

Research and Development at Shionogi

Be a Game Changer

March 19, 2020

Shionogi & Co., Ltd.

SHIONOGI

Agenda

1. **Introduction**
   - **Isao Teshirogi**, Ph.D., President and CEO
2. **Research**
   - **Ryuichi Kiyama**, Ph.D., Corporate Officer, Senior Vice President, Pharmaceutical Research Division
3. **Development**
   - **Toshinobu Iwasaki**, Ph.D., Senior Executive Officer, Senior Vice President, Global Development Division
4. **CMC**
   - **Yasuyoshi Isou**, Ph.D., Corporate Officer, Senior Vice President, CMC R&D Division
5. **Summary**
   - **Isao Teshirogi**, Ph.D., President and CEO
6. **Q&A**

1. Introduction
- Research and Development in SGS2020
~ Overview ~ -

Isao Teshirogi, Ph.D., President and CEO

Cited from presentation material of FY2013 R&D, partially modified

Selection of Therapeutic Area in SGS2020

Core Therapeutic Areas: Capitalize on our strengths

Infectious Diseases

- Expand anti-HIV drug discovery platform into other anti-viral discovery areas
- Accelerate research and development for multi-drug-resistant bacteria
- Pursue drug discovery for emerging and re-emerging infectious disease

Pain/Neuropathy

- Strengthen R&D for treatment of pain
- Enter neurology/psychiatric areas, starting with Alzheimer's disease and ADHD
- Pursue discovery of neuro-regeneration drugs that may improve synapse and neural function

Innovative Frontier Medicines: Establish our next core therapeutic areas

Obesity/Geriatric Metabolic Disease

- Progress R&D for anti-obesity drugs
- Pursue research for complicated /refractory/geriatric condition

Oncology/Immunological Disease

- Progress cancer peptide vaccines
- Pursue research into novel immuno-modulating therapies

- Make the most of our know-how and assets in our areas of strength and evolve into leadership positions
- Leverage modalities and alliances to cultivate new areas that contribute to medium- to long-term growth

Cited from presentation material of Updates to SGS2020

Growth Strategy for 2020

Grow sustainably as a drug discovery-based pharmaceutical company contributing to a more vigorous society through improved healthcare

Region to grow	Keys to growth
Japan/US **Development in EU/Asia**	**Addressing society's needs**
Infectious disease **Pain/CNS**	**Balance of innovation and health economic efficiency**

Cited from presentation material of Updates to SGS2020

Pursuing More Efficient R&D with Small Molecule Drug Discovery

SONG for you!

Contribute throughout the healthcare value chain by leveraging our capabilities in small molecule drug discovery, creating novel drugs whose innovation brings both health and economic benefits

Open innovation

- Identify novel research concepts

Drug discovery engine

- New SAR* platforms
- Expand platform to include peptides

Development design

- Effective and efficient drug pre-registration and post-marketing product development

Biomarker R&D

pursuing synergies with our pipeline

Utilization of big data

* Structure-Activity Relationship

R&D vision and KPI for SGS2020

R&D vision

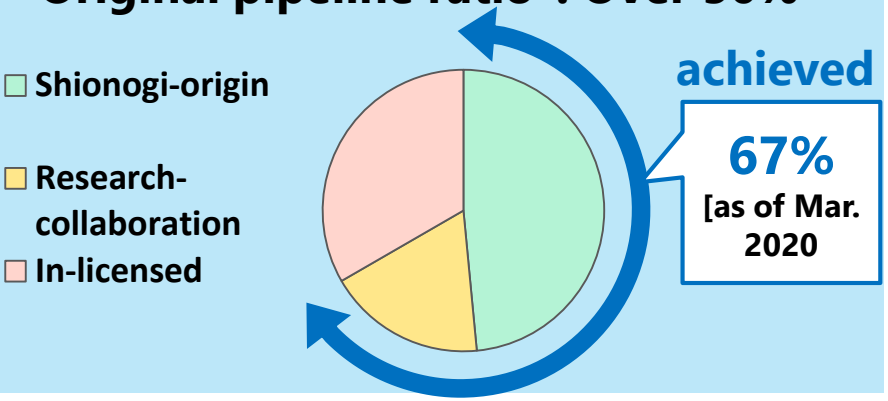
Research: Innovation in drug discovery to meet societal needs

CMC: Research and Development of original CMC technology

Development: Advance reliability and innovation together

KPI of Efficiency:

Original pipeline ratio*: Over 50%





* Proprietary origin compounds in the development pipeline（Includes development candidates and results from joint research with partners）

Cited from presentation material of FY2018 Financial Results

Strategic Investment in FY2018

Obtained pipeline and new technology through strategic investment

Infectious Disease

- Drug candidates for mycobacterial disease (Hsiri)
- Collaborative research on anti-RS virus drug (Ube)
- Collaborative research on prophylaxis and treatment for Malaria (Nagasaki Univ.)
- Nitric Oxide inhaled antimicrobial drug candidates (Vast)
- Technology for Antimicrobial Resistance (Nemesis)

Promote research on the world's top 3 infectious diseases, and other refractory infectious diseases

⇒Establish a global presence in infectious disease area

Pain/CNS

- Anti-depressant candidate, S-812217 (Sage)
- Drug candidate for cognitive and memory deficits, BPN-14770 (Tetra)
- Digital medicine candidate AKL-T01, AKL-T02 (Akili)

Obtained new pipeline assets

⇒Provide new treatment options based on novel mechanisms

Modality

- PDC* technology (PeptiDream)
- Regenerative medicine product candidate, ADR-001 (Rohto)

Obtain new modalities

⇒Meet unmet needs that small molecule drugs cannot solve

Collaborated with 10 new partners for beyond 2020

* Peptide drug conjugates

Enhance Assets and Maximize Value Through Alliances

SONG for you!

	Overcoming drug discovery hurdles, expanding product indications and pipeline	Advancing development, maximizing product value
Infectious diseases	Heiri Therapeutics, 長崎大学 NAGASAKI UNIVERSITY, VAST THERAPEUTICS THE NEW FIGHT, NEMESIS BIOSCIENCE, TB ALLIANCE, GHIT Fund, DNDi Drugs for Neglected Diseases initiative, BIOCRYST, UBE, Nissan Chemical CORPORATION	gsk, ViiV Healthcare, Roche, AMR CENTRE
Pain/CNC	Lilly, Sage Therapeutics, Takeda, AKILI, mundipharma, 帝國製薬株式会社, tetra, KISSEI, 徳島大学, BIKEN	biodelivery SCIENCES, SANDOZ A Novartis Division, ferrer, MOLTENI FARMACEUTICI
Frontier areas	SANOFI, DAINIPPON SUMITOMO PHARMA, AMRYT PHARMA, STALLERGENES GREER, FUNDEP, PHARMAIN	AstraZeneca, DUCHESNAY, MedImmune, ILDONG, EDDING亿腾 PHARM

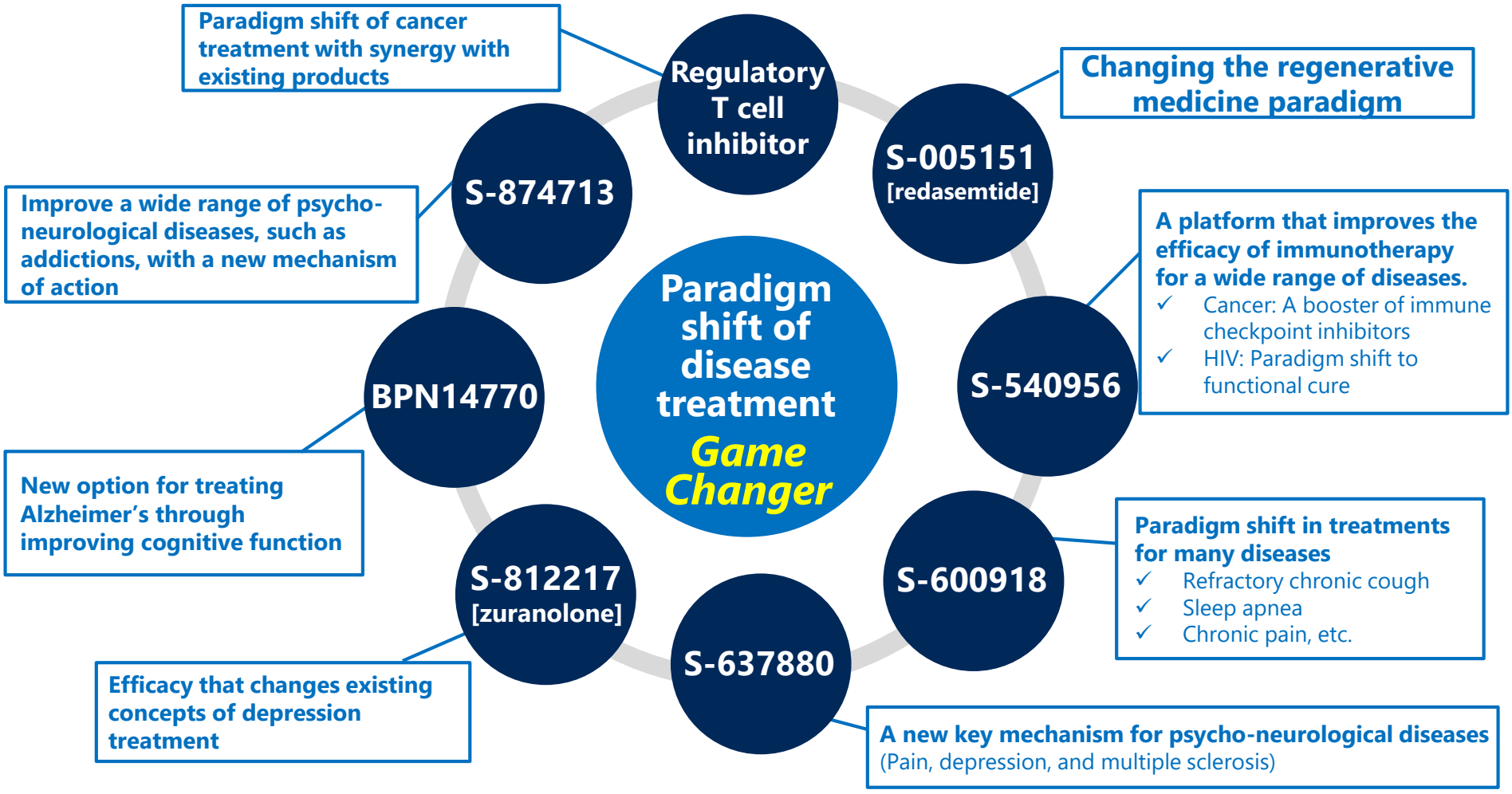
	Acquiring new modalities	Generating operational synergies	IT reform, pursuit of great efficiency
Creation of novel innovation	Middle-sized molecules drug discovery: PeptiDream, PeptiStar, OncoTherapy Science, Inc. Regenerative medicine: StemRIM, NEVER SAY NEVER ロート製薬	Vaccine, diagnosis: UMN, Aillis	M3, Inc., accenture, 大阪大学 OSAKA UNIVERSITY, Croit

Growth Drivers Discovered/Acquired in SGS2020

Disease area	Research	Pre-clinical development	Clinical development	Launched
Infectious diseases three major infections, severe infections, influenza, and emerging/re-merging infectious diseases etc.	Drug discovery program to challenge unmet needs	S-540956 (HIV)	S-648414 (HIV)	Xofluza® (Influenza) cefiderocol* (Multidrug resistant Gram-negative bacterial infection) Juluca® (HIV) Dovato® (HIV)
Psycho-neurological diseases depression, ADHD, dementia, autism, and pain etc.		BPN14770 (Alzheimer's disease etc.) S-874713 (Psycho-neurological diseases) S-109802 [botulinus toxin] (Post-stroke spasticity)	S-812217 [zuranolone] (Depression) S-600918 (refractory chronic cough etc.) S-637880 (Pain etc.) SDT-001 [app.] (ADHD)	naldemedine** (Opioid-induced constipation) Intuniv® (ADHD) Vyvanse® (ADHD)
New growth areas immuno-oncology, guided regeneration, and fibrotic disease etc.		S-723595 (NASH) S-540956 (Cancer) Regulatory T cell inhibitor (Cancer)	S-005151 [Redasemtide] [HMGB1 peptide] (Epidermolysis bullosa, ischemic stroke) S-770108 [Pirfenidone inhalation] (IPF)	Infectious disease Psycho-neurological disease New growth area

Growth Drivers Created from FY2014 to present
ADHD: attention deficit hyperactivity disorder
* brand name in US: Fetroja®, brand name in EU: Fetcroja®, details are shown in p.117
** brand name in Japan and US: Symproic®, brand name in EU: Rizmoic®

The World We Envision Based on Our Core Pipeline



Create products and services for diseases with no satisfactory treatment options, and contribute to solving social issues

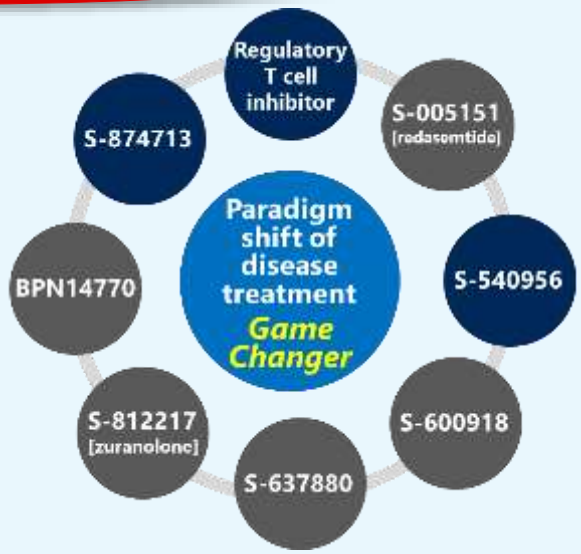
Biggest Management Issue Facing Shionogi

Transpiring around 2028

Overcoming the "HIV Product Patent Cliff" for Sustainable Growth

Research

Ryuichi Kiyama, Ph.D.
Corporate Officer
Senior Vice President
Pharmaceutical Research Division



R&D Vision Beyond 2020

R&D vision

Create innovations beyond the borders of medical/pharmaceutical fields, unbound from existing concepts, showing every consideration for social issues

- **Create solutions that go beyond existing concepts via expanded modalities and flexible disease area strategies**
  - To further enhance our strength in small molecule drug discovery and establish a presence in peptide drug discovery and nucleic acid drug discovery.
  - To further enhance/extend approaches to drug discovery through alliances
  - To pursue what patients really suffer from through flexible disease area strategies
- **Collaboration with a wide range of business partners**
  - To flexibly adapt to changes in external environments through collaboration with other companies
- **Realize high-level business operations**
  - To expand multi-level preparations for the HIV patent cliff with a keen focus on timelines

Establish new platforms combining the strengths of our company with those of our business partners

Therapeutic Area Strategies Beyond 2020

Therapeutic Area Strategies

While focusing on infectious and psycho-neurological diseases as our core fields, we will pursue other therapeutic areas with high social and medical need, while establishing a research management system that enables flexible and clear prioritization.

Infectious diseases

Protecting the world from the threat of infectious diseases as a leader in the area

- ✓ To provide new benefits to HIV/influenza patients
- ✓ To contribute to global health by dealing with the three major infectious diseases and AMR

Psycho-neurological diseases

Paradigm shift in the treatment of psycho-neurological diseases

- ✓ To realize optimal therapy through objective diagnosis/stratification
- ✓ To provide a wide range of treatment options through discovery of innovative drugs with new mechanism of action

New growth areas

Address diseases with substantial unmet needs affecting many patients

- ✓ To aggressively pursue disease areas with great social need, and to reshuffle priorities flexibly and rapidly according to the potential of “drug seeds”

Re-appeared

Growth Drivers Discovered/Acquired in SGS2020

SONG for you!

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ADHD: attention deficit hyperactivity disorder

Research

Therapeutic Area	Project	Indication	Pages
Immuno-oncology	**Regulatory T cell inhibitor**	Cancer	P.18-23
Immuno-oncology	**S-540956** **Nucleic acid adjuvant**	Cancer	P.24-27
Psycho-neurological diseases	**S-874713**	Various psycho-neurological diseases	P.28-32
Infectious diseases	**HIV franchise** **Long-acting/functional cure**	HIV infection	P.33-36
Infectious diseases	**Vaccine for prophylaxis**	Influenza virus infection	P.37, 38
Infectious diseases	**Corona virus infection treatment, diagnosis**	Corona virus infection	P.39-41
-	**Peptide drugs**	-	P.42-46

Regulatory T cell inhibitor, S-540956
Cancer

Status and Challenges of Immuno-Oncology

Market forecast for cancer therapeutics (by category) *

Market

CY2017 $130bn

↓

CY2024 $205bn

Market of ICI and Immunomodulator

CY2017 $21bn

↓

CY2024 $61bn

Status and challenges of ICI treatment

ICI Treatment

- Majority of the market: Anti-PD-1 / PD-L1 antibodies (Opdivo®, Keytruda®, etc.)
- Major treatment: Combination therapy

Challenges

- Ineffective / weak against some cancer types (Colon cancer, pancreatic cancer, prostate cancer, etc.)
- Ineffective for many patientfor ICI treatment (70-90% of targeted patients)

Large unmet medical need
Pursued new therapeutics with significant efficacy in patients that do not respond to existing ICIs

ICI：Immune checkpoint inhibitor

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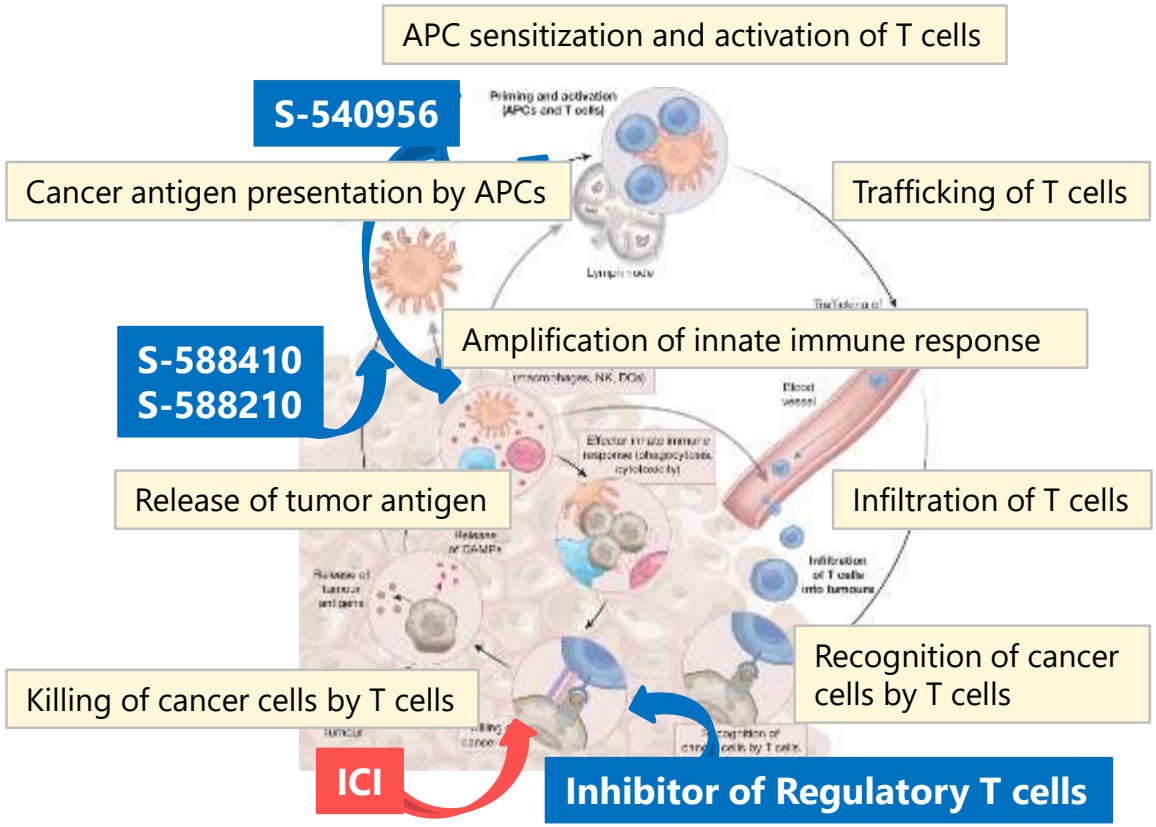
Unique Immuno-Oncology Assets Innovated by SHIONOGI

Diverse modalities with different mechanisms

- **Cancer peptide vaccine*** (S-588410、S-588210)
  - Inducing cancer-specific immune response and exerting cancer cytotoxicity
- **Nucleic acid TLR9 agonist** (S-540956)
  - Strong immune activation enhances cancer immune response
- **Anti-CCR8 antibody** (Regulatory T cell inhibitor)
  - Releasing cancer immunosuppressive mechanisms and exerting strong antitumor effects



Building a cancer platform that enables various treatment approaches

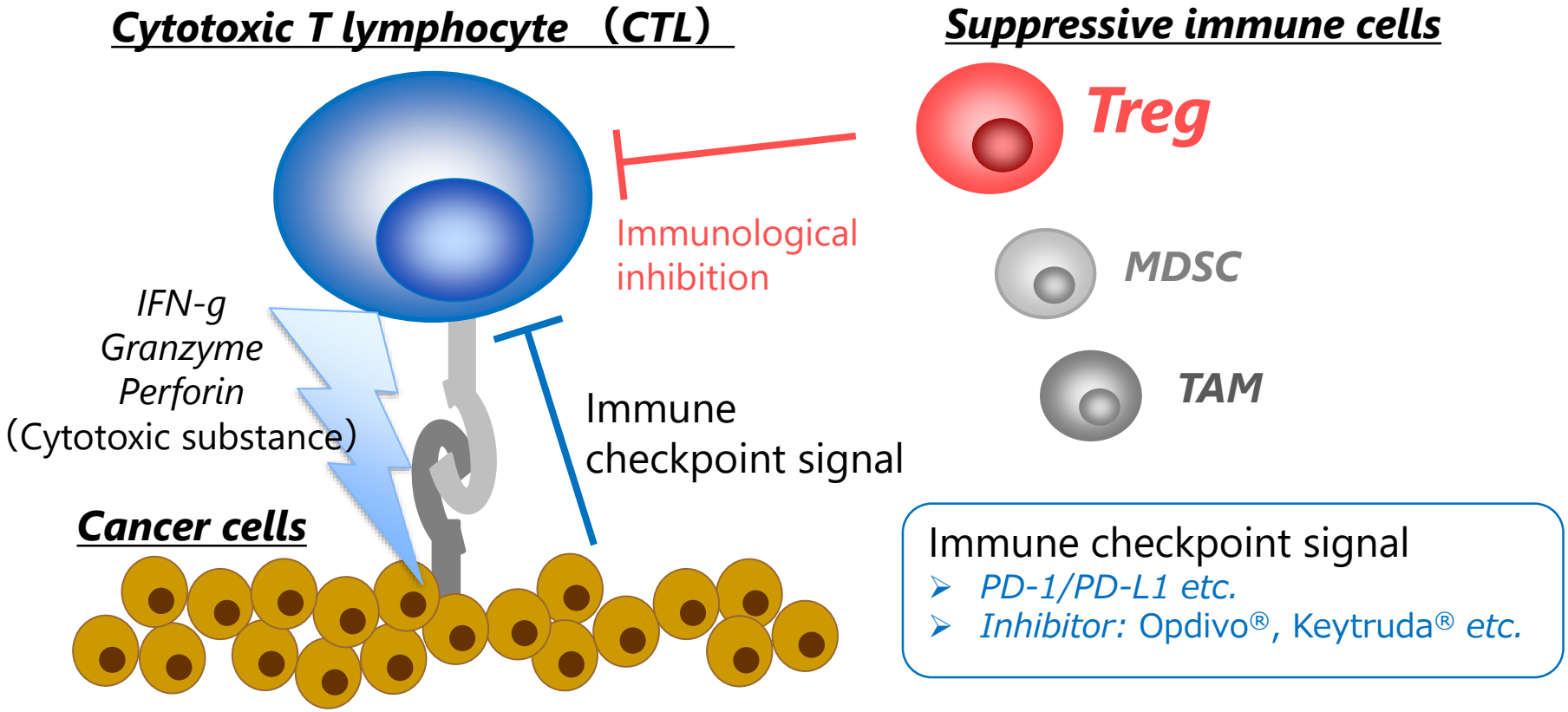
* Cancer peptide vaccine: profiles are shown in p.133-136

APC：Antigen presenting cells ICI：Immune Checkpoint Inhibitor

図：Nature. 2019 Oct;574(7776):45-56 より

Collaboration Research on CoMIT with Osaka University

Tumor immune-related cells in the intra-tumoral microenvironment



Immune checkpoint signal
- *PD-1/PD-L1 etc.*
- *Inhibitor:* Opdivo®, Keytruda® *etc.*

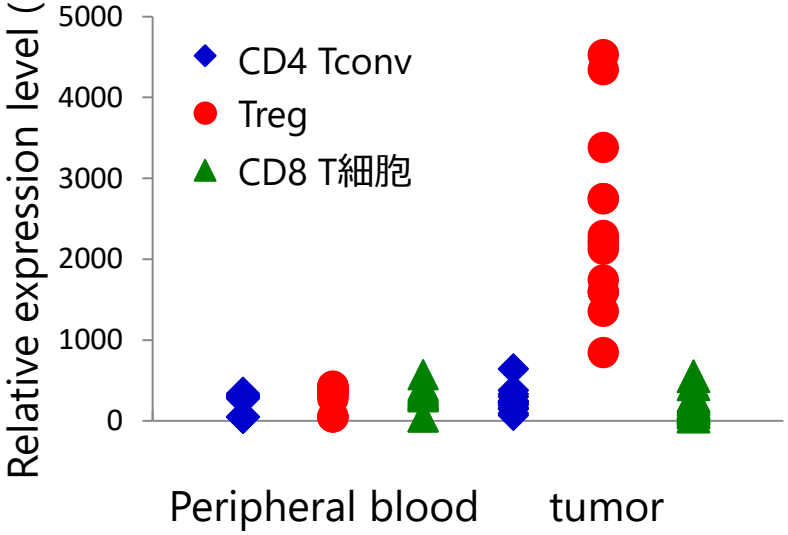
Search for treatments selectively inhibiting Treg in the tumor microenvironment

CoMIT: Center of medical innovation and translational research
MDSC: Myeloid-derived suppressor cells
Treg: Regulatory T cells
TAM: Tumor associated macrophages

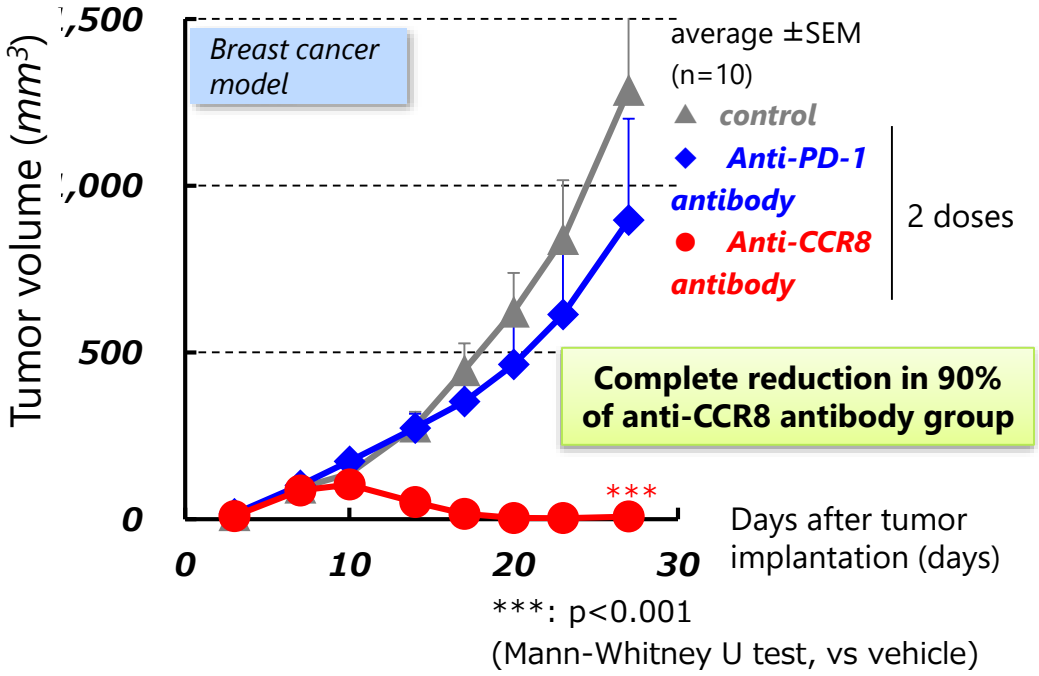
Discovery of Regulatory T-cell Inhibitor

Identification of CCR8, an anti-tumor target selectively overexpressed in tumor Treg

Expression of CCR8 in Treg in human renal carcinoma



Anti-tumor effect of anti-CCR8 antibody (non-clinical)



***: p<0.001
(Mann-Whitney U test, vs vehicle)

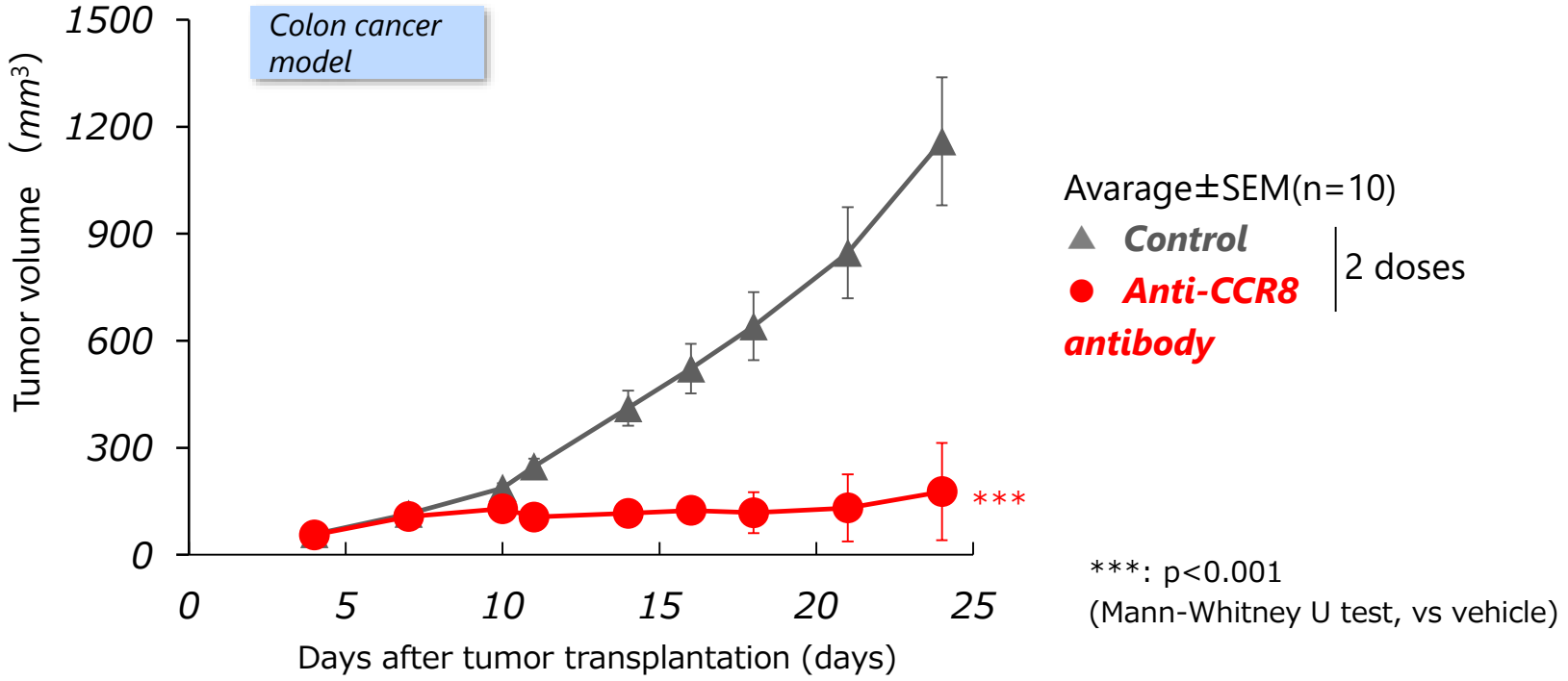
Profile: A drug with the ability to completely cure cancers for which ICI does not work

Treg: Regulatory T cells
CD4 Tconv: CD4 T cells without ICI: Immune checkpoint inhibitor

