SHIONOGI & CO., LTD.

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R&D Day

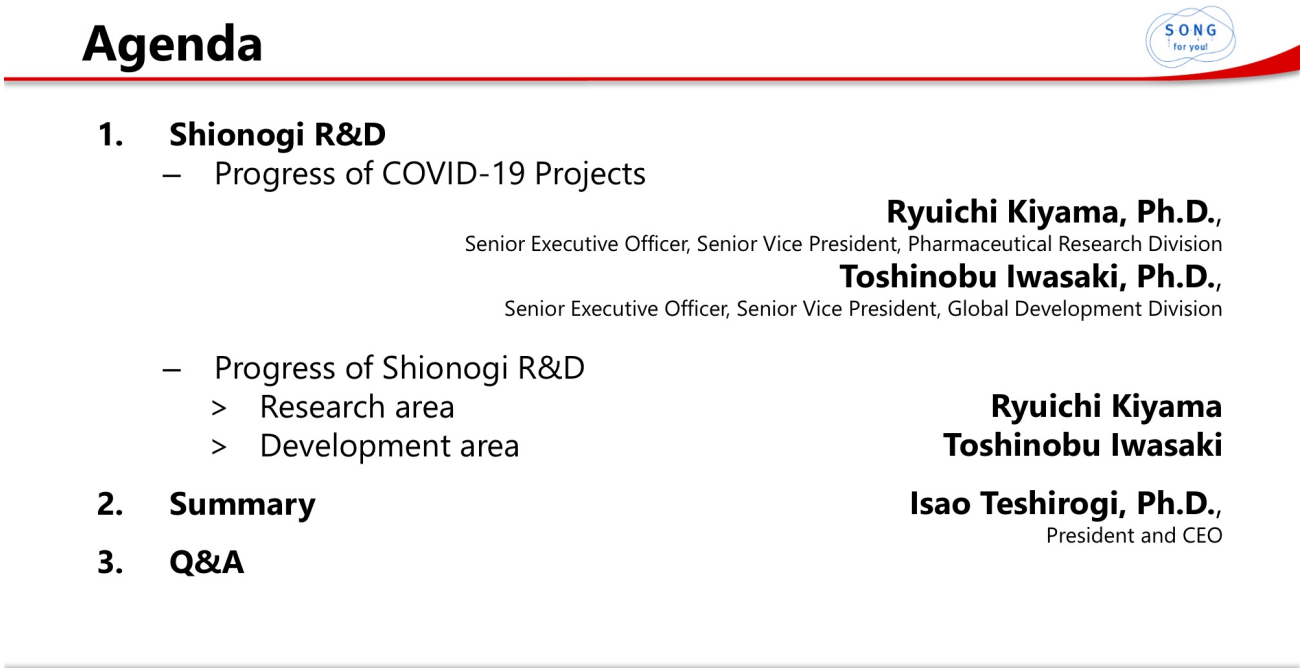
September 29, 2021

Presentation

Kyokawa: Hello. I am Kyokawa, Vice President of Corporate Communications at SHIONOGI & CO., LTD. Thank you very much for joining us today.

For more than 10 years, Shionogi has regularly held R&D briefings in mid or late March. Although today's event is 6 months late, we believe that given the progress in COVID-19 vaccination, now is an appropriate time to hold this event.

We are pleased to open the 2021 Shionogi R&D Day.



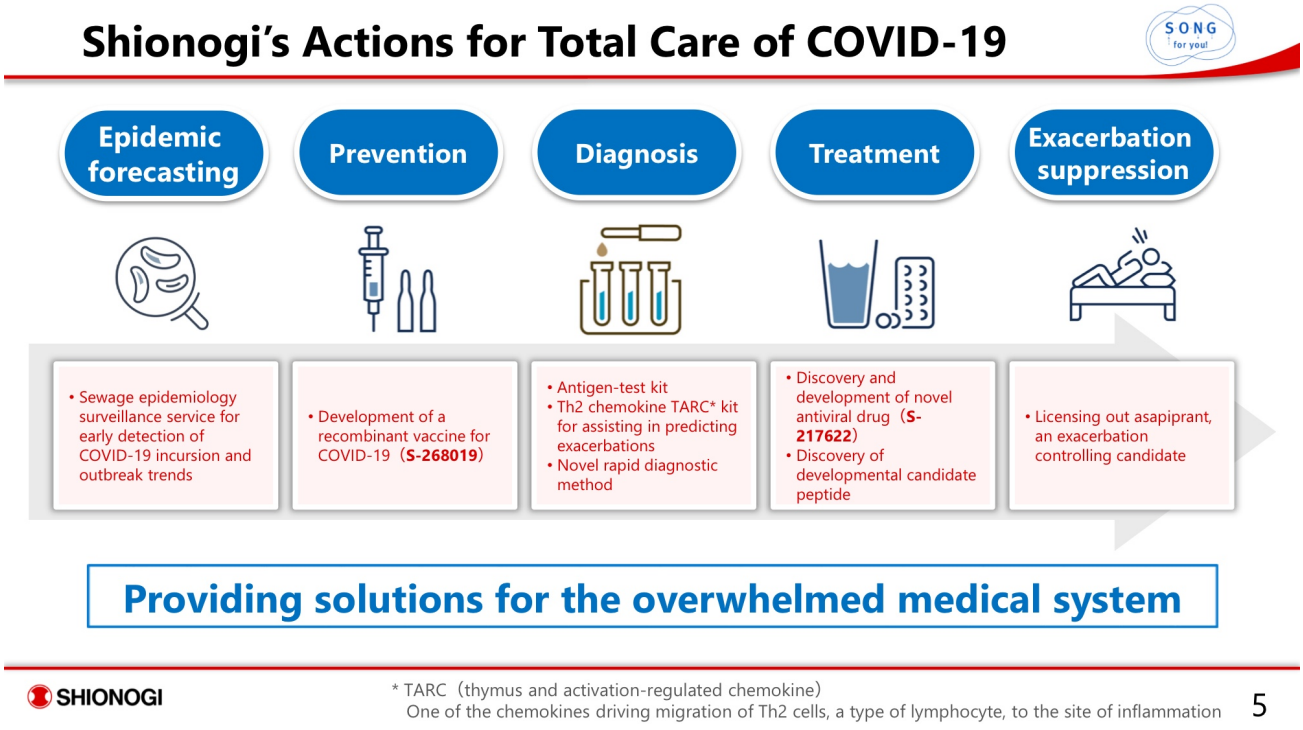
Kyokawa: I will now describe the itinerary for today's session.

Dr. Kiyama and Mr. Iwasaki will begin by explaining the progress of COVID-19-related projects in their respective areas of responsibility. Next, they will talk about overall progress in research and development. Finally, Dr. Teshirogi will say a few words to wrap up the presentations. This will be followed by a question-and-answer session. Thank you.

For the Q&A session, we will be taking questions from both participants at the venue and from participants via telephone, so we will inform you when the time for questions has come. The session is scheduled to end at 12:00.

So, let's get started.

I will now hand over to Dr. Kiyama, who will discuss the progress of COVID-19-related projects. Thank you.



Kiyama: I'd like to start by talking about COVID-19-related projects.

Please see page 5. Shionogi is making comprehensive efforts to bring COVID-19 to an early end.

From the left, in the area of epidemic prediction, we have the sewage epidemiological survey service. The aim here is early detection of viral outbreaks. Next, in the area of prevention, is the vaccine. As for diagnosis, we have a newly approved TARC kit for predicting disease severity. In the area of treatment, I would like to introduce some data on small molecule therapeutics. This will be the main focus of today's presentation. We will also cover peptide drug discovery, which we are working on in parallel. In addition, we are working on the PGD2 antagonist asapiprant, which we licensed out to BioAge Labs, for the prevention of severe disease.

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

Let's start with S-217622, a small molecule therapeutic agent. Please see page 7.

Recently, treatments such as remdesivir and antibody cocktail therapy have been put to practical use, but in order to make COVID-19 a disease comparable to influenza and restore society to a state of normality, we believe that it is necessary to have 3 things in place. These are diagnostic agents, vaccines, and therapeutic agents. Here, we think there should be a particular focus on oral agents that can be used on an outpatient basis.

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

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* Structure activity relationship: Correlation between structure and antiviral activity

Please see page 8. Shionogi has been working on antiviral drugs for many years, and during the pandemic we have reaffirmed our strength in this field.

As you can see in the 3 squares at the top, after COVID-19 started spreading, we put 80% of our research staff to work in this area. This was a bold shift in resources, and required quick decision-making.

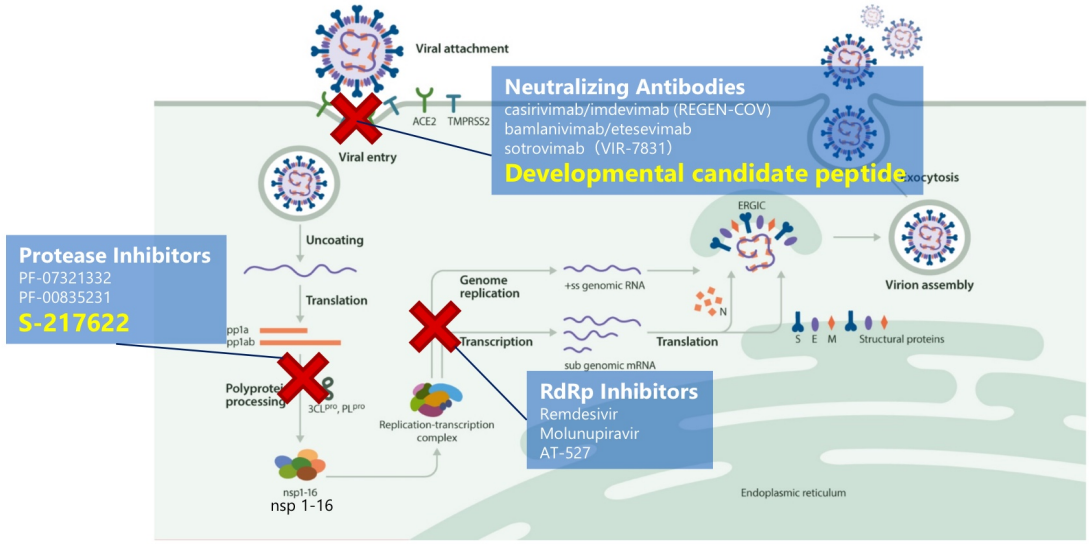
In addition, we have a long track record in virus research and small molecule compound design. We have been working on coronavirus research and drug discovery for several years.

In addition, we have strong relationships with the infectious diseases KOLs in Japan. We have also built partnerships with organizations such as Hokkaido University.

Regarding S-217622, we have gone from launching the research program to candidate compound in about 9 months. We were able to find a development candidate within about 4 months of the start of SAR. After that, we were able to start clinical trials within another 4 months.

However, what I hope you'll appreciate here is that we are not skipping any of the required tests. We also took the risk of conducting tests on large animals in parallel from an early stage in order to speed up the process. I am proud to say that we have been the fastest in the world in terms of discovering original therapeutic agents for COVID-19.

S-217622：3C-Like protease



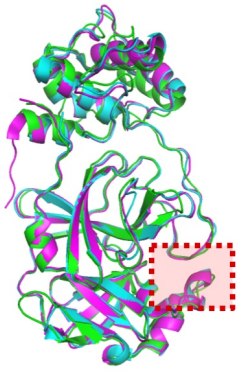
Please see page 9. Here is a representation of the life cycle of the SARS-CoV-2 virus.

In addition to vaccines, such as the antibody cocktail that is now widely talked about, there are drugs that suppress the initial adhesion of viruses to cells, as indicated by the cross at the top.

We believe that there are 2 enzymes that play a major role in the replication cycle after the virus enters the cell: the protease represented on the left and the polymerase on the right. These are the 2 drug targets: the oral drugs currently being developed worldwide aim to suppress 1 of these 2. We are aiming to suppress protease, shown here on the left.

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

Let's go to page 10. This slide covers why we chose this 3CL-protease as a drug target.

As mentioned in the text box, this protein is highly conserved in the coronavirus genus. The image on the left is an X-ray superimposition of the protein structure in SARS, MERS, and SARS-CoV-2. As you can see, the structure is very well preserved. Therefore, we anticipate that the drug will be able to respond to new pandemics in the future.

Another motivation for targeting this protein is its low homology with human proteases. This reduces the risk of side effects and safety concerns.

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

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

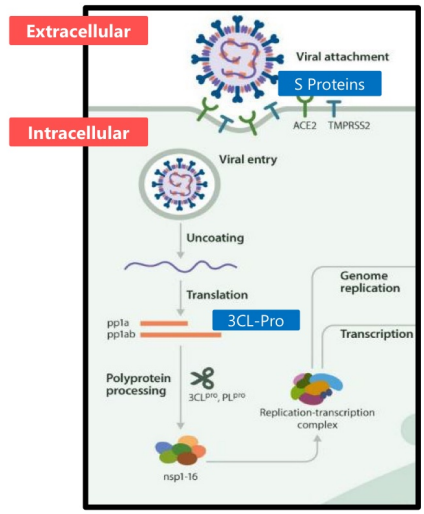
Please see page 11. The following table shows the effect of S-217622 on the 3CL-protease of different well-known viral strains.

