SHIONOGI 140th Anniversary

S-O-N-G for you!

Research and Development at Shionogi

March 14, 2019

Shionogi & Co., Ltd.

SHIONOGI

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

Stage	Disease Area	Project	Indication	Pages in the slide
Clinical	Infectious disease	**S-004992**	Tuberculosis	P.87-88
	Pain/CNS	**S-600918**	Refractory/unexplained chronic cough	P.89-94
		S-637880	Neuropathic pain	P.95-96
		S-812217	Depression	P.25, 97-99, 148
	Others	**S-770108**	Idiopathic pulmonary fibrosis	P.32, 53, 100-103
Pre-clinical	Infectious disease	**Novel HIV drug**	HIV	P.20-21
	Others	**S-540956 (Nucleic acid adjuvant)**	Infectious disease prophylaxis etc.	P.17-18
Research	Infectious disease, Pain/CNS, Others	**Peptide**	Infectious disease, Pain/CNS, Others	P.31-32

Other Next Growth Drivers 1/2

Stage	Disease Area	Project	Indication	Pages in the slide
Clinical	Infectious disease	**Xofluza™**	Influenza virus infection	P.30, 55, 69-77, 142-146
		Cefiderocol	Multidrug-resistant Gram-negative bacterial infections	P.55, 78-80
	Pain/CNS	**Intuniv®**	ADHD	P.55, 81-83
		Lisdexamfetamine	ADHD	P.55, 84-85
		SDT*-001	ADHD	P.25, 105-109, 149
		S-005151	Acute ischemic stroke ,Epidermolysis bullosa	P.110
	Others	**ADR-001**	Decompensated liver cirrhosis	P.33, 110, 147
		SR-0379	Cutaneous ulcer	P.111
		S-588410	Esophageal cancer	P.111, 150
		S-588210	Solid tumor	P.111

* STD: Shionogi Digital Therapeutics

Other Next Growth Drivers 2/2

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

* 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

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**

* CNS: Central nervous system

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* CNS: Central nervous system

Cited from FY2017 R&D presentation

Synergistic Research Innovation for Our Society

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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

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Cited from FY2017 R&D presentation

FY2018 Plans for Research

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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)

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* PDPS: Peptide Discovery Platform System

** PET: Positron emission tomography

*** NASH: nonalcoholic steatohepatitis

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Challenges and Tactics for Research

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Development candidate products and developed products for this 3 years

FY2016
- Developed: 1 product (target: more than 3)
- Candidates: 3 products (target: more than 2)

FY2017
- Developed: 4 products (target: more than 2)
- Candidates: 2 products (target: 1)

FY2018
- Developed: 0 product (target: 2)
- Candidates: 2 products (target: 3)

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**

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Our New Drug Discovery Strategies for Infectious Diseases

HIV	Influenza	AMR*
The world's 3 major infectious diseases	**Hard to Treat Bacteria**	**Prevention Cure**
Worldwide epidemic for a long time	**Worldwide momentum for beating AMR* and difficult bacteria**	**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

Cited from FY2017 R&D presentation

Success in Nucleic Acid Drug Discovery

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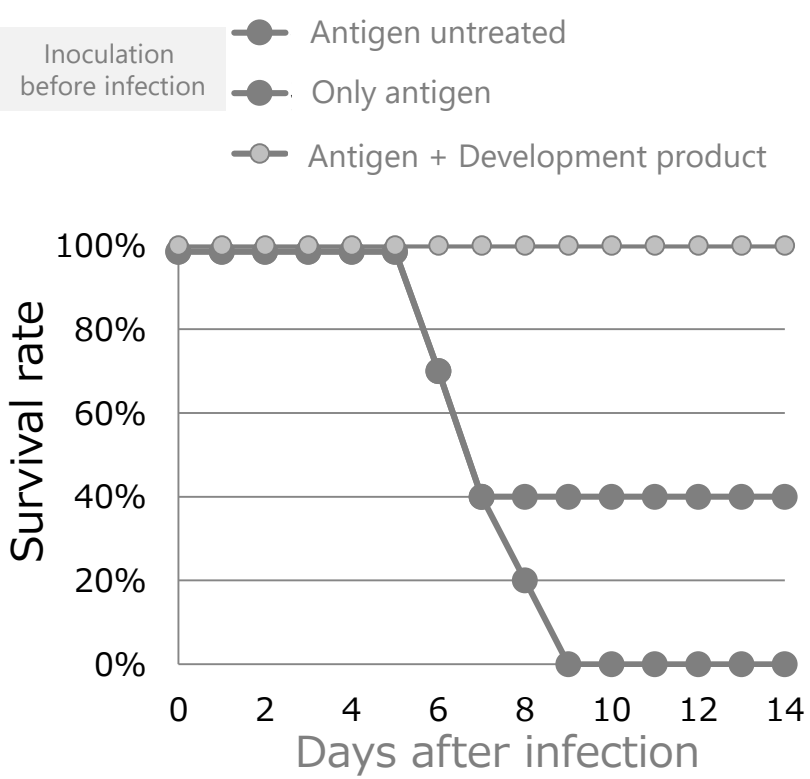
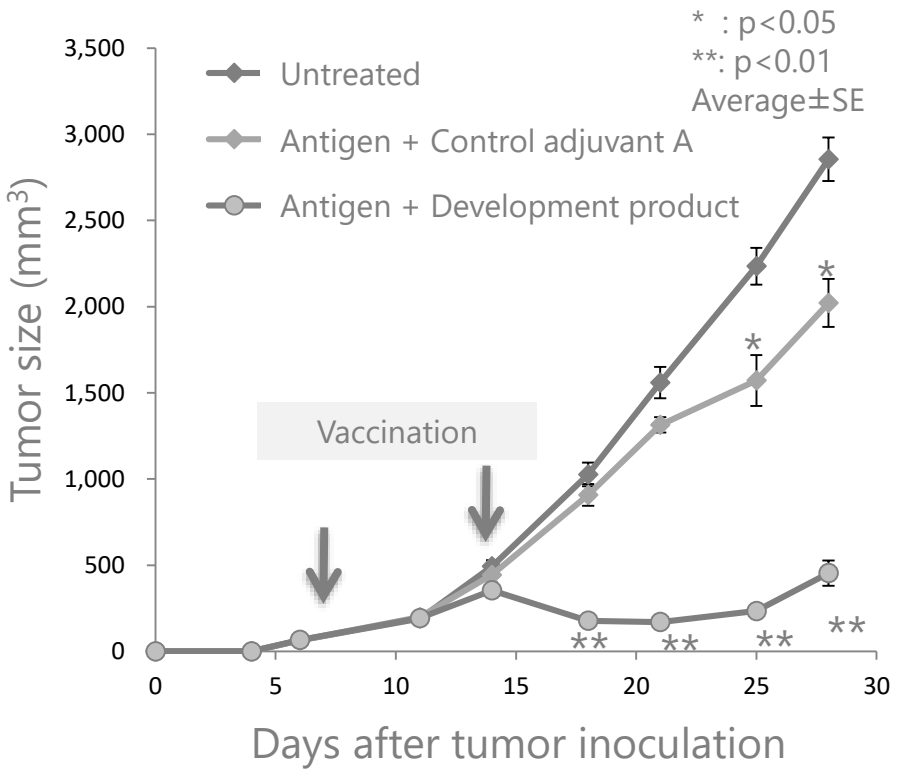
Infectious disease vaccine adjuvant effect (nonclinical)

To initiate clinical trials in 2020



Cancer vaccine adjuvant effect (nonclinical)

To initiate clinical trials in 2019



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)

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		Research		Preclinical	Clinical	Market
The world's 3 major infectious diseases	HIV	HIV LAP*1	HIV LAP	HIV Oral	Cabotegravir	Dolutegravir
	TB*2 /NTM*3	Novel mechanism TB/NTM	Hsiri	S-004992		
	Malaria	Nagasaki				
Hard to Treat Bacteria	AMR*4	Novel β-Lactam	Novel β-Lactam	Novel anti bacteria	Cefiderocol	Doripenem
		Nemesis	Vast			
	Fungus	Fungus	Fungus			
Prevention	Vaccine	UMN		S-540956 (adjuvant)		
	Other Virus	PDPS*5	Ube (RS virus)	Anti-Influenza virus		Baloxavir
		PDPS				

(This figure shows representative portfolio)

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

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HIV	Tuberculosis	Malaria
* New patients 1.8M Death 0.9M	* New patients 10.4M Death 1.7M	* 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	Beating resistance Shortening treatment period	Providing epoch-making drug and vaccine
Preparing novel LAP following cabotegravir Focused investment on HIV cure	Efficient discovery research combination with NTM**** Proactive alliance and collaboration	Conducting open innovation based on collaboration with Nagasaki Univ.

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* Epidemiology: Cited from WHO Fact sheets

*** LAP: Long acting parenteral administration

** AE/DDI: adverse effect / drug-drug interaction

**** 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

Improvement of **Drug burden**

Forwarding **a novel mechanism drug** as best partner for Dortegravir

Advanced regimen of 2 drugs

Focused investment in FY2019

Improvement of **Drug adherence**

Development from oral administration to **LAP***

Greater QOL improvement

Next generation of HIV treatment

More improvement of **QOL**

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

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Tuberculosis/NTM*, Malaria		Hard to Treat Bacteria	
Hsiri (Collaboration)	**Nagasaki Univ.** (Collaboration)	**Nemesis** (Funding)	**Vast** (Funding)
Drug for anti acid-fast bacillus with **novel mechanism**	World-wide presence in **Emerging and Re-emerging Infectious Diseases**	Breaking resistance gene by **Bacteriophage** and **CRISPR-Cas**	Utilizing **NO*** ** which has wide sterilization potential

Our stepping stone for creating novel treatments for TB and NTM**

Commitment for creating novel values utilizing Shionogi's know-how

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

* NTM: Non-Tuberculosis Mycobacterium ** TB: Tuberculosis *** NO: Nitric oxide

Our Vision in CNS Disease Area

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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

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

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

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* 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）

	Research	Preclinical	Clinical	NDA/launch
Depression	SK PJ 2nd		S-812217	Cymbalta®
ADHD	Early PG / Late PG		SDT-001	Intuniv® / lisdexamfetamine
Alzheimer's disease /Cognitive and memory deficits	SK PJ 1st / Early PG / PDC / Late PG	BPN14770		
Other CNS disorders	SK PJ 1st / Early PG			
Pain	PDPS / Early PG		S-637880 / S-600918	Cymbalta® / OxyContin® TR / Symproic®

(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

SAGE Therapeutics
Novel antidepressant
S-812217

- $GABA_A$ PAM*
- **Rapid onset** & **Strong efficacy** & **Sustainable efficacy**
- Possibility to **expand indications** with a focus on depression

Tetra Discovery Partners
Drug candidate for cognitive and memory deficits
BPN14770

- PDE4D** NAM***
- **Significant reduction of side effects**
- Possibility to **expand indications** marked by cognitive and memory deficits

Akili Interactive
ADHD digital therapeutics
SDT-001

- **Therapeutic application**
- **Activate the cerebral cortex** that becomes dysfunctional with ADHD
- **Improvement of treatment environment by digital sharing of information**

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
***NAM: Negative allosteric modulator
** PDE4D: Phosphodiesterase 4D

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

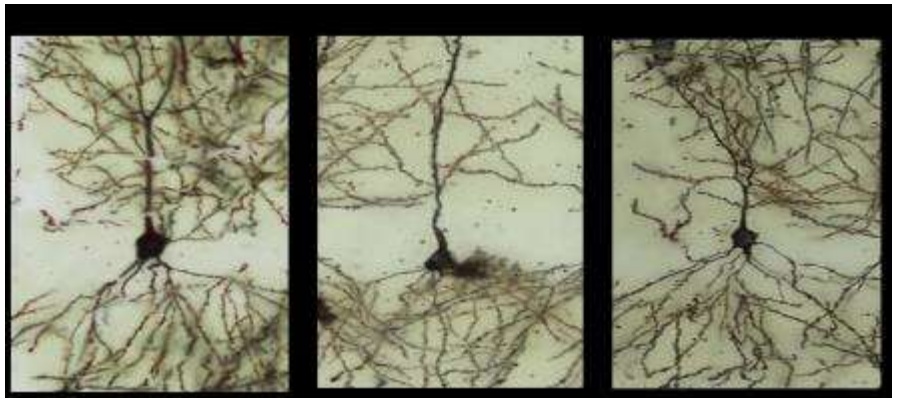
PDE4 NAM**
→ Activation of cAMP/CREB pathway
It plays a core role in cognitive function. Nerve activity is stimulated by activating this pathway, driving enhancement of cognitive function.

BPN14770 Efficacy (non-clinical)

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

control（normal）　Aβ1-42 hippocampal administration AD***model

＋ BPN14770



(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)**

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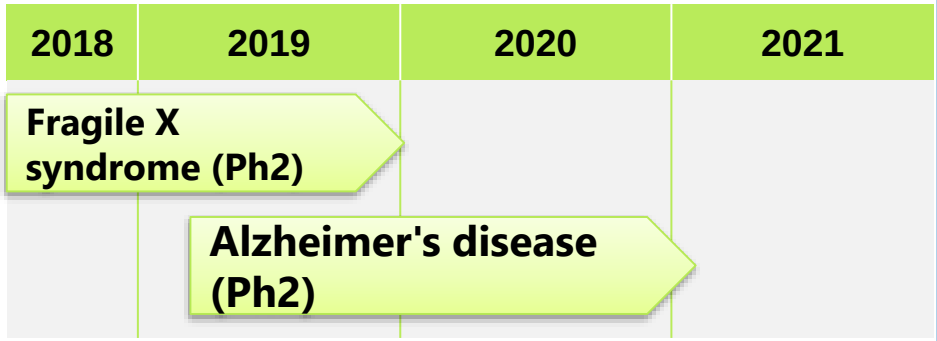
* PDE4: Phosphodiesterase 4　** NAM: Negative allosteric modulator
*** AD: Alzheimer's disease　*** PDE4D: Phosphodiesterase 4D

R&D Timeline of BPN14770

Development plan of Tetra in US

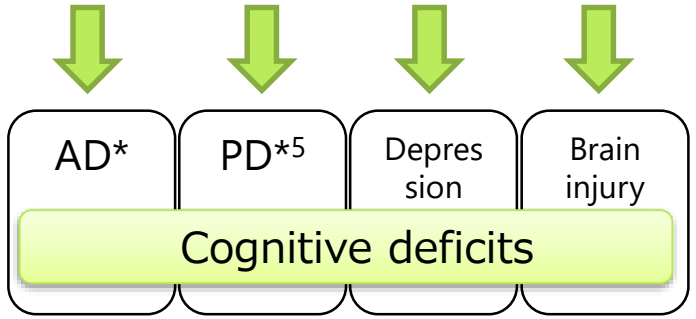


- **Fragile X syndrome:** Confirming therapeutic potential of the drug in a small number of patients, receiving orphan drug designation from FDA
- **AD*1:** Seeking to improve symptoms of cognitive dysfunction in early Alzheimer's (MCI*2)

Research plan of SHIONOGI

Seeking to various target indications with cognitive deficits through collaborative research

BPN14770 (PDE4D*3 NAM*4)



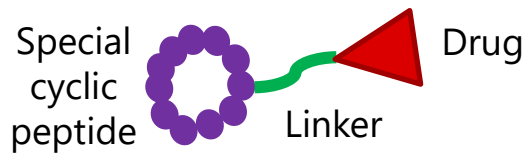
US: To accelerate development of FXS*6 and AD by Tetra
Japan: To seek various indications and develop formulations for the future clinical phase

*1 AD: Alzheimer's disease *2 MCI: Mild Cognitive Impairment *3 PDE4D: Phosphodiesterase 4D
*4 NAM: Negative allosteric modulator *5 PD: Parkinson's disease *6 FXS: Fragile X syndrome

CNS Drug Discovery Future Leveraging PDC

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)



Novel target from SK PJ etc.

Application stage
(establishment of platform)

Establishment of Brain delivery platform

Making it possible to deliver drugs into the brain independent of molecular weight and physical properties

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.

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.

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.

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.