Discovery of Regulatory T-cell Inhibitor

Creation of humanized development candidate antibody showing the same effect as mouse antibody

Anti-tumor evaluation of development candidate antibody using CCR8 humanized mouse model



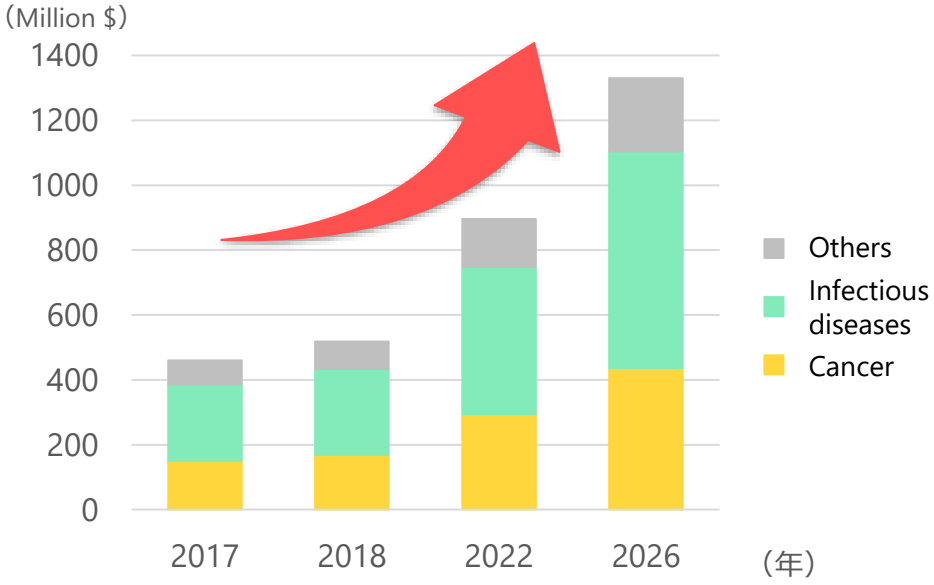
Accelerating research to achieve early clinical entry

Status and Challenges of Vaccine Adjuvants

Market and vaccine adjuvants competitors

Forecast of vaccine adjuvants

Growth markets, infectious diseases and cancer



Major Launched Vaccine Adjuvants and Indications

adjuvant	products（companies）	indications
Alum	Gardasil (MSD) etc.	Cervical cancer
MF59	CELTURA (Novartis)	H1N1 influenza
AS03	Arepanrix H1N1 (GSK)	H1N1 influenza
AS04	Cervarix（GSK）	Cervical cancer
1018-ISS	Heplisav-B（Dynavax）	Hepatitis B

Issues of products on the market

- **Side effects such as inflammation**
- **Weak induction of cellular immunity**

Need for an adjuvant that induces cell-mediated immunity with fewer side effects

* Global Vaccine Adjuvants Market Outlook (2017-2026)

S-540956, Nucleic Acid TLR9 Agonist

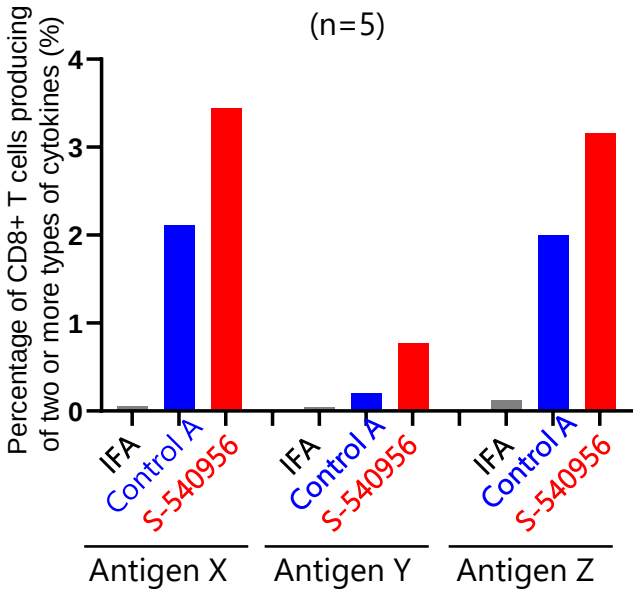
Features of S-540956（non-clinical）

Excellent immune enhancement

Evaluation of functional CTL induction

(Cytokine evaluated: IFNγ/IL-2/TNFα)

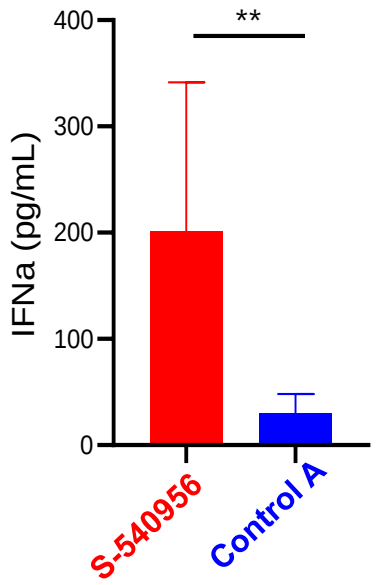
(n=5)



High IFNα induction

In vitro evaluation of human PBMC

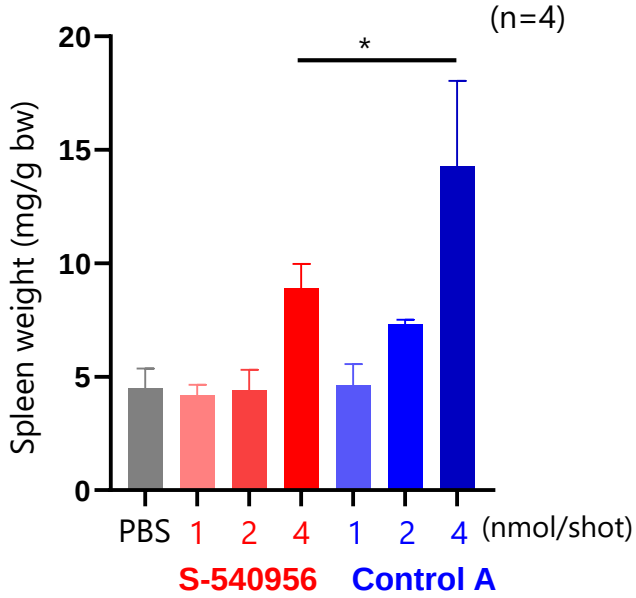
(n=5)



Low safety concerns

Effects on the spleen

(n=4)



*: $p<0.05$
**: $p<0.01$
(Mann-Whitney U test)

Day0, 2, 4: Intramuscular injection
Day7: Mesurement

Leveraging the features of S-540956, we can develop new therapies for oncology and infectious diseases (such as HIV functional cure)

CTL: Cytotoxic T cells　　PBMC：Peripheral blood mononuclear cells
IFA：Incomplete Freund Adjuvant (Montanide)

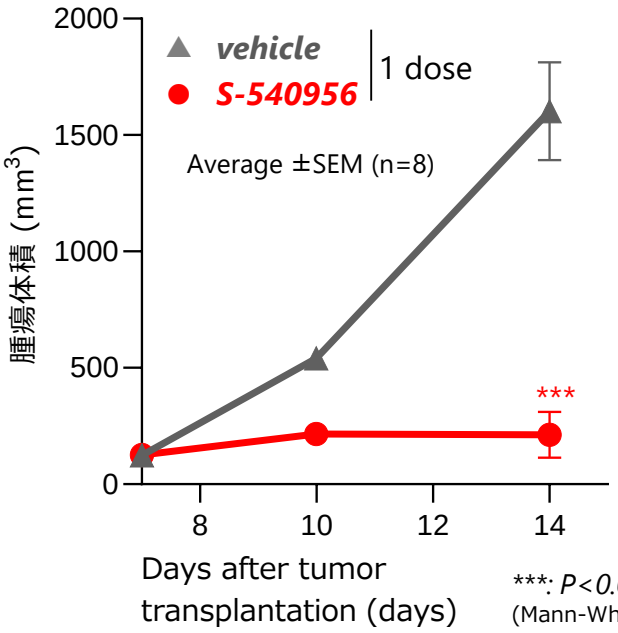
Antitumor Effect of S-540956 (Sole Administration)

Showing efficacy by intratumoral and subcutaneous administration

Lymphoma model

Antitumor effect of intratumoral administration

(Effective at 1/10 dose than subcutaneous administration)

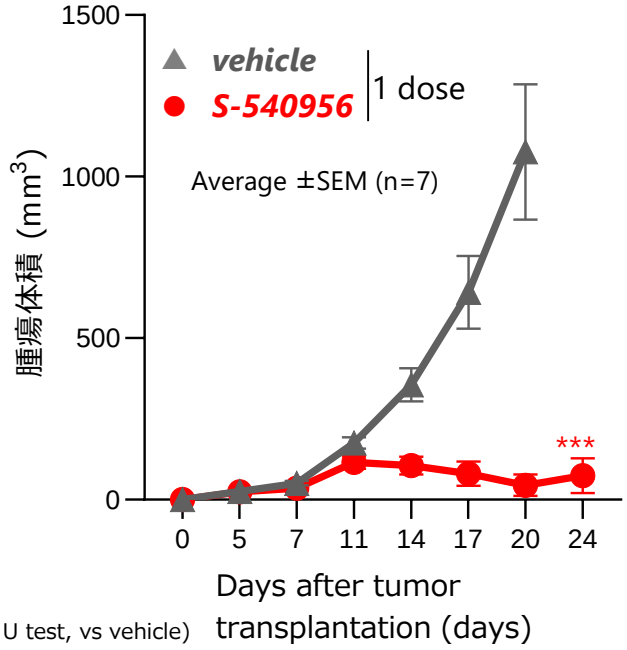


***: P<0.001
(Mann-Whitney U test, vs vehicle)

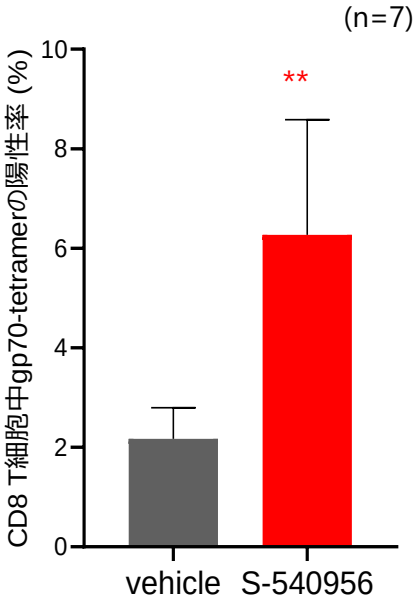
Colon cancer model

Subcutaneous administration distal from the tumor

Antitumor effect



CTL inducibility

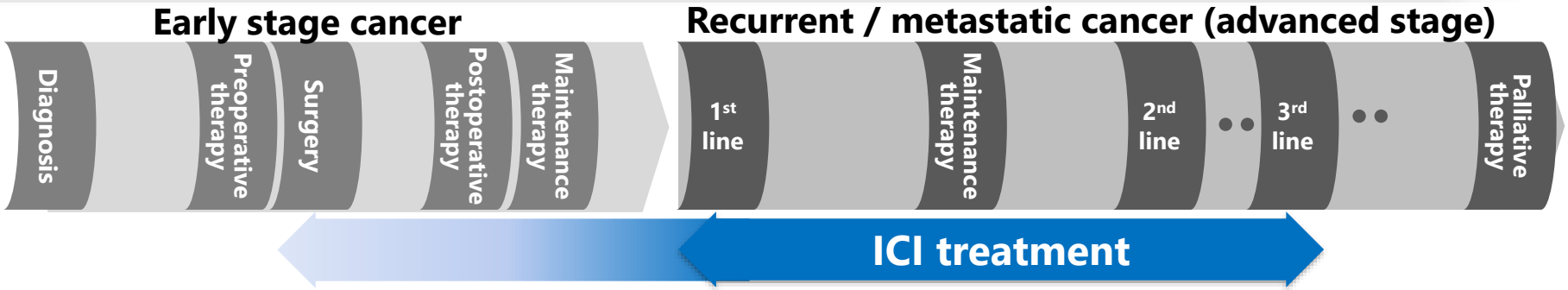


**: P<0.01
(Mann-Whitney U test, vs vehicle)

By immunostimulation, it triggers CTL from cancer-specific antigens and exerts antitumor effect.

CTL: Cytotoxic T cells

Positioning of Immuno-Oncology Assets



Unmet needs： Ineffective / weak cancer types, ineffective patients

Immuno-oncology assets that can be complemented and concomitant with existing ICI treatment for each patient segments

- Peptide vaccine
- Peptide vaccine ＋ICI
- S-540956 ＋ICI
- Regulatory T cell inhibitor
- Reguatory T cell inhibitor ＋ICI
- Peptide vaccine＋ S-540956
- Peptide vaccine＋ S-540956 ＋ICI
- Peptide vaccine＋ S-540956＋Regulatory T cell inhibitor ＋ICI

Providing treatment, or potentially a complete cure, for patients who have relapsed or are refractory after treatment with existing ICIs, and for cancer types not indicated for ICI

ICI: Immune checkpoint inhibitor

S-874713
Psycho-Neurological Diseases

S-874713, Dopamine D3 Receptor Inhibitor

Potential to ameliorate a wide range of mental illness symptoms based on the mechanism

Features of S-874713

- Selective inhibitor of D3 receptor
- Activates of prefrontal cortex and nucleus accumbens through D3 receptor inhibition
- Avoids side effects associated with D2 receptor inhibition

Disease	ADHD	Addiction	LID	Depression	Autism
Estimated pathological mechanism	Hypoactivity in the prefrontal cortex and nucleus accumbens	Elevated expression of D3 receptors	Elevated expression of D3 receptors	Prefrontal cortex hypoactivity	Hypoactivity in the nucleus accumbens
Problems that can be resolved	Inattention, hyperactivity, and impulsivity	Dependence on opioids and alcohol	Dyskinesia associated with Parkinson's disease treatment	Decreased motivation and loss of interest	Difficulties in social communication

Non-clinical efficacy is being confirmed
Focused on accelerating progression

ADHD: Attention deficit hyperactivity disorder LID: Levodopa-induced dyskinesia

Current Status and Challenges of ADHD Treatment

Patient number and market size in Japan, US and Europe*

Patients	Market
2014年 26.54 million	2014年 $ 6.1bn
↓	↓
2024年 34.13 million	2024年 $ 13.9bn

Feature and challenges of ADHD treatment

Non-central stimulants
（Intuniv®, Strattera®, etc.）

- Less concern for addiction and side effects, or overdosage
- Moderate effect compared to central nervous system stimulants

Central stimulants
（Vyvanse®, Concerta®, etc.）

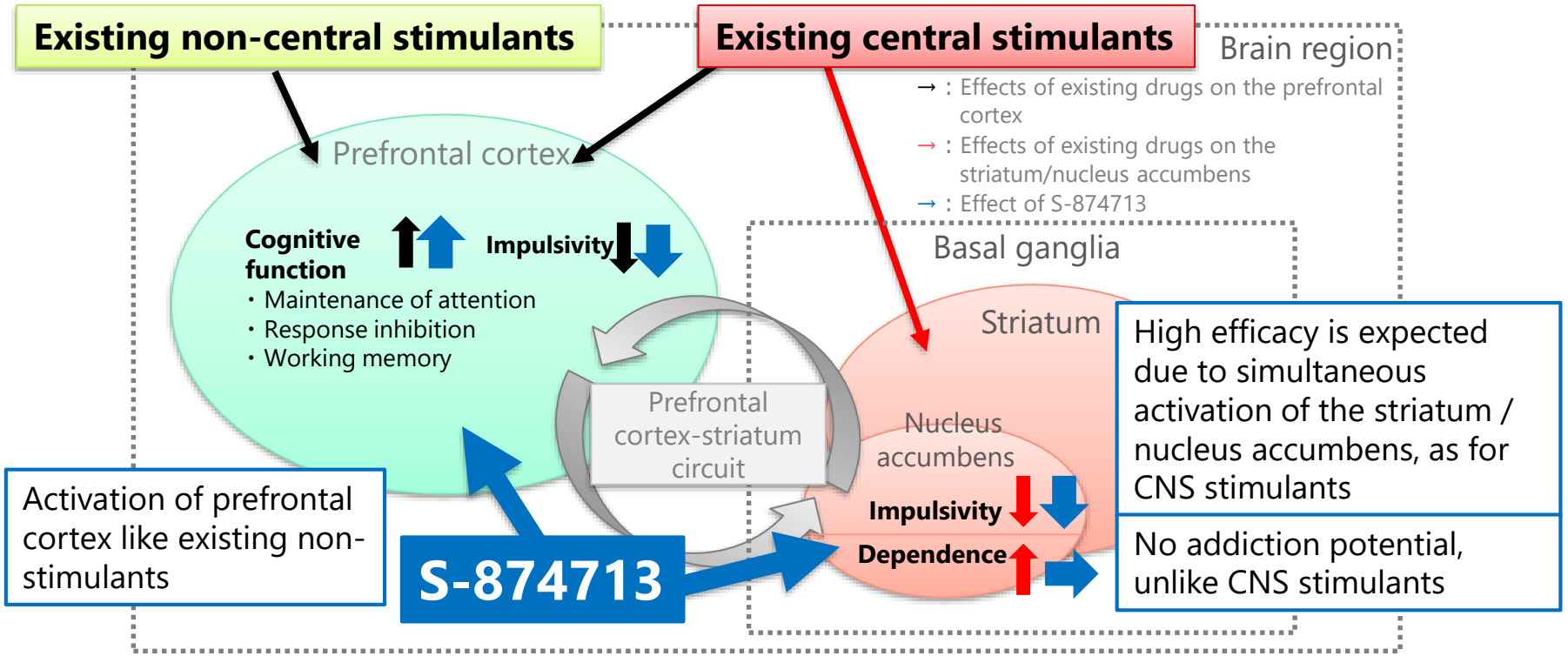
- Highly effective for hyperactivity / impulsivity
- Addiction and safety concerns

Improvement of balance between efficacy and side effects is expected

* GlobalData 2016

Mode of Action of S-874713

Mode of action of S-874713 and existing drugs for ADHD

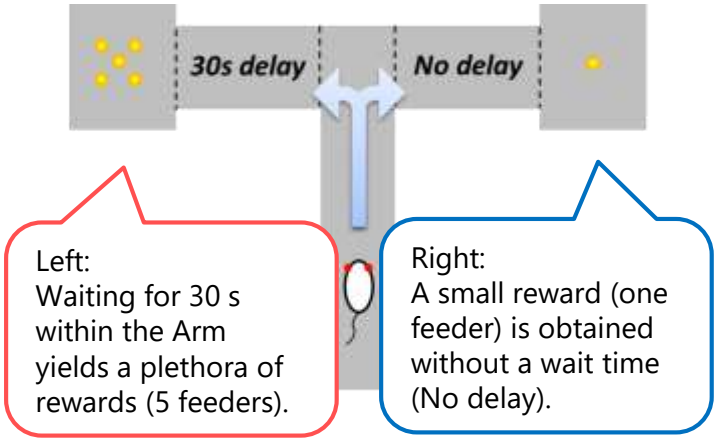


S-874713 shows a strong efficacy by acting on both the prefrontal cortex as well as the striatum / nucleus accumbens, while avoiding addiction.

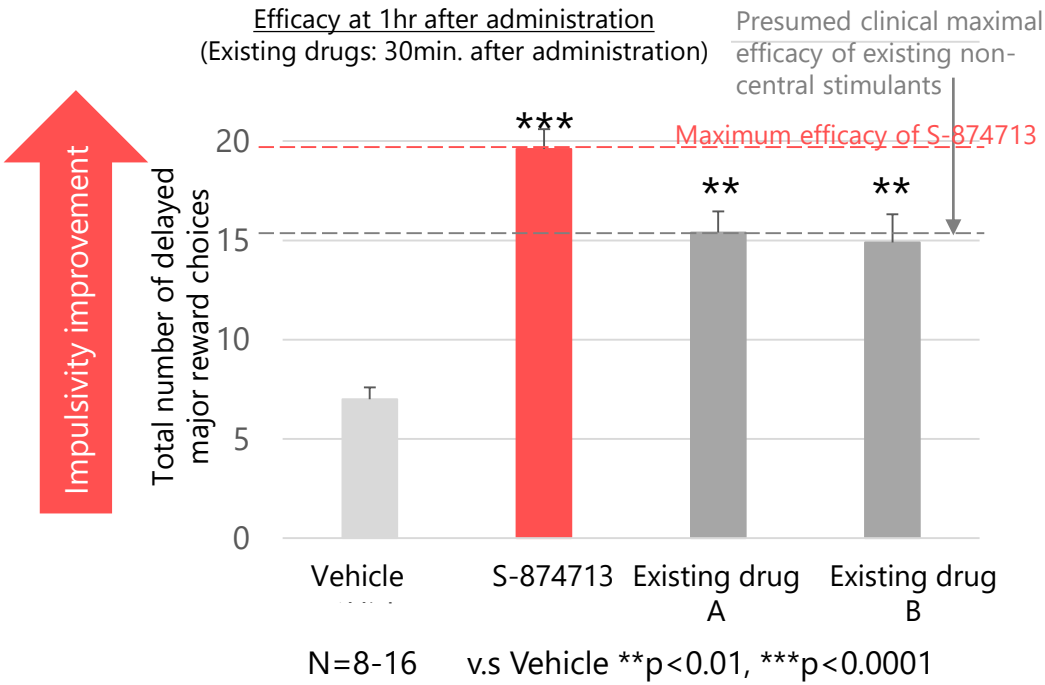
Pharmacological Action of S-874713

Potential for greater efficacy than existing non-stimulants

Back-translational evaluation system for abnormalities (impulsivity) in reward system in ADHD patients



Impulsiveness evaluation (non-clinical)



Low addiction risk and increased effects on attention / cognition
Aiming to be the No. 1 company in the ADHD area by offering a full range of effective therapies

Progress in Infectious Disease Area

R&D Vision for Addressing Infectious Diseases

3 major infectious diseases | **Influenza** | **Refractory infections**

Creation of anti-infective drugs to address residual unmet needs



Providing new treatment options for refractory infections, including three major infections and AMR

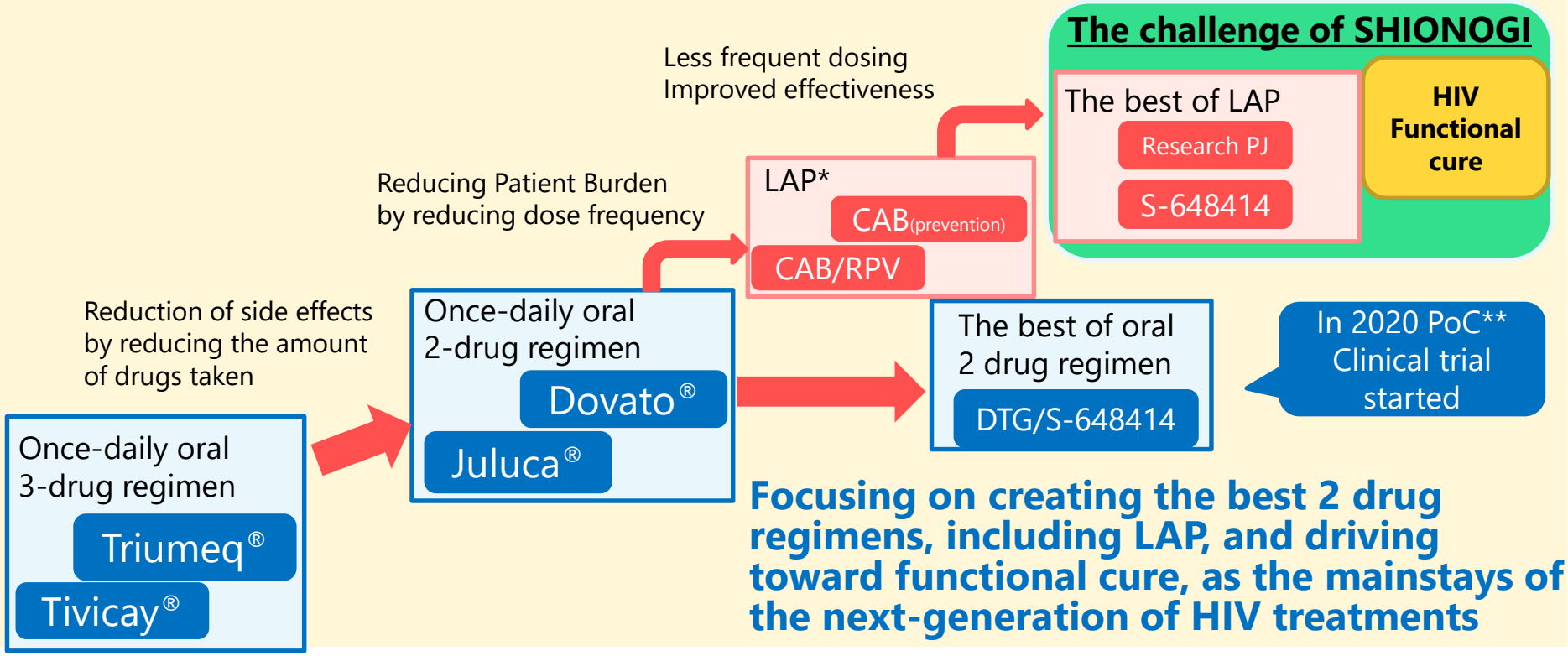
Achieving Total Care for Infectious Diseases in response to social and unmet medical needs

A new approach to infectious disease treatment using therapeutic vaccines

Creation of a vaccine with superior preventative efficacy

Challenges for Developing Anti-HIV Drugs

Anti-HIV drug market will be changed by the availability of generics for DTG in 2028 or after. Improving on these options requires reducing the overall burden and stress of HIV treatment on patients.

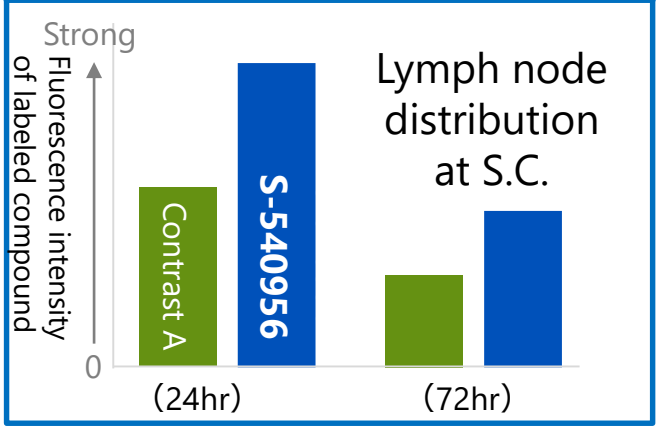


* LAP: Long acting parenteral administration
CAB: cabotegravir, RPV: rilpivirine, DTG: dolutegravir

Efforts to Discover HIV Functional Cure

The ultimate vision for functional cure discovery as a company that discovers HIV therapeutics

Lymph node transfer of S-540956



"Kick & Kill"

Activate intracellular latent HIV viruses, then eliminate them using drugs and the immune system

With high nodal transferability and immune-enhancing effect of S-640956 is one of the best approaches to HIV functional cure

Entry into HIV cure using approaches that capitalize on S-540956 characteristics

Entry into Vaccine Business

Entered the vaccine business by making UMN Pharma a wholly-owned subsidiary

UMN Pharma

Possessing a vaccine manufacturing platform that allows the production of homogeneous and stable antigens without the need for viral culture

Characteristics of platform technology (BEVS) of UMNs

Four "S" enables stable supplies

- **S**afer: Only viral genes need to be available
- **S**table: Antigenicity does not change during manufacturing
- **S**calable: Complex culture conditions are not required
- **S**peedy: Manufactured 2 months after genetic information is available

Starting with a **preventive influenza vaccine**

By fully integrating the strengths of UMN into the strengths of Shionogi in infectious disease, we have expanded our business area into prevention.

Future Development of Vaccine Business

Exploiting the strengths of Shionogi in infectious diseases to enter the preventive and therapeutic vaccine businesses

Infectious disease Preventive vaccine	Infectious disease treatment Therapeutic Vaccine
Creation of vaccines to prevent infectious diseases, including influenza	Creation of therapeutic vaccines to replace existing treatments for infectious diseases where relapse or reactivation is a problem

Combining antigens, adjuvants and routes of administration to continually create optimized vaccines

Contributing to fortify new drug discovery platforms and expand the pipeline

Fight Against COVID-19*

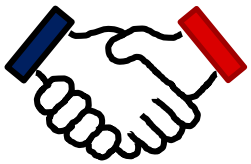
Collaboration with Hokkaido University Research Center for Zoonosis Control

Hokkaido University Research Center for Zoonosis Control

SHIONOGI

Strengths

- One of the best research laboratories for infectious diseases
- Experts in various infectious diseases
- Promotion of research and education about zoonotic diseases with another research base in Africa



Strengths

- Infectious disease is one of its core therapeutic areas
- Strong drug discovery capability using various modalities such as small and medium-sized molecules
- Deliver solutions through prevention, diagnosis, and treatment

Based on the knowledge from previous research, we initiated drug discovery research for COVID-19 as well as emerging and re-emerging infectious diseases.

*Coronavirus disease 2019

Exploratory Data About the Novel Coronavirus (flash report)

Promising compounds for the novel coronavirus have been found from internal *in vitro* studies

(EC_{50} : μM)

Compounds	Novel coronavirus* In-house data	Novel coronavirus* published data**	Previous coronavirus*** In-house data
Compound-1	0.10	—	0.40
Compound-2	Ongoing	—	0.22
Compound-3	Ongoing	—	0.25
Remdesivir	0.64	0.77	Ongoing
Favipiravir	132	62	>400

To reduce the societal anxiety and economic impact of the pandemic of novel viruses such as SARS, MERS and SARS-CoV-2, we will continue drug discovery and prepare for pandemic of coronavirus in the future as our mission as a pharmaceutical company which focuses on infectious diseases as one core therapeutic area

SHIONOGI

* SARS-CoV-2
**Cell Research (2020) 30:269–271 ***OC43

Fight Against COVID-19*

Business Partnership with Micro Blood Science Inc. for an IgG/IgM Antibody-test Kit

Difficulties in the current diagnosis

- PCR is an essential test for confirming infectious patients
- PCR presents problems in terms of simplicity and rapidity, such as requiring dedicated measuring equipment and requiring a relatively long time to obtain test results

- **Rapid IgG/IgM antibody-test kit for the COVID-19, imported by MBS from a Chinese cooperative company, Vazyme Biotech, Co., Ltd.**
  - This test kit, which is very convenient and uses only a drop of blood, provides rapid test results in 10 minutes
  - It also demonstrates high performance with a sensitivity of 94% and a specificity of 97% (according to Vazyme's clinical trial data in China)
- **Shionogi will progress discussions with MBS regarding the distribution and sales of this kit**

Contribute to early diagnosis and following treatment for COVID-19, leading to safe and reliable society

*Coronavirus disease 2019

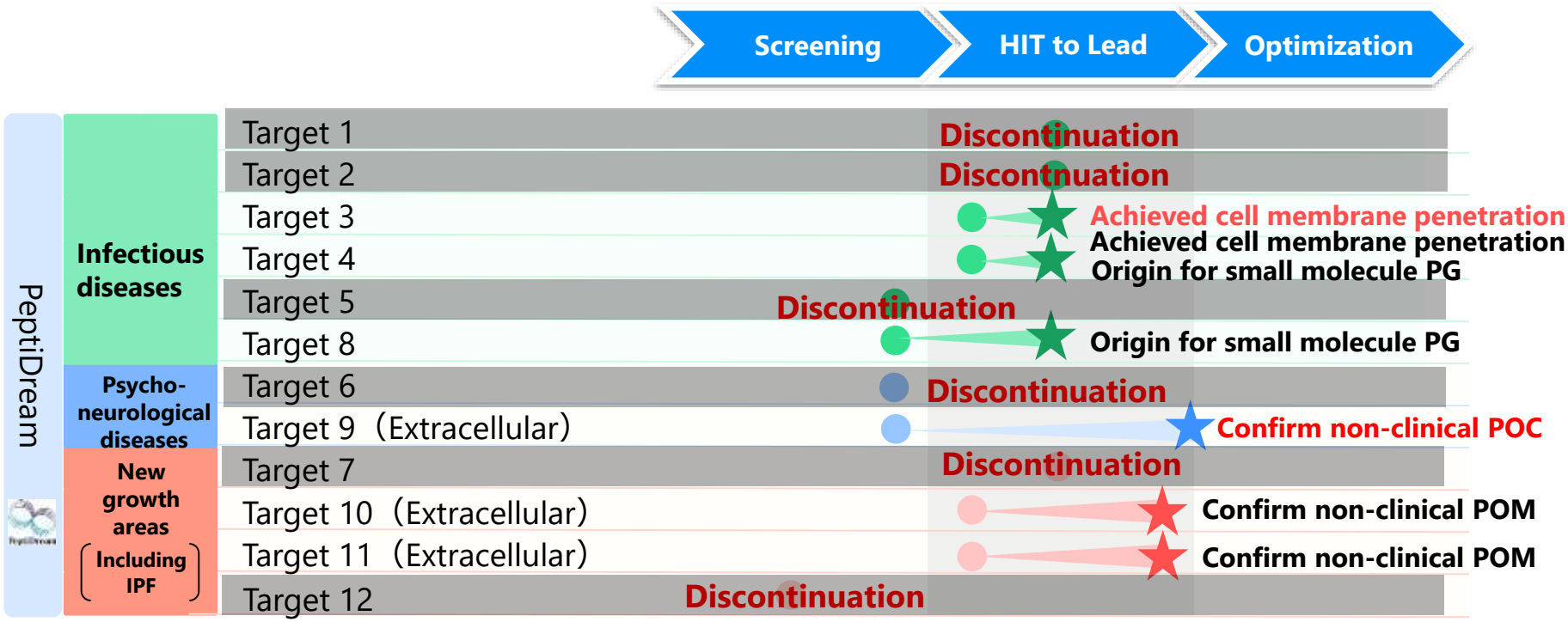
Progress in Peptide Drug Discovery

Progress in Peptide Drug Discovery

Focused Program (PG) portfolio : narrowed down from 12PG to 6PG

Confirmed POC in non-clinical models in priority PGs

Obtained highly active peptides for intracellular targets



To prioritize our efforts, we have narrowed down PDPS PGs and accelerated the development of fundamental technologies to permeabilize peptides across cell membranes and to use peptides as a starting point for discovery of small-molecule lead compounds.

