropathic pain</td>
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<td>S-812217</td>
<td>Depression</td>
<td>P.25, 97-99, 148</td>
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<td></td>
<td>Others</td>
<td>S-770108</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>P.32, 53, 100-103</td>
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<td>Pre-clinical</td>
<td>Infectious disease</td>
<td>Novel HIV drug</td>
<td>HIV</td>
<td>P.20-21</td>
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<td></td>
<td></td>
<td>S-540956</td>
<td>Infectious disease prophylaxis etc.</td>
<td>P.17-18</td>
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<tr>
<td></td>
<td>Others</td>
<td>Peptide</td>
<td>Infectious disease, Pain/CNS, Others</td>
<td>P.31-32</td>
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<tr>
<td>Stage</td>
<td>Disease Area</td>
<td>Project</td>
<td>Indication</td>
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<td>Clinical</td>
<td>Infectious disease</td>
<td><strong>Xofluza™</strong></td>
<td>Influenza virus infection</td>
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<td><strong>Cefiderocol</strong></td>
<td>Multidrug-resistant Gram-negative bacterial infections</td>
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<td>Pain/CNS</td>
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<td><strong>Intuniv®</strong></td>
<td>ADHD</td>
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<td><strong>Lisdexamfetamine</strong></td>
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<td>P.55, 84-85</td>
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<td></td>
<td></td>
<td><em><em>SDT</em>-001</em>*</td>
<td>ADHD</td>
<td>P.25, 105-109, 149</td>
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<td></td>
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<td><strong>S-005151</strong></td>
<td>Acute ischemic stroke, Epidermolysis bullosa</td>
<td>P.110</td>
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<tr>
<td>Others</td>
<td></td>
<td><strong>ADR-001</strong></td>
<td>Decompensated liver cirrhosis</td>
<td>P.33, 110, 147</td>
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<tr>
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<td><strong>SR-0379</strong></td>
<td>Cutaneous ulcer</td>
<td>P.111</td>
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<td></td>
<td></td>
<td><strong>S-588410</strong></td>
<td>Esophageal cancer</td>
<td>P.111, 150</td>
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<tr>
<td></td>
<td></td>
<td><strong>S-588210</strong></td>
<td>Solid tumor</td>
<td>P.111</td>
</tr>
</tbody>
</table>

* STD: Shionogi Digital Therapeutics
<table>
<thead>
<tr>
<th>Stage</th>
<th>Disease Area</th>
<th>Project</th>
<th>Target indication</th>
<th>Pages in the slide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical</td>
<td>Others</td>
<td>S-723595</td>
<td>NASH*</td>
<td>P.32-34</td>
</tr>
<tr>
<td>Research</td>
<td>Infectious Disease</td>
<td>Collaboration with Nemesis</td>
<td>Refractory infectious disease</td>
<td>P.22, 135</td>
</tr>
<tr>
<td>Research</td>
<td>Infectious Disease</td>
<td>Collaboration with Vast</td>
<td>Refractory infectious disease</td>
<td>P.22, 136</td>
</tr>
<tr>
<td>Research</td>
<td>Infectious Disease</td>
<td>Collaboration with Hsiri</td>
<td>Mycobacterial diseases (tuberculosis, NTM** disease)</td>
<td>P.22, 137</td>
</tr>
<tr>
<td></td>
<td>Infectious Disease</td>
<td>Collaboration with Nagasaki Univ.</td>
<td>Malaria, Emerging re-emerging infectious diseases</td>
<td>P.20, 22</td>
</tr>
<tr>
<td>Pain/CNS</td>
<td></td>
<td>BPN14770</td>
<td>cognitive and memory deficits</td>
<td>P.25-27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Collaboration with PeptiDream (PDC***)</td>
<td>Technology to improve the migration of medicines through the BBB up to the brain BBB****</td>
<td>P.28</td>
</tr>
</tbody>
</table>

* NASH: non-alcoholic steatohepatitis  * NTM: Non-Tuberculosis Mycobacterium  ** PDC: Peptide Drug Conjugate  **** BBB: blood-brain barrier
Research

Takeshi Shiota, Ph.D.
Senior Vice President
Pharmaceutical Research Division
R&D Vision

Research: Innovation in drug discovery to meet societal needs

CMC: Research and Development of original CMC technology

Development: Advance reliability and innovation together

Actions:

- Continuous generation of new development products and drug candidates
- Wider range of research programs for peptide drugs
- Strategic investments for expansion/refocusing of disease area strategy and acquiring new technologies
- Progression of biomarker research to increase probability of clinical success
Agenda: Pharmaceutical Research Division

• **Goals of drug discovery research and Shionogi's vision**
  – Innovation in drug discovery to meet societal needs

• **Targets and accomplishments in FY2018 (Summary)**
  – Development products & drug / biomarker research

• **Accomplishments and review of FY2018 (Topic)**
  – Research Issues and approaches to solve them
  – Output of FY2018
    > Disease strategies and strategic collaborations (infectious diseases / CNS*)
    > Research approaches for Influenza
    > Peptide drug discovery
    > Novel drug candidate

• **Targets for FY2019**
Agenda: Pharmaceutical Research Division

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• **Targets for FY2019**

* CNS: Central nervous system
Synergistic Research Innovation for Our Society

Issues for Drug Industry: Appropriate balancing between producing of novel medicine and social economy for medical & social needs

Concept for Drug Discovery
- Powerful research points of infectious diseases and CNS
- Getting profound social issues in the future
- Flexible research scope shift to “more valuable area”

Drug Discovery Modalities
- SAR Engine for small molecule drug discovery
- Acquiring new modalities
- Expanding the productive power of our original “SAR* engine”

We produce novel medicines meeting medical & societal needs faster than other companies

* SAR: Structure activity relationship
Agenda: Pharmaceutical Research Division

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• Targets for FY2019

* CNS: Central nervous system
FY2018 Plans for Research

Innovation in Drug discovery to Meet Societal Needs

10 or more development products to be generated by FY2020

• Continuous generation of development candidates and development products
  – Generate 3 development candidates (2 candidates in FY2017)
  – Generate 2 development products (4 products in FY2017)

• Initiating actions to improve productivity
  – Launch 5 programs using PDPS, and obtain hit peptides
  – Launch new business corporation to promote drug discovery
  – Launch new open recruitment project, FINDS Targets*, to acquire novel drug targets
  – Launch clinical trial using novel PET** imaging marker to improve development productivity

* FINDS Targets: Shionogi original research open innovation competition
** PET: Positron emission tomography
Accomplishments in FY2017

Internal accomplishments

### Infectious diseases
- Created a novel drug candidate for Influenza

### CNS
- Conducted a novel PET** imaging biomarker for more efficient clinical trials

### Technology
- Started 5 new research programs utilizing PDPS* technology

### Others
- Created a novel drug candidate for NASH**

- 2 development candidates (target: 3 candidates)
- 0 development products (target: 2 products)
- 5 PDPS research programs (target: 5 programs)

* PDPS: Peptide Discovery Platform System
** PET: Positron emission tomography
*** NASH: nonalcoholic steatohepatitis
Agenda: Pharmaceutical Research Division

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    > Peptide drug discovery
    > Novel development candidate

• **Targets for FY2019**

* CNS: Central nervous system
## Challenges and Tactics for Research

Development candidate products and developed products for this 3 years

<table>
<thead>
<tr>
<th>Year</th>
<th>Developed</th>
<th>Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY2016</td>
<td>1 product</td>
<td>3 products</td>
</tr>
<tr>
<td>FY2017</td>
<td>4 products</td>
<td>2 products</td>
</tr>
<tr>
<td>FY2018</td>
<td>0 product</td>
<td>2 products</td>
</tr>
</tbody>
</table>

**Marked challenges**
- To accelerate establishment of drug discovery know-how in CNS and novel infectious disease areas
- To avoid late research phase discovery failures due to off-target side effects

**Strengthening SHIONOGI drug discovery infrastructure via strategic investment**
- Strengthening pipeline in CNS and Infectious diseases
- Acceleration of mid-stage drug discovery + expanding to new modalities

**Step changes in drug discovery productivity**
Agenda: Pharmaceutical Research Division

• **Goals of drug discovery research and Shionogi's vision**
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• **Targets for FY2019**

* CNS: Central nervous system
Our New Drug Discovery Strategies for Infectious Diseases

HIV

The world’s 3 major infectious diseases
Worldwide epidemic for a long time

Influenza

Hard to Treat Bacteria
Worldwide momentum for beating AMR* and difficult bacteria

AMR*

Prevention Cure
Realizing a release from infectious diseases

Proactive investment for tuberculosis and malaria

Creating a novel drug utilizing new modalities

Collaboration with UMN Pharma**, utilizing original adjuvant

* AMR: Antimicrobial resistance
** UMN Pharma: Collaboration from FY2017
Maximizing the value of a novel nucleic acid adjuvant arising from Shionogi internal research via collaborative efforts with the National Institutes of Biomedical Innovation, Health and Nutrition
Generating New Opportunities for Drug Discovery Through Strategic Investment (Infectious Diseases)

<table>
<thead>
<tr>
<th>Research</th>
<th>Preclinical</th>
<th>Clinical</th>
<th>Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV LAP*1</td>
<td>HIV LAP</td>
<td>HIV Oral</td>
<td>Cabotegravir</td>
</tr>
<tr>
<td>HIV LAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel mechanism TB/NTM</td>
<td>Hsiri</td>
<td>S-004992</td>
<td></td>
</tr>
<tr>
<td>Nagasaki</td>
<td></td>
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</tr>
</tbody>
</table>

| Hard to Treat Bacteria    | Novel β-Lactam       | Novel antibacteria | Cefiderocol        | Doripenem          |
| Fungus                    | Nemesis              |                    |                    |                    |
| AMR*4                     | Vast                 |                    |                    |                    |

| Preventive                | PDPS*5               | Anti-Influenza virus|                    | Baloxavir          |
| Vaccine                   | Ube (RS virus)       |                    |                    |                    |

- HIV: The world's 3 major infectious diseases
- TB*2 /NTM*3: Tuberculosis / Non-Tuberculosis Mycobacterium
- Malaria: Hard to Treat Bacteria
- AMR*4: Antimicrobial resistance
- Prevention: Fungus
- Other Virus: Vaccine

Constructing a deeper pipeline and more drug discovery opportunities through strategic investment

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*1 LAP: Long acting parenteral administration  
*2 TB: Tuberculosis  
*3 NTM: Non-Tuberculosis Mycobacterium  
*4 AMR: Antimicrobial resistance  
*5 PDPS: Peptide Discovery Platform System
Our Vision for Beating the World’s 3 Major Infectious Diseases

**HIV**
- New patients: 1.8M
- Death: 0.9M

**Tuberculosis**
- New patients: 10.4M
- Death: 1.7M

**Malaria**
- Patients: 200M
- Death: 0.44M

**Should be solved:**
- Drug burden
- Drug adherence
- Multi-drug resistance
- Long therapies (difficult accomplishment)
- AE/DDI**
- Drug resistance
- No efficient vaccine

**Our vision and approaches:**

**Creating and expanding the use of LAP***
- Realizing cure
- Preparing novel LAP following cabotegravir
- Focused investment on HIV cure

**Beating resistance**
- Shortening treatment period
- Efficient discovery research combination with NTM***
- Proactive alliance and collaboration

**Providing epoch-making drug and vaccine**
- Conducting open innovation based on collaboration with Nagasaki Univ.

* Epidemiology: Cited from WHO Fact sheets
** AE/DDI: adverse effect / drug-drug interaction
*** LAP: Long acting parenteral administration
**** NTM: non-tuberculosis mycobacteria
HIV Drug Formulation for LAP

Issues of HIV treatment: Patients have to take pills for decades => QOL improvement is demanded

Clinical stage in FY2019

Forwarding a novel mechanism drug as best partner for Dortegravir

Focused investment in FY2019

Development from oral administration to LAP*

Next generation of HIV treatment

Creating novel LAP following cabotegravir (Research)

We provide necessary approaches to satisfy clinical demands for improving QOL

* LAP: Long acting parenteral administration
# Strategic Investment in Infectious Diseases

## Tuberculosis/NTM*, Malaria

<table>
<thead>
<tr>
<th>Hsiri (Collaboration)</th>
<th>Nagasaki Univ. (Collaboration)</th>
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<tbody>
<tr>
<td>Drug for anti acid-fast bacillus with novel mechanism</td>
<td>World-wide presence in Emerging and Re-emerging Infectious Diseases</td>
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</table>

## Hard to Treat Bacteria

<table>
<thead>
<tr>
<th>Nemesis (Funding)</th>
<th>Vast (Funding)</th>
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</thead>
<tbody>
<tr>
<td>Breaking resistance gene by Bacteriophage and CRISPR-Cas</td>
<td>Utilizing NO*** which has wide sterilization potential</td>
</tr>
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</table>

### Creating novel drugs built on synergies between partner’s expertise and our SAR engine

- Our stepping stone for creating novel treatments for TB** and NTM
- Commitment for creating novel values utilizing Shionogi’s know-how

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* NTM: Non-Tuberculosis Mycobacterium  
** TB: Tuberculosis  
*** NO: Nitric oxide
### Our Vision in CNS Disease Area

**As is**

Symptoms vary widely even in the same disease. Effective therapies must be based on deep understanding of the mechanisms of brain function.