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* Scientific Reports, volume 8, Article number: 9633 (2018)

** Cap-dependent endonuclease

*** Neuraminidase inhibitor

Progression of Peptide Drug Discovery

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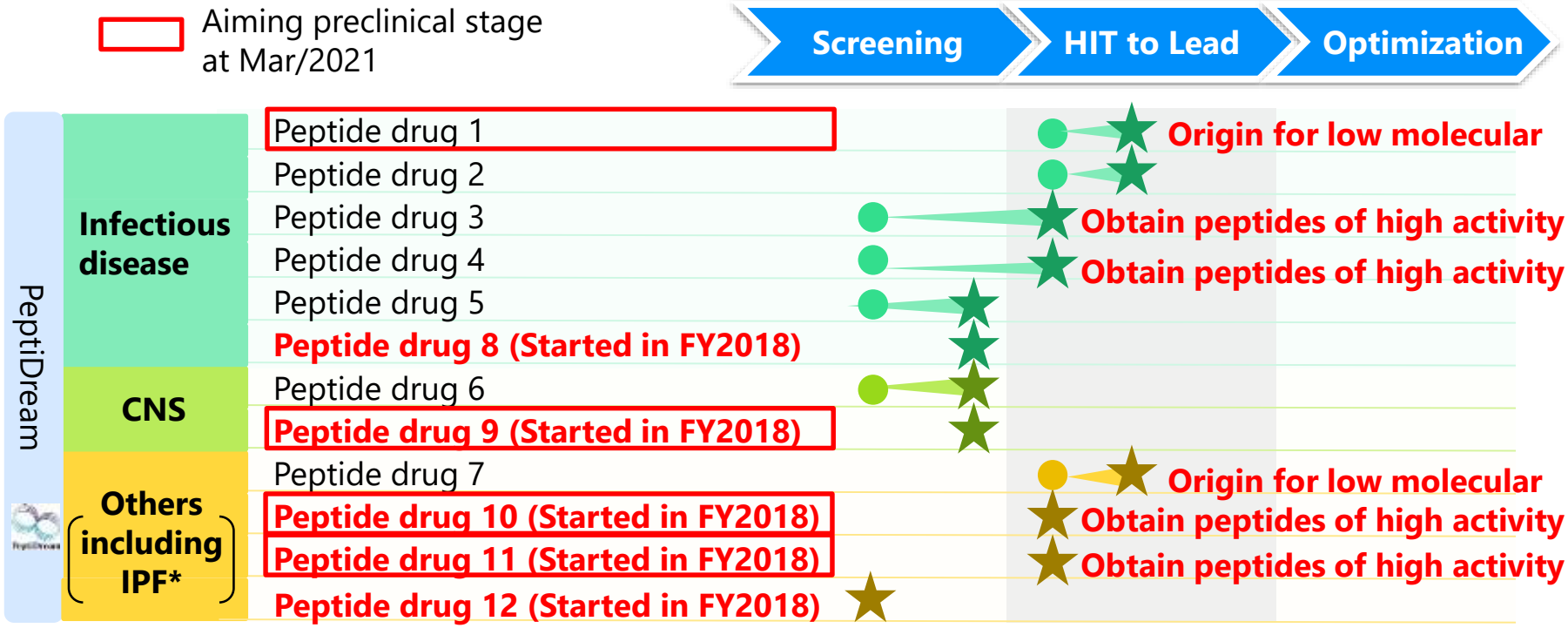
PDPS Drug Discovery Platform

Started 5 new research programs

Found 2 peptides for low molecular compounds

Aiming preclinical stage at Mar/2021



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)

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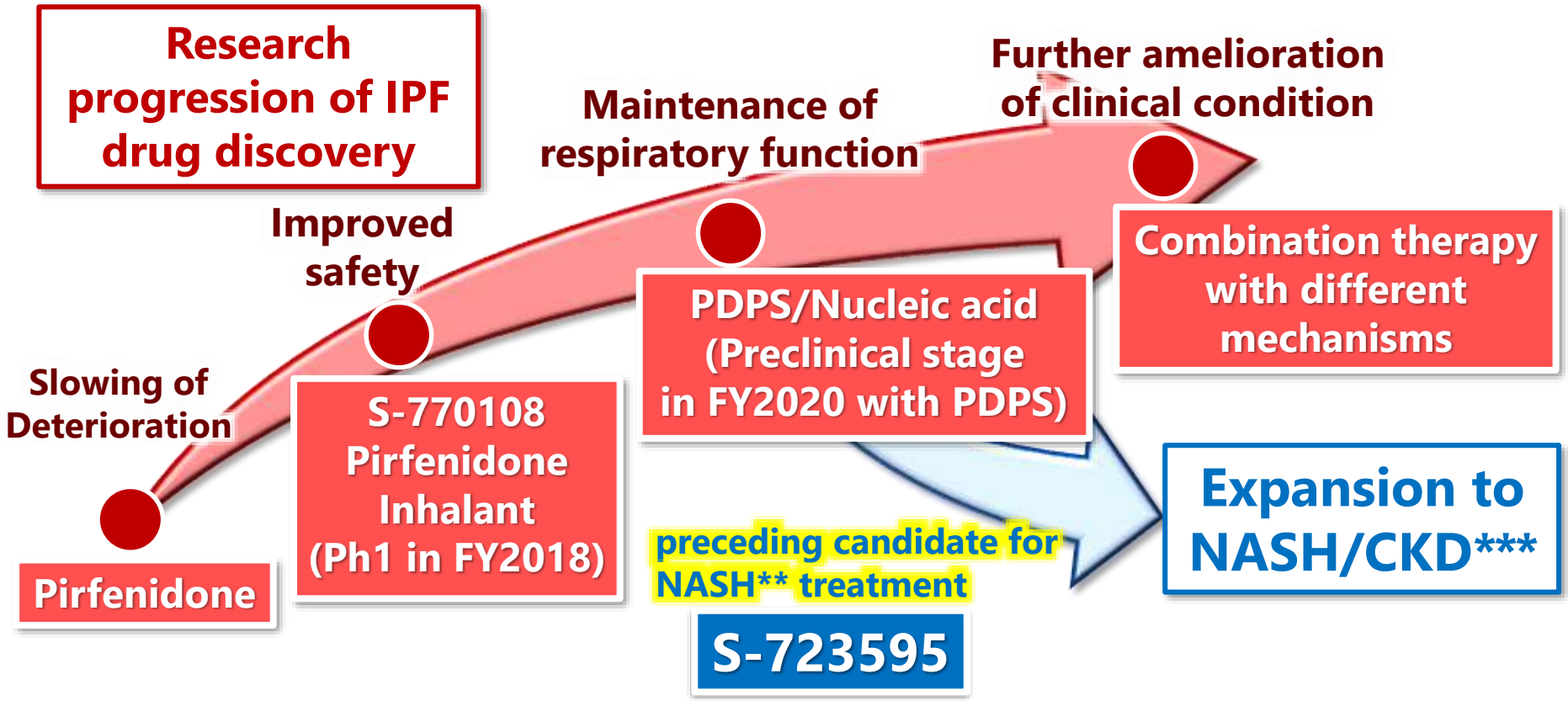
As of Mar. 2018

As of Mar. 2019

* IPF: Idiopathic pulmonary fibrosis

Expansion beyond IPF* to Other Diseases

Research activity and expansion beyond IPF



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

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* IPF: Idiopathic pulmonary fibrosis ** NASH: Non-alcoholic steatohepatitis
***CKD: Chronic kidney disease

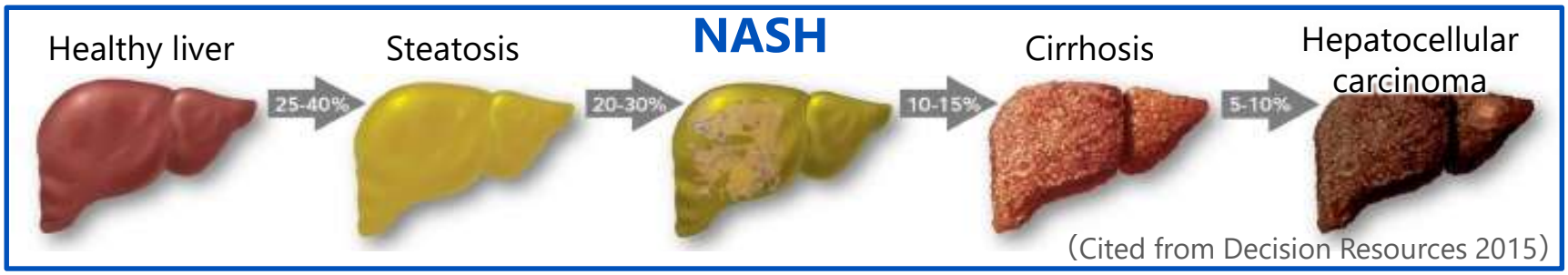
Product Pipeline in Liver Disease

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

Mulpleta®

Platelet depletion



Increasing number of patients

(Exercise and diet therapy)

Increasing risk of cirrhosis

S-723595

LCM of IPF*** drug**

No drug

ADR-001**

NEVER SAY NEVER ROHTO

Created a drug candidate for NASH treatment with novel mechanism

* 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

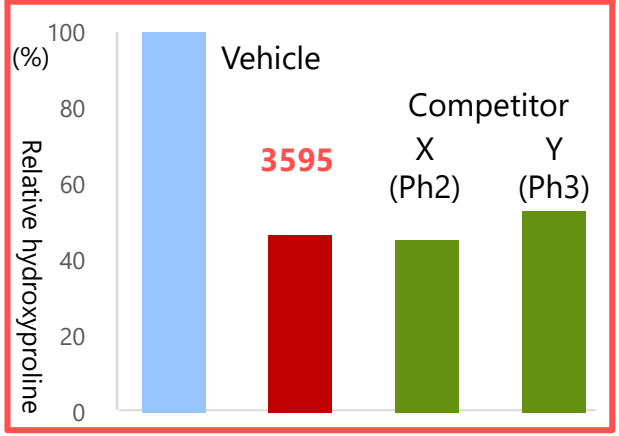
Novel Drug Candidate S-723595

Created a novel drug candidate with unique mechanism reducing ectopic fat

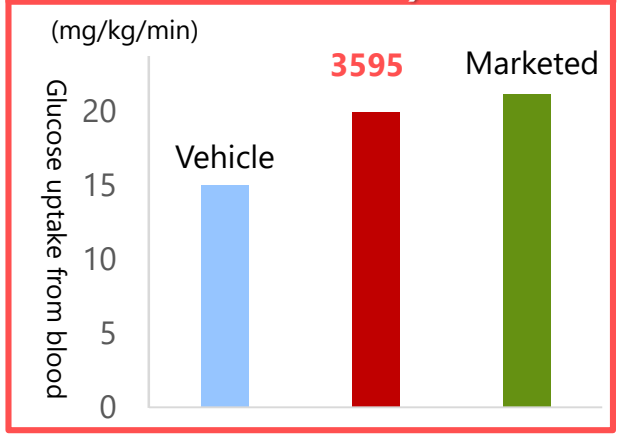
Metabolic syndrome → **Accumulation of ectopic fat** → **Deteriorating condition**

S-723595 decreases ectopic fat

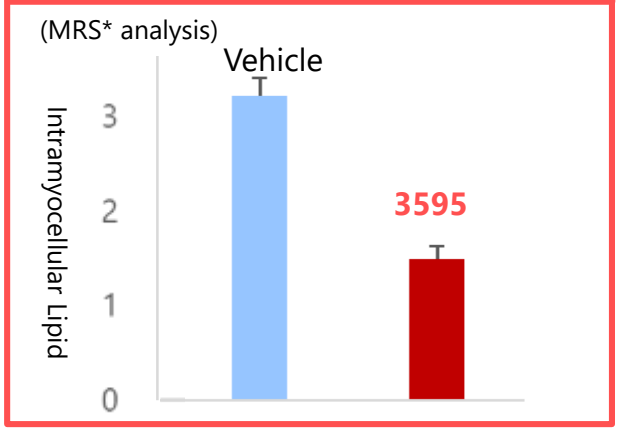
Decreasing fibrosis in liver (for NASH drug)



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



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



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

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  - 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

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

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

CMC

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

R&D Vision

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

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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
- Supporting a Longer Healthy Life
- Growing Difficulty in Drug Discovery
- More Stringent Global Quality Control

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

From Presentation of FY2017

Targets for FY2018 (1)

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

From Presentation of FY2017

Targets for FY2018 (2)

Rapid/High Quality NDAs and Launches

Xofluza™	Completion of NDA and Preparation for Launch in the US, Completion of NDA for Pediatric Granular Formulation in Japan
Lisdexamfetamine	Approval in Japan, Launch
Rizmoic® (Naldemedine)	Completion of Preparation for Launch in EU
Mulpleta®	Completion of Preparation for Launch in the US
Cefiderocol	Completion of NDA preparation in the US

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)

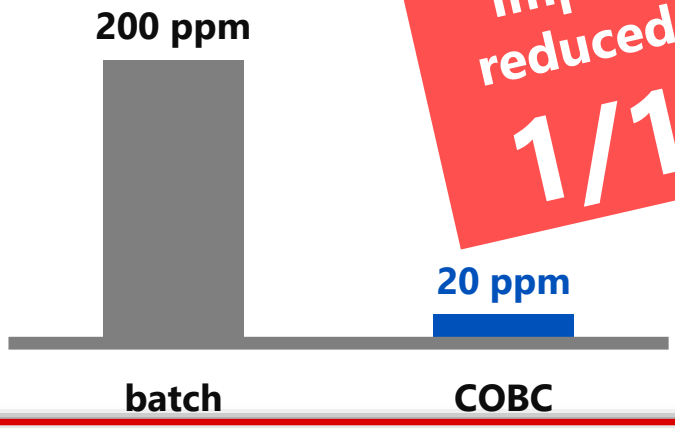
Crystallization for Continuous Manufacturing

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

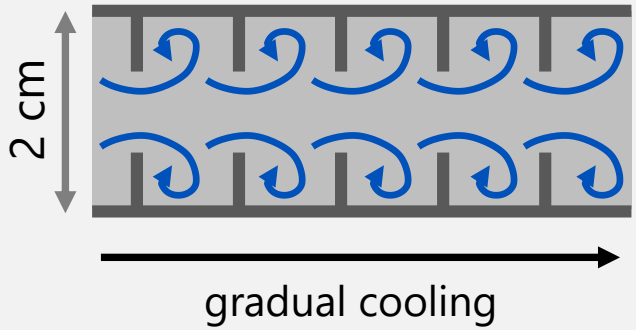
Comparison of impurity amount



Impurity reduced to 1/10

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



Consistently produce **high quality APIs**

establishing **continuous manufacturing system** with flow reactors

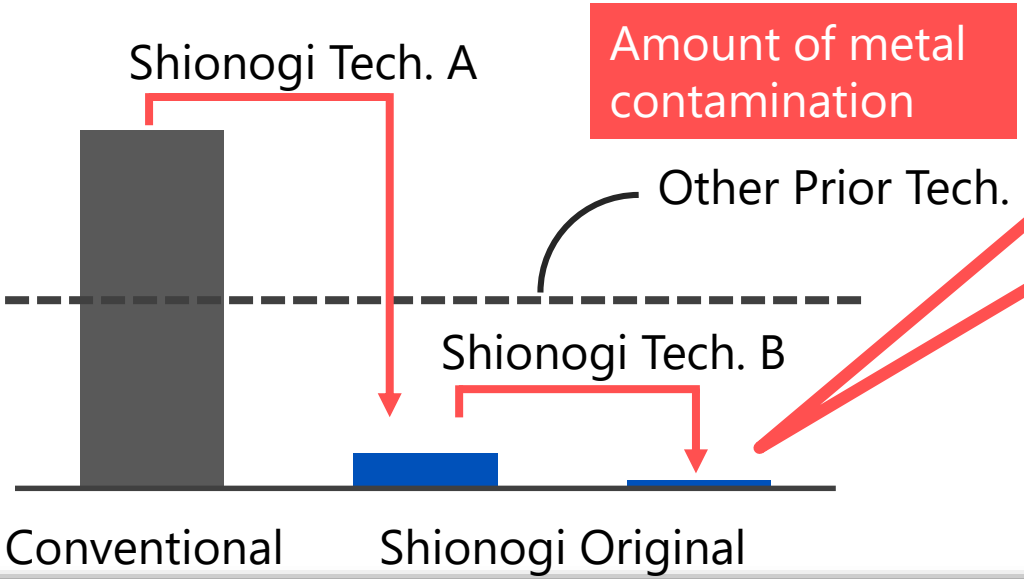
Novel Nanotechnology for Formulation of Low Solublllity APIs

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**

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 -15ºC is necessary)

A API Free base

Patent applied

Salt selection

B Organic acid — Improve purity by forming organic acid salt

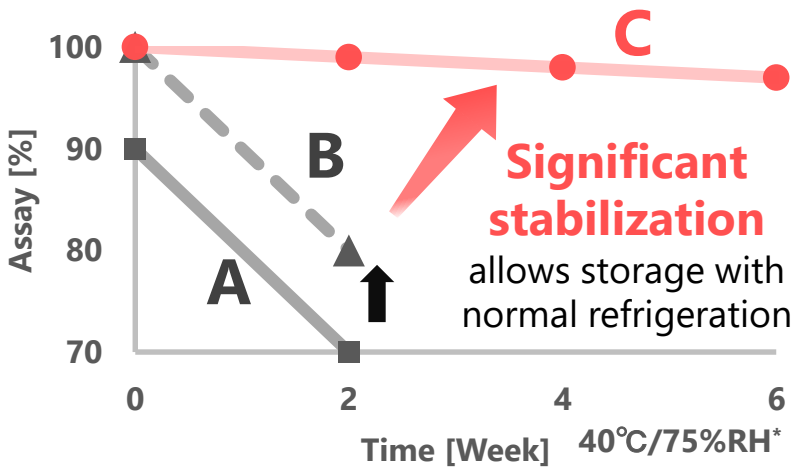
Stabilization

C Sugar, NaCl, Organic acid

Cefiderocol drug product
Protected by 3 components

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

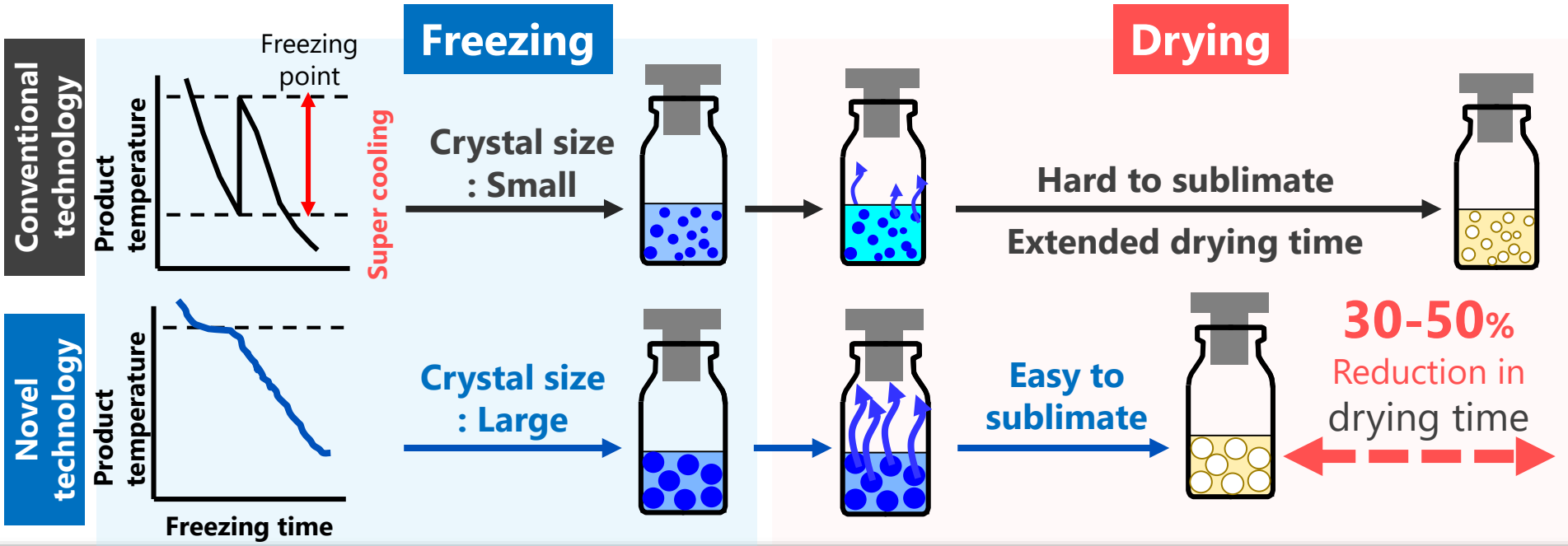
Importance: Lyophilization is an effective technology for stabilization and sterilization of unstable mid-large molecule API

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.