A similar level of effect is seen in the WK-521, alpha, beta, gamma, and delta strains. The reason for this is, of course, the major mutation sites shown on the right side of the page. As you can see, mutations in all strains have occurred in the spike protein on the surface, not in the protease.

Only the beta strain has a mutation in protease, the K90R mutation. This is an amino acid mutation located slightly away from the active site of the protease. We assessed activity on the K90R-mutant enzyme in vitro, and confirmed that the mutation has no effect on the activity of our compound, S-217622.

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

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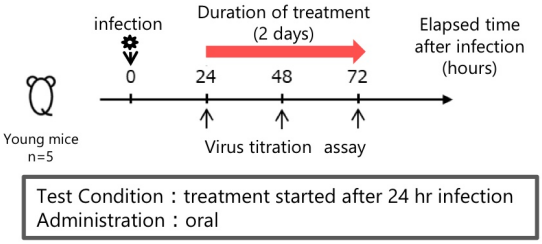
On page 12, I would like to talk a little bit about our thoughts on this word “mutation” and mutant coronavirus strains. The term “mutant strain” refers to a spontaneous mutation of the spike protein. As a strategy for survival, viruses try to increase their infectivity and find new hosts by mutating the spike proteins on their surface. This occurs through a series of spontaneous mutations. Because of this, host selection pressure is applied regardless of the presence or absence of drugs, and mutations occur 1 after another.

On the other hand, enzymes have evolved to maximize their function, so mutations in them are generally not selected for and are not propagated. If an artificial mutation pressure such as an enzyme inhibitor is applied, the wild strains die out, and new resistant strains emerge as a result of selection pressure. These new strains are typically less infective and less able to propagate.

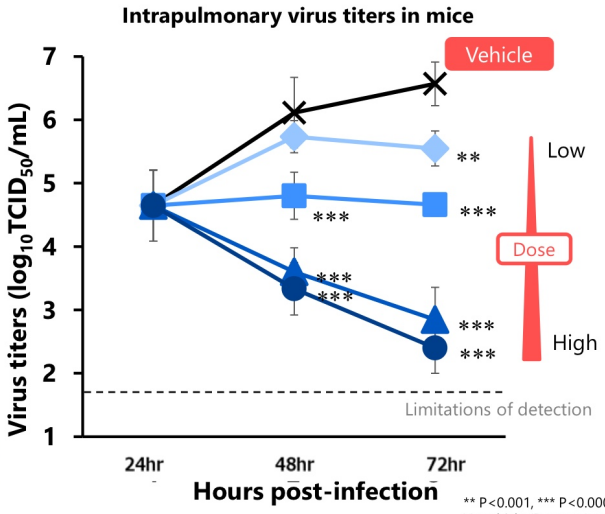
As is written here in blue, we believe that a clear distinction should be made between viral strains that emerge due to host selection pressure, such as the delta strain, and drug-resistant strains caused by enzyme inhibition. I'm sorry if this explanation has gone on a bit.

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

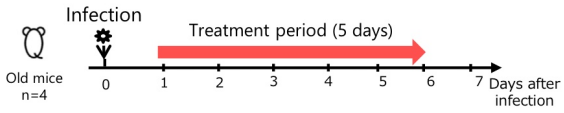


On page 13, I will introduce the drug efficacy evaluation for S-217622.

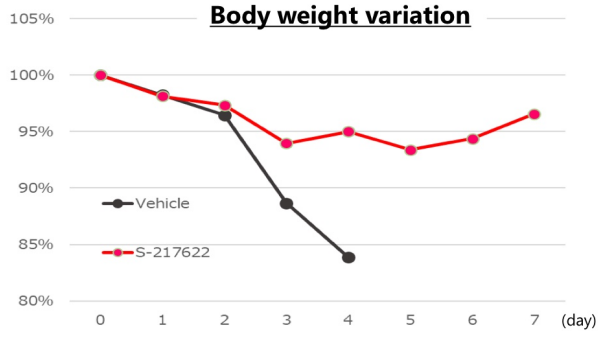
This is an in vivo model using mice. Drug administration started 24 hours after infection with SARS-CoV-2 and continued for 2 days. The drug was administered orally.

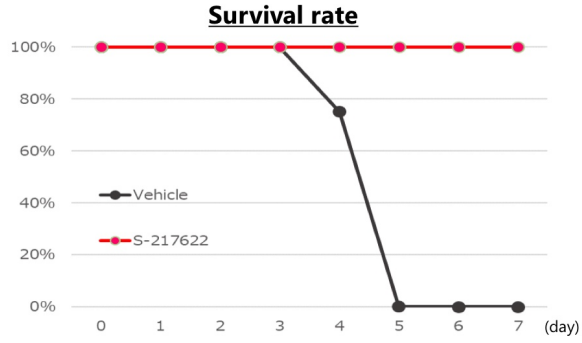
As is written on the right side, when the virus titer in the lungs is measured after 24 hours, the virus level in the vehicle group continues to increase, while the virus titer in the S-217622 group decreases in a dose-dependent manner.

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

Let's go to page 14. This is another evaluation of drug efficacy in mice. The study drug was administered 24 hours after infection for a period of 5 days.

On the left side of the graph, we can see dramatic weight loss in the vehicle group, with death occurring on the fourth or fifth day. In the drug group, which received S-217622, there was almost no change in weight.

In the survival rate graph on the right, all animals in the vehicle group, shown by the black line, died by day 5. On the other hand, all animals in the S-217622 group survived. This indicates that S-217622 can be expected to be effective in reducing disease severity.

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**

Iwasaki: I will now present the progress of development.

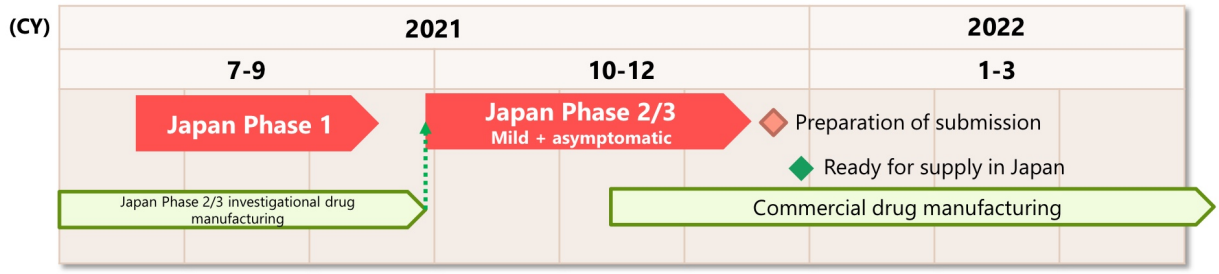
Please see page 15.

Based on the results of the non-clinical studies, we submitted a clinical trial report to the Japanese regulatory authorities in July and started Phase 1 trials. Single and repeated doses have been administered, and we are now in the follow-up phase. In terms of safety, no major problems have been observed.

In terms of pharmacokinetics, we have been able to obtain the blood drug concentrations that we expected from the non-clinical studies, and there has been no effect of diet. Results so far suggest a very favorable safety profile.

With these results, we are now starting Phase 2/3 in Japan as planned. This was announced in the press yesterday.

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

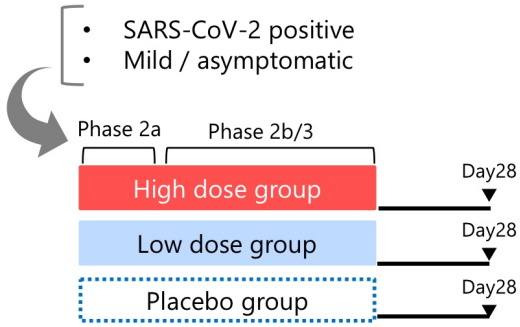
This is page 16. Future plans are shown here.

Phase 1 has been completed, and as announced yesterday, we are moving to Phase 2/3 trials. The goal of these trials is to evaluate antiviral efficacy and symptomatic improvement—so-called clinical efficacy—in asymptomatic patients or mildly ill patients in Japan.

This will be a large study, with roughly 2,000 patients. We are considering filing an application in Japan based on the results. Of course, vaccines are important, but therapeutic drugs also have a large role to play. Faced with these societal needs, we are preparing to file this application so that we can supply these drugs as soon as possible. This will depend on the negotiations with the regulatory authorities, but we are considering to submit an application by the end of this year, while working to complete preparations for domestic supply.

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



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* Number of subject is TBD

This is page 17. An overview of the trials is shown here.

The target population is asymptomatic patients or mildly ill patients. Asymptomatic patients and those with mild symptom patients are treated at home or in hotels, so we are also conducting tests in these areas. Assessment is divided into 2 parts: Phase 2a, and Phase 2b and III.

First of all, we would like to see how quickly the antiviral effect can be observed in Phase 2a, which consists of about 60 patients. We are planning to move straight into Phase 2b and Phase 3.

The drug is administered once daily as a tablet for 5 days. We feel this is a very user-friendly formulation.

We received a report yesterday that the First Patient In has been completed. Since the number of patients is decreasing dramatically, our mission is to complete the trials as soon as possible, while seeking the cooperation of the regulatory authorities and KOLs on how to accelerate the enrolment process.

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

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* Primary endpoint: Mortality rate / hospitalization rate

This is page 18. The global development plan is shown here.

We are now facing the problem of high rates of serious illness, hospitalization, and mortality. We hear a lot about antibody cocktail therapy at the moment. For patients with mild disease, there is a great need for drugs that are easy to take orally. We are preparing for the global trials in parallel for discussions with the FDA and other agencies.

This concludes the section on S-217622.

S-268019

COVID-19 vaccine

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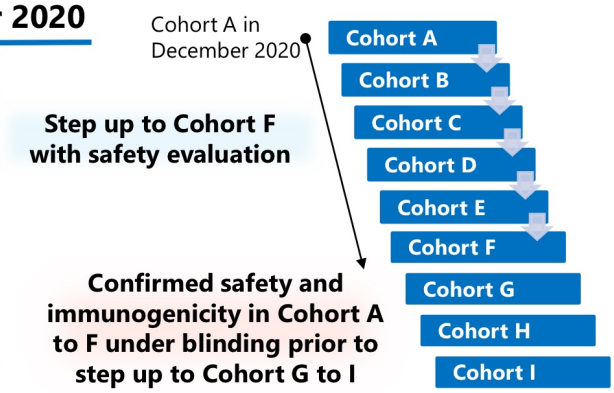
Let's jump to page 19 for an explanation of the vaccine situation.

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.

SHIONOGI * 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

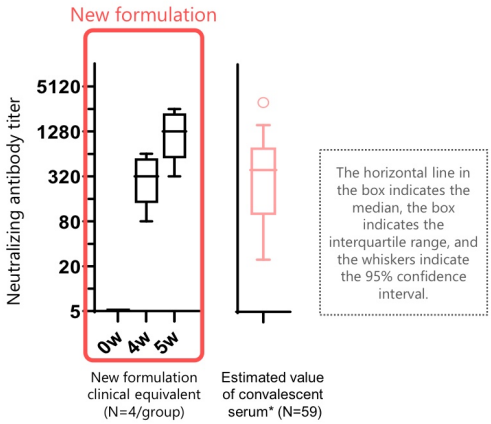
This is page 20.

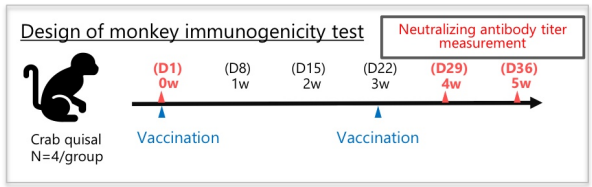
Since last December, we have been conducting Phase 1/2 to assess safety and measure neutralizing antibody titers. As you can see in the outline here, we tried different doses and combinations of antigens and adjuvants, but unfortunately, we were unable to raise sufficient neutralizing antibodies.

Initially, based on the research results of SARS and MERS, we used an adjuvant aimed at this, which was less likely to cause VDE, considering the importance of the balance between Th1 and Th2. As a result, we were able to confirm that a certain level of cellular immunity was induced. However, the neutralizing antibody titer, which is the key factor, did not increase sufficiently, so we gave up on the adjuvant and changing to a new adjuvant, we started preclinical trials.

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.

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This research is supported by AMED under Grant Number JP21nf0101626

Next, page 21.

As you can see in the graph on the left side, the red boxes indicate the neutralizing antibody titer observed in the serum of recovered animals. With this new formulation, we were able to obtain the same or better neutralizing antibody level after 4 or 5 weeks in 4 cases. We started Phase 1/2 administration in August this year using this new formulation.