### Issues

<table>
<thead>
<tr>
<th>Diagnosis/stratification of patients with biomarkers</th>
<th>Understanding the mechanisms of brain function</th>
<th>Appropriate therapeutic options</th>
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</thead>
<tbody>
<tr>
<td>・Development of biomarker in order to diagnose and stratify patients</td>
<td>・Development of evaluation index in common with human and animals (MTC*)  ・Development of non-clinical evaluation and discovery of novel drug targets (SK PJ**)</td>
<td>・Acquisition of novel drug candidate  ・Acquisition of digital medicine  ・Collaborative research for new PDC***discovery  ・Start research to develop non-drug therapy</td>
</tr>
</tbody>
</table>

Seek to provide the correct therapy based on the correct diagnosis, using objective approaches such as biomarkers.

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**Note:**

* MTC: Milner Therapeutic Consortium  
** SK PJ: Collaboration project of Shionogi and Kyoto Univ.  
*** PDC: Peptide Drug Conjugate
**Creation of Drug Discovery Opportunities by Strategic Business Investment (CNS/Pain)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Research</th>
<th>Preclinical</th>
<th>Clinical</th>
<th>NDA/launch</th>
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</thead>
<tbody>
<tr>
<td><strong>Depression</strong></td>
<td>SK PJ 2nd</td>
<td></td>
<td>S-812217</td>
<td>Cymbalta®</td>
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<tr>
<td><strong>ADHD</strong></td>
<td>Early PG</td>
<td>Late PG</td>
<td>SDT-001</td>
<td>Intuniv®</td>
</tr>
<tr>
<td><strong>Alzheimer’s disease</strong></td>
<td>SK PJ 1st</td>
<td>Early PG</td>
<td>BPN14770</td>
<td></td>
</tr>
<tr>
<td>/Cognitive and memory deficits</td>
<td>PDC</td>
<td>Late PG</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other CNS disorders</strong></td>
<td>SK PJ 1st</td>
<td>Early PG</td>
<td>S-637880</td>
<td>Cymbalta®</td>
</tr>
<tr>
<td></td>
<td>PDPS</td>
<td>Early PG</td>
<td>S-600918</td>
<td>OxyContin®</td>
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<td>Symproic®</td>
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(This figure shows representative portfolio)

To accelerate drug discovery based on the symptoms, we acquired new assets and build a stronger pipeline.
The Next Growth Drivers in CNS Disease Area

### Three strategic investment products

<table>
<thead>
<tr>
<th>SAGE Therapeutics</th>
<th>Tetra Discovery Partners</th>
<th>Akili Interactive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Novel antidepressant S-812217</strong></td>
<td><strong>Drug candidate for cognitive and memory deficits BPN14770</strong></td>
<td><strong>ADHD digital therapeutics SDT-001</strong></td>
</tr>
<tr>
<td>- GABA$_A$ PAM*</td>
<td>- PDE4D** NAM***</td>
<td>- Therapeutic application</td>
</tr>
<tr>
<td>- Rapid onset &amp; Strong efficacy &amp; Sustainable efficacy</td>
<td>- Significant reduction of side effects</td>
<td>- Activate the cerebral cortex that becomes dysfunctional with ADHD</td>
</tr>
<tr>
<td>- Possibility to expand indications with a focus on depression</td>
<td>- Possibility to expand indications marked by cognitive and memory deficits</td>
<td>- Improvement of treatment environment by digital sharing of information</td>
</tr>
</tbody>
</table>

Expanding our pipeline into a wider range of treatment options

In-house ADHD PG products to progress into pre-clinical phase next year

* PAM: Positive allosteric modulator
** PDE4D: Phosphodiesterase 4D
*** NAM: Negative allosteric modulator
Tetra: Novel Cognitive Function Improving Drug

**Tetra discovery partners**

- Biotechnology R&D company in Michigan State, USA
- Search drugs for novel mechanisms against PDE4* by protein structure-based drug design

**BPN14770 Efficacy (non-clinical)**

BPN 14770 improves neuronal plasticity in Alzheimer’s disease model.

<table>
<thead>
<tr>
<th>control (normal)</th>
<th>Aβ1-42 hippocampal administration AD***model</th>
<th>+ BPN14770</th>
</tr>
</thead>
</table>

(Brain histochemistry)

Confirmed improvement of cognitive function also in behavior evaluation

**Avoiding side effects while maintaining therapeutic efficacy using an allosteric modulator distinct from existing development products (PDE4D**** inhibitor)**

* PDE4: Phosphodiesterase 4
** NAM: Negative allosteric modulator
*** AD: Alzheimer's disease
**** PDE4D: Phosphodiesterase 4D
R&D Timeline of BPN14770

Development plan of Tetra in US

<table>
<thead>
<tr>
<th>Year</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
</tr>
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<tbody>
<tr>
<td>Fragile X syndrome (Ph2)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer's disease (Ph2)</td>
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- **Fragile X syndrome**: Confirming therapeutic potential of the drug in a small number of patients, receiving orphan drug designation from FDA
- **AD**: Seeking to improve symptoms of cognitive dysfunction in early Alzheimer's (MCI)*2

Research plan of SHIONOGI

Seeking to various target indications with cognitive deficits through collaborative research

- BPN14770 (PDE4D*3 NAM*4)
- AD*1
- PD*5
- Depression
- Brain injury
- Cognitive deficits

US: To accelerate development of FXS*6 and AD by Tetra
Japan: To seek various indications and develop formulations for the future clinical phase

To start collaboration research with PD* to build a platform for delivery of compounds to the brain that will be designed to improve the migration of medicines through the BBB**

**PDC** (Peptide Drug Conjugate)

- Special cyclic peptide
- Linker
- Drug

**Establishment of Brain delivery platform**
Making it possible to deliver drugs into the brain independent of molecular weight and physical properties

**Application stage**
(establishment of platform)

**Validation stage**
(Collaboration research with PD)

**Early practical use of brain delivery technology**
Early entering into clinical stage by high possibility establishment of POC***

To maximize CNS drug discovery, accelerate the establishment of brain delivery platform by medium molecule

* PD: PeptiDream
** BBB: Blood Brain Barrier
*** POC: Proof of concept
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• Targets for FY2019

* CNS: Central nervous system
Research Approaches for Influenza

Features of Influenza Viruses
- The error-prone properties of the RNA virus inevitably create diverse variant viruses during genome replication due to a lack of proofreading activity.
- The I38 variants with reduced susceptibility to Xofluza emerged in some patients.

Characterization of I38 variants
- Reduced replicative fitness of the I38 variants* due to reduced CEN** activity may be associated with reduced transmission capability, that requires further studies.

Combination Dosing Regimen
- Combination use of medicines from different classes is the current standard for the current HIV therapy.
- Combination with NAI*** & multiple dosing regiments is required for severely ill influenza patients.

Efficacy in Combination
- Reduced emergence of I38 variants with higher antiviral activity was confirmed in combination with NAI in nonclinical studies.
- A clinical trial in seriously ill, hospitalized patients is ongoing to explore the dose regimen in combination.

Shionogi will identify the optimal dosing regimen for Xofluza for influenza treatment in various populations supported by extensive non-clinical approaches.

* Scientific Reports, volume 8, Article number: 9633 (2018)
** Cap-dependent endonuclease
*** Neuraminidase inhibitor
## Progression of Peptide Drug Discovery

### PDPS Drug Discovery Platform

<table>
<thead>
<tr>
<th>Started 5 new research programs</th>
<th>Found 2 peptides for low molecular compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aiming preclinical stage at Mar/2021</td>
<td>Screening</td>
</tr>
<tr>
<td><strong>Infectious disease</strong></td>
<td></td>
</tr>
<tr>
<td>Peptide drug 1</td>
<td>Origin for low molecular</td>
</tr>
<tr>
<td>Peptide drug 2</td>
<td></td>
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<tr>
<td>Peptide drug 3</td>
<td></td>
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<tr>
<td>Peptide drug 4</td>
<td></td>
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<tr>
<td>Peptide drug 5</td>
<td></td>
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<tr>
<td>Peptide drug 8 (Started in FY2018)</td>
<td></td>
</tr>
<tr>
<td>Peptide drug 6</td>
<td></td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td></td>
</tr>
<tr>
<td>Peptide drug 9 (Started in FY2018)</td>
<td></td>
</tr>
<tr>
<td>Peptide drug 7</td>
<td></td>
</tr>
<tr>
<td><strong>Others including IPF</strong>*</td>
<td></td>
</tr>
<tr>
<td>Peptide drug 10 (Started in FY2018)</td>
<td></td>
</tr>
<tr>
<td>Peptide drug 11 (Started in FY2018)</td>
<td></td>
</tr>
<tr>
<td>Peptide drug 12 (Started in FY2018)</td>
<td></td>
</tr>
</tbody>
</table>

**Expanding peptide drug discovery as a core technology (IPF as the initial focus indication for identification of a candidate to progress into preclinical stage in FY2020)**

*IPF: Idiopathic pulmonary fibrosis*
Expansion beyond IPF* to Other Diseases

Research activity and expansion beyond IPF

- **Research progression of IPF drug discovery**
- **Slowing of Deterioration**
- **Improved safety**
- **Pirfenidone**
  - S-770108 Pirfenidone Inhalant (Ph1 in FY2018)

- **Maintenance of respiratory function**
  - PDPS/Nucleic acid (Preclinical stage in FY2020 with PDPS)

- **Further amelioration of clinical condition**
  - Combination therapy with different mechanisms

- **Expansion to NASH/CKD***
  - S-723595 preceding candidate for NASH** treatment

Accelerating drug discovery research for IPF utilizing PDPS technology with consideration for expansion into NASH and CKD

---

* IPF: Idiopathic pulmonary fibrosis  
** NASH: Non-alcoholic steatohepatitis  
***CKD: Chronic kidney disease
Product Pipeline in Liver Disease

**NASH* development and commercial environment**
- No approved drug for NASH (Some drugs are used off-label, including certain anti-diabetics and Vitamin E)
- Low success rate in achieving primary endpoint in Ph2
- Combination therapy with different mechanisms are required due to complex underlying cause

- Increasing number of patients
  (Exercise and diet therapy)

- Increasing risk of cirrhosis

- No drug

- Created a drug candidate for NASH treatment with novel mechanism

<table>
<thead>
<tr>
<th>Healthy liver</th>
<th>Steatosis</th>
<th>NASH</th>
<th>Cirrhosis</th>
<th>Hepatocellular carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Healthy liver image" /></td>
<td><img src="image2" alt="Steatosis image" /></td>
<td><img src="image3" alt="NASH image" /></td>
<td><img src="image4" alt="Cirrhosis image" /></td>
<td><img src="image5" alt="Hepatocellular carcinoma image" /></td>
</tr>
</tbody>
</table>

(Cited from Decision Resources 2015)

- **S-723595**
- **ADR-001****
- **LCM** of IPF*** drug

* NASH: Non-alcoholic steatohepatitis  ** LCM: Lifecycle management  *** IPF: Idiopathic pulmonary fibrosis  **** ADR-001: Cellular and Tissue-based Product prepared from mesenchymal stromal cells (MSC) derived from allogeneic adipose tissue
Novel Drug Candidate S-723595

Created a novel drug candidate with unique mechanism reducing ectopic fat

- **Metabolic syndrome**
- **Accumulation of ectopic fat**
- **Deteriorating condition**

S-723595 decreases ectopic fat

**Decreasing fibrosis in liver (for NASH drug)**

- **Vehicle**
- **Competitor X (Ph2)**
- **Competitor Y (Ph3)**

**Improving insulin resistance (A lot of NASH patients have insulin resistance)**

- **Vehicle**
- **3595**
- **Marketed**

**Reducing ectopic fat in muscle (Unique profile of our compound)**

- **Vehicle**
- **3595**

This candidate has also body weight decreasing function

S-723595 has a unique mechanism and can be a strong partner for other NASH development compounds

* MRS: Magnetic Resonance Spectroscopy
Agenda: Pharmaceutical Research Division

- **Goals of drug discovery research and Shionogi's vision**
  - Innovation in drug discovery to meet societal needs
- **Targets and accomplishments in FY2018 (Summary)**
  - Development products & drug / biomarker research
- **Accomplishments and review of FY2018 (Topic)**
  - Research Issues and approaches to solve them
  - Output of FY2018
    - Disease strategies and strategic collaborations (infectious diseases / CNS*)
    - Research approaches for Influenza
    - Peptide drug discovery
    - Novel drug candidate
- **Targets for FY2019**

* CNS: Central nervous system
FY2018 Plans for Research

Innovation in Drug discovery to Meet Societal Needs

10 or more development products to be generated by FY2020

• Continuous generation of development candidates and development products
  – Generate **3 development candidates** (2 candidates in FY2017)
  – Generate **2 development products** (4 products in FY2017)

• Initiating actions to improve productivity
  – Launch **5 programs** using PDPS, and obtain hit peptides
  – Launch **new business corporation** to promote drug discovery
  – Launch **new open recruitment project, FINDS Targets***, to acquire novel drug targets
  – Launch clinical trial using **novel PET** imaging marker to improve development productivity

*Cited from FY2017 R&D presentation

* FINDS Targets: Shionogi original research open innovation competition
** PET: Positron emission tomography
FY2019 Plans for Research

Innovation in Drug discovery to Meet Societal Needs

10 or more development products to be generated by FY2020

- Continuous generation of development candidates and development products
  - Generate **4 development candidates** (2 candidate in FY2018)
  - Generate **2 development products** (0 products in FY2018)
  - Raising PDPS programs to preclinical Late phase