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



Pulmonary Drug Delivery Technology for Inhaled Pirfenidone

Achievements and next issue

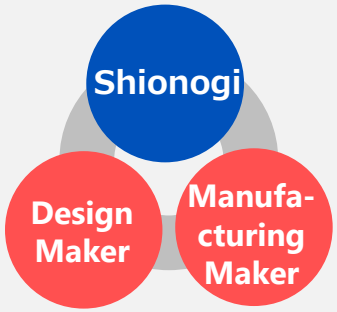
Achievements

- 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

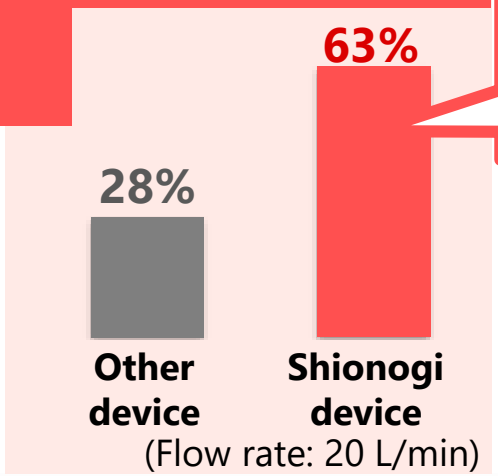


Inhalation device co-developed with other companies

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



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

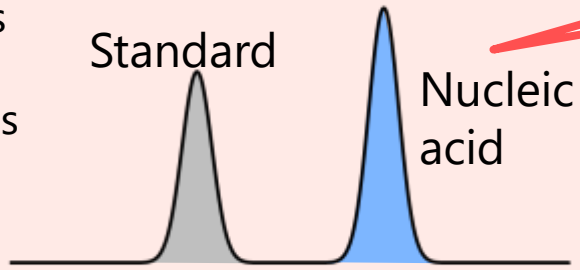
- Development of method: **1 week**
- Reference standards available on the **market**
- Accuracy assured by using high-purity universal standards

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

^{31}P-NMR spectra



Accurate, reliable and rapid evaluation

Contributed to efficient and rapid drug development with higher quality

SHIONOGI

* 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**
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- **Targets for FY2019**
  - Targets for FY2019
  - Towards Further Advances in CMC Technologies: Collaboration with Outside Organizations

Targets for FY2019 (1)

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

Xofluza™	Approval in Taiwan, Launch Launch for pediatric granule formulation in Japan
Lisdexamfetamine	Launch in Japan
Intuniv®	Approval in Japan, Launch
Cefiderocol	Approval in the US, Launch

Toward Further Advances in CMC Technologies:
Collaboration with Outside Organizations

PHARMAIN
Enabling and improving human therapeutics

Collaborative research utilizing PGCTM Platform Technology

umn

Capital and business alliance, technology for prophylactic vaccine against infection disease

VAST THERAPEUTICS
THE NEW FIGHT

R&D for Nitric Oxide inhaled antimicrobial drug candidate

BIKEN
一般財団法人 阪大微生物病研究会

Process technology development for "A2NTX" Botulinum Toxin bio-pharmaceutical

ACADEMIA

Collaboration with academia, university, laboratory etc.

SAGE
THERAPEUTICS

Collaborative research of "SAGE-217" for the treatment of MDD*

PeptiStar

Creation of CMO* for revolutionizing production of API for constrained peptides

tetra
RESTORING CLARITY OF THOUGHT

Collaborative research of "BPN14770" for the treatment of cognitive and memory deficits

Hsiri Therapeutics

Collaborative research for the treatment of Mycobacterial diseases

*MDD: major depressive disorder

Development

Toshinobu Iwasaki, Ph.D.
Senior Vice President
Development Division

R&D Vision

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

From Presentation of FY2017

Development Targets for FY2018

Issues for FY2017

Accuracy of clinical trial planning

Progress of global studies

Increasing outsourcing fees

- **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 skillis in forecasting and planning
  - Using feasibility studies to increase predictability

NDA Submissions: 3 (4 indications)

Approvals: 3

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 alignement
- 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

①Mulpleta®：US
②Xofluza™：US
③Lusutrombopag：EU
④Rizmoic®/Naldemedine：EU

Achievements in FY2018: NDA Submissions and Approvals

Product (indication)	Phase I	Phase II	Phase III	NDA submission	Approval
Mulpleta® (Thrombocytopenia)				US(2017.12) EU(2018.1)	US(2018.8) EU(2019.2)
Rizmoic®/Naldemedine (Opioid-induced constipation)				EU(2017.3)	EU(2019.2)
Lisdexamfetamine (ADHD(pediatric))			high-dose study	Japan(2017.4)	(Japan* 2019.2)
Xofluza®/Xofluza™ ①Influenza virus infection ②Influenza virus infection (granule) ③Influenza virus infection (granule・Weight under 20kg)			Global : High Risk study completed(2018.8) Japan : ・Granule study completed(2018.7) ・High-dose study for children ongoing	①US(2018.4) ②Japan(2018.4) ③Japan(2018.8)	①US(2018.10) ②Japan (2018.9)
Cefiderocol (Multidrug-resistant Gram-negative bacterial infections)			Global : 2 clinical studies** ongoing	US(2018.12)	
Intuniv® (ADHD(adult))			Japan : extension study completed(2019.1)	Japan(2018.8)	

*Passed Drug Committee Meeting
** CR : Carbapenem-resistant
** HAP/VAP/HCAP: hospital-acquired pneumonia/ventilator-associated pneumonia /health care-associated pneumonia

Achievements in FY2018 ：Phase II ～ III

Product (indication)	Phase I	Phase II	Phase III	NDA submission	Approval
Xofluza®(Influenza virus infec(prophylaxis))			Japan：initiated(2018.7)		
OxyContin®TR (Treatment of moderate to severe chronic pain)			Japan：initiated(2018.5)		
S-588410 (Bladder cancer)		Japan・EU：completed(2019.3)			
S-120083 (Inflammatory pain)		US：completed (2018.10)			
S-600918 (Neuropathic pain or Refractory Chronic Cough)	Multiple dose study Completed in FY2017	Japan：initiated (2018.6)			
SR-0379 (Skin ulcers(Pressure ulcers, diabetic ulcers, etc))		Japan：Skin ulcers subjects initiated(2018.6)			

Achievements in FY2018 ：Phase I

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

* 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

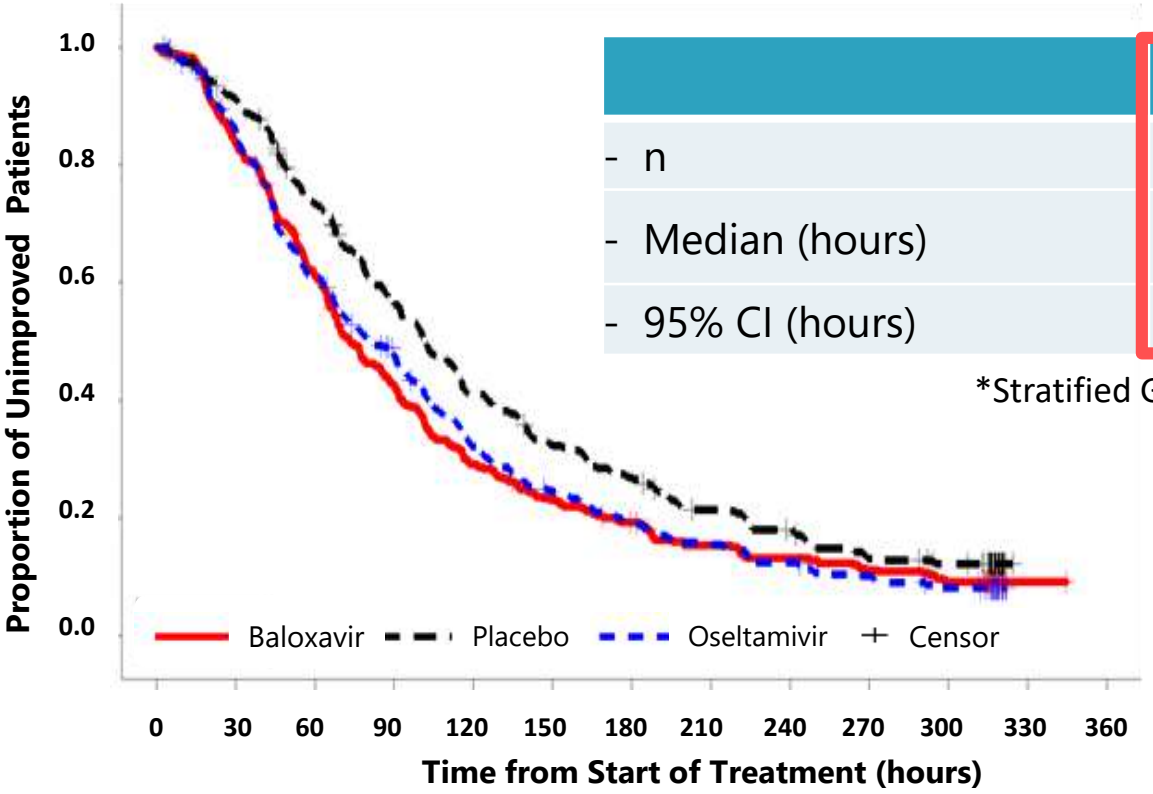
Japan： Phase III new dosage for children (for granule)
Japan： Phase III Post Exposure Prophylaxis Study
Taiwan：NDA submission

Future plans

Japan： NDA submission for new dosage for children
Japan： NDA submission for prophylaxis indication
Taiwan：approval

* N Engl J Med. 2018;379(10):913-923. Antiviral Res. 2019;163:75-81.
Antiviral Res. 2018;160:109-117. Sci Rep. 2019;9(1):3466

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



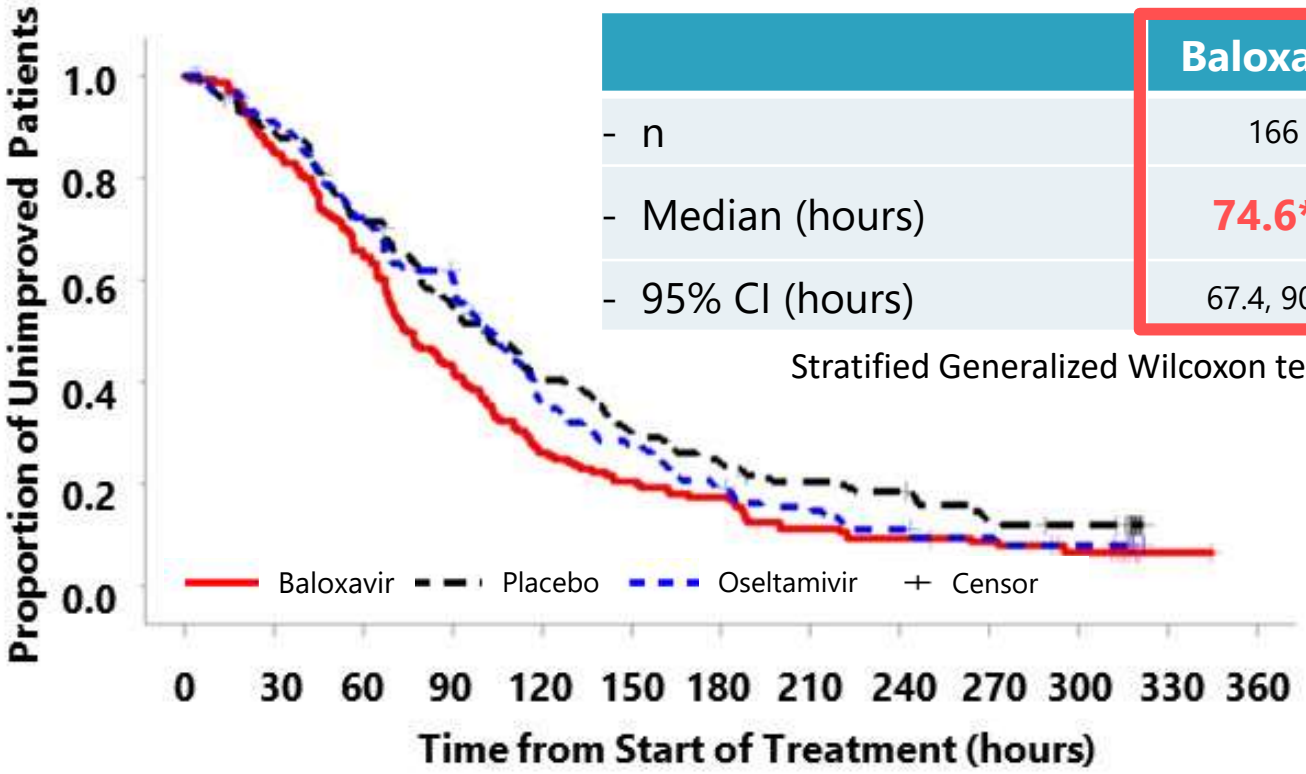
	Baloxavir	Placebo	Oseltamivir
- n	385	385	388
- Median (hours)	73.2*	102.3	81.0
- 95% CI (hours)	67.2, 85.1	92.7, 113.1	69.4, 91.5

*Stratified Generalized Wilcoxon test, P<.0001 vs placebo

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	Placebo	Oseltamivir
- n	166	167	148
- Median (hours)	74.6*#	100.6	101.6
- 95% CI (hours)	67.4, 90.2	82.8, 115.8	90.5, 114.9

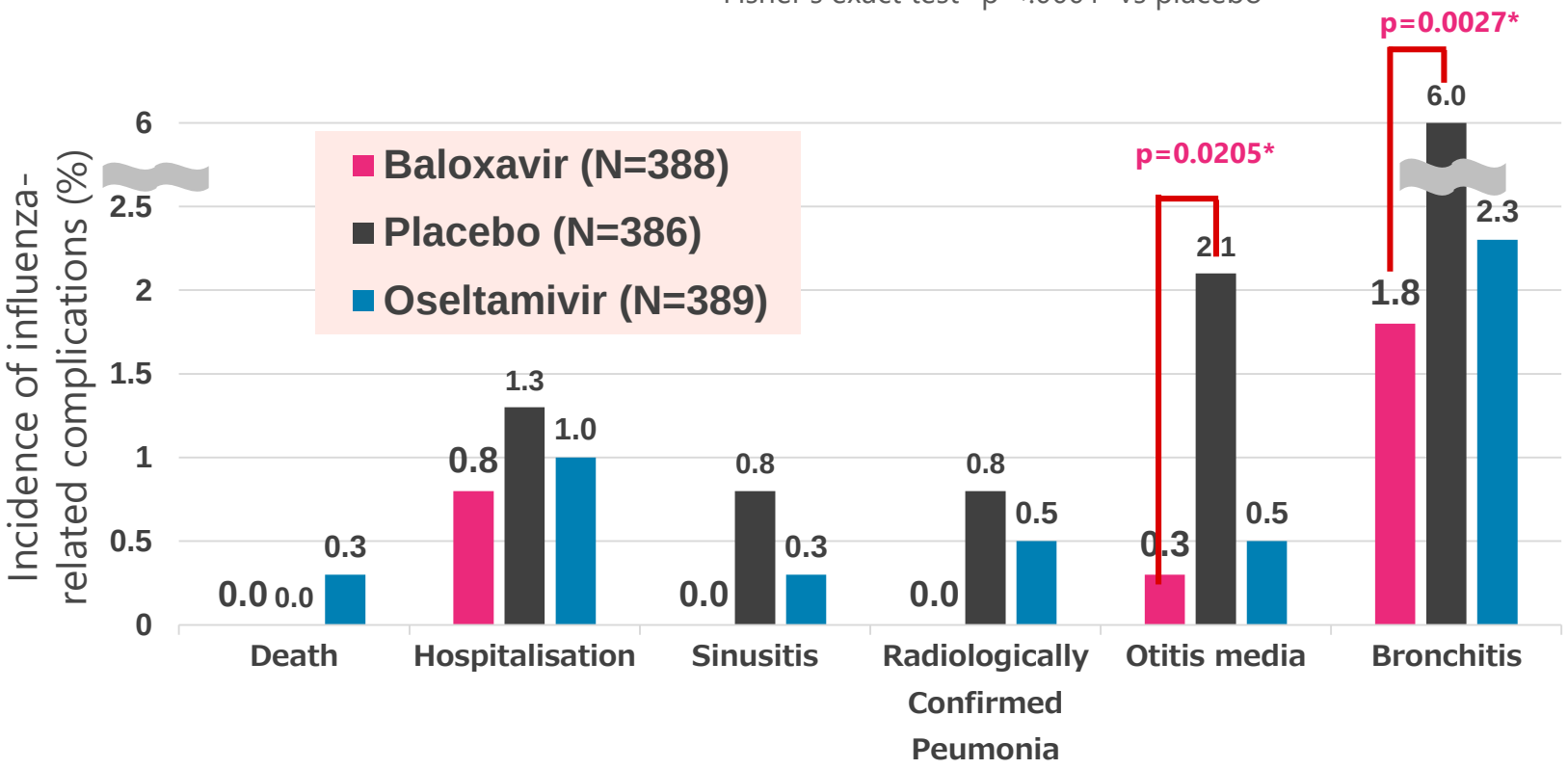
Stratified Generalized Wilcoxon test, P<.05 vs *placebo or #oseltamivir

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

Xofluza™ Incidence of Influenza-related Complications in High Risk Patients

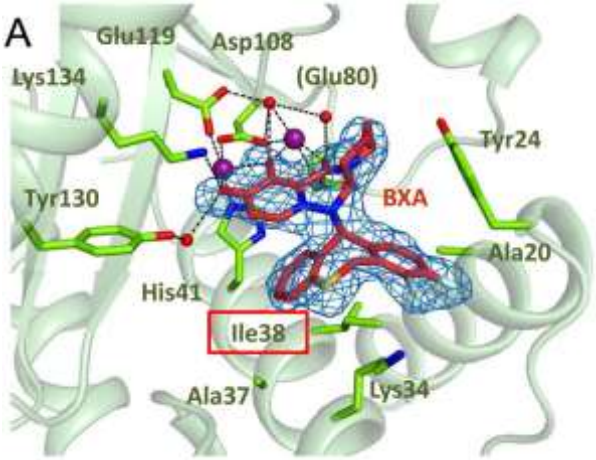
	Baloxavir N = 388	Placebo N = 386	Oseltamivir N = 389
Patients with any complications	2.8%* (11/388)	10.4% (40/368)	4.6% (18/389)

*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 38th 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.