We have completed 2 doses of the drug and are waiting for the results to be analyzed, but there are no problems in terms of safety.

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

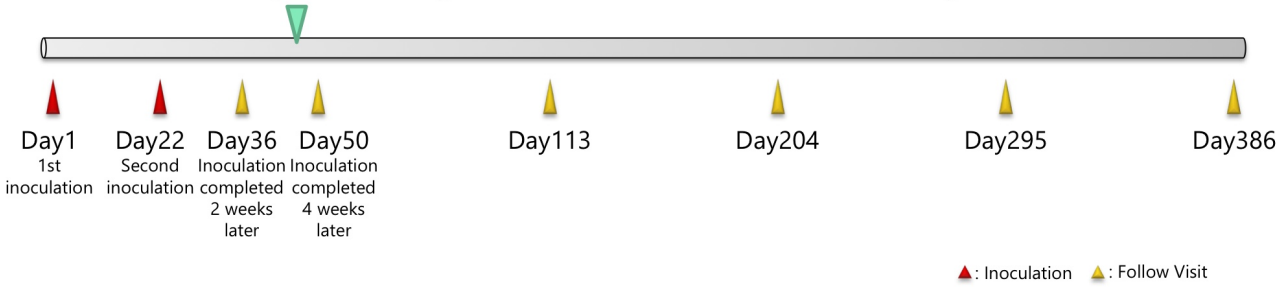
This research is supported by AMED under Grant Number JP21nf0101626

A summary of this is shown on page 22.

We are hoping to publish the results soon.

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

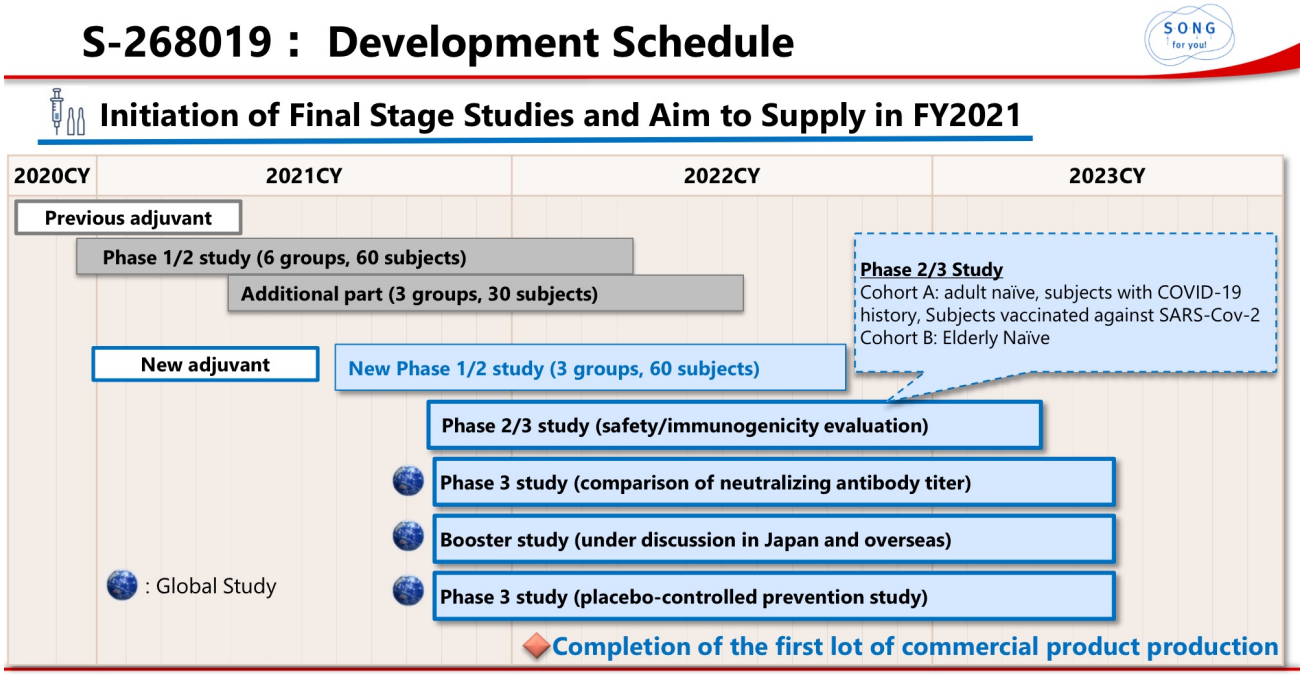
Scheduled Initiation of Phase 2/3 Study in Japan in late October

This research is supported by AMED under Grant Number 21nf0101626

This is page 23.

As for the schedule, on the 24th of this month, all 60 subjects reached 36 days of post-vaccination observation. The most important thing is whether the level of neutralizing antibodies will go up. We have completed this observation.

Although some adverse events have occurred, we believe that the safety profile is acceptable.



The graph on page 24 is a bit complicated and difficult to read, but we are currently negotiating with the regulatory authorities on what kind of tests to conduct. Normally, prevention of disease is the best way to go, but a study of 30,000 or 40,000 cases is necessary. While vaccination has progressed to 50% in developed countries, this study of 30,000 or 40,000 cases is very difficult from the standpoint of ethics and feasibility.

In addition, we have received a new proposal from the government to put together a data package of 3,000 cases, consisting mainly of Japanese people. We are now preparing for both of these situations.

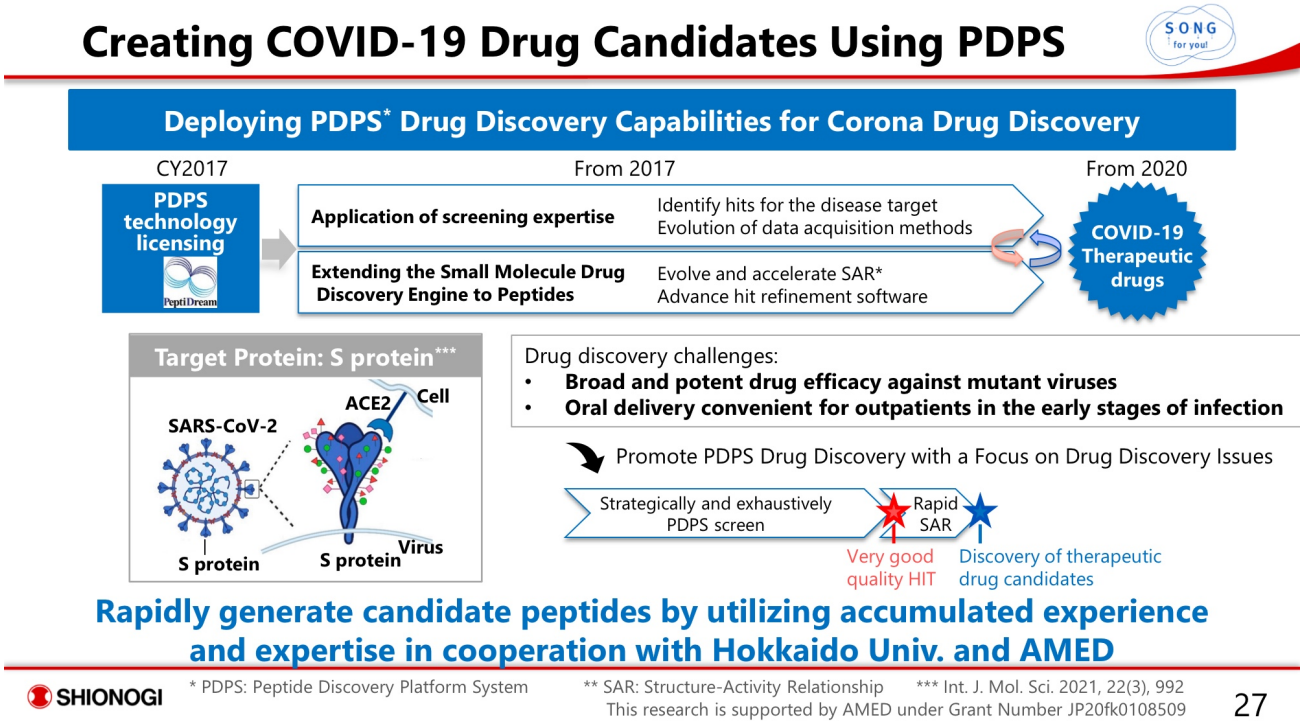
As I will explain in a little more detail on page 24, we will conduct safety and immunogenicity studies in Phase 2/3. This study will recruit adult naive patients, those previously infected, and those who have been vaccinated. We have not narrowed down the conditions or assumptions there. In addition, since elderly people are at higher risk, we are planning to collect data on elderly people and measure their antibody titers separately.

Next, we are planning to conduct a drug-controlled neutralizing antibody titer comparison study, which is an equivalence or superiority study. The goal of this is to see how the antibody titer differs from that of existing vaccines.

In addition to the Phase 2/3 and Phase 3 studies, the booster study will be very important in view of the actual use of the drug in the future. 1 proposal is to formulate an application package with a total of 3,000 cases.

In parallel, we are now considering 2 studies: a standardized onset suppression study and a global study of tens of thousands of cases.

This concludes the section on the progress of vaccine development.



Kiyama: Next, I will talk about other initiatives with the goal of halting the COVID-19 pandemic.

Please proceed to page 27.

We licensed the PDPS peptide screening technology from PeptiDream in 2017 and have been accumulating screening know-how.

This is not just a matter of screening peptides using PDPS to obtain hit peptides. By extending the small molecule drug discovery engine that we have cultivated so far to these peptides, we have continued to work on the process of transforming hit peptides into drugs. We have been able to apply this to the treatment of COVID-19.

On the lower left of page 27, there is a picture of the S protein, which is a target for vaccines and antibody therapy. Because it repeats mutation, it is possible to prevent mutations by using multiple antibodies, such as the antibody cocktail that is currently in use. This is where our accumulated experience and know-how came in handy, as we were able to identify potentially useful compounds.

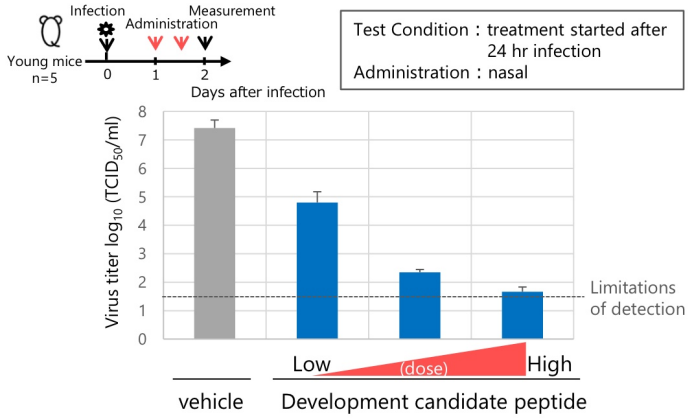
Nonclinical Drug Efficacy of Development Candidate Peptides

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



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

SHIONOGI

This research is supported by AMED under Grant Number JP20fk0108509

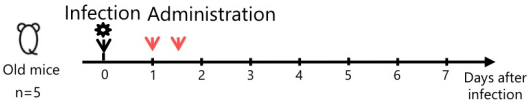
This is page 28. The following table shows the in vitro antiviral activity against each virus strain.

As you can see from the WK-521 strain to the delta strain, we have achieved an EC50 in the order of single digit nanomolar.

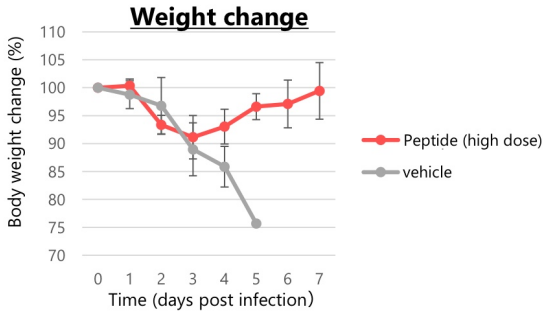
The graph on the right shows the results of evaluation using a mouse lung infection model. We administered the drug twice, 24 hours and 36 hours after viral infection. The results showed that the virus was suppressed to almost below the detection limit when measured 2 days later. The route of administration is nasal.