Summary of FY2018
Strengthened our pipeline in infectious diseases and CNS by strategic investment

Plans for FY2019
Continually generate new development products by focusing on research areas of infectious diseases and CNS, and by focusing on progress of development candidates

* Research core means “infectious diseases” and “CNS”
CMC

Ryuichi Kume, Ph. D.
Senior Vice President
CMC R&D Division
R&D Vision

Research: Innovation in Drug Discovery to Serve Society

CMC: Research and Development of original CMC technology

Development: Advance reliability and innovation together

Actions:
By Implementing world-class, cutting-edge CMC Research/Technology
- Providing the Best Possible Medicine
- Improving Medical Economics
- Increasing the Success Rate of Drug Development
Agenda: CMC R&D Division

• To Achieve SGS2020
  – Mission for CMC R&D Division
  – Changes in the Environment and What CMC Research can Do to Respond

• Achievements in FY2018
  – Product Development and Maximizing the Value of Our Products by CMC Technologies
  – NDA Submissions and Market Launches of Pipeline Products

• Targets for FY2019
  – Targets for FY2019
  – Towards Further Advances in CMC Technologies: Collaboration with Outside Organizations
Agenda: CMC R&D Division

• **To Achieve SGS2020**
  – Mission for CMC R&D Division
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  – Targets for FY2019
  – Towards Further Advances in CMC Technologies: Collaboration with Outside Organizations
Mission for CMC R&D Division

Create Valuable Products Meeting Society’s Needs

- Providing the Best Possible Medicine
  - Creation of Products with High Product Features and Quality Function
  - Delivering Relief Reliably to All People

- Improving Medical economics
  - Continuous CoGs* Reduction and Treatment, QOL and Social Productivity improvement
  - Development Demonstrating Cost-Effectiveness

- Increasing Success Rate of Our Drug Development
  - Application of CMC Technology at Early R&D Stage
  - Providing New Solutions for Drug Discovery Research

*CoGs: Cost of Goods
Changes in the Environment and What CMC Research can Do to Respond

External Environment Changes

• Aging of Society, Health Economy-Oriented
• Acceleration of Industry-Academia and Industry-Industry Collaboration
• Stemming the Rising Tide of Drug-Resistant Bacteria and Viruses

Increasing inhibition factor on CMC-related
Increasing inhibition factor not only on efficacy and safety but also on CMC-related, e.g. low absorption of new drug and high manufacturing cost

Increasing Importance of CMC Contribution to Drug Development

• Acceleration of drug development
• Maximizing the value of new drugs through formulation technology
• Systems that ensure appropriate cost and quality
• Efficient strategic planning and execution through NDA filing and post-launch
Agenda: CMC R&D Division

• **To Achieve SGS2020**
  – Mission for CMC R&D Division
  – Changes in the Environment and What CMC Research can Do to Respond

• **Achievements in FY2018**
  – Product Development and Maximizing the Value of Our Products by CMC Technologies
  – NDA Submissions and Market Launches of Pipeline Products

• **Targets for FY2019**
  – Goal in FY2019
  – Towards Further Advances in CMC Technologies: Collaboration with Outside Organizations
Maximize the Value of our Compounds

NME and LCM* through CMC Technologies

NME  
Moving Projects forward to Drug Candidate status using Innovative and Advanced CMC Technologies  
➡ Advance ≥ 4 Projects by 2020  
➡ FY2017: 0 Project   FY2018: 2 Projects

Developing Revolutionary CMC Technologies through In-House Development and Collaborations  
➡ Develop ≥ 3 Technologies by 2020  
➡ FY2017: 2 Tech.   FY2018: 1 Tech.

LCM  
Develop New LCMs Utilizing Improved CMC Technology  
➡ Advance ≥ 2 Projects by 2020  
➡ FY2017: 1 Project   FY2018: 1 Project

Collaborate to apply CMC core competencies across the value chain, beyond the traditional role of CMC

Targets for FY2018 (1)
## Targets for FY2018 (2)

### Rapid/High Quality NDAs and Launches

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xofluza™</td>
<td>Completion of NDA and Preparation for Launch in the US, Completion of NDA for Pediatric Granular Formulation in Japan</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>Approval in Japan, Launch</td>
</tr>
<tr>
<td>Rizmoic® (Naldemedine)</td>
<td>Completion of Preparation for Launch in EU</td>
</tr>
<tr>
<td>Mulpleta®</td>
<td>Completion of Preparation for Launch in the US</td>
</tr>
<tr>
<td>Cefiderocol</td>
<td>Completion of NDA preparation in the US</td>
</tr>
</tbody>
</table>

**Rapid/high quality NDAs that reliably meet the requirements of global regulatory authorities**

- Drug development with predictive risk assessment and proactive resolution
- No delays in approval of NDA submissions due to quality of filing package and excellent communication with authorities
Achievement in FY2018 (1)

Maximize the Value of the Compound

NME and LCM by CMC Technologies

**NME**
Moving Projects forward to Drug Candidates Status using Innovation and Advanced CMC Technologies

➡️ **Advance ≥ 4 Projects by 2020**
FY2017: 0 Project
FY2018: 2 Projects (Novel mechanism anti-HIV medicine, S-540956 (vaccine adjuvant))

Developing Revolutionary CMC Technologies through In-House Development and Collaborations

➡️ **Advance ≥ 3 Technologies by 2020**
FY2017: 2 Tech.
FY2018: 1 Tech. (Nanotechnology)

**LCM**
Develop New LCMs Utilizing Improved CMC Technology

➡️ **Advance ≥ 2 Projects by 2020**
FY2017: 1 Project
FY2018: 1 Project
Research and Development of Original CMC Technology

– Crystallization for Continuous Manufacturing
– Novel Nanotechnology for Formulation of Low-solubility APIs
– Cefiderocol Stabilization Technology
– Novel Lyophilization Technology for Productivity Improvement
– Pulmonary Drug Delivery Technology for Inhaled Pirfenidone
– Development of Quantitative NMR (q-NMR)
Crystallization for Continuous Manufacturing

**Importance of Crystallization**

Crystallization is the most effective method to eliminate impurities in a drug substance. It determines the quality. However,

- Achieving consistent crystallization is difficult with complex compound structures
- Extended processing times can result in compound degradation

**Continuous Crystallization**

A continuous oscillatory baffled crystallizer (COBC) is a tube containing periodically spaced orifice baffles to allow efficient mixing → purer crystal with narrow crystal size distribution

**Comparison of impurity amount**

<table>
<thead>
<tr>
<th></th>
<th>COBC</th>
<th>Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impurity</td>
<td>20 ppm</td>
<td>200 ppm</td>
</tr>
<tr>
<td>Reduced</td>
<td>1/10</td>
<td></td>
</tr>
</tbody>
</table>
Novel Nanotechnology for Formulation of Low Solubility APIs

Benefits and challenge

Benefits of Nanotechnology
• Improve BA
• Reduce food-effect
• Design prolonged-release injectable suspension

Challenge: Metal contamination risk from the equipment used in process

Solution to challenge
Not shown in detail - Patent in preparation

Drastic reduction of metal contamination compared to Conventional Technology

Advanced formulation development of Nano drug product with the lowest metal contamination in the world

<table>
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<tr>
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<tbody>
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</tr>
</tbody>
</table>

Amount of metal contamination
Cefiderocol Stabilization Technology

**Challenges**

- Hard to obtain high-purity API because it is difficult to crystallize.
- Challenging to develop drug product because API is highly unstable. (Storage below -15°C is necessary)

**Solutions to the challenges**

- **Improvement of API purity** by comprehensive salt screening to find more crystallizable salt form
- **Stabilization of cefiderocol** by protective effects of 3 excipients

**Challenges**

- Improvement of API purity by comprehensive salt screening to find more crystallizable salt form
- Stabilization of cefiderocol by protective effects of 3 excipients

**Solutions to the challenges**

- Improvement of API purity by comprehensive salt screening to find more crystallizable salt form
- Stabilization of cefiderocol by protective effects of 3 excipients

**Technological advancements simplified and accelerated the development of cefiderocol**

*RH; Relative Humidity
Novel Lyophilization Technology for Productivity Improvement

Importance and challenges

**Importance:** Lyophilization is an effective technology for stabilization and sterilization of unstable mid-large molecule API

**Challenge:** Supercooling prior to freezing causes micro ice crystal formation, resulting in extended drying time.

Development of novel technology

Addition of sterilized ice fog prior to freezing prevents supercooling and increases the ice crystal size to shorten the drying time.

**Importance and challenges**

**Importance:** Lyophilization is an effective technology for stabilization and sterilization of unstable mid-large molecule API

**Challenge:** Supercooling prior to freezing causes micro ice crystal formation, resulting in extended drying time.

**Development of novel technology**

Significant reduction of drying time allows production of drug product at an **affordable price**

**Conventional technology**

- **Product temperature**
- **Freezing point**
- **Freezing time**

**Novel technology**

- **Product temperature**
- **Freezing point**
- **Freezing time**

**Freezing**

- **Super cooling**
- **Crystal size:** Small

**Drying**

- **Hard to sublimate**
- **Extended drying time**

- **Easy to sublimate**
- **30-50% Reduction in drying time**
Pulmonary Drug Delivery Technology for Inhaled Pirfenidone

**Achievements and next issue**

**Achievements**
- Micronized API and optimized API-carrier formulation for high efficiency of pulmonary drug delivery
- Clinical Inhalation device developed for maximum performance

**Next Challenge**
- **Design of commercial device**

**Design of commercial device**

Inhalation device co-developed with other companies

Commercial design of devise with **high inhalation efficiency and ease of use** is under development

**Emitted dose evaluation of clinical inhaler device**

High pulmonary drug delivery achieved even for IPF* patients with low inhalation flow rate

<table>
<thead>
<tr>
<th>Other device (Flow rate: 20 L/min)</th>
<th>Shionogi device</th>
</tr>
</thead>
<tbody>
<tr>
<td>28%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Competitive results were shown with clinical device against others.

**More rapid progression of inhaled pirfenidone towards commercialization**

*IPF: Idiopathic pulmonary fibrosis*
Development of Quantitative NMR (q-NMR)

**Conventional method**

**Commonly used HPLC** method
- Development of a test method: 1 month
- Require setting reference standards: Setting & Control: 1 month
- Accuracy affected by external factors (Ex. purity of reference standard)

**Better method: q-NMR**

Utilization of q-NMR**: Emerging technology in recent years
- Development of method: 1 week
- Reference standards available on the market
- Accuracy assured by using high-purity universal standards

**Quick and accurate method**

- Applicable to nucleic acids for which it is difficult to set reference standards
- Quantification of phosphorus atoms determined nucleic acids’ content

31P-NMR spectra

- Standard
- Nucleic acid

Accurate, reliable and rapid evaluation

Contributed to efficient and rapid drug development with higher quality

---

* HPLC: High Performance Liquid Chromatography
** NMR: Nuclear Magnetic Resonance
Achievements in FY2018 (2)

• Rapid/high quality NDAs and launches
  – Xofluza™
    > NDA (Apr. 24), Approval (Oct. 24), 2 months acceleration of US launch (Nov. 7) in the US
    > NDA in Taiwan (Jun. 29), NDA and launch of pediatric granule formulation in Japan
  – Lisdexamfetamine (Pediatric AD/HD)
    > Passed First Committee on New Drugs in Japan (Feb. 21)
  – Intuniv® (Adult ADHD)
    > NDA for additional indication in Japan (Aug. 10)
  – Rizmoic ® (Naldemedine)
    > Approval in EU (Feb. 22)
  – Mulpleta®/Lusutrombopag
    > Approval in the US (Jul. 31), 1 month acceleration of launch (Aug. 30)
    > Approval in EU (Feb. 22)
  – Cefiderocol
    > Progress as scheduled for approval in the US: US application acceptance (Feb. 12)
Agenda: CMC R&D Division

• To Achieve SGS2020
  – Mission for CMC R&D Division
  – Changes in the Environment and What CMC Research can Do to Respond

• Achievements in FY2018
  – Product Development and Maximizing the Value of Our Products by CMC Technologies
  – NDA Submissions and Market Launches of Pipeline Products

• Targets for FY2019
  – Targets for FY2019
  – Towards Further Advances in CMC Technologies: Collaboration with Outside Organizations
Maximize the Value of the Compound

NME and LCM by CMC Technologies

**NME**
Advancing products to drug candidates status using advanced CMC technology
⇒ **Advance ≥ 4 Projects by 2020**
   FY2017: 0 Project  FY2018: 2 Projects
   **FY2019: 1 Project**

Developing revolutionary CMC technologies through in-house development and collaborations
⇒ **Advance ≥ 3 Technologies by 2020**
   FY2017: 2 Tech.  FY2018: 1 Tech.
   **FY2019: 1 Tech.**

**LCM**
Develop new LCMs utilizing improved CMC technology
⇒ **Advance ≥ 2 Projects by 2020**
   FY2017: 1 Project  FY2018: 1 Project
   **FY2019: 1 Project**
## Targets for FY2019 (2)