SHIONOGI

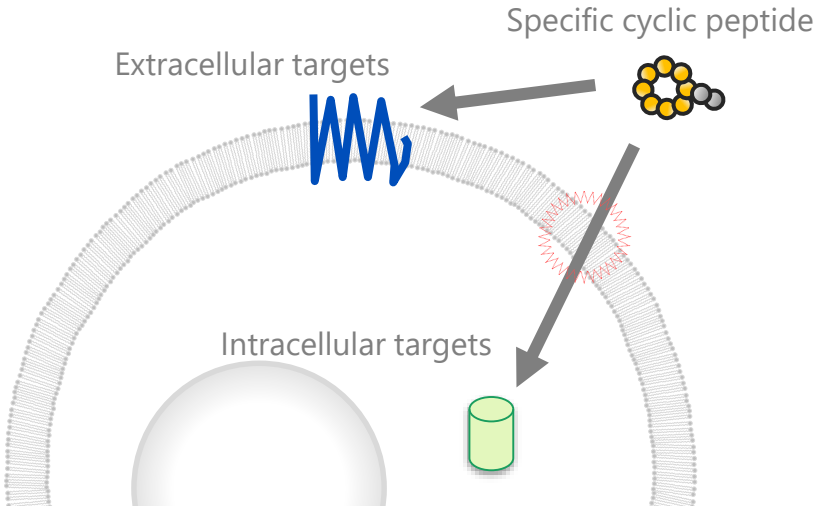
As of Mar. 2020

As of Mar. 2021

PDPS: Peptide Discovery Platform System
IPF: Idiopathic Pulmonary Fibrosis
POC: Proof of Concept
POM: Proof of Mechanism

Expectations and Challenges for Peptide Drug Discovery

Extracellular targets	Intracellular targets
Exploring new medical needs by utilizing various administration routes such as oral, pulmonary, and transdermal	Aggressive approach for high-difficulty targets (proteases, protein-protein interactions)



Issues：Cell membrane permeability

Peptides have low membrane permeability and are expected to have limited effects on intracellular targets

- **To establish peptide membrane permeation technology**
- **To establish technology to generate small molecule leads (which leads may be membrane-permeable) based on peptide structures**

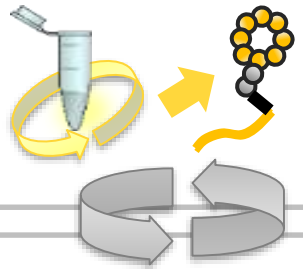
Combine our small molecule drug discovery capabilities with PDPS technology to establish a unique peptide drug discovery platform for highly difficult drug discovery targets

Establishment of Technology for Cell Membrane-Permeable Peptides

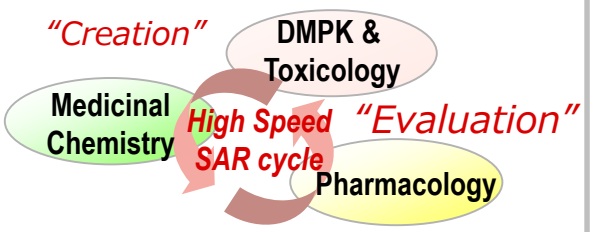
We have achieved intracellular translocation of peptides by combining our strengths of small molecule drug discovery and PDPS technology.

PDPS platform

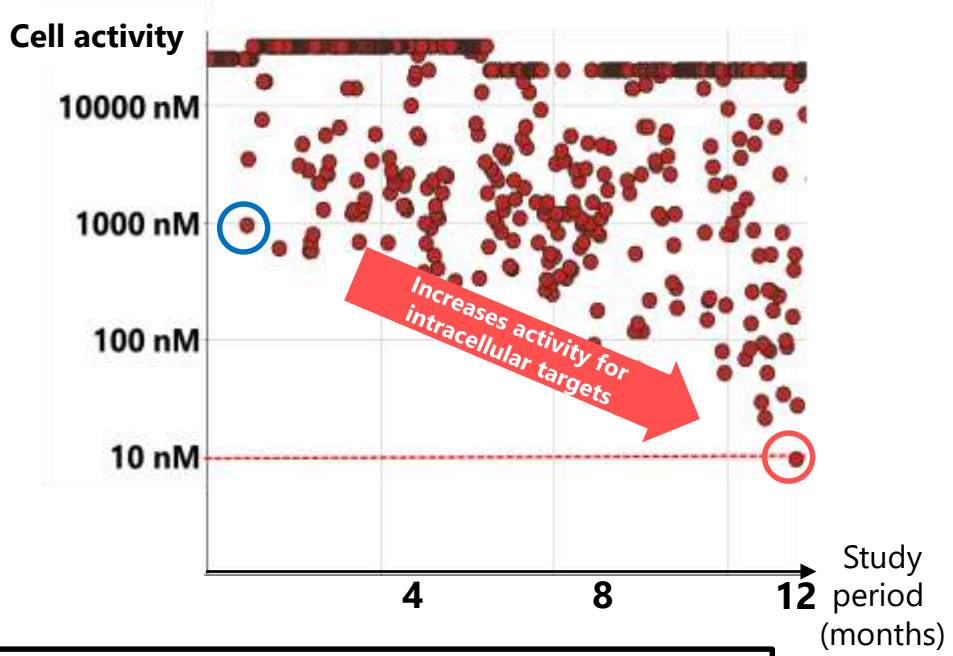
Special cyclic peptide



Our original SAR engine



Approximately one year from start to reach activity below 10 nM



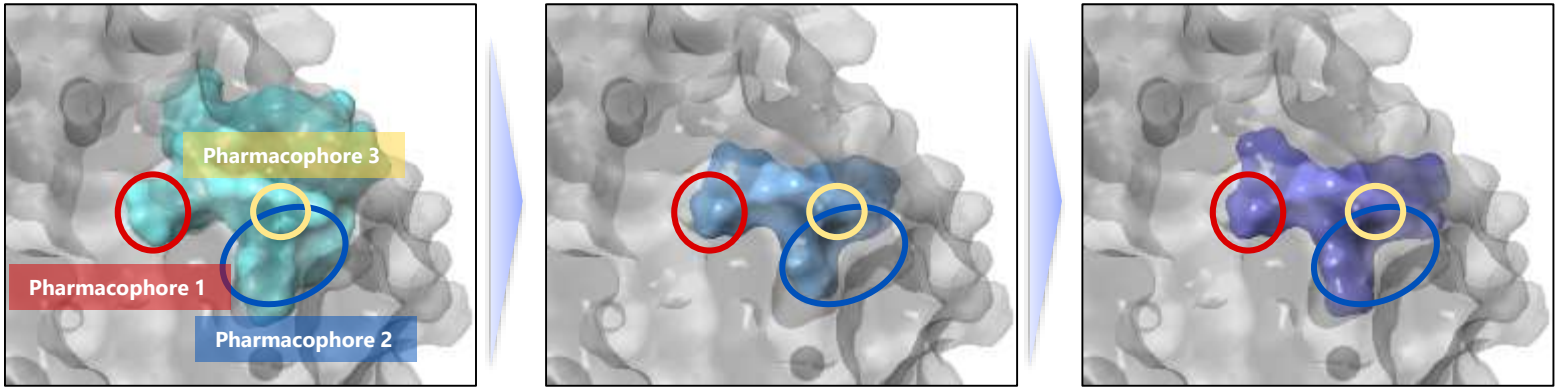
Issues：Expansion of know-how to turn active peptide molecules into lead peptides and pharmaceuticals

Structural optimization of intracellular target-directed PDPS hit peptides to obtain lead peptides

Establishment of Technology to Transform Hit Peptides into a Small-molecule Lead Compounds

We have leveraged pharmacophore information from peptide/target complexes to create highly active small molecules.

Target A



Peptide
(molecular weight=1192)
IC_{50} = 104 nM

Small molecule
(molecular weight= 517)
IC_{50} = 54000 nM

Small molecule
(molecular weight=592)
IC_{50} = 1.1 nM

Issues：Construction of know-how for small molecule design and SAR development

To provide innovative new drugs at a affordable price, we will technologies to transform hit peptides into small-molecule lead compounds and evolve our small-molecule drug discovery platforms.

SAR: structure activity relationship

Research

Therapeutic Area	Project	Indication	Plan in FY2020-2021
Immuno-oncology	**Regulatory T cell inhibitor**	Cancer	**Initiation of clinical study in FY2021**
Immuno-oncology	**S-540956** **Nucleic acid adjuvant**	Cancer	**Initiation of clinical study in FY2020**
Psycho-neurological diseases	**S-874713**	Various psycho-neurological diseases	**Initiation of clinical study in FY2020**
Infectious diseases	**HIV franchise** **Long-acting/functional cure**	HIV infection	**S-540956: Initiation of clinical study in FY2020** **S-648414: PoC in FY2020**
Infectious diseases	**Vaccine for prophylaxis**	Influenza virus infection	**Initiation of clinical study in FY2021**

Progress research activities for core pipeline assets to initiate clinical development and continuously create new growth drivers

Development

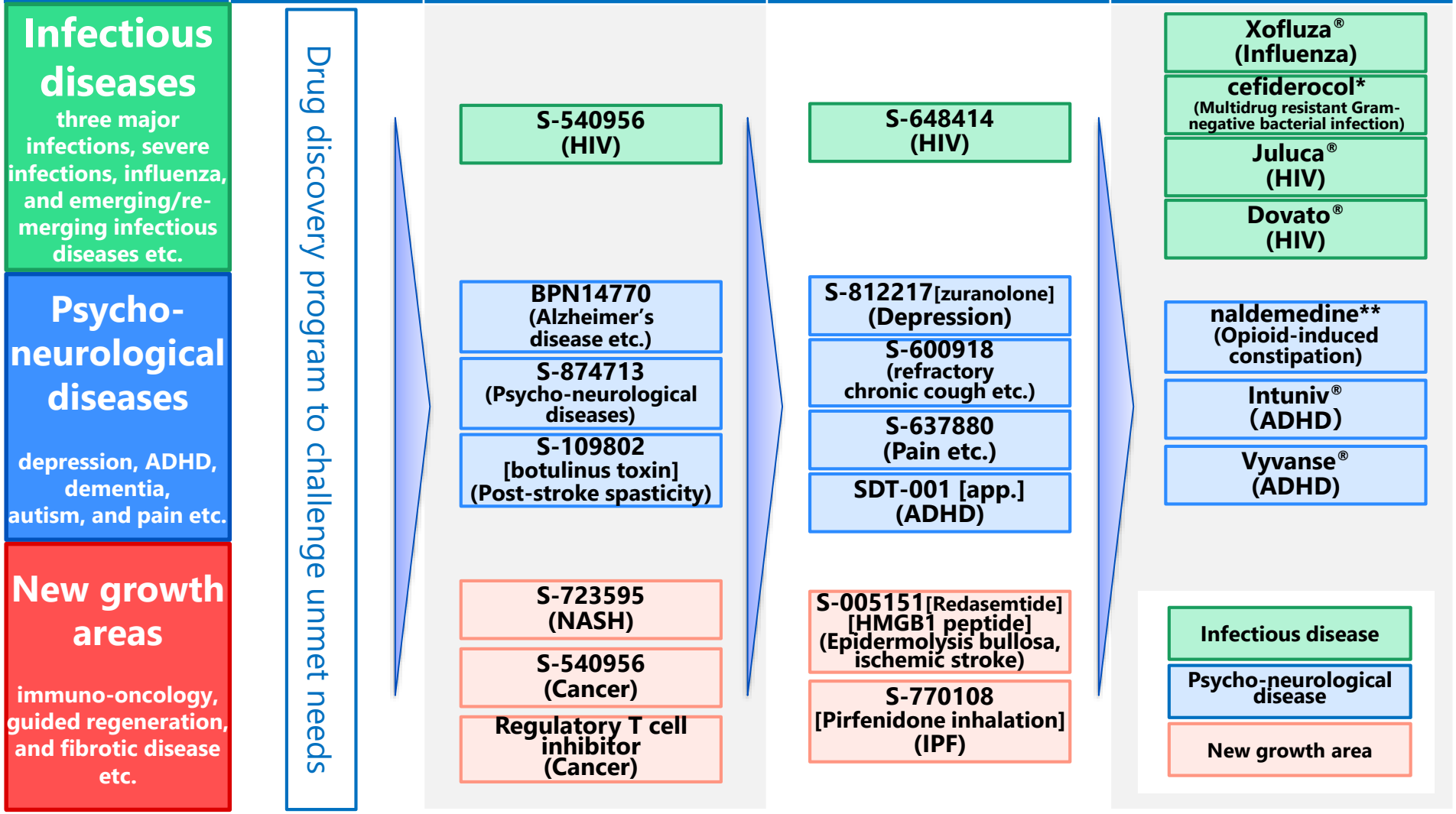
Toshinobu Iwasaki, Ph.D.
Senior Executive Officer
Senior Vice President
Global Development Division



Re-appeared

Growth Drivers Discovered/Acquired in SGS2020

SONG for you!



Growth Drivers Created from FY2014 to present
ADHD: attention deficit hyperactivity disorder
* brand name in US: Fetroja®, brand name in EU: Fetcroja®, details are shown in p.117
** brand name in Japan and US: Symproic®, brand name in EU: Rizmoic®

Development

Current Stage	Therapeutic Area	Project	Indication	Pages
Japan: pre-clinical US: Phase 2	Psycho-neurological diseases	**BPN14770**	Alzheimer's disease	P.51-57
Phase 1*		**S-812217 [zuranolone]**	Depression	P.58-63
Phase 2		**S-600918**	Refractory chronic cough etc.	P.64-69
Phase 1		**S-637880**	Neuropathic pain	P.70, 71
Phase 2		**SDT-001**	ADHD (Treatment app.)	P.72-77
Phase 2	Guided regeneration	**S-005151 [redasemtide]**	Epidermolysis bullosa, Ischemic stroke etc.	P.78-85
Phase 1	Fibrotic disease	**S-770108**	Idiopathic pulmonary fibrosis	P.86-88
Phase 1	Infectious diseases	**S-648414**	HIV infection	P.89-91
Launched		**Xofluza®**	Influenza virus infection	P.92-97

Projects in red are core pipelines with which we desire paradigm shift of disease treatment

* S-812217: Phase 3 studies are being conducted by Sage

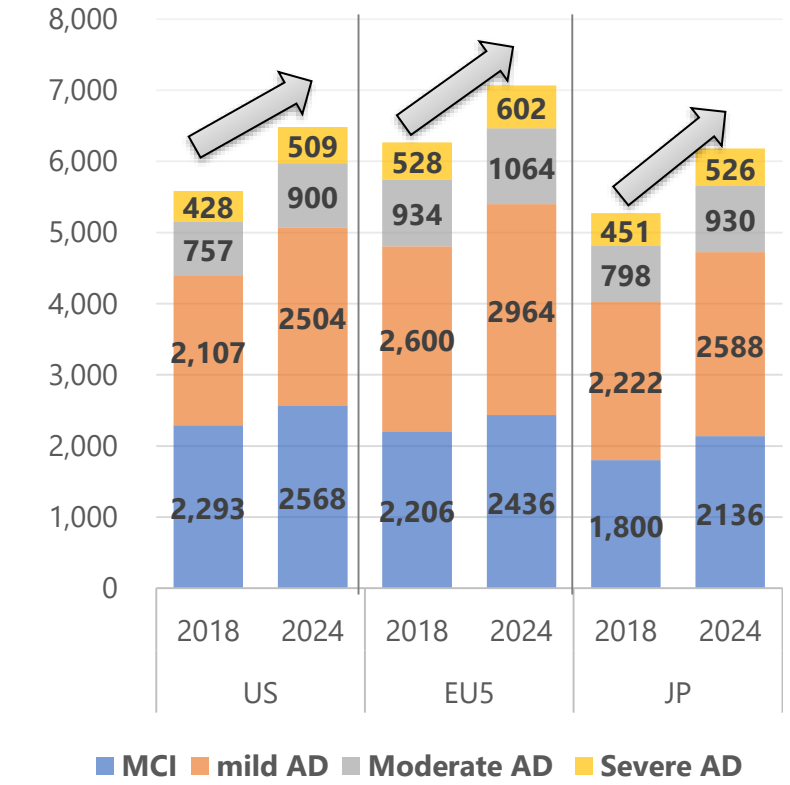
BPN14770
Alzheimer's Disease (AD)

- **Origin**: Tetra Therapeutics
- **Mechanism of action** : Phosphodiesterase 4D negative allosteric modulator
- **Characteristics**：Improvement of cognitive function and Inhibition of AD progression

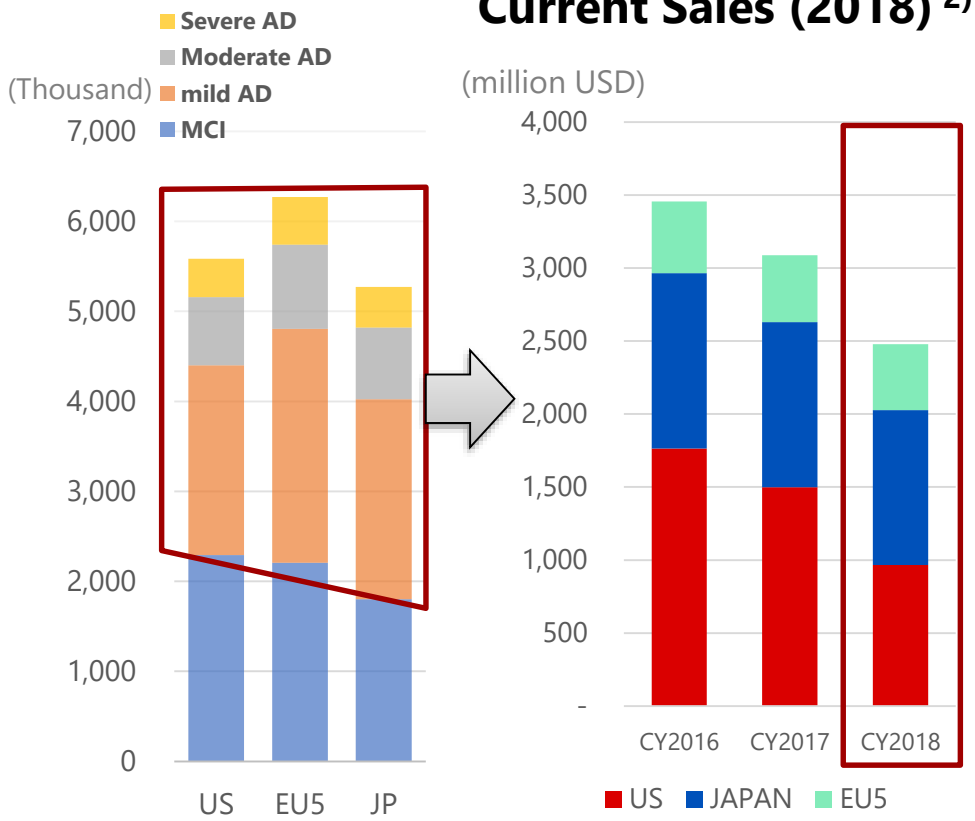
- **Development stage (as of Mar.2020)**:
  - ✓ Japan: Phase 1 study in preparation
  - ✓ US: AD (and FXS) Phase 2 study is being conducted by Tetra therapeutics
- **Plans for FY2020**:
  - ✓ Japan: Phase 1 study will be initiated → completed
  - ✓ US: Phase 2 study will be completed
  - ✓ Global: Phase 2b and Phase 3 studies will be initiated

Sales forecast in AD

Prevalence (2018→2024) [1)]



Current Sales (2018) [2)]



The number of AD [4)] patients including MCI [3)] is extremely large in all areas (US, EU, JP), and the number is expected to increase in the future.

Sales of existing drug in 2018: 2.5 billion USD (7MM)

Market size in AD shrinking year after year due to GE, however, is expected to expand because drugs with new mechanisms of action can expand the target market to include mild cognitive impairment (MCI).

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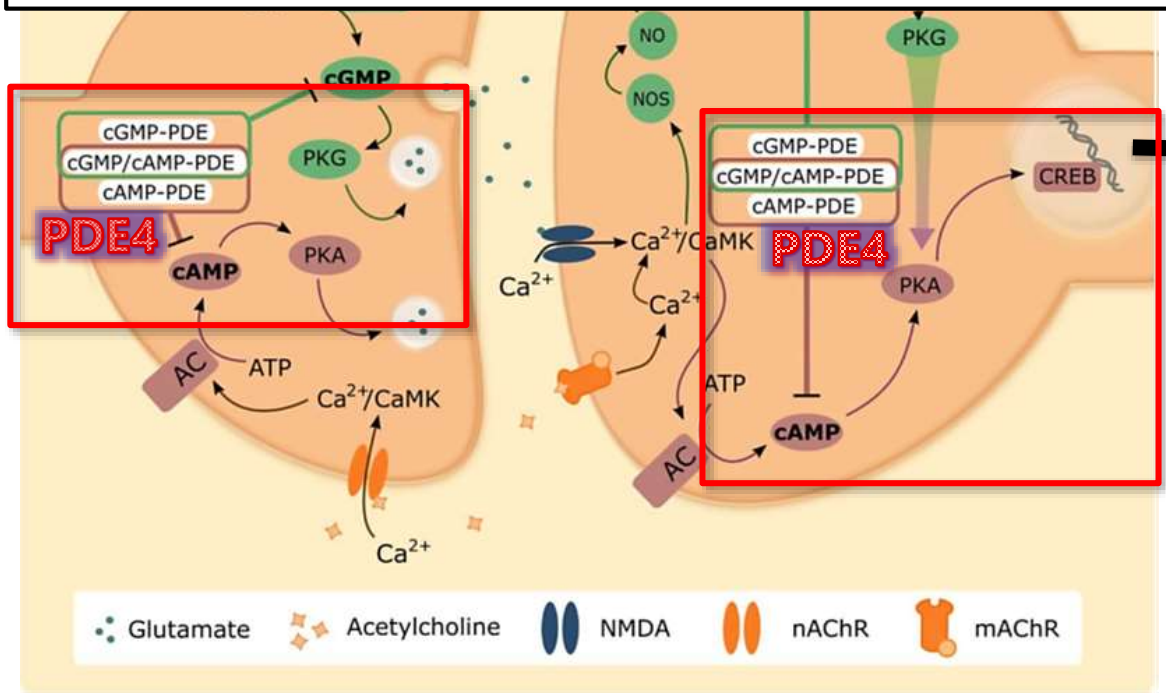
[1)] Decision Resources Group Landscape & Forecast Alzheimer's Disease June . 2019 [2)] IQVIA Analytics Link
[3)] Mild Cognitive Impairment 軽度認知機能障害 [4)] Alzheimer's disease アルツハイマー型認知症

Characteristics of BPN14770

Phosphodiesterase (PDE) reduces cAMP in neurons

cAMP increase ⇒ activation of PKA-CREB pathway ⇒ gene expression change ⇒ enhancement of synaptic/neuronal function



Gene expression change
Protein distribution

- **Synaptic plasticity and growth**
- **Neurogenesis**
- **Neuroprotection**
- **LTP/LTD**

Memory / Learning / Cognition

BPN14770 increases cAMP by negative modulation of PDE4D, resulting in improvement and maintenance of cognitive function by altering the expression of neuronal genes

Heckman PRA et al.,
Neurosci Biobehav Rev. 2018;87:233-254

PKA: Protein kinase A
CREB: cAMP response element binding protein

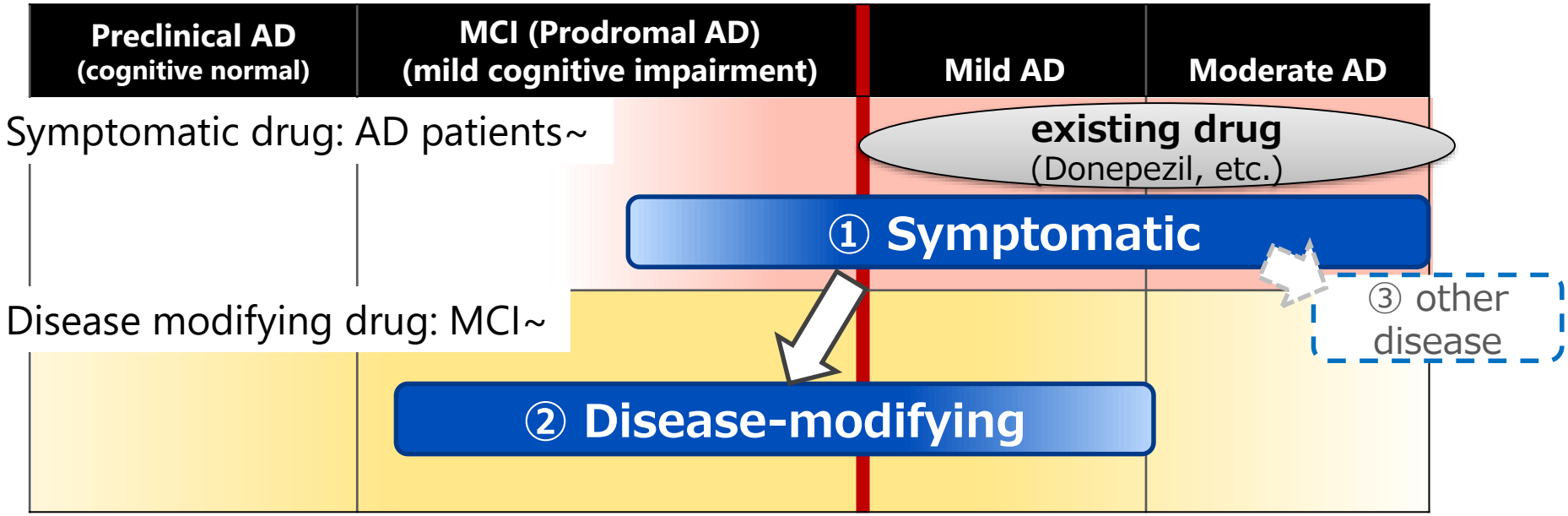
Position of BPN14770 in AD treatment

BPN14770 has a potential to be both a "symptomatic drug" and a "disease-modifying drug"

① **Early approval as a cognitive enhancer (symptomatic drug) after AD onset**

② **Expanding to be a disease-modifying drug for early AD (including MCI) after confirming its potential to prevent AD progression**

③ **Additional potential as a cognitive-enhancing drug in other dementia and psychiatric diseases**

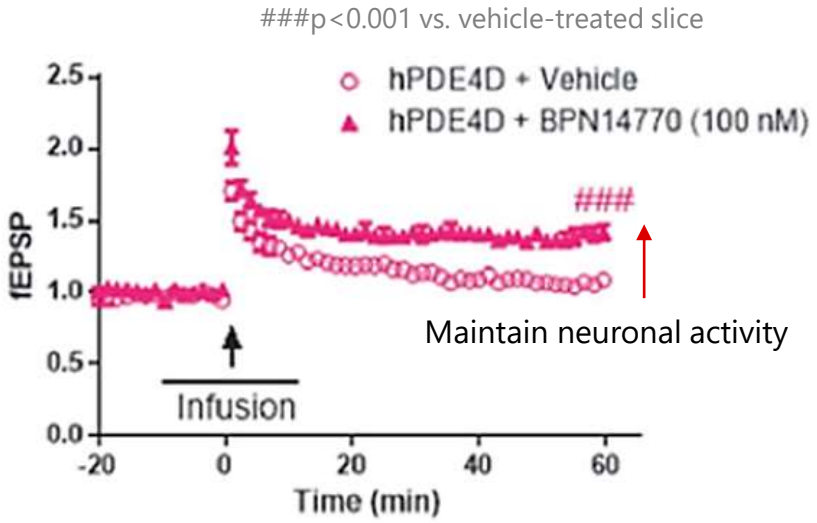


Non-Clinical Study: Symptomatic Effects

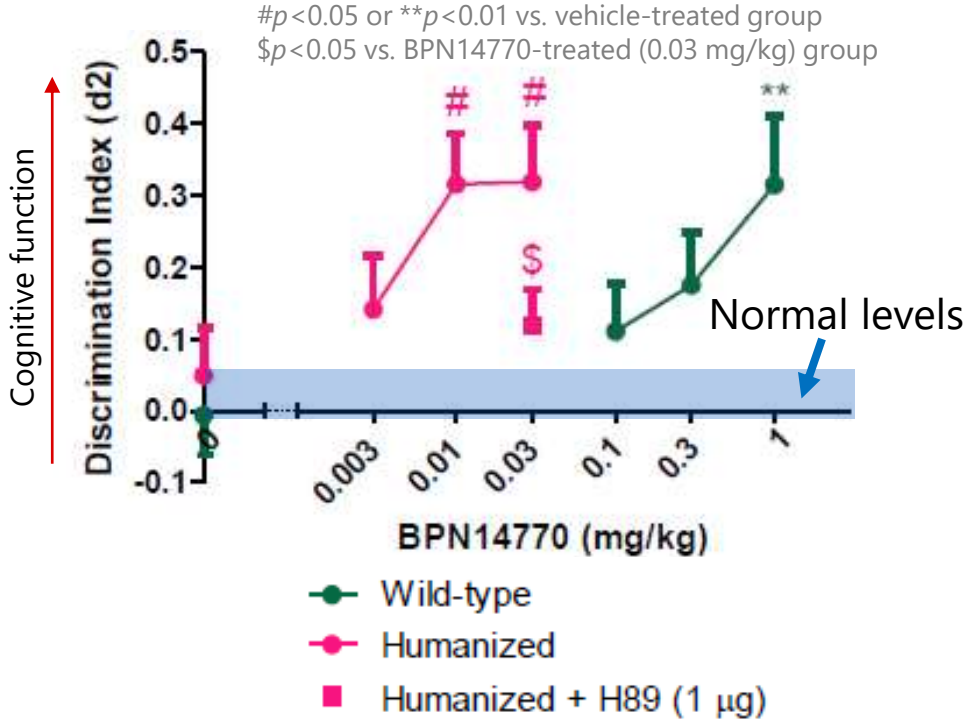
Effects on cognitive function (symptomatic)

BPN14770 can induce synaptic LTP (long-term potentiation) in hippocampal slices and improve the cognitive function of normal mice

Neuronal plasticity (synaptic LTP)



Cognitive function (novel object recognition test)