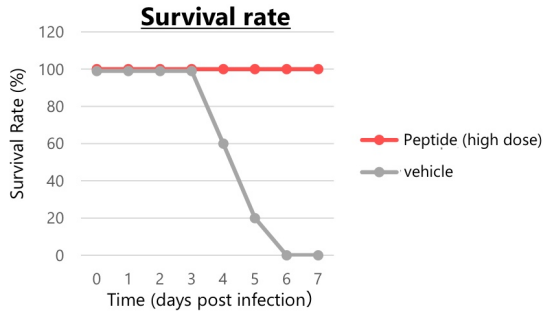
Nonclinical Drug Efficacy of Development Candidate Peptides

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



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





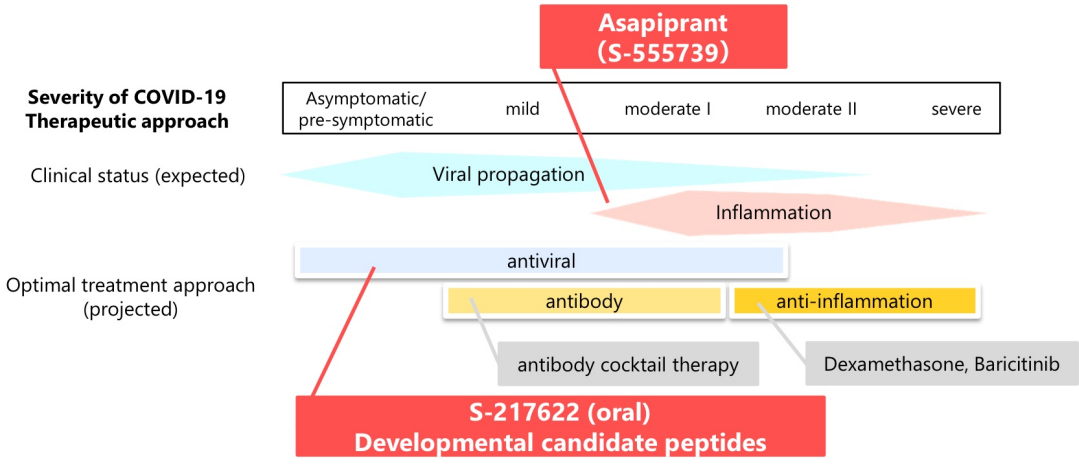
Single-day administration is expected to reduce the severity of the effect even in patients at high risk of severe disease

This research is supported by AMED under Grant Number JP20fk0108509

On page 29, we show the results of survival rate and weight variation, similar to those for the small molecule drug shown earlier.

In the same way, we administered peptides nasally 24 hours and 36 hours after infection. The results showed that there was no change in body weight, which was notably different from the vehicle group. Regarding survival rate, all subjects in the vehicle group had died by the 6th day, while all subjects in the peptide group survived.

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

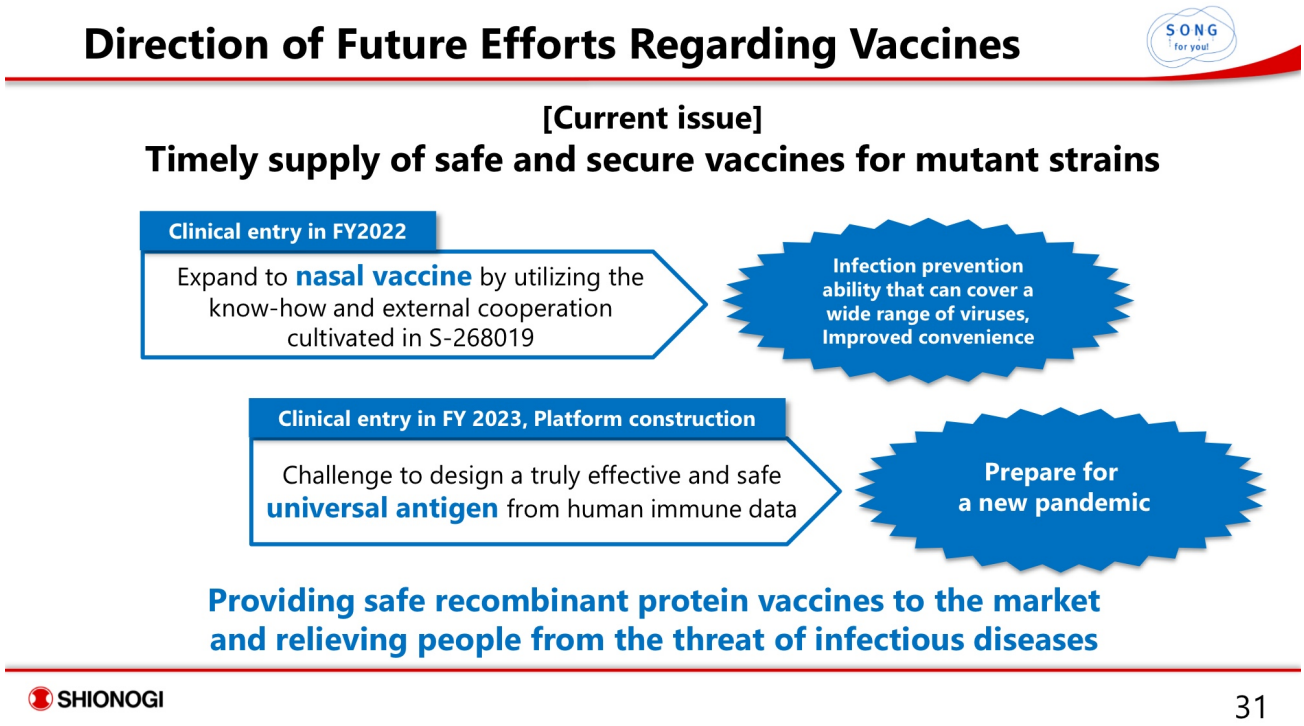
* Referring to the "Eighth Edition of the Concept of Drug Treatment for COVID-19" of the Japanese Society of Infectious Diseases

Let's go to page 30. This is a summary of our approach to COVID-19 therapeutics.

In the area of asymptomatic to mild disease, the virus is still multiplying very rapidly, and we believe that antiviral drugs should be used here. We will proceed with S-217622 and peptides that are candidates for development in parallel.

On the other hand, in moderate to severe cases, the body is reacting to the virus and inflammation is the main cause of injury. Therefore, treatment other than antivirals, including anti-inflammatory therapy, will be necessary.

It is very important to strike the virus effectively at an early stage. By preventing cases of severe infection, it will be possible to reduce the load on the medical system. We would like to supply medicines that allow people to treat themselves at home.



Let's go to page 31. Returning to the subject of vaccines for a moment, I would like to explain the direction of Shionogi's vaccine initiatives in the future.

At present, we are working on the development of a vaccine using intramuscular injection, and in the future we will develop a booster dose. At present, immunity acquired by intramuscular injection is very effective in preventing the onset of illness as well as the development of severe disease. However, we are still not satisfied with its ability to prevent infection, and we are also concerned about its broad applicability to future mutant strains. Therefore, we are now considering the development of nasal vaccines.

Therefore, we need universal antigens that can respond to any new pandemic or new strain. We would like to take up the challenge of designing such a universal antigen.

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

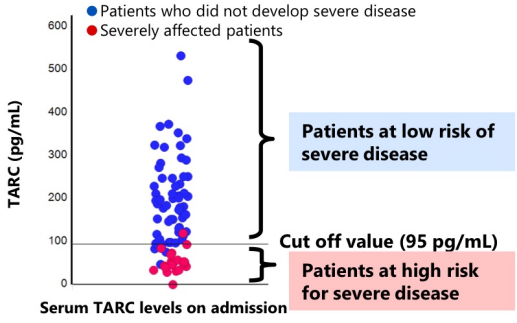
Let's go to page 32.

As of July this year, the Biomarker Research and Development Department was incorporated into the Pharmaceutical Research Division, which I am in charge of, and the organizational structure was changed. The Biomarker Research and Development Division is working on biomarkers and diagnostic reagents, and we would like to further strengthen the linkage with pharmaceutical research and development.

We are also working on the development of surrogate markers that can replace neutralizing antibody titers for earlier evaluation, highly sensitive antigen test reagents that are as accurate as PCR, and prediction of severe disease. Page 33 shows some detailed data on the prediction of severe disease.

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

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* 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

HISCL TARC is a marker for atopic dermatitis that Shionogi has been marketing as a diagnostic agent for some time. If the serum concentration of this TARC component is 95 pg/mL or lower, patients are at high risk of severe disease, as depicted by the red dots. If it is over 95 pg, patients are at low risk of severe disease.

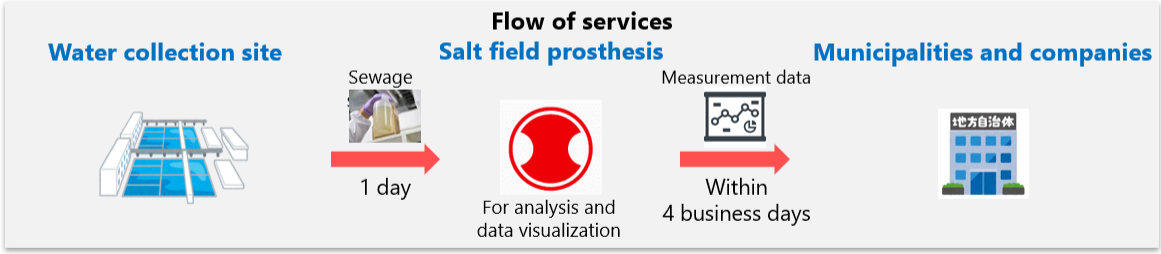
As shown in the table on the right, 94.7% of patients with a positive TARC value, that is, 95 pg or less, will develop severe disease. In addition, for patients with a negative TARC value and95 pg or more, 93.2% of the cases are mild, and the product can provide a highly predictive diagnosis with a sensitivity of 95% and a specificity of 93%.

The data shown here are backward-looking data. We are currently conducting prospective clinical trials in actual clinical settings after the product is launched.

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
- Discussing a business alliance with Shimadzu that leverages the strengths of both parties



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

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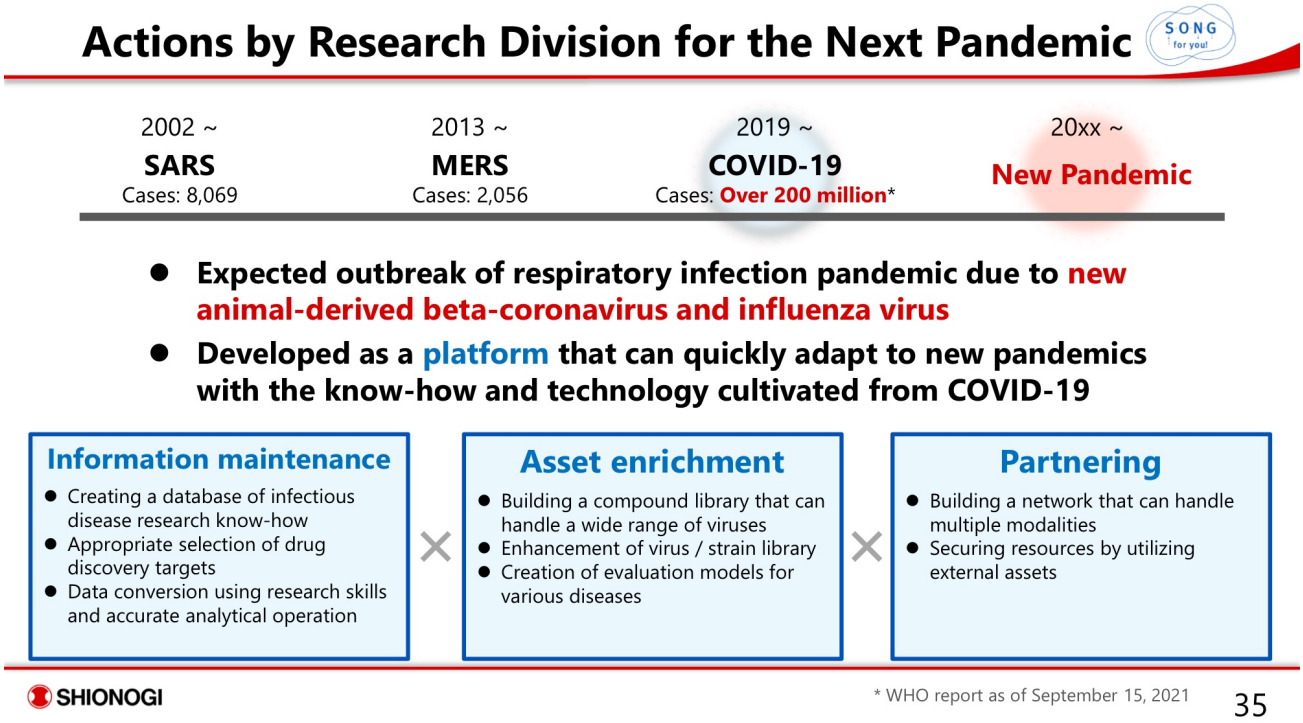
* https://www.cas.go.jp/jp/seisaku/ful/taisakusuisin/bunkakai/dai4/ict_teigen.pdf

** 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

Moving on to page 34, we have made various announcements on this subject previously, but we are also accelerating our efforts to apply sewage epidemiology to benefit society.

