Shionogi R&D Day 2021

September 29, 2021

SHIONOGI & Co., Ltd.

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Agenda

1. **Shionogi R&D**
   - Progress of COVID-19 Projects

Ryuichi Kiyama, Ph.D.,
Senior Executive Officer, Senior Vice President, Pharmaceutical Research Division
Toshinobu Iwasaki, Ph.D.,
Senior Executive Officer, Senior Vice President, Global Development Division

   - Progress of Shionogi R&D
     - > Research area — **Ryuichi Kiyama**
     - > Development area — **Toshinobu Iwasaki**

2. **Summary** — **Isao Teshirogi, Ph.D.,** President and CEO
3. **Q&A**

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1. **Shionogi R&D**
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     - > Research area
     - > Development area

Ryuichi Kiyama
Toshinobu Iwasaki

2. **Summary**

Isao Teshirogi, Ph.D.,
President and CEO

3. **Q&A**

Progress of COVID-19 projects

Shionogi's Actions for Total Care of COVID-19

Epidemic forecasting	Prevention	Diagnosis	Treatment	Exacerbation suppression
				
• Sewage epidemiology surveillance service for early detection of COVID-19 incursion and outbreak trends	• Development of a recombinant vaccine for COVID-19（**S-268019**）	• Antigen-test kit • Th2 chemokine TARC* kit for assisting in predicting exacerbations • Novel rapid diagnostic method	• Discovery and development of novel antiviral drug（**S-217622**） • Discovery of developmental candidate peptide	• Licensing out asapiprant, an exacerbation controlling candidate

Providing solutions for the overwhelmed medical system

* TARC（thymus and activation-regulated chemokine）
One of the chemokines driving migration of Th2 cells, a type of lymphocyte, to the site of inflammation

S-217622

COVID-19 therapeutic drug

The Need for COVID-19 Oral Antivirals

- **In order for COVID-19 to be managed like influenza, the following is required**
  - ✓ Diagnostics
  - ✓ Vaccines
  - ✓ Therapeutic drugs: Antiviral drugs (especially oral drugs that can be used as an outpatient)
- **Therapeutic agents currently available in Japan**
  - ✓ Remdesivir (antiviral drug: intravenous injection)
  - ✓ COVID-19 antibody (cocktail, etc.: intravenous injection)
  - ✓ Suppressors of exacerbation (dexamethasone, etc.)

Especially while the infection continues to spread, the burden on the medical field is heavy

⇒ The need for oral antivirals is high

Re-deploying Strengths through Corona Therapeutic Drug Research

Bold resource shifts focused on COVID-19 research coupled with rapid decision-making

Shionogi's original drug discovery platform based on our knowledge of antiviral research and small molecule compound design"

Fusion of different strengths through collaboration with external partners, such as Hokkaido University and others

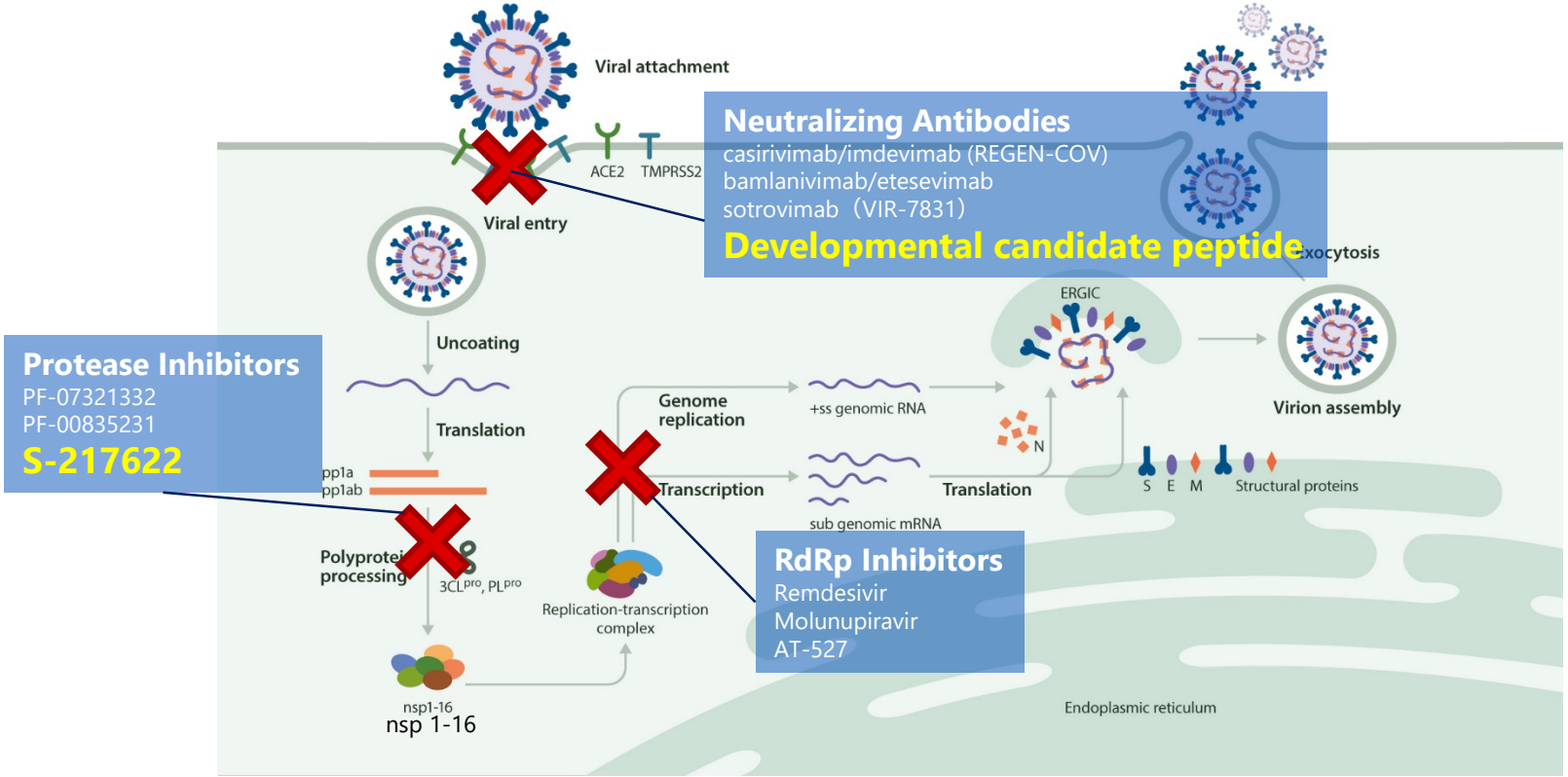
- **Upon selecting a SARS-CoV-2 specific compound, enter clinical stage with top-class speed**
  - Progressing at an unprecedented rate by conducting multiple required tests in parallel

- Approximately **9 months** after launching the project (approximately **4 months** from the start of SAR*) for the creation of SARS-CoV-2 specific compounds
- Identified discovered development candidates including S-217622
  - Traditionally, the probability that a drug will reach the market is 1 in 25,000, and it takes five years from the start of drug discovery to a development candidate. "
- Clinical study initiated about 4 months after the discovery of S-217622

Re-deploying our strengths that created Tivicay and Xofluza to meet the need for small molecule drug discovery

* Structure activity relationship: Correlation between structure and antiviral activity

S-217622：3C-Like protease



S-217622: 3CL-protease As a Drug Discovery Target

Superimposition of X-ray structures of various coronaviruses*

SARS-CoV (2BX4)
SARS-CoV-2 (6Y2E)
MERS-CoV (5C3N)

Amino acid sequence homology of SARS-CoV-2
- SARS-CoV: >95%
- MERS-CoV: >60%

Reason for 3CL-pro selection
- ✓ Highly conserved in the genus Coronavirus
- ✓ Active-center amino acids have low homology with human proteases, reducing safety concerns
- ✓ Drug discovery experience with diverse viral protease targets
- ✓ The X-ray complex structure has already been clarified*, enabling rapid drug discovery using structural information
- ✓ Compared with the S protein, natural mutations that are not drug-induced mutations are less likely to occur (details on p.12)

Targets for drug discovery that can address new mutant viruses and the next pandemic

*Protein Data Bank

S-217622: Antiviral Efficacy Against Mutant Strains

Evaluation using monkey-derived cells

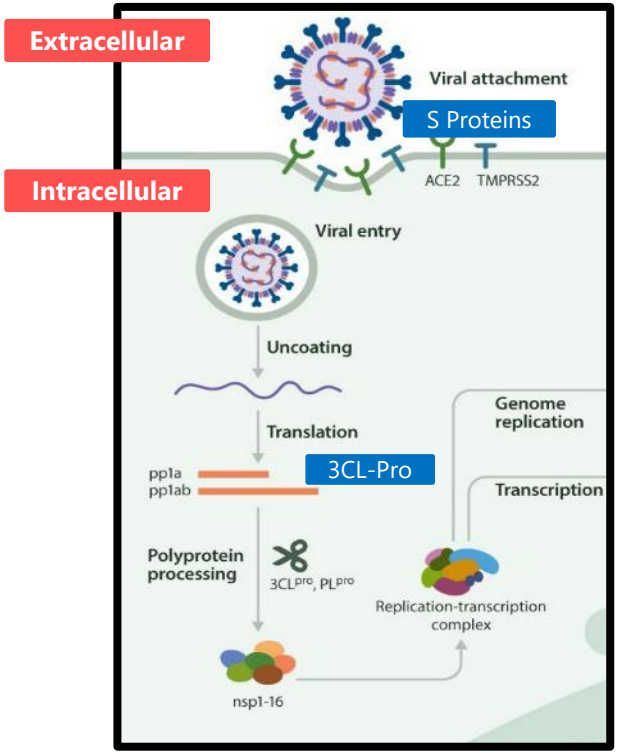
Virus strain	EC50 (μM)	Major mutation site	
		Spike-protein	3CL-protease
WK-521 strain	**0.37**	-	-
α strain (QHN001/QHN002/QK002)	**0.31/0.46/0.33**	N501Y, D614G	-
β strain (TY8-612)	**0.40**	K417N, E484K, N501Y, D614G	K90R*
γ strain (TY7-501/TY7-503)	**0.50/0.43**	K417T, E484K, N501Y, D614G	-
δ strain (TY11-927-P1)	**0.41**	L452R, T478K, D614G	-

It is active against a wide range of strains, including the δ strain creating the current wave of the pandemic

* Inhibitory assessment using K90R enzyme confirmed no effect on drug efficacy

SARS-CoV-2 Mutation

Cell invasion and growth process of SARS-CoV-2



Spontaneous mutations in the S protein

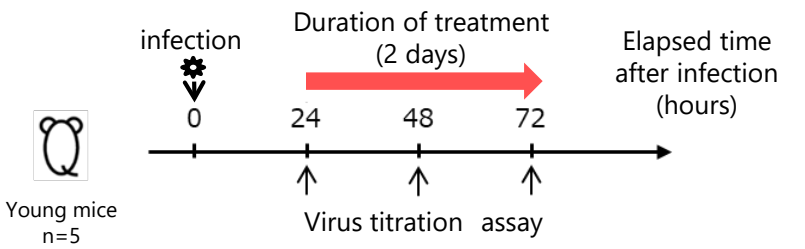
- Used for adhesion to and invade host cells, new mutations may increase infectivity or expand opportunities for new host infections.
- As a survival strategy of the virus, the mutation is replicated and expanded by the application of selective pressure irrespective of the use of any drug

Drug resistance mutations in enzyme inhibitors

- Enzymes required for viral growth have low genetic diversity because mutations have negative effects (such as reduced substrate binding capacity)
- Drug-resistant strains selected to withstand the selective pressure of enzyme inhibitors often have reduced proliferative and pathogenicity due to decreased enzyme activity

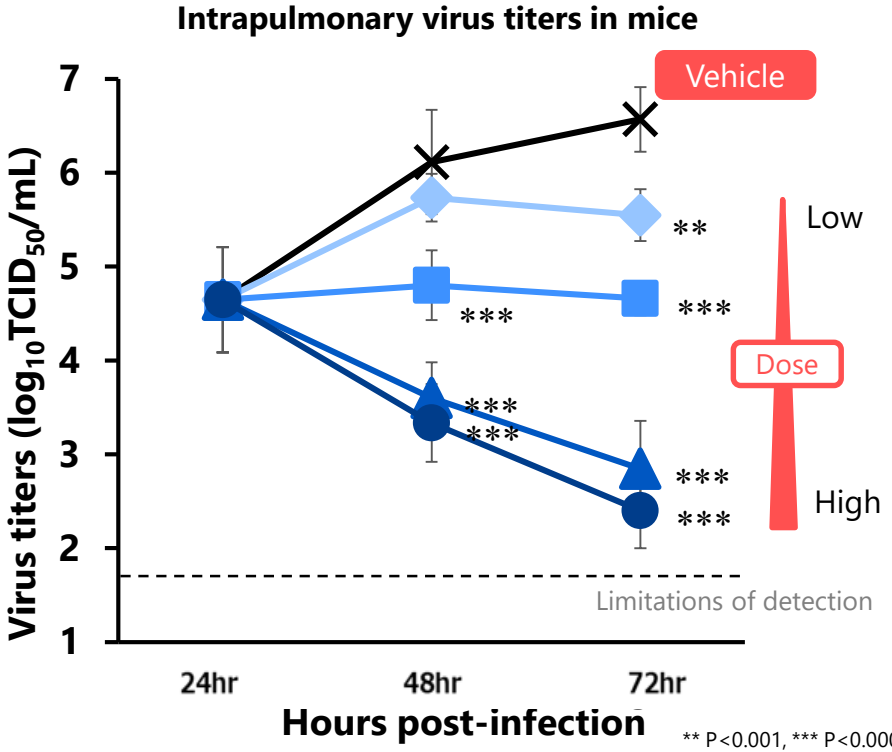
Virus strains selected by host pressure, such as δ strains, and drug-resistant strains selected by enzyme inhibition have distinct differences in their proliferative and virulence potential which should be recognized

S-217622: Efficacy in Mouse Model



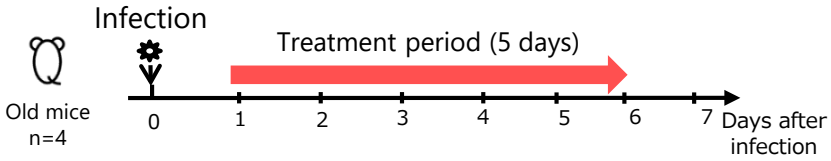
Test Condition：treatment started after 24 hr infection
Administration：oral

Confirming a dose-dependent viral reduction effect of S-217622 in the 48-72 h post-infection period when the virus is replicating in the body

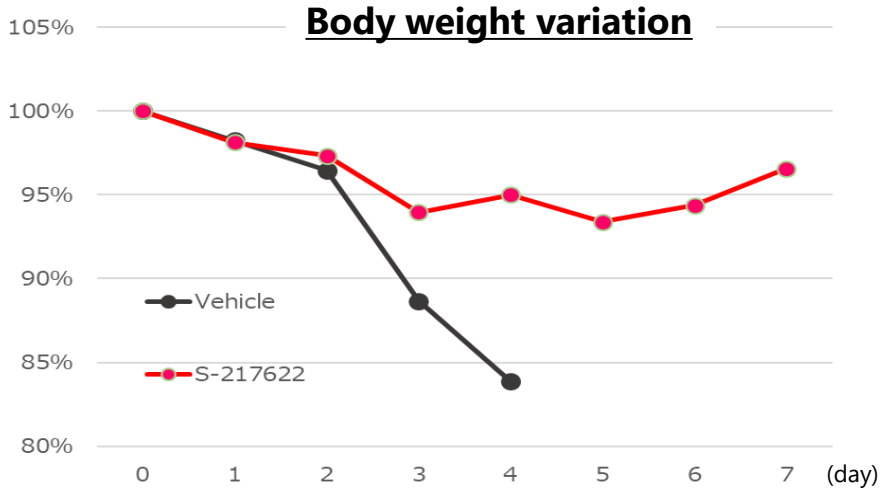


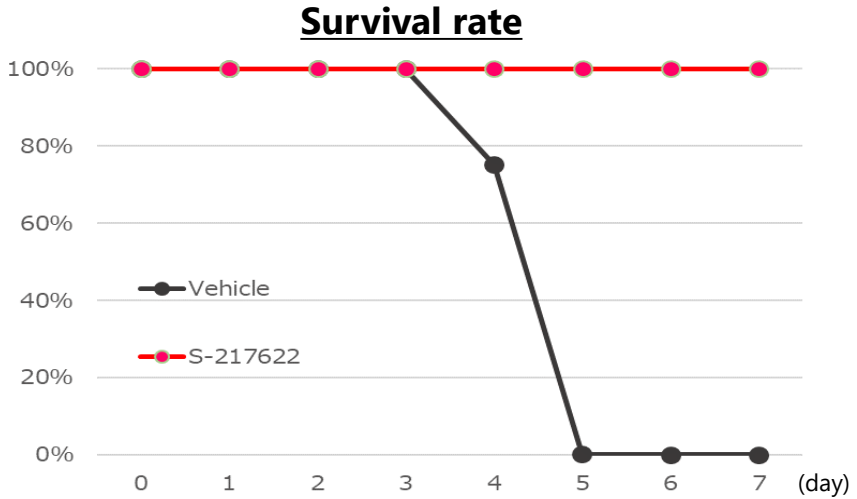
** P<0.001, *** P<0.0001
Vs vehicle (Dunnett's method)