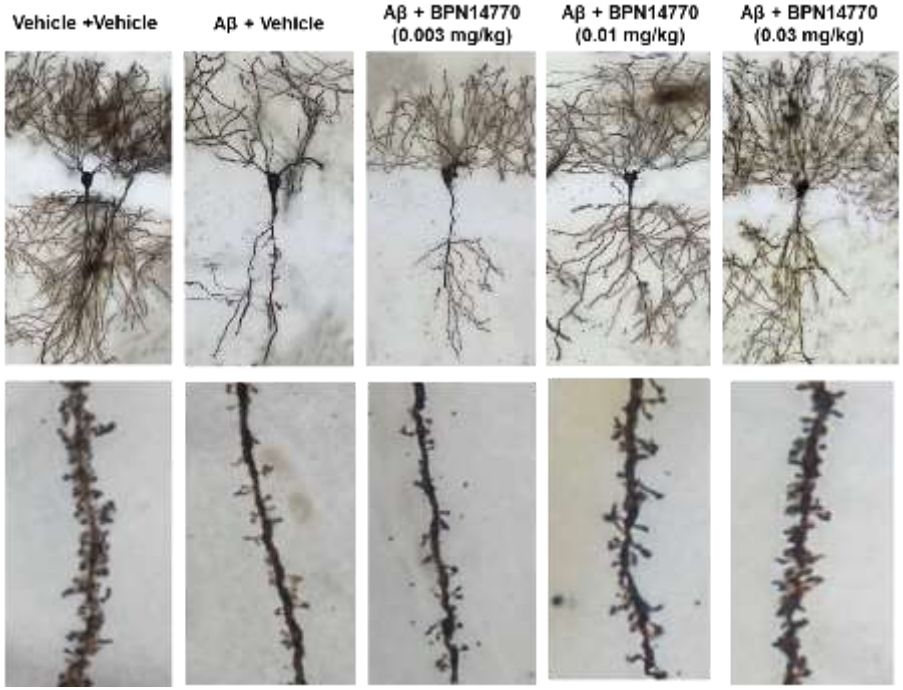
Zhang C et al., Neuropsychopharmacology. 2018;43:2299-2309

Non-Clinical Study: Inhibition of AD Progression

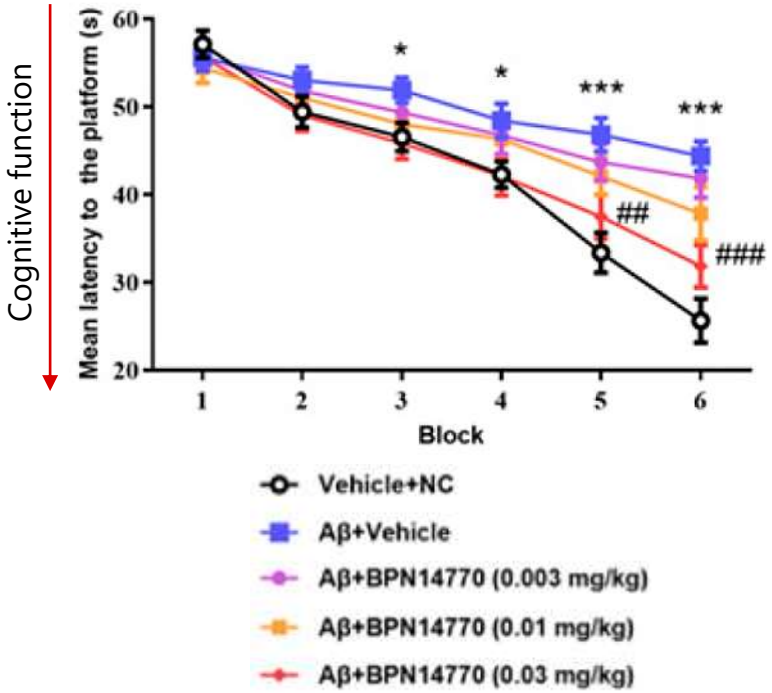
Effects on neuronal impairment (inhibition of AD progression) in hippocampus β-amyloid (Aβ) infusion models

BPN14770 can Inhibit the Aβ-induced neuronal impairment (structural change: reduction of dendrites and spines) and cognitive dysfunction (14 days treatment after Aβ-infusion)

Neuronal impairment
(Golgi staining, CA1 in hippocampus)



Cognition (Morris Water Maze test)



Cui SY et al., J Pharmacol Exp Ther. 2019;371:250-259

*p<0.05, ***p<0.001 vs. vehicle-treated control group
##p<0.01, ###p<0.001 vs. vehicle-treated Aβ1-42 group

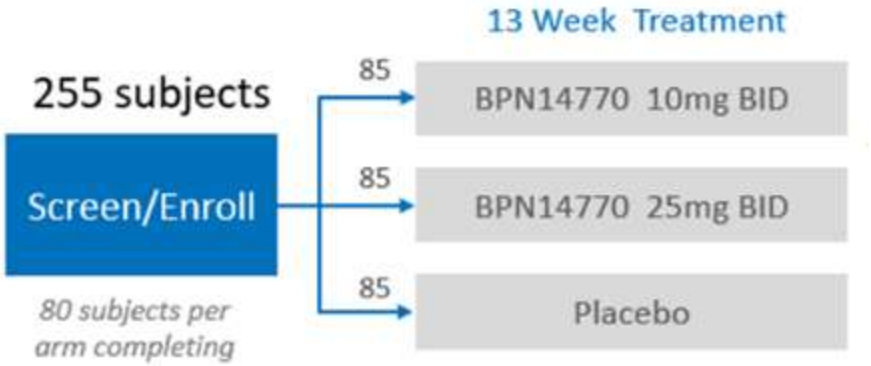
Rapid Enrollment of AD Phase 2 Study in US

PROTOCOL 201 EARLY ALZHEIMER'S TRIAL DESIGN

ClinicalTrial.gov Identifier: NCT03817684

Early Alzheimer's Disease (MCI (mild cognitive impairment) + mild AD)

CDR-MB > 0.5 or 1; MMSE ≥ 20; RBANS-DMI ≤ 85;
Currently receiving a stable dose regimen of donepezil or another cholinesterase inhibitor



Primary endpoint：**RBANS-DMI**
Secondary endpoints：**RBANS total score, ADCS-ADL, MMSE** score, **CDR-SB, CGI-I, ADCOMS**

RBANS-DMI: Repeatable Battery for the Assessment of Neurological Status
DMI: Delayed Memory Index
ADCS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory
MMSE: Mini-Mental State Evaluation
CDR-SB: Clinical Dementia Rating sum of boxes score
CGI-I: Clinical Global Impression – Improvement
ADCOMS: Composite endpoint based on AD Composite Score

Based on the AD Ph2 topline results, Shionogi will decide to make Tetra a wholly owned subsidiary of Shionogi if certain conditions are met. Then, global development of BPN14770 and research to identify follow-up compounds (Best in Class) will be initiated.

S-812217 [zuranolone]
Depression

- **Origin**: Sage Therapeutics
- **Mechanism of Action**: $GABA_A$ Receptor Positive Allosteric Modulator
- **Characteristics**:
  - ✓ Rapid onset: efficacy shown in 24 hours after the first dosing
  - ✓ Strong efficacy: efficacy is greater than available antidepressants
  - ✓ Long-acting: efficacy is durable after completing 2 weeks of dosing
  - ✓ Better medication adherence: No need for dose adjustment, including titration and tapering, once daily dosing for 14 days
- **Development stage (as of Mar. 2020)**:
  - ✓ Japan (Shionogi): Phase 2 study to be initiated in March
  - ✓ US (Sage): Phase 3 studies on-going (Protocol of Phase 3 studies may be amended upon completion of relevant correspondence with the FDA
- **Plans for FY2020**:
  - ✓ Japan: Ph2 ongoing
  - ✓ US: Meeting with FDA to discuss development strategy

Social impact of Depression in Japan

Antidepressant market & work productivity loss due to depression

5M Patients

- Ca. **5M patients** with depression in Japan[1)]
  - The most prevalent non-fatal diseases

160 B yen Market

- Current antidepressant market in Japan : Ca. **160 B yen**: Cymbalta® maintains top-share

40M days/year & 400 B yen losses

- Absence from work for **40M days/year** in total
- Work productivity loss equivalent to ca. **40 B yen** [2)]
  - The largest impact amongst all diseases

Major unmet medical needs with current therapies

Insufficient Efficacy

- Remission rate after the first treatment using SSRI[3)]: 36.8%[4)]
- Cumulative remission rate after changing anti-depressants up to 3 times[5)]: ca. 67% in total[4)]

Slow Onset

- 2-8 weeks are needed for onset of efficacy
- Prolonged debilitation and increased risks of deterioration or suicide due to slow onset[6)]

Complicated regimen

- Dose adjustment is necessary to mitigate adverse events

SHIONOGI

1) WHO, Depression and Other Common Mental Disorders Global Health Estimates, 2) Collins JJ, et al. J Occup Environ Med 2005; 47, 3) QIDS-C16 score 5 or less, 4) Am J Psychiatry 2006; 163:1905–1917, 5) treatment algorithm for antidepressant drugs of SSRI, SNRI, Nassa or tricyclics, 6) JAMA. 2004;292:338-343

Target Product Image

Novel antidepressant with breakthrough profile

＜First-line antidepressant＞

- Rapid onset results in earlier remission earlier and return to normal life
- Provides an efficient option both in terms of speed and medical economy, which available depression treatments have yet to satisfy
- Potential to improve complicated depression

Unmet needs in depression treatment

- Slow onset
- Insufficient efficacy
- Prolonged treatment period
- Concomitant insomnia or anxiety

zuranolone

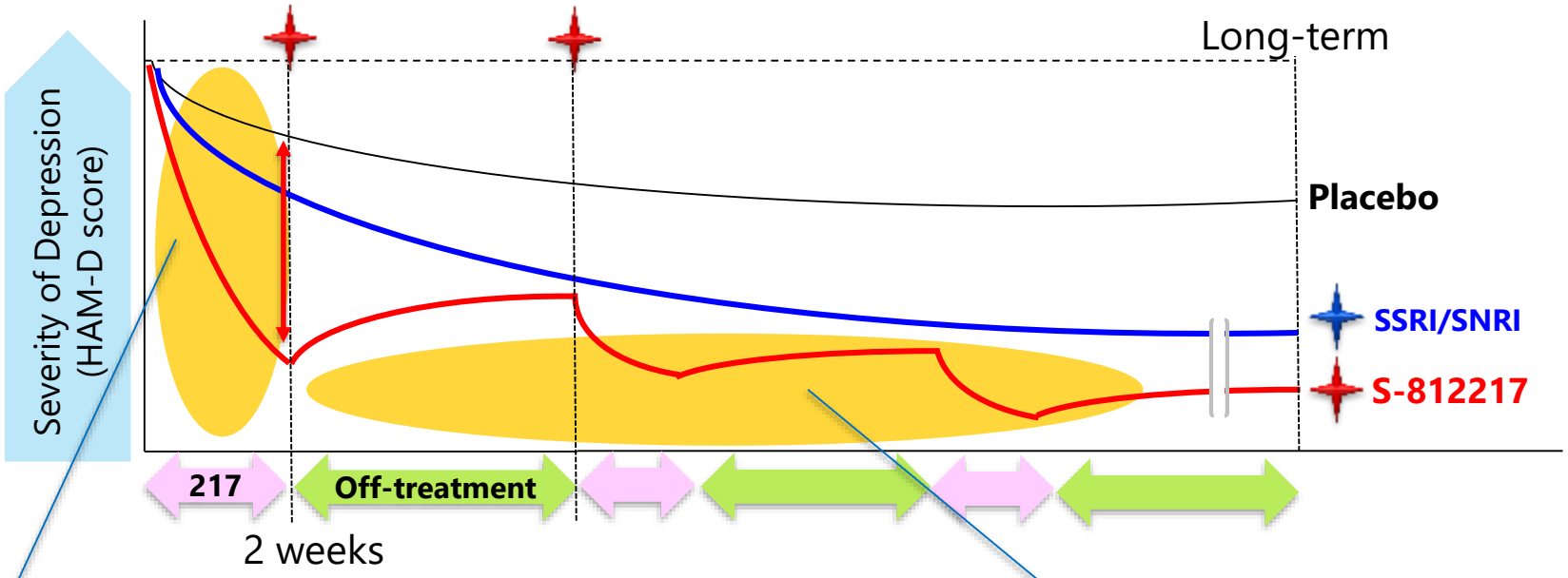
Resolve unmet needs

Values of S-812217

- **Rapid onset of action**
- **Greater efficacy**
- **Durable effect**
- **Improve insomnia and anxiety**

Potential to be effective across a broader range of depressant symptoms

Depression Improvement by S-812217



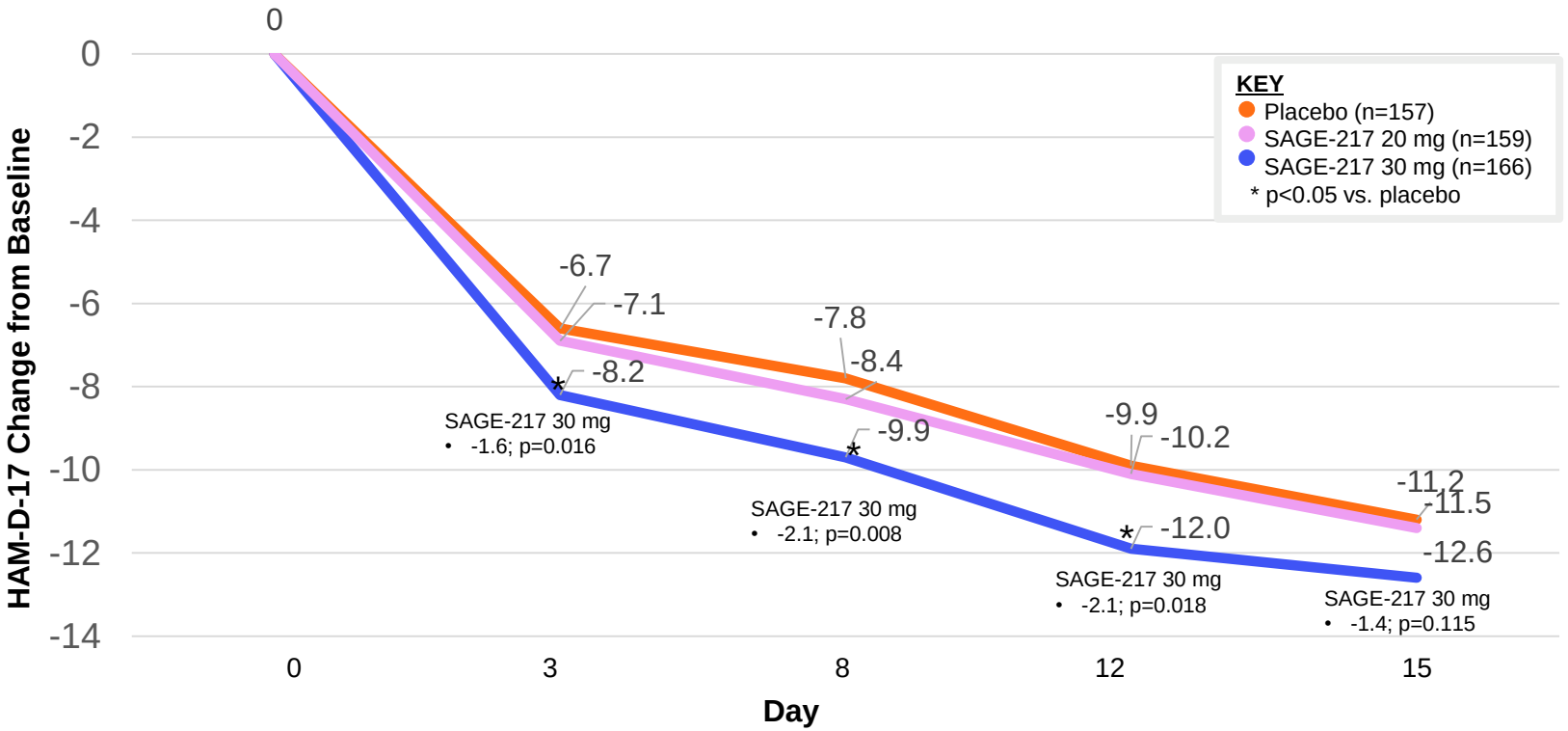
First, achieves remission earlier (Important unmet need)

Repeated treatment cycles to suppress relapse
Shorten depression treatment period leading more quickly to medication-free life

US Phase 3 Pivotal: Topline Results

SAGE-217 Primary Efficacy Measure

HAM-D Total Score LS Mean Change From Baseline Through Day 15



Rapid onset of effect for SAGE-217 30 mg was seen beginning at Day 3 with maintenance of effect through Day 15; statistical separation from placebo observed Days 3 – 12

9

The primary endpoint at Day 15 was not met.
Rapid onset was seen Day 3 to Day 12.

Next Step

zuranolone efficacy

- Rapid onset was confirmed in the US Phase 3 pivotal study, MDD-301
- Based on the previous phase 2 studies of MDD-201 and PPD-201, rapid onset and greater efficacy, which are unmet needs in depression treatment, are anticipated.
  - Especially, resolving the issue of slow onset, which can result in prolonged or more debilitation, and increase suicidal risk, is key.
- In general, clinical trials in depression, even with market-approved antidepressants, often resulted in study failure.

Shionogi will continue to invest in S-812217 to demonstrate S-812217 superior potential for rapid onset and greater efficacy in JP Phase 2 study.

S-600918
Refractory Chronic Cough etc.

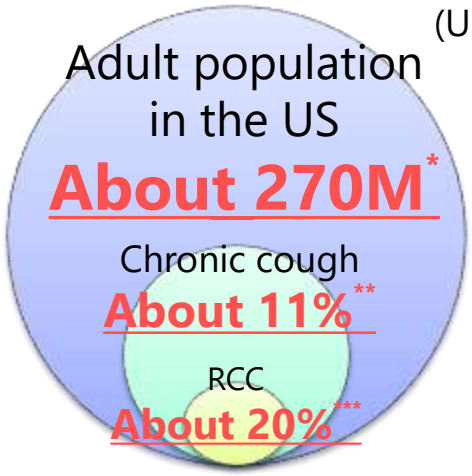
- **Origin**: in-house
- **Indication**: Refractory chronic cough, Sleep apnea syndrome, Neuropathic low back pain
- **Mechanism of action**: $P2X_3$ receptor antagonist
- **Characteristics**:
  - ✓ Once-daily, oral
  - ✓ Well-tolerated safety profile
- **Development stage (as of Mar. 2020)**:
  - ✓ Global: Phase 2b dose finding study for refractory chronic cough is ongoing
  - ✓ Japan: PoC study for sleep apnea syndrome will start
- **Plans for FY2020**:
  - ✓ Preparation for other LCM indications

Contributions to Societal Needs

Refractory Chronic Cough (RCC)

- **Cough lasting ≥ 8 weeks**
- **Underlying causes: asthma, sinobronchial syndrome, GERD etc.**
- **Persisting cough despite appropriate treatment(s)**

Estimated number of RCC patients



About 6 million patients are suffering from RCC in the US

There are no approved drugs

Centrally-acting antitussives have CNS side effect concerns

Reduce self-consciousness and improve QoL by providing relief from long-lasting cough

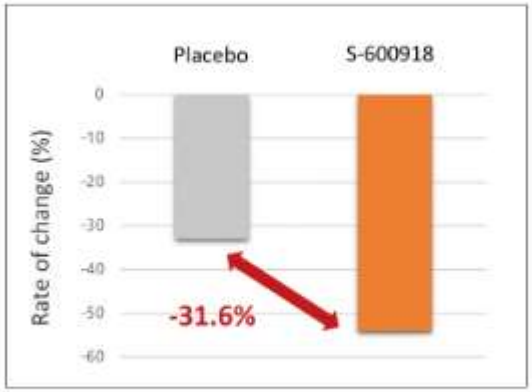
GERD: Gastroesophageal Reflux Disease

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

Presentation of PoC Study at ERS2019

PoC study results were presented as late-breaking abstract at European Respiratory Society International Congress 2019

Primary Endpoint: Cough Frequency in Daytime



Study drug	N = 31 S-600918	Placebo
n	31	30
Estimated rate of change (%)	-54.1	-33.0
Rate of change adjusted by placebo (%)	-31.6	---
P-value	0.0546	---

The rate of change adjusted by placebo was -31.6% (p = 0.0546)
No significant sequence or period effect was observed

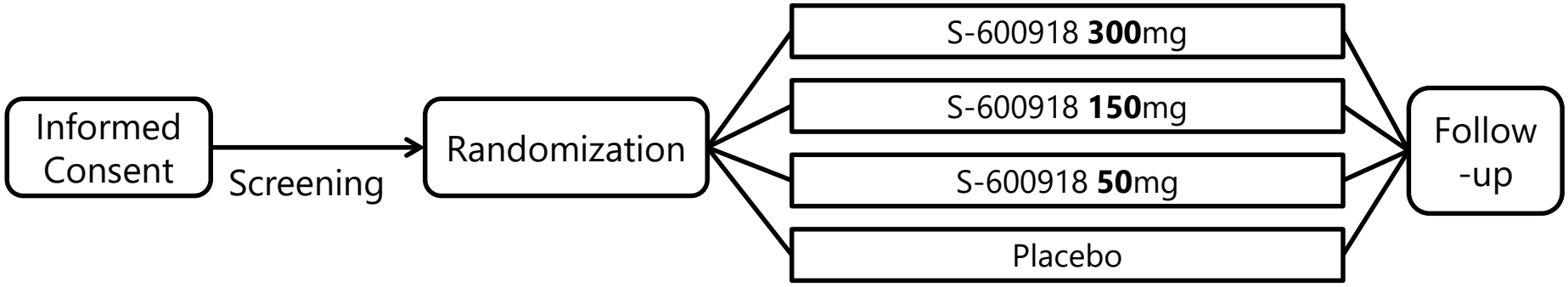
【Efficacy】
The rate of change in hourly cough frequency during the daytime adjusted by placebo was -31.6% (p=0.0546).

【Safety】
No significant difference in the incidence of AEs. Taste-related AEs, reported in similar drugs, was observed in 2/31 (6.5%) during S-600918 treatment.

AE: Adverse Event

Study Design of Phase 2b Dose Finding Study

Population	Refractory chronic cough
Endpoints	Efficacy (cough frequency, QoL etc.), safety, pharmacokinetics
Primary endpoint	Hourly cough frequency in 24 hours
Design	Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group
Region	Japan, US, EU
Number of patients	Total of 372 patients
Treatment duration	4 weeks, once daily administration
Protocol ID	1812VA323 (NCT04110054, JapicCTI-195079, 2019-002283-27)



【Current status】
FPI: Achieved in Feb. 2020

【Next milestone】
LPI: Expected by the end of 2020

Potential roles of $P2X_3$ in Disease

Characteristics of S-600918

- Selective antagonist of $P2X_3$ receptor, $P2X_3R$
- Inhibits activity of sensory nerves that expresses $P2X_3R$
- Reduced risk of side effects due to high selectivity for $P2X_3R$ vs. $P2X_{2/3}R$

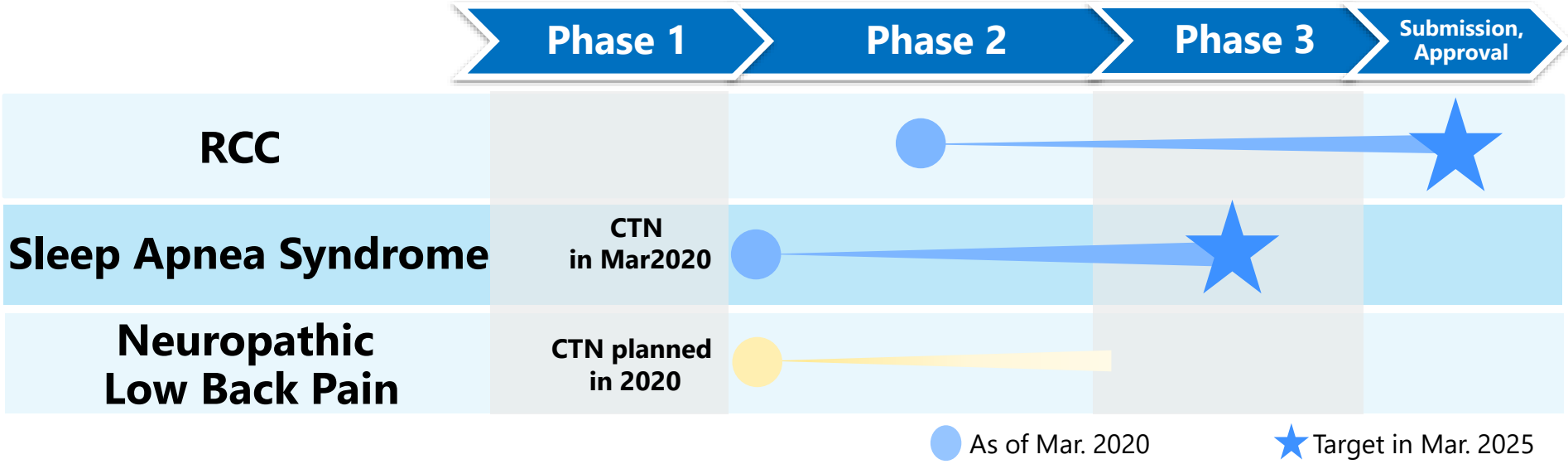
Possibility to show efficacy for diseases/conditions that have hypersensitivity of $P2X_3$

Cough	Pain	Sleep apnea	Itch	Hypertension
• Inhibition of vagus nerve • Confirmed efficacy in clinical trials	• Inhibition of primary afferents • Confirmed efficacy in animal models	• Inhibition of carotid body	• Some reports indicate that $P2X_3R$ shows efficacy in animal models	

To maximize the value of S-600918, LCM planning is ongoing

S-600918 supplemental information: shown in appendices, p.130-132

LCM Development Plan



Sleep Apnea Syndrome

- Estimated number of patients in 7 major markets: 25M*1
- No approved drug
- Low tolerability/convenience of CPAP and MAD treatments

Drug treatment contributes to patients' usability

Neuropathic Low Back Pain

- Estimated number of patients in 7 major markets: 22M*2
- In some cases, existing drugs are ineffective
- Even when effective, CNS side effects are a concern

High unmet medical need for effective and safe treatment

*1: Estimation based on Epidata, Jammnet data *2: Decision Resource
*3 Continuous Positive Airway Pressure, MAD: mandibular advancement device

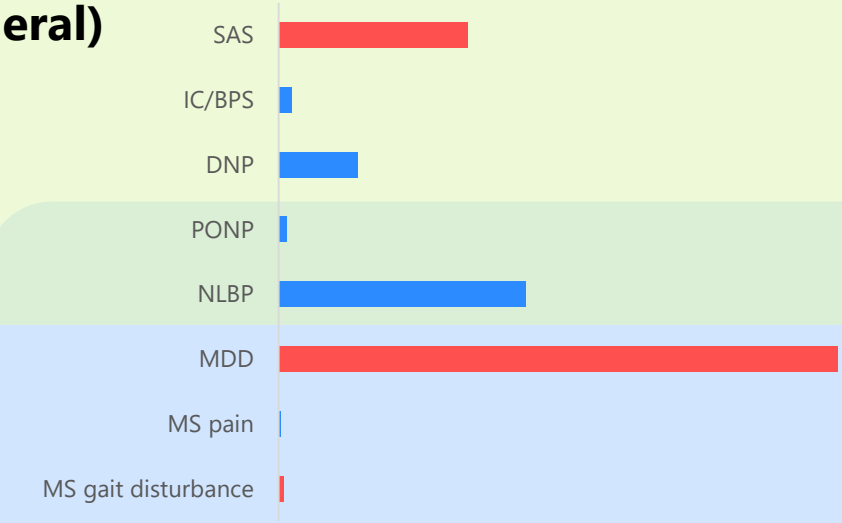
S-637880
Neuropathic pain

- **Origin**: in-house
- **Mechanism of action**: Not disclosed
- **Characteristics**: expected to be effective in peripheral and central neuropathic pain
- **Development stage (as of Mar. 2020)**: Ph1 multiple dose study (Japan, ongoing)
- **Plans for FY2020**:
  - ✓ Completion of Phase 1 MAD study
  - ✓ Initiation of Phase 2a study

New Opportunity in Pain Area

One clinical study will start in FY2020 to evaluate both S-600918 and S-637880 in one. It is important to develop analgesics esp. for Japanese pain market after Cymbalta® and Oxycontin® family.
Neuropathic low back pain was selected to leverage the strength of two compounds which are expected to be effective in peripheral and central neuropathic pain, respectively.

Diseases where S-637880 is expected to work (peripheral)



Diseases where S-637880 is expected to work (central)

SAS: Sleep apnea syndrome
IC/BPS: Interstitial cystitis/bladder pain syndrome
DNP: Diabetic neuropathic pain
PONP: Postoperative neuropathic pain
NLBP: Neuropathic low back pain
MDD: Major Depressive Disorder
MS: Multiple Sclerosis

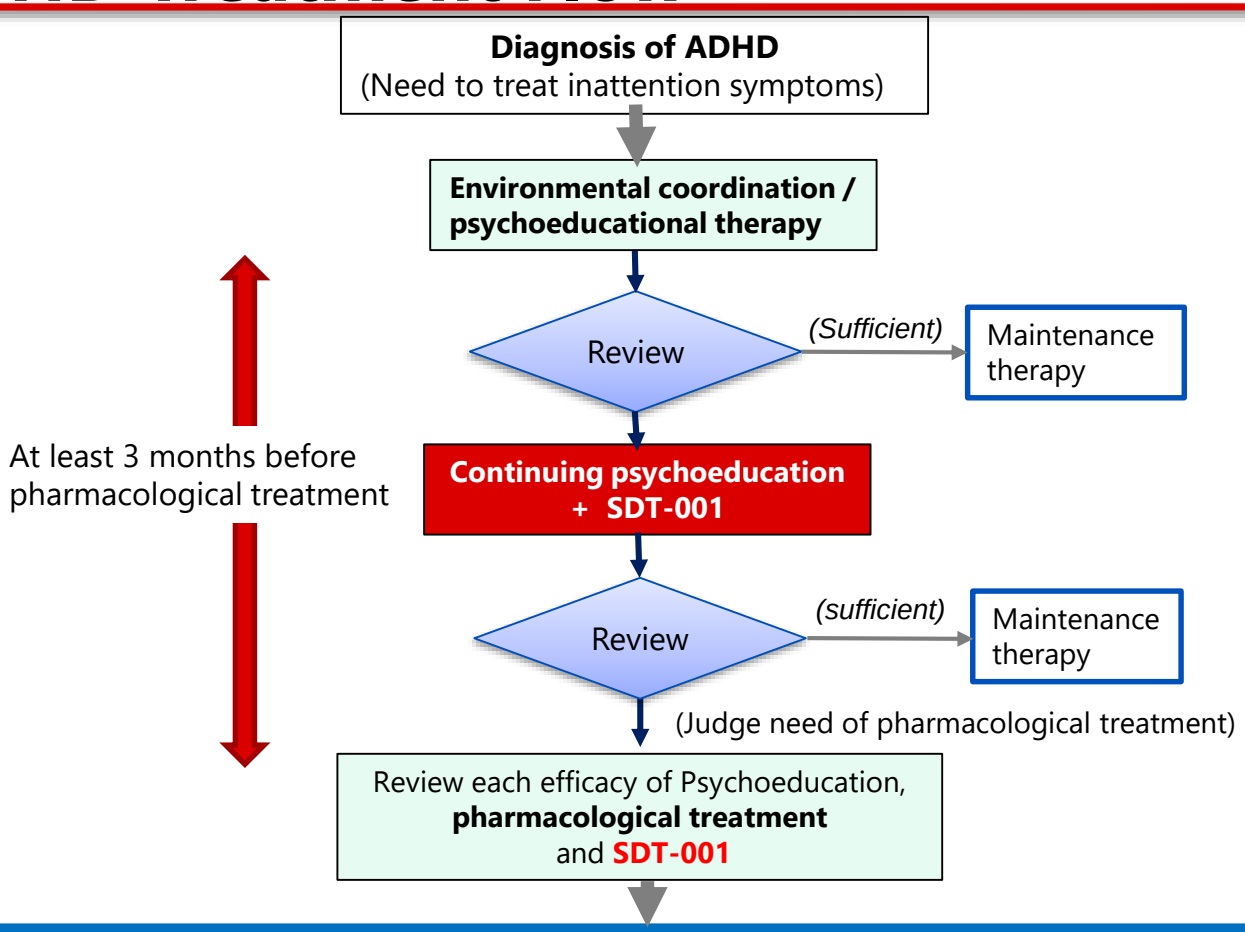
Pain Others

Bars show market potential (patient number)

SDT-001
Inattention symptoms of pediatric ADHD patients

- **Origin**: Akili
- **Mechanism of action**: Continuous activation of cerebral cortex through multitasking challenge with optimized difficulty for individual patients
- **Characteristics**: Digital therapeutic application
- **Development stage (as of Mar. 2020)**: Initiation of Phase 2 exploratory study (Japan)
- **Plans for FY2020**: Phase 2 study is ongoing (Japan)

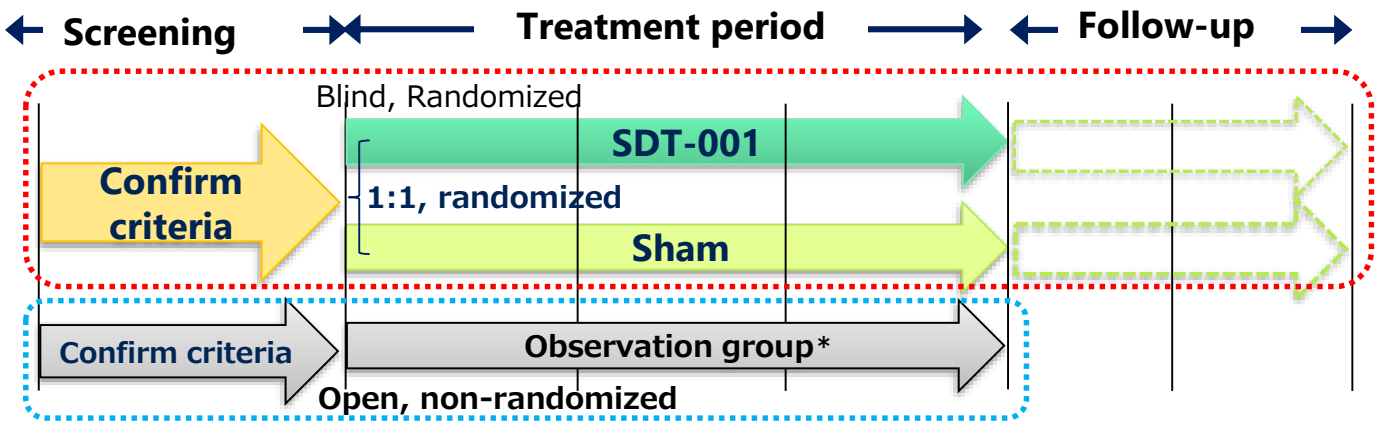
Expected Clinical Position of SDT-001 in ADHD Treatment Flow



1. **ADHD patients currently have no options other than pharmacological treatment if psychoeducation is ineffective.**
2. **SDT-001 could be a new, evidence-based, treatment option for the treatment of ADHD before initiating pharmacological treatment.**
3. **SDT-001 could potentially be used alongside pharmacological treatment.**

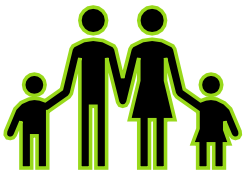
Summary of Phase 2 Study

Exploratory study to evaluate the efficacy and safety of SDT-001 in Japan

Objective	● To initially assess the efficacy/safety of SDT-001 compared to sham (exclude core mechanism of SDT-001). ● Collect reference data from psychoeducation-only group (include environmental coordination).
Study design	 *continue only psychoeducation (include environmental coordination).
Treatment method	SDT-001 or sham everyday for 6 weeks.
Efficacy endpoint	● Change from baseline in each ADHD symptoms score ● Change from baseline in TOVA (Test of Variable Attention, objective measurements of inattention) score, etc.