### Rapid/High Quality NDAs and Launches

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
</tr>
</thead>
</table>
| Xofluza<sup>TM</sup> | Approval in Taiwan, Launch  
<p>|                | Launch for pediatric granule formulation in Japan                      |
| Lisdexamfetamine | Launch in Japan                                                         |
| Intuniv&lt;sup&gt;®&lt;/sup&gt;  | Approval in Japan, Launch                                               |
| Cefiderocol      | Approval in the US, Launch                                              |</p>
<table>
<thead>
<tr>
<th><strong>Collaborative research utilizing PGCTM Platform Technology</strong></th>
<th><strong>Capital and business alliance, technology for prophylactic vaccine against infection disease</strong></th>
<th><strong>R&amp;D for Nitric Oxide inhaled antimicrobial drug candidate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACADEMIA</strong></td>
<td><strong>Collaboration with academia, university, laboratory etc.</strong></td>
<td><strong>Collaborative research of “SAGE-217” for the treatment of MDD</strong>*</td>
</tr>
<tr>
<td><strong>Process technology development for “A2NTX” Botulinum Toxin biopharmaceutical</strong></td>
<td><strong>Collaborative research of “BPN14770” for the treatment of cognitive and memory deficits</strong></td>
<td><strong>Collaborative research for the treatment of Mycobacterial diseases</strong></td>
</tr>
<tr>
<td><em><em>Creation of CMO</em> for revolutionizing production of API for constrained peptides</em>*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* MDD: major depressive disorder
Development

Toshinobu Iwasaki, Ph.D.
Senior Vice President
Development Division
R&D Vision

Research: Innovation in drug discovery to benefit society

CMC: Research and Development of original CMC technology

Development: Advance reliability and innovation together

Actions:
• Enhance global functions
• Develop ability for cost management
• Promote innovation in drug development
Agenda: Global Development Division

• Achievements in FY2018
  – Current Status and Actions
  – Pipeline
  – Top-priority products
    > Xofluza®
    > Cefiderocol
    > ADHD*(Intuniv® / Lisdexamfetamine)
  – High-priority projects
    > S-004992
    > S-600918
    > S-637880
    > S-812217
    > S-770108
  – Challenge to new modality
    > SDT-001
    > ADR-001, S-005151, SR-0379, Cancer Peptide Vaccine

• Targeted Milestones for FY2019
  – Current Status and Actions
  – Pipeline
Development Targets for FY2018

Issues for FY2017

- Establish development framework that can respond flexibly to environmental changes
  - Centralized management and oversight for global clinical trials
  - Rapid decision making by data driven approach
- Cost saving by streamlining development packages and focusing clinical trials
  - Increasing skillsets in forecasting and planning
  - Using feasibility studies to increase predictability

NDA Submissions: 3 (4 indications)  Approvals: 3

From Presentation of FY2017
Actions in FY2018

Establish development framework that can respond flexibly to environmental changes

- Optimizing resource allocation using visualization tools for global planning
- Establishing Global Function Head for cross-regional alignment
- Implementing data analysis platform for internal and external data related to drug development

Cost saving by streamlining development packages and focusing clinical trials

- Conducting clinical trials with most efficient use of resources
- Accomplishing Xofluza pivotal study in one influenza reason in Japan
- Clear prioritization regarding timing of study conduct

NDA Submitted:3(5 indications)
Targeted:3(4 indications)

①Xofluza™: US
②Xofluza®(granule): Japan
③Xofluza®(granule・New dosage for children): Japan
④Intuniv®(Adult): Japan
⑤Cefiderocol: US

Approved:3(4 indications)
Targeted:3

①Mupleta®: US
②Xofluza™: US
③Lusutrombopag: EU
④Rizmoic®/Naldemedine: EU
# Achievements in FY2018: NDA Submissions and Approvals

<table>
<thead>
<tr>
<th>Product (indication)</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>NDA submission</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EU(2018.1)</td>
<td>EU(2019.2)</td>
</tr>
<tr>
<td>Rizmoic®/Naldemedine (Opioid-induced constipation)</td>
<td></td>
<td></td>
<td></td>
<td>EU(2017.3)</td>
<td>EU(2019.2)</td>
</tr>
<tr>
<td>Lisdexamfetamine (ADHD(pediatric))</td>
<td></td>
<td></td>
<td>high-dose study</td>
<td>Japan(2017.4)</td>
<td>Japan* 2019.2</td>
</tr>
<tr>
<td>Xofluza®/Xofluza™</td>
<td></td>
<td></td>
<td></td>
<td>Global : High Risk study completed(2018.8)</td>
<td>US(2018.4)</td>
</tr>
<tr>
<td>① Influenza virus infection</td>
<td></td>
<td></td>
<td></td>
<td>Japan : Granule study completed(2018.7)</td>
<td>② Japan(2018.4)</td>
</tr>
<tr>
<td>② Influenza virus infection (granule)</td>
<td></td>
<td></td>
<td></td>
<td>③ Japan(2018.8)</td>
<td>① US(2018.10)</td>
</tr>
<tr>
<td>③ Influenza virus infection (granule • Weight under 20kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>② Japan (2018.9)</td>
</tr>
<tr>
<td>Cefiderocol (Multidrug-resistant Gram-negative bacterial infections)</td>
<td></td>
<td></td>
<td></td>
<td>Global : 2 clinical studies** ongoing</td>
<td>US(2018.12)</td>
</tr>
<tr>
<td>Intuniv® (ADHD(adult ))</td>
<td></td>
<td></td>
<td></td>
<td>Japan : extension study completed(2019.1)</td>
<td>Japan(2018.8)</td>
</tr>
</tbody>
</table>

**Passed Drug Committee Meeting  
** HAP/VAP/HCAP: hospital-acquired pneumonia/ventilator-associated pneumonia  
** CR : Carbapenem-resistant  
/health care-associated pneumonia
# Achievements in FY2018: Phase II ~ III

<table>
<thead>
<tr>
<th>Product (indication)</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>NDA submission</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xofluza®<em>(Influenza virus infection)</em> (prophylaxis)</td>
<td></td>
<td></td>
<td>Japan:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>initiated(2018.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OxyContin®*TR (Treatment of moderate to severe chronic pain)</td>
<td></td>
<td></td>
<td>Japan:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>initiated(2018.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-588410 (Bladder cancer)</td>
<td></td>
<td></td>
<td>Japan • EU:</td>
<td>completed(2019.3)</td>
<td></td>
</tr>
<tr>
<td>S-120083 (Inflammatory pain)</td>
<td></td>
<td></td>
<td>US:</td>
<td>completed (2018.10)</td>
<td></td>
</tr>
<tr>
<td>S-600918 (Neuropathic pain or Refractory Chronic Cough)</td>
<td>Multiple dose study Completed in FY2017</td>
<td>Japan: initiated (2018.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR-0379 (Skin ulcers (Pressure ulcers, diabetic ulcers, etc))</td>
<td></td>
<td></td>
<td>Japan:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skin ulcers subjects initiated(2018.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Achievements in FY2018: Phase I

<table>
<thead>
<tr>
<th>Product (indication)</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>NDA submission</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-770108 (Idiopathic Pulmonary Fibrosis)</td>
<td>Japan: Single and multiple dose study completed (2018.10) &lt;br&gt; UK: Lung deposition study (in preparation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-637880 (Neuropathic pain)</td>
<td>Japan: Single dose study completed (2019.3) &lt;br&gt; Japan: PET receptor occupancy study ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-005151 (stroke)</td>
<td>Japan: Study in Healthy adults (Including the elderly*) initiated (2018.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-812217 (Depression)</td>
<td>Japan: Single and multiple dose study initiated (2018.10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-004992 (Tuberculosis)</td>
<td>Asia (China): initiate</td>
<td>postponed to FY2019</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-588210 (Solid tumor)</td>
<td>UK: Study in patients with solid tumor initiated (2018.11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ICH-E7 defines older people over 65 years old
Top-priority products

Xofluza®
Cefiderocol
ADHD(Intuniv®/ Lisdexamfetamine)
Xofluza™
Influenza Virus Infection
Profile: Xofluza™

**Indication**
Influenza virus infection

**Mechanism of action**
Cap-dependent endonuclease inhibition (novel mechanism of action)

**Special characteristics**
- Single oral dose
- Potent antiviral activity against seasonal influenza (type A and B viruses) and virus with potential pandemic risk including highly pathogenic avian viruses
- Confirmed safety/tolerability

**Stage**
- Japan: Phase III new dosage for children (for granule)
- Japan: Phase III Post Exposure Prophylaxis Study
- Taiwan: NDA submission

**Future plans**
- Japan: NDA submission for new dosage for children
- Japan: NDA submission for prophylaxis indication
- Taiwan: approval

---

Xofluza™  Time to Improvement of Influenza Symptoms in High Risk Patients

Early improvement of symptoms confirmed in high risk patients

US: Completed sNDA for high risk indication
Japan: Updated the package insert with these data
Xofluza™ Time to Improvement of Influenza Symptoms in High Risk Patients (Influenza B)

Baloxavir significantly reduced in time to improvement of influenza symptoms compared with oseltamivir for influenza B infected high risk patients.

<table>
<thead>
<tr>
<th></th>
<th>Baloxavir</th>
<th>Placebo</th>
<th>Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>166</td>
<td>167</td>
<td>148</td>
</tr>
<tr>
<td>Median (hours)</td>
<td>74.6*#</td>
<td>100.6</td>
<td>101.6</td>
</tr>
<tr>
<td>95% CI (hours)</td>
<td>67.4, 90.2</td>
<td>82.8, 115.8</td>
<td>90.5, 114.9</td>
</tr>
</tbody>
</table>

Stratified Generalized Wilcoxon test, P<.05 vs *placebo or #oseltamivir
Xofluza™ Incidence of Influenza-related Complications in High Risk Patients

<table>
<thead>
<tr>
<th></th>
<th>Baloxavir (N=388)</th>
<th>Placebo (N=386)</th>
<th>Oseltamivir (N=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.0</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>0.8</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Radiologically Confirmed Pneumonia</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Otitis media</td>
<td>0.0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Patients with any complications: 2.8%* (11/388) for Baloxavir, 10.4% (40/368) for Placebo, 4.6% (18/389) for Oseltamivir.

*Fisher’s exact test  p < .0001  vs placebo

Lower incidence of influenza-related complications was demonstrated in patients at risk for complication.
Influenza A Viral Variants With Reduced Susceptibility To Baloxavir (PA/I38 Variants) Were Seen In Clinical Trials

PA/I38 variants, viruses harboring amino acid substitution at the position 38\textsuperscript{th} in PA, such as PA/I38T (isoleucine to other amino acids), show reduced susceptibility to baloxavir.

Reduced replicative fitness of these variants due to reduced CEN activity of the variants with substitutions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion of PA/I38 variant emergence (patients with I38/total patients)</th>
<th>Type/subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A/H1N1pdm</td>
</tr>
<tr>
<td>Phase 2 study</td>
<td>2.2% (4/182)</td>
<td>3.6% (4/112)</td>
</tr>
<tr>
<td>Phase 3 OwH* study</td>
<td>9.7% (36/370)</td>
<td>0% (0/4)</td>
</tr>
<tr>
<td>Pediatric study (T0822)</td>
<td>23.4% (18/77)</td>
<td>0% (0/2)</td>
</tr>
<tr>
<td>Phase 3 High Risk study</td>
<td>5.2% (15/290)</td>
<td>5.6% (1/18)</td>
</tr>
<tr>
<td>NIID Surveillance Data\textsuperscript{1}</td>
<td>8.2% (16/194)</td>
<td>1.8% (2/110)</td>
</tr>
</tbody>
</table>

\textsuperscript{1}https://www.niid.go.jp/niid/en/flu-m/flutoppage/2132-flu/flu-dr-e/8652-flu-r-e20190304.html (Table 1)
No Consistent Trend On The Impact Of Emergence Of PA/I38 Variants For Clinical Symptoms Across Three Studies

**Time to Alleviation of Symptoms in Patients with/without PA/I38 Variants**

**Phase 3 OwH* Study (adults and adolescents)**
- Baloxavir
  - Patients with PA/I38 variants (n=36)
  - Patients without PA/I38 variants (n=334)
- Placebo (n=230)

**Pediatric Study (6M - 12yo)**
- Baloxavir
  - Patients with PA/I38 variants (n=17)
  - Patients without PA/I38 variants (n=59)

**Phase 3 High Risk study (adults and adolescents)**
- Baloxavir
  - Patients with PA/I38 variants (n=15)
  - Patients without PA/I38 variants (n=275)
- Placebo (n=385)

* OwH: Otherwise healthy
Robust Ongoing Activities Generating Important Data In Key Populations - Provides Further Insights Into PA/I38 Variants

<table>
<thead>
<tr>
<th>STUDY</th>
<th>STUDY FOCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STATUS</strong></td>
<td><strong>CLINICAL APPROACH</strong></td>
</tr>
<tr>
<td>ONGOING</td>
<td>PEDIATRICS STUDIES AT HIGHER DOSING</td>
</tr>
<tr>
<td>ONGOING</td>
<td>SEVERELY ILL &amp; HOSPITALIZED PATIENTS</td>
</tr>
<tr>
<td>ONGOING</td>
<td>POST EXPOSURE PROPHYLAXIS</td>
</tr>
<tr>
<td>ONGOING</td>
<td>DRUG SUSCEPTIBILITY SURVEILLANCE</td>
</tr>
<tr>
<td>PLANNED</td>
<td>REDUCED TRANSMISSION</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STATUS</th>
<th>NON-CLINICAL APPROACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONGOING</td>
<td>NEXT GENERATION SEQUENCING</td>
</tr>
<tr>
<td>ONGOING</td>
<td>TRANSMISSION STUDY IN FERRET MODELS</td>
</tr>
<tr>
<td>ONGOING</td>
<td>COMBINATION W/NAI &amp; MULTIPLE DOSING REGIMENS</td>
</tr>
</tbody>
</table>