S-217622: Assessment of Drug Efficacy in Mice



Test Condition：treatment started 24 hr after infection
Administration：oral





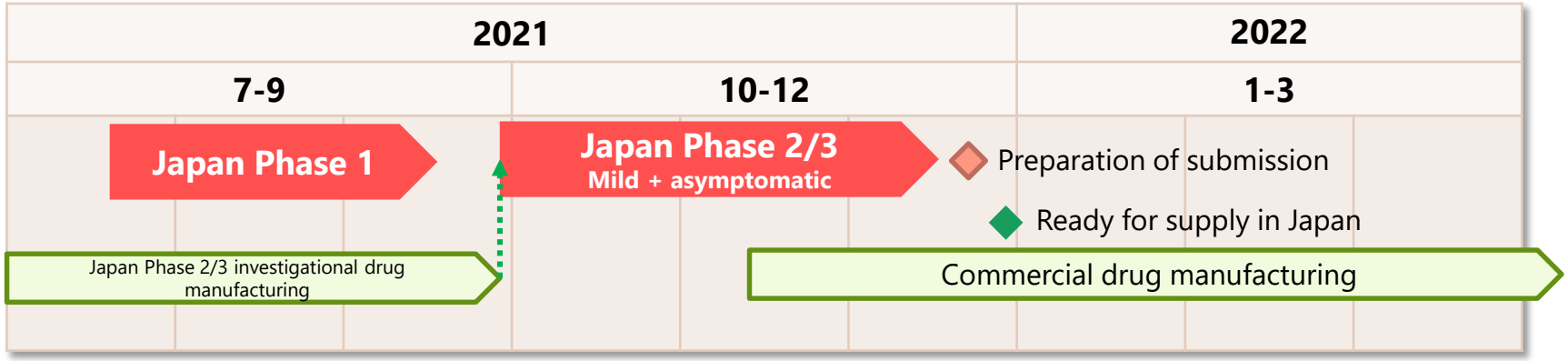
It is expected that S-217622 will reduce the sequelae of infection

S-217622: Summary of Phase 1 Study

- **Safety**
  - No major clinical adverse events have been identified
- **Pharmacokinetics**
  - Drug concentrations obtained were above the target
  - No food effect on efficacy and safety identified

- **Confirmed tolerability and absence of major safety issues at this time**
- **Will conduct Phase 2/3 at the originally planned dose**

S-217622: Domestic Clinical Trial Schedule And Supply

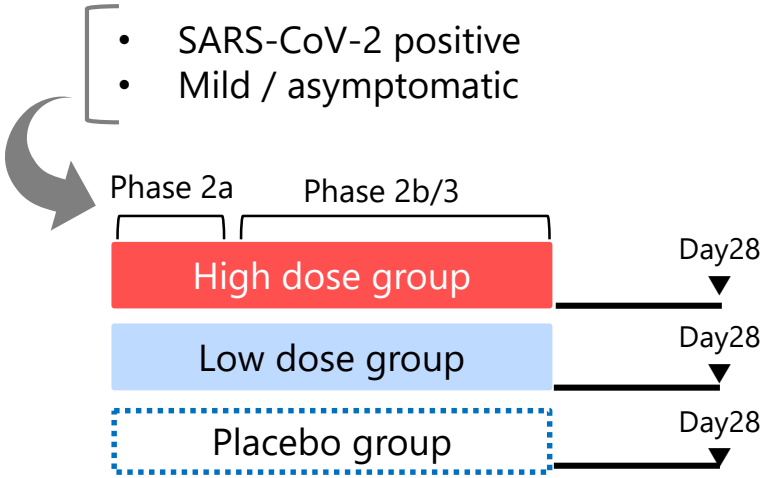


- **Domestic clinical trial and commercial drug supply plans**
  - Will submit data on symptom improvement/symptom occurrence reduction and antiviral effect in mild and asymptomatic patients from Japan Phase 2/3
  - Preparation of domestic submission by the end of 2021

We intend to provide oral therapeutic agents that can be easily taken by large number of asymptomatic and mild patients with limited treatment options

S-217622: Design of Domestic Phase 2/3 Study

Study title	A Phase 2/3 Study of S-217622 in Participants Infected with SARS-CoV-2
subject	Asymptomatic or mild COVID-19 patients
Clinical trial design	Multicenter, randomized, double-blind, placebo-controlled study
Treatment group	High dose group, low dose group, placebo
Primary endpoint	Phase 2a: Change in virus titer from baseline Phase 2b/3: Mild: Time to resolution of COVID-19 symptoms, Asymptomatic: Proportion of participants with occurrence of COVID-19 symptoms
Dosage	Oral administration, once a day for 5 days (tablet)
Number of subject*	Total about 2,100 subjects



* Number of subject is TBD

S-217622: Global Development Plan

Global COVID-19 situation

- **High severity rate, hospitalization rate, mortality rate**
- **Existing antibodies, which are therapeutic agents for mild to moderate patients, are administered by injection and expensive**

- **Improving the medical environment and reducing the burden with simple oral therapeutic agents can have great social significance**
- **Global Phase 3 study is being designed to meet worldwide unmet needs**
  - Plan to assess the same endpoints as used for other anti COVID-19 drugs*
  - Discussions with FDA and EMA will be initiated in 3Q 2021 (October-December)

Initiate discussions with regulatory authorities and accelerate the start of the global phase 3 study
Prepare to provide oral therapeutic agents globally as soon as possible

* Primary endpoint: Mortality rate / hospitalization rate

S-268019

COVID-19 vaccine

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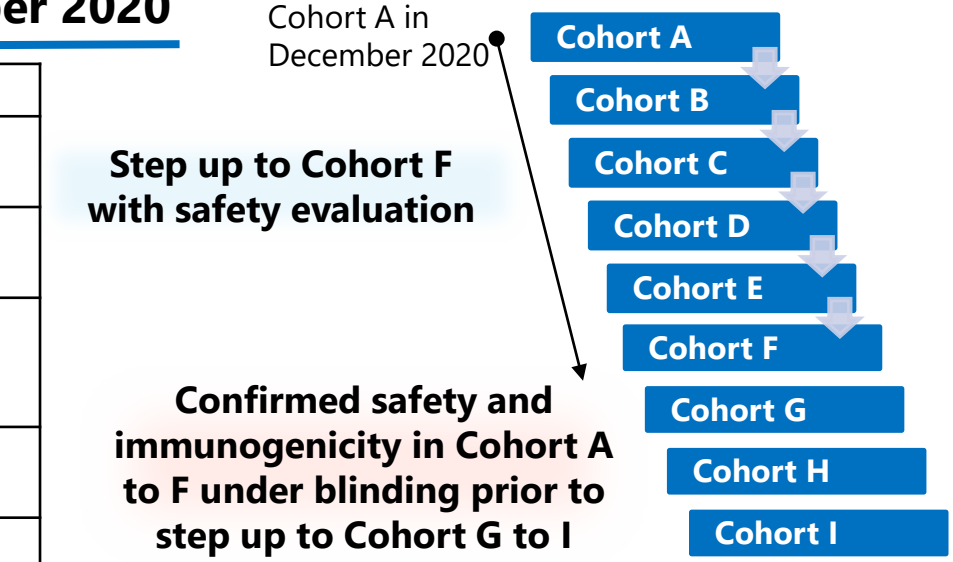
S-268019: Efforts for Commercialization of Domestic Vaccine

Initiated Phase 1/2 Study in December 2020

Design	Randomized, double-blind
Subject	Japanese healthy adult men and women (20-64 years old)
Main Purpose	Safety and tolerability at the time of 2 doses
Primary Endpoints	Adverse Events/Vaccine Reactions/Serious Adverse Events/Frequency of Specific Adverse Events, Vital Signs, Laboratory Tests, Electrocardiogram
Secondary Endpoints	Neutralizing antibody titer Anti-S protein IgG antibody titer
Number of Subjects	10 subjects in each cohort (Active drugs: 8 subjects, Placebo: 2 subjects)



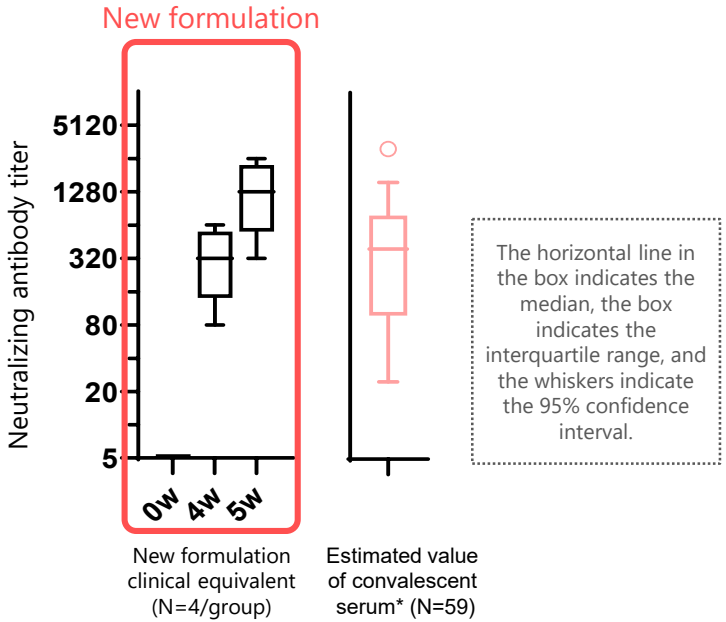
- Considering the importance of Th1> Th2 type balance from research results on SARS* and MERS*2, we selected an adjuvant that is less likely to cause VDE*3/ADE*4 and has a clinical record of administration
- Although clinical trials were conducted at a wide range of doses and confirmed high safety and constant induction of cell-mediated immunity, the neutralizing antibody titer was not sufficiently high.

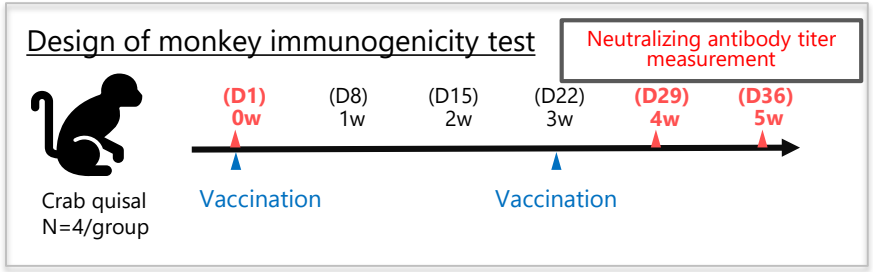
* SARS：Severe Acute Respiratory Syndrome
*2 MERS：Middle East Respiratory Syndrome
*3 VDE：Vaccine induced Disease Enhancement
*4 ADE：Antibody-Dependent Enhancement

This research is supported by AMED under Grant Number JP21nf0101626

S-268019: Change to New Adjuvant

Monkey immunogenicity test:
Neutralizing antibody titer Day29 / 36





- Confirmed similar neutralizing antibody titer compared to convalescent serum by combination of new adjuvant
- **Phase 1/2 trial dosing with new adjuvant initiated in August**
- In Phase 3, verification by comparison of neutralizing activity is under discussion with the regulatory agency.

This research is supported by AMED under Grant Number JP21nf0101626

S-268019: Phase 1/2 Study with New Adjuvant

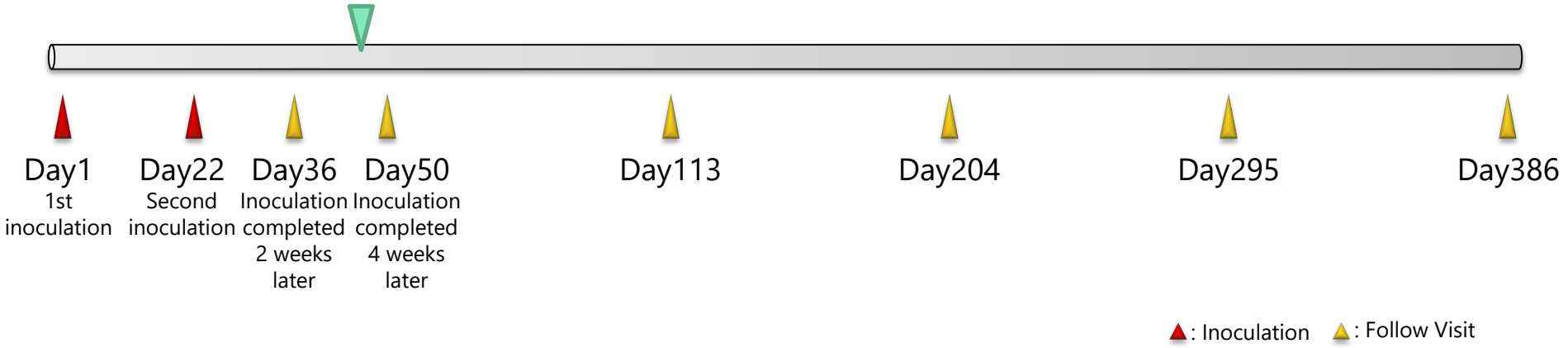
Initiated Phase 1/2 Study with New Adjuvant in August 2021

Design	Randomized, double-blind
Subject	Japanese healthy adult men and women (20-64 years old)
Main Purpose	**Safety, tolerability**
Secondary Purpose	Immunogenicity (neutralizing antibody titer, IgG antibody titer, cell-mediated immunity)
Primary Endpoints	Adverse Events/Vaccine Reactions/Serious Adverse Events/Frequency of Specific Adverse Events, Vital Signs, Laboratory test, Electrocardiogram results
Target Number of Subjects	60 subjects in 3 groups (Active drug: 24 subjects x 2 groups, Placebo: 12 subjects)
Dosing Regimen	Intramuscular injection, 2 inoculations (Day 1 and Day 22)
Dose	Antigen 5 μg, Antigen 10 μg, Placebo
Study Period	August 2021-September 2022

This research is supported by AMED under Grant Number JP21nf0101626

S-268019: Phase 1/2 Study with New Adjuvant

9/24 Completed Day 36 observation for all 60 subjects



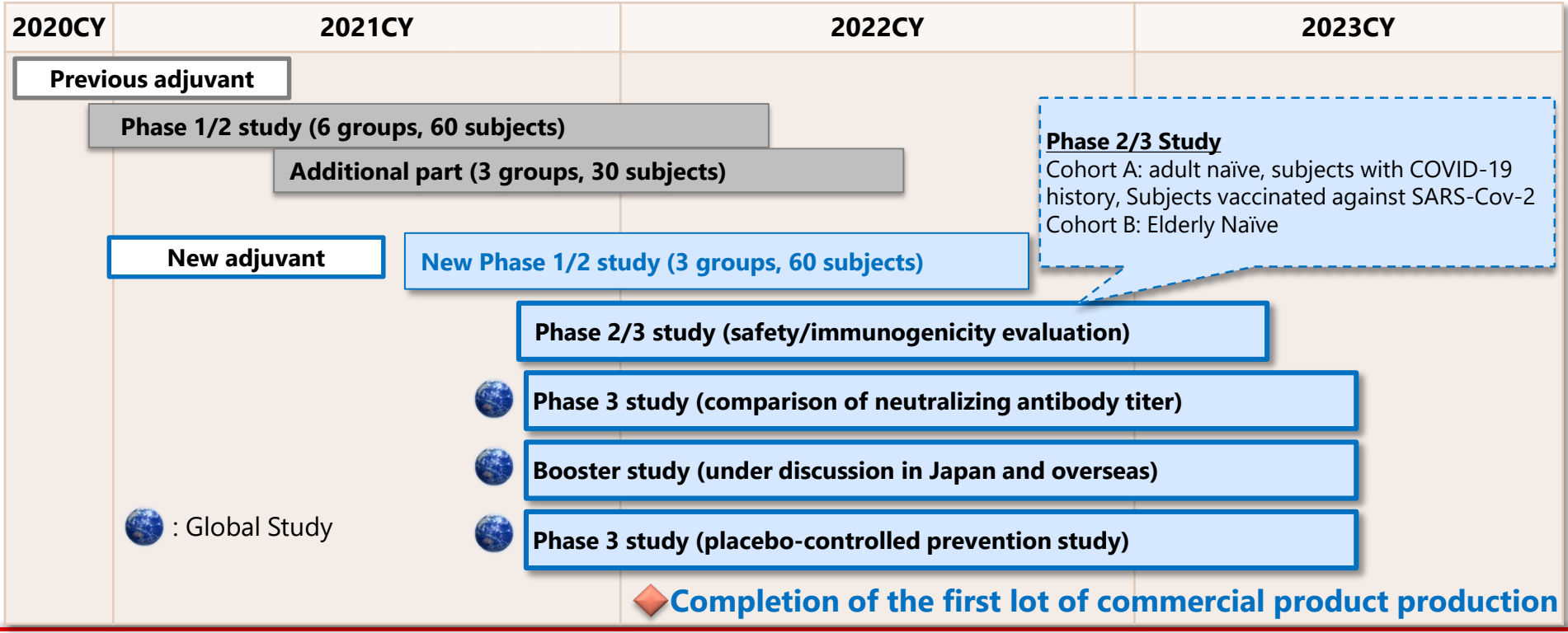
No serious adverse events or adverse events leading to discontinuation

Scheduled Initiation of Phase 2/3 Study in Japan in late October

This research is supported by AMED under Grant Number 21nf0101626

S-268019： Development Schedule

Initiation of Final Stage Studies and Aim to Supply in FY2021



Phase 1/2 studies are supported by AMED under Grant Number JP21nf0101626

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1. **Shionogi R&D**
   - Progress of COVID-19 Projects

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     Senior Executive Officer, Senior Vice President, Pharmaceutical Research Division
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Research area

Actions for COVID-19

Creating COVID-19 Drug Candidates Using PDPS

Deploying PDPS* Drug Discovery Capabilities for Corona Drug Discovery

CY2017

PDPS technology licensing

PeptiDream

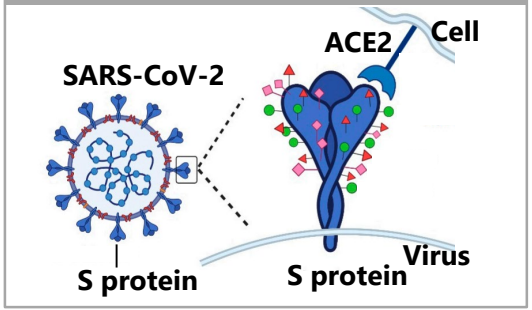
From 2017

Application of screening expertise	Identify hits for the disease target Evolution of data acquisition methods
Extending the Small Molecule Drug Discovery Engine to Peptides	Evolve and accelerate SAR* Advance hit refinement software

From 2020

COVID-19 Therapeutic drugs

Target Protein: S protein***



Drug discovery challenges:

- **Broad and potent drug efficacy against mutant viruses**
- **Oral delivery convenient for outpatients in the early stages of infection**

Promote PDPS Drug Discovery with a Focus on Drug Discovery Issues

Strategically and exhaustively PDPS screen → Rapid SAR

Very good quality HIT

Discovery of therapeutic drug candidates

Rapidly generate candidate peptides by utilizing accumulated experience and expertise in cooperation with Hokkaido Univ. and AMED

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* PDPS: Peptide Discovery Platform System