Proposal for a Total ADHD Treatment Solution

Family



Physician



Information sharing via IT



Digital therapy



Drug

Intuniv® (Pediatric and adult indication)

Vyvanse® (Pediatric indication, Planning of adult development)

1. Provide digital therapy or medication customized for medical or social needs of patient.
2. Sharing symptom status and monitoring between family and physician through digital device

Improve the paradigm of care for ADHD patients

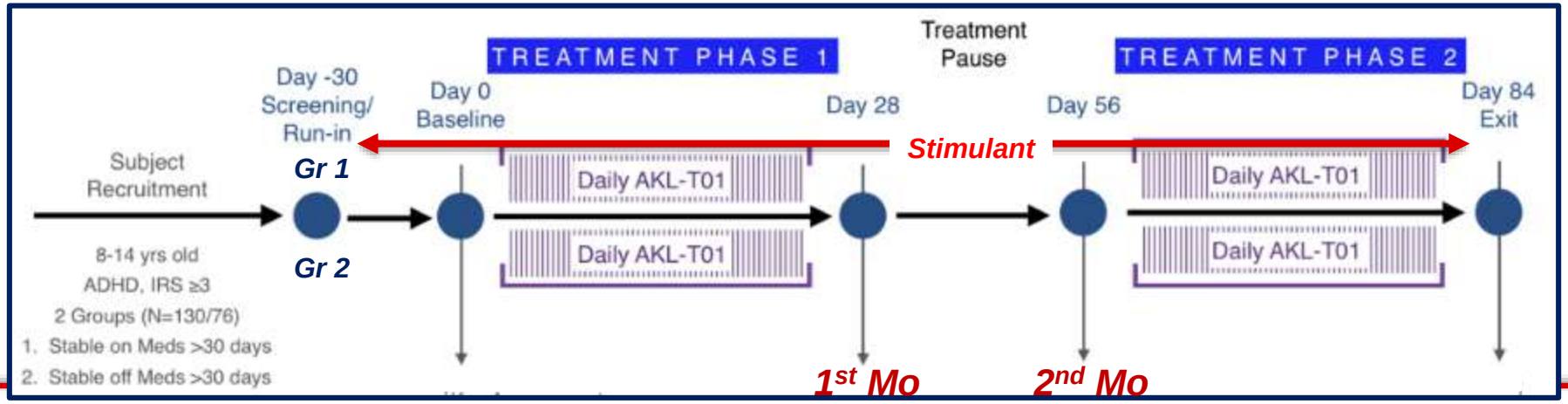
AKL-T01 Adjunctive Study (US, Akili)

Primary objective： To determine the effects of combining AKL-T01 (SDT-001) as adjunctive treatment to stimulant medication in pediatric ADHD patient.

Endpoints： Primary: IRS (impairment rating scale, Scale of life difficulty)
Secondary: ADHD-RS-IV, TOVA, CGI-I
Exploratory: Academic Performance Test (calculation, silent reading)

Target： Pediatric ADHD patient, ages 8 to 14 years
On medication group：consistently on stimulant medication (for ≥ 30 days) prior to enrollment
Off medication group：consistently off stimulant medication (for ≥ 30 days) prior to enrollment

Method： A 1-month AKL-T01 1st treatment phase, a 1-month pause in AKL-T01 treatment phase, followed by a 1-month AKL-T01 2nd treatment phase. The participants on stimulant medication remained on medication for the 3 months and the ones off of medication remained off.



Interim Report of Adjunctive Study：Efficacy

- The IRS demonstrated significant improvement from baseline at 1st month and 2nd month. (It is similar in ADHD-RS and CGI-I).
- Each outcome demonstrated similar improvement in both the on-stimulant and off-stimulant cohorts. Further improvement is also shown after a 2nd month of treatment.

Cohort	IRS (Change from baseline)	
	1st month	2nd month
Off-medication	0.53	0.96
On-medication	0.68	1.04

S-005151 [redasemtide] Dystrophic Epidermolysis Bullosa, Acute Ischemic Stroke etc.

- **Origin**: Stemrim
- **Mechanism of action**: Mobilization of mesenchymal stem cells (MSCs) to peripheral blood
- **Characteristics:**
  - ✓ Drip intravenous infusion
  - ✓ Induction of regeneration by mobilized MSCs

- **Development stage (as of Mar. 2020)** :
  - ✓ Dystrophic Epidermolysis bullosa (DEB): Follow up study after Investigator-initiated Phase 2 study (Japan)
  - ✓ Acute ischemic stroke (AIS): Phase 2 study (Japan)
- **Plans for FY2020:**
  - ✓ DEB: Completion of follow up study, PMDA meeting (Japan)
  - ✓ AIS: Conduct Phase 2 study (Japan)

Mechanism of Action

Promote tissue regeneration

In vivo self-regeneration mechanism discovered by collaborative research with academia and venture

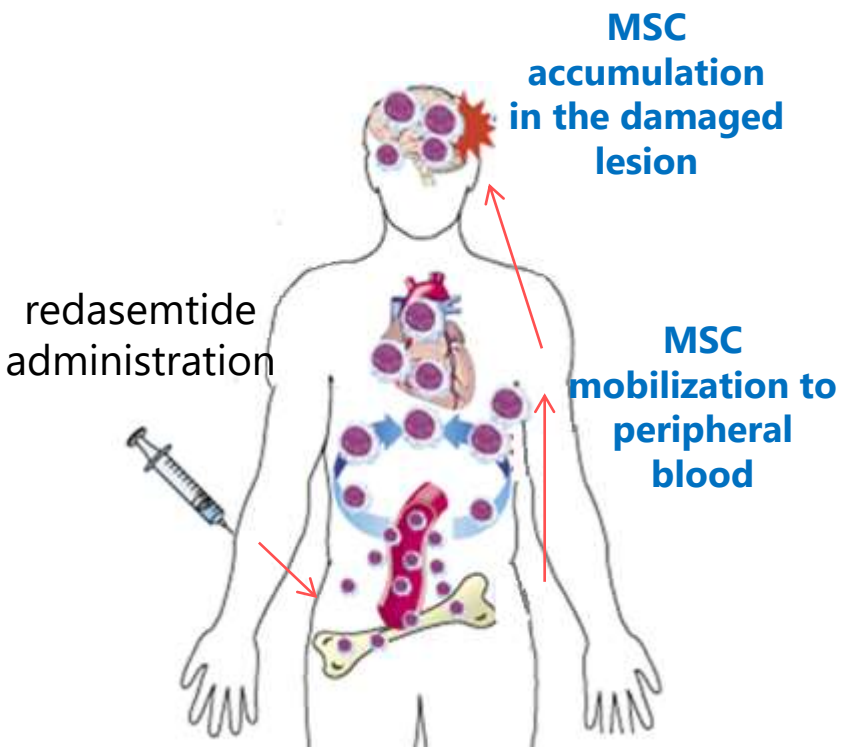
Regeneration-inducing factor → **Drug discovery seeds**

Bone marrow ⇄ Peripheral blood circulation ⇄ Damaged tissue

Mesenchymal stromal cells (MSC)

StemRIM

Suggested action of redasemtide

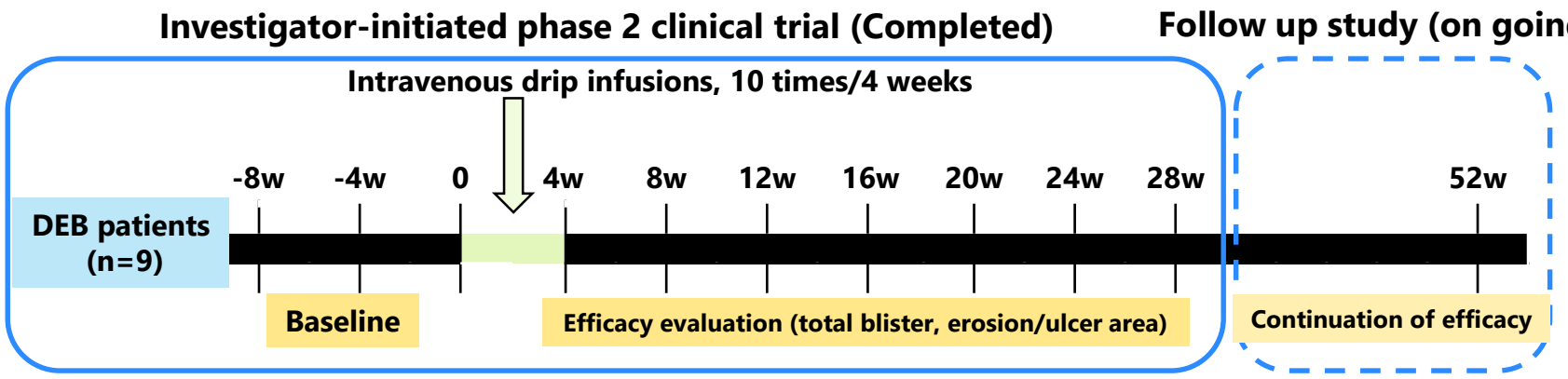


This peptide with regeneration-inducing effects arose from drug seeds derived from a collaboration with the Osaka University-originated venture, Stemrim

Study Result of DEB Clinical Study (Flash Result)

Study Design

Study title (UMIN ID: UMIN000029962)	Investigator-initiated phase 2 clinical trial of KOI2 for Dystrophic Epidermolysis Bullosa (DEB) patients*
Subjects	DEB patients , N=9
Study site	Osaka University, Toho University, Keio University
Primary endpoint	Percentage change from baseline in the total area of blisters, erosions/ulcers on the whole body
Dose and usage	Intravenous drip infusions, 10 times/4 weeks, 1 time/day [1w: 4 days/week, 2-4ws: 2 days/week]

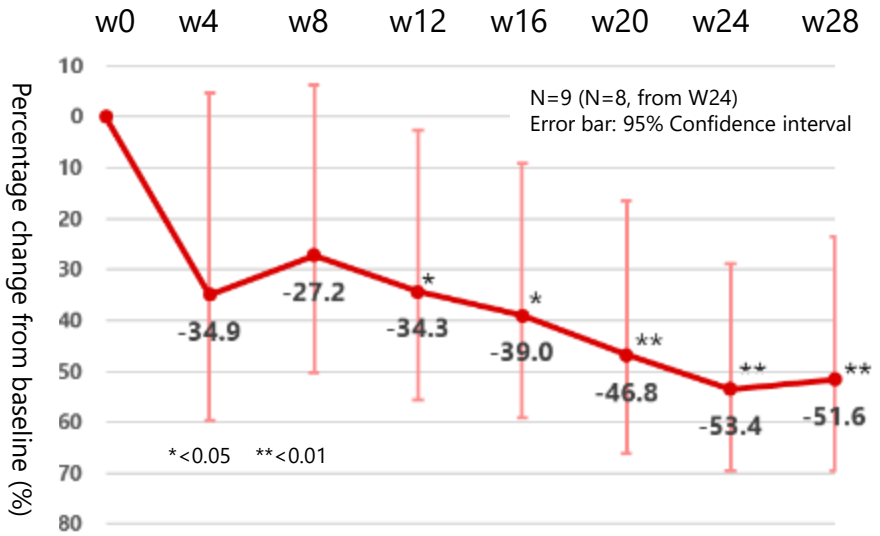


Confirmed efficacy of redasemtide in DEB patients (Flash result, next page)

*This clinical trial was supported by AMED (AMED Study No. JP19lm0203018, Representative: Katsuto Tamai, Site: Oosaka University).

Percent Change from Baseline in the Total Area of Blisters, Erosions/Ulcers on the Whole Body (Flash Result)

Total (n=9)

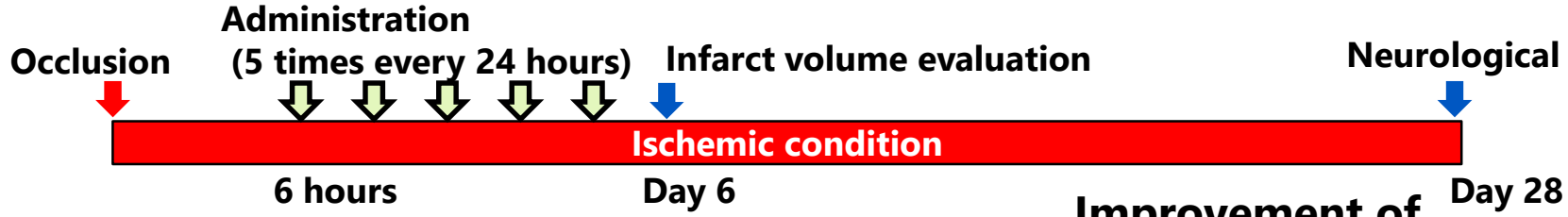


Statistically significant improvement (After week12)

This result suggests that **redasemtide might be effective in lesions on the entire body**, differing from other regenerative medicines whose efficacy is limited to the site of administration

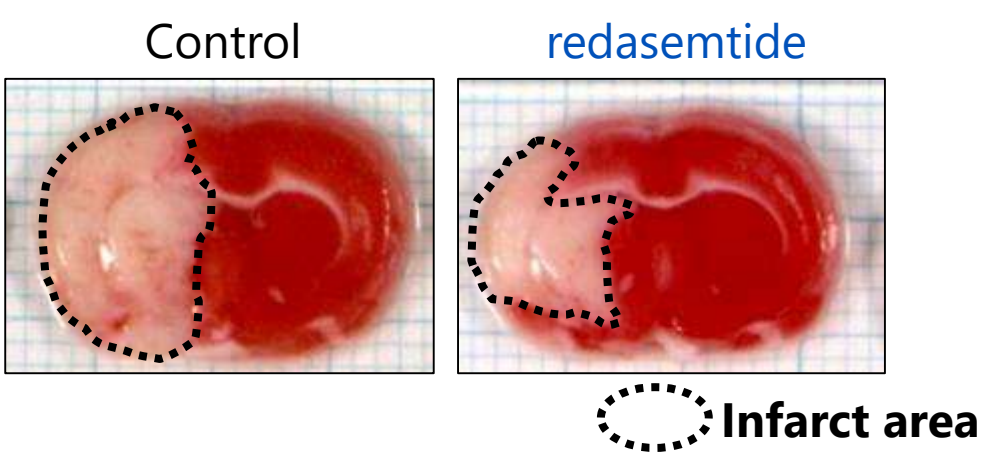
Acute Ischemic Stroke - Efficacy and Target Segments

Rat permanent occlusion model prepared by MCAO*
Administration of redasemtide was started from 6 hours after MCAO.



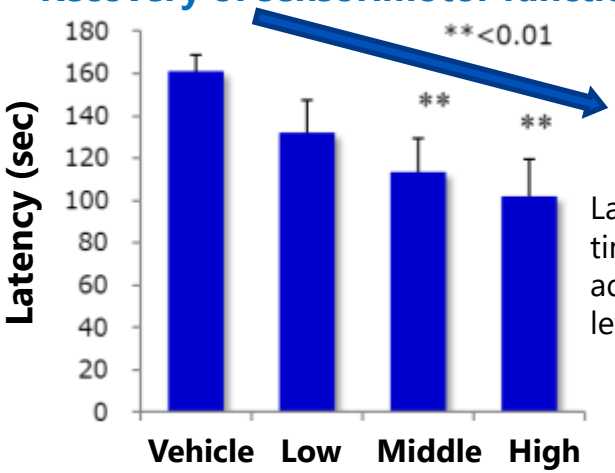
Neuroprotective effect

Infarct size reduction



Improvement of neurological deficits

Recovery of sensorimotor function



Latency shows the time to remove the adhesive tape from left forelimb.

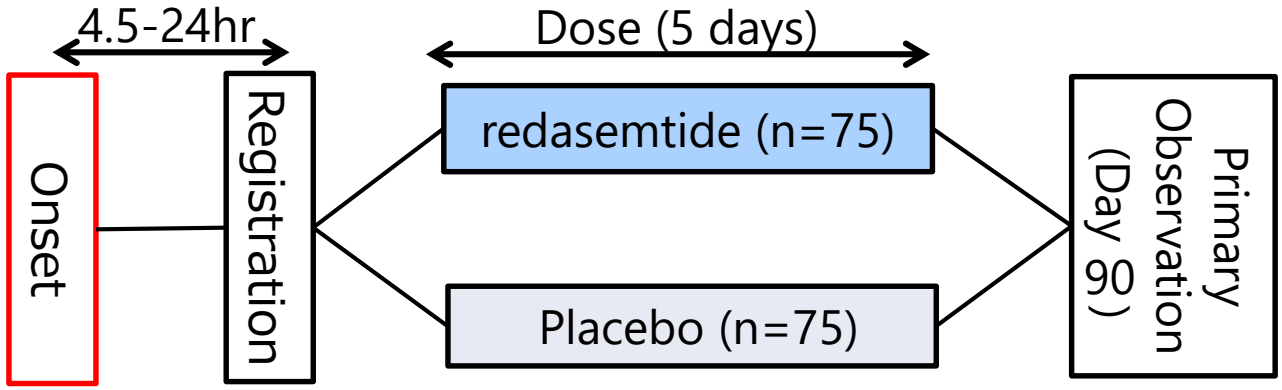
These results indicate that redasemtide may be effective in the patients without reperfusion within 24 hours after the onset of ischemic stroke.**

SHIONOGI

* Middle cerebral artery occlusion
** Six hours efficacy in rats was estimated to 24 hours efficacy in human by the mismatched region analysis

Study Design:
Acute Ischemic Stroke Phase 2 Study

Subjects	Acute Ischemic Stroke patients within 4.5 to 24 hours after the onset of ischemic stroke
Study design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group
Target sample size	150
Primary endpoint	modified Rankin Scale (mRS) 90 days after the first dose
Dosage	Once daily, 5 days (90 min infusion)
Location	Japan
Protocol ID	1810P2221 (JapicCTI-194963)

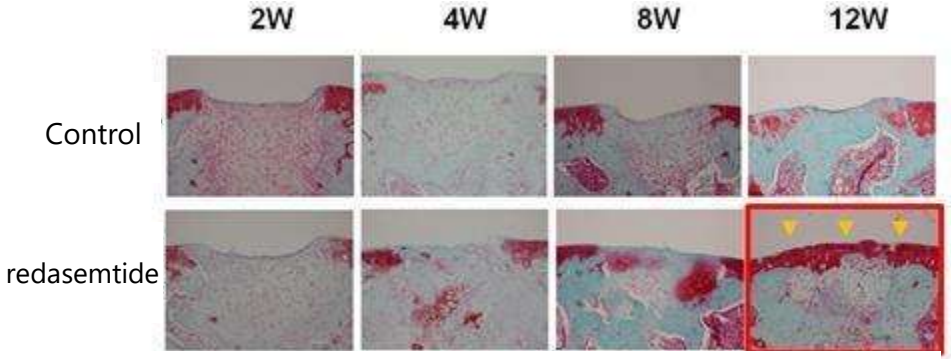


Nov, 2019: First Patient In

Sep, 2021: Last Patient Out

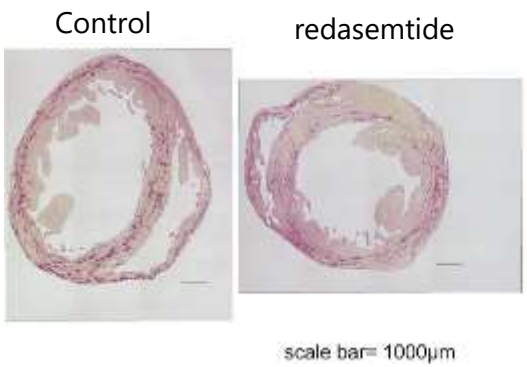
Non Clinical Study Report

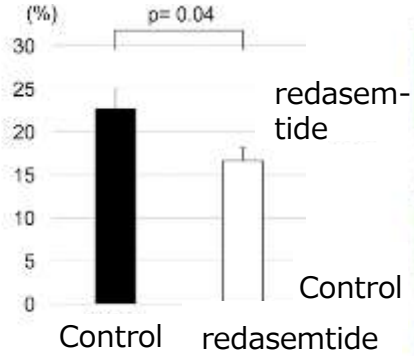
Cartilage regeneration in rat joints



(collaborative research by Osaka University and STEMRIM)

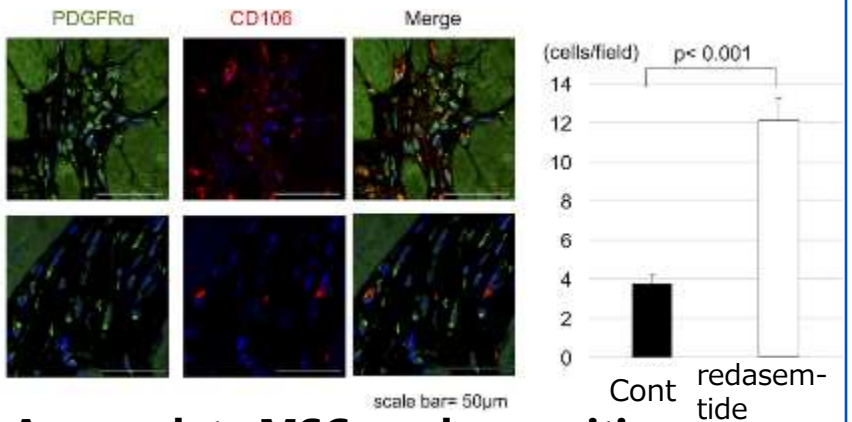
Efficacy in a hamster model of dilated cardiomyopathy (PLOS ONE | https://doi.org/10.1371/journal.pone.0202838 December 5, 2018)





Reduced the degree of myocardial fibrosis

(collaborative research by Osaka University and STEMRIM)



Accumulate MSC marker positive cells in myocardium

LCM Plan

Cirrhosis of the liver

- Improve liver function
- Provide new treatment opportunities for patients without effective treatment

Knee osteoarthritis

- Cartilage regeneration
- Provide new treatment opportunities that can contribute to improving QOL in an aging society

Cardiomyopathy

- Reduce myocardial fibrosis
- Provide new treatment opportunities for patients without effective treatment

Licensed exclusive development, manufacturing and marketing rights worldwide from STEMRIM

Plan to start physician initiated clinical study based on the nonclinical evidence

Maximize the value of S-005151 as a regeneration-inducing drug with strong collaboration with academia

S-770108
Idiopathic Pulmonary Fibrosis

- **Origin**: in-house
- **Mechanism of action**: Antifibrotic
- **Characteristics**:
  - ✓ Oral pirfenidone is recommended treatment for IPF as per international guidelines
  - ✓ Inhaled dry powder formulation accompanied by a specifically developed inhaler device
  - ✓ By directly delivering the drug to the site of action in the lungs, a substantial reduction in systemic exposure and improved safety profile can be expected
- **Development stage (as of Mar. 2020)**: Lung deposition study under preparation (UK)
- **Plans for FY2020**: Examine the ability to reach the lungs during the lung deposition study (UK)

S-770108 Development Approach

Oral Pirfenidone (Pirespa® & Esbriet®)

[Efficacy]

- Efficacy established in pivotal trials[1-3)]
  - Reduction in rate of lung function decline ; (Forced) vital capacity
  - Maintenance of 6 minute walk test distances
  - Extended progression free survival
- Improved survival (reduced mortality)[4)]

Recognized in international guidelines as a recommended treatment for IPF (2015)[5)]

[Safety]

- High incidence of side-effects
  - Photosensitivity (14.4%)
  - Loss of appetite (27.9%), Nausea (8.0%)
- Over half of patients fail to reach the recommended maintenance dose (1800 mg)
- Around 20% of patients discontinue the drug due to side-effects

(Figures from Japanese domestic PMS study[6)])

- **Greatly reduce systemic exposure by directly delivering the drug to the lungs**
- **Achieve efficacy while reducing the incidence of side-effects related to the oral formulation, while maintaining adequate concentration in the lungs and improved adherence.**
- **Assessing global development plans**

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 Overall Development Strategy

① Preclinical，Pharmacodynamics
Assess the effective lung dose required during inhalation in animal models

② Phase 1 Pharmacokinetic study (Completed)
- Well tolerated, good safety profile
- Pharmacokinetics：Approximately 1/100 of that seen after an oral dose

③ IPF patient inhalation study (Japan, 2019)
- Assess inhalational flow rates obtainable by IPF patients using the device, then utilize these flow rates during the lung deposition study④

④ Lung deposition study (UK, Healthy volunteers, FY2020)
- Using inhalational flow rates identified in ③，examine lung deposition parameters (particularly in the outer lung) after drug inhalation
- Determine whether sufficient amount of drug reaches the peripheral lung for efficacy to be expected

⑤ Late phase trials
Demonstrate the safety and efficacy in IPF patients

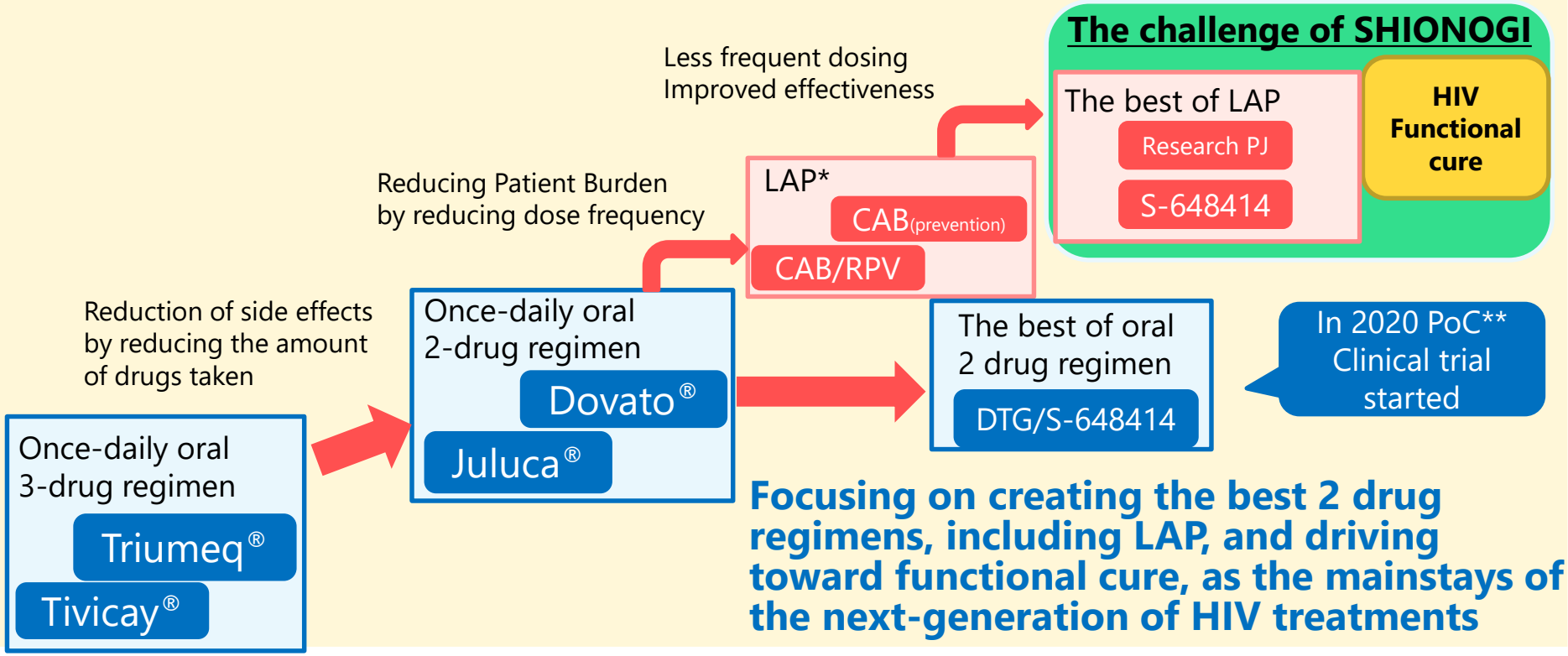
- **The lung deposition study is key for inhaled drug development as it may allow us to forego dose-ranging studies and increase development speed**
- The physiochemical properties of pirfenidone powder prevented the application of previously utilized ^{99m}Technetium radiolabeling methods (Wet, Dry methods), a new hybrid method was developed for this project, which is undergoing process validation

S-648414
HIV

- **Origin**: in-house
- **Mechanism of action**: Not disclosed
- **Characteristics**:
  - ✓ New mechanism of action
  - ✓ Excellent efficacy against viruses resistant to other anti-HIV drugs
- **Development stage (as of Mar. 2020)** : Phase 1 study ongoing (US)
- **Plans for FY2020**:
  - US: Complete Ph1
  - US: Initiate Phase 2 study (POC)

Challenges for Developing Anti-HIV Drugs

Anti-HIV drug market will be changed by the availability of generics for DTG in 2028 or after. Improving on these options requires reducing the overall burden and stress of HIV treatment on patients.