Shionogi will accomplish this through a robust ongoing development plan that includes surveillance, clinical and non-clinical assessments as well as timely publications.
Combinational Effect of Baloxavir and NAI

Viral load and emergence of I38 variants 5 days post single dose in highly immunocompromised mouse model with shedding infectious virus continuously

Shionogi confirmed decreased risk of emergence of I38 variants in combination with NAI, that is a therapy applied in the ongoing SEVERELY ILL & HOSPITALIZED PATIENTS STUDY
Cefiderocol
Multidrug-resistant Gram-negative bacterial infection
## Profile: Cefiderocol

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidrug-resistant Gram-negative bacteria infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Mechanism of action</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-wall synthesis inhibition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Special characteristics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Injectable siderophore cephalosporin</td>
</tr>
<tr>
<td>• Wide range of Gram-negative pathogens</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Stage</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Global: CREDIBLE-CR*: carbapenem-resistant Gram-negatives study</td>
</tr>
<tr>
<td>Global: APEKS**-NP***: hospital-acquired pneumonia/ventilated-associated pneumonia study</td>
</tr>
<tr>
<td>US: NDA submission in 2H FY2018 (QIDP**** designated compound)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Future plan</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EU: MAA submission in 1H FY2019 (Accelerated Assessment)</td>
</tr>
<tr>
<td>US, EU: Approval</td>
</tr>
<tr>
<td>Global: Pediatric Program</td>
</tr>
</tbody>
</table>

*Carbapenem Resistant, ** Acinetobacter, Pseudomonas, E. coli, Klebsiella, Stenotrophomonas, ***Nosocomial Pneumonia, ****Qualified infectious disease product
US NDA & EU MAA

US New Drug Application

• Submitted for the indication of “Complicated urinary tract infections (cUTI), including pyelonephritis”
• FDA Accepted the NDA
  - PDUFA Goal: 14 Aug 2019
• Planned supplemental NDA for HABP/VABP with the results of APEKS-NP

EU Marketing Authorization Application

• Planned MAA for the indication of “Treatment of infections due to aerobic Gram-negative bacteria with limited treatment options” in 1H FY2019
  - Granted Accelerated Assessment (review timeline: about 8 months, anticipated timeline from filing to approval: about 10 months, provided accelerated review is maintained.)

Approval in US and EU in FY2019
Intuniv®/ Lisdexamfetamine ADHD (Attention-deficit/hyperactivity disorder)
## Intuniv®: Profile

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th>ADHD (Attention-deficit/hyperactivity disorder)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Selective alpha 2a adrenergic receptor agonist</td>
</tr>
</tbody>
</table>
| **Special characteristics** | • Taken once-daily (AM/PM), Intuniv controls ADHD core symptoms (hyperactivity-impulsivity and inattention) significantly compared to the placebo.  
• Safety of clinical dose established by extensive data accumulated in overseas commercialization.  
• Approved as monotherapy and adjunctive therapy to stimulants in the US and Canada. Approved as monotherapy in the EU. |
| **Stage** | Japan: Pediatric ADHD: on the market, Adult ADHD: August 2018 sNDA filing  
US, Canada, EU: on the market (Shire/Takeda) |
| **Future plan in Japan** | Approval for Adult ADHD indication in Japan |
Results from completed long-term study* was submitted to health authority

*A long-term (1 year) Study in Adult ADHD Patients. Subjects included patients who completed the preceding phase 3 DBT and the patients who were newly enrolled in this study.

【Summary of study results】

- The ADHD-RS-IV with adult prompts Total Score and CAARS sub-scale Score were significantly improved at all evaluated points, as compared to the baseline (P < 0.0001)
- Intuniv long-term administration neither increased onset of AEs nor developed new AEs, suggesting to pose no significant problems with the safety.
Lisdexamfetamine: Profile

**Indication**
ADHD (Attention-deficit/hyperactivity disorder)

**Mechanism of action**
To block the reuptake of norepinephrine and dopamine and increase their release

**Special characteristics**
- Taken once-daily, S-877489 controls ADHD core symptoms significantly compared to placebo
- Comparable safety profile to CR methylphenidate
- Compound aiming to decrease risk of dependence or abuse*

**Stage**
Japan: Pediatric ADHD: Under PMDA review
US, Canada, Brazil, EU and Israel: on the market (Shire/Takeda)

**Future plan in Japan**
Pediatric ADHD indication launch in FY2019

*Lisdexamfetamine is a pharmacologically inactive prodrug. After ingestion, it is gradually converted to the active element. The risk of dependence and abuse is low, because it has a resistance to the hydrolysis by enzyme except in red blood corpuscles, and slowly convert to the active element after nasal administration or intravenous administration.
Shionogi will manage the distribution control system strictly to prevent inappropriate prescription or illegal use after marketing of lisdexamfetamine, and provide it only to those patients for whom it is an appropriate treatment.

Lisdexamfetamine handling should be managed carefully. Shionogi will construct the system to use it safely.

Contribution:
- Improvement of patient’s QOL
- To create the society where individual patient’s originality will be respected and demonstrated.
High-priority projects

【In Development Stage 】
S-004992
S-600918
S-637880
S-812217
S-770108
S-004992
Anti-Tuberculosis
Profile: S-004992

**Indication**

Tuberculosis

**Mechanism of action**

Inhibition of mycolic acid synthesis in the Mycobacterium tuberculosis

**Special characteristics**

- Orally active against both drug-sensitive and drug-resistant strains of Mycobacterium tuberculosis
- Potentially offering potent efficacy from a pharmacokinetics perspective (high lung concentrations, low plasma protein binding)

**Development stage**

Phase I study is getting prepared
Nonclinical studies are underway to confirm the competitive efficacy and safety of metabolite impurity
S-600918
Neuropathic Pain • Refractory Chronic Cough
Profile: S-600918

Indication
Neuropathic Pain, Refractory Chronic Cough (RCC)

Mechanism of Action
P2X$_3$ Receptor Antagonist

Special characteristics
- Once-daily, oral
- Good and well-tolerated safety profile

Stage
Japan: Proof of concept study for RCC

Future Plan
Global: Dose-finding study for RCC will be initiated
Markets of Refractory Chronic Cough

- There are **no approved drugs** for RCC
- **Long-term use** of centrally-acting antitussive is **not recommended**, and **CNS side effects** are also observed

![Diagram showing estimated number of RCC patients]

It is estimated about 6 million patients are suffering from RCC in the US

Safe and effective treatments are needed

---

* United Nations Population Database, **Song WJ et al., 2015**, ***Levine BM et al., 2008***
P2X<sub>3</sub> Receptor and Cough Reflex

- **P2X<sub>3</sub> receptor**
  - ATP (adenosine triphosphate) -gated ion channel
  - Mainly expressed in peripheral nervous system and mediates neuronal sensitization
  - Assembled by three P2X<sub>3</sub> subunits, homo-trimer (P2X<sub>2/3</sub> hetero-timer also exists)

ATP, ligand of P2X<sub>3</sub> receptors, induces the cough reflex

P2X<sub>3</sub> receptors are expressed in nerves which are associated with the cough reflex

P2X<sub>3</sub> receptors are involved in the cough reflex

**Overview of Proof of Concept Study**

<table>
<thead>
<tr>
<th>Screening</th>
<th>1st period</th>
<th>Wash-out</th>
<th>2nd period</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>2-3 weeks</td>
<td>2 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Population**
- Patients with refractory/unexplained chronic cough

**Design**
- Placebo-controlled, multi-center, randomized, double-blind, cross-over comparison

**Efficacy Endpoints**
- To evaluate the rate of change in the number of coughs per hour in 24 hours, in the daytime, in the nighttime and so on.
- To evaluate the change in the Leicester Cough Questionnaire etc.,

**No. of patients**
- 30 patients

*Informed consent*
Results of Proof of Concept Study

Coughs per hour in the daytime

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>S-600918</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of change (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughs per hour in the daytime</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-31.6%  
(p=0.0546)

Leicester Cough Questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>S-600918</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p=0.0415)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Coughs per hour in 24 hours

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>S-600918</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of change (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughs per hour in 24 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-30.9%  
(p=0.0386)

Safety

- The incidence of AEs related to the taste disturbance was lower than the competitor.

Proceed to a dose-finding study
S-637880
Neuropathic Pain
Profile: S-637880

**Indication**
Neuropathic Pain, etc.

**Mechanism of action**
Not disclosed (new mechanism)

**Special characteristics**
To expect efficacy for peripheral and central neuropathic pain

**Stage**
Japan: SAD study (completed)
Japan: PET receptor occupancy study

**Future plans**
Japan: MAD study
Global: Phase 2 study
S-812217
Depression
Profile: S-812217

Indication
Depression (Major Depressive Disorder)

Mechanism of Action
GABA<sub>A</sub> Receptor Positive Allosteric Modulator

Special characteristics
• Breakthrough profiles
  ✓ **Rapid onset**: efficacy shown in 24 hours after the first dosing
  ✓ **Strong efficacy**: efficacy is greater than available antidepressants
  ✓ **Sustainable**: efficacy is durable after completing 2 weeks dosing
  ✓ **Better medication adherence**: No need for dose adjustment including titration and tapering, once daily dosing for 14 days
• The US FDA designed breakthrough therapy

Stage by Shionogi
Japan: Ph1 ongoing

Stage by Sage
US: PPD Ph3 completed
US: MDD Ph3 ongoing

Future plans
Japan: Initiate clinical study in MDD

PPD: postpartum depression, MDD: major depressive disorder
Concept for S-812217 Development

Creating a more vigorous society

Novel mechanism of action | Rapid onset, Strong and Sustainable Efficacy

Potential paradigm shift in the treatment of depression providing new benefit to patients

Novel antidepressant following Cymbalta®

- Launching new CNS products contributing to sales beyond 2020

Social impact of Depression in Japan

- 5M patients with depression in Japan\(^1\), the largest population among non-fatal diseases
- Depression results in an aggregate absence from work of 40M days/year, and a productivity loss equivalent to 40B yen\(^2\), the biggest impact among all diseases

---

1) WHO, Depression and Other Common Mental Disorders Global Health Estimates
S-770108
Idiopathic Pulmonary Fibrosis
Profile: S-770108 (Inhaled Pirfenidone formulation)

Indication
Idiopathic Pulmonary Fibrosis

Mechanism of action
Anti-fibrotic

Special characteristics
- Dry Powder for Inhalation (Highly convenient)
- Novel Dry Powder Inhaler specifically designed for S-770108
- High level of safety and tolerability

State
Japan: Phase I single and multiple dose trial completed

Future plans
UK: Commence a trial using radiolabeled S-770108 to evaluate the lung penetration potential
S-770108 Development Strategy

Oral Pirfenidone (Pirespa® & Esbriet®)

[Efficacy]
- Efficacy established in confirmatory trials¹,²,³
  - Suppression of lung function decline; (forced) vital capacity
  - Maintenance of 6 minute walk test distance
  - Extended progression-free survival
- Life prolongation (reduced mortality)⁴
Internationally recognised in recent treatment guidelines as a recommended treatment for IPF (2015)⁵

[Safety]
- Frequent Adverse Events
  - Photosensitivity reactions (14.4%)
  - Decreased appetite (27.9%), Nausea (8.0%)
- Over half of patients do not reach the recommended maintenance dose (1800 mg)
- Around 20% of patients discontinue treatment due to adverse events
(Figures from Japanese PMS data⁶)

- Large reduction of systemic exposure by delivering pirfenidone directly into the lungs
- Large reduction in adverse event frequency, attainment of a high concentration in the lungs, and improved adherence are expected, allowing the full potential of pirfenidone to be fulfilled

S-770108 Development Status and Plans

Phase I Single and Repeated dose study : Complete

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Healthy male subjects (Caucasian and Japanese)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Single dose part: No adverse events reported</td>
</tr>
<tr>
<td></td>
<td>Repeated dose part (three doses/day)</td>
</tr>
<tr>
<td></td>
<td>Temporary cough was reported in some subjects directly following inhalation, however these events were all mild and resolved without intervention. No other adverse events were reported.</td>
</tr>
</tbody>
</table>

Large reduction in systemic exposure (blood drug concentration) compared to oral pirfenidone

- It is assumed that the current safety concerns (GI events, photosensitivity) with oral pirfenidone can be avoided with this inhaled formulation

Lung deposition study : Commencing FY2019 (UK)

To evaluate whether or not S-770108 is delivered to, and reaches an potentially effective concentration in the peripheral regions of the lung (the area affected by IPF)
Challenge to new Treatment Modalities

SDT-001
ADR-001
S-005151
SR-0379
Cancer Peptide Vaccine
SDT (Shionogi Digital Therapeutics)
Introduction of A New Treatment Option for ADHD Symptoms

Shionogi will provide a new treatment option for medical and social needs of ADHD patients

Introduction of AKL-T01: Akili digital non-drug prescription treatment

- Treatment program based on cerebral mechanism (Nature)
- Verification by clinical studies (submitted to FDA)
- Utilizes digital technology
- Through accumulation, sharing and analysis of data, identify the best possible treatment optimized for each patient

Selective Stimulus Management engine

Nature. 2013 Sep 5;501(7465):97-101
Mechanism of AKL-T01 (SDT-001)

A substantial body of literature demonstrates that ADHD patients have hypoactivity in the cerebral cortex, and activation of the cerebral cortex is linked to improvements in ADHD symptoms. AKL-T01 incorporates adaptive, simultaneous cognitive tasks automatically optimized for each patient and activates their cerebral cortex.