** SAR: Structure-Activity Relationship

*** Int. J. Mol. Sci. 2021, 22(3), 992

This research is supported by AMED under Grant Number JP20fk0108509

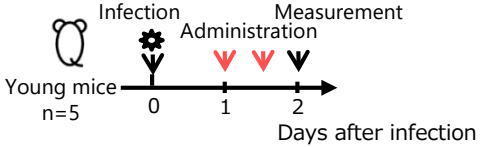
Nonclinical Drug Efficacy of Development Candidate Peptides

The developmental candidate peptides exhibited broad and strong antiviral effects against each mutant strain

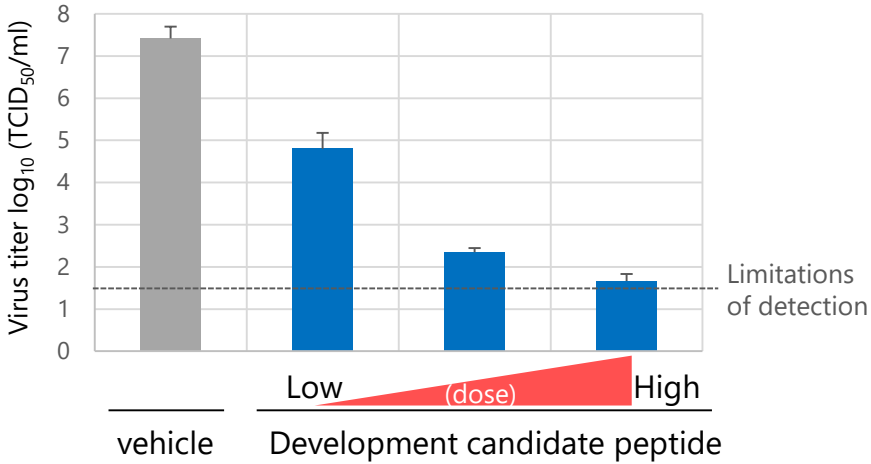
Evaluation using monkey-derived cells

Virus strains	EC_{50} (nM)
WK-521 strain	4.2
α strain	8.5
β strain	2.2
γ strain	6.4
δ strain	7.8

Evaluation using a mouse lung infection model



Test Condition : treatment started after 24 hr infection
Administration : nasal

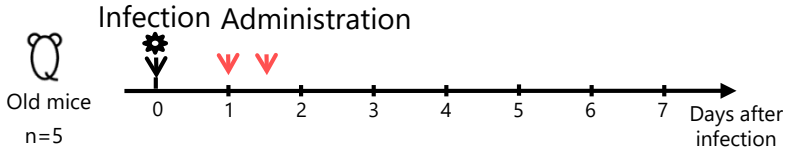


Single-day administration is expected to improve symptoms with rapid viral elimination

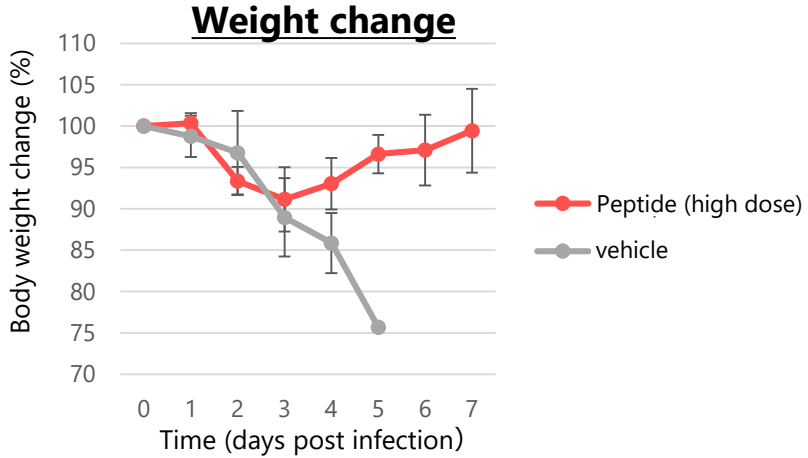
This research is supported by AMED under Grant Number JP20fk0108509

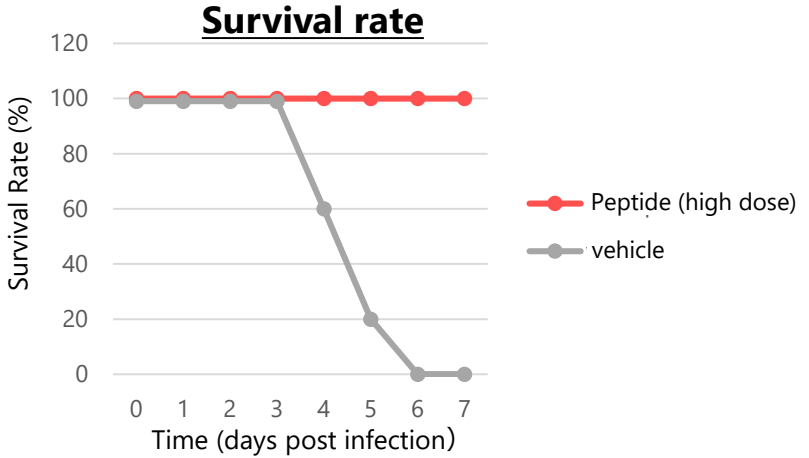
Nonclinical Drug Efficacy of Development Candidate Peptides

The developmental candidate peptide maintained weight and survival in an aged mouse model



Test Condition：treatment started after 24 hr infection
Administration：nasal

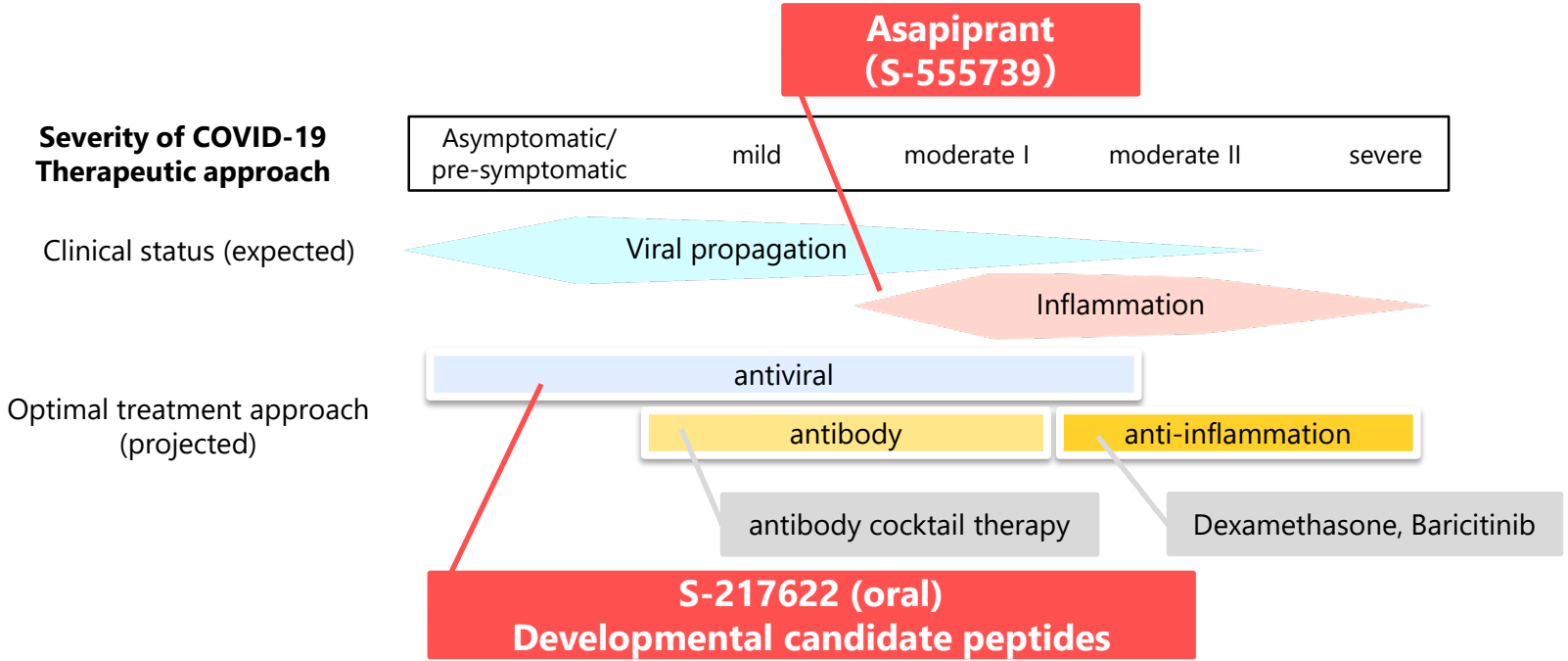




Single-day administration is expected to reduce the severity of the effect even in patients at high risk of severe disease

This research is supported by AMED under Grant Number JP20fk0108509

Positioning* of COVID-19 Drugs



Our mission is to develop a portfolio of drugs to assist patients across the spectrum of COVID-19 disease and restore normality to the medical system

* Referring to the "Eighth Edition of the Concept of Drug Treatment for COVID-19" of the Japanese Society of Infectious Diseases

Direction of Future Efforts Regarding Vaccines

[Current issue]

Timely supply of safe and secure vaccines for mutant strains

Clinical entry in FY2022

Expand to **nasal vaccine** by utilizing the know-how and external cooperation cultivated in S-268019

Infection prevention ability that can cover a wide range of viruses, Improved convenience

Clinical entry in FY 2023, Platform construction

Challenge to design a truly effective and safe **universal antigen** from human immune data

Prepare for a new pandemic

Providing safe recombinant protein vaccines to the market and relieving people from the threat of infectious diseases

Biomarker Initiatives in The Area of Infectious Diseases

- Since July 2021, the Department of Biomarker Research and Development has been under the Pharmaceutical Research Division to further promote the development of biomarkers/diagnostics supporting proper use of pharmaceuticals, adding value, improving diagnosis in target areas, etc. from the research stage

Initiatives as Biomarker R&D Dept. for COVID-19

Establishment of in-house vaccine efficacy metrics

Obtaining evidence and providing information on antibody titers

Test for the pathogen

Testing to meet medical needs

- High-sensitivity antigen test (lumira)
- Simple rapid test, etc.

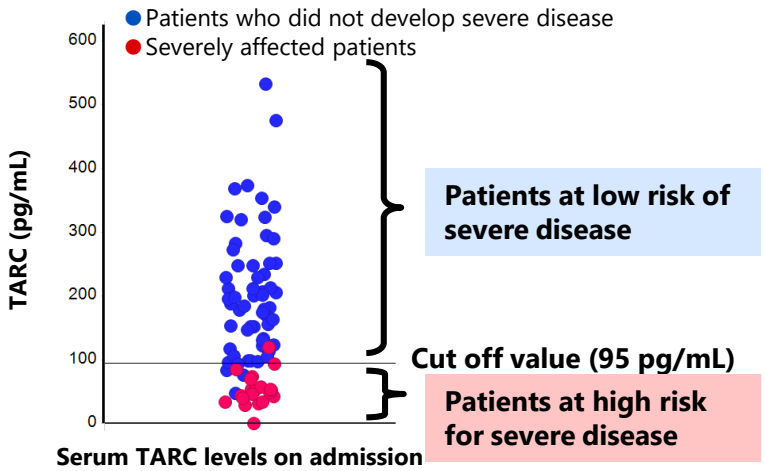
Prediction of severity

Early assessment of the risk of severe disease

- Selection of subjects for administration of therapeutic drugs by HISCL®TARC

Results of HISCL ® TARC* Clinical-Performance Test

Severity of corona patients by TARC measurements ** Risk determination



- Days from onset to TARC determination in critically ill individuals (19 patients) averaging 6.3 days (1-10 days)
- Days from onset to TARC determination for those who did not become severely ill (59 patients): mean 7.7 days (0-28 days)
- Clinical Study Period: January to May 2020

Relationship between Positive Determination by TARC and Severity in Early-Onset Individuals

Positive cases with TARC levels below the cutoff (95.0 pg/mL) obtained on admission

		Severity	
		Severe (moderate II or higher with respiratory failure) group	Mild (moderate I or less) group
TARC	Positive	**94.7% (Sensitivity)**	6.8%
	Negative	5.3%	**93.2% (Specificity)**

Continue efforts to maximize optimize treatment and development by providing rapid and accurate feedback on actual use after product launch, as well as obtaining data prior to commercialization

* TARC(thymus and activation-regulated chemokine): One of a group of chemokines that induce Th2 cells, one of the lymphocytes, to migrate to sites of inflammation

** Severe: Moderate II or higher with respiratory failure

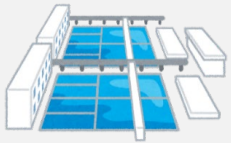
Efforts to Apply Sewage Epidemiology to Benefit Society

Successful development of a highly sensitive Hokkaido Univ.-Shionogi method (tentative) and construction of an inspection system

- Since June 2021, the Sewage Epidemiology Surveillance Service for new coronaviruses has started
- Included in Suggestions by the Subcommittee on Control of New Coronavirus Infections*
- The Law identifies** use for sewage surveillance by the Investigation Committee on New Coronaviruses, which is jurisdictional to the Ministry of the Republic
- Expanding services by contracting with multiple municipalities
- Conducted a survey at the Tokyo 2020 Olympic and Paralympic Athletes Village
- Discussing a business alliance with Shimadzu that leverages the strengths of both parties

Flow of services

Water collection site



Sewage

1 day

Salt field prosthesis

For analysis and data visualization

Measurement data

Within 4 business days

Municipalities and companies

Even in areas where the number of infected people is relatively low, due to a sensitive evaluation system, it is expected to capture the prevalence of new coronaviruses

* https://www.cas.go.jp/jp/seisaku/ful/taisakusuisin/bunkakai/dai4/ict_teigen.pdf

** Media publication: (Link)-(Link) of publication of new coronavirus (Link)RNA (Link) levels of incoming sewage at sewage treatment sites (Link)(mlit.go.jp)(Link) of the Ministry of Land, Infrastructure, Transport and Tourism

Actions by Research Division for the Next Pandemic

2002 ~	2013 ~	2019 ~	20xx ~
SARS	**MERS**	**COVID-19**	**New Pandemic**
Cases: 8,069	Cases: 2,056	Cases: **Over 200 million***	

- **Expected outbreak of respiratory infection pandemic due to new animal-derived beta-coronavirus and influenza virus**
- **Developed as a platform that can quickly adapt to new pandemics with the know-how and technology cultivated from COVID-19**

Information maintenance

- Creating a database of infectious disease research know-how
- Appropriate selection of drug discovery targets
- Data conversion using research skills and accurate analytical operation

×

Asset enrichment

- Building a compound library that can handle a wide range of viruses
- Enhancement of virus / strain library
- Creation of evaluation models for various diseases

×

Partnering

- Building a network that can handle multiple modalities
- Securing resources by utilizing external assets

* WHO report as of September 15, 2021

Research area

S-648414, S-365598

HIV infection

Global HIV Drug Discovery Trends

In anticipation of the penetration of oral GE products into the HIV market after 2028, companies have shifted focus **long-acting formulations** that bring a range of benefits to patients

- **Partnership between Gilead and Merck** (March,2021)
  - Announced a partnership for joint development of long-acting formulations
- **GSK** announced Vision for pursuing Integrase-based long-acting regimen (Jun,2021)
- High demand from patients who participated in the clinical trial

S-648414

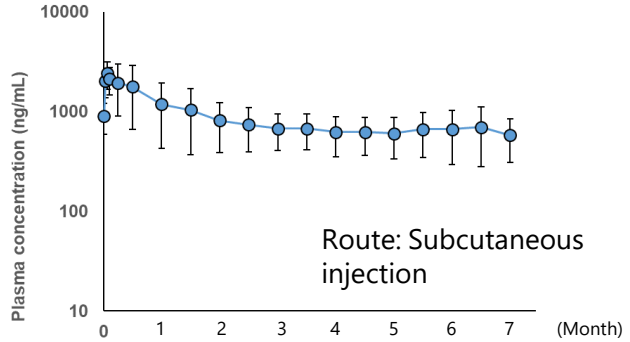
– Difficult to formulate a long-acting formulation that meets patient needs

→ Development discontinued

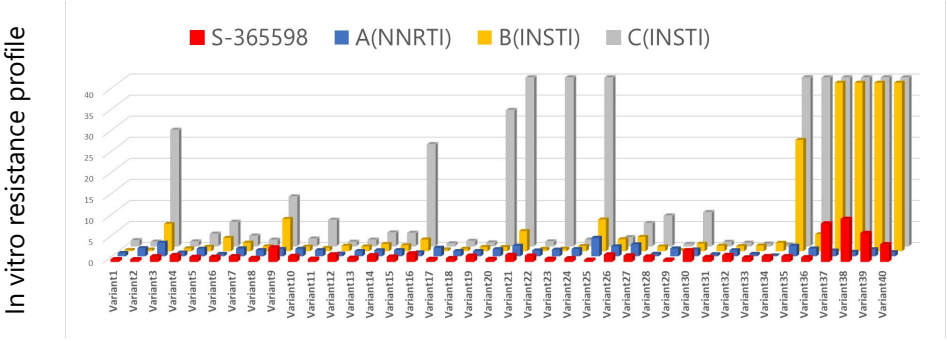
Shift Towards Ultra Long-Acting Formulations

- **S-365598**
  - **Third-generation HIV integrase inhibitors**
  - Targeting creation of ultra-long-acting HIV regimens with dosing intervals of three months or longer
  - Potent anti-HIV activity, including against mutant viruses

Persistence Assessment Results in Monkeys*



Resistance profile**



Creating compounds with the potential to form ultra-long regimens that meet patient needs

* Exploratory studies in which QA was not implemented
** QA Not performed

Agreement with ViiV Healthcare for S-365598

Announced a licensing agreement with ViiV for the third-generation HIV integrase inhibitor, S-365598, to create ultra-long-acting regimens (announced September 28, 2021)

Dolutegravir

Taken by 17 million people globally

Cabotegravir

1st long-acting regimen for treatment

S-365598

Further improvement in QOL for people living with HIV

Intend to initiate first time in human studies by 2023

- **Financial provisions**
  - Upfront payment: £20M
  - Development milestone: £15M
  - Royalty: Aligned with royalty levels in existing Integrase Inhibitors agreement
  - **Shionogi contributes to development costs** up to an annual maximum

- **Collaborating with ViiV, bring forward innovative approaches for HIV**
- **Continuing to pursue new drug discovery with the aim of cure of HIV**