We have implemented a test called the Hokkaido Univ.-Shionogi method, which was developed in collaboration with a professor at Hokkaido University, and we are currently starting epidemiological survey services in June 2021. The system is also being used for sewage surveillance by the investigative committee under the jurisdiction of the Ministry of Land, Infrastructure, Transport, and Tourism. We are currently expanding our services by signing contracts with several local governments. In addition, we have actually been taking measurements at the Olympic and Paralympic villages, and we are getting very good results here as well. We are also currently discussing a business alliance with Shimadzu Corporation that will leverage the strengths of both companies.



Finally, page 35.

The SARS epidemic occurred in 2002. In the past 20 years, we have had 3 pandemics of the genus *Betacoronavirus*. It is short-sighted to think that this will not happen again in 3 or 5 years. We will continue to conduct research on the possibility of a pandemic of respiratory infections. This includes new types of *Betacoronavirus* of animal origin and infections such as avian influenza causing infections in humans.

As you can see in the 3 blue squares below, in terms of information maintenance, we have created a database of our know-how in infectious disease research. We were able to mobilize 80% of the researchers in 2 weeks. In the future, we would like to create a database of skills, so that we can develop even more advanced resource operations.

In addition to the compound library that can handle a wide range of viruses, which I think is a library that only Shionogi is capable of having, we will also enhance the library of viruses and strains.

In addition to our own company, we would like to collaborate with external academic KOL professors to further build a network that can support multiple modalities.

These are Shionogi's initiatives for COVID-19.

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

Next, I would like to report on HIV infection.

As you can see on page 37, the current trend in HIV drug discovery is that once-daily administration has already become the norm.

From 2028 onwards, oral compounds, including the compounds we are providing now, will become generics. Companies are clearly shifting to more convenient, long-acting drugs and LAP drugs.

The business alliance between Gilead and Merck was announced in March this year, and it seems that Gilead has shifted its focus from conventional cures to long-acting drugs.

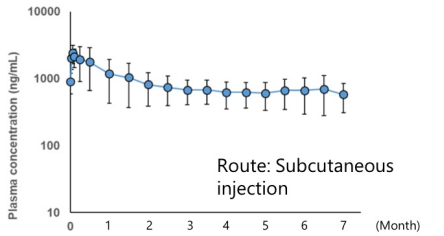
From the comments of clinical trial participants, it is clear that the act of taking the medicine every morning reminds them that they are infected, and they want a drug that will make them forget about the treatment for a certain period of time.

However, it was difficult to create a long-acting formulation that would meet the needs of these patients, and we made the difficult decision to discontinue the development of S-648414. We are still working on the compounds that we are making in this project, so we are now switching to the evaluation of the backup compounds.

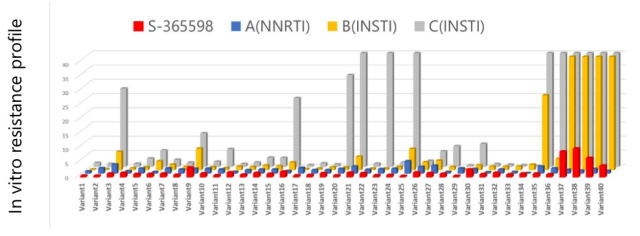
Shift Towards Ultra Long-Acting Formulations

- **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

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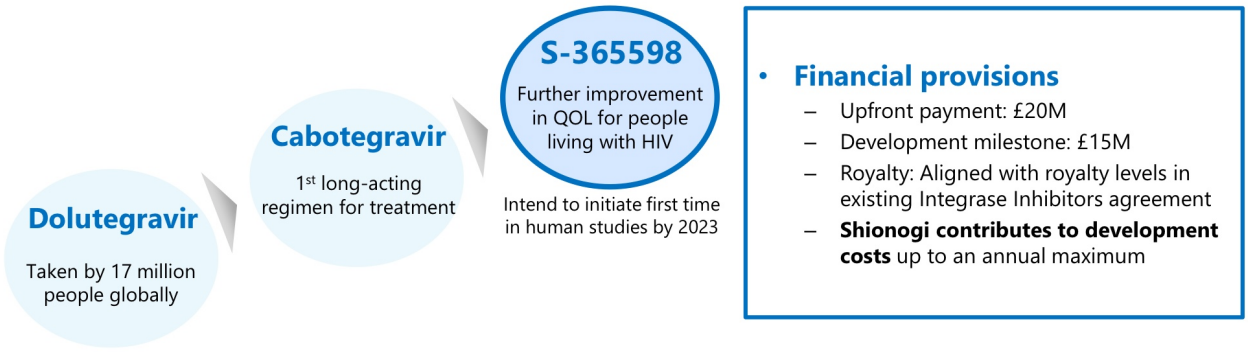
* Exploratory studies in which QA was not implemented
** QA Not performed

On the other hand, as you can see on page 38, we have recently developed another compound, S-365598, which we consider to be a third-generation integrase inhibitor. As shown in the graph on the left, I believe that it will be an ultra-long-acting drug that lasts more than 3 months after a single administration. In the graph below, the persistence of the drug was evaluated in monkeys, and it was proved in non-clinical studies that the drug concentration could be maintained beyond 6 months.

As for the drug efficacy against mutant viruses, as shown in the graph on the right, the yellow and gray are the existing integrase inhibitors, which have shown broad drug efficacy against highly mutant strains. As you can see on the right side, it has been observed in clinical practice that the efficacy of drugs against virus strains with multiple amino acid mutations inevitably decreases. However, S-365598, represented by this red bar, has been able to maintain very high anti-HIV activity.

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)



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

Let's go to page 39.

As announced yesterday, we have entered into a licensing agreement with ViiV for S-365598, a third-generation integrase inhibitor, which is an ultra-long-acting drug.

We have been providing ViiV with dolutegravir and cabotegravir, which are used by many patients worldwide. That makes this the third drug.

As announced yesterday, the agreement includes an upfront payment of £20M, development milestone payments of £15M, and royalties on the same terms as the existing integrase inhibitors.

We are not only licensing out this technology, but we also include in the contract that we will be responsible for a part of the research and development. However, there is an upper limit to the annual figure.

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

As for other areas, I would like to introduce a compound called S-309309, which is in the obesity area.

Let's go to page 41.

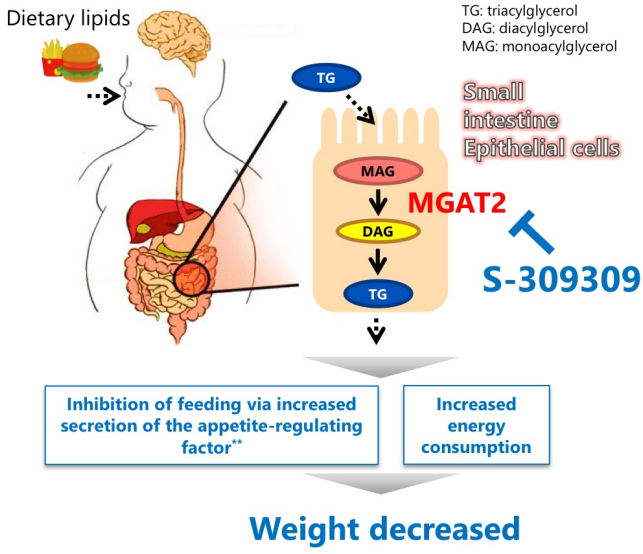
Although Shionogi has been working on obesity for more than 20 years, we have not been able to show any results.

In the meantime, a number of anti-obesity drugs have been launched by various companies. More than 200 million people still suffer from the disease in Japan, the US, and Europe, and the drug treatment rate is still in the single digits percent.

The reason for this, as you all know, is that existing drugs inevitably have side effects that are centrally mediated, and their effects do not last. Drug efficacy is not sustainable, and insurance reimbursement is discontinued. As a result, high cost is a major problem. I believe that the unmet needs that remain today are high safety, sustained efficacy, and low economic burden.

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)**



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

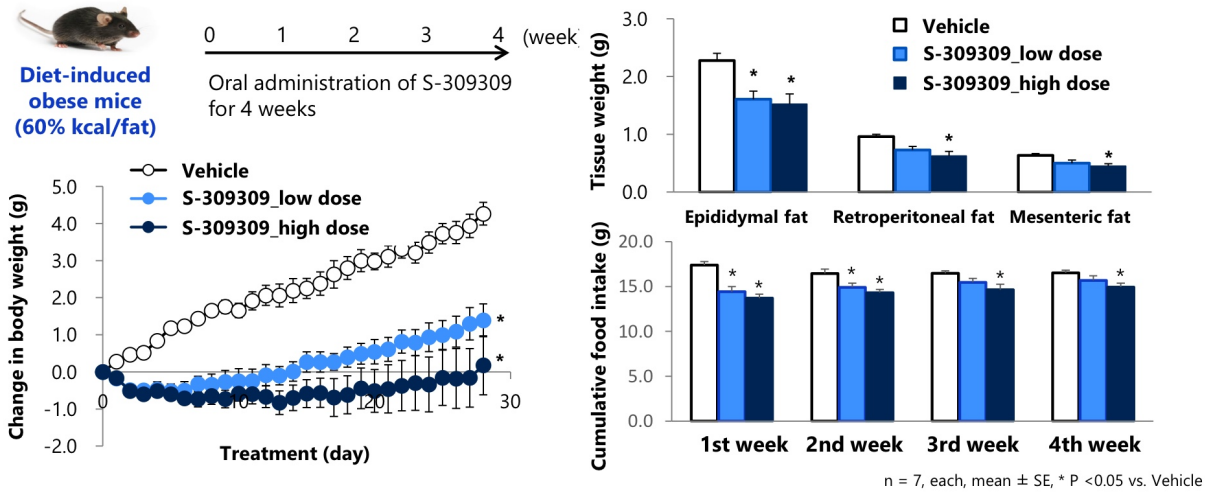
Let's go to page 42.

This compound, S-309309, is an enzyme that resynthesizes triglycerides, called MGAT2, in small intestinal epithelial cells.

When triglycerides, or neutral fats, are taken into the body from food, they are broken down into monoacylglycerols in the digestive tract, absorbed, and then re-synthesized into triglycerides in the epithelial cells of the small intestine for further absorption into the body. This drug suppresses that process.

This results in the inhibition of the absorption of triglycerides, the inhibition of food intake, and the enhancement of energy expenditure, which all combine to produce a strong inhibitory effect on weight gain.

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



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

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

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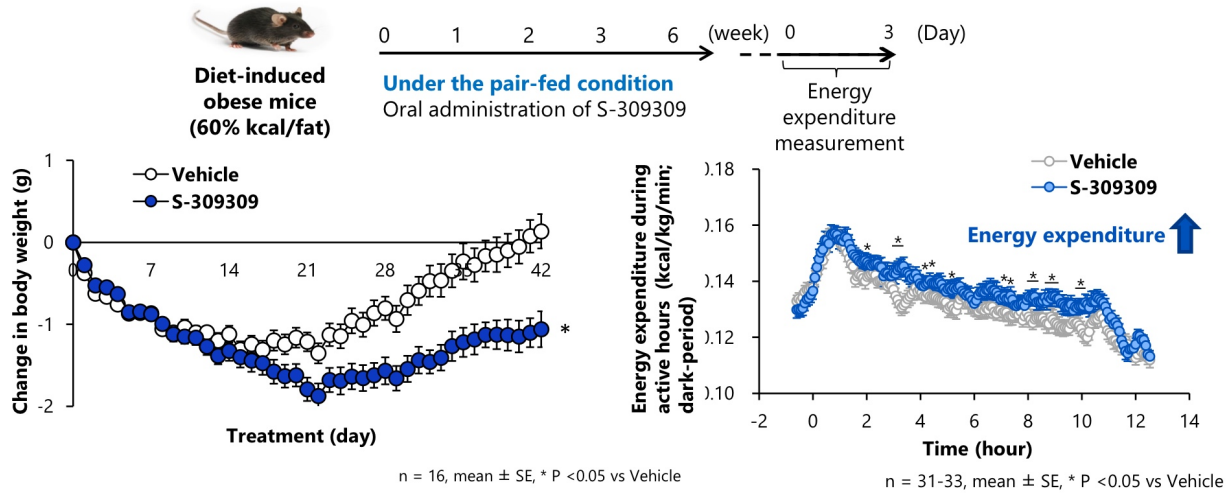
** Epididymal fat, retroperitoneal fat, mesenteric fat

On page 43, we show you some data.

Repeated oral administration of this compound to DIO mice and diet-induced obese mice for 4 weeks significantly suppressed body weight compared to the Vehicle group.

The top bar graph on the right shows the weight of different tissues, and the cumulative amount of food intake is at the bottom.