Multiple tasks + Optimized for patient

Simultaneous activities: Steering and Tapping
- Steering: avoid obstacles
- Tapping: touch special targets

Assess the difference between 1st and 2nd exercise grades (patient ability)

Real-time optimization of the performance of simultaneous tasks for each patient

Continuous activation
- Continuously activate cerebral cortex
- Improve inattention

Closed-Loop

Nature. 2013 Sep 5;501(7465):97-101
AKL-T01 Pivotal study

Akili has conducted a pivotal study of AKL-T01: A multi-center, double-blind, randomized, active-controlled study in the US.

<Study summary>
- Object (Sample size): ADHD patients ages 8 to 12 (n=348)
- Treatment period: 4 weeks (25 minutes/day, 5 days/week)
- Control: active control app
- Primary endpoint: Test of Variables of Attention (TOVA)* Attention Performance Index (API) scores

<Result>
- The change of TOVA-API from baseline was significantly improved in AKL-T01 group compared to the active control group (p=0.006).

* TOVA is medical instrument based on Continuous Performance Task (CPT). Inattention and impulse are objectively assessed.
Vision: An Integrated Suite of ADHD Therapies

Shionogi will provide new treatment options to address the medical and social needs of ADHD patients

1. Provide digital therapy alongside drug therapy
2. Utilize digital technology to monitor and share symptom and treatment effectiveness data between the family and the physician

Improve the paradigm of care for ADHD patients
Challenge to New Treatment Modalities

**ADR-001** licensed from Rohto Pharmaceutical Co., Ltd.

- **Regenerative medicine product for the treatment of decompensated decompensated liver cirrhosis**
  - ADR-001 is prepared from adipose-derived mesenchymal stem cells (MSCs) using a culture method with serum-free medium developed by Rohto.
  - Adipose tissue contains a large number of MSCs and can be obtained less invasively than bone marrow.
  - ADR-001 can be manufactured and stocked on a large scale and this treatment can be provided efficiently smoothly to patients.
- **Phase I/II study in patients with decompensated decompensated liver cirrhosis is now underway by Rohto (Japan)**
  - Plan to obtain “conditional and time-limited approval of a regenerative medical product”* using data from the Phase I/II study.

* A regulation developed to promptly and safely receive approval for regenerative medicine products. It allows conditional and time-limited approval if clinical trials of the product indicate that it is likely to be effective.

**S-005151** licensed from StemRIM Inc.

- **Epidermolysis bullosa : Conducting Investigator-initiated Phase II study**
- **Acute ischemic stroke : Completed Phase I study in Japan**
  - IND submission for the phase 2 study on April 2019
Challenge to New Treatment Modalities

SR-0379 licensed from FanPep CO., Ltd., (a biotechnology venture company based on technology of Osaka University)

• Skin ulcers (Pressure ulcers, diabetic ulcers, etc): Phase II is ongoing (Japan)
  • Topical liquid spray, easy to use
  • Contribute to increment in social needs from home medical care
  • 2019 first half of fiscal: Confirm the result of Phase II study

Cancer Peptide Vaccine (CPV) licensed from OncoTherapy Science, Inc.

• S-588410 (Esophageal cancer) : Completed exploratory study* to evaluate tumor-infiltrating CTL** (See Appendix 150page for details)
  • Activated-CTL infiltration and PD-L1 expression in the tumor were induced by S-588410.
  • High efficacy of combination therapy with CPV and a PD-(L)1 inhibitor can be expected in patients with low PD-L1 expression.
• S-588210 (Solid tumor) : Initiated Ph1 study in patients with solid tumor
  • S-588210 has restricted affinity for HLA-A*02:01 which is dominant in Caucasian, and its target antigens are the same as those of S-588410.
  • Once the safety and tolerability of S-588210 monotherapy is confirmed, clinical studies in combination with S-588210 and a PD-(L)1 inhibitor will start.

• Future development plan
  • Accelerate the CVP development globally with the addition of S-588210 to the CPV pipeline
    ✓ CPV monotherapy for prevention of recurrence or maintenance after chemo/radiotherapy
    ✓ Combination therapy with CPV and a PD-(L)1 inhibitor for advanced cancer

* Interim analysis result was published in ESMO 2018, **cytotoxic T lymphocyte
Development Targets for FY2019
Development Targets for FY2019

Efficient Global Operation

• “One Global Shionogi” with Global Functions
  – Efficient decision-making by Global Function Head, and clear role and responsibility for each function
  – Understanding of environment and requirements in each region and planning of regulatory strategy to support development and registration of new modalities

• Cost Management
  – Accurate budget control by comprehensive planning
  – Enhancement of management ability for outsourcing activity and associated costs

• Data-Driven Development
  – Quality management and performance evaluation for development activities based on analysis of all accumulated data
  – Development of new endpoints and supportive clinical evidence using digital technologies

Vision

Balance between efficiency and innovation

Development Innovation

NDA Submissions: 2(3 indications)  Approvals: 4(5 indications)
### Target Milestones for FY2019: NDA Submission and Approvals

Maximize products value and Challenge for applying new modality to clinical use

<table>
<thead>
<tr>
<th>Product (indication)</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>NDA submission</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisdexamfetamine (ADHD(pediatric))</td>
<td></td>
<td></td>
<td></td>
<td>Japan(2017.4)</td>
<td>Japan</td>
</tr>
<tr>
<td>Intuniv® (ADHD(adult ))</td>
<td></td>
<td></td>
<td></td>
<td>Japan(2018.8)</td>
<td>Japan</td>
</tr>
<tr>
<td>Xofluza® (Influenza virus infec) ①granule(weight under 20kg) ②granule(new dosage for children(weight under 20kg) ③prophylaxis</td>
<td></td>
<td>Japan : High-dose study for children completion Prophylaxis study completion</td>
<td></td>
<td>①Japan(2018.8)</td>
<td>①Japan</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>②Japan</td>
<td>②Japan</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>③Japan</td>
<td>③Japan</td>
</tr>
<tr>
<td>OxyContin®TR (Treatment of moderate to severe chronic pain)</td>
<td></td>
<td></td>
<td></td>
<td>Japan : completion</td>
<td>Japan</td>
</tr>
</tbody>
</table>

Stage up
## Target Milestones for FY2019: Phase I ~ III

<table>
<thead>
<tr>
<th>Product (indication)</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>NDA submission</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-812217 (Depression)</td>
<td>Japan: Single and multiple dose study completion</td>
<td></td>
<td>Japan: initiate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rizmoic®/Naldemedine (Opioid-induced constipation(pediatric))</td>
<td></td>
<td></td>
<td>EU: initiate</td>
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<td></td>
</tr>
<tr>
<td>Cefiderocol (Multidrug-resistant Gram-negative bacterial infections(pediatric))</td>
<td></td>
<td></td>
<td>Global: Safety and PK study initiate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-600918 (Neuropathic pain or Refractory Chronic Cough)</td>
<td>Japan: POC study completion Global: Dose-finding Study initiate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR-0379 Skin ulcers(Pressure ulcers, diabetic ulcers, etc)</td>
<td>Japan: POC study completion</td>
<td></td>
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</tr>
<tr>
<td>S-770108 (Idiopathic Pulmonary Fibrosis)</td>
<td>UK: Lung deposition study initiate</td>
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</tr>
</tbody>
</table>
## Target Milestones for FY2019: Phase I ~ III

<table>
<thead>
<tr>
<th>Product (indication)</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>NDA submission</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-005151 (stroke)</td>
<td>Japan: Study in Healthy adults (Including the elderly) completion</td>
<td>Japan: initiate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>S-637880 (Neuropathic pain)</td>
<td>Japan: Multiple dose study completion</td>
<td>Global: initiate</td>
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<tr>
<td>Naldemedine (POI*)</td>
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<tr>
<td>Novel HIV Drug (HIV virus infection)</td>
<td></td>
<td>US: initiate</td>
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<td></td>
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<tr>
<td>SDT-001 (ADHD)</td>
<td></td>
<td>Japan: initiate</td>
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</tr>
</tbody>
</table>

* Post operative ileus
Development Targets for FY2020 from FY2017

Goals

10 or more compounds, including out-licensed products and products currently approved in a limited number of countries, to be launched globally

Direction for FY2020

Establish global development framework

- One Global SHIONOGI
  - Sharing fundamental policies, mission and decisions
  - Standardization of Roles & Responsibilities and business processes

Fast and accurate making decision

- Strategy-based prioritization
- ROI* based efficient investment
- Science-based go/no-go decision

Efficient development

- Control development costs
- Reduce development time

FY2017
3 compounds

FY2018
7 compounds

FY2019
9 compounds

FY2020
10 compounds

* Return on investment
### Current situation for development targets through FY2020

#### Goals

**10 or more compounds**, including out-licensed products and products currently approved in a limited number of countries, to be launched globally

<table>
<thead>
<tr>
<th>Launched</th>
<th>NDA submission / NDA submission (in preparation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Before SGS2020(FY2014)]</td>
<td></td>
</tr>
<tr>
<td>• Osphena®/ Senshio*</td>
<td></td>
</tr>
<tr>
<td>1. TIVICAY®</td>
<td></td>
</tr>
<tr>
<td>[From SGS2020(FY2014)]</td>
<td></td>
</tr>
<tr>
<td>2. Triumeq®</td>
<td></td>
</tr>
<tr>
<td>3. Symproic®</td>
<td></td>
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<tr>
<td>4. Julica®</td>
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<tr>
<td>5. Mulpleta®</td>
<td></td>
</tr>
<tr>
<td>6. Xofluza®</td>
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<tr>
<td>7. Osphena® (Vaginal dryness)</td>
<td></td>
</tr>
</tbody>
</table>

8. Cefiderocol
   - US/EU: launch in FY2019

9. DTG/3TC (HIV): First 2-drug regimen for naïve patients
   - Launch in FY2019

10. CAB+RPV (HIV): First long acting injection
    - 1H 2019: NDA/MAA submission in US and EU
    - US: launch in FY2019

---

DTG: dolutegravir, RPV: rilpivirine, 3TC: lamivudine, CAB: cabotegravir

---

*Scheduled to be achieved in FY2020*

*After approval of Osphena for the treatment of Vaginal dryness in US, it will be regarded as globally launched product*
Summary

Isao Teshirogi, Ph.D., President and CEO
To continue to discover next growth drivers ~ Achievement in FY2018 ~

➢ Steady progress of R&D especially for the 8 high-priority projects*

➢ In-licensing of novel platform candidates
  – Expanded opportunities to discover novel medicines by 10 strategic collaborations
    ✓ Hsiri, Nemesis, SAGE, Rohto, Vast, Ube, Tetra, PeptiDream, Nagasaki Univ., Akili

➢ Steady progress of existing platforms
  – Advancing and strengthening foundation for HIV treatment and prevention through progress of DTG/CAB franchise

Further strengthen, expand, and accelerate drug-discovery both on our own and through external collaboration

---

DTG/CAB Franchise - HIV Treatment Platform

Tivicay®, Triumeq®  Launch: 2013~
• Key drug for 3-drug regimen

Juluca® (DTG/RPV)  Launch: 2017~
• First 2-drug regimen for maintenance therapy
• Dec. 2018: Launched in Japan

DTG/3TC  Launch: 2019~
• First 2-drug regimen for naïve patients
  ➢ PDUFA action date is anticipated in 6 months (priority review voucher)
  → Plan to be approved by Apr. 2019

CAB+RPV  Launch: 2019~
• First long acting injection (monthly or bimonthly)
• Aug. 2018: positive results from ATLAS,
  Oct. 2018: positive results from FLAIR
• Mar. 7, 2019: ATLAS/FLAIR data presentation at CROI
• In 2019: NDA/MAA submission in US and EU (monthly injection)
  ATLAS 2M (bimonthly injection) study data

CAB prophylaxis  Launch: 2021~
• First long-acting injectable for prophylaxis
  (bimonthly injection)

Continued excellent progress in expanding the platform and its value

Progress from Feb. 1, 2019 to Mar. 14, 2019
DTG: Dolutegravir, CAB: Cabotegravir, RPV: Rilpivirine, 3TC: Lamivudine
CAB+RPV: Positive Results (48week)  
(ATLAS study: switch, FLAIR study: naive)

- **Viral Suppression**
  - CAB+RPV had similar efficacy to a comparator group*, and **two studies met their primary endpoint**.
    - ATLAS: CAB+RPV 92.5%, CAR* 95.5%
    - FLAIR: CAB+RPV 93.6%, Triumeq® 93.3%

- **Patient-reported Treatment Satisfaction**
  - **Significantly greater increase in treatment satisfaction** reported with CAB+RPV vs previous oral.
  - **Most patients preferred CAB+RPV** over previous oral therapy**.
    - ATLAS: CAB+RPV 86.4%, CAR 2.3%
    - FLAIR: CAB+RPV 90.8%, Triumeq® 0.7%

- **Safety, Tolerability**
  - Treatment with CAB+RPV was well-tolerated, and similar to the results of Phase IIb

- **Confirmed Virologic Failure (CVF)**
  - Low confirmed virologic failure rate (1%) across both treatment arms, and similar to the results of Phase IIb
    - ATLAS: CAB+RPV 3 subjects (1%), CAR 4 subjects
    - FLAIR: CAB+RPV 3 subjects (1%), Triumeq® 3 subjects

---

* ATLAS: current antiretroviral therapy (CAR), the existing three-drug regimen once a day. FLAIR: Triumeq®
** in FLAIR, ARV therapy-naive adults received induction therapy with oral Triumeq® for 20 weeks and were randomly assigned to continue oral Triumeq® or switch to CAB+RPV
ATLAS study: Patient-reported Treatment Satisfaction

Source: CROI, Mar. 7, 2019

ATLAS: High Participant Satisfaction (HIVTSQs) and Preference for Injectable Therapy

<table>
<thead>
<tr>
<th>HIVTSQs Total Score*</th>
<th>50</th>
<th>55</th>
<th>Improvement</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB LA + RPV LA</td>
<td></td>
<td></td>
<td>+6.43</td>
<td></td>
</tr>
<tr>
<td>CAR</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Week 24*</td>
<td>+1.05</td>
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<td></td>
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</tr>
<tr>
<td>Week 44*</td>
<td>+0.44</td>
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</tbody>
</table>

- The CAB + RPV group were more satisfied with the monthly injectable treatment compared with participants receiving CAR

Difference (95%CI)

- Week 24*: 5.39 (4.17–6.60), p<0.001
- Week 44*: 5.68 (4.37–6.98), p<0.001

Patient Preference Survey (LA Arm)

Single-item question on participants' preference at Week 48
- ITT-E population: 86% (266/308) preferred LA; 2% (7/308) preferred daily oral therapy
  - Responding participants: 97% (266/273) preferred the LA regimen over previous oral therapy

CAB, cabotegravir; CAR, current antiretroviral; HIVTSQs, HIV Treatment Satisfaction Questionnaire (Status); ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine

*Adjusted mean change from baseline; adjusted for baseline score, sex, age, race, and baseline third agent class. Error bars show 95% confidence interval. n=300 for CAB + RPV at Week 24 and n=300 at Week 48; n=283 for CAR at Week 24 and n=204 at Week 48.