Research area

S-309309

Obesity

Unmet Need for Anti-obesity Drugs and Required Profile

- Growing obese population: More than 200 million obese people in Japan, the US and Europe
- Low drug treatment rate for obesity: 0.4%-2.3%

Safety concerns	Insufficient effect	Economic burden
• Central nervous system side effects (CV* risk, anxiety, dizziness, insomnia, paresthesia) • Gastrointestinal side effects of GLP-1 analogs	• Long-term potent effect (weight loss of 8%-10% / year required) • Clinical satisfaction low with currently approved drugs.	• Low insurance reimbursement rate (about 70% out of pocket) • High drug price of about $40/day for GLP-1 analogs

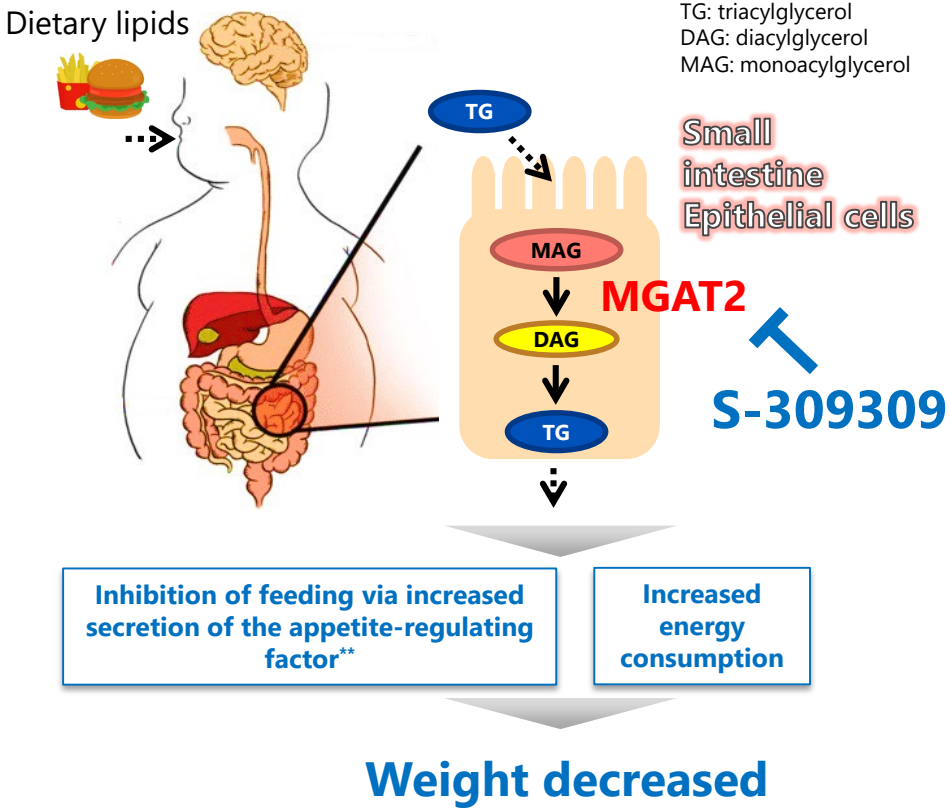
Required anti-obesity drug profile

- Good safety profile: continuous treatment without clinically significant safety concerns
- Sustained potent effect: weight loss of 10% / year or more
- Low economic burden: affordable drug price, insurance reimbursement

*cardiovascular

S-309309: Non-clinical Findings

- **Strongly inhibits MGAT2*, an enzyme involved in triglyceride resynthesis of small intestinal epithelial cells**
- **Exerts anti-obesity effects by a novel mechanism of action that is not present in existing drugs (right panel)**
  - ✓ Suppression of TG absorption (decrease in energy amount)
  - ✓ Appetite suppression
  - ✓ Increased energy consumption
- **Strong inhibition of body weight gain**
  - ✓ Exert stronger effects than existing drugs
  - ✓ Therapeutic effect in combination with a new GLP-1 formulation (Semaglutide)
- **No toxicity concerns in non-clinical safety studies (GLP)**



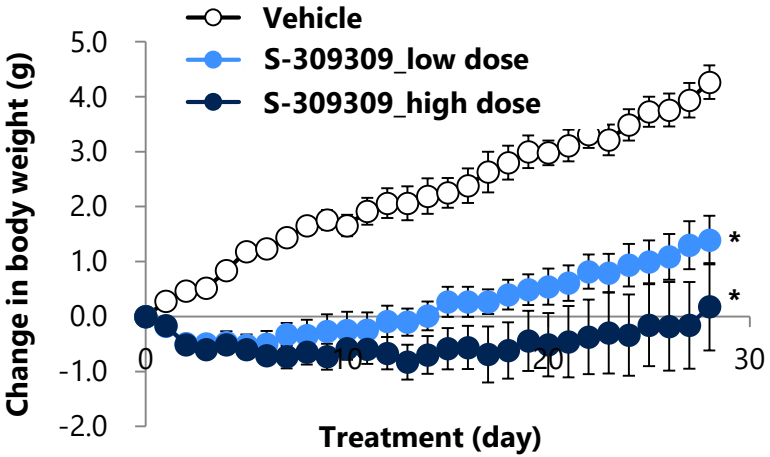
*Monoacylglycerol acyltransferase 2 ** GLP-1, PYY, etc.

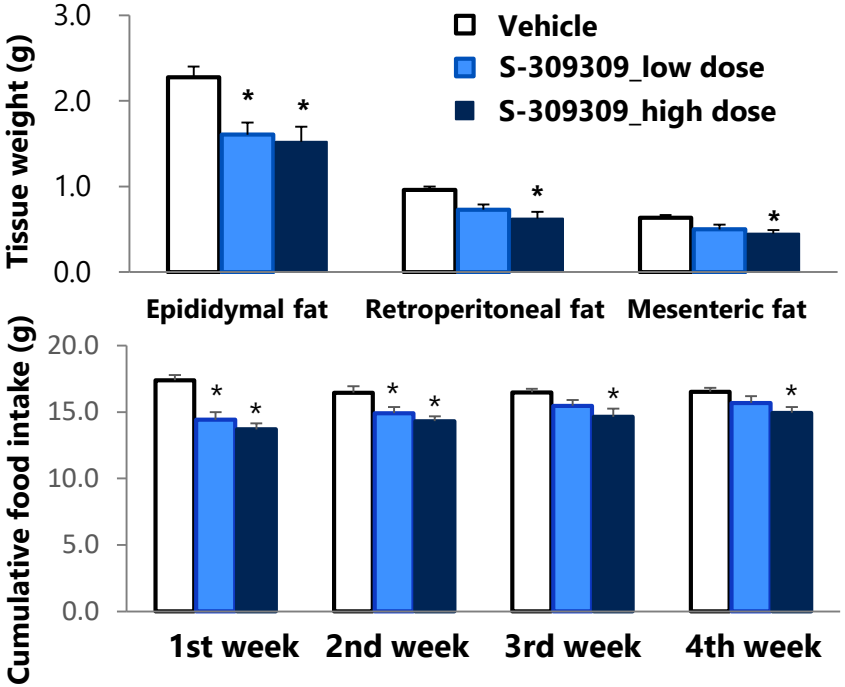
S-309309: Effect on Body Weight, Visceral Fat, and Food Intake

Diet-induced obese mice (60% kcal/fat)

0 1 2 3 4 (week)

Oral administration of S-309309 for 4 weeks





n = 7, each, mean ± SE, * P <0.05 vs. Vehicle

S-309309 reduced body weight and visceral fat weight following decrease in food intake**

** Epididymal fat, retroperitoneal fat, mesenteric fat

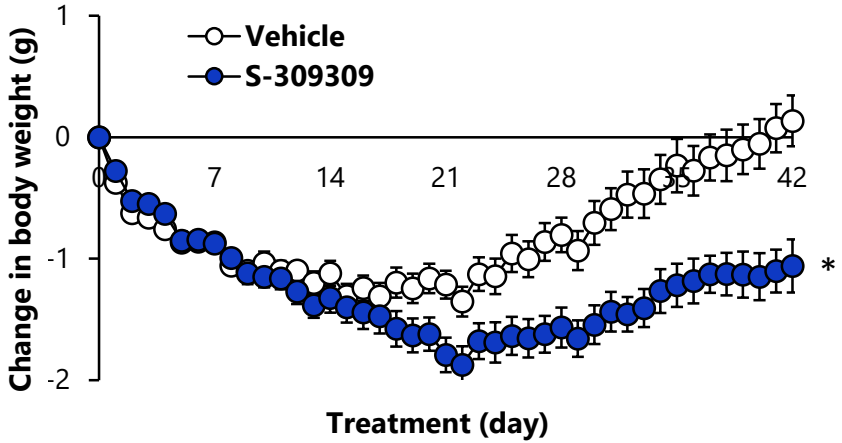
S-309309: Effect on Increased Energy Expenditure

Diet-induced obese mice (60% kcal/fat)

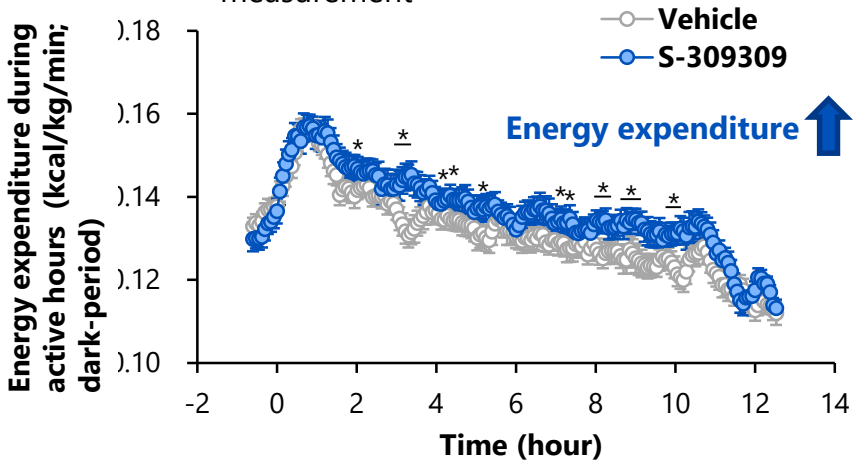
0 1 2 3 6 (week) 0 3 (Day)

Under the pair-fed condition
Oral administration of S-309309

Energy expenditure measurement



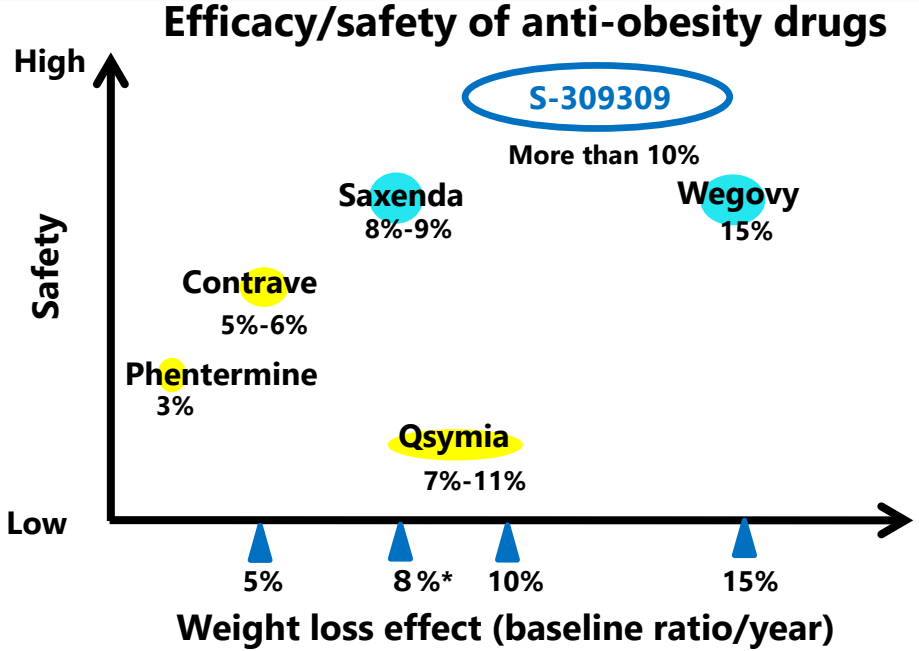
n = 16, mean ± SE, * P <0.05 vs Vehicle



n = 31-33, mean ± SE, * P <0.05 vs Vehicle

S-309309 induced a weight reduction and increased energy expenditure under pair-fed condition

S-309309: Target product profile



Limitations with approved drugs

Oral preparations
- Central nervous system side effects (CV risk, anxiety, dizziness, insomnia, paresthesia)
- Insufficient medicinal effect

GLP-1 injection
- High drug price ($ 40/day)
- Frequent gastrointestinal symptoms (dose should be titrated for up to 4 months to reach maintenance dose and avoid side effects)

S-309309: First-line drug in the treatment of obesity

- **No safety concern, The most potent efficacy among oral drugs (10%/year weight loss)**
- **Lower economic burden than GLP-1 analogs, affordable price suitable for long-term treatment**

* 1st benchmark of FDA guidelines (5% weight loss / year compared to placebo)

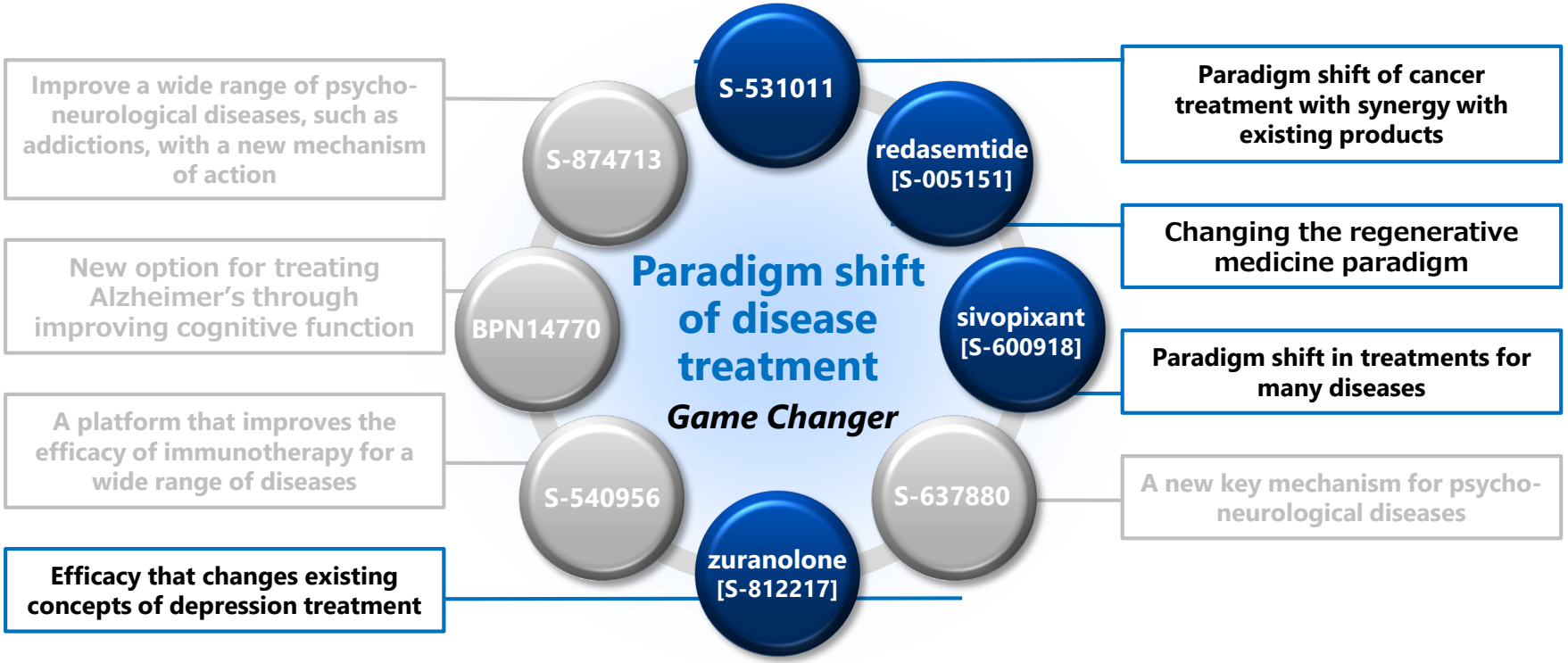
Agenda

1. **Shionogi R&D**
   - Progress of COVID-19 Projects

     Ryuichi Kiyama, Ph.D.,
     Senior Executive Officer, Senior Vice President, Pharmaceutical Research Division
     Toshinobu Iwasaki, Ph.D.,
     Senior Executive Officer, Senior Vice President, Global Development Division

   - Progress of Shionogi R&D
     - > Research area — **Ryuichi Kiyama**
     - > Development area — **Toshinobu Iwasaki**
2. **Summary** — **Isao Teshirogi, Ph.D.,** President and CEO
3. **Q&A**

The Outcome We Envision from our Core Pipeline



Creating products and services for diseases with high unmet medical needs

Development area

S-600918 [sivopixant]

Refractory chronic cough (RCC)

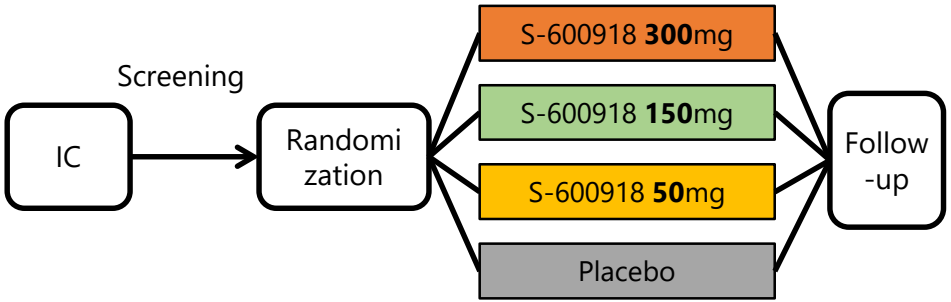
Sleep apnea syndrome (SAS)

Sivopixant: Refractory Chronic Cough (RCC)