* LAP: Long acting parenteral administration
CAB: cabotegravir, RPV: rilpivirine, DTG: dolutegravir

Single Oral Dose Study Results and Future Development

Phase 1 single oral dose study (preliminary results)

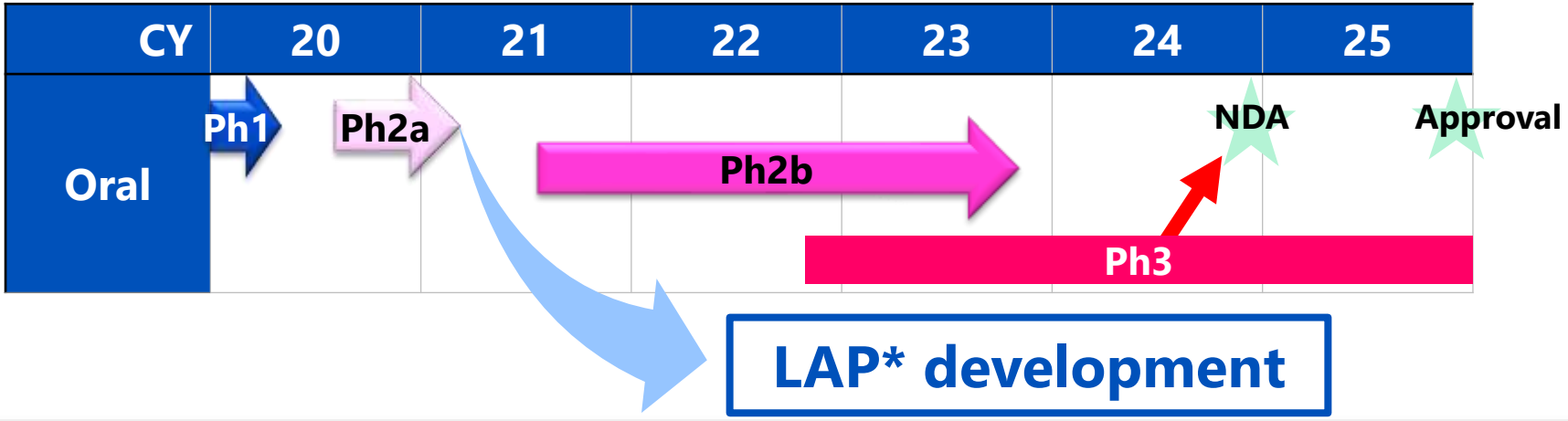
- Safety : No major concern
- PK : Achieved a target drug concentration for efficacy at low dose

Excellent safety and efficacy profile expected

Initiate PoC study once safety and tolerability at multiple doses are confirmed

Deliver the best 2 drug treatment with DTG

- Next step, development of LAP



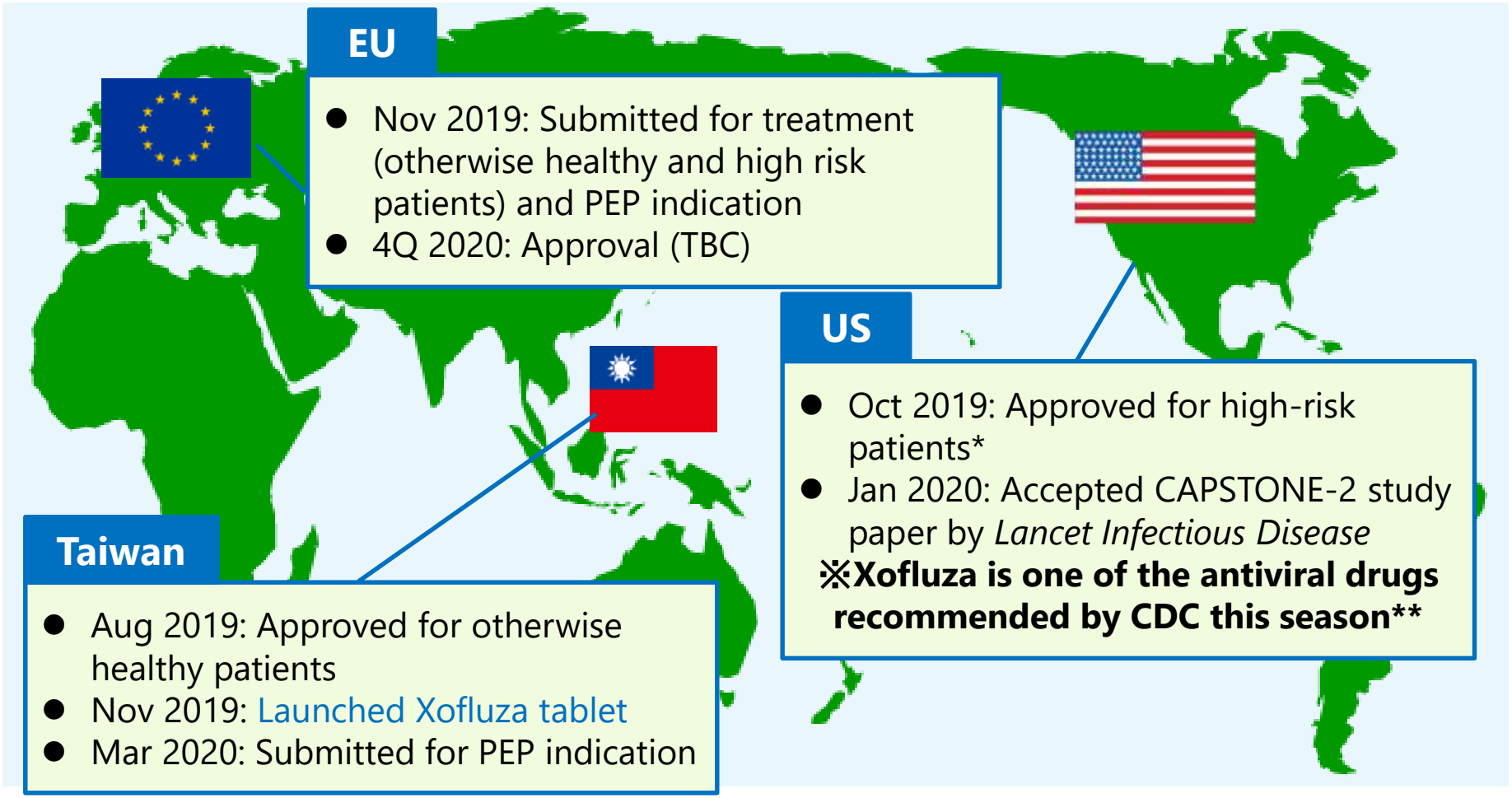
PK: Pharmacokinetics DTG: Dolutegravir * LAP: Long acting parenteral administration

Xofluza®
Influenza Virus Infection

- **Origin**: in-house
- **Mechanism of action**: Cap-dependent endonuclease inhibition
- **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

- **Development stage (as of Mar. 2020)** :
  - ✓ Japan: Submitted post-exposure prophylaxis indication (Oct 2019), Completed patients enrollment in Japan high-dose pediatric study
  - ✓ Taiwan: Launched Xofluza tablet (Nov 2019), Submission for post-exposure prophylaxis (Mar 2020)
  - ✓ US: Approved for otherwise healthy patients and high-risk patients
  - ✓ EU: Submitted for treatment (otherwise healthy and high risk patients) and post-exposure prophylaxis indication (Nov 2019)
  - ✓ Global: Hospitalized study, reduced transmission study, pediatric study (under 1 year old) are ongoing
- **Plans for 2020FY**:
  - ✓ Japan: Complete Japan high-dose pediatric study
  - ✓ Global: Complete hospitalized study and pediatric study

Outside Japan: Smooth Development Progress to Support its Full Potential



EU

- Nov 2019: Submitted for treatment (otherwise healthy and high risk patients) and PEP indication
- 4Q 2020: Approval (TBC)

US

- Oct 2019: Approved for high-risk patients*
- Jan 2020: Accepted CAPSTONE-2 study paper by *Lancet Infectious Disease*

※Xofluza is one of the antiviral drugs recommended by CDC this season**

Taiwan

- Aug 2019: Approved for otherwise healthy patients
- Nov 2019: Launched Xofluza tablet
- Mar 2020: Submitted for PEP indication

Increase product platform by adding indications in major markets in collaboration with Roche group

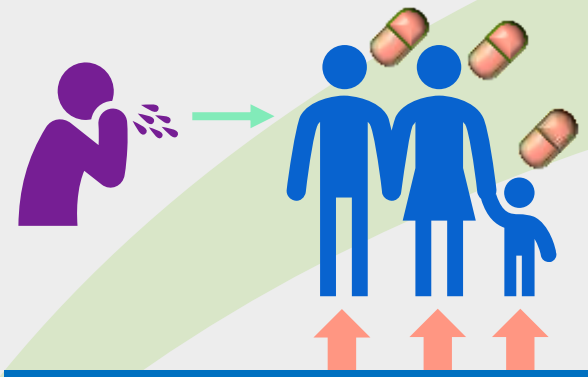
*high-risk patients：patients at high risk of flu complications　PEP：Post-exposure prophylaxis

** https://www.cdc.gov/flu/treatment/baloxavir-marboxil.htm

Strong Antiviral Effect: Confirmed Prophylaxis and Reduced Transmission Effects of Xofluza

- Post-exposure prophylaxis study

Confirm post-exposure prophylaxis effect in household contacts treated with Xofluza

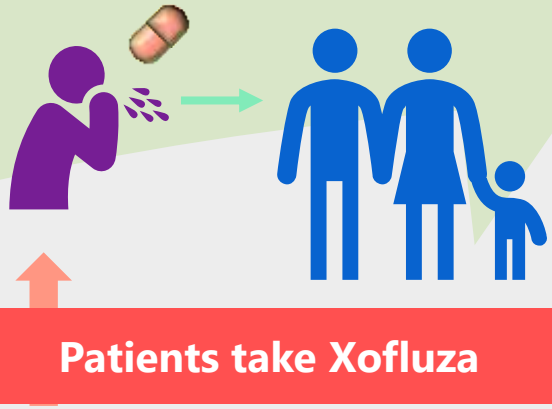


Household contacts who have index patients took Xofluza

Confirmed post-exposure prophylaxis effect

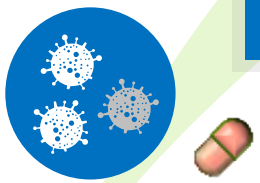
- Reduced transmission study
- Collaborative observational study with a clinic in Japan

Confirmed reduced transmission effect in patients treated with Xofluza



Patients take Xofluza

Confirmed reduced transmission effect following post-exposure prophylaxis effect driven by strong antiviral effect of Xofluza



Xofluza®
Strong antiviral effect

I38-substituted Virus: Characteristics Based on Clinical/Non-clinical and Surveillance Data

- **Association between the incidence of I38-substituted viruses and clinical symptoms:**
  In all age populations, the rate was higher in A/H3N2, **though the median time to alleviation of illness tended to be longer in some younger pediatric populations, the tendency is not apparent in 6-12 years old pediatric patients**
- **Susceptibility・replicative capacity・competitive fitness:**
  Though I38-substituted virus from clinical isolates showed reduced susceptibility to Xofluza, **replicative capacity of substituted viruses was comparable to the wild-type. In competitive fitness experiment, wild-type became dominant under co-infection of wild-type and I38-substituted viruses**
- **Transmission:**
  According to the surveillance results in prior season, **several human-to-human transmission cases were found, but large-scale transmission of I38-substituted viruses has not been seen in this season or prior seasons**

Statement for Xofluza use issued by JAID* and JPS**

12 to19 years of age and adults： No decision on a recommendation for XOFLUZA use has been made at present due to limited clinical data

Children <12 years of age： Careful consideration of the XOFLUZA use, taking into account the high rates of emergence of variant viruses

Continue to collect further data and analyses to characterize I38-substituted virus

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*JAID (The Japanese Association for Infectious Disease) http://www.kansensho.or.jp/modules/guidelines/index.php?content_id=37

**JPS (JAPAN PEDIATRIC SOCIETY) http://www.jpeds.or.jp/uploads/files/2019-2020_influenza_all.pdf

I38-substituted virus: Actions for Surveillance

- **Purpose of surveillance:**
  Investigate susceptibility of flu viruses to Xofluza, incidence of substituted virus emergence and clinical outcomes in patients with I38-substituted viruses

2018/19 | 2019/20 | 2020/21 | 2021/22 | 2022/23 | 2023/24 | 2024/25 year

▶ **Drug use result survey: Niigata university** -> **Surveillance results uploaded in Shionogi website* twice a month**

Number of samples: 100 strains/year
Period: 6 seasons from 2018/19 season

▶ **Domestic surveillance (JPA surveillance)**

Number of patients: 300 patients/season
Period: 2-3 seasons from 2019/20 season

▶ **Global surveillance (Roche):**
Under discussion

Investigate characteristics of I38-substituted viruses in collaboration with Roche group

Disclose the surveillance results in a timely manner
Continue to investigate characteristics and transmissibility of I38-substituted viruses

* Shionogi Xofluza website https://www.shionogi.co.jp/med/p_xofluza/flu_virus_info/
JPA: Japan Physicians Association

Detection of I38-Substituted Viruses in This Season

- **NIID: Detection of antiviral drug-resistant viruses in Japan during the 2019/2020 influenza season (as of Mar. 16, 2020)**

	A(H1N1)pdm09	A(H3N2)	B
Resistant (%)	1* (0.2%)	0 (0.0%)	0 (0.0%)
Number of viruses tested	515	36	15

*In accordance with WHO's provisional standards, defined as a reduced susceptibility virus when three fold or more susceptibility reduction is confirmed, patient without treatment

- **Drug use result survey result（Conducted by Niigata university: as of Mar. 18, 2020）**

Frequency of influenza patients with PA/I38 mutations in Japan during 2019/20 influenza season

Mutation / Type/Subtype	Pre-treatment	Post-treatment with baloxavir	
		Based on all treated cases	Based on sequence-positive in the second sample
A(H1N1)pdm09	0% (0/158*)	2.1% (1/48*)	4.2% (1/24*)
A(H3N2)	–	–	–
A(H1N1)pdm09 and A(H3N2)	– (1**/1)	–	–
B	– (0/1)	–	–

*E199D was detected in pre- and post-treatment samples collected from one patient. The susceptibility test is assessing.
**A patient with mixed infection of A(H1N1)pdm09 and A(H3N2) harboring PA/I38T. The A(H1N1)pdm09 sequencing was unavailable.

- **In this season, I38-substituted viruses with reduced susceptibility have been rarely observed in pre-treatment samples**
- **Spread of I38-substituted viruses have not been observed**

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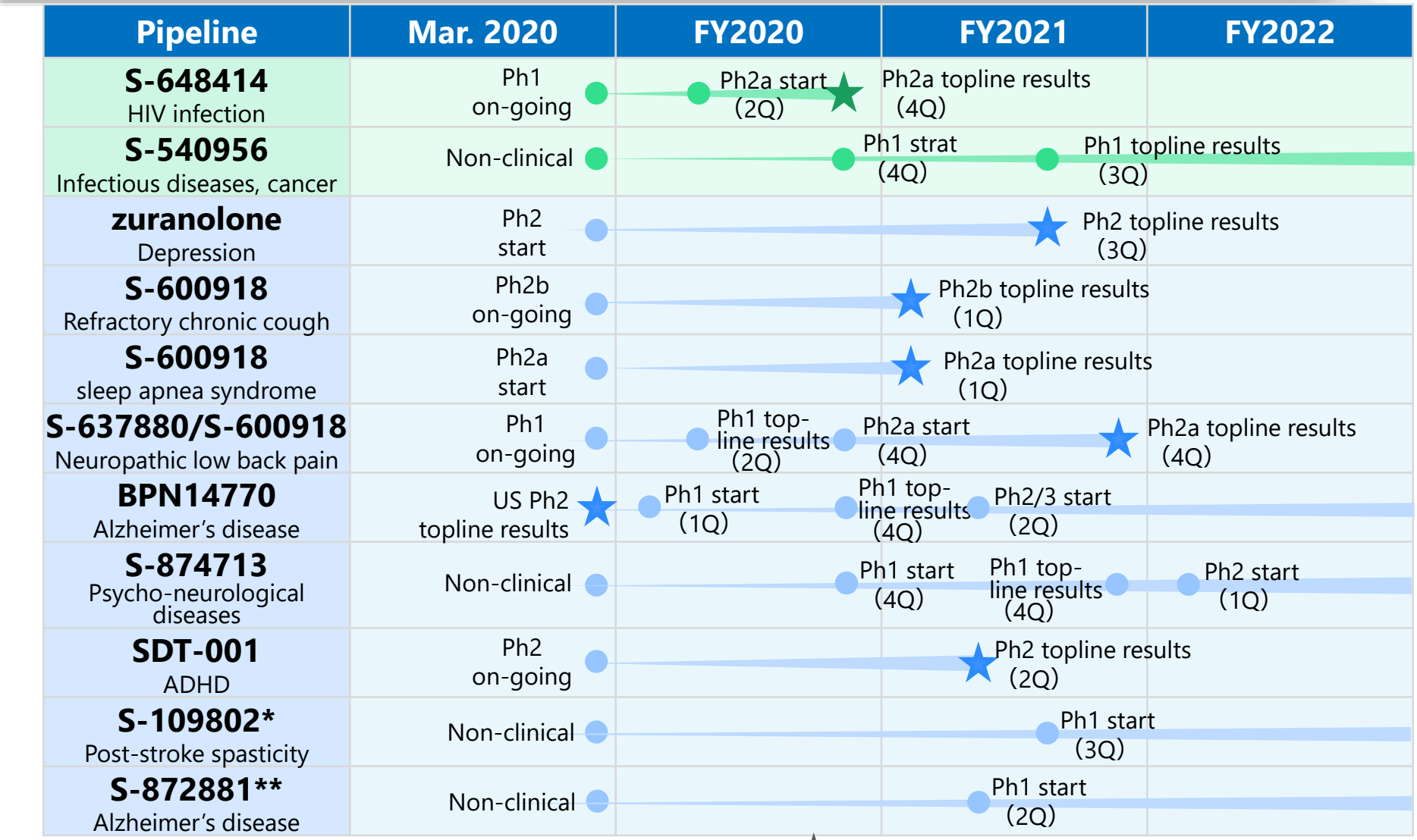
NIID: National Institute of Infectious Diseases
NIID Antiviral resistance surveillance in Japan https://www.niid.go.jp/niid/ja/influ-resist.html
Niigata University Antiviral Susceptibility http://www.med.niigata-u.ac.jp/pub/category/influenzasearch/

Development Timelines

Key Events for Major Pipeline Compounds



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* S-109802: Profiles are shown in appendices, p.137-139

** S-872881: Profiles are shown in appendices, p.140, 141

Key Events for Major Pipeline Compounds

Pipeline	Mar. 2020	FY2020	FY2021	FY2022
redasemtide Epidermolysis bullosa	sponsor investigator top-line results ★		Launch	
redasemtide ischemic stroke	Ph2 on-going		★ Ph2 topline results (3Q)	
Regulatory T cell inhibitor Cancer	Non-clinical		Ph1 start (2Q)	
S-588410 Esophagus cancer	Ph3 on-going	★ Ph3 topline results (1Q)		
S-588210 Solid tumor	Ph1 on-going	Ph1 topline results (2Q)		
S-770108 Idiopathic pulmonary fibrosis	Preparation for lung deposition study (LD study)	LD study start (1Q) / LD study topline results (3Q)	Ph2/3 strat (2Q)	
S-723595* NASH	Non-clinical	Ph1 start (3Q)	Ph1 topline results (3Q)	Ph2a start (3Q)
S-309309** Obesity	Non-clinical		Ph1 start (2Q)	Ph1 topline results / Ph2a start (4Q)

★ Ph2 or Ph3 top-line results are anticipated

* S-723595: Profiles are shown in appendices, p.142, 143

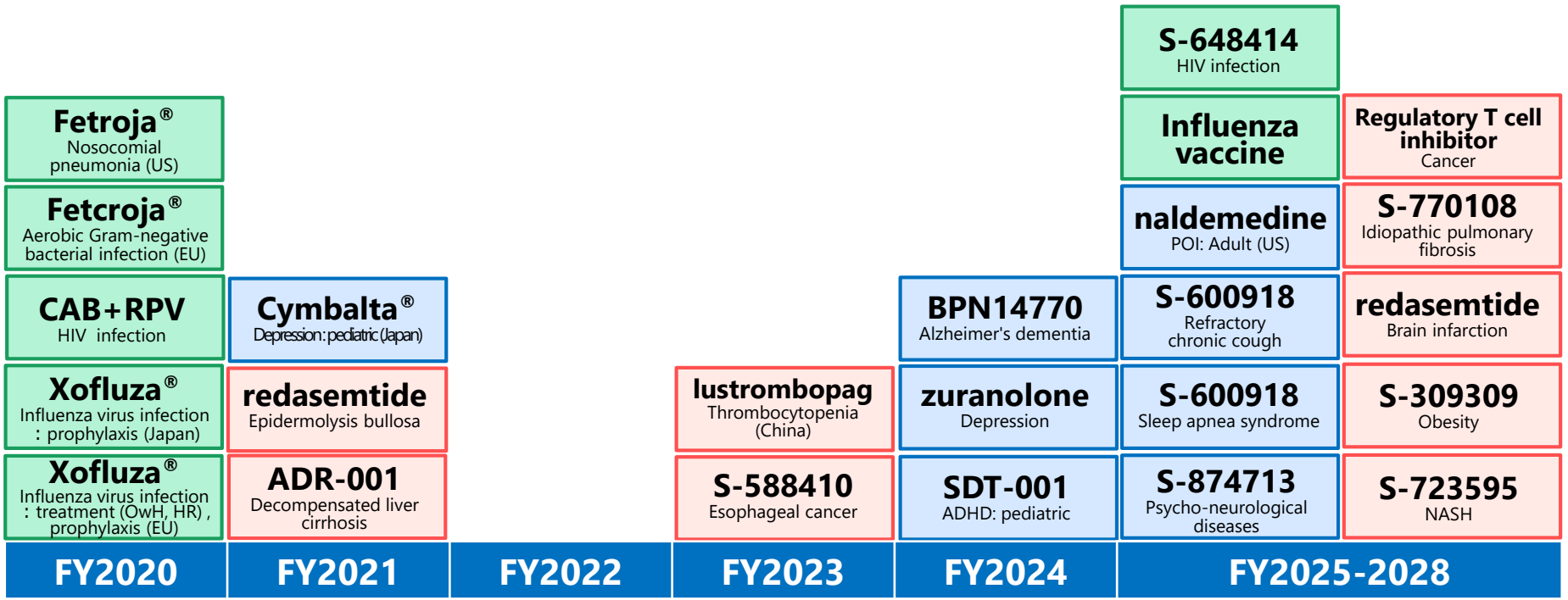
** S-309309: Profiles are shown in appendices, p.144, 145

Launch/sNDA Approval Target

Infectious disease

Psycho-neurological diseases

New growth areas



Launch innovative drugs continuously

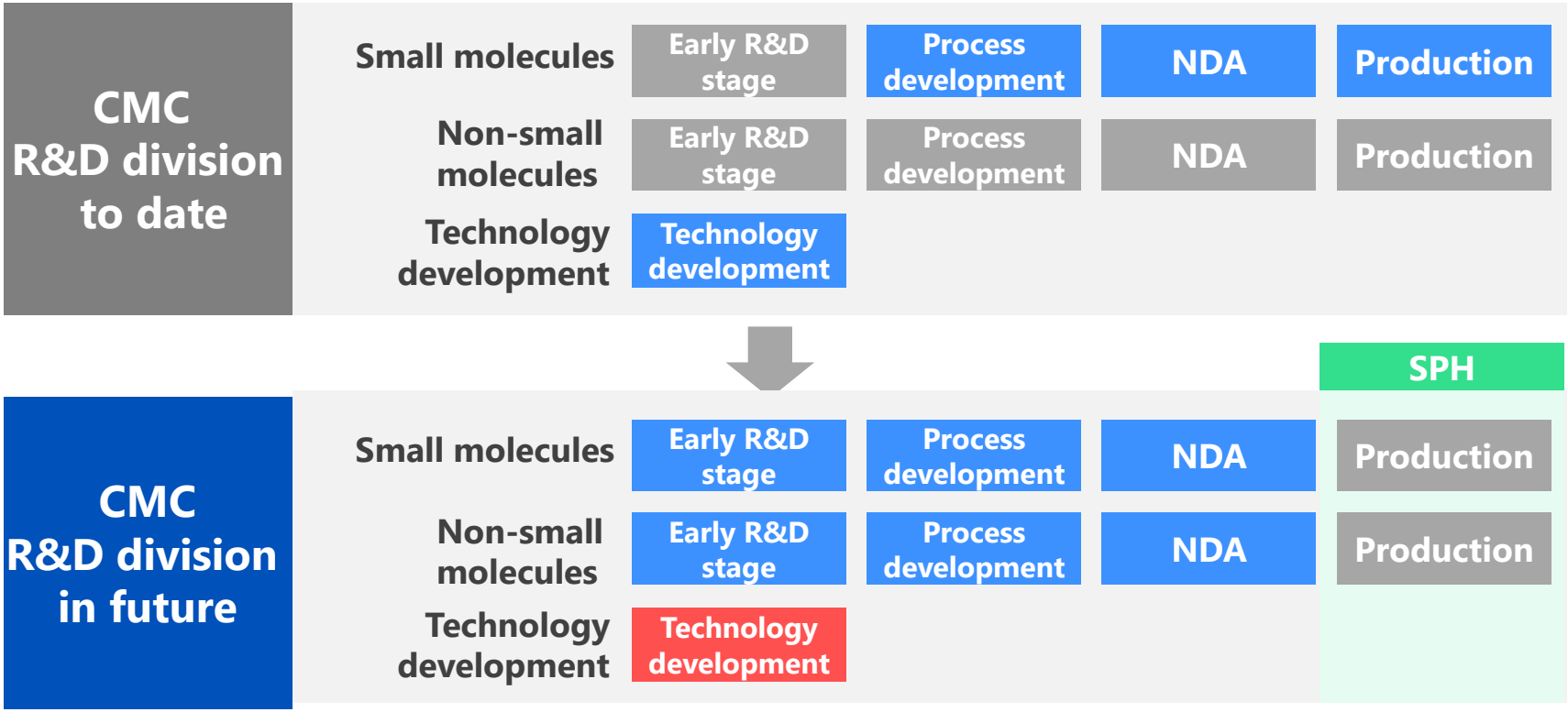
* Addition of data to the label
POI: Post Operative Ileus

CAB: cabotegravir, RPV: rilpivirine

CMC Research & Development

Yasuyoshi Isou, Ph.D.
Corporate Officer
Senior Vice President
CMC R&D Division

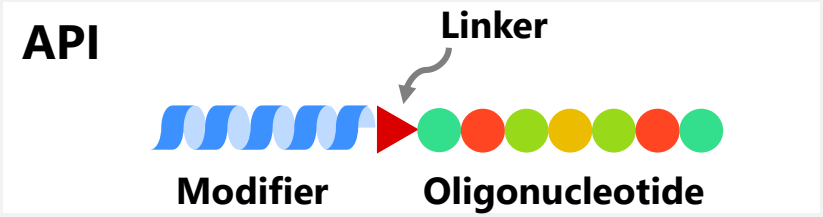
Changes in the Role of CMC R&D Division



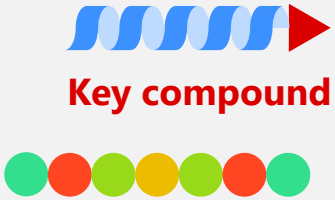
- Manufacturing function is unified into Shionogi Pharma (SPH)
  ➡ **Optimization of overall group companies**
- Expanding the scope of modalities beyond **small molecules to non-small molecules**
  - Application of legacy technologies/knowhow acquired through small molecule experience
- To further strengthen new technology development for the future

New Manufacturing Approach for a Specialty Oligonucleotide Drug

Instability of Key Compound



Primary Approach



Low Productivity
Key Compound is **too unstable** to produce

Stability of Key Compound

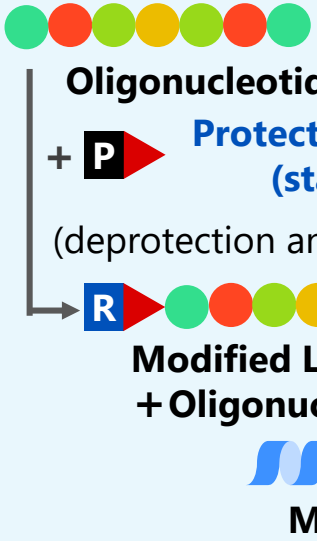
Primary Approach

- decomposed with unacceptable rate even in a freezer

New Approach

- Stable at room temperature for a couple of months

New Approach with Stable Key Compound



The novel protected linker was successfully developed and applied to manufacturing through collaboration between Med. Chem. and CMC.

Efficient manufacturing approach
for Oligonucleotide drug was established.

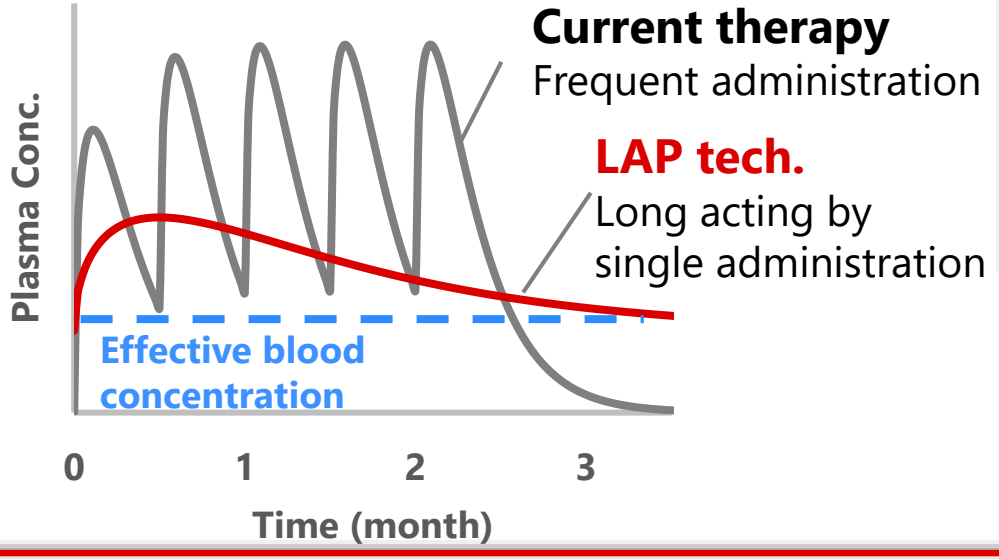
Maximizing the Value of Our Products by Long Acting Parenteral Technology

Current therapies

Everyday oral administration for many years

- High medication burden for patients
- Risk of disclosure of therapy and constant reminder of disease

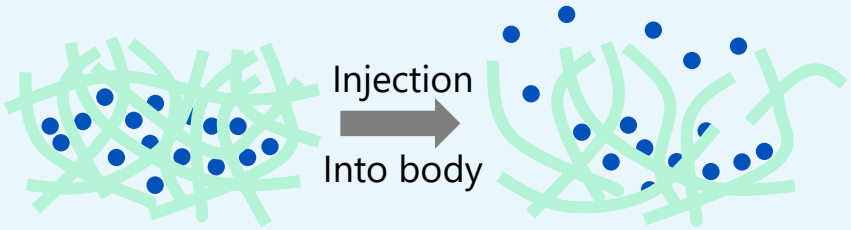
Schematic diagram on Plasma concentration of API



Current therapy
Frequent administration

LAP tech.
Long acting by single administration

Long Acting Parenteral (LAP) tech.



Polymer matrix
API

Polymer matrix swells and gradually expands by absorbing moisture
➡Sustained API release

➡ **Seek to achieve new treatment paradigm through long-acting release of product**

Product development for medical needs of patients
by combination of therapeutic potential of compound and LAP tech.

Feasible Peptide Drug Manufacturing Methods

1: Peptide Drug

Typically High-cost

- Traditional manufacturing protocols: Solid Phase Peptide Synthesis (SPPS) has **Low-productivity**.

2: Productivity Improvement with Micro Wave (MW) Irradiation

MW irradiation improves the productivity of SPPS

- Acceleration of reaction time

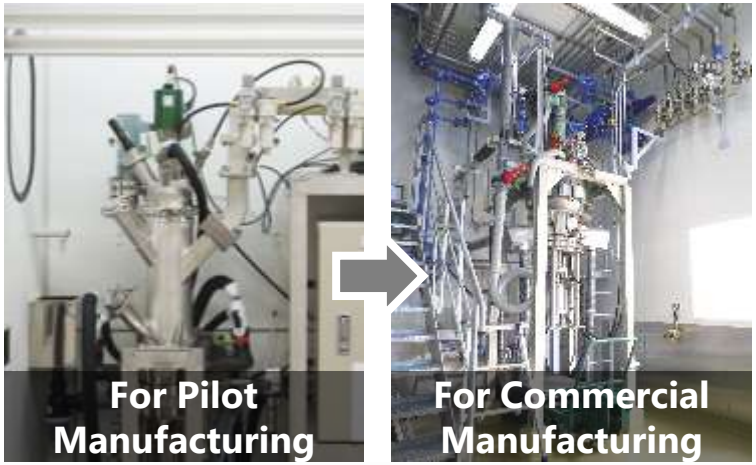
40hrs ➡ 1h

Announced at the 2017 R&D briefing meeting

3: From Lab. to Mfg.

Introduction of MW equipment in Commercial Mfg.

- Substantial lead-time required to implement special equipment.



4: Implementation in Mfg. Facility

Seamless introduction of MW equipment has been achieved through a technical alliance with PeptiStar Inc.

PeptiStar

Cost Reduction of Peptide Drug is Achieved by **Productivity Improvement**

Photos provided by PeptiStar Inc.