Source: CROI 2019; Seattle, WA. Abstract 1475

Conference on Retroviruses and Opportunistic Infections; March 4–7, 2019; Seattle, WA
**FLAIR study: Patient-reported Treatment Satisfaction**

**Source:** CROI, Mar. 7, 2019

### FLAIR: High Participant Satisfaction (HIVTSQc) and Preference for Injectable Therapy

<table>
<thead>
<tr>
<th>HIVTSQc Mean Total Score</th>
<th>0</th>
<th>Improvement</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB LA + RPV LA (n=263)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DTG/ABC/3TC (n=266)</td>
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</tbody>
</table>

- **Week 48**
  - 29.6% improvement
  - 25.5% improvement
  - Difference (95% CI): 4.1 (2.8–5.5), p<0.001

- Change in satisfaction with current treatment vs induction phase treatment was significantly higher for LA vs DTG/ABC/3TC
  - HIVTSQs exhibited a ceiling effect, with very high baseline satisfaction scores in both groups (data not shown)†

### Patient Preference Survey

Single-item question on participants’ preference at Week 48:

- **ITT-E population:** 91% (257/283) preferred LA; 1% (2/283) preferred daily oral therapy
  - **Responding participants:** 99% (257/259) preferred the LA regimen over previous oral therapy

---

**SHIONOGI**

CROI: Conference on Retroviruses and Opportunistic Infections 124
# Actions to Create Further Growth Drivers

**1: Generate a Large Variety of Compounds in Phase I (Infectious disease, Pain/CNS)**

### Focus on 8 projects marked by red frame in FY2019

<table>
<thead>
<tr>
<th>Infection Disease</th>
<th>Preclinical (Basic research)</th>
<th>Preclinical (Early phase)</th>
<th>Preclinical (Late phase)</th>
<th>Preclinical (Candidate)</th>
<th>Phase I</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV virus infection</td>
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<tr>
<td>Opioid</td>
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<tr>
<td>SK PJ1: Alzheimer’s disease</td>
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<tr>
<td>RS virus infection</td>
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<tr>
<td>SK PJ2: Other CNS disease</td>
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<tr>
<td>MTC</td>
<td></td>
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<tr>
<td>Influenza virus infection</td>
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<tr>
<td>Bacterial infection</td>
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<tr>
<td>Fungus infection</td>
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<tr>
<td>Bacterial infection</td>
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<tr>
<td>Fungus infection</td>
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<tr>
<td>Industry-academic collaboration in UK</td>
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<tr>
<td>Vaccine for prevention</td>
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<tr>
<td>Participation in consortium</td>
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<tr>
<td>Malaria (Nagasaki Univ)</td>
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</tbody>
</table>

**Infectious disease**

- HIV virus infection
- Influenza virus infection
- Bacterial infection
- Fungus infection
- RS virus infection
- Bacterial infection
- Fungus infection
- Industry-academic collaboration in UK
- Vaccine for prevention
- Participation in consortium
- Malaria (Nagasaki Univ)

**Pain/CNS**

- ADHD
- Cognitive and memory disorder
- Opioid
- Alzheimer’s disease
- SK PJ1: Alzheimer’s disease
- SK PJ2: Other CNS disease
- MTC

- Under discussion on the timing of initiating Phase I with the partner

**Actions**

1. **Generate a Large Variety of Compounds in Phase I**
   - Focus on 8 projects marked by red frame in FY2019
   - Phase I in FY2019
   - Phase I in FY2019

**As of Mar. 2019**

**Target milestones as of Mar. 2021**

---

*Focus on 8 projects marked by red frame in FY2019*
### Actions to Create Further Growth Drivers

**1: Generate a Large Variety of Compounds in Phase I (Others)**

<table>
<thead>
<tr>
<th>Project</th>
<th>Phase</th>
<th>Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-723595</strong> (NASH)</td>
<td></td>
<td></td>
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<tr>
<td>Obesity</td>
<td></td>
<td></td>
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<tr>
<td>Hypertrophic scars</td>
<td></td>
<td>Discontinued</td>
</tr>
<tr>
<td><strong>S-540956</strong> (Nucleic acid adjuvant)</td>
<td></td>
<td></td>
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<tr>
<td>Cancer metastasis</td>
<td></td>
<td></td>
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<tr>
<td><strong>Peptide project 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peptide project 2</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Peptide project 3</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Peptide project 4</strong></td>
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<tr>
<td><strong>Peptide project 5</strong></td>
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<td></td>
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<tr>
<td><strong>Peptide project 6</strong></td>
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<tr>
<td><strong>Peptide project 7</strong></td>
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<tr>
<td><strong>Peptide project 8</strong></td>
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<tr>
<td><strong>Peptide project 9</strong></td>
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<td><strong>Peptide project 10</strong></td>
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<tr>
<td><strong>Peptide project 11</strong></td>
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<tr>
<td><strong>Peptide project 12</strong></td>
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</tr>
</tbody>
</table>

**Focus on 8 projects marked with red frame in FY2019**

- As of Mar. 2019
- Target milestones as of Mar. 2021
**Actions to Create Further Growth Drivers**

2: To expand the Phase II and III pipeline

**Focus on 8 projects marked with red frame in FY2019**

### Infectious disease
- **S-004992** (Tuberculosis)
  - Created by C&O, Chinese subsidiary

### Pain/CNS
- **S-600918** (Refractory/unexpected chronic cough)
- **S-637880** (Neuropathic pain)
  - Potential effectiveness for various pain types
- **S-812217**
  - Depression
  - Antidepressant candidate following Cymbalta®

### Collaboration
- **S-005151** (Acute ischemic stroke)
  - Peptide with regeneration-inducing effects

### Others
- **SDT-001** (ADHD)
  - Digital medicine

---

**As of Mar. 2019**

**Target milestones as of Mar. 2021**
Actions to Create Further Growth Drivers
2: To expand the Phase II and III pipeline

Focus on 8 projects marked with red frame in FY2019

<table>
<thead>
<tr>
<th>In-house</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADR-001</strong> (Decompensated liver cirrhosis)</td>
<td><strong>SR-0379</strong> (Cutaneous ulcer)</td>
</tr>
<tr>
<td>Cellular and tissue-based product candidate</td>
<td>Functional peptide which enhances cellular proliferation and vascular formulation</td>
</tr>
<tr>
<td><strong>S-770108</strong> (Idiopathic pulmonary fibrosis)</td>
<td><strong>S-588410</strong></td>
</tr>
<tr>
<td>• Using dry powder inhalation technology to minimize side effects</td>
<td>Relapse prevention of esophagus cancer</td>
</tr>
<tr>
<td>Cancer peptide vaccine</td>
<td><strong>S-588210</strong> Treatment for solid tumor</td>
</tr>
<tr>
<td><strong>S-588210</strong> Treatment for solid tumor</td>
<td>Cancer peptide vaccine</td>
</tr>
</tbody>
</table>

As of Mar. 2019 Target milestones as of Mar. 2021

Phase I | Phase II | Phase III
## Pipeline (as of Mar. 14, 2019)

### Preclinical (target indication*)

<table>
<thead>
<tr>
<th>Influenza virus infection</th>
<th>HIV virus infection</th>
<th>RS virus infection</th>
<th>Bacterial infection</th>
<th>Mycobacterium disease</th>
<th>Fungus infection</th>
<th>Vaccine for prevention</th>
<th>Peptide</th>
<th>ADHD</th>
<th>Opioid</th>
<th>Alzheimer’s disease</th>
<th>Cognitive and memory deficits</th>
<th>Post-stroke spasticity</th>
<th>Peptide</th>
<th>Obesity</th>
<th>S-723595 NASH</th>
<th>Cancer metastasis</th>
<th>S-540956 Nucleic acid adjuvant</th>
<th>Peptide</th>
</tr>
</thead>
</table>

### Phase I

<table>
<thead>
<tr>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

### Phase II

<table>
<thead>
<tr>
<th><strong>Cefiderocol</strong> Multidrug-resistant Gram-negative bacterial infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-120083</strong> Inflammatory pain</td>
</tr>
<tr>
<td><strong>S-707106</strong> Type2 diabetes</td>
</tr>
<tr>
<td><strong>S-488210</strong> Head and neck squamous cell carcinoma</td>
</tr>
<tr>
<td>epertinib Malignant tumor</td>
</tr>
<tr>
<td><strong>S-588410</strong> Bladder cancer</td>
</tr>
</tbody>
</table>

### Phase III

<table>
<thead>
<tr>
<th><strong>Cefiderocol</strong> Multidrug-resistant Gram-negative bacterial infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baloxavir Marboxil (Taiwan) Influenza virus infection</td>
</tr>
</tbody>
</table>

### Filed

<table>
<thead>
<tr>
<th><strong>Oxycodone</strong> Moderate to severe chronic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lisdexamfetamine</strong> ADHD (pediatric)</td>
</tr>
<tr>
<td><strong>Intuniv®</strong> ADHD (adult)</td>
</tr>
</tbody>
</table>

### In Japan

<table>
<thead>
<tr>
<th><strong>S-812217</strong> Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-600918</strong> Neuropathic pain</td>
</tr>
<tr>
<td><strong>S-637880</strong> Neuropathic pain</td>
</tr>
<tr>
<td><strong>S-010887</strong> Neuropathic pain</td>
</tr>
<tr>
<td><strong>S-005151</strong> Acute ischemic stroke</td>
</tr>
<tr>
<td><strong>S-770108</strong> Idiopathic pulmonary fibrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cefiderocol</strong> Multidrug-resistant Gram-negative bacterial infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-600918</strong> Refractory/unexpected chronic cough</td>
</tr>
<tr>
<td><strong>S-237648</strong> Obesity</td>
</tr>
<tr>
<td><strong>S-525606</strong> Allergic rhinitis caused by Japanese cedar allergen</td>
</tr>
<tr>
<td><strong>S-588410</strong> Bladder cancer</td>
</tr>
<tr>
<td><strong>SR-0379</strong> Cutaneous ulcer</td>
</tr>
<tr>
<td><strong>ADR-001</strong>* Decompensated liver cirrhosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cefiderocol</strong> Multidrug-resistant Gram-negative bacterial infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Xofluza™</strong> Influenza virus infection (prophylaxis)</td>
</tr>
<tr>
<td><strong>Xofluza™</strong> Influenza virus infection (New dosage for children)</td>
</tr>
<tr>
<td><strong>Cymbalta®</strong> Depression (pediatric)</td>
</tr>
<tr>
<td><strong>Oxycodeone</strong> Moderate to severe chronic pain</td>
</tr>
<tr>
<td><strong>S-588410</strong> Esophageal cancer</td>
</tr>
</tbody>
</table>

### Progress from Feb. 1, 2019 to Mar. 14, 2019

* Target indication may include some projects

** In preparation for Phase I

*** In Phase I/II
## Pipeline - Out-licensed (as of Mar. 14, 2019)

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Filed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GSK3342830 Multidrug-resistant Gram-negative bacterial infections</td>
<td></td>
<td>DTG/3TC Treatment for HIV infection TANGO study (maintenance)</td>
<td>DTG/3TC (EU/US) Treatment for HIV infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAB LAP Prevention for HIV infection</td>
<td>Xofluza™ Influenza virus infection (High risk patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAB+RPV LAP Treatment for HIV infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Xofluza™ Severe influenza virus infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Xofluza™ Influenza virus infection (pediatric)</td>
<td></td>
</tr>
</tbody>
</table>