- Phase 2b dose finding study

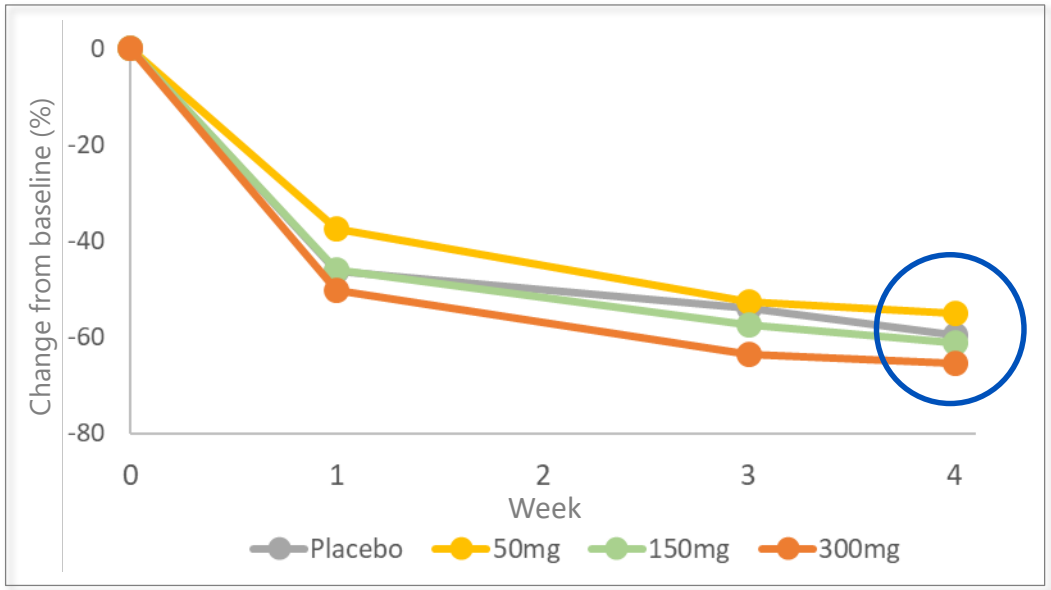
Patients	Refractory/Unexplained chronic cough
Endpoints	Efficacy (cough counts, QoL etc.) , Safety, PK
Primary endpoint	Cough Counts per hour in 24hr
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group
Regions	Japan, US, Europe
No. of patients	372
Dosing regimen	Once daily, 4 weeks

Last Patient Last Visit (LPLV) was completed in Dec. 2020 successfully, as minimizing impact of COVID-19



Sivopixant: RCC (Primary Endpoint)

- Cough counts per hour in 24hr (FAS, Full Analysis Set)

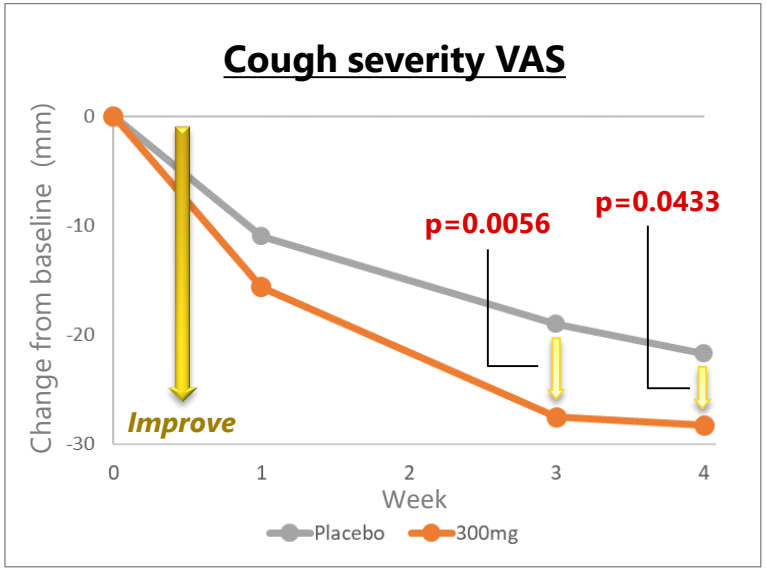


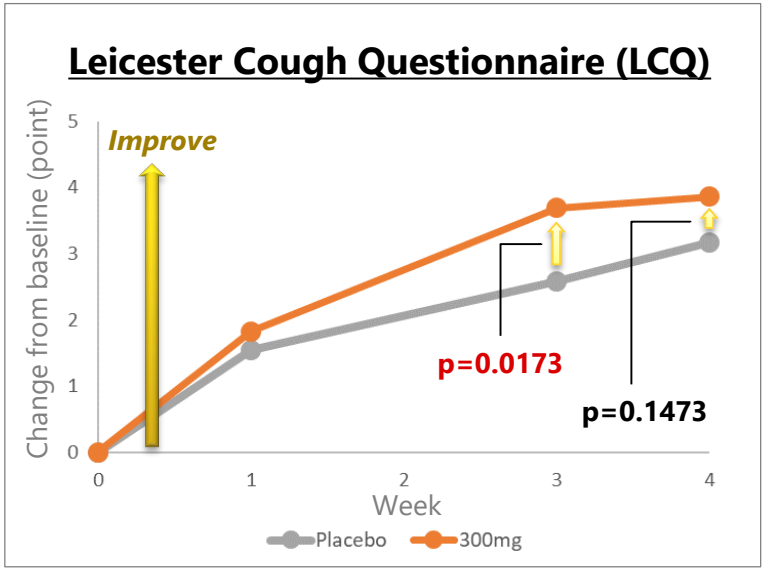
	N	Placebo-adjusted change (at 4wks)	P-value
Placebo	102	—	—
50 mg	100	13.17%	0.3532
150 mg	102	- 1.77%	0.8935
300 mg	96	- 12.47%	0.3241

Primary endpoint was not met
(statistical significance was not observed in any of sivopixant groups)

Sivopixant: RCC (Secondary Endpoints)

- Cough severity VAS, cough-specific QoL questionnaire at 300 mg



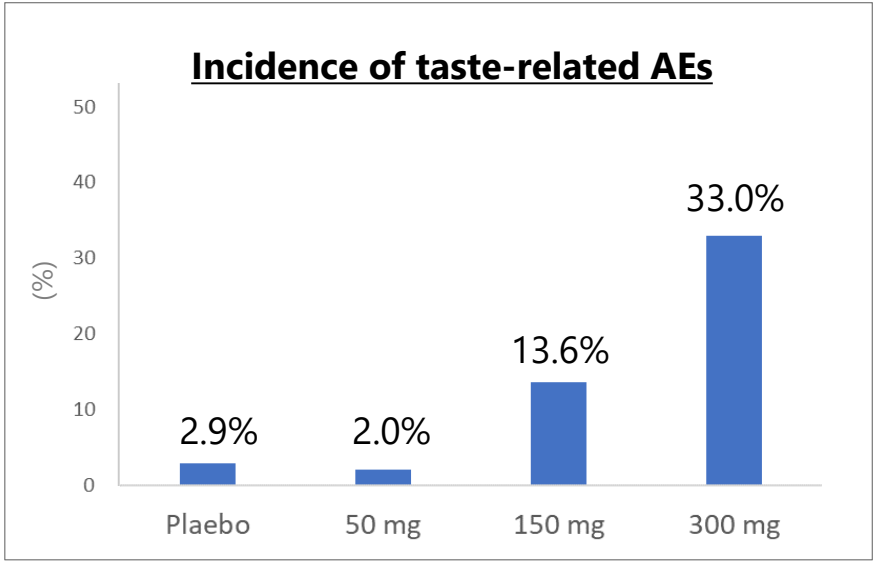


Sivopixant 300 mg dose group showed a tendency toward efficacy in some secondary endpoints

VAS: Visual Analogue Scale, LCQ : Leicester Cough Questionnaire

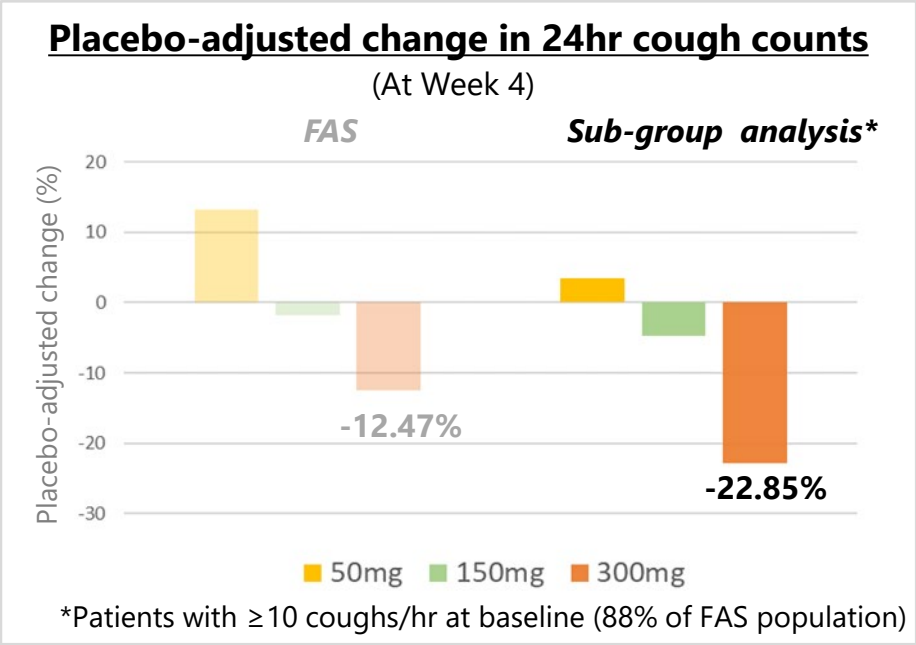
Sivopixant: RCC (Secondary Endpoints)

- Safety, taste-related AEs (Safety Analysis Population)



- **1-month administration of sivopixant was well tolerated**
  - ✓ **Discontinuation ratio was less than 5% in any of sivopixant groups**
- **On the other hand, incidence of taste-related AEs increased dose-dependently**

S-600918: RCC (Next steps)



*Patients with ≥10 coughs/hr at baseline (88% of FAS population)

For the next phase

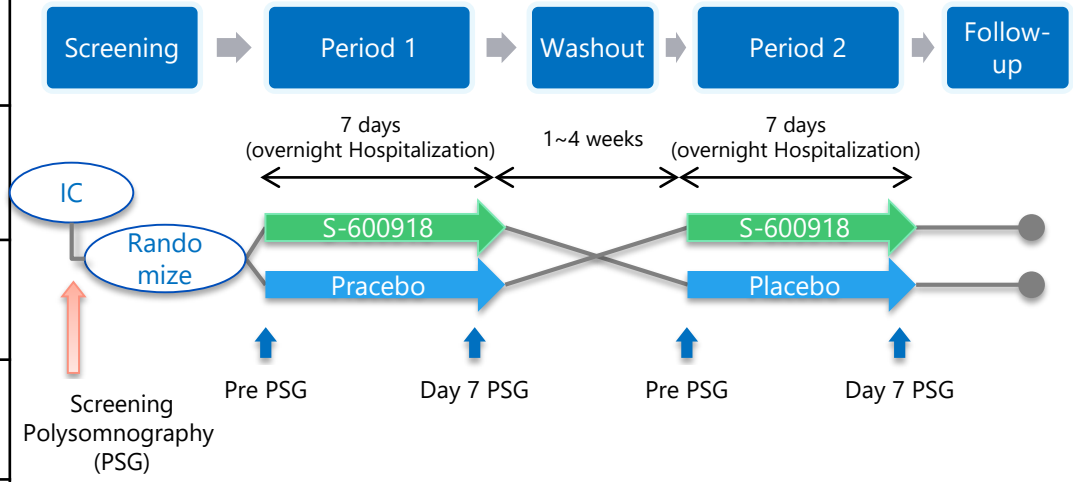
- To determine clinical optimal dose
- To manage placebo effect
- To differentiate from competitors

Taking post-hoc analysis into consideration as well, appropriateness of dose selection, Ph3 study design etc. will be discussed at EoPh2 meetings
→ Aiming to submit IND/CTA/CTN by the end of FY2021

Sivopixant : Sleep Apnea Syndrome (SAS)

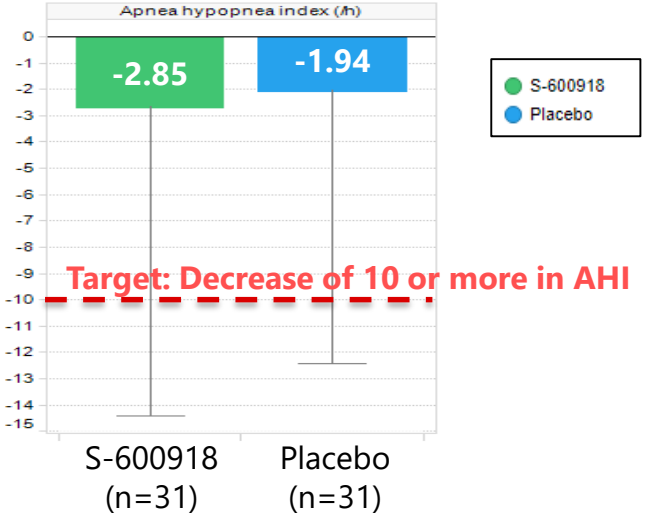
- Overview of Proof of Concept (PoC) Study

Target Patients	Moderate to severe sleep apnea syndrome patients (15≤ Apnea-Hypopnea Index (AHI) <50)
Study design	Placebo controlled, Multi study sites, Randomized, Crossover assignment, Double blind
Endpoints	Apnea-Hypopnea Index (AHI) change from baseline, etc.
Dosing	S-600918 300 mg, Placebo for 7 days (Once a day, before bedtime, oral)
Enrollment	33 participants



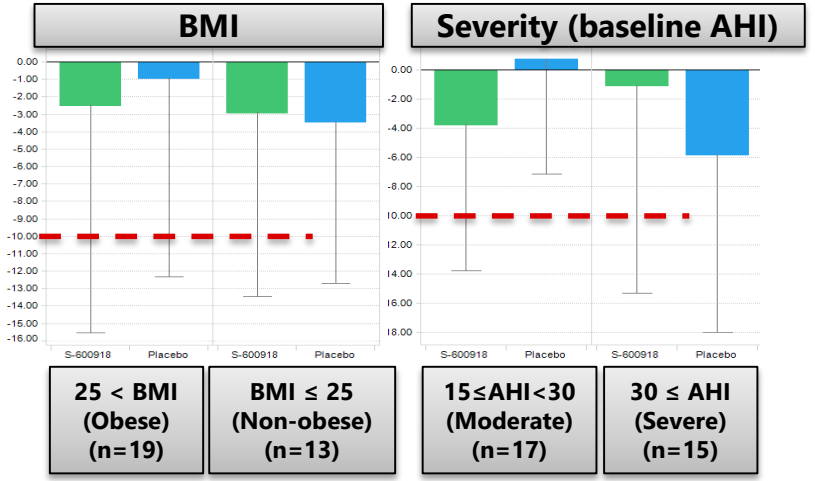
Sivopixant: SAS (Result in PoC study)

- Primary endpoint：Apnea-Hypopnea Index (Change in AHI at Day 7 from baseline)



No major safety concerns were identified

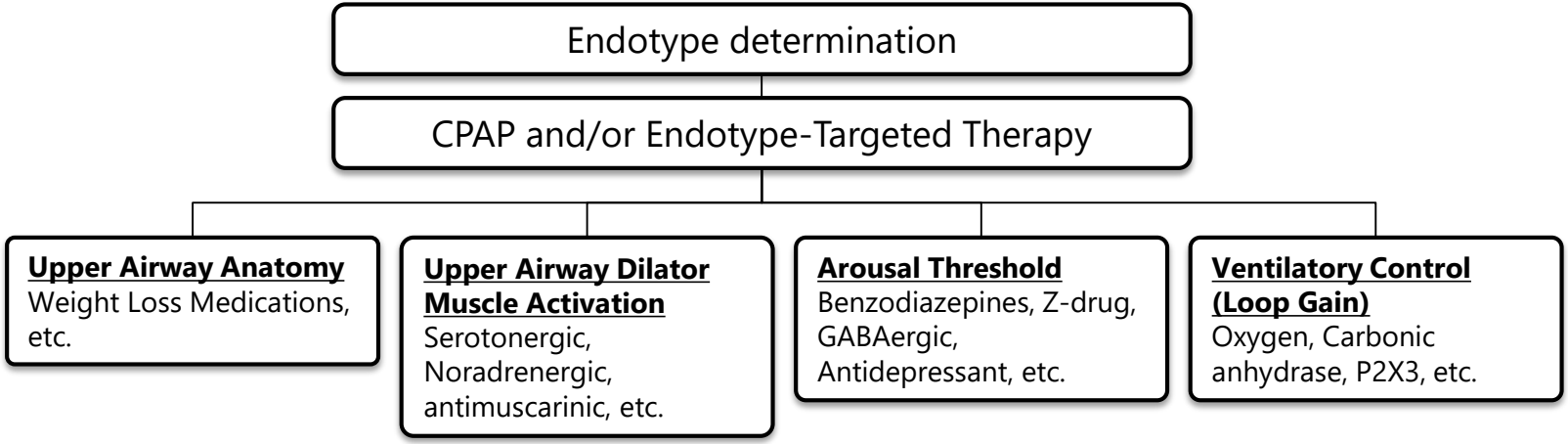
No meaningful efficacy is seen in moderate to severe SAS patients



Sivopixant: Next Action for SAS

- **Suspended/discontinued the development of S-600918 for general SAS (moderate to severe)**
- Exploratory the classification of the endotype in SAS (including background factors), and identify the therapy for each endotype (Precision Medicine)

⇒ Pursuing research and development in SAS by utilizing the experience of PoC study



Reffered to L Tranto-Montemurro et al., J Clin Med. 2019
Targeting Endotypic Traits with Medications for the Pharmacological Treatment of Obstructive Sleep Apnea.

Development area

S-005151 [redasemtide]

- Dystrophic Epidermolysis Bullosa : Investigator initiated study was completed and the efficacy on DEB patients was confirmed. Additional clinical study is in preparation.
- Acute Ischemic Stroke : Phase 2 study is ongoing, LPI was achieved.
- Chronic Liver Disease : Investigator initiated Phase 2 study is ongoing.
- Knee Osteoarthritis : Investigator initiated Phase 2 study is ongoing.
- Cardiomyopathy : Investigator initiated study is in preparation.