Study	Proportion of PA/I38 variant emergence (patients with I38/total patients)	Type/subtype		
		A/H1N1pdm	A/H3	B
Phase 2 study	2.2% (4/182)	3.6% (4/112)	0% (0/14)	0% (0/56)
Phase 3 OwH* study	9.7% (36/370)	0% (0/4)	10.9% (36/330)	2.7% (1/37)
Pediatric study (T0822)	23.4% (18/77)	0% (0/2)	25.7% (18/70)	0% (0/6)
Phase 3 High Risk study	5.2% (15/290)	5.6% (1/18)	9.2% (13/141)	0.8% (1/131)
NIID Surveillance Data[1]	8.2% (16/194)	1.8% (2/110)	17.9% (14/78)	0% (0/6)

[1]https://www.niid.go.jp/niid/en/flu-m/flutoppage/2132-flu/flu-dr-e/8652-flu-r-e20190304.html (Table 1)

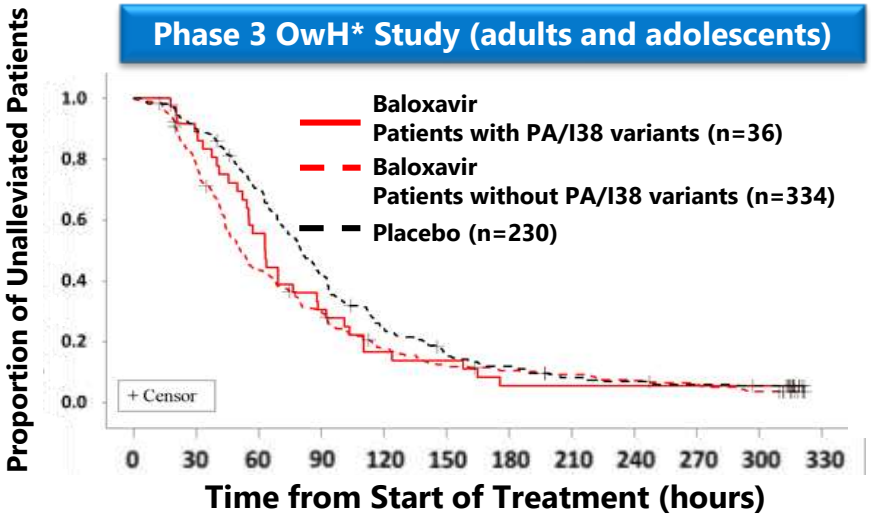
* OwH: Otherwise healthy

Sci Rep 2018;8:9633

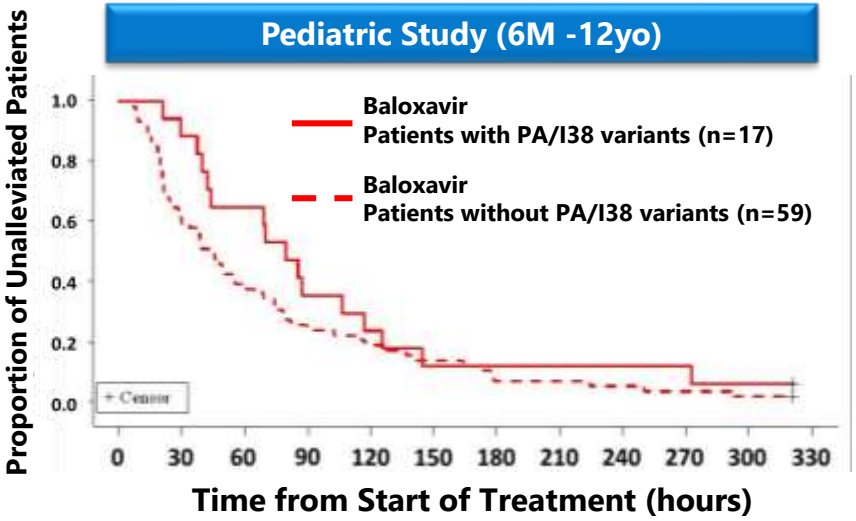
No Consistent Trend On The Impact Of Emergence Of PA/I38 Variants For Clinical Symptoms Across Three Studies

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

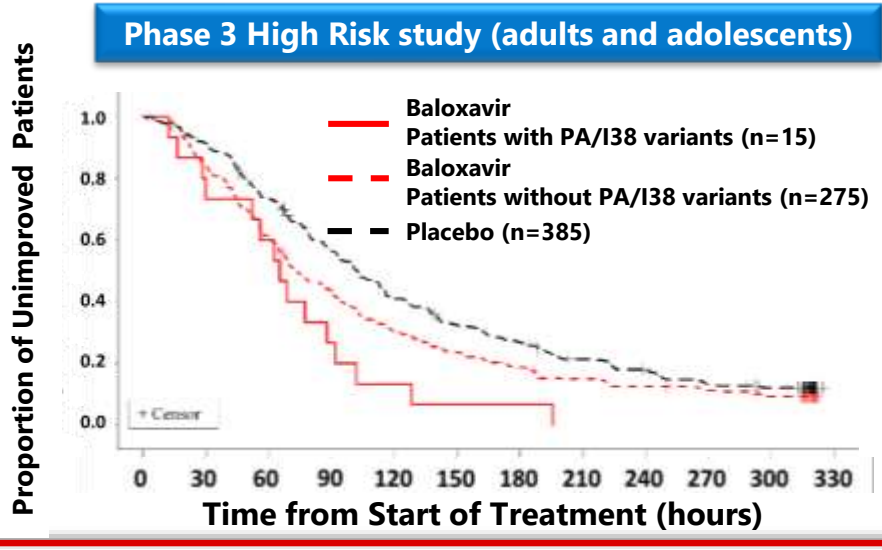
Phase 3 OwH* Study (adults and adolescents)



Pediatric Study (6M -12yo)



Phase 3 High Risk study (adults and adolescents)



* OwH: Otherwise healthy

Robust Ongoing Activities Generating Important Data In Key Populations - Provides Further Insights Into PA/I38 Variants

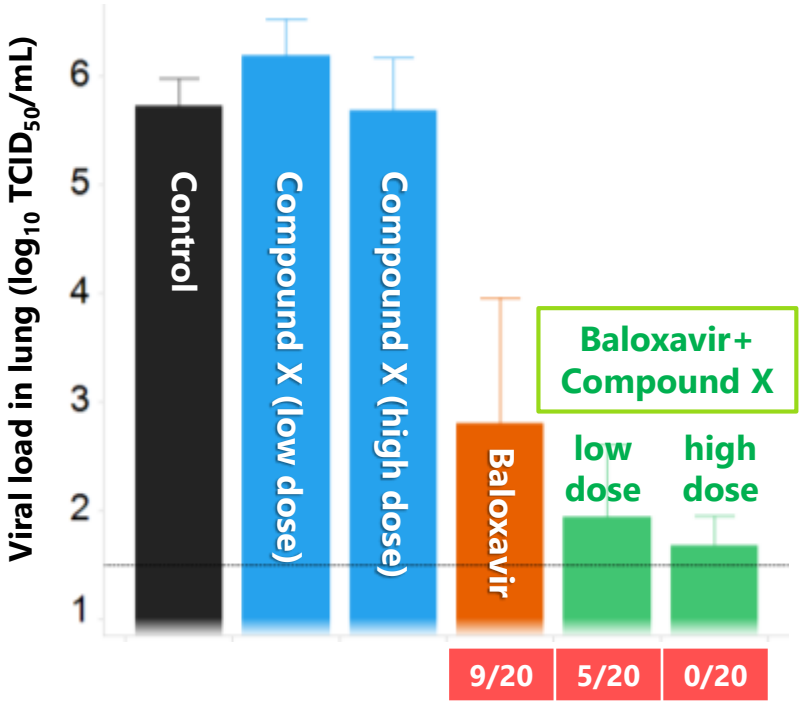
STUDY		STUDY FOCUS
STATUS	**CLINICAL APPROACH**	
ONGOING	**PEDIATRICS STUDIES AT HIGHER DOSING**	Assesses safety, PK and efficacy at higher dose.
ONGOING	**SEVERELY ILL & HOSPITALIZED PATIENTS**	Explores combination therapy with NAIs and multiple dosing in hospitalized patients.
ONGOING	**POST EXPOSURE PROPHYLAXIS**	Assessing prophylactic efficacy of baloxavir and the risk of transmission of I38 variants.
ONGOING	**DRUG SUSCEPTIBILITY SURVEILLANCE**	Resistance monitoring in the clinical setting.
PLANNED	**REDUCED TRANSMISSION**	Clinical assessment for reduced transmission to household contacts from patients treated with baloxavir and possible risk of transmission of I38 variants.

STATUS	NON-CLINCAL APPROACH	
ONGOING	**NEXT GENERATION SEQUENCING**	Sensitive and quantitative detection of I38 variants in post-dose clinical specimens.
ONGOING	**TRANSMISSION STUDY IN FERRET MODELS**	Explores effect of baloxavir on transmission and assess risk of transmission of I38 variants in ferrets
ONGOING	**COMBINATION W/NAI & MULTIPLE DOSING REGIMENS**	Explores combination with NAI & multiple dosing regiments for severely ill patients.

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

Indication

Multidrug-resistant Gram-negative bacteria infection

Mechanism of action

Cell-wall synthesis inhibition

Special characteristics

- Injectable siderophore cephalosporin
- Wide range of Gram-negative pathogens

Stage

Global: CREDIBLE-CR*: carbapenem-resistant Gram-negatives study
Global: APEKS**-NP***: hospital-acquired pneumonia/ ventilated-associated pneumonia study
US： NDA submission in 2H FY2018 (QIDP**** designated compound)

Future plan

EU: MAA submission in 1H FY2019 (Accelerated Assessment)
US, EU: Approval
Global: Pediatric Program

*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

Indication

ADHD (Attention-deficit/hyperactivity disorder)

Mechanism of action

Selective alpha 2a adrenergic receptor agonist

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

Intuniv® Adult: Long-term Study

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.

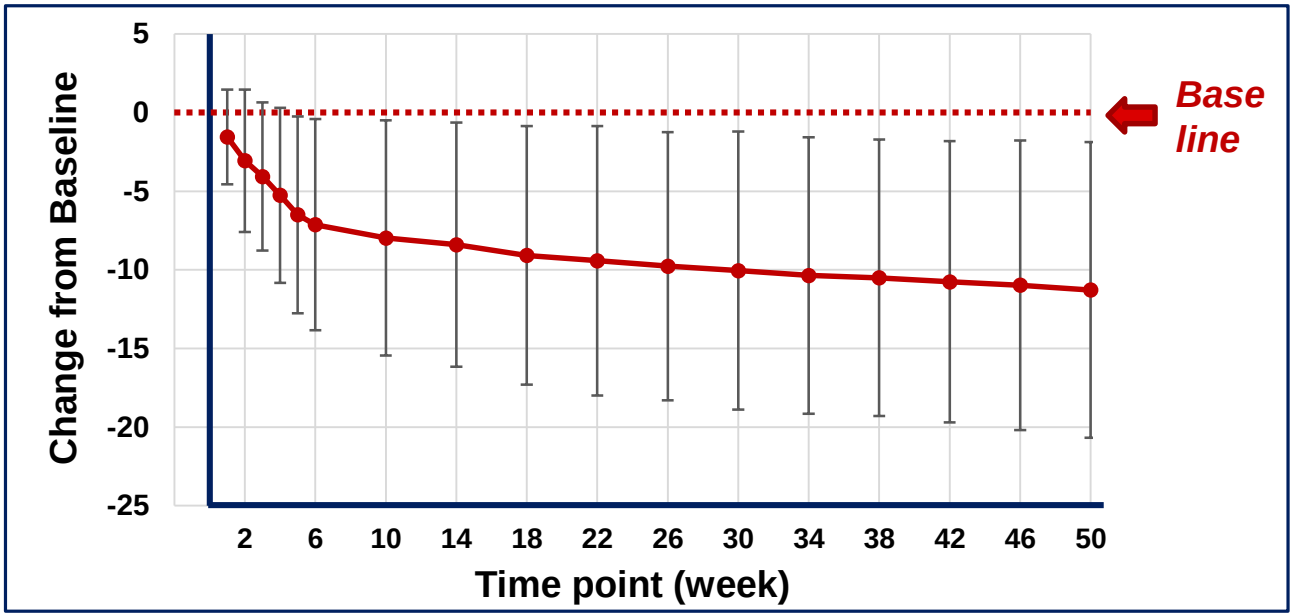


Figure: The change of ADHD-RS-IV with adult prompts Total Score (Mean ± SD)

【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)

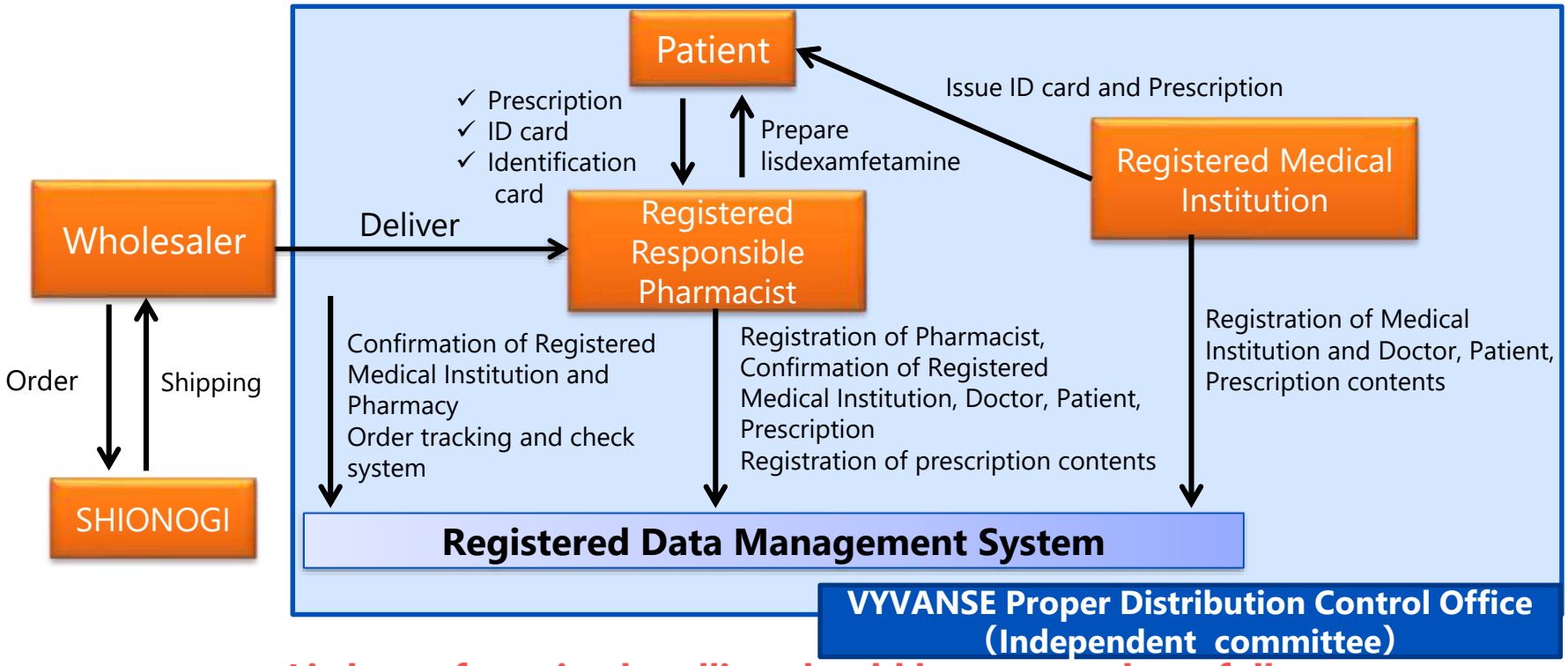
Future plan in Japan

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

Lisdexamfetamine: Distribution Control

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

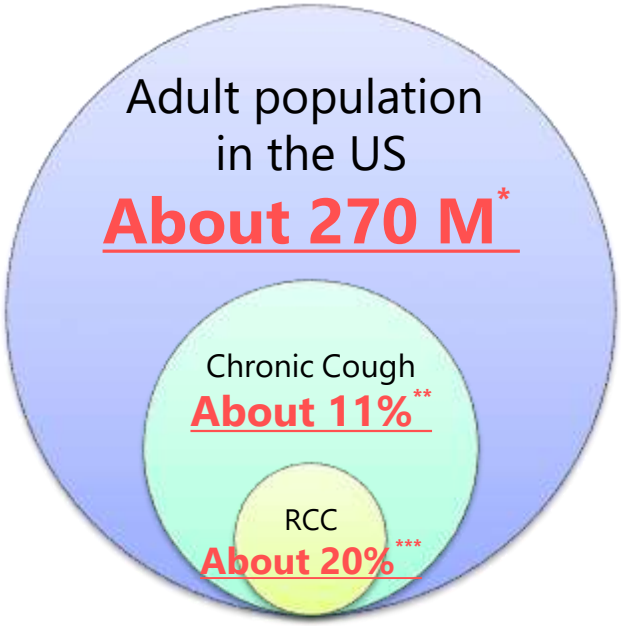
Future Plan

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

Estimated number of RCC patients (US, 2025)



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

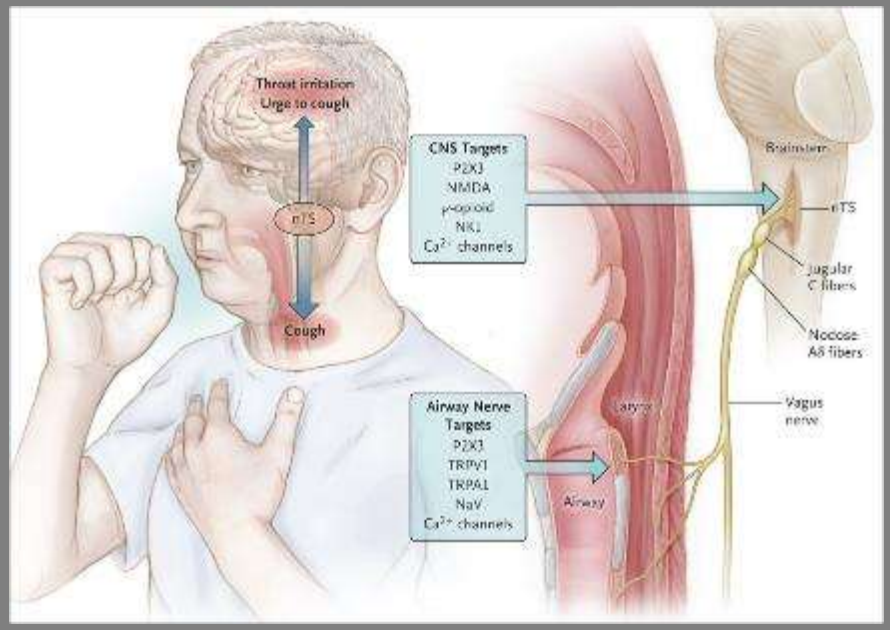
Safe and effective treatments are needed

* United Nations Population Database、** Song WJ et al.、2015、*** Levine BM et al、2008

$P2X_3$ Receptor and Cough Reflex

- **$P2X_3$ receptor**
  - ATP (adenosine triphosphate) -gated ion channel
  - Mainly expressed in peripheral nervous system and mediates neuronal sensitization
  - Assembled by three $P2X_3$ subunits, homo-trimer ($P2X_{2/3}$ hetero-timer also exists)

Neuronal Pathways Controlling Cough、and Targets of Available Antitussive Agents and of Those in Development.