S-309309: Effect on Increased Energy Expenditure



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

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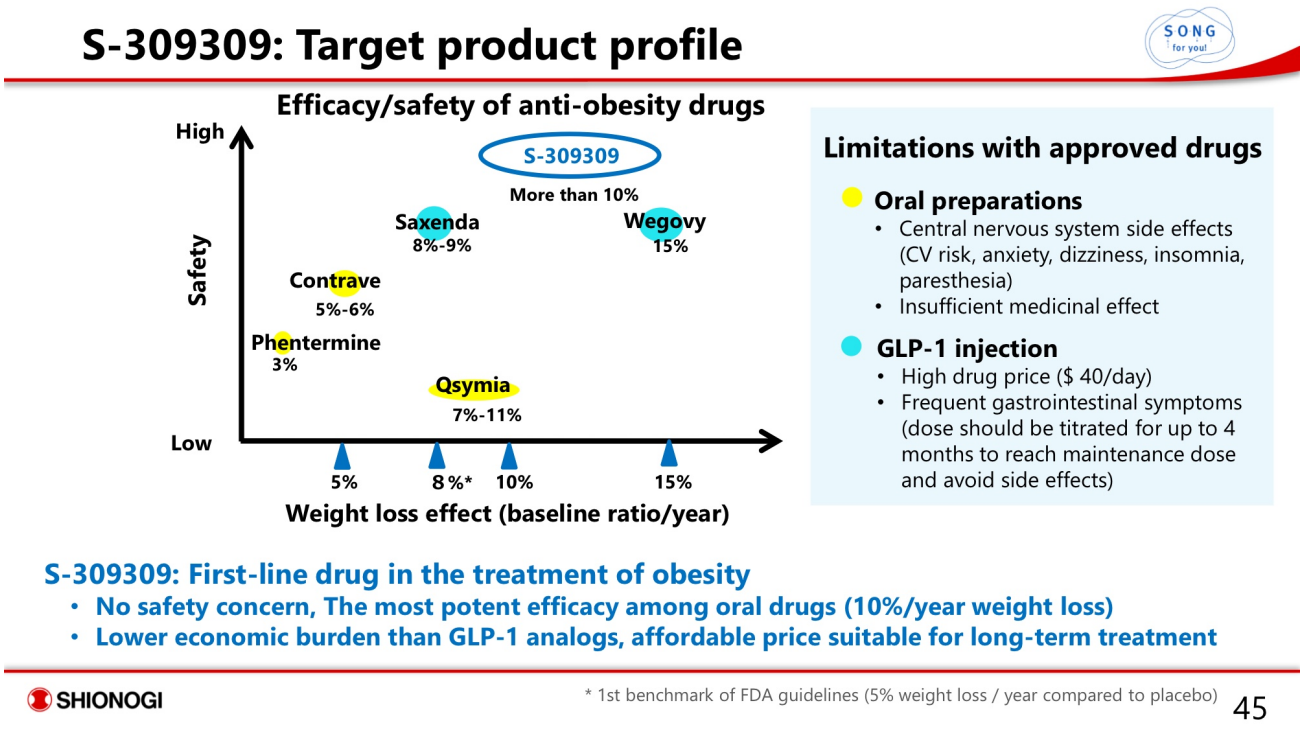
Please go to the next page, page 44.

In this data, the amount of food intake was the same for both the vehicle group and the actual drug group. In other words, the same amount of food was given to both groups. As you can see, the actual drug group lost more weight, and the graph on the right shows that energy consumption increased in the actual drug group during the nighttime activity period.



Page 45, last slide.

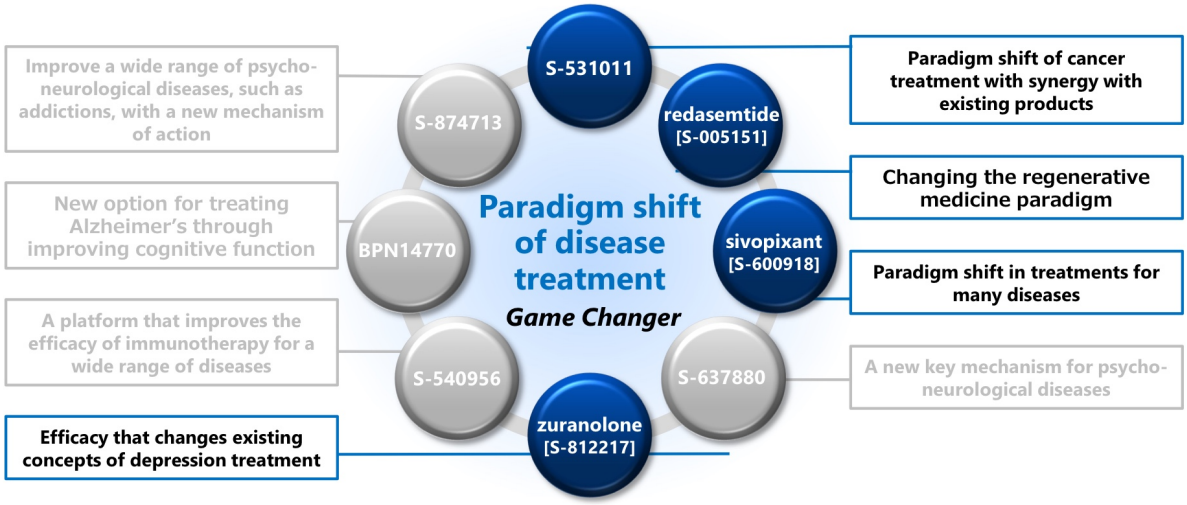
If we take the safety on the vertical axis and the weight loss effect on the horizontal axis, we can see that the weight loss effect will be stronger and the safety will be overwhelmingly higher than that of conventional oral drugs, such as Qsymia, where central side effects are a concern. The safety of the drug is anticipated to be very high.

In addition, GLP-1 injections, Saxenda and Wegovy, also have a higher weight loss effect than Dulaglutide and Saxenda. In terms of safety, we believe that our compound has a higher level of safety.

As for GLP-1 injection, the high drug price of $40 per day has been a problem, but we are hopeful that we can deliver this drug to patients at an appropriate price.

That is all.

The Outcome We Envision from our Core Pipeline



Creating products and services for diseases with high unmet medical needs

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Iwasaki: I will continue with a discussion of development progress from page 46.

Please see page 47.

At last year's R&D briefing, we introduced 8 key products that are changing the paradigm of disease treatment. Among them, I would like to explain about the 4 main items where progress has been made.

Development area

S-600918 [sivopixant]

Refractory chronic cough (RCC)
Sleep apnea syndrome (SAS)

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This is page 48.

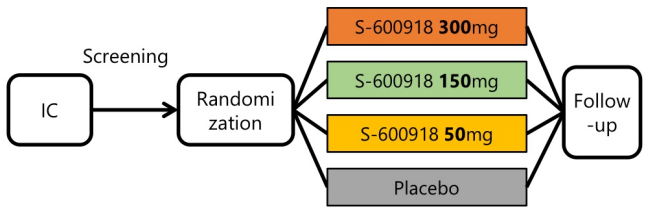
We will report the results of the P2X3 inhibitor sivopixant, or S-600918, on chronic cough and sleep apnea.

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



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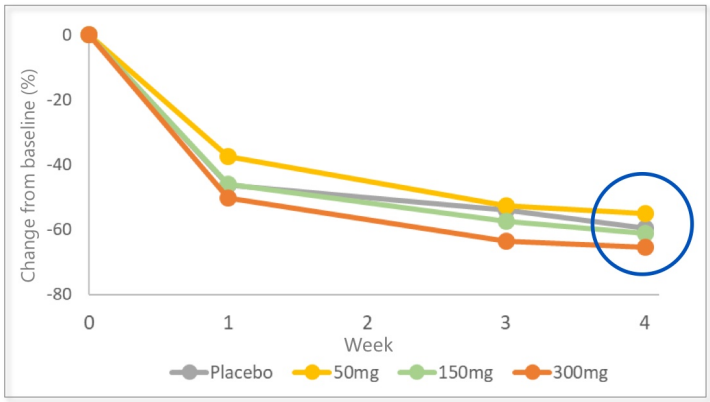
This is page 49.

A similar drug to this one is being developed by MSD and Bayer.

The outline of Phase 2b is based on a PoC study in which 372 patients were tested globally in Japan, the US, and Europe using 3 groups of actual drug and placebo with the endpoint of cough frequency per hour over 24 hours.

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)

This is page 50.

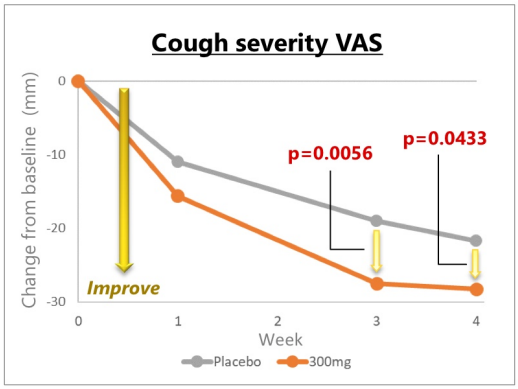
You can see the results here. The orange line is 300 mg, green is 150 mg, yellow is 50 mg, and gray is placebo.

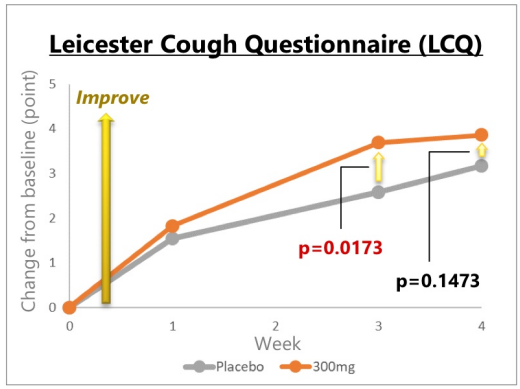
As you can see below, the results did not show a statistically significant difference compared with the placebo. However, looking at the cause of this, the placebo effect was higher than expected. We believe this was the cause of not observing a statistically significant effect.

Looking at the actual change in coughing frequency, it is almost the same as the results of PoC or other companies, so I guess that the placebo had a significant effect.

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

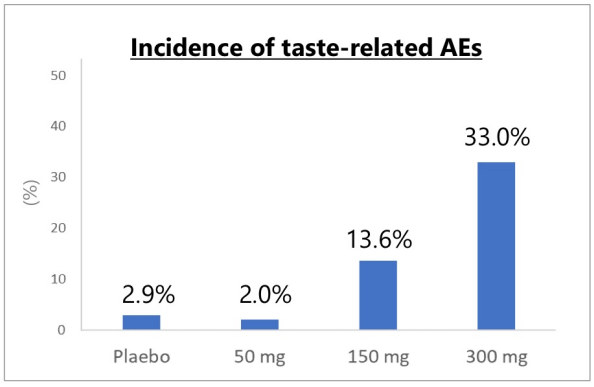
VAS: Visual Analogue Scale, LCQ : Leicester Cough Questionnaire

This is page 51. This slide shows secondary endpoints.

We believe that it is very important to evaluate not only the number of coughs, but also carry out a subjective assessment of whether the patient can live a normal life. We believe that quality of life is important, so from that perspective, we have confirmed a trend of efficacy in the 300 mg dose group in multiple secondary assessments, including the VAS for cough severity and the LCQ, which is a so-called QoL questionnaire specific to cough.

Sivopixant: RCC (Secondary Endpoints)

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



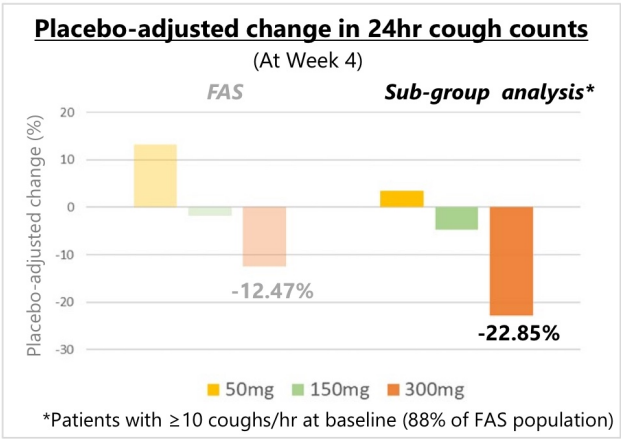
- **1-month administration of sivopixant was well tolerated**
  - ✓ **Discontinuation ratio was less than 5% in any of sivopixant groups**
- **On the other hand, incidence of taste-related AEs increased dose-dependently**

This is page 52.

1 of the biggest problems with this kind of drug is that it causes taste abnormalities.

The incidence of this symptom was 13.6% for the 150 mg group and 33% for the 300 mg group. This tolerance level will need to be evaluated in the future, but overall, this drug has a good profile in 1-month administration. In fact, the discontinuation rate due to adverse events was less than 5%.

S-600918: RCC (Next steps)



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

SHIONOGI

This is page 53.