### Stage progression (from Jan. 31, 2019)
- Cefiderocol: Phase II → Filed (US)
- Xofluza™: Phase III (high risk patients) → sNDA (US)
- Naldemedine (Rizmoic®): File → Approve (EU)
- Lustrombopag: File → Approve (EU)

### Discontinuation (from Mar. 15, 2018)
- Janssen/Shionogi β-secretase inhibitor (Phase III)
- Diabetes (preclinical): target indication was changed to NASH
- Hypertrophic scars (preclinical)
Toward Sustainable Growth Beyond 2020

To continue to discover next growth drivers

Achievement in FY2018

Further strengthen, expand, and accelerate drug-discovery on our own and through external collaboration

➢ Steady progress of R&D especially for 8 high-priority projects
➢ Novel platforms: created new opportunities to discover novel medicines by strategic collaboration

Challenge for FY2019

Progress R&D and create novel platform

➢ Focus resources on 8 high-priority projects
➢ Maximize value of in-licensed projects

Toward FY2020

Abundant pipeline in Phase I ~ Phase II in FY2020
# Targets for FY2018 (Summary)

<table>
<thead>
<tr>
<th>Research</th>
<th>Achievements in FY2017</th>
<th>Achievements in FY2018</th>
<th>Targets for FY2019</th>
<th>Targets from FY2017 to FY2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug candidate: 2 candidates</td>
<td>Drug candidate: 2 candidates</td>
<td><strong>4 candidates</strong></td>
<td>10 development products</td>
<td></td>
</tr>
<tr>
<td>Development products: 4 products</td>
<td>Development products: 0 products</td>
<td><strong>3 products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moving projects forward to drug candidate: 0 project</td>
<td>Moving projects forward to drug candidate: 2 projects</td>
<td><strong>1 project</strong></td>
<td>4 or more projects</td>
<td></td>
</tr>
<tr>
<td>Obtaining revolutionary CMC technologies: 2 technologies</td>
<td>Obtaining revolutionary CMC technologies: 1 technology</td>
<td><strong>1 technology</strong></td>
<td>3 or more technologies</td>
<td></td>
</tr>
<tr>
<td>Developing new LCMs: 1 project</td>
<td>Developing new LCMs: 1 project</td>
<td><strong>1 project</strong></td>
<td>2 or more projects</td>
<td></td>
</tr>
<tr>
<td>NDA submissions: 4 compounds (6 indications)</td>
<td>NDA submissions: 3 compounds (5 indications)</td>
<td><strong>2 compounds (3 indications)</strong></td>
<td>10 or more compounds to be launched globally*</td>
<td></td>
</tr>
<tr>
<td>Approvals: 4 compounds</td>
<td>Approvals: 3 compounds</td>
<td><strong>4 compounds</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Targets by FY2020
Q&A
Appendix

- Research
Acquire knowledges about the novel modality “Symbiotics©” an approach to the problem of AMR

1) Insert plasmid* designed specifically to inactivate antibiotic-resistant genes into phage**
   * DNA molecule, ** Virus that infects to bacteria

2) Deliver plasmid into antibiotic-resistant bacteria

3) Modification of antibiotic-resistant genes by inserted plasmid
   ⇒ Inactivation of antibiotic-resistant genes

Expanding therapeutic options to AMR as a leading company in the infectious disease field
Antibacterial mechanism of NO:
Increasing oxidant stress to the bacterial cell and then show a **broad antibacterial spectrum**

Appropriate formulations are needed for localization and stable exposure of NO at lung

**Attractive BIOC51 potential:**
Sustainable NO yielding **at lung** by nebulizer

**Low risk** of generating resistant bacteria in contrast to marketed antibiotics

**Toward a novel useful modality effective against AMR**
Hsiri: Novel Drug for Mycobacterial Disease

Collaboration vision of Hsiri and Shionogi

Creating an novel drug with powerful effect by inhibiting common factor between TB and NTM
Appendix

- CMC
Stabilization Technology for Solid Dosage Form

**Without stabilization**

- **Moisture**
- **API**
- **Increment of decomposition**

Requirement for stabilization technology because of recent tightened regulation for degradant impurities

**Stabilized formulation**

- **Moisture**
- **Stabilizer**
- **Suppressing decomposition**

Protecting molecular bonds with stabilizer

**Reduce degradation of API**

- **Amount of decomposition**
- **Month**
- **Degradation reduced by 1/10**

Use technology to allow product development to proceed efficiently with high quality

Applicable across multiple APIs

SHIONOGI
In Silico Formulation Design/Dissolution Simulation (F-CAD)

Conventional simulation
Required extended simulation time due to numerous input factors

F-CAD simulation
- Rapid simulation using simplified input factors
- High predictability of dissolution

Rapid and accurate formulation design by In Silico
- Optimization of formulation to achieve the target dissolution profile
- Formulation resilient to process parameter variability
- Dissolution simulation and analysis of risk of changes in formulation

Accelerate and increase probability of successful formulation development while reducing time and cost spent on trial-and-error experimentation
Appendix

• Development
# Post Exposure Prophylaxis Study

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To evaluate the efficacy of a single, oral dose of baloxavir compared with placebo for the prevention of influenza virus infection in household members of influenza infected index patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td>Household members who live with an influenza infected index patient</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Double-blind, multicenter, randomized, placebo-controlled study</td>
</tr>
<tr>
<td><strong>Dosage/administration</strong></td>
<td>Single oral dose (10-80 mg)</td>
</tr>
<tr>
<td><strong># enrollment / Region</strong></td>
<td>750／Japan</td>
</tr>
</tbody>
</table>

**Index Patients** ➔ **Standard of Care (Anti-influenza drug)**

**Subject**

- **Household Member (s)**
  - **baloxavir**
  - **placebo**

**1:1**

**Primary endpoint**: Incidence of influenza infected subjects

750 subjects recruitment was completed.
### Seriously-ill Hospitalized Study

<table>
<thead>
<tr>
<th><strong>Subject</strong></th>
<th>Patients requiring hospitalization for severe influenza who aged ≥12 years and weighing ≥40 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Double-blind, multinational, randomized, parallel-group study</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Time to clinical improvement defined as:</td>
</tr>
<tr>
<td></td>
<td>Time to hospital discharge OR</td>
</tr>
<tr>
<td></td>
<td>Time to NEWS2 of ≤2 maintained for 24 hours</td>
</tr>
<tr>
<td><strong>Study period</strong></td>
<td>35 days (Treatment period: 10 days, Follow-up period 25 days)</td>
</tr>
</tbody>
</table>

#### Treatment period

- **Baloxavir 40/80 mg** +SOC (Neuraminidase inhibitor)
- **Placebo** +SOC (Neuraminidase inhibitor)

#### Screening

1:2

#### Follow-up period

Day1, Day4, Day5, Day7, Day10, Day11, Day35

*NEWS2: National Early Warning Score 2 (Score index based on several vital signs)*

**Sponsor**: F. Hoffmann-La Roche Ltd

Baloxavir or Placebo

SOC: standard-of-care
HR Study: Change of Viral Titer and Improvement of Symptoms in Patients at Risk for Complication (Type B)

Mean in Virus Titer

Change from Baseline in Influenza Virus Titer (log_{10} TCID_{50}/mL)

<table>
<thead>
<tr>
<th>Time from Start of Treatment (hours)</th>
<th>Baloxavir (n)</th>
<th>Placebo (n)</th>
<th>Oseltamivir (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>153</td>
<td>159</td>
<td>139</td>
</tr>
<tr>
<td>30</td>
<td>150</td>
<td>154</td>
<td>133</td>
</tr>
<tr>
<td>60</td>
<td>148</td>
<td>150</td>
<td>131</td>
</tr>
<tr>
<td>90</td>
<td>145</td>
<td>145</td>
<td>126</td>
</tr>
<tr>
<td>120</td>
<td>145</td>
<td>145</td>
<td>123</td>
</tr>
</tbody>
</table>

*p<0.05 vs placebo, #p<0.05 vs Oseltamivir
Test: van Elteren test;
Stratification factors:
region, composite symptom scores at baseline and preexisting and worsened symptom.

Time to Improvement of Influenza Symptoms

Median:

<table>
<thead>
<tr>
<th></th>
<th>Baloxavir</th>
<th>Placebo</th>
<th>Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>166</td>
<td>167</td>
<td>148</td>
</tr>
<tr>
<td>Median</td>
<td>74.6*#</td>
<td>100.6</td>
<td>101.6</td>
</tr>
</tbody>
</table>

Unit of Median: hours,
*p<0.05 vs placebo, #p<0.05 vs Oseltamivir
Pediatric (Granule) Study: Change of Viral Titer and Body Temperature in Patients <20 kg by Virus Type/Subtype

Mean in Virus Titer by Virus Type/Subtype

Mean Body Temperature by Virus Type/Subtype

Analysis Population: ITTI and Subset of patients who were positive for influenza virus titer at baseline

Virus titer (log\(_{10}\) TCID\(_{50}\)/mL)

Day 1  Day 2  Day 3  Day 4  Day 6  Day 9

Analysis Population: ITTI
Dosage and Plasma Concentration 72 Hours After Treatment in Pediatric Patients Whose Body Weight Less Than 20 kg

10kg≤BW<20kg : 10mg
BW<10kg : 1mg/kg

10kg≤BW<20kg : 20mg
BW<10kg : 2mg/kg
(<3months old: 1mg/kg)

Plasma concentration 72 hours after treatment in pediatric patients at the high dose is equivalent with that in adults
# ADR-001: Phase I / II study

<table>
<thead>
<tr>
<th><strong>Objectives</strong></th>
<th>To assess safety and preliminary clinical activity of ADR-001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Patients with decompensated liver cirrhosis</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Single group assignment, ascending 3 doses</td>
</tr>
<tr>
<td><strong>Subject / Location</strong></td>
<td>15 pts / Japan</td>
</tr>
<tr>
<td><strong>Sponsor</strong></td>
<td>ROHTO Pharmaceutical Co., Ltd.</td>
</tr>
</tbody>
</table>

**ADRs-001**

- Adipose tissue obtained by liposuction
- Cell culture facility

**Timeline**

- **Screening**
- **Intravenous administration**
- **Efficacy evaluation**
- **Safety evaluation**
- **Efficacy evaluation**

**Timepoints**

- 4 week
- 8 week
- 12 week
- 16 week
- 20 week
- 24 week
S-812217: PPD Ph3 ROBIN study

Sponsored by Sage
Study period: Dec 2016 to Dec 2018

Severe PPD patients (HAM-D score ≥26)

Treatment period for 14 days

S-812217 (SAGE-217) 30mg

Placebo

Primary endpoint on Day 15

Follow up for 4 weeks

- Efficacy: met the primary and secondary endpoints
  - Statistically significant differences in the reduction in HAM-D total score of SAGE-217 vs placebo were first observed on Day 3 and maintained through the 4 week follow-up.

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Treatment period (2 weeks)</th>
<th>Follow up (4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 3 (first observation)</td>
<td>Day 15(treatment completion)</td>
</tr>
<tr>
<td>Reduction in HAM-D total score</td>
<td>Placebo</td>
<td>-9.8</td>
</tr>
<tr>
<td></td>
<td>SAGE-217</td>
<td>-12.5 (p=0.0255)</td>
</tr>
<tr>
<td>Remission rate (HAM-D ≤7, %)</td>
<td>Placebo</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>SAGE-217</td>
<td>-</td>
</tr>
</tbody>
</table>

- Safety: Well-tolerated. The most common adverse events (≥5%) were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, nausea, sedation, vomiting, abnormal dreams and hyperhidrosis.

Successful and consistent with MDD-Ph2 study data

PPD: postpartum depression 1) Hamilton Rating Scale for Depression
Summary of TOVA

**T.O.V.A.** (Test of Variables of Attention)

- Objective measurements
- The response time or error to the target occurring randomly are measured.
- Inattention and impulse are objectively assessed.
- FDA cleared and CE Medical Device Directive compliant

TOVA is one of the three objective Continuous Performance Test (CPT) approved by FDA (2017) for the monitoring of inattention and inhibitory control.
• Published data in ESMO2018
  – CD8-positive TILs were increased in all patients after vaccination
  – PD-L1 expression was induced in 7 out of 8 patients

  **Pre-treatment**  **After 6 time treatment**

• Strategy of CPV-ICI combination therapy
  – CPV: Increase tumor specific TIL
  – ICI: Inhibition of immunosuppressive mechanism

→ Synergistic effect of combination therapy can be expected even in patients who have failed each monotherapy
Appendix

- Others
ATLAS Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints

ATLAS study: Viral Suppression

Source: CROI, Mar. 7, 2019

CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

*Adjusted for sex and baseline third agent class.

FLAIR Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints

<table>
<thead>
<tr>
<th>Virologic Outcomes</th>
<th>Adjusted Treatment Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAB LA + RPV LA (n=283)</td>
</tr>
<tr>
<td>Proportion (%)</td>
<td>DTG/ABC/3TC (n=283)</td>
</tr>
<tr>
<td>Virologic nonresponse (≥50 c/mL)</td>
<td>2.1 : 2.5</td>
</tr>
<tr>
<td>Virologic success (&lt;50 c/mL)</td>
<td>93.6 : 93.3</td>
</tr>
<tr>
<td>No virologic data</td>
<td>4.2 : 4.2</td>
</tr>
</tbody>
</table>

Primary endpoint: LA noninferior to DTG/ABC/3TC (≥50 c/mL) at Week 48

Key secondary endpoint: LA noninferior to DTG/ABC/3TC (<50 c/mL) at Week 48

3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

*Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).

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