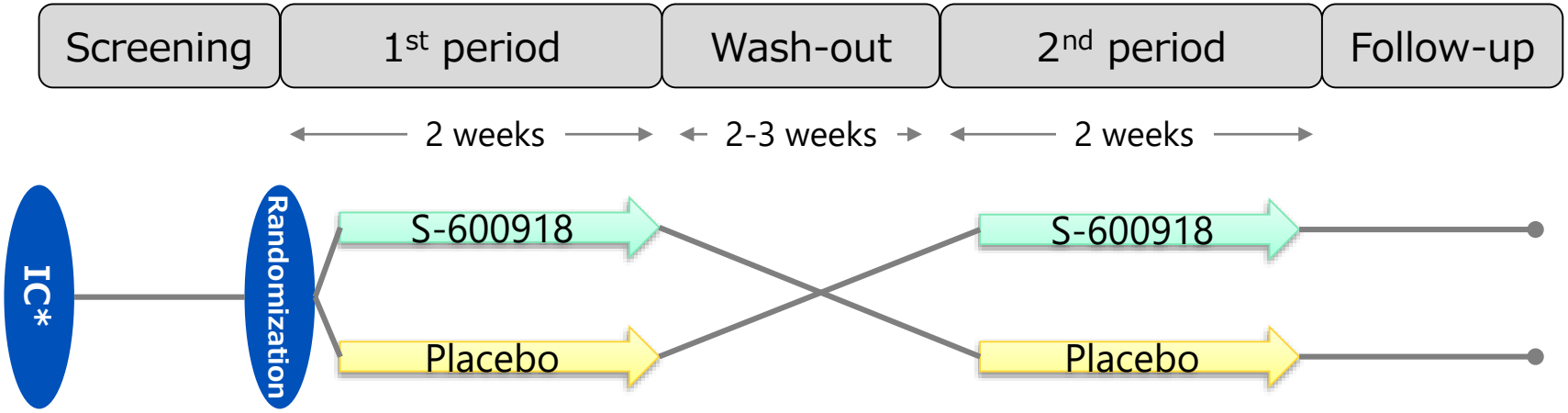
Smith JA、Woodcock A. N Engl J Med 2016;375:1544-1551.

P2X3 receptors are expressed in nerves which are associated with the cough reflex

ATP, ligand of P2X3 receptors, induces the cough reflex

$P2X_3$ receptors are involved in the cough reflex

Overview of Proof of Concept Study

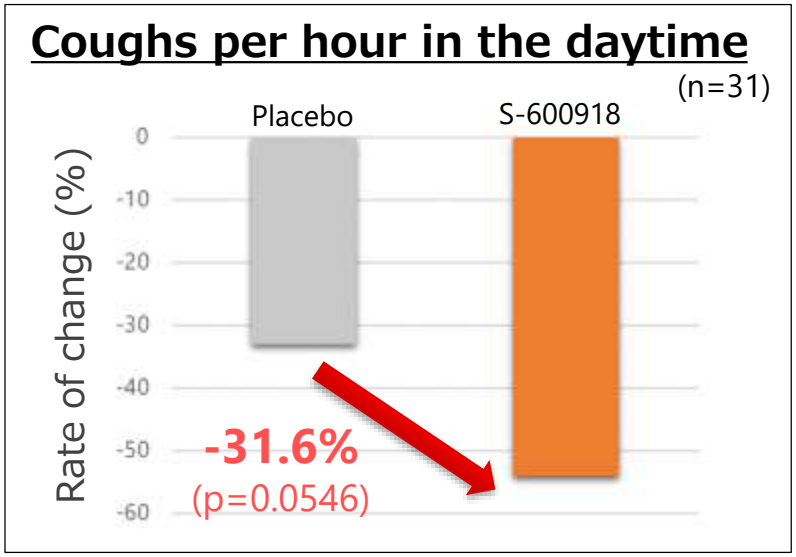


Population	Patients with refractory/unexplained chronic cough
Design	Placebo-controlled, multi-center, randomized, double-blind, cross-over comparison
Efficacy Endpoints	To evaluate the rate of change in the number of coughs per hour in 24 hours, in the daytime, in the nighttime and so on. To evaluate the change in the Leicester Cough Questionnaire etc.,
No. of patients	30 patients

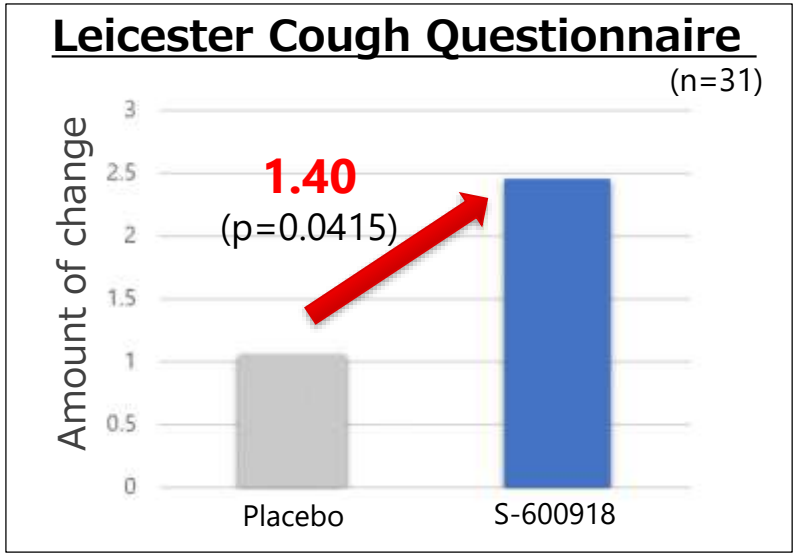
*Informed consent

Results of Proof of Concept Study

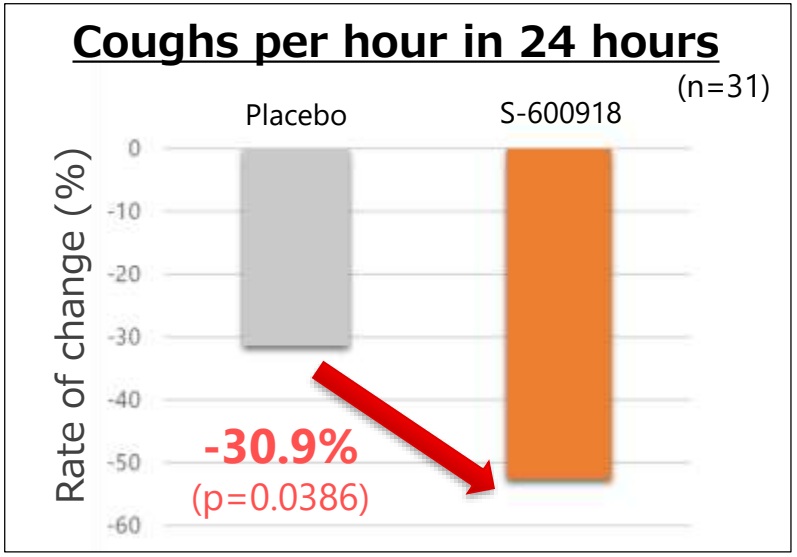
Coughs per hour in the daytime



Leicester Cough Questionnaire



Coughs per hour in 24 hours



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

$GABA_A$ 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

SONG for you!

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、
2) Collins JJ、et al. J Occup Environ Med 2005; 47

S-770108
Idiopathic Pulmonary Fibrosis

Profile: S-770108 (Inhaled Pirfenidone formulation)

SONG for you!

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 trials[1、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 data[6)])

- **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**

1) Eur Respir J. 2010;35(4):821-9、 2) Lancet. 2011;377(9779):1760-9、 3) N Engl J Med. 2014;370(22):2083-92
4) Lancet Respir Med. 2017;5(1):33-41 5) Am J Respir Crit Care Med. 2015;192(2):e3-19. 6) Respir Investig. 2015;53(5):232-41

S-770108 Development Status and Plans

Phase I Single and Repeated dose study : Complete	
Subjects	Healthy male subjects (Caucasian and Japanese)
Safety	Single dose part: No adverse events reported
	Repeated dose part (three doses/day) 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.

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 Continuous activation

Simultaneous activities: Steering and Tapping

Steering : avoid obstacles

Tapping : touch special targets

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

Closed-Loop

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

Continuously activate cerebral cortex → **Improve inattention**

SHIONOGI

Nature. 2013 Sep 5;501(7465):97-101

AKL-T01 Pivotal study

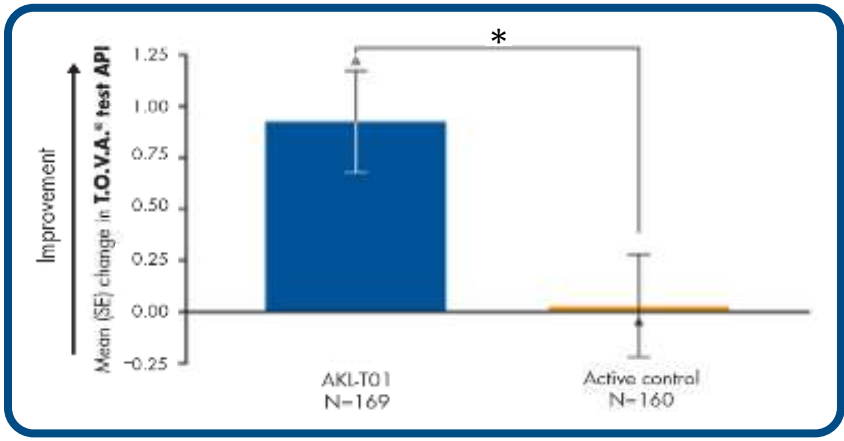
Akili has conducted a pivotal study of AKL-T01:
A multi-center, double-blind, randomized, active-controlled study in the US.

＜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.

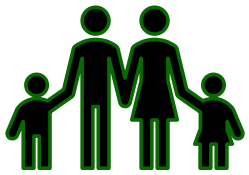
JAACAP. October 2018 Vol 57,Issue10、Suppl、S172

Vision: An Integrated Suite of ADHD Therapies

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

Family

Physician



Information sharing by IT

Digital therapy

Drug

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 on going (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

Vision: Balance between efficiency and innovation

Efficient Global Operation — Balance — Development Innovation

- **"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

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

Product (indication)	Phase I	Phase II	Phase III	NDA submission	Approval
Lisdexamfetamine (ADHD(pediatric))				Japan(2017.4)	Japan
Intuniv® (ADHD(adult))				Japan(2018.8)	Japan
Cefiderocol (Multidrug-resistant Gram-negative bacterial infections)			Global：2 clinical studies completion	US(2018.12) EU	US EU
Xofluza® (Influenza virus infec) ①granule(weight under 20kg) ②granule(new dosage for children(weight under 20kg) ③prophylaxis			Japan：High-dose study for children completion Prophylaxis study completion	①Japan(2018.8) ②Japan ③Japan	①Japan
OxyContin®TR (Treatment of moderate to severe chronic pain)			Japan：completion	Japan	

Target Milestones for FY2019: Phase I ～ III

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

Target Milestones for FY2019: Phase I ～ III

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

* Post operative ileus

⇨ Stage up

Development Targets for FY2020 from FY2017

Direction for FY2020

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

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**

* 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**

launched

[Before SGS2020(FY2014)]

- Osphena®/ Senshio*

1. **TIVICAY®**

[From SGS2020(FY2014)]

2. **Triumeq®**
3. **Symproic®**
4. **Julica®**
5. **Mulpleta®**
6. **Xofluza®**
7. **Osphena®(Vaginal dryness)**

NDA submission / NDA submission(in preparation)

8. **Cefiderocol**
   - US：FY2018，EU：FY2019
   - US/EU： launch in FY2019
9. **DTG/3TC(HIV：First 2-drug regimen for naïve patients**
   - Sep. 2018: MAA submission in EU, Oct. 2018: NDA submission in US (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

Toward Sustainable Growth Beyond 2020

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

1: Novel HIV drug, 2: S-004992 (Tuberculosis), 3: S-600918 (Refractory/unexplained chronic cough, Neuropathic pain), 4: S-637880 (Neuropathic pain), 5: S-812217 (Depression), 6: Adjuvant for vaccine, 7: S-770108 (Idiopathic pulmonary fibrosis), 8: Peptide drug

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**
- Nov. 2017-Jun. 2018: Approved in US, EU, CAN, AUS
- Dec. 2018: Launched in Japan

DTG/3TC **Launch: 2019~**
- **First 2-drug regimen for naïve patients**
- Sep. 2018: MAA submission in EU, Oct. 2018: NDA submission in US (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

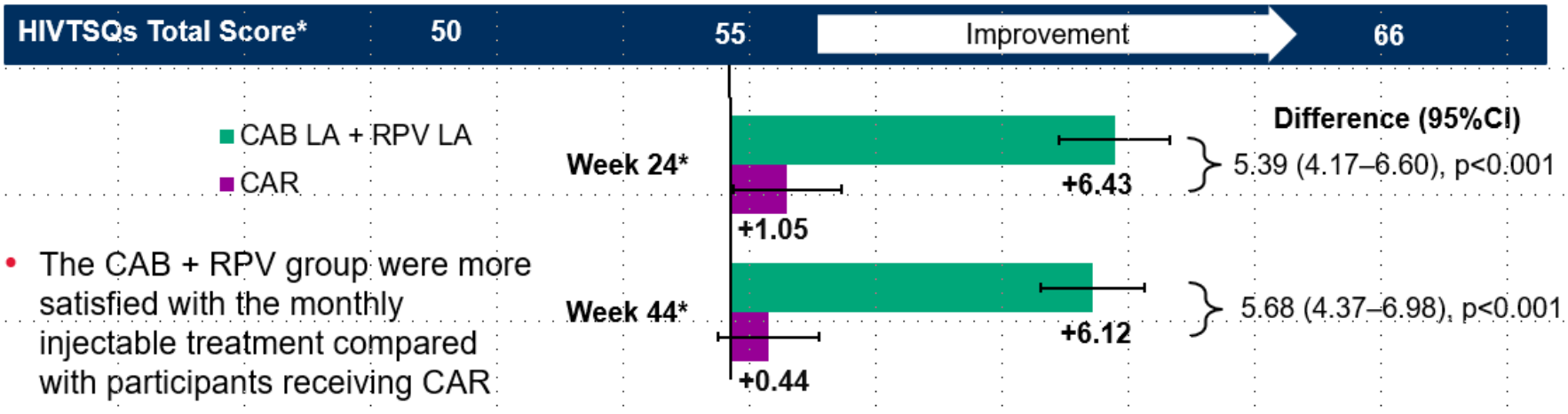
SHIONOGI

* ATLAS：current antiretroviral therapy (CAR), the existing three-drug regimen once a day、FLAIR：Triumeq®
** in FLAIR, ARV therapy-naïve 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



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

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=288 for CAR at Week 24 and n=294 at Week 48.

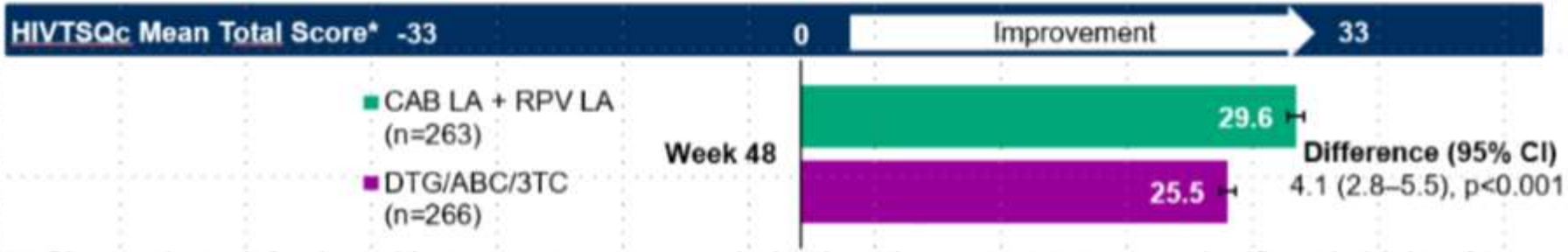
Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475.

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



- 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**

3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; HIVTSQc, HIV Treatment Satisfaction Questionnaire (change version); HIVTSQs, HIV Treatment Satisfaction Questionnaire (status version); ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine; SE, standard error.

*Adjusted for baseline HIV-1 RNA (< vs ≥100,000 c/mL), sex, age, and race, ± SE. Based on observed dataset of participants who completed the questionnaire at Week 48 or early withdrawal; †Maintenance (Day 1) HIVTSQs baseline mean score comparable between both arms with the same mean value of 59 out of 66 points.

Orkin C, et al. CROI 2019; Seattle, WA. Abstract 3947.