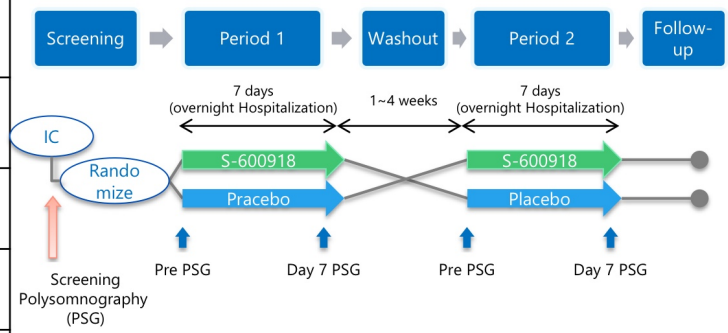
As for what to do in the future, we are working on several sub-analyses. In addition, we are proud to say that P2X3 itself is effective in treating cough and chronic cough.

The issues are as I've just outlined, and the placebo effect is quite pronounced. With the Phase 2b results, we would like to proceed to Phase 3. Before that, however, we would like to consult with the FDA and other regulatory authorities to make a final decision on whether to proceed. However, we are preparing for global trials and are aiming to submit a global clinical trial notification by the end of this fiscal year.

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

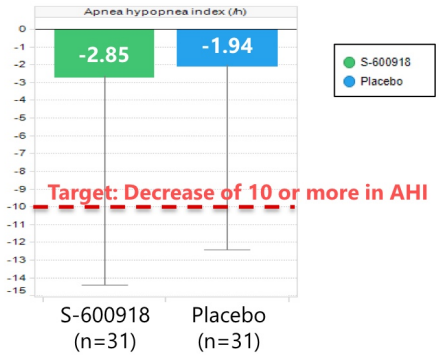


This is page 54. We are pleased to report the results of a PoC study on sleep apnea syndrome.

In Japan, we used the endpoint of AHI in 33 patients and looked at the difference in the amount of change in the endpoint in a crossover study.

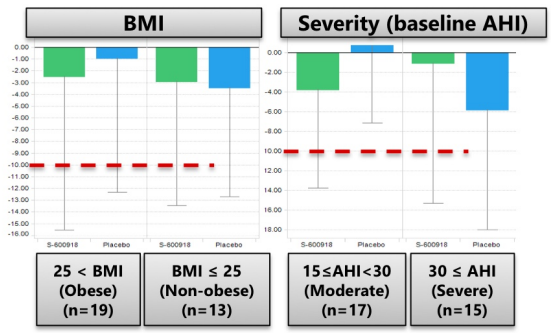
Sivopixant: SAS (Result in PoC study)

- 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



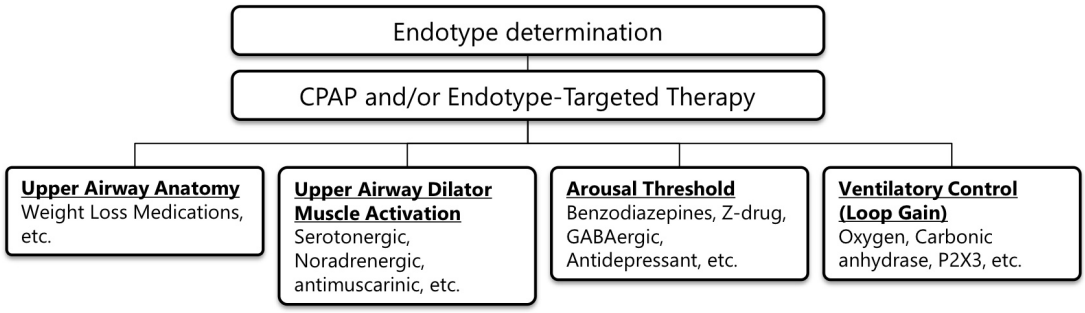
You can find the results on page 55.

Clinically, we expected to see a decrease in the AHI of 10 or more, but the results were less than 3, and there was no significant difference from the placebo.

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



SHIONOGI

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

In terms of safety, there were no taste abnormalities, but the results were not achieved. As you can see on page 56, the development of this drug for sleep apnea syndrome has been suspended.

However, sleep apnea can lead to heart disease later on, so there is a need to treat this condition. In addition, management with a CPAP device is very inconvenient, so we would like to continue pursuing drug therapy for sleep apnea in the future.

Therefore, since there are various patterns of sleep apnea syndrome, we will continue to search for ways to divide these patterns into different types of patients, and consider the ways in which we can expect therapeutic effects.

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.

SHIONOGI

Next, I will explain about redasemtide. This is page 57.

Currently, we are conducting clinical trials for these 5 diseases.

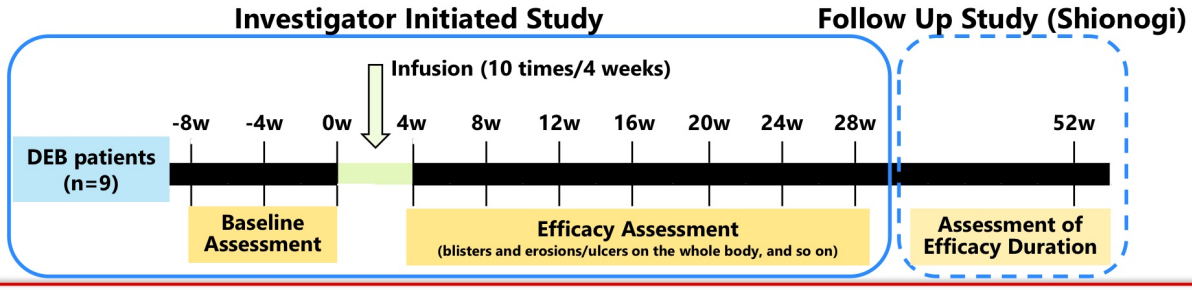
Redasemtide: Dystrophic Epidermolysis Bullosa

- **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)]

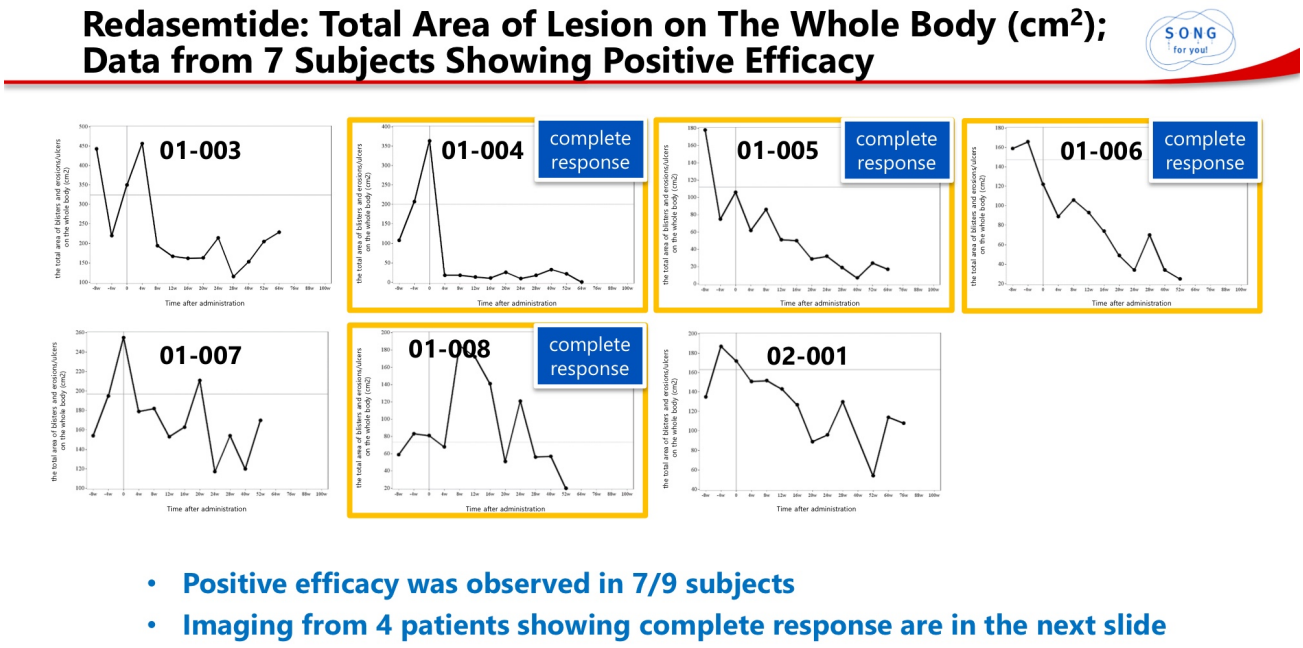


SHIONOGI

First, I would like to report on the progress of dystrophic epidermolysis bullosa. This is page 58.

This is a physician-led clinical trial being conducted mainly at Osaka University. It is a physician-led clinical trial, and as you can see here, we evaluated for 28 weeks. At that time, the efficacy evaluation was based on

systemic blisters, erosions, and ulcers. Since 28 weeks is not enough time for observation, we have taken the initiative in conducting additional research up to 52 weeks.



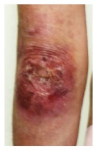
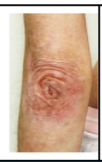
The result is shown on page 59.

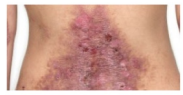
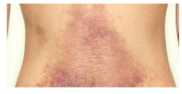
First of all, as for the area of systemic lesions, we administered the drug individually. It is very difficult to collect patients because the number of patients is close to that for an orphan drug disease. We targeted 9 cases.

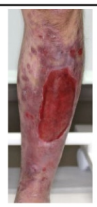
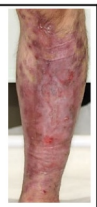
It is very rare for this disease to improve in a certain direction, as it can worsen again with just a little contact with the affected area.

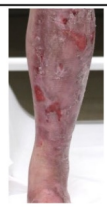
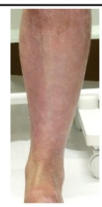
From this point of view, the yellow boxes show a generally consistent trend of improvement, and we expect that redasemtide will have a therapeutic effect on epidermolysis bullosa.

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

SHIONOGI

* 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

On page 60, you can see the actual clinical progress.

In particular, the patient on the lower right, who has a thigh ulcer, showed a clear improvement after 75 weeks. According to the treating physician, this kind of significant improvement is very rare, so we can expect efficacy from Redasemtide.

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**

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

- Additional Clinical Study (tentative)

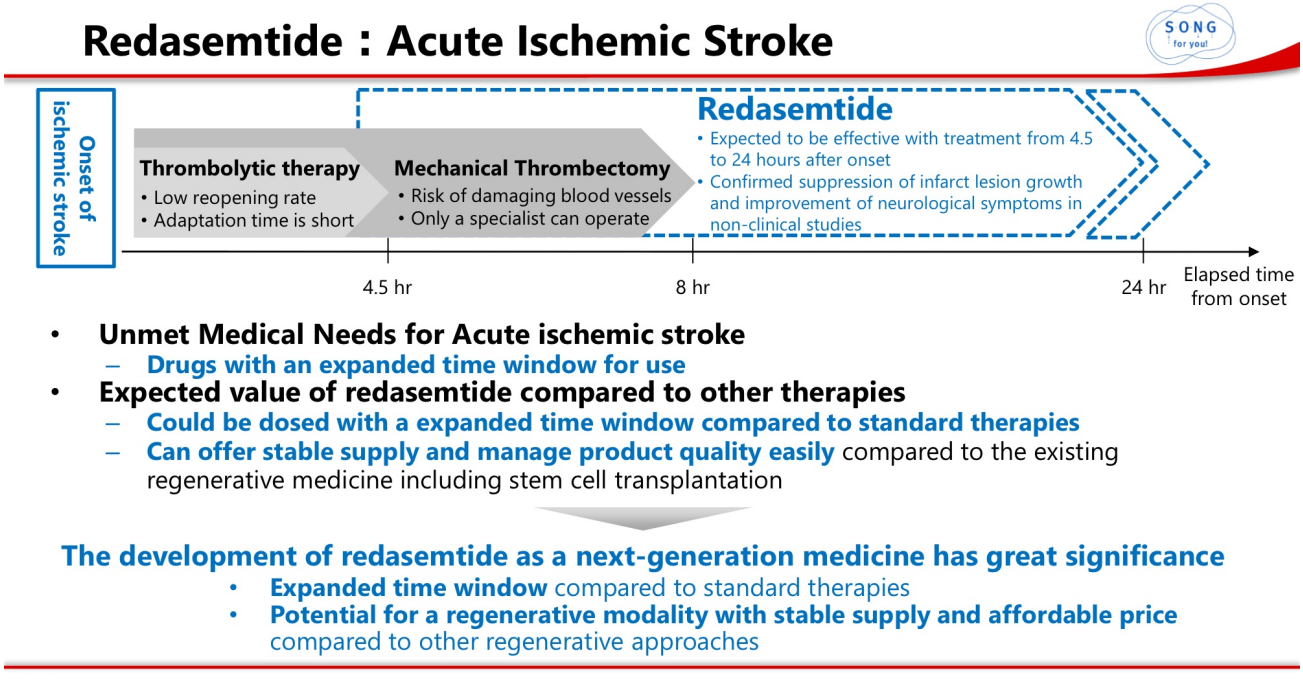
Target Population	Dystrophic epidermolysis bullosa patients
Primary objective	Epithelialization of refractory ulcer
Dosage	Drip intravenous infusion, 10 times/4 weeks [Week 1: 4 days, Week 2-4: 2 days/week (1 dosage/3-4 days)]

SHIONOGI

With these results, we explored the possibility of applying as a drug. We negotiated with the regulatory authorities, and as you can see on page 61, the regulatory authorities themselves have high expectations for

the efficacy of this drug. However, the number of cases is still very small, so they have asked us to accumulate more cases to see if the results are reproducible.