Oral Formulation Technology Development for Peptide Drug

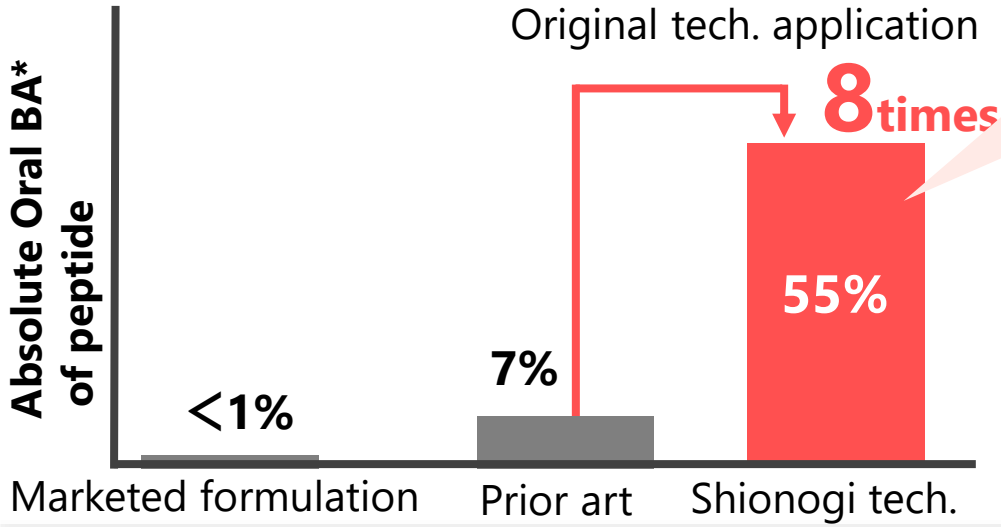
Advantages and challenges of oral formulation

Advantages of oral formulation

- **Most common administration method**
- **Easy for self-administration by patients**

Challenges for Oral formulation

- Oral formulation for is hard to achieve for **degradable and/or poorly absorbable** compounds
- Low absolute oral BA, especially peptide/medium-sized molecules



Development of oral adsorption improvement technology

Technology to achieve better oral absorption than prior approaches is under development.

Future plan

Further improving technology robustness, application to other compounds and initiate human clinical study

Oral formulation of peptide/medium-sized molecules will be accelerated

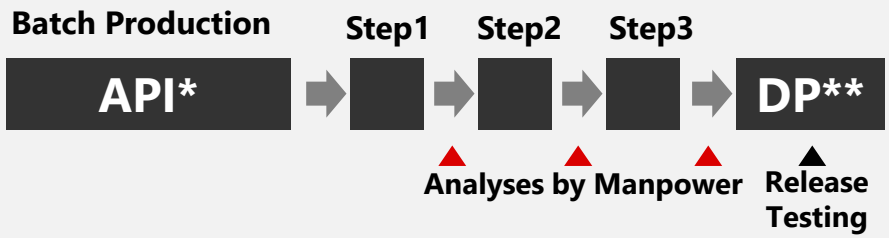
*BA：Bioavailability. Results of animal study.

Drug Product Manufacturing Productivity Improvement with Continuous Production

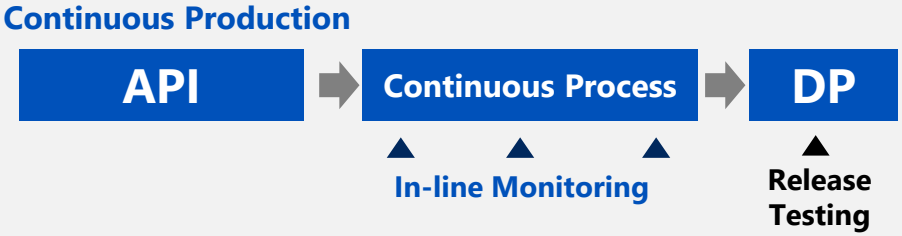
Continuous Production/ Monitoring Technology

Batch to Continuous Production

- In-line sensors for continuous manufacturing contributes **cost reduction** by saving the testing tasks performed by humans.
- The production amount can be increased without changing scale, which cuts down on scale-up experiments, thereby also **reducing cost and time for drug product development.**

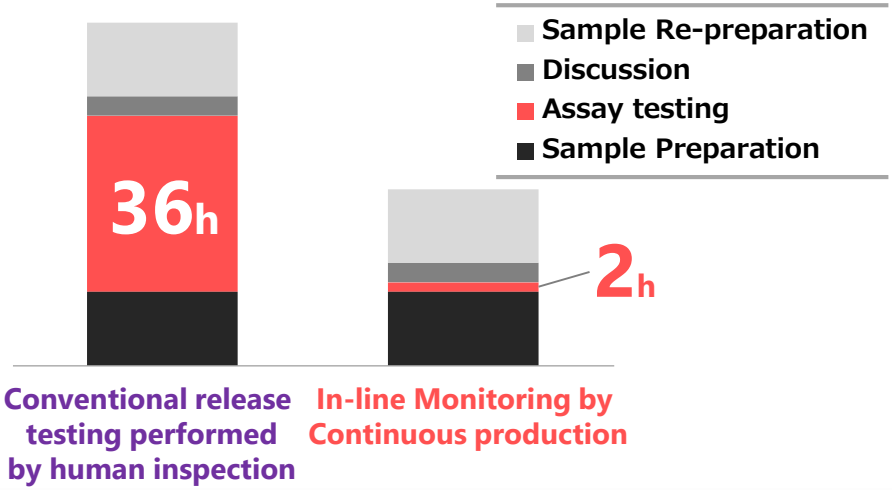


Scale-up experiments for commercial production consumes a lot of APIs and other materials, leading to **high cost and long time for drug product development.**



No need for scale-up experiments; production amount can be increased only extending the time. Continuous production of drug product **makes cost and time smaller.**

API Assay Evaluation Time for Each Batch



Contribute to cost/time reduction through continuous production and in-line monitoring technology

*API: Active Pharmaceutical Ingredients
** DP: Drug Product

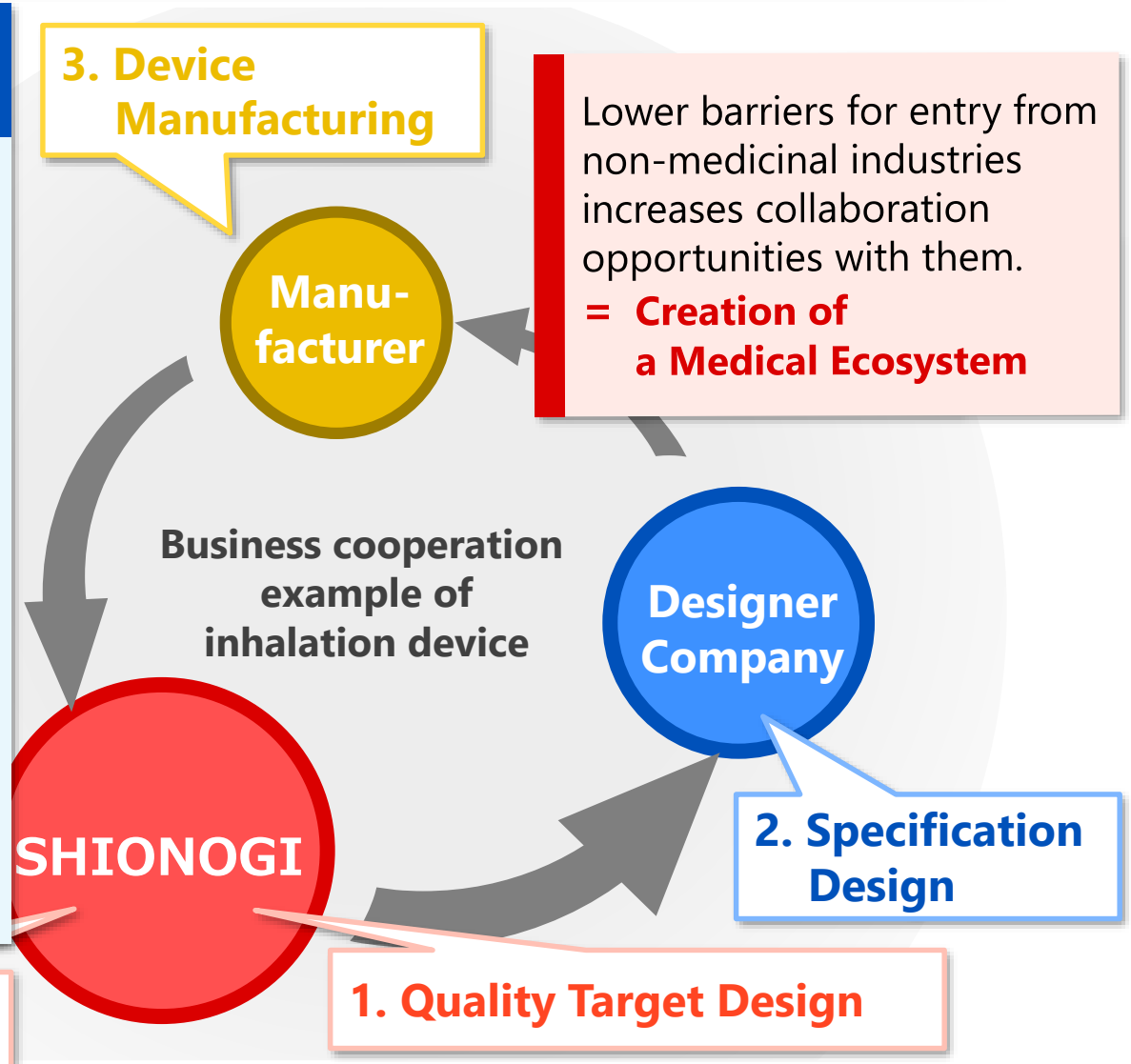
Device Development Through Collaboration

Choosing the Best Administration Route

The key to maximizing value is selection of administration route that matches the properties of the drug substance, such as pulmonary, nasal, transdermal, or subcutaneous injection, in addition to general oral administration.

➡ Especially for specific routes of administration require tailored devices

➡**A product development system through design and collaboration with manufacturers** is required rather than in-house only.



Next Targets: New Modalities

Strengths

Small Molecules

Xofluza®
S-600918
HIV franchise

Lean and agile R&D

Peptide

Peptides

Built an efficient manufacturing system with PeptiStar

Next Targets

Oligonucleotide

S-540956

Acquired manufacturing know-how through the external partner

Antibody

Regulatory T-Cell Inhibitor

Acquired manufacturing know-how through the external partner

Vaccine

Vaccine for Prevention/Therapy

Built a CMC function of vaccines with BEVS technologies of UMN

Cell

ADR-001

Preparing for NDA submission (JP) with Rohto

To expand the scope
by acquiring know-how of new modalities

BEVS: protein expression technologies employing insects cells and so on

Strengths of Shionogi CMC

Provide solutions for research and development with high probability of success

- Relieving drug seeds that are difficult to commercialize, ex) Improved absorption of poorly soluble drugs

Creation of completely new added value through product research

- Create new value and contribute to the creation of new products augmenting the company's growth

Improve industrial productivity

- Contribute to technology development for cost reduction, such as cost reduction and production efficiency improvement

Create unexpected value from Shionogi's production technology

Summary
- for growth beyond 2020 -

Isao Teshirogi, Ph.D., President and CEO

Aiming for Sustainable Growth in 2020 and Beyond

R&D Vision

Create innovations beyond the borders of medical/pharmaceutical fields, unbound from existing concepts, showing every consideration for social issues

- **Achieve a Phase 1-Phase 2 lineup of highly-differentiated products**

Beyond 2020

- **Focus resources on our key products with the goal of bringing them to market as soon as possible**
- **Continue to hone our proprietary drug discovery capabilities to become the chosen collaborator of other companies and other industries**
- **Develop a new platform leveraging our proprietary strengths, augmented and networked via partnering**

Overcome "HIV product patent cliff" for sustainable growth

Overcoming the HIV Product Patent Cliff -1-

SONG for you!

Development projects with the potential to become blockbusters (Prior to PoC confirmation)

Infectious disease	S-540956 (HIV)	S-648414 (HIV)	Vaccine (Influenza)	Corona virus infection treatment (against pandemic)
Psycho-neurological disease	BPN14770 (Alzheimer's disease etc.)	S-874713 (Psycho-neurological disease)	S-637880 (Pain etc.)	S-109802 [botulinus toxin] (Post-stroke spasticity)
New growth domains	S-540956 (Cancer)	Regulatory T cell inhibitor (Cancer)	S-770108 [Pirfenidone inhalation] (IPF)	S-723595 (NASH)

Large-scale development projects with plans for expansion of indications and regions of commercialization (After PoC confirmation)

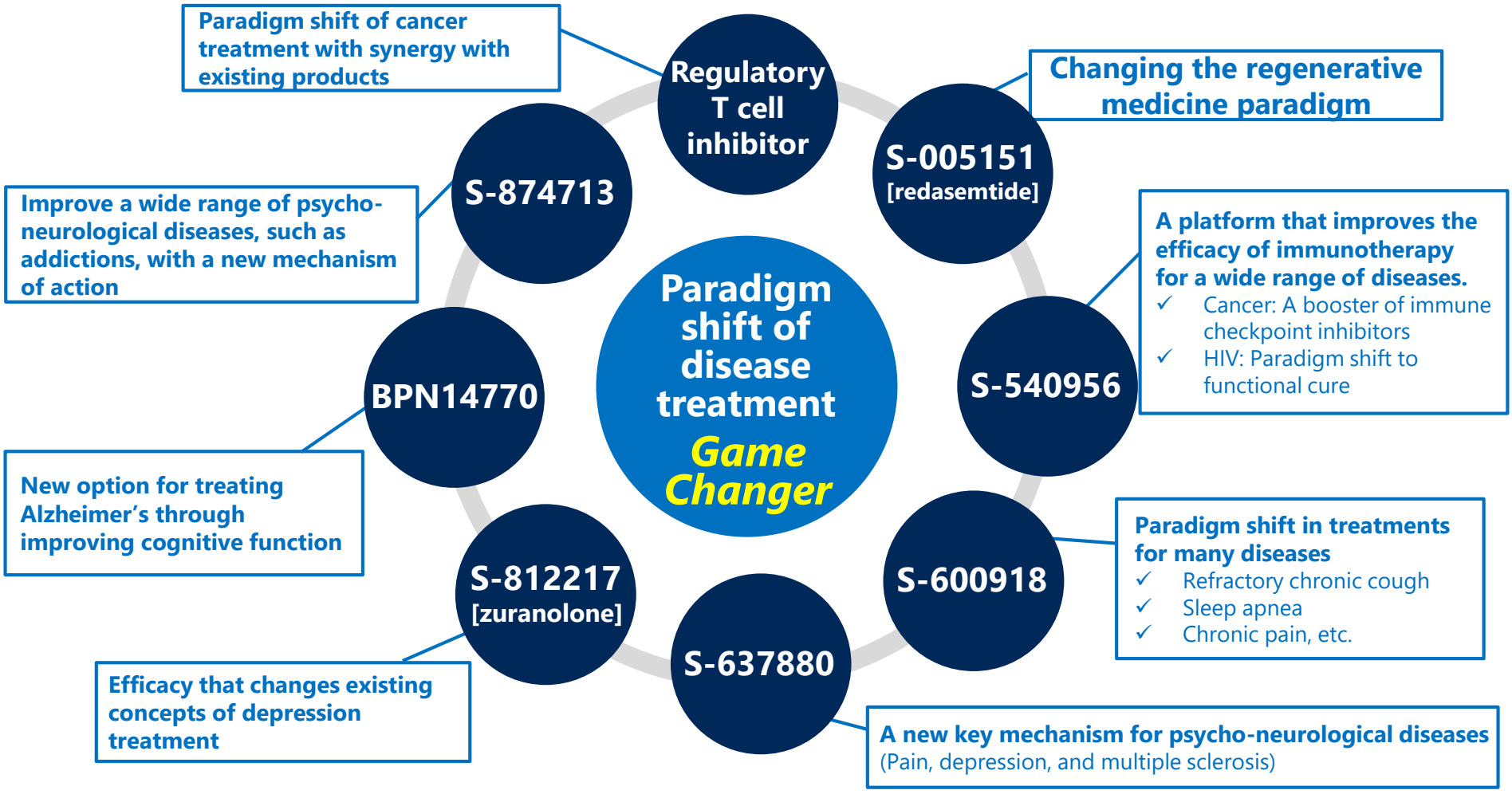
cefiderocol (Multidrug resistant Gram-negative bacterial infection)	naldemedine (Opioid-induced constipation)	S-600918 (Refractory chronic cough etc.)	S-812217 (Depression)	S-005151 [HMGB1 peptide] (Epidermolysis bullosa, ischemic stroke)
Further expand launch from the US and EU	Expand indications, adding POI to OIC	Develop additional indications beyond refractory chronic cough	Expand markets beyond Japan	Bring patient benefit through regeneration induction potential in multiple indications

PoC：Proof of concept

POI: Post Operative Ileus

Re-appeared

The World We Envision Based on Our Core Pipeline



Create products and services for diseases with no satisfactory treatment options, and contribute to solving social issues

Re-appeared

Next Targets: New Modalities

SONG for you!

Strengths

Small Molecules

Xofluza®
S-600918
HIV franchise

Lean and agile R&D

Peptide

Peptides

Built an efficient manufacturing system with PeptiStar

Next Targets

Oligonucleotide

S-540956

Acquired manufacturing know-how through the external partner

Antibody

Regulatory T-Cell Inhibitor

Acquired manufacturing know-how through the external partner

Vaccine

Vaccine for Prevention/Therapy

Built a CMC function of vaccines with BEVS technologies of UMN

Cell

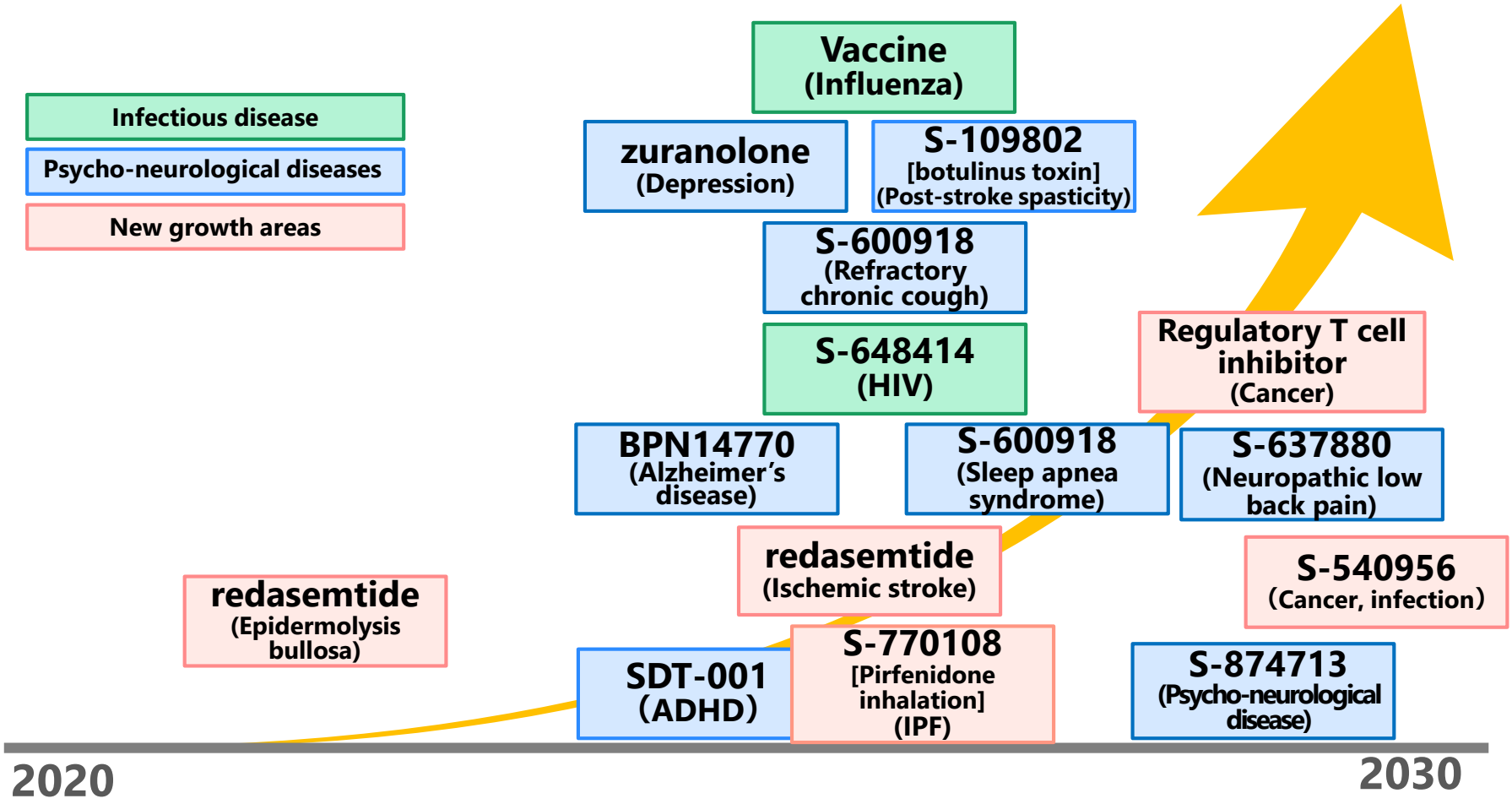
ADR-001

Preparing for NDA submission (JP) with Rohto

To expand the scope by acquiring know-how of new modalities

BEVS: protein expression technologies employing insects cells and so on

Overcoming the "HIV Product Patent Cliff" -2-
- Launch timing of core pipelines（planned）-



Advance R&D pipeline with tight focus on the timeline up to the HIV product patent cliff

Activities to Fight Infectious Diseases

Development of cefiderocol
（brand name in US：Fetroja®, brand name in EU：Fetcroja®）

- Feb.2020: Launch in US for the treatment of complicated urinary tract infections*
- Feb.2020: Positive CHMP opinion for the treatment of infections due to aerobic Gram-negative bacteria*

* Patients with no or limited treatment options

Shionogi's response to the threat of AMR is evaluated positively by the Access to Medicines Foundation

- Selected as one of the most highly rated companies in 2020, following 2018
- In the 2020 report, evaluated higher than in the 2018 report
- Active investment in R&D for antibiotics
  (the highest ratio of antibiotic R&D investment to income)
- The following points were noted favorably
  - Active surveillance of drug resistance
  - Separated the evaluation of sales representatives from the antibiotic sales levels achieved



2020 Antimicrobial Resistance Benchmark
https://accesstomedicinefoundation.org/publications/2020-antimicrobial-resistance-benchmark

Solving Societal Issues through R&D

Contributing to SDGs with R&D



To protect the health and wellbeing of everyone by solving what patients suffer focusing on infectious diseases and psycho-neurological diseases



To create innovation by utilizing various modalities from preemptive measures/prevention, diagnosis, treatment to prognosis



To establish new platforms and create innovation through cooperation with business partners that have different strengths than us

Contributing to the fulfillment of SDGs through proprietary drug discovery and the creation of healthcare innovations in cooperation with other companies

Q&A

Appendix

Pipeline (as of Mar. 19, 2020)

SONG for you!

Preclinical (target indication*)	Phase 1	Phase 2	Phase 3	Submission
Influenza virus infection	**Global**	**Naldemedine** Post operative ileus		**Fetcroja® (EU)** Aerobic Gram-negative bacterial infection
HIV infection	**S-648414** HIV infection	**Rizmoic®**** Opioid-induced constipation (pediatric)		
RS virus infection	**S-117957** Insomnia	**S-600918** Refractory chronic cough		
Bacterial infection	**S-237648** Obesity	**S-120083** Inflammatory pain		
Mycobacterium disease	**S-588210** Solid tumor	**S-707106** Type2 diabetes		
Fungus infection		**S-488210** Head and neck squamous cell carcinoma		
Vaccine for prevention influenza		**Epertinib** Malignant tumor		
Peptide		**S-588410** Bladder cancer		
S-874713 Psycho-neurological disease	**In Japan**			
Opioid	**zuranolone** Depression	**cefiderocol** Complicated urinary tract infections	**cefiderocol** Nosocomial pneumonia	**Oxycontin®TR** Moderate to severe chronic pain
S-872881 Alzheimer's disease	**S-600918** Neuropathic pain	**SDT-001** Inattentive ADHD (pediatric)	**Xofluza®** Influenza virus infection (High-dose for children)	**Xofluza®** Influenza virus infection (prophylaxis)
BPN14770 Alzheimer's disease	**S-637880** Neuropathic paiin	**S-600918** Refractory chronic cough	**Cymbalta®** Depression (pediatric)	**Xofluza®** Influenza virus infection (granule, <20 kg)
S-109802 Post-stroke spasticity	**S-010887** Neuropathic pain	**Redasemtide** Acute ischemic stroke	**S-588410** Esophageal cancer	
Peptide	**S-770108** Idiopathic pulmonary fibrosis	**Redasemtide** Epidermolysis bullosa		**Infectious disease**
S-309309 Obesity		**S-237648** Obesity		**Psycho-neurological diseases**
S-723595 NASH		**S-588410** Bladder cancer		**New growth areas**
Cancer metastasis		**SR-0379** Cutaneous ulcer		
S-540956 Nucleic acid adjuvant		**ADR-001**** Decompensated liver cirrhosis		
Peptide				

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* Target indication may include some projects

** In Phase 1/2

Pipeline
- Major Out-Licensed Pipeline (as of Mar. 19, 2020)

Preclinical (target indication*)	Phase 1	Phase 2	Phase 3	Submission
	GSK3342830 Multidrug-resistant Gram-negative bacterial infections		**Dovato®** Treatment for HIV infection TANGO study (maintenance)	**Xofluza® (EU)** Influenza virus infection (treatment [OwH, HR], prophylaxis)
			CAB LAP Prevention for HIV infection	**CAB+RPV LAP** Treatment for HIV infection
			Xofluza® Severe influenza virus infection	
			Xofluza® Influenza virus infection (pediatric, <1 year old)	
			Xofluza® Influenza virus infection (transmission)	

Infectious disease

Psycho-neurological diseases

New growth areas

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

Target Milestones for FY2019: Approval and Submission

Product (indication)	Phase 1	Phase 2	Phase 3	Submission	Approval
Vyvanse® (ADHD(pediatric))			Achieved (Mar.)	Japan(2017.4)	Japan
Intuniv® (ADHD(adult))			Achieved (Jul.)	Japan(2018.8)	Japan
Cefiderocol (US: Complicated urinary tract infections, including pyelonephritis , EU: Aerobic Gram-negative bacterial infection)	Approval (US) (Nov.) CHMP positive opinion (EU) (Feb.)		Global: CR study completion Global: Nosocomial pneumonia study completion	US(2018.12) EU(2019.3)	US (2019.11) EU
Xofluza® (Influenza virus infection) ①granule (weight under 20kg) ②prophylaxis			Japan： High-dose study for children: completion	①Japan(2018.8)	①Japan
	Achieved (Oct.)		Prophylaxis study completion	②Japan(2019.10)	
OxyContin®TR (Treatment of moderate to severe chronic pain)	Achieved (May)		Japan： Completion	Japan	

Target Milestones for FY2019: Phase 1 - 3

Product (indication)	Phase 1	Phase 2	Phase 3	Submission	Approval
S-812217 [zuranolone] (Depression)	Japan: Single and multiple dose study completion ⇨	Japan: initiate			
Rizmoic® (Opioid-induced constipation(pediatric))	EU: Phase I/II study Initiate		Achieved (Q3)		
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	Achieved (Q2)		
SR-0379 (Skin ulcers (Pressure ulcers, diabetic ulcers, etc))		Japan: POC* study completion	Achieved (Q3)		
S-770108 (Idiopathic Pulmonary Fibrosis)	UK: Lung deposition study initiate				

Target Milestones for FY2019: Phase 1 - 3

Product (indication)	Phase 1	Phase 2	Phase 3	Submission	Approval
Redasemtide [S-005151] (stroke)	Japan：Study in Healthy adults (Including the elderly) completion	Japan：initiate	Achieved (Q1)		
S-637880 (Neuropathic pain)	Japan：Multiple dose study completion	Global：initiate			
Naldemedine (POI*)		Global：initiate	Achieved (Q3)		
Novel HIV Drug (HIV virus infection)	US：initiate	Achieved (Q2)			
SDT-001 (ADHD)		Japan：initiate	Achieved (Q4)		

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Progress from Feb. 3, 2020 to Mar. 19, 2020

Planned

Completed

* Post operative ileus

BPN14770 Supplemental

BPN14770
Summary of Phase 1 Study

BPN14770 demonstrated positive safety and tolerability with an absence of dose limiting side effects common to marketed drugs that inhibit all four subtype of PDE4, for example, roflumilast and apremilast cause nausea, vomiting and diarrhea in up to 15-20% of patients

Tolerability and Safety

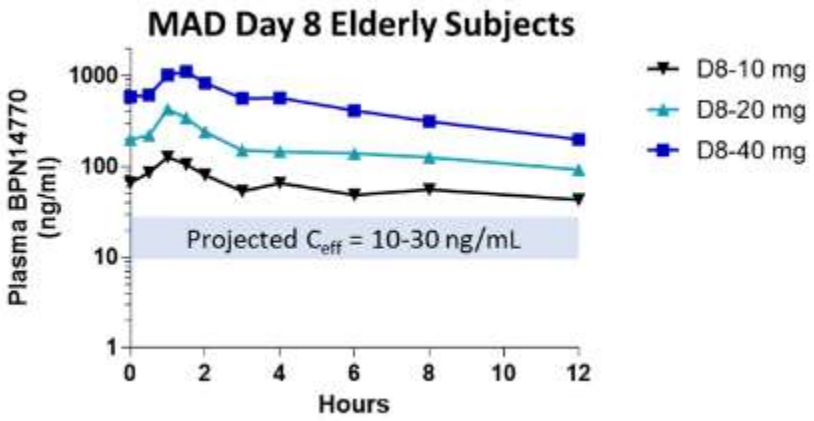
Well tolerated with few adverse events

- Adverse events mild or moderate with no SAEs
- Emetic threshold demonstrated at 75 mg as a single dose
  - Transient nausea and emesis occurred at C_{max}
  - No diarrhea
- Well tolerated at up to 40 mg bid in elderly and 50 mg bid in young subjects over 8 days of dosing without nausea, emesis or diarrhea
  - Sporadic headaches seen in elderly subjects dosed at 40 mg bid
- No clinically significant changes in laboratory tests, vital signs, or ECGs
- No dose limiting toxicity

Efficacy

Cognitive benefit in elderly subjects

- Improvement in speed of processing time in elderly subjects at 10 and 20 mg bid but not at 40 mg
- Improvement in 24 hr recall of a word list in elderly subjects at 20 and 40 mg bid



BPN14770
Justification for Phase 2 Dose Selection

- Preclinical Rationale
  - Efficacy observed in preclinical models at ~10-30 ng/ml
    - ✓ High tolerability in rodents, dogs and primates
- Clinical rationale for Phase 2 doses: **10 and 25 mg b.i.d.**
  - Healthy volunteers showed most robust cognitive effects after multiple doses of 10 and 20 mg b.i.d.
  - 40 mg b.i.d. had some efficacy but headaches were observed
  - 25 mg b.i.d. yields over 3x exposure at steady state compared to 10 mg b.i.d.
  - Phase 2 doses are associated with plasma concentrations ~10 – 30-fold higher than concentrations required for full preclinical effects

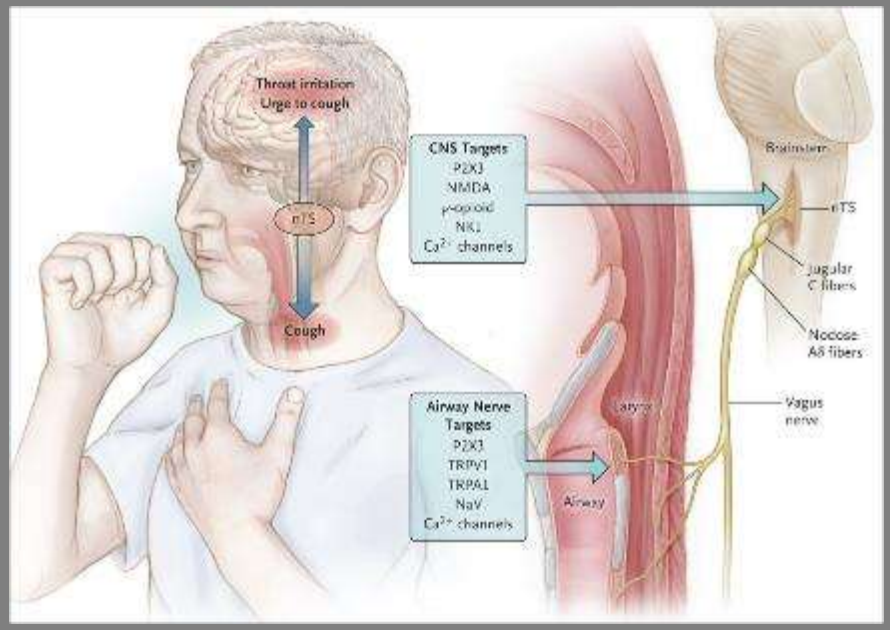
S-600918 Supplemental

Cited from FY2018 R&D Day

$P2X_3$ 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.