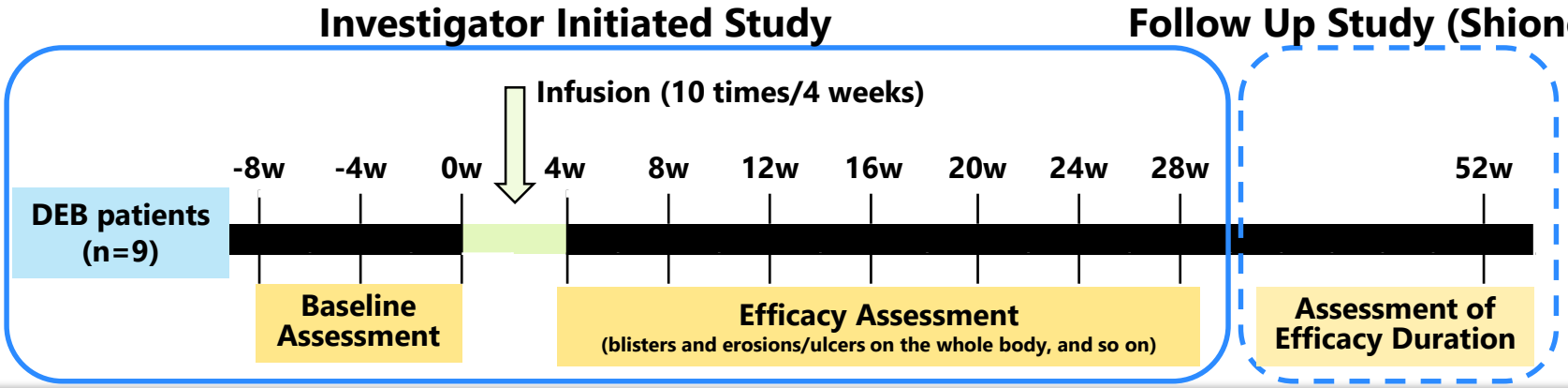
Redasemtide: Dystrophic Epidermolysis Bullosa

- **Outline of Clinical Studies for Epidermolysis Bullosa**

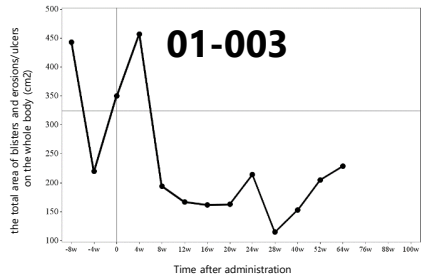
Shionogi conducted the follow up study for assessing the efficacy until all subjects reached 52 weeks after administration

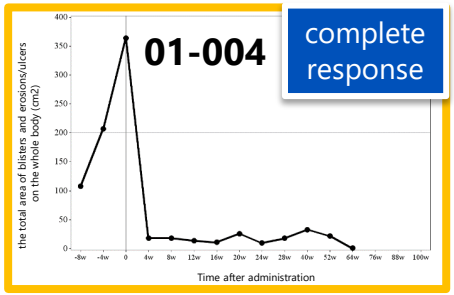
Investigator Initiated Study

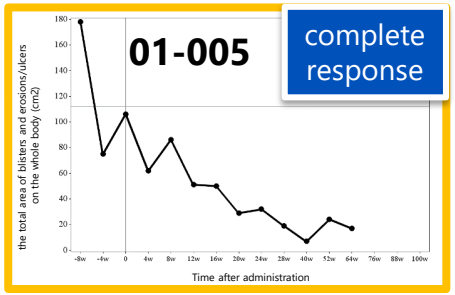
Target Population	Dystrophic Epidermolysis Bullosa (DEB) patients, n=9 (active drug only)
Primary objective	Percentage change from baseline in the total area of blisters and erosions/ulcers on the whole body
Dosage	Drip intravenous infusion, 10 times/4 weeks [Week 1: 4 days, Week 2-4: 2 days/week (1 dosage/3-4 days)]

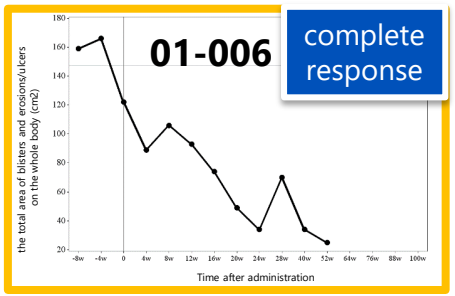


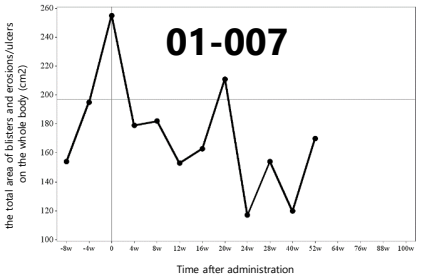
Redasemtide: Total Area of Lesion on The Whole Body (cm^2); Data from 7 Subjects Showing Positive Efficacy

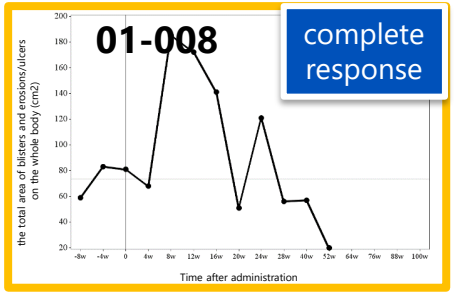


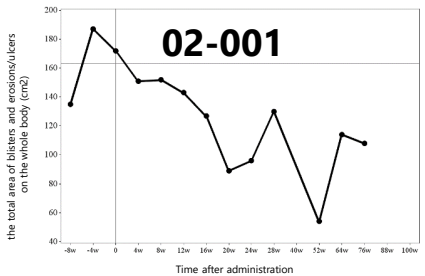






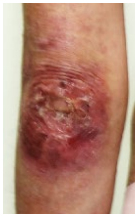
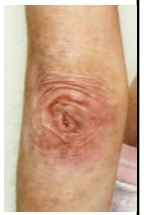


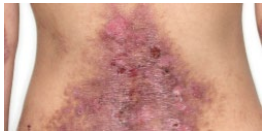
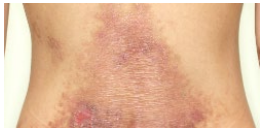


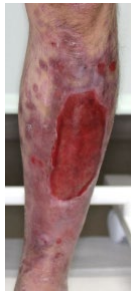
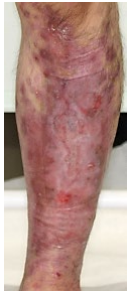


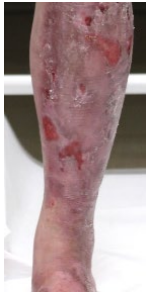
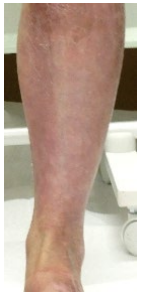
- **Positive efficacy was observed in 7/9 subjects**
- **Imaging from 4 patients showing complete response are in the next slide**

Redasemtide: Clinical Course of 4 patients

Drastic improvement of elbow*refractory scar (**No. 01-004**)			
0w		28w	
	Blisters and erosions were on the scar.		The scar was disappeared, blisters and erosions also almost disappeared.

Drastic improvement of back refractory scar (**No. 01-005**)	
0w	28w
Erosions and scabs were on the scar. 	Dramatical improvement of scar, erosions and scabs 

Drastic improvement of lower leg refractory ulcer (**No. 01-006**)			
0w		28w	
	Refractory ulcer was on the scar (no healed for a long time)		The scar became milder and epithelializatio n of refractory ulcer was observed.

Drastic improvement of lower leg refractory scar (**No. 01-008**)			
0w		75w**	
	Skin ulcer on the inflammator y scar		Dramatical improvement of scar, disappearance of ulcer

* The region in which the lesion is persistent because the external force is routinely applied ** The 120th Annual Meeting of the Japanese Dermatological Association; Educational Lecture presented by Dr. Tamai

Redasemtide: Dystrophic Epidermolysis Bullosa

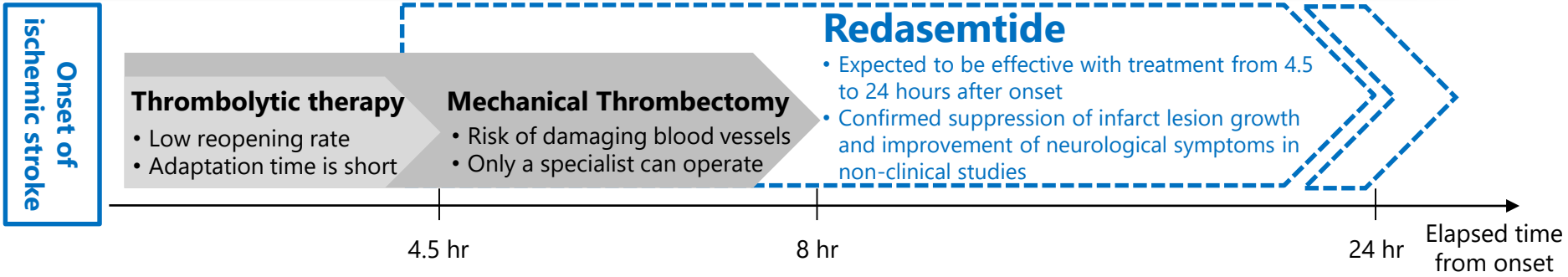
- **NDA Preparation**
  - The result of discussion with PMDA
    - > Dramaticl improvement was observed in the Investigator initiated study, however, **additional efficacy data is needed for NDA**

- Additional Clinical Study (tentative)

Target Population	Dystrophic epidermolysis bullosa patients
Primary objective	Epithelialization of refractory ulcer
Dosage	Drip intravenous infusion, 10 times/4 weeks [Week 1: 4 days, Week 2-4: 2 days/week (1 dosage/3-4 days)]

An additional clinical study is planned to confirm the reproducibility of the Investigator initiated study results

Redasemtide：Acute Ischemic Stroke



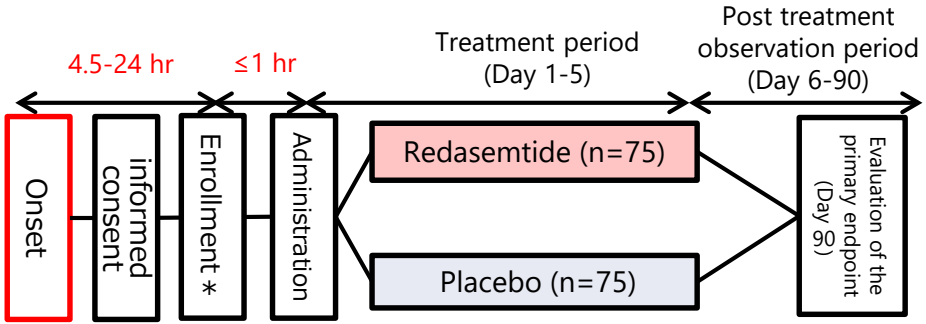
- **Unmet Medical Needs for Acute ischemic stroke**
  - **Drugs with an expanded time window for use**
- **Expected value of redasemtide compared to other therapies**
  - **Could be dosed with a expanded time window compared to standard therapies**
  - **Can offer stable supply and manage product quality easily** compared to the existing regenerative medicine including stem cell transplantation

The development of redasemtide as a next-generation medicine has great significance

- **Expanded time window** compared to standard therapies
- **Potential for a regenerative modality with stable supply and affordable price** compared to other regenerative approaches

Redasemtide：Acute Ischemic Stroke PoC study

Primary objective	To evaluate the efficacy and safety of redasemtide compared to placebo in patients with acute ischemic stroke (**Within 4.5-24 hours of onset**, Male or female patients aged ≥ 60 to < 85 years)
Study design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group
Sample size	Redasemtide (1.5 mg/kg): 75 subjects Placebo: 75 subjects 150 subjects in total
Dosage	90 minutes intravenous infusion, Once daily, 5 days
Primary endpoint	modified Rankin Scale (mRS**) 90 days after the first administration



Standard therapies except for t-PA and endovascular recanalization therapy can be used

＊ Allocation factor: NIHSS, Time from onset of acute ischemic stroke to enrollment

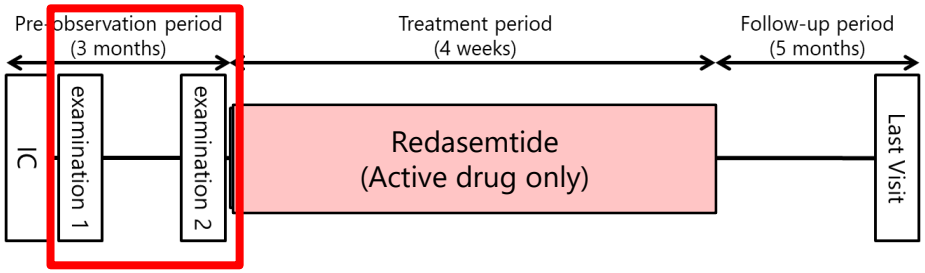
Completion of enrollment of the last subject was achieved as planned even in coronavirus crisis (Jul-2021)

Last observation in Oct-2021
Top-line result will be available in 3Q-2021 (October-December)

** modified Rankin Scale: A scale commonly used to measure the degree of disability or dependence in daily activities of people suffering from stroke or other causes of neuropathy

Redasemtide : Chronic Liver Disease Investigator initiated Phase 2 study

Primary objective	To evaluate the efficacy and safety of Redasemtide in patients with chronic liver disease.
Study design	Single center, non-randomized, single arm, open label
Target population	**Patients with chronic liver disease whose liver stiffness is 4 kPa or more measured by MR elastography. 10 patients in total.**
Dosage	• **1.5 mg/kg (free form),** 90 minutes intravenous infusion • Cohort A: 4 times / 4 weeks [once a week] • Cohort B: 7 times / 4 weeks [Week 1: 4 days, Week 2-4: once a week (1 dosage/3-4 days)]
Study duration	**Pre-observation: 3 months** **Treatment and follow-up: 6 months**
Site	**Division of Gastroenterology and Hepatology, Niigata University Medical and Dental Hospital**

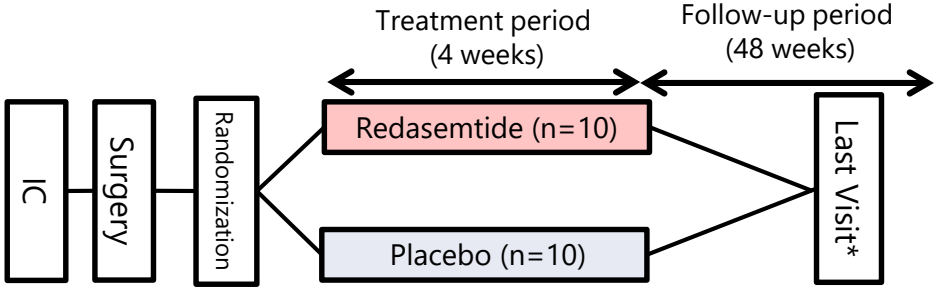


Efficacy and safety of redasemtide are exploratorily evaluated by improvement of fibrosis, inflammation and liver function in patients whose pathophysiology is stable during 3-month pre observation period.

Ongoing: Administration to 1st patient was achieved on Mar-2021

Redasemtide: Knee Osteoarthritis Investigator initiated Phase 2 study

Primary objective	To evaluate the efficacy and safety of redasemtide compared to placebo in patients with knee osteoarthritis (OA)
Study design	Single center, randomized, placebo-controlled, double blinded, parallel-group
Target population	**Patients with knee OA who have undergone high tibial osteotomy (HTO) and microfracture**
Sample size	Redasemtide (1.5 mg/kg) : 10 subjects Placebo: 10 subjects 20 subjects in total
Dosage	90 minutes intravenous infusion, 8 times / 4 weeks [1 dosage/3-4 days].
Study duration	**12 months after the initial administration**
Site	**Department of Orthopaedic Surgery, Hirosaki University**



*joint cartilage biopsy at follow-up surgery of HTO (plate removal)

Efficacy and safety of redasemtide compared to placebo are exploratorily evaluated with structural/functional endpoint and QOL in patients with knee osteoarthritis (OA) who undergone high tibial osteotomy and arthroscopic microfracture.

Ongoing: Administration to 1st patient was achieved in Feb-2021

High tibial osteotomy: Surgery to reduce knee pain by correcting the O-leg to the X-leg so that the load is applied to the outside and reducing the burden on the inside.
Arthroscopic microfracture: A treatment that promotes the outflow of stem cells, which may differentiate into articular cartilage cells, from the bone marrow to the damaged part by making a small hole in the subchondral bone of the mother bed of the damaged cartilage.