Conference on Retroviruses and Opportunistic Infections; March 4–7, 2019; Seattle, WA

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

Preclinical (Basic research) → Preclinical (Early phase) → Preclinical (Late phase) → Preclinical (Candidate) → Phase I

Infectious disease

In-house

- **HIV virus infection** — Phase I in FY2019
- Influenza virus infection — Phase I in FY2019
- Bacterial infection
- Bacterial infection
- Fungus infection

Collaboration

- RS virus infection (UBE / UBE INDUSTRIES,LTD.)
- Bacterial infection
- Fungus infection (Nissan Chemical CORPORATION)
- Industry-academic collaboration in UK
- Vaccine for prevention (UMN)
- Participation in consortium (DNDi)
- Malaria (Nagasaki Univ)

Pain/CNS

In-house

- ADHD — Phase I in FY2020

Collaboration

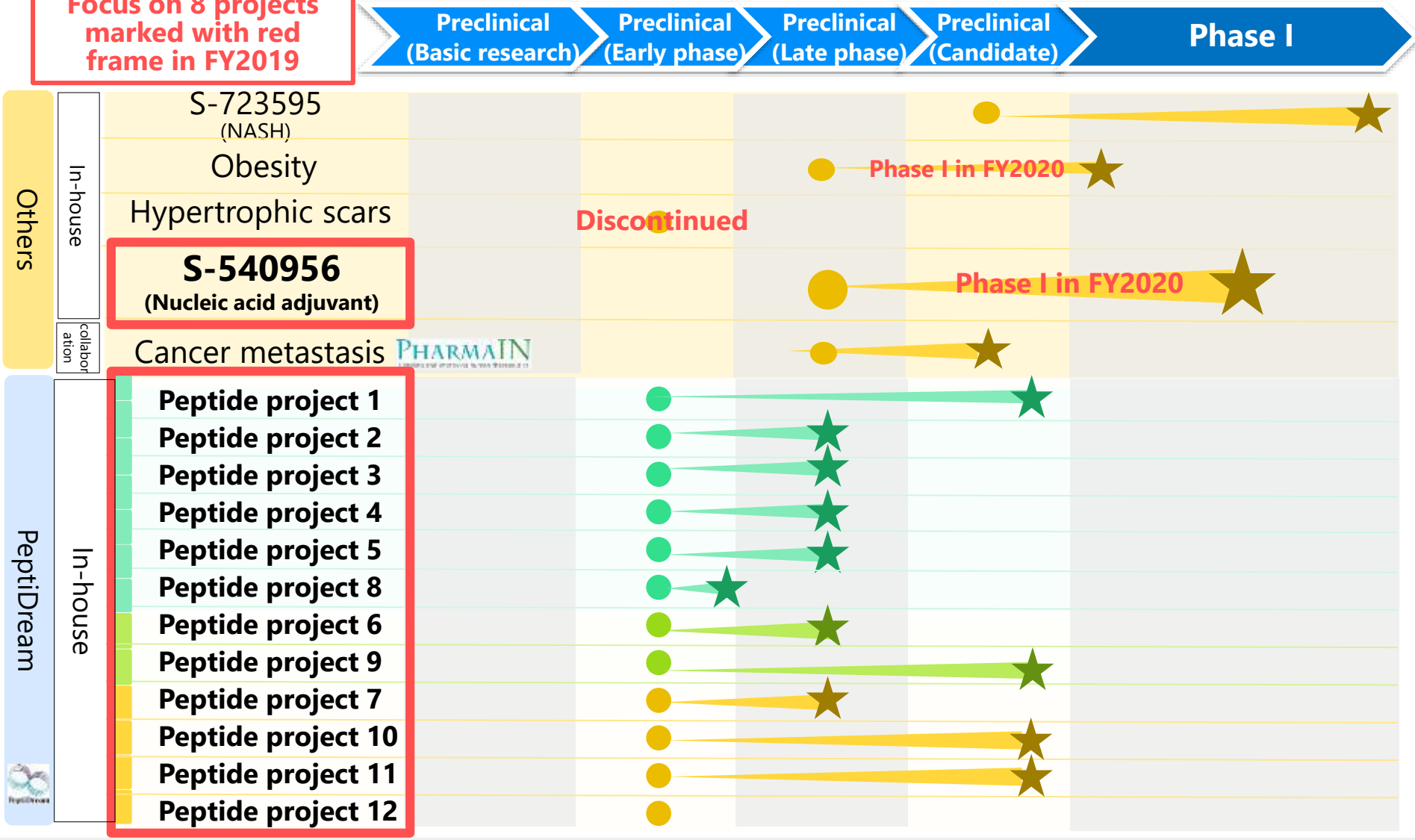
- Cognitive and memory disorder (tetra)
- Opioid
- Alzheimer's disease
- SK PJ1: Alzheimer's disease
- SK PJ2: Other CNS disease
- MTC

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

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

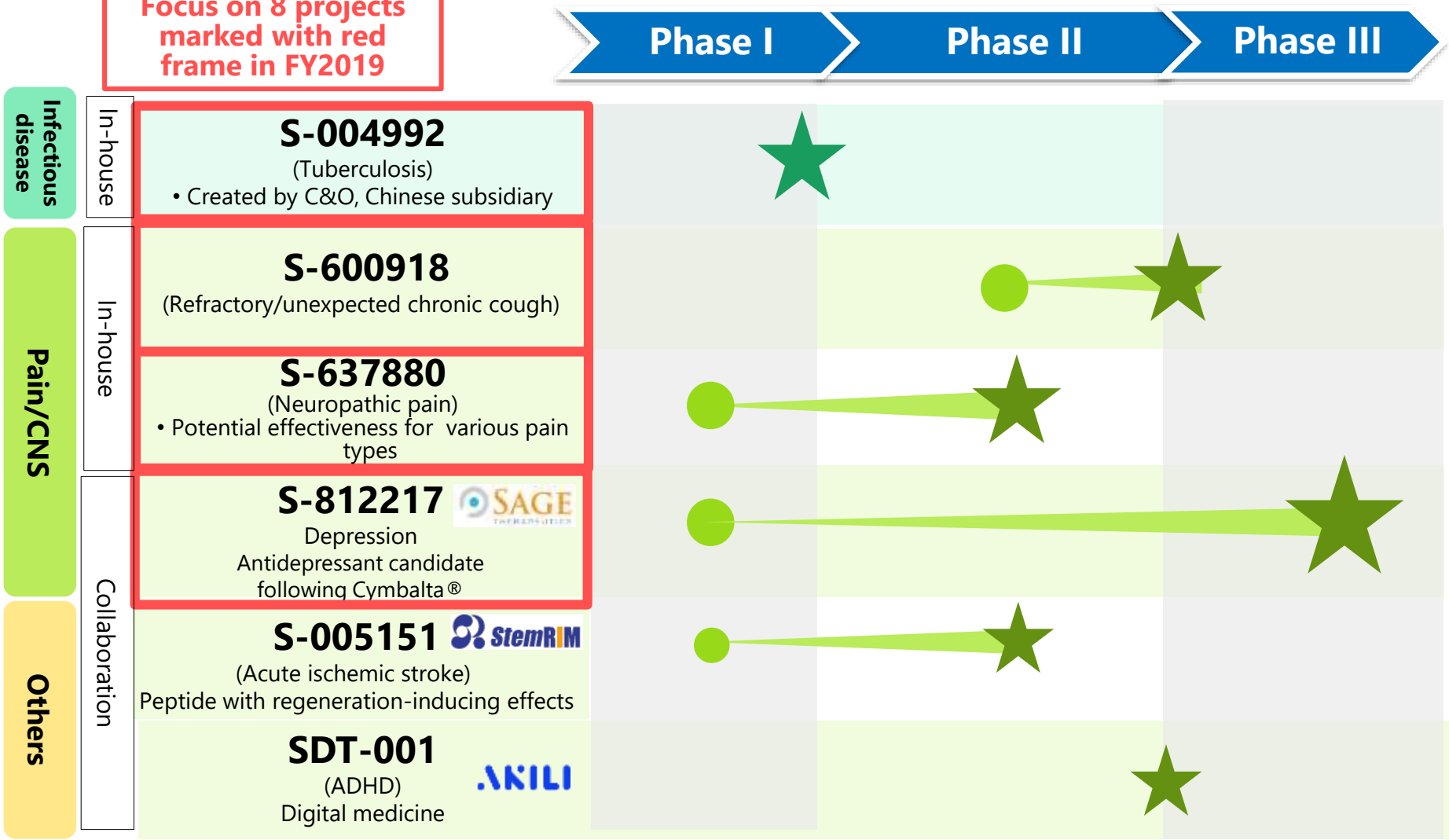
Actions to Create Further Growth Drivers
1: Generate a Large Variety of Compounds in Phase I (Others)

Focus on 8 projects marked with red frame in FY2019



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



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

Others

In-house

S-770108
(Idiopathic pulmonary fibrosis)
- Using dry powder inhalation technology to minimize side effects

Collaboration

ADR-001
(Decompensated liver cirrhosis)
Cellular and tissue-based product candidate

SR-0379
(Cutaneous ulcer)
Functional peptide which enhances cellular proliferation and vascular formulation

S-588410
Relapse prevention of esophagus cancer
Cancer peptide vaccine

S-588210
Treatment for solid tumor
Cancer peptide vaccine

Pipeline (as of Mar. 14, 2019)

Preclinical (target indication*)	Phase I	Phase II	Phase III	Filed
Influenza virus infection	**Global**			
HIV virus infection	S-004992** Tuberculosis	S-120083 Inflammatory pain	Cefiderocol Multidrug-resistant Gram-negative bacterial infections	Cefiderocol Multidrug-resistant Gram-negative bacterial infections
RS virus infection	S-117957 Insomnia	S-707106 Type2 diabetes		Baloxavir Marboxil (Taiwan) Influenza virus infection
Bacterial infection	S-237648 Obesity	S-488210 Head and neck squamous cell carcinoma		
Mycobacterium disease	S-588210 Solid tumor	epertinib Malignant tumor		
Fungus infection		S-588410 Bladder cancer		
Vaccine for prevention	**In Japan**			
Peptide	S-812217 Depression	Cefiderocol Multidrug-resistant Gram-negative bacterial infections	Cefiderocol Multidrug-resistant Gram-negative bacterial infections	Oxycodone Moderate to severe chronic pain
ADHD	S-600918 Neuropathic pain	S-600918 Refractory/unexpected chronic cough	Xofluza™ Influenza virus infection (prophylaxis)	Lisdexamfetamine ADHD (pediatric)
Opioid	S-637880 Neuropathic pain	S-237648 Obesity	Xofluza™ Influenza virus infection (New dosage for children)	Intuniv® ADHD (adult)
Alzheimer's disease	S-010887 Neuropathic pain	S-525606 Allergic rhinitis caused by Japanese cedar allergen	Cymbalta® Depression (pediatric)	
Cognitive and memory deficits	S-005151 Acute ischemic stroke	S-588410 Bladder cancer	Oxycodone Moderate to severe chronic pain	
Post-stroke spasticity	S-770108 Idiopathic pulmonary fibrosis	SR-0379 Cutaneous ulcer	S-588410 Esophageal cancer	
Peptide		ADR-001*** Decompensated liver cirrhosis		
Obesity				
S-723595 NASH				
Cancer metastasis				
S-540956 Nucleic acid adjuvant				
Peptide				

- Infectious diseases
- Pain/CNS
- Other

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)

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

- **Infectious diseases**
- **Pain/CNS**
- **Others**

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)

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

DTG: Dolutegravir 3TC: Lamivudine RPV: Rilpivirine CAB：Cabotegravir

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)

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

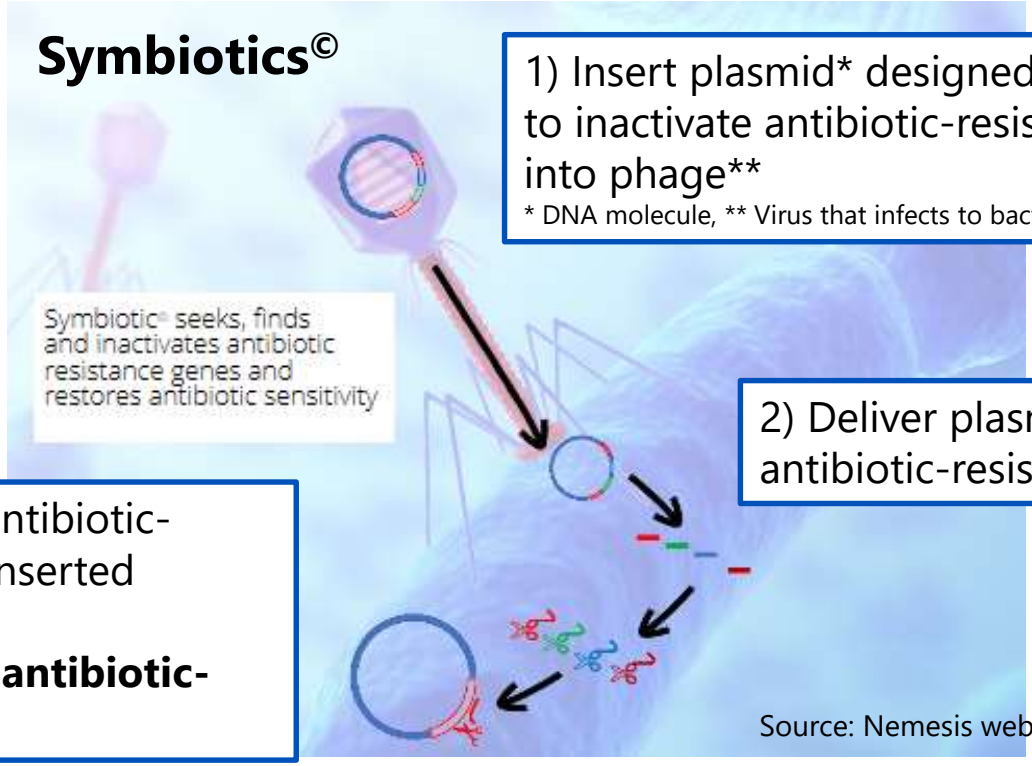
Q&A

Appendix

- Research

Nemesis：Novel Technology for Antimicrobial Resistance (AMR)

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**

Source: Nemesis website, partially modified

Expanding therapeutic options to AMR as a leading company in the infectious disease field

Vast: Novel NO Releasing Compound

Broad antibacterial spectrum of NO at lung

Antibacterial mechanism of NO:

Increasing oxidant stress to the bacterial cell and then show a **broad antibacterial spectrum**

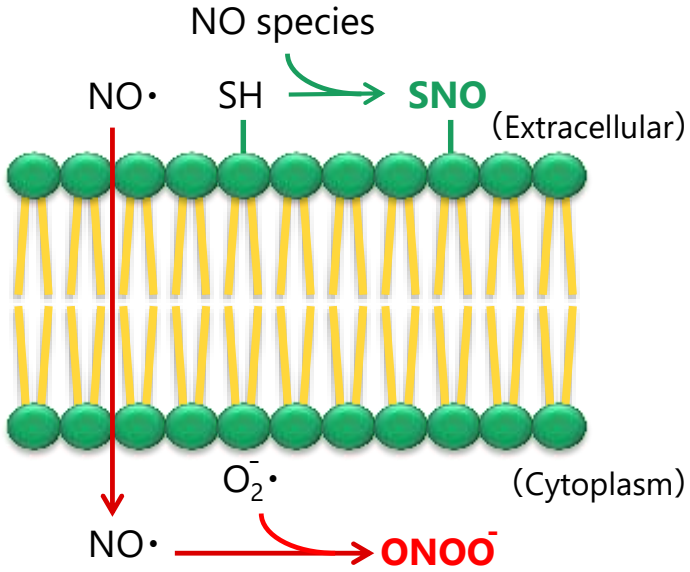
Appropriate formulations are needed for localization and stable exposure of NO at lung

Attractive BIOC51 potential:

Sustainable NO yielding **at lung** by nebulizer

Low risk of generating resistant bacteria in contrast to marketed antibiotics

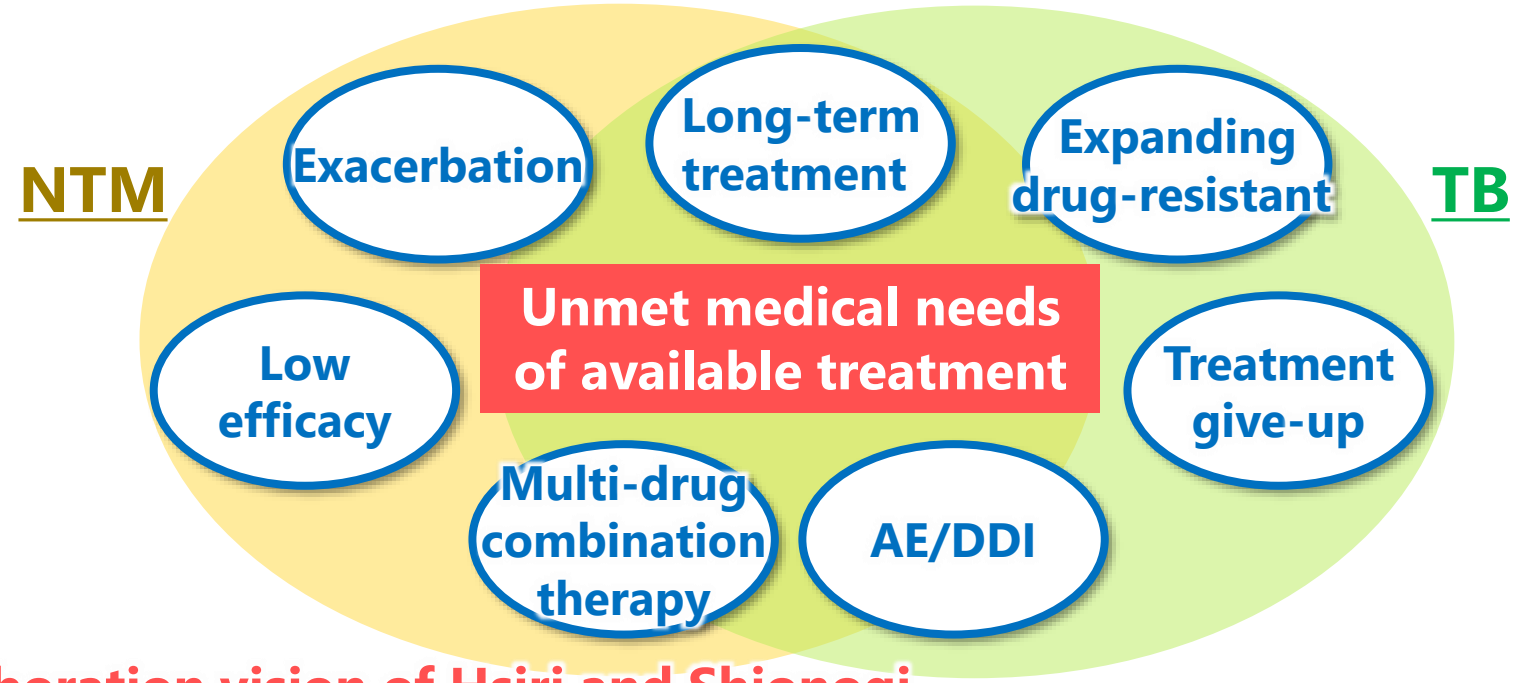
Antibacterial mechanism of NO



Toward a novel useful modality effective against AMR

Hsiri：Novel Drug for Mycobacterial Disease

Collaboration using evaluation assets and promising compounds which show powerful inhibition against TB and NTM



Collaboration vision of Hsiri and Shionogi

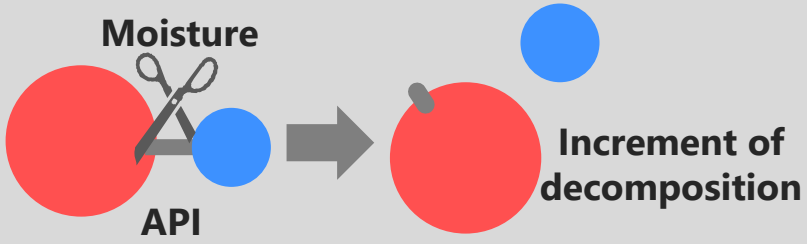
Creating an novel drug with powerful effect by inhibiting common factor between TB and NTM

Appendix

- CMC

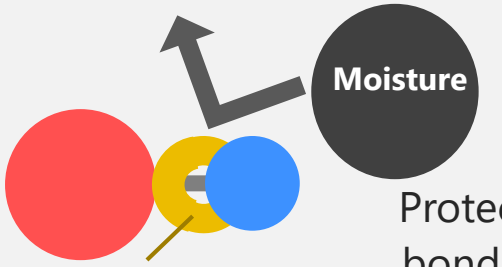
Stabilization Technology for Solid Dosage Form