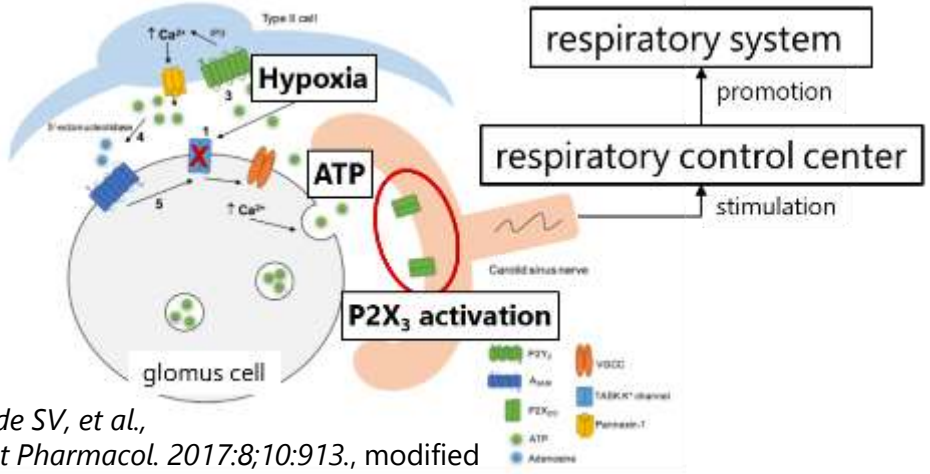
P2X3 receptors are expressed in nerves which are associated with the cough reflex

ATP, ligand of P2X3 receptors, induces the cough reflex

$P2X_3$ receptors are involved in the cough reflex

$P2X_3$ Receptors in Respiratory response

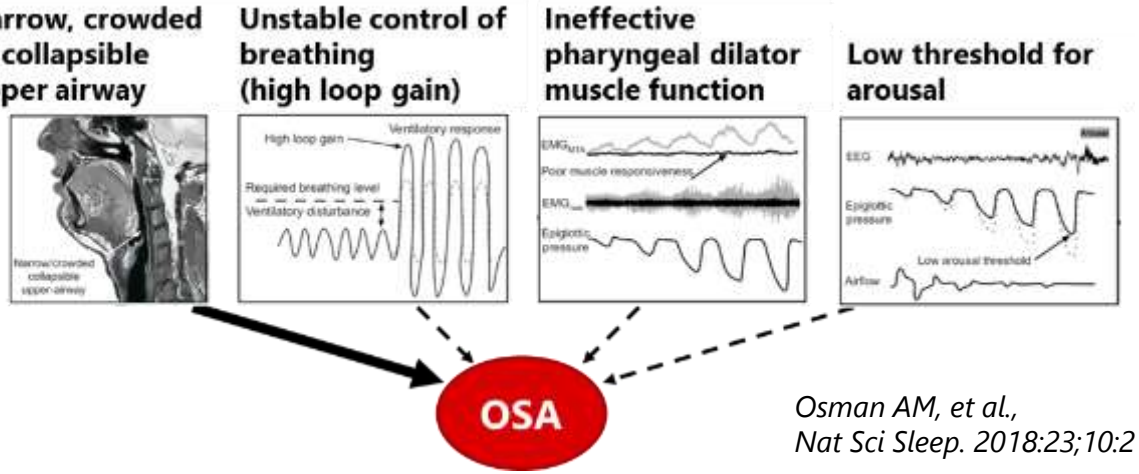
Carotid body: PaO2 Monitoring



Conde SV, et al.,
Front Pharmacol. 2017:8;10:913., modified

- $P2X_3$ receptors express in neurons projected to Carotid body (hypoxic response)
- Hypoxia release ATP from glomus cells, ATP activate the $P2X_3$ receptors.
- Respiratory center is stimulated by activation of $P2X_3$ receptors and promote the ventilation
- **Inhibition of P2X3 receptor suppresses hypoxic respiratory response**

Schematic of the anatomical and non-anatomical causes of OSA



Osman AM, et al.,
Nat Sci Sleep. 2018:23;10:21-34., modified

Cancer Peptide Vaccines
Esophageal cancer, lung cancer, bladder cancer, head & neck cancer, ovarian cancer, etc.

- **Origin**: OncoTherapy Science, Inc.
- **Mechanism of action**:
  - ✓ Vaccination with peptides derived from tumor-associated antigen selectively and highly expressed in tumor cells
  - ✓ The peptides can effectively induce cancer-cell specific CTLs*, which elicit the antitumor effect
- **Characteristics**:
  - ✓ 2 vaccine products (S-588410, S-588210) restricted to dominant HLA types of either Japanese or Caucasian
  - ✓ 5-peptide cocktail vaccine will exert efficacy against many types of cancer
- **Development stage (as of Mar. 2020)** :
  - ✓ S-588410: JP/ Esophageal cancer Phase 3, NSCLC Phase 2 (investigator initiated)
  - ✓ S-588210: UK/ Phase 1
  - ✓ S-588210/PD-(L)1 inhibitor combo study (investigator initiated): UK/ Bladder cancer Phase1b/2, Singapore/ Gastric cancer Phase 1b
- **Plans for 2020FY**:
  - ✓ S-588410: Key open for Ph3 for esophageal cancer to evaluate the prevention of relapses after surgery
  - ✓ S-588210: Confirmation of safety and CTL* inducibility

* CTL: cytotoxic T cells

S-588410 - Results of Exploratory Study of for Esophagus Cancer

[Results]

- S-588410 induced peptide-specific CTL* in oesophageal tumour tissues
  - S-588410 peptide-reactive T-cell receptors detected after administration
- Tumor-infiltrating CD8, PD-1positive CD8 and PD-L1 expressing cells were markedly increased
- Confirmed well tolerated, with a good safety profile of S-588410

[Conclusion]

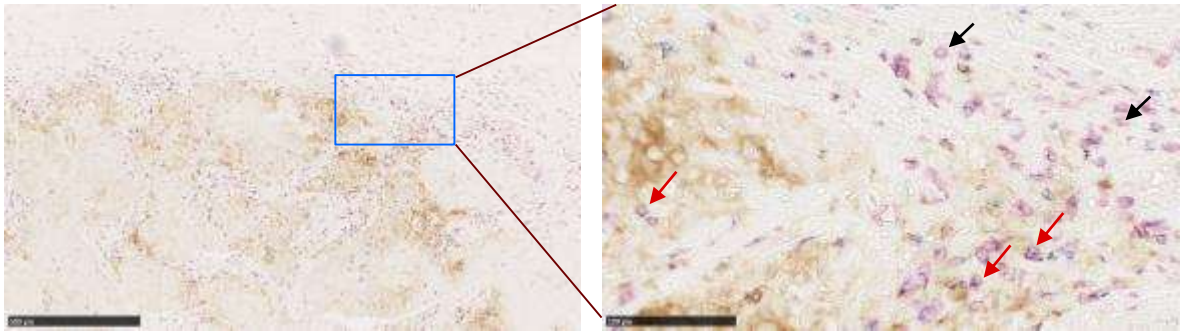
- S-588410 suggests the potential for inductions of antigen-specific tumor immunity and PD1/PD-L1 pathways
- Combination of S-588410 and PD-(L)1 inhibitors promises to be more effective than monotherapy

CD8 (red)/Granzyme B(blue) / PD-L1 (brown)

Before treatment

After treatment

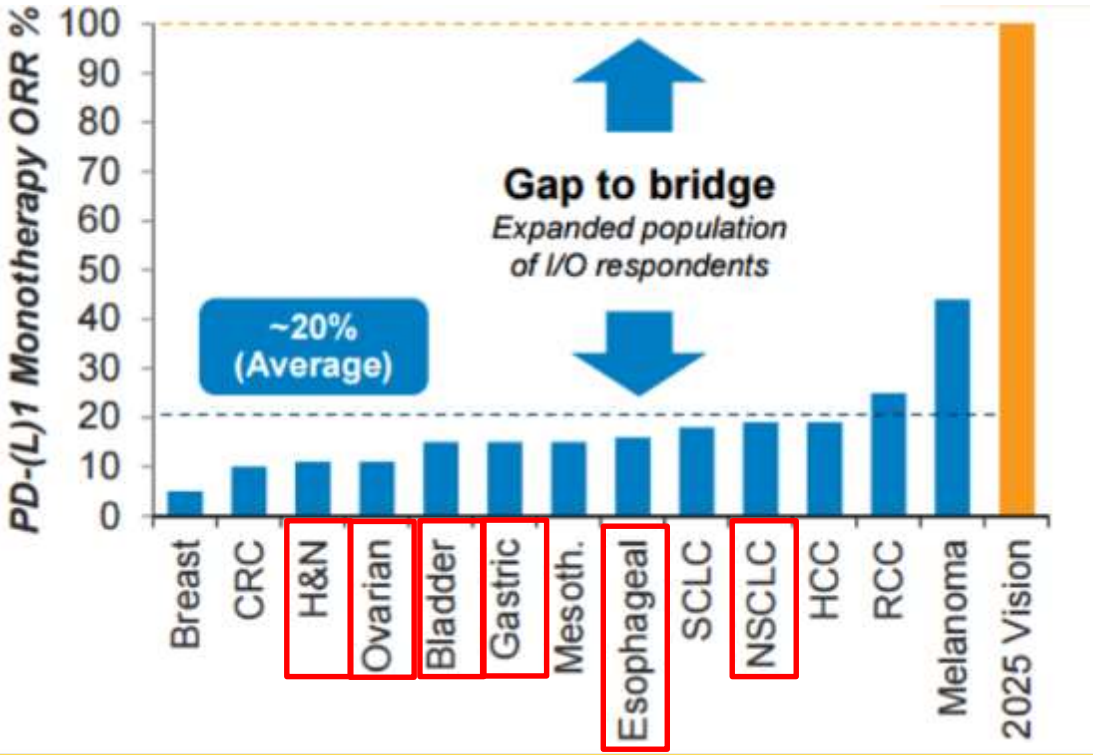




* CTL: cytotoxic T cells

Poster was presented at European Society for Medical Oncology 2019 Congress

Efficacy and Challenges of PD-(L)1 Inhibitors



- **No clear effect in more than 80% of patients with monotherapy**
- **No clear effect in patients with less than 1% of PD-L1 expression level.**

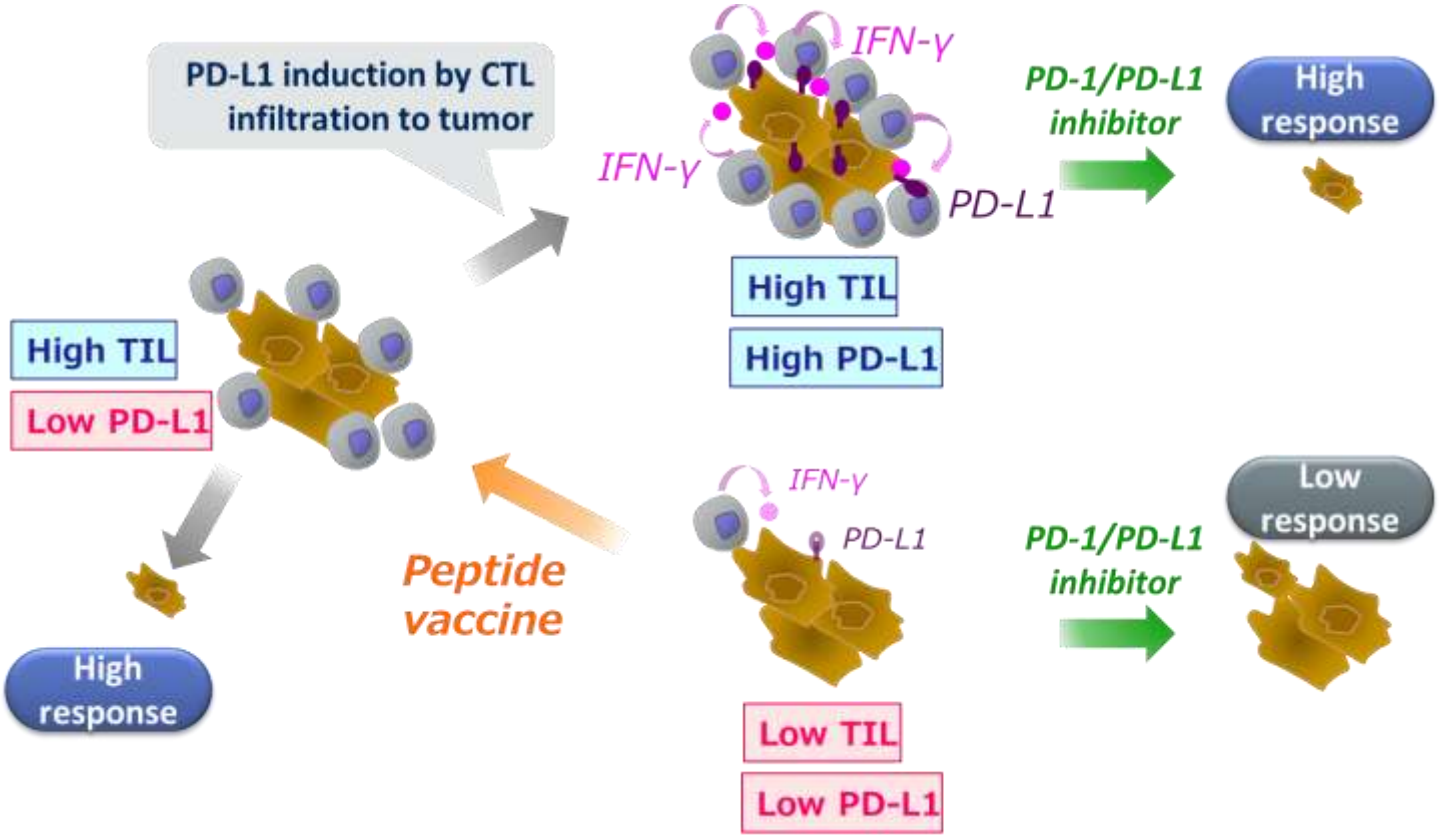
Combination drugs that Increase PD-(L)1 Inhibitor Sensitivity and Increase may respond to Rates are highly desired.

It is expected that PD-(L)1 inhibitor sensitivity can be increased by PD-L1 expression, and that efficiency can be increased by combining vaccine with a PD-(L)1 inhibitor.

ORR; Overall response rate (overall response rate).
I/O: Immuno-Oncology

Source: BMS Investor Presentation (March 31、2016)

Effect of Combination with PD-(L)1 Inhibitors



- Cancer Peptide Vaccines induce Cancer-Specific TILs
- PD-(L)1 inhibitor releases immunosuppressive mechanisms

Patients with advanced cancer who do not respond to monotherapy may respond to combination therapy

CTL: Cytotoxic T lymphocyte
TIL: Tumor infiltrating lymphocyte

Referred from "Science 3 April 348; 56-61 (2015)"

S-109802
Upper and lower limb spasticity post-stroke

- **Origin**: Tokushima University
- **Mechanism of action**: Inhibition of acetylcholine release from neurons, and suppress the hyperactive muscles
- **Characteristics (based on non-clinical data)**:
  - ✓ High affinity to neuron receptors, and efficiently enter into neurons, and show high inhibitory effect on hyperactive muscles.
  - ✓ Low spreading from injected muscle, and low risk of adverse reactions
  - ✓ Low antigenicity and low risk of neutralizing antibody formation.
- **Development stage (as of Mar. 2020)** : Pre-clinical
- **Plans for 2020FY**:
  - ✓ Pre-clinical studies are ongoing
  - ✓ Preparation of manufacturing drug products for Phase 1（Phase 1 study will be started in FY2021）

Product Summary S-109802 (A2 type botulinum toxin)

Frontier	Post-stroke upper and lower limb spasticity and cervical dystonia	In-license from Tokushima Univ.

【Characteristics】
- Inhibit acetylcholine release from neurons, and suppress hyper-active muscles (spasticity, dystonia, spasm)
- Compared to A1 type botulinum toxin (Botox®), A2 toxin exhibits -
  - Higher affinity to neuron receptors, and captured in neurons more efficiently, and with more potent inhibitory action on hyperactive muscles.
    → More spastic muscles can be treated with high toxin activity
  - Lower spreading to adjacent muscles and lower transport to other sites of the body, could cause lower risk of adverse reactions.
    → Lower risk of adverse reactions from spreading, and can inject more safely in face and neck
- Low antigenicity - low risk of neutralizing antibody formation and attenuation of efficacy
- Co-development with Biken (Biken is in charge of manufacturing)

Progress in FY2019	【Biken】 • Drug substance : Establishment of cultivation and purification methods for A2 toxin. • Drug product : Establishment of preparation for drug product for pre-clinical studies. • Analysis : Development of quality tests for drug substance and drug product. 【Shionogi】 • Pre-tox and pre-pharmacology studies of A2 toxin.
Plan in FY2020	• Perform GLP (repeated dose tox, safety pharmacology) & pharmacological studies • Set-up for manufacturing investigational product for Phase 1 studies.

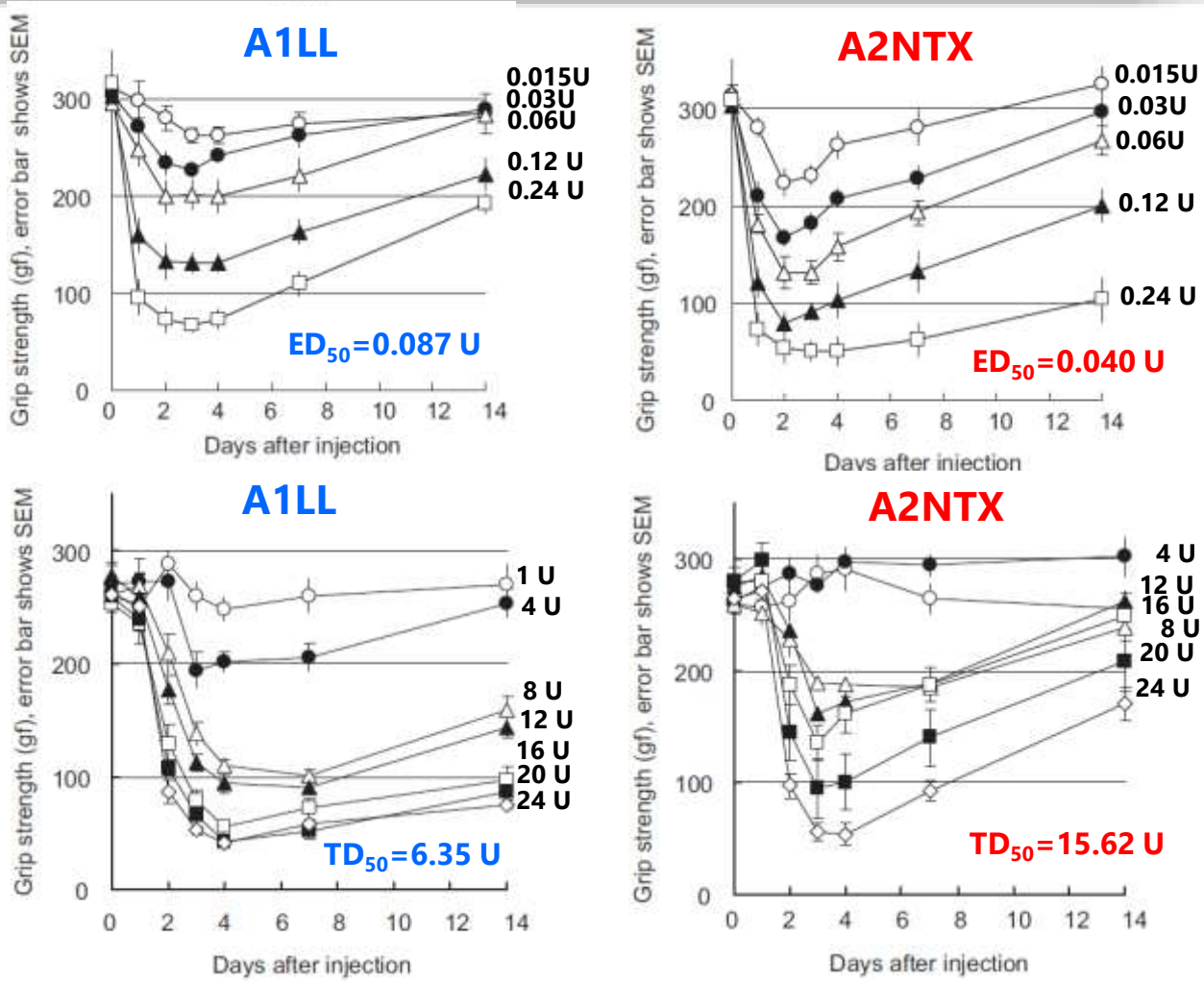
Grip Strength Assay in Rats

Grip strength in ipsilateral foreleg

A1LL (Botox) or A2NTX is injected in rat foreleg, and grip strength in ipsilateral foreleg and contralateral foreleg were evaluated.

Toxicon 2011:57;93-99

Grip strength in contralateral foreleg



A2NTX showed more potent inhibitory action on the injected foreleg than A1LL, while showing lower activity on the contralateral site.

→ Potent action on injected muscle, with little effect on other sites of the body.

S-872881
Alzheimer's Disease (AD)

- **Origin**: in-house
- **Mechanism of action**: β-secretase (BACE1) inhibitor
- **Characteristics (based on non-clinical data)** :
  - ✓ Disease-modifying effect (Prevention and Inhibition of progress for AD)
  - ✓ Back-up compounds of Atabecestat, reducing risk liver tox and CV
  - ✓ Expected to reduce the cognitive worsening by high selectivity against BACE2
- **Development stage (as of Mar. 2020)** : Pre-clinical
- **Plans for 2020FY**: Pre-clinical studies are ongoing

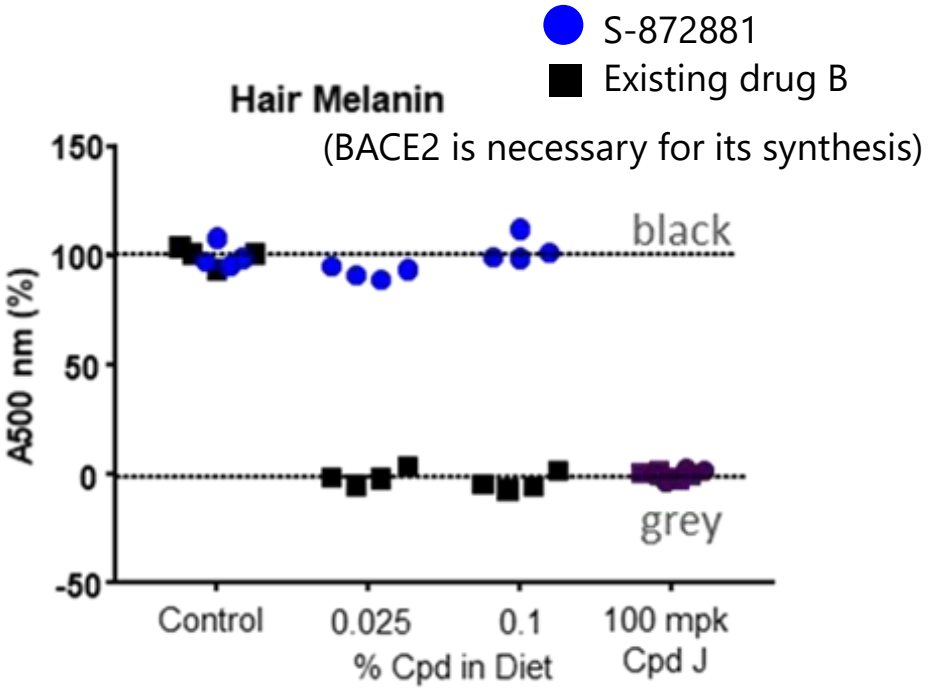
S-872881_Novel Drug Candidate for the Treatment of AD

S-872881 is highly selective for BACE1

In vitro selectivity

	Ki (nM)	
	BACE1	BACE1/2 selectivity
S-872881	0.9	**Over 150-fold**
Existing drug A	0.8	12-fold

In vivo selectivity (non-clinical)



To elucidate the mechanism of cognitive deterioration of the preceding compounds, as well as to establish a clinical evaluation system that can trace the deterioration of cognitive function

S-723595
Nonalcoholic steatohepatitis (NASH)

- **Origin**: in-house
- **Mechanism of action**: Not disclosed
- **Characteristics (based on non-clinical data)**:
  - ✓ Improvement of liver fibrosis comparable to OCALIVA® (obeticholic acid) *
  - ✓ Improvement of liver fibrosis even in models and conditions where obeticholic acid and similar competitor drugs do not work
  - ✓ Risk reduction of elevated blood triglycerides like a side effect of similar competitor drugs
- **Development stage (as of Mar. 2020)** : Pre-clinical
- **Plans for 2020FY**: Start of Phase 1 study

* OCALIVA® (obeticholic acid): a drug for the treatment of primary biliary cholangitis (PBCs). The only late-phase study in NASH confirmed improved fibrosis stages (as of January 2020)

Cited from FY2018 R&D Day, partially modified

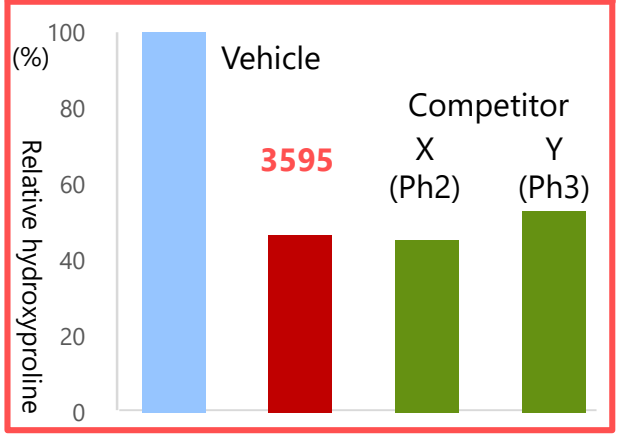
Novel Drug Candidate S-723595

Created a novel drug candidate with unique mechanism reducing ectopic fat

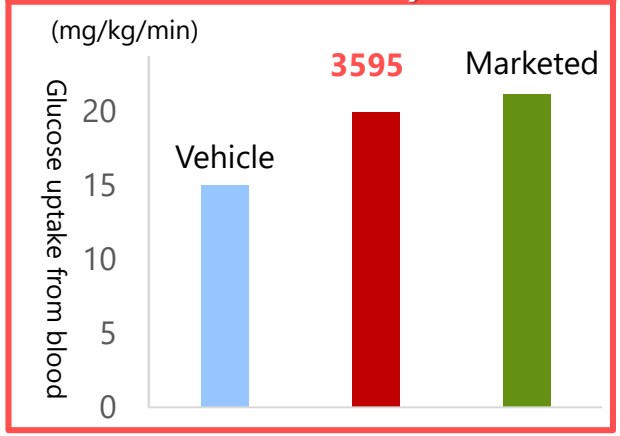
Metabolic syndrome → **Accumulation of ectopic fat** → **Deteriorating condition**

S-723595 decreases ectopic fat

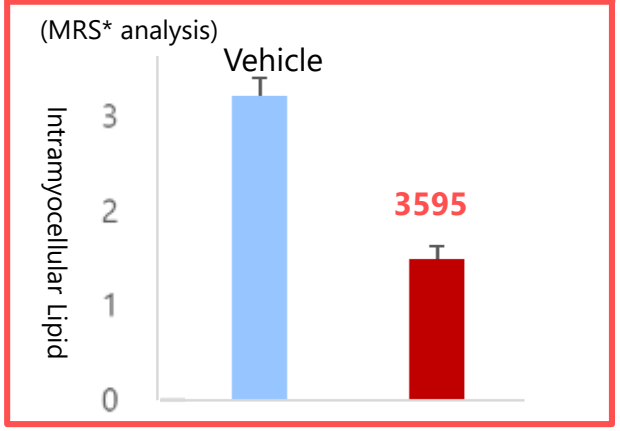
Decreasing fibrosis in liver (NASH endpoint)



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

Evidence from pre-clinical studies support pursuit as a new option for the treatment of NASH. Phase 1 study will start FY2020.

* MRS: Magnetic Resonance Spectroscopy

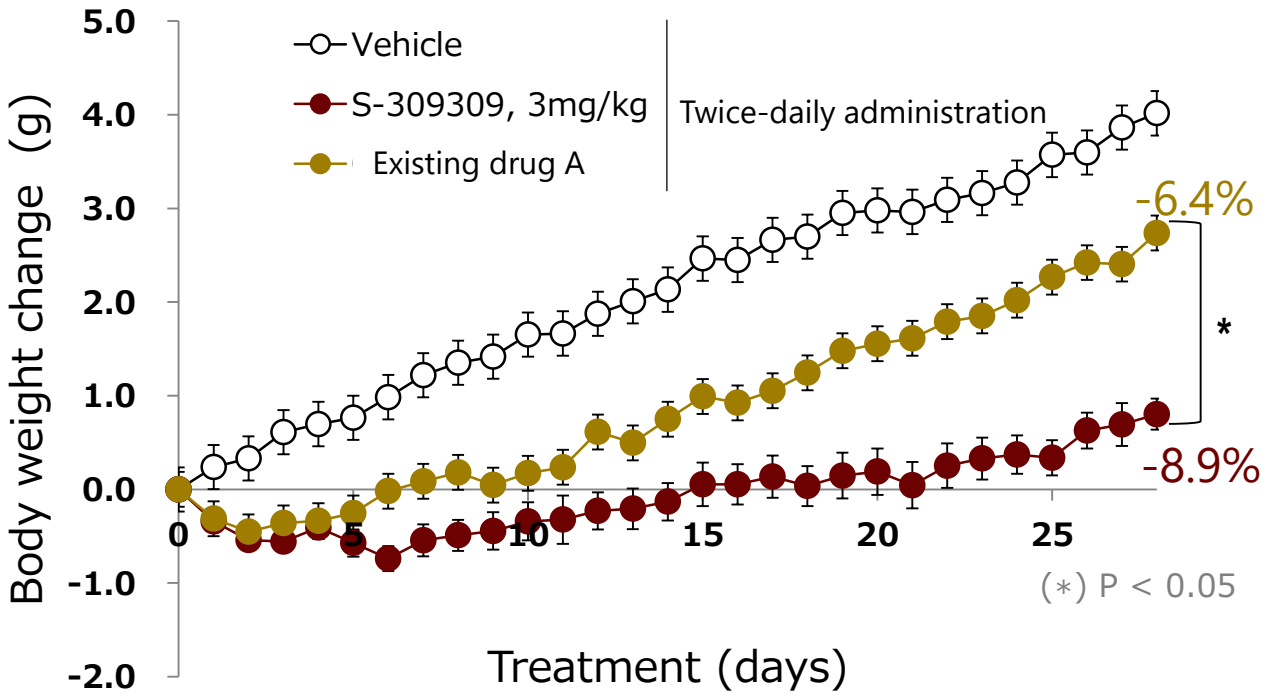
S-309309
Obesity

- **Origin**: in-house
- **Mechanism of action**: Not disclosed
- **Characteristics (based on non-clinical data)** :
  - ✓ Rapid and robust weight loss for people who have difficulty managing diet and exercise
  - ✓ Weight loss efficacy superior to QSYMIA® (phentermine and topiramate) extended-release capsules, for oral use
  - ✓ Safe and easy to use. Central side effects and steatorrhea are infrequent.
- **Development stage (as of Mar. 2020)** : Pre-clinical
- **Plans for 2020FY**: Pre-clinical studies are ongoing

S-309309_Novel Anti-obesity Drug Candidate

Confirms superior efficacy compared to existing small molecule drug

Anti-obesity effects in a diet-induced obesity model



Achieve rapid and reliable weight loss effects for people who have difficulty managing diet and exercise

Forward-Looking Statements

- Forecast or target figures in this material are neither official forecasts of earnings and dividends nor guarantee of target, achievement and forecasts, but present the midterm strategies, goals and visions. Official earnings guidance should be referred to in the disclosure of the annual financial report (*kessan tanshin*) in accordance with the rules set by Tokyo Stock Exchange.
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