Development area

S-812217 [zuranolone]

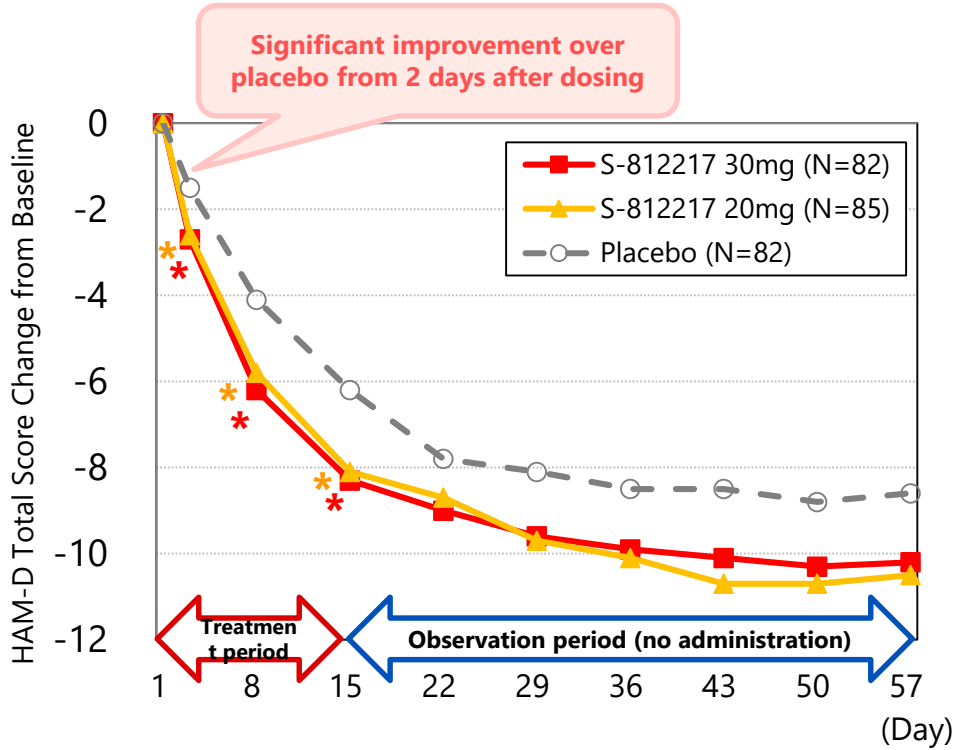
Depression

Zuranolone: Domestic Phase 2 Study Outline

Subject	Patients with moderate to severe major depressive disorder
Primary endpoint	Change of total score of Hamilton Depression Rating Scale for 17 items (HAM-D17) 2 weeks after administration (Day 15) from baseline
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group controlled trial
Area	Japan
Target number of patients	80 patients in each group, 240 patients in total
Administration method / administration period	Once daily for 2 weeks

- **Unmet needs for existing depression treatment**
  - ✓ **Necessity for long-term medication until the therapeutic effect is exhibited**
  - ✓ Insufficient therapeutic effect
  - ✓ Long-term drug treatment
  - ✓ Insomnia and anxiety
- **Expected value provided by zuranolone**
  - ✓ **Immediate therapeutic effect**
  - ✓ Strong improvement of depressive symptom
  - ✓ Sustained therapeutic effect after drug withdrawal
  - ✓ Improvement of insomnia symptoms associated with depression
- Increasing needs for **quick onset of therapeutic effects** and improvement of insomnia associated with depression in COVID-19 pandemic

Zuranolone: Domestic Phase 2 Study Results



Efficacy

- **Achieved the primary endpoints at both 20 mg and 30 mg**
  - ✓ Significant improvement over placebo from Day 3 (first observation) to Day 15 (end of administration) at 20 mg and 30 mg of change in total HAM-D score from baseline
  - ✓ Response rate** was significantly improved on Day 8 and Day 15 compared to placebo

⇒ Confirm the "Quick onset"

  - ✓ Throughout the observation period from Day 15 to Day 57, although there was no significant difference from placebo, trend in continuous therapeutic effect was observed.

Safety

- **Confirmed the safety**
  - ✓ All adverse events were mild or moderate, with no new concerns

SHIONOGI

* P<0.05 vs Placebo

** Percentage of patients who improved ≥50% in HAM-total score from baseline

Zuranolone: Development strategy

Features of zuranolone

- **Quick onset**
  - Effective 2 days after dosing (existing antidepressants take 4-6 weeks)
- **Durability**
  - Durability is indicated for 6 weeks after the end of the treatment period
- **Ease to use**
  - High adherence to complete administration in 2 weeks
- **Safety**
  - Mild / moderate with no new concerns

- **Product positioning that takes advantage of these 4 characteristics**
- **Phase 3 study will be started in 4Q of FY2021, JNDA filing in FY2023, approval in FY2024**

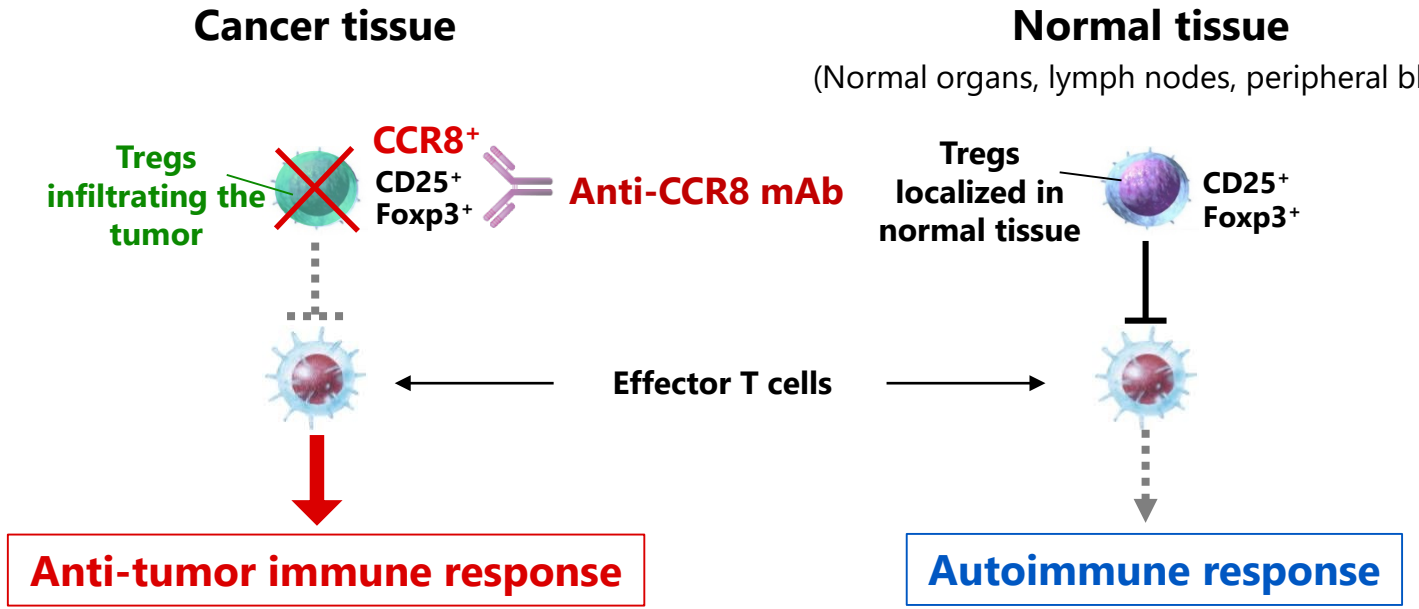
* From treatment introduction after depression diagnosis to remission (disappearance of depressive symptoms) (Source: Depression Treatment Guidelines, Key Points of Depression Treatment-10)

Development area

S-531011

Solid tumor

S-531011: Therapeutic drug concept



Selective removal of tumor-infiltrating Tregs can be expected to reduce the risk of autoimmune disease and enhance anti-tumor immunity.

S-531011: Phase 1b/2 Study

Study title	A Phase 1b/2, multicenter, open-label study of S-531011 as monotherapy and in combination with an immune checkpoint Inhibitor (ICI) in participants with locally advanced or metastatic solid tumors
Arms	Part A-1: Dose escalation, S-531011 monotherapy Part A-2: Dose escalation, S-531011 combination therapy with ICI Part B: Dose Expansion, S-531011 monotherapy Part C: Dose Expansion, S-531011 combination therapy with ICI
Enrollment	Part A-1: 24 participants, Part A-2: 18 participants, Part B, C: 232 participants
Tprimary endpoint	Part A: Safety and tolerability Part B, C: Antitumor efficacy * (ORR **)
Secondary endpoint	Part A: Antitumor efficacy (ORR), progression-free survival (PFS), progression-free survival (OS) Part B, C: Safety, tolerability Part A, B, C: Pharmacokinetics, biomarker (CCR8 tissue staining, TMB***)
Usage	S-531011, ICI once every three weeks, up to 1 year
Region and number of sites	Part A: Japan/US (each 3 sites), Part B, C: North America / Asia / Europe (35 sites in total)

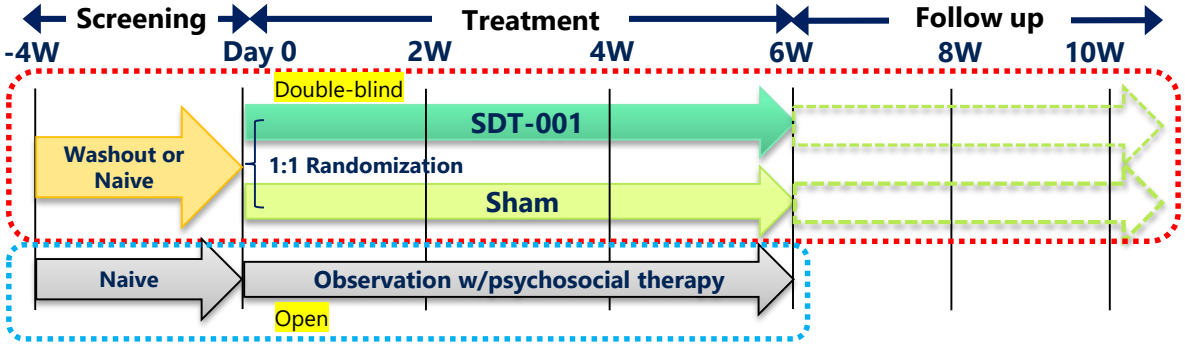
* Evaluation evaluation for RECIST Ver1.1, ** Overall response rate, ***Tumor Mutation Burden

Development area

SDT-001

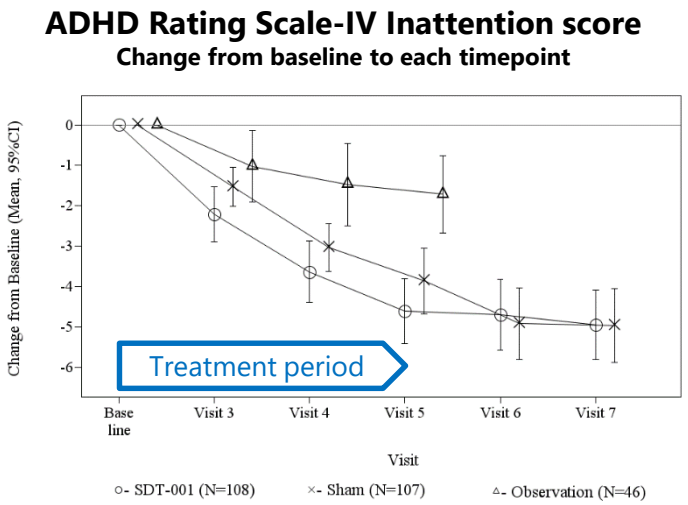
Inattentive ADHD (pediatric)

SDT-011: Phase 2 Study Protocol

Objective	Evaluate efficacy & safety of SDT-001 in pediatric ADHD patients comparing with Sham*. Evaluate efficacy of SDT-001 and appropriateness of Sham in comparison to Observation cohort. *Appli. w/similar appearance excluding core mechanism of Dual task & Difficulty adjustment
Study design	
Target patients	Patients who were judged to be ineffective in psychosocial treatment including environmental adjustment in both SDT-001 / Sham / Observation。
Target sample size	247 patients (106 patients each for SDT-001/Sham group, 35 patients for Observation cohort)
Duration	Once daily (25min) for 7 days/week，6-weeks
Endpoints	• Change in ADHD RS Inattention subscale scores from baseline to each timepoints • Change in TOVA ACS from baseline to each timepoints, etc.

TOVA: The Test of Variables of Attention, ACS: Attention Composite Score

SDT-001: Phase 2 study in pediatric ADHD



Treatment group	Change from Baseline	Week 6（Visit 5） vs Sham	
	Mean (SD)	Difference of LS Mean [95% CI]	p-value
SDT-001	-4.6（4.2）	-0.8 [-1.9, 0.3]	0.1750
Sham	-3.9（4.2）		
Observation	-1.7（3.2）		

Post-hoc analysis*	Estimated efficacies vs Observation group**	
	Estimated difference at Week 6 (Visit 5) compared with Observation group [95% CI]	p-value
SDT-001	-2.5 [-3.7, -1.4]	<0.0001
Sham	-1.7 [-2.9, -0.5]	0.0051

*Observation group not randomized in this study
**Analysis by inverse probability weighting with propensity score (Reference values)

- **Efficacy**
  - SDT-001 showed larger improvements in clinical endpoints; ADHD Rating Scale-IV Inattention score and Hyperactivity/Impulsivity and Total scores, CGI-I etc. compared with Sham though not statistically significant
  - Analysis with propensity score (Reference values) suggested that SDT-001 can show efficacies in various endpoints vs Observation cohort (existing psychosocial therapy including environmental adjustment)
- **Safety**
  - Adverse device reactions were irritability and headache, 1 each in SDT-001 and Sham group, somnolence in 2 events（Sham）, asthenopia in 1 events（Sham）tinnitus and nausea in 1 event（SDT-001）, and all the events were mild in severity

SDT-001 : Device with core-mechanism (Dual task＋difficulty adjustment for individual), Sham : Sham application in appearance as same as possible (Device with single task), CGI-I : Clinical Global Impression–Improvement

SDT-001: Development Strategy

US Akili

- **EndeavorRX**
  Prescribed by self-financed medical treatment and insurance reimbursement after FDA approved in 2020,6,15
  Indications: a digital therapeutic indicated to improve attention function as measured by computer-based testing in children ages 8-12 years old with primarily inattentive or combined type ADHD, who have a demonstrated attention issue
- **ADHD (13-17 years old),(adult) open label test underway** **510 (K) application planned**
- **Clinical trial of COVID-19 brain fog underway** **Joint research with academia***

Japan

- **Improving the treatment paradigm for ADHD**
  Providing a new concept of treatment (digital treatment app) for pediatric ADHD patients who are concerned about side effects of drug treatment and long-term administration
- **Scheduled to consult with PMDA regarding Phase 3 implementation**

* Weill Cornell Medicine, NewYork-Presbyterian Hospital and Vanderbilt University Medical Center

Development area

S-770108

Idiopathic Pulmonary Fibrosis

S-770108: Rationale for Development

Oral pirfenidone (Pirespa® & Esbriet®)

- The efficacy in IPF is established in pivotal studies[*, 2*, 3*], and recommended IPF therapy in the international guideline*[4]
- High incidence of adverse drug reactions*[5]
  - Photosensitivity reactions (14.4%)
  - Decreased appetite (27.9%)、Nausea (8.0%)
- In more than half of the patients, the recommended dose level (1800 mg) cannot be achieved due to adverse drug reactions (ADR)[5*].
- Approximately 20% of patients discontinued the treatment due to adverse events[5*]

Inhaled pirfenidone (S-770108)

- **Administered directly in the lung by inhalation, systemic exposure will be markedly reduced (1/50)**
- **Incidence of ADRs would be greatly decreased, and high drug concentration in the lung and superior adherence could enhance the efficacy.**

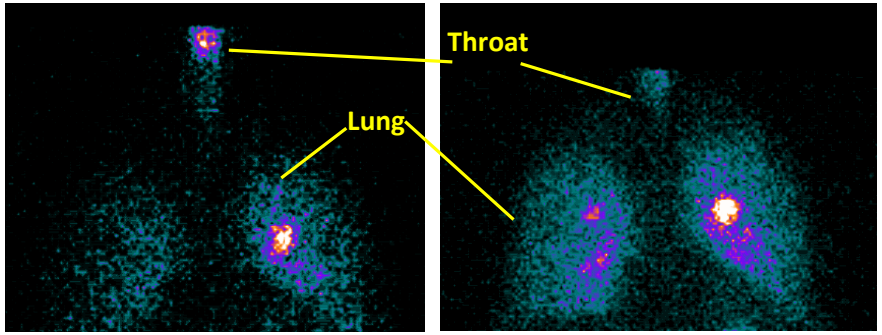
* Eur Respir J. 2010;35(4):821-9, 2* Lancet. 2011;377(9779):1760-9, 3* N Engl J Med. 2014;370(22):2083-92
4* Am J Respir Crit Care Med. 2015;192(2):e3-19. 5* Respir Investig. 2015;53(5):232-41

S-770108

- Lung deposition study (Phase 1)
  - Pirfenidone deposition (concentration) in the lung was evaluated during a lung deposition study conducted in 2020, in place of a Phase 2 dose-finding study, to allow progression to the Phase 3 program.
  - During the lung deposition study, deposition parameters in healthy subjects were evaluated at two different Inhalation flow rates, achievable by the target IPF patient population, which were identified during a previous clinical research study*

Flow rate : 15 L/min
Flow rate that the majority of IPF patients can produce

Flow rate : 30 L/min
Flow rate achievable by healthy subjects, and more mild IPF patients



Scintigraphic image in one subject

Lung delivery and deposition of S-770108 was confirmed at both inhalation flow rates.

The higher flow rate is estimated to deliver a larger amount of drug in the lung in IPF patients.

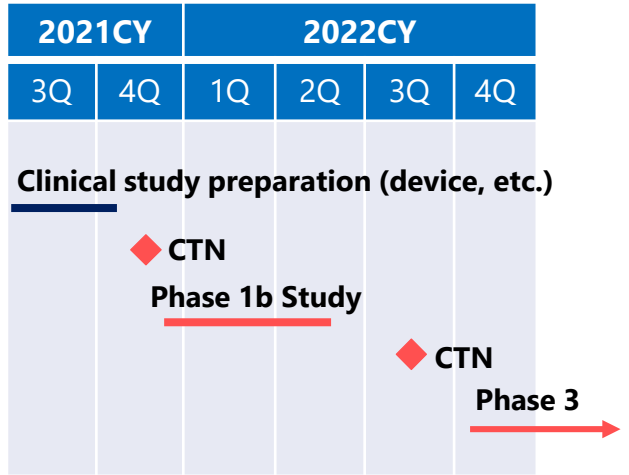
* After training healthy subjects to achieve the target inspiratory rate, inhale S-770108 at that inspiratory rate and evaluate lung deposition.