Without stabilization



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

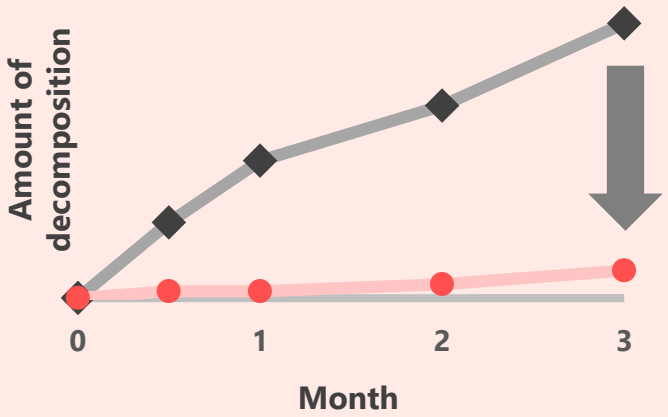
Stabilized formulation



Protecting molecular bonds with stabilizer

Suppressing decomposition

Reduce degradation of API



Applicable across multiple APIs

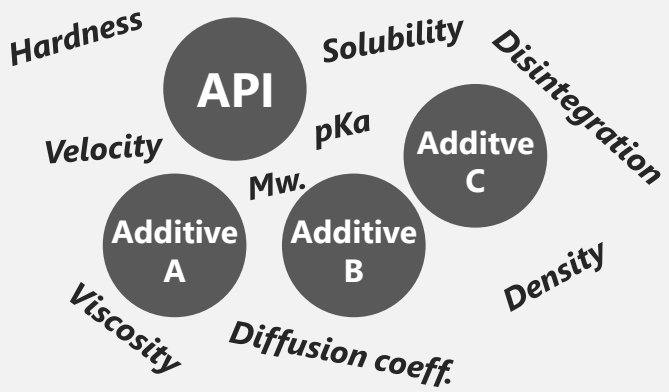
Degradation reduced by **1/10**

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

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

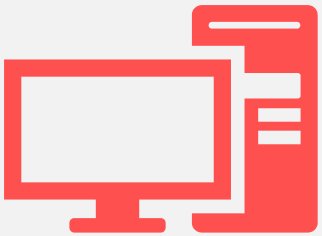
Conventional simulation

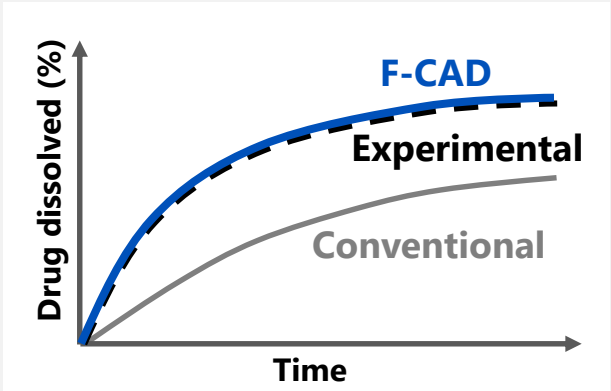
Required extended simulation time due to numerous input factor



F-CAD simulation

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





Rapid and accurate formulation deesign 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

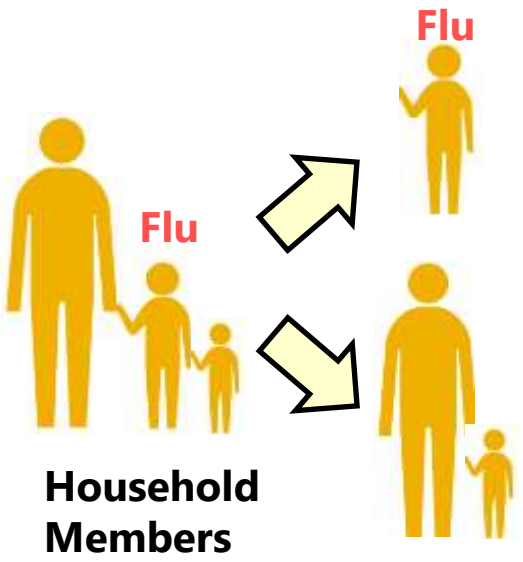
Accelerate and increase probability of successful formulation development while reducing time and cost spent on trial-and-error experimentation

Appendix

- Development

Post Exposure Prophylaxis Study

Objective	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
Subjects	Household members who live with an influenza infected index patient
Study Design	Double-blind, multicenter, randomized, placebo-controlled study
Dosage/administration	Single oral dose (10-80 mg)
# enrollment / Region	750／Japan



Index Patients → Standard of Care (Anti-influenza drug)

Subject

Household Member (s) → 1:1

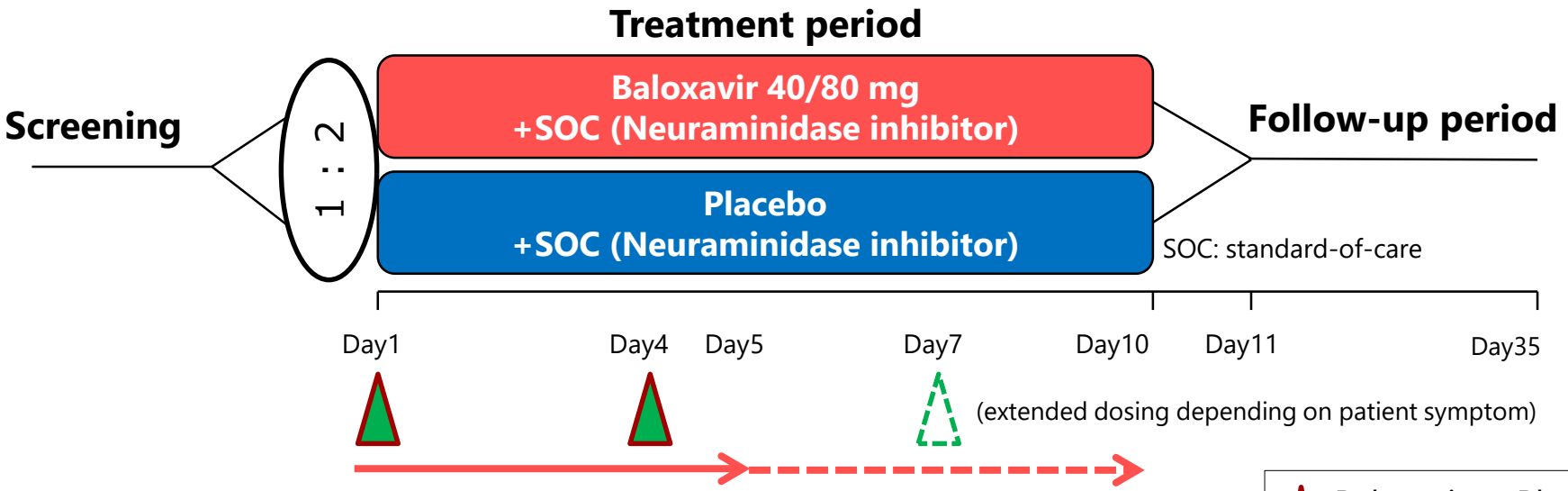
- **baloxavir** → observation : 10 days
- **placebo** → observation : 10 days

750 subjects recruitment was completed.

Primary endpoint：Incidence of influenza infected subjects

Seriously-ill Hospitalized Study

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

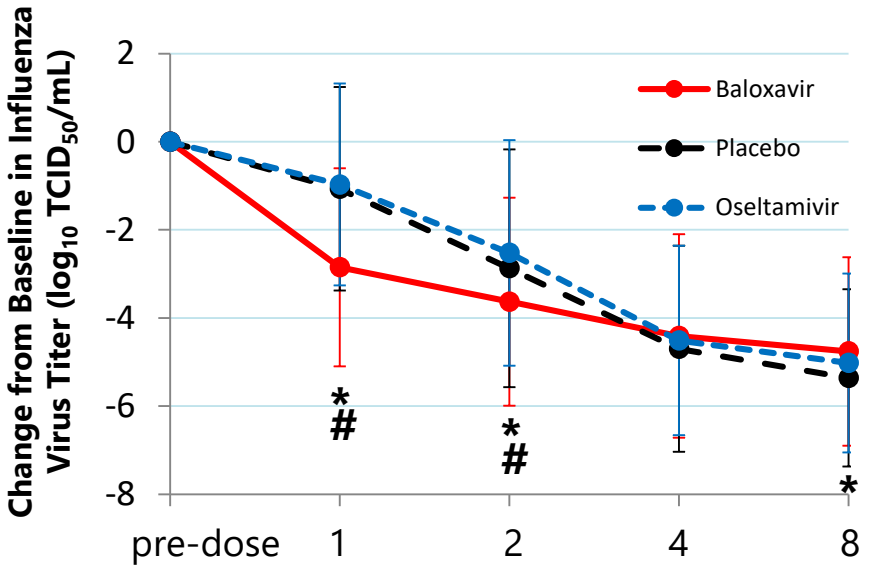


Sponsor：F. Hoffmann-La Roche Ltd

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

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

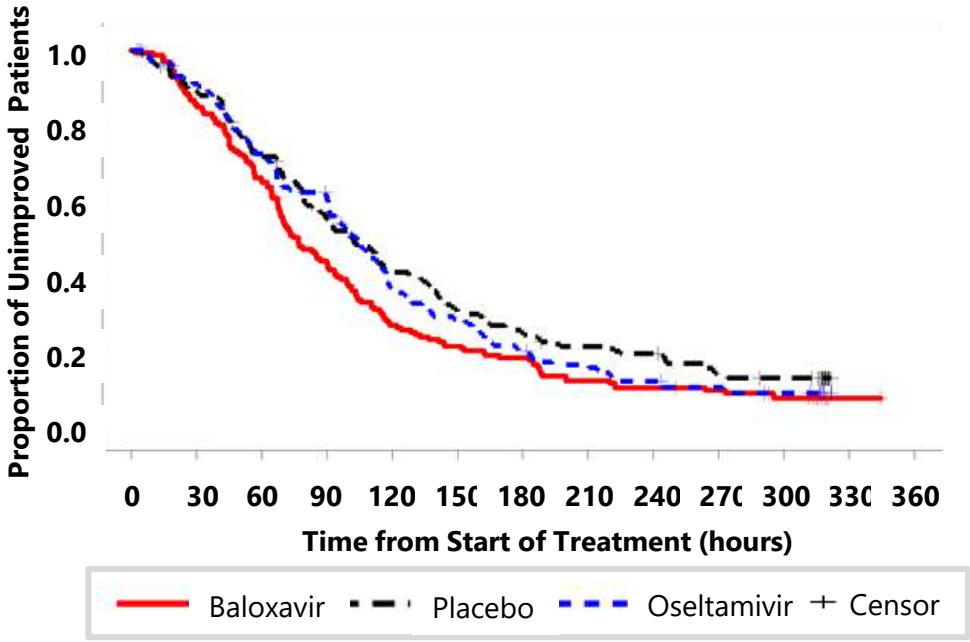
Mean in Virus Titer



Baloxavir (n)	153	150	148	145	145
Placebo (n)	159	154	150	145	145
Oseltamivir (n)	139	133	131	126	123

*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

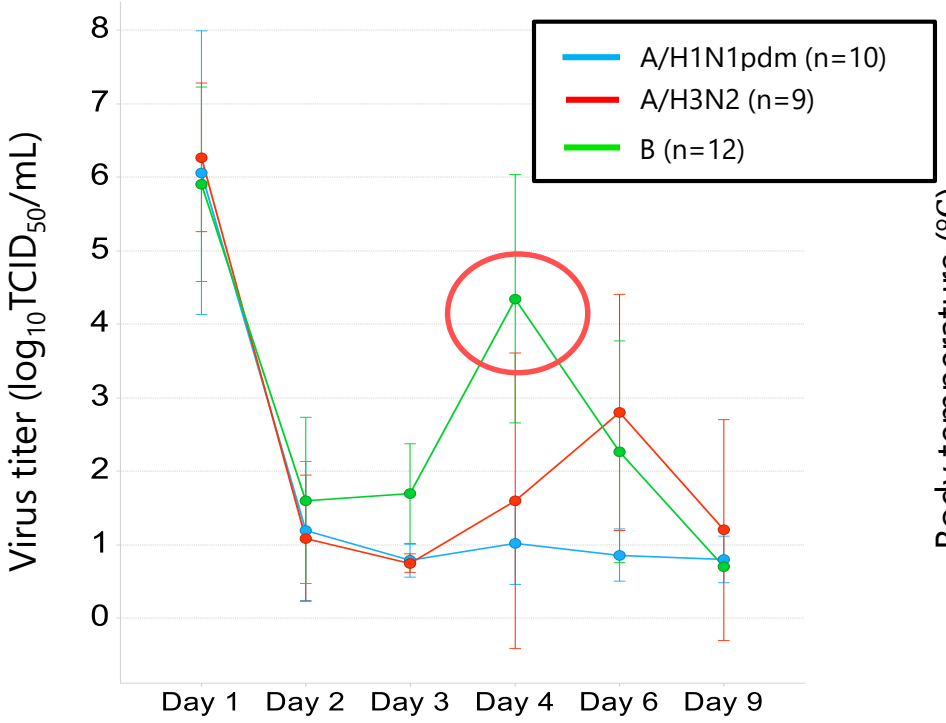


	Baloxavir	Placebo	Oseltamivir
n	166	167	148
Median	**74.6*#**	**100.6**	**101.6**

Unit of Median: hours,
*p<0.05 vs placebo, #p<0.05 vs Oseltamivir

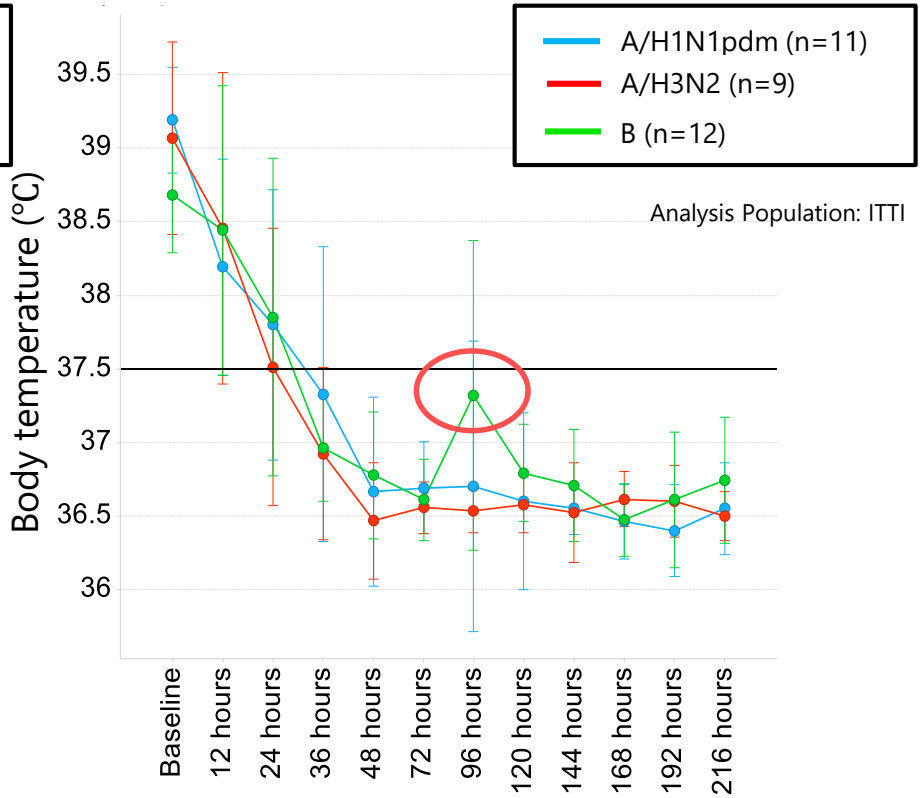
Pediatric (Granule) Study: Change of Viral Titer and Body Temperature in Patients ≤20 kg by Virus Type/Subtype

Mean in Virus Titer by Virus Type/Subtype



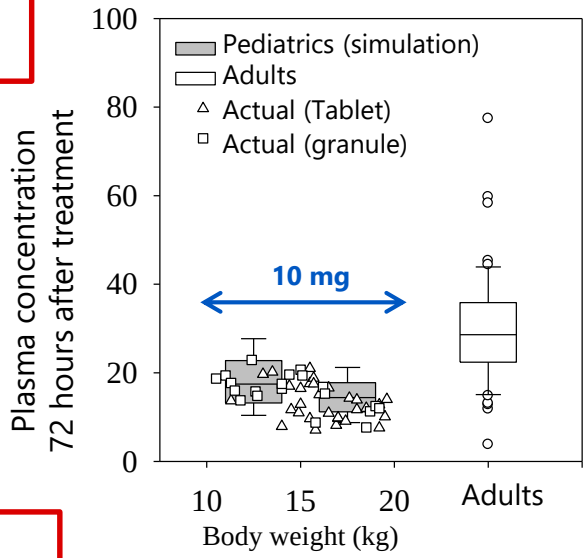
Analysis Population: ITTI and Subset of patients who were positive for influenza virus titer at baseline

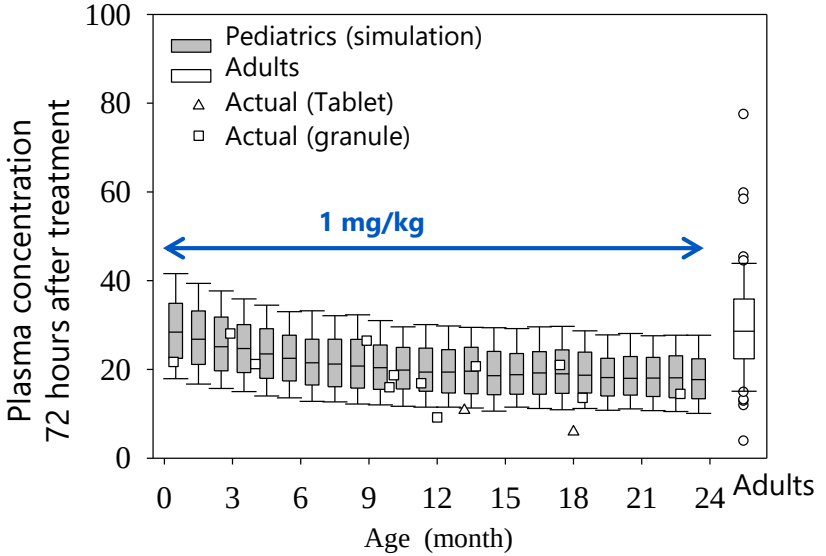
Mean Body Temperature by Virus Type/Subtype



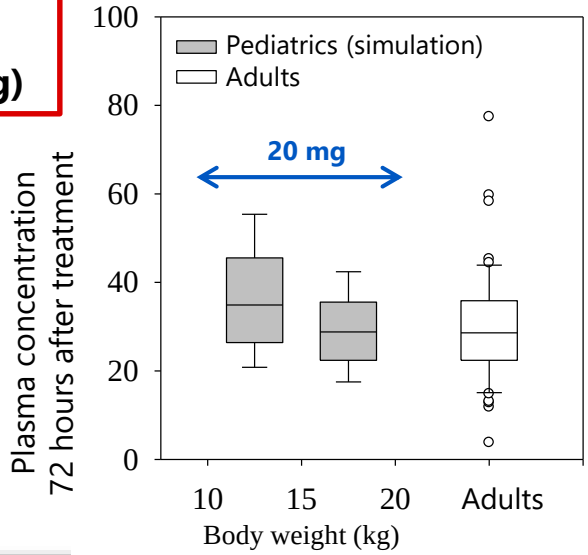
Dosage and Plasma Concentration 72 Hours After Treatment in Pediatric Patients Whose Body Weight Less Than 20 kg

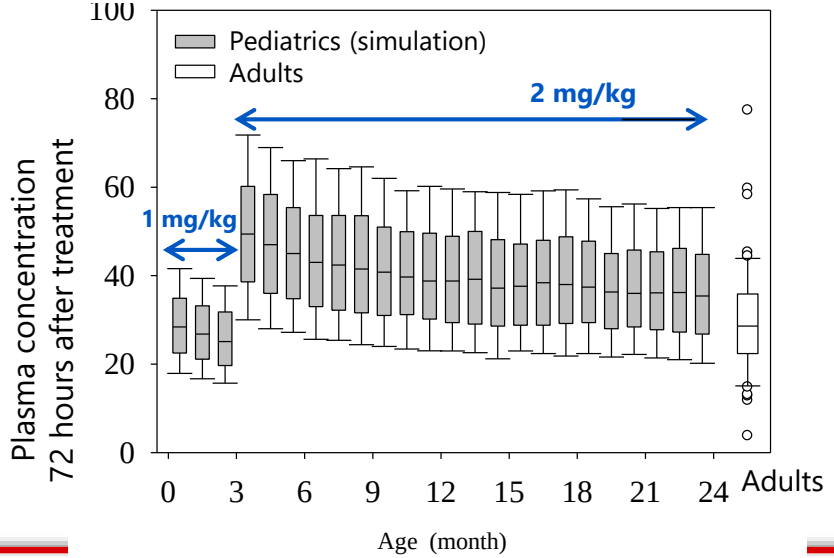
10kg≤BW<20kg : 10mg
BW<10kg : 1mg/kg

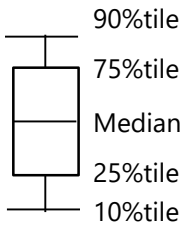




10kg≤BW<20kg : 20mg
BW<10kg : 2mg/kg
(<3months old: 1mg/kg)



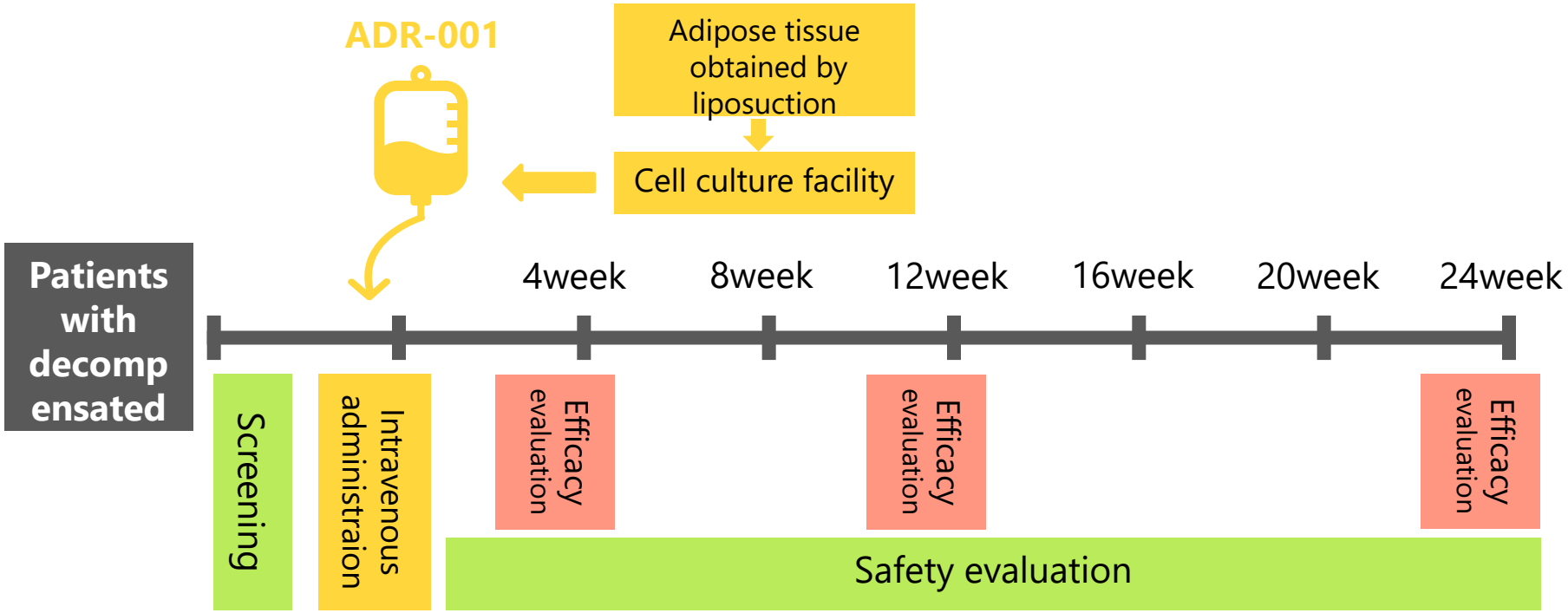




Plasma concentration 72 hours after treatment in pediatric patients at the high dose is equivalent with that in adults

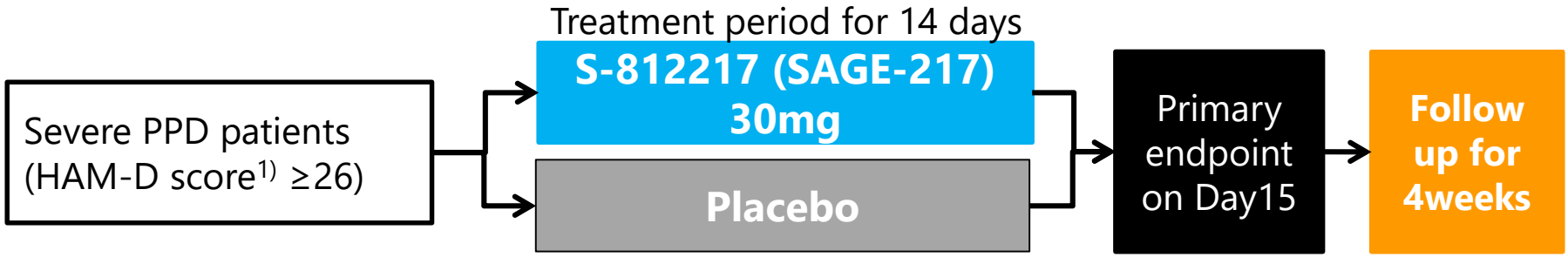
ADR-001: Phase I / II study

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



S-812217: PPD Ph3 ROBIN study

Sponsored by Sage
Study period: Dec 2016 to Dec 2018



- 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.

Efficacy		Treatment period (2 weeks)		Follow up (4 weeks)
		Day 3 (first observation)	Day 15(treatment completion)	Follow up completion
Reduction in HAM-D total score	Placebo	-9.8	-13.6	-15.1
	SAGE-217	-12.5 (p=0.0255)	-17.8 (p=0.0029)	-19.2 (p=0.0027)
Remission rate (HAM-D ≤7, %)	Placebo	-	23%	30%
	SAGE-217	-	45% (p=0.0122)	53% (p=0.0102)

- 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

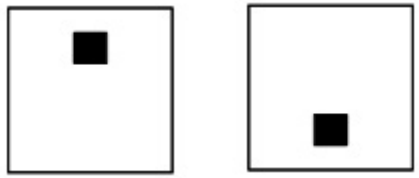
Primary Endpoint in the AKL-T01 Pivotal Study

Summary of TOVA

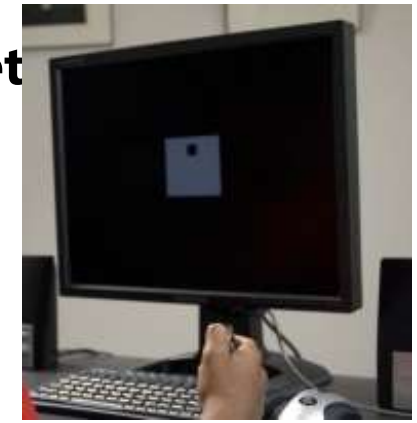
T.O.V.A.® (Test of Variables of Attention)

- **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**

Target **Non-Target**



Respond only to the target.



TOVA is one of the three objective Continuous Performance Test (CPT) approved by FDA (2017) for the monitoring of inattention and inhibitory control .

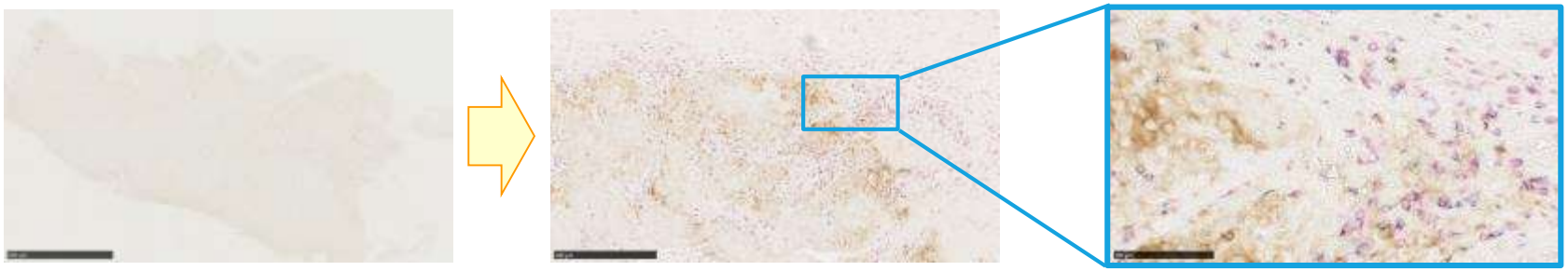
T.O.V.A. Professional Manual. Los Alamitos, CA. The TOVA Company, 2018.

S-588410

- 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

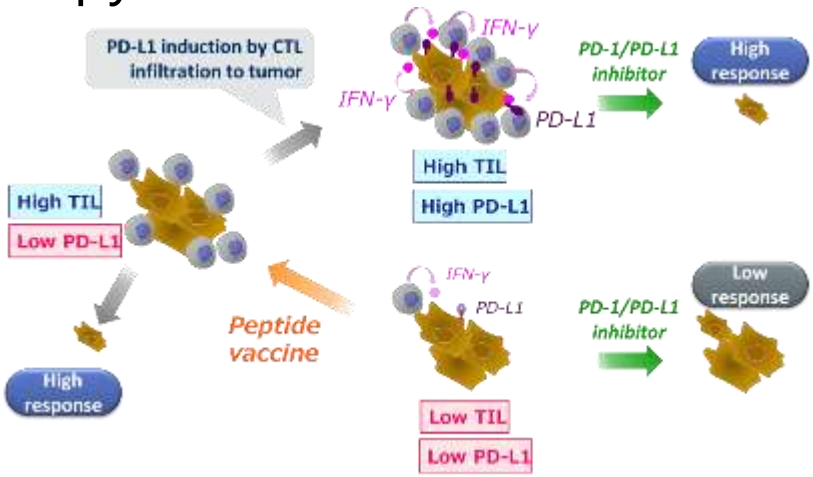
Red: CD8
Brown: PD-L1
Blue: GranzymeB

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



TIL: Tumor infiltrating lymphocyte
CPV: Cancer Peptide Vaccine

ICI: Immune Checkpoint Inhibitor
Referred from "Science 3 April 348; 56-61 (2015)"

Appendix

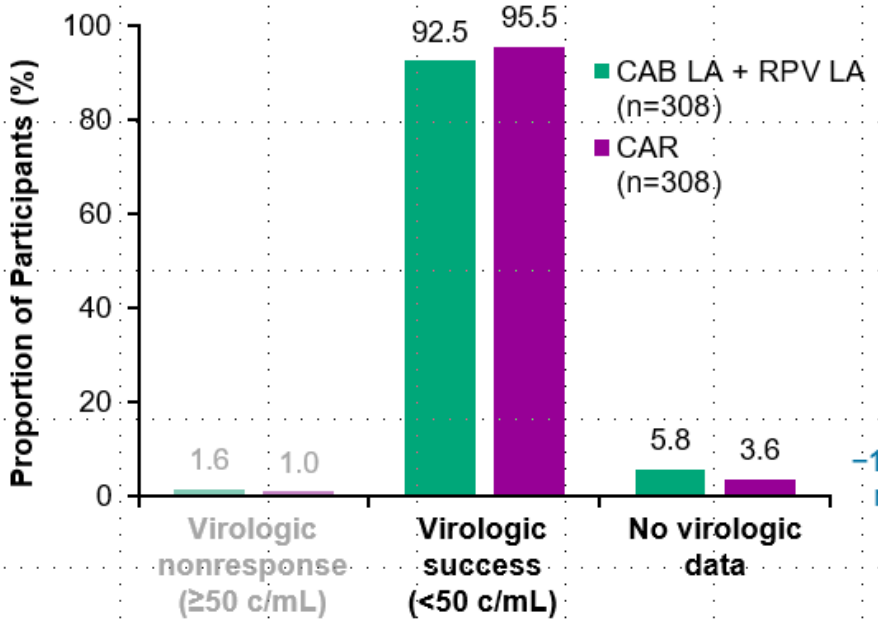
- Others

ATLAS study: Viral Suppression

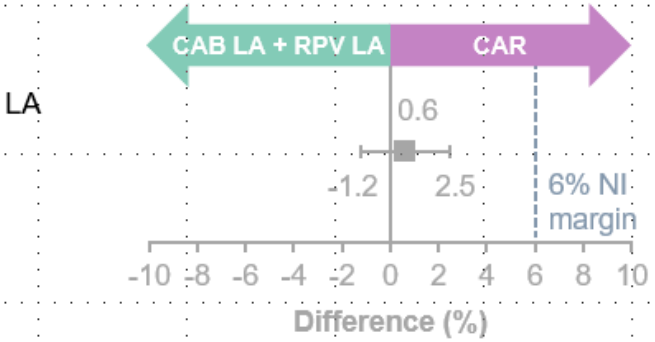
Source: CROI, Mar. 7, 2019

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

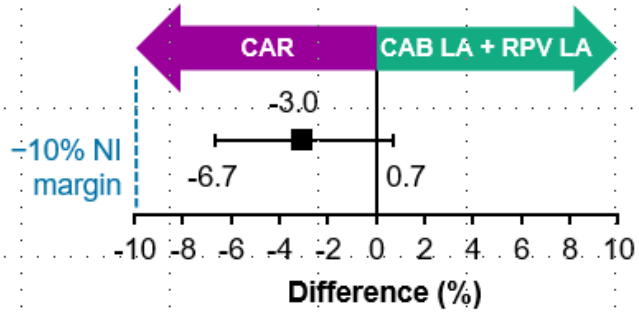
Virologic Outcomes



Adjusted Treatment Difference (95% CI)*



Primary endpoint:
LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48



Key secondary endpoint:
LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

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.

Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475.

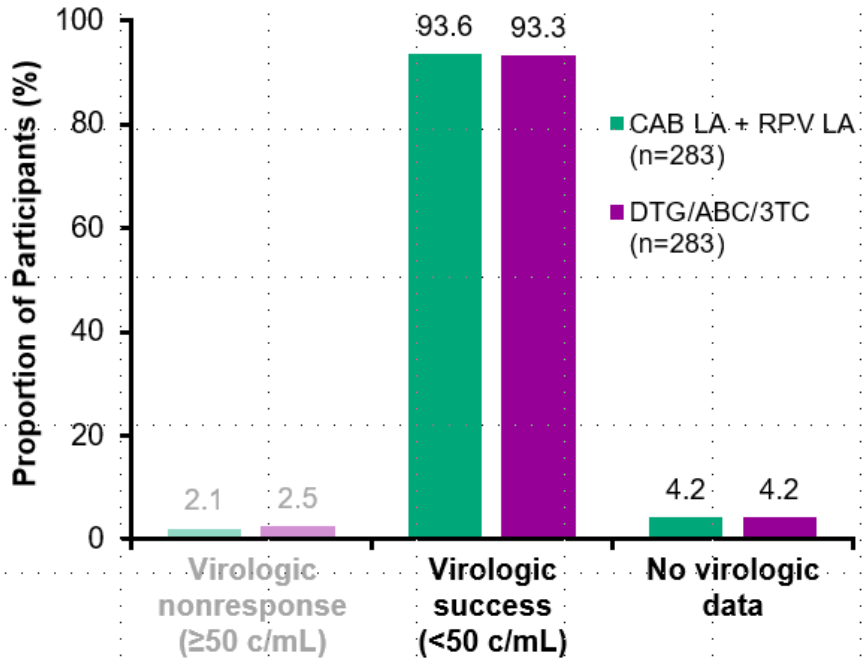
Conference on Retroviruses and Opportunistic Infections; March 4–7, 2019; Seattle, WA

FLAIR study: Viral Suppression

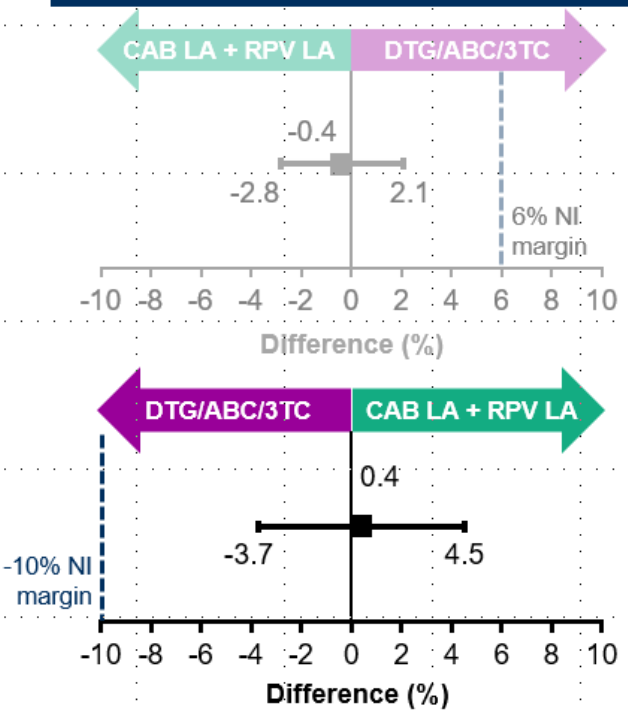
Source: CROI, Mar. 7, 2019

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

Virologic Outcomes



Adjusted Treatment Difference (95% CI)*



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).

Orkin C, et al. CROI 2019; Seattle, WA. Abstract 3947.

Conference on Retroviruses and Opportunistic Infections; March 4–7, 2019; Seattle, WA

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