Therefore, although we have not yet decided on the specific number of cases or the time frame, we are planning to conduct additional clinical trials with a small number of cases to accumulate cases of efficacy, and then we will set a schedule for filing an application.



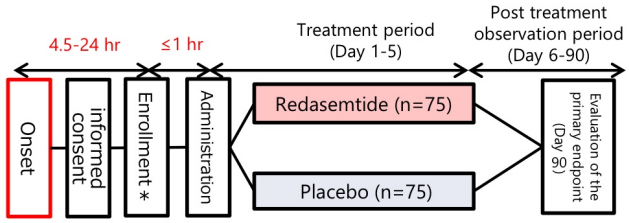
This is page 62. This is a clinical trial for acute ischemic stroke.

At present, thrombolytic therapy or mechanical thrombus retrieval therapy is the mainstay of treatment, but since these measures must be taken within 8 hours of the onset of symptoms, time constraints are 1 of the problems that prevent effective treatment.

If we can extend the so-called treatment window with redasemtide, more patients can be treated. In addition, we are currently conducting clinical trials for acute cerebral infarction, not for regenerative medicine, but for this drug because of its simple quality control and low cost.

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

SHIONOGI

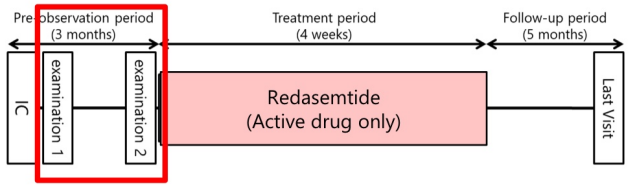
The summary is on page 63.

The main objective is the efficacy and safety of redasemtide, especially in patients who are within 4.5 to 24 hours of the episode and with an extended treatment window. The study was conducted in Japan, with 75 groups in both the placebo and treatment groups. The drug was administered intravenously once daily for 90 minutes, for a total of 5 days. The primary endpoint of the study was mRS.

We were worried about the progress of the clinical trials because of the coronavirus pandemic and the fact that this kind of hospital accepts coronavirus patients. However, by expanding the number of facilities, we are able to complete the registration in July this year and obtain the results in December this year, which is on schedule.

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**



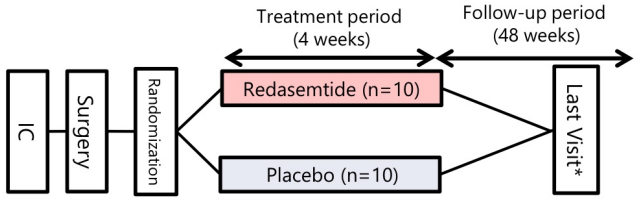
Efficacy and safety of redasemtide are exploratorily evaluated by improvement of fibrosis, inflammation and liver function in patients whose pathophysiology is stable during 3-month pre observation period.

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

In addition, on page 64, we have started a physician-led clinical trial for chronic liver disease based on the non-clinical data that we introduced at Niigata University last year. The first case was administered in March of this year.

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.

Page 65 shows a study that Hirosaki University is conducting a physician-led clinical trial for osteoarthritis of the knee.

This relates to osteotomy, and if cartilage regeneration is achieved through the administration of redasemtide, it will greatly contribute to the effectiveness of the treatment and the improvement of the patient's QoL. We

have high expectations for this. As for this investigator-initiated clinical trial, the first case was administered in February this year.

This concludes the Redasemtide part of the presentation.

Development area

S-812217 [zuranolone]

Depression

SHIONOGI

From page 66 onward, this is S-812217, or zuranolone, a drug introduced by Sage Pharmaceuticals, Inc.

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

SHIONOGI

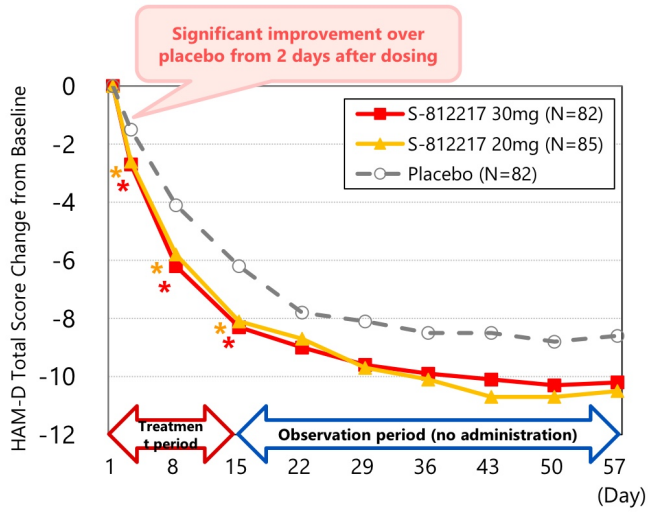
Please see page 67. The results and summary of the Phase 2 study in Japan are shown here.

The unmet needs of existing treatments with depression are shown here. 1 of them is that they need to take the drug for a long time before the therapeutic effect is realized. There are also symptoms of inadequate treatment, prolonged medication, insomnia, and anxiety.

For these unmet medical needs, S-812217 is expected to provide immediate therapeutic effects. It is also expected to improve insomnia since it is said to have a strong effect on depressive symptoms, to maintain the therapeutic effect after drug withdrawal, and to improve depressive symptoms when insomnia is cured.

To see the effect on these unmet needs, we conducted a Phase 2 study with 240 patients, including 2 doses of each drug and a placebo, administered once a day for 2 weeks. The endpoint is the amount of change in HAM-D.

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

The results are shown on page 68.

Yellow is 20 mg, red is 30 mg, and the circle is placebo. This asterisk indicates that a statistically significant difference was achieved during the 2-week treatment period.

As a result, the final assessment also showed statistical significance for both 20 mg and 30 mg. In addition, the early improvement that we were aiming for as 1 of the features of the drug was statistically significant after both 2 and 8 days of administration, confirming its immediate efficacy.

In addition, we are now following up on the duration of the treatment. Although the treatment was discontinued after 2 weeks, the effect was sustained even after that. The safety profile is mild to moderate, and no new concerns have been identified.

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**

SHIONOGI

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

This is page 69.

The characteristics of zuranolone are summarized here: it is fast-acting, and it is effective from 2 days after the start of administration. As a reference, existing antidepressant medications take 4 to 6 weeks to work. This can be very anxiety-inducing, especially for first-time patients, so I think they will be very relieved if they can expect results from the second or third day of medication.

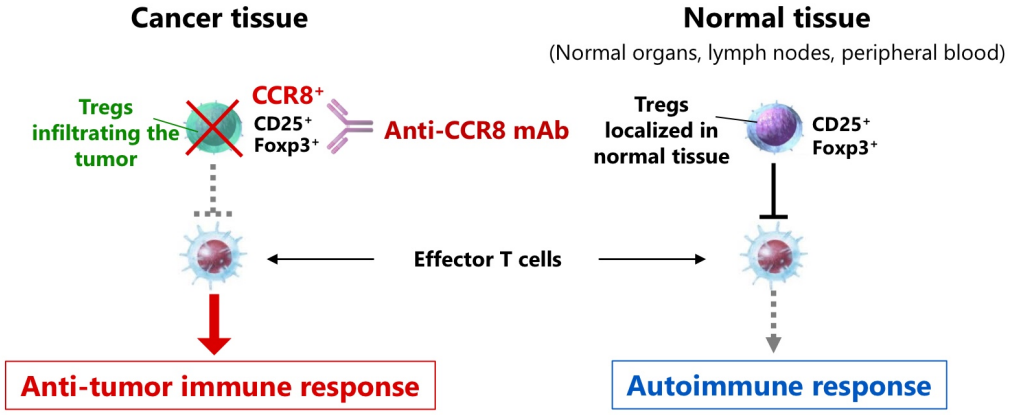
Regarding persistence, the effect of the drug has been suggested to last for 6 weeks after administration at this time.

As for convenience, no dose adjustment is required, and since the 30 mg dose has a good safety profile, we believe that a once-daily 30 mg dose will provide a simple treatment option.

There are no safety concerns about the product. We are aiming to position the product by taking advantage of these 4 characteristics.

We are thinking to start Phase 3 by the end of this fiscal year, submit a domestic application in FY2023, and have it approved in FY2024.

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.

Next is page 71, S-531011. This slide shows the treatment concept.

It has been found that modulating tumor immunity by PD-1/PD-L1 inhibition has excellent therapeutic effects, and the search for novel immunomodulating target molecules with different mechanisms of action is now very much underway.

On the other hand, targeting molecules that are also expressed in normal tissues may cause side effects due to the autoimmune response, so we were aiming to develop drugs that target only tumor immunity. Through joint research with Osaka University, we identified a molecule called CCR8, which is expressed only on regulatory T cells, or Treg cells, that are found in cancer tissues.

S-531011 is an anti-CCR antibody, and as I mentioned earlier, we are developing it based on the concept of responding only to tumor immunity and controlling autoimmune responses.

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)

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

As you can see on page 72, we are currently conducting Phase 1 clinical trial registration in Japan and the United States. Each of these has been submitted and accepted, and we are aiming to have our first patient in by the end of this year.

We have a clinical trial structure intended to find the so-called MTD with single-agent treatment. At the same time, we would like to look at the safety of using the drug in combination therapy. After confirming the safety of the drug, we are now designing a study to investigate the anti-tumor effect of the drug as a single agent or in combination.

At the same time, we will conduct biomarker validation such as CCR8 tissue staining and tumor gene mutation levels. The dosage and administration of S-531011 and ICI will be administered once every 3 weeks for up to 1 year.

Since Japan is the first country to enroll and start the test, we are planning to conduct Part A in Japan and the United States first, and then expand to Asia and Europe.

Development area

SDT-001

Inattentive ADHD (pediatric)

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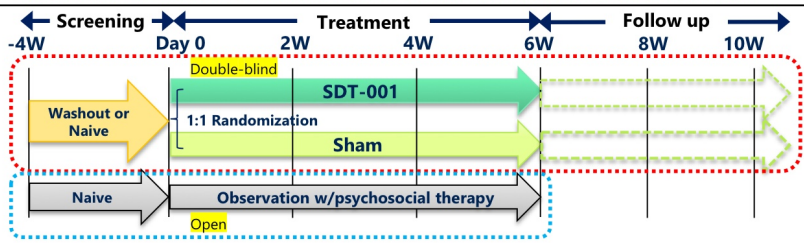
Next is page 73, SDT-001.

This is a so-called ADHD treatment application, a digital application introduced by Akili Interactive in the United States.

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.

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

A summary of the trial is shown on page 74.

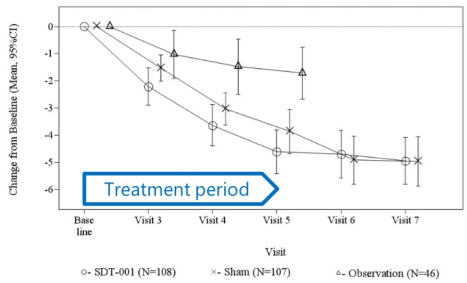
This is a game application that utilizes a brain function called dual tasking. By having the children do both things at the same time in the game, we can improve their attention span, which will ultimately lead to the treatment of ADHD.

This SDT-001 treatment incorporates such a program. In the control group, the program was removed and a game called “Sham” was created to compare the results. As a reference, counseling is now being used as a standard treatment, so we also took data on the effects of counseling and standard treatment as a reference, and compared them.

We evaluated 106 patients in the Sham group/SDT-001 group and 35 patients in the follow-up group for 6 weeks. The score, or endpoint, is the amount of change from baseline in ADHD RS and what is considered normal. We are also measuring TOVA, which is an endpoint that specifically looks at attention.

SDT-001: Phase 2 study in pediatric ADHD

ADHD Rating Scale-IV Inattention score
Change from baseline to each timepoint



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

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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

On page 75, the results are shown in the graph on the left, which is a little hard to see. The triangles are for standard therapy, the crosses are for Sham, and the circles are for the SDT-001 group.

As you can see in the yellow box, no statistically significant difference was obtained between SDT-001 and Sham. However, in the observation group, although it was a follow-up analysis, statistical significance was achieved.

Although the results of SDT-001 and Sham were not statistically significant, the SDT-001 group showed greater improvement