S-770108: Future Development Plan

Plan to initiate Japan Ph1b study in Oct prior to conduction of Phase 3 study with the new inhalation device

- **Obtain inhalation flow profiles with the new inhalation device in IPF patients** (during screening)
- Evaluate safety, tolerability, and PK in IPF patients when the drug is inhaled 3 times a day for 15 days (To evaluate the long-term acceptability of S-770108 treatment)

Title	Ph1 study of S-770108 in IPF patients
Objective	Primary : Safety, tolerability Secondary: Pharmacokinetics Exploratory: Inhalation parameters
Design	Open
Target patients	20 IPF patients (8 or more subjects with <75% %FVC)
Study drug	S-770108 (6 mg/cap, 2 capsules/dose, 3 times a day)
Device	New inhalation device
Treatment period	15 ± 3 days
Study period	Oct 2021 (CTN) – Apr 2022.4 (LPLV)



Under discussion with regulatory agencies to minimize timeline disruption caused by device change

Development milestones

Development Products in FY2021: Major Progress Plans 1/2

Category	Pipeline	Indication	Milestone	Achievement
COVID-19	S-217622	Treatment of COVID-19	Japan: Submission, Approval	
			Japan: Initiation of Phase 2/3	◎Sep
			Japan: Initiation of Phase 1	◎Jul
			Global: Initiation of Phase 3	
	S-268019	Prevention of COVID-19 (COVID-19 Vaccine)	Japan: supply	
			Global: Initiation of Phase 3	
Core 8PJ	S-531011	Solid cancer	Japan, US: Initiation of Phase 1b/2	◎Aug
	S-600918	Refractory/unexplained chronic cough	Global: Initiation of Phase 3	
	S-812217	Depression	Japan: Initiation of Phase 3	
	S-005151	Epidermolysis bullosa	Japan: Initiation of follow up study	
	BPN14770	Alzheimer's disease	Japan: Initiation of Phase 2	◎Apr
		Fragile X syndrome	Global: Initiation of Phase 2	◎Aug
	S-540956	Infectious disease、Cancer	US: Initiation of Phase 1	
	S-874713	Psycho-neurological disease	Japan: Initiation of Phase 1	

Development Products in FY2021: Major Progress Plans 2/2

Category	Pipeline	Indication	Milestone	Achievement
Others	S-309309	Obesity	US: Initiation of Phase 1	
	S-770108	Idiopathic pulmonary fibrosis	Japan: Initiation of Phase 1b	
	SDT-001	Inattention symptom in ADHD patients (pediatric)	Japan: Initiation of Phase 3	
	Xofluza®Granules	Influenza virus infection (pediatric, body weight <20kg)	Japan: supplemental approval	
	S-649266 ［Cefiderocol Tosilate Sulfate Hydrate］	Various infectious diseases	Japan: Submission	

Agenda

1. **Shionogi R&D**
   - Progress of COVID-19 Projects

     Ryuichi Kiyama, Ph.D.,
     Senior Executive Officer, Senior Vice President, Pharmaceutical Research Division
     Toshinobu Iwasaki, Ph.D.,
     Senior Executive Officer, Senior Vice President, Global Development Division

   - Progress of Shionogi R&D
     - > Research area — **Ryuichi Kiyama**
     - > Development area — **Toshinobu Iwasaki**

2. **Summary** — **Isao Teshirogi, Ph.D.,** President and CEO
3. **Q&A**

Agenda

1. **Shionogi R&D**
   - Progress of COVID-19 Projects

Ryuichi Kiyama, Ph.D.,
Senior Executive Officer, Senior Vice President, Pharmaceutical Research Division
Toshinobu Iwasaki, Ph.D.,
Senior Executive Officer, Senior Vice President, Global Development Division

   - Progress of Shionogi R&D
     - > Research area — **Ryuichi Kiyama**
     - > Development area — **Toshinobu Iwasaki**

2. **Summary** — **Isao Teshirogi, Ph.D.,** President and CEO
3. **Q&A**

Appendix

Other 8 Core Projects

- Progress and future plan

S-540956

- **Preparing for Phase 1 study**
  - Objective: Confirmation of safety and immune response as a vaccine adjuvant
  - Scheduled for US IND in December 2021
- **Pursuing collaborations with antigen researchers and companies**

S-874713

- **Preparing for Phase 1 study**
  - Objective: Confirmation of safety and setting of clinical dose
  - Scheduled to start clinical trial in the 2nd half of 2021
- **Considering disease with high medical and value potential**

BPN14770

- **Started Phase 2 trial in Alzheimer's disease (AD) and Fragile X syndrome (FXS)**
  - AD: started Domestic Phase 2 study on April
  - FXS: started US Phase 2b study on August, discussions with FDA for Phase 3 study
- **Accelerating the Phase 2 study for early transition to the Phase 3 study**

S-637880

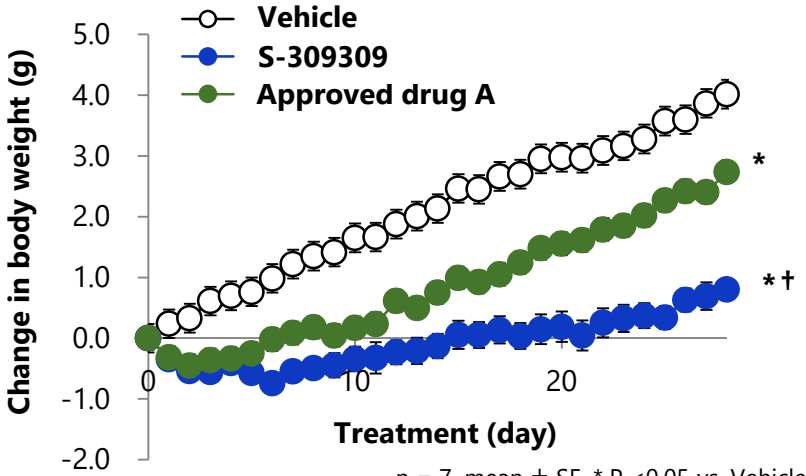
- **Phase 2a study for neuropathic low back pain is underway in Japan**
- **Considering development in other diseases such as multiple sclerosis**

S-309309: Comparison of Efficacy with Approved Drugs

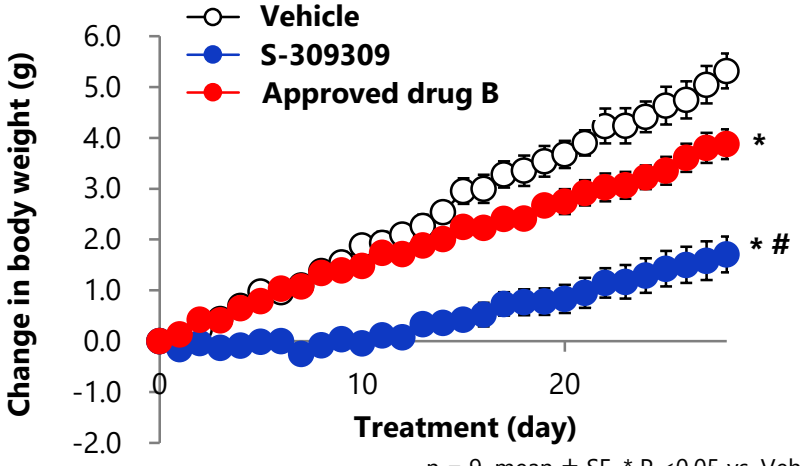
Diet-induced obese mice (60% kcal/fat)

0 1 2 3 4 (week)

Administration of S-309309, approved drug A or drug B for 4 weeks



n = 7, mean ± SE, * P <0.05 vs. Vehicle,
† P <0.05 vs. appproved drug A



n = 9, mean ± SE, * P <0.05 vs. Vehicle,
# P <0.05 vs. approved drug B

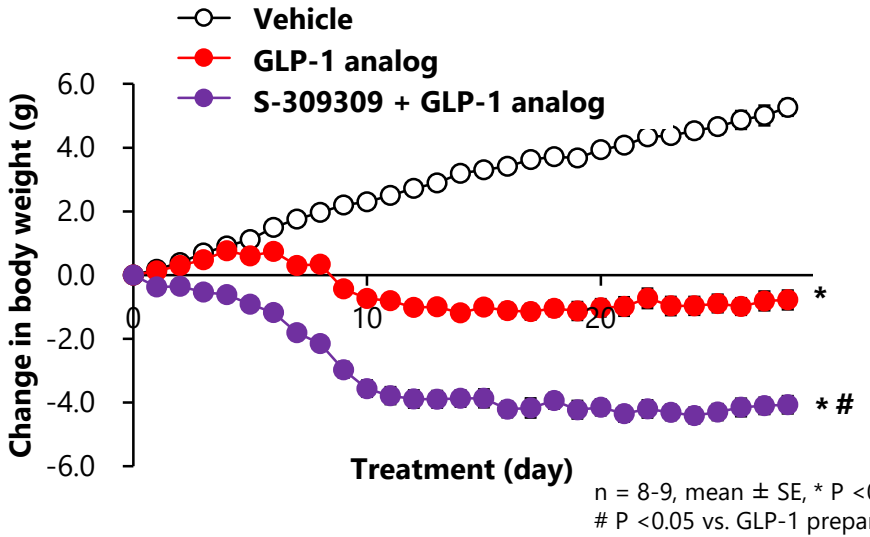
S-309309 showed a stronger anti-obesity effect than approved anti-obesity drugs

S-309309: Effect of Combined Use with GLP-1 Analog

Diet-induced obese mice (60% kcal/fat)

0 1 2 3 4 (week)

Administration of S-309309, GLP-1 preparation, or both agents for 4 weeks



n = 8-9, mean ± SE, * P <0.05 vs. Vehicle, # P <0.05 vs. GLP-1 preparation

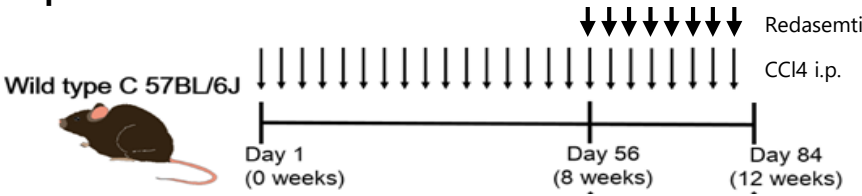
S-309309 had an add-on effect when co-administered with an approved GLP-1 analog

Redasemtide: Chronic Liver Disease

Efficacy in CCl4-induced liver cirrhosis model mice (1)

Research result at Division of Gastroenterology and Hepatology, Niigata University Medical and Dental Hospital

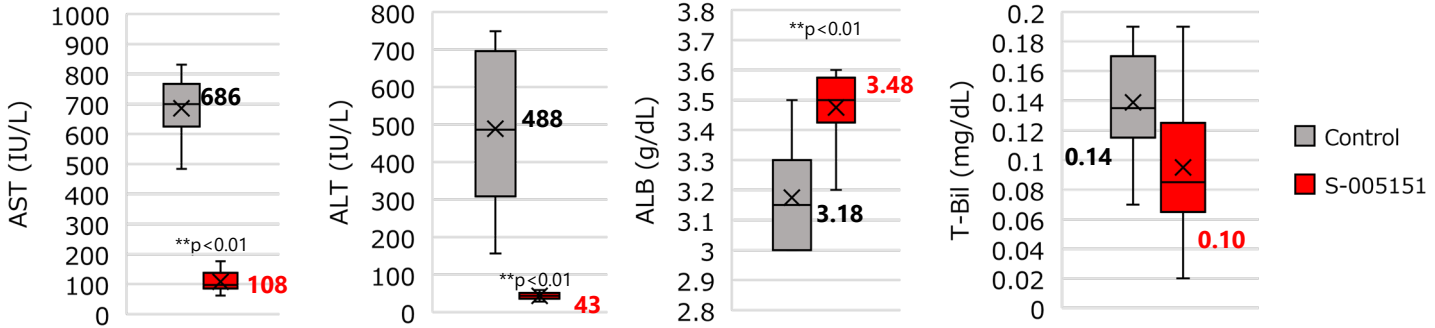
Experiment overview



- CCl4 exposure: 12 weeks (twice a week)
- Treatment duration: 4 weeks (after the 8 weeks exposure of CCl4)
- Dose: 3.5 mg/kg, 8 times (twice a week for 4 weeks)
- Evaluation: after 12 weeks exposure of CCl4 (3 says after the last exposure)

Liver damage indicators (AST, ALT), Liver function indicators (ALB, T-Bil) in Serum

Control: n=8
Redasemtide: n=8
numbers in figures are mean value

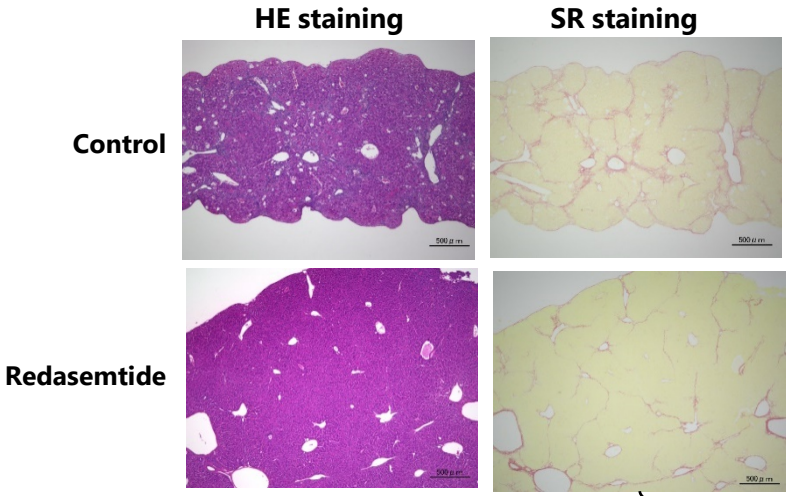


Redasemtide: Chronic Liver Disease

Efficacy in CCl4-induced liver cirrhosis model mice (2)

Research result at Division of Gastroenterology and Hepatology, Niigata University Medical and Dental Hospital

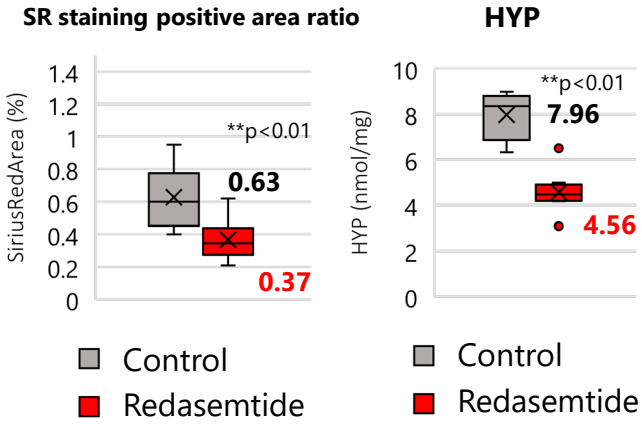
【Tissue sample】



Redasemtide group retain normal liver morphology in comparison to Control group

Quantification of SR staining positive area ratio

【Markers for tissue fibrosis】



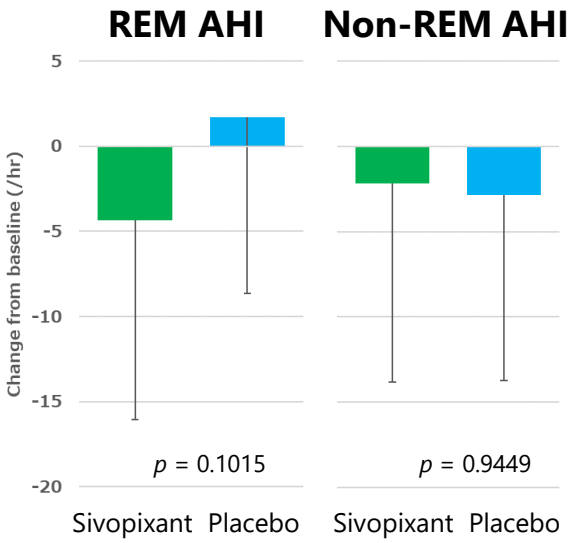
Control: n=8, redasemtide: n=8
numbers in figures are mean value

HYP: Hydroxyproline. It is contained in collagen. HYP content is useful as measure of tissue fibrosis level because it is known increase of HYP and liver fibrosis are correlated.
SR: Sirius-Red staining. It is used for the detection of collagen.

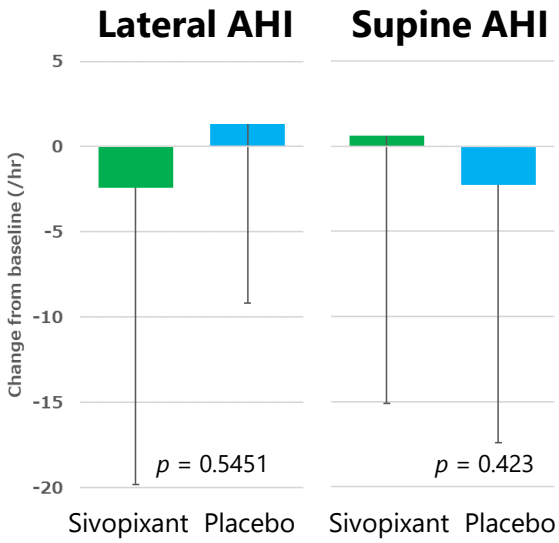
Sivopixant: SAS (Ad-hoc Analysis in PoC Study)

- Changes in the Apnea-Hypopnea index (AHI) for each condition

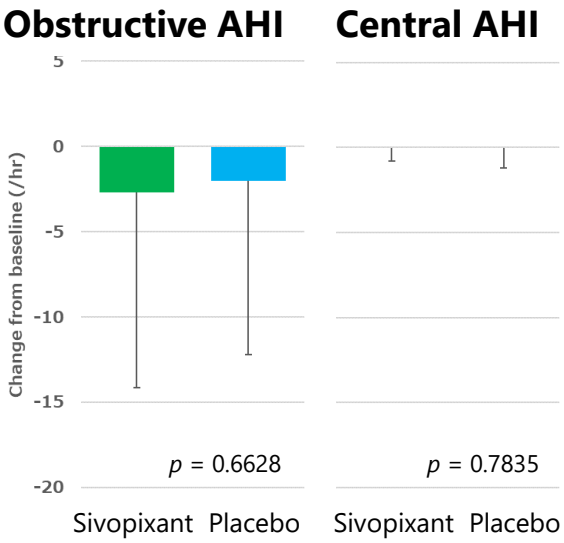
Sleep Stage



Position



Category



No significant changes were found in any AHI indicators analyzed

Sewage Epidemiological Survey in The Olympic and Paralympic Athletes' Village

Contributed to infection control by conducting sewage epidemiological surveys in the Olympic and Paralympic athletes' villages

- Joint conduction with the Univ. of Tokyo, Hokkaido Univ., Osaka Univ. and volunteer research team MARCO
- Sewage was sampled from manholes at three points in the athlete's village, and SARS-CoV-2 quantitative survey and genome analysis were conducted using the Hokkaido Univ.-Shionogi method (tentative)
- Investigation result
  - **It was often detected in sewage in areas where no SARS-CoV-2 infection positive person were reported, but it is thought that this is because the detection sensitivity of the Hokkaido Univ.-Shionogi method (tentative) is high**
    - > It is possible that viral RNA excreted from pre-infected persons, who are generally considered to be non-infectious, and subclinical infected persons with a small amount of virus was also detected
  - **SARS-CoV-2 sequence was confirmed by genome analysis, and mutant strain was detected**
  - **If it was not detected in sewage* for 3 consecutive days, it was not detected in humans**

* Passive sampling: Water is sampled by immersing the lumber in sewage for 24 hours and sampling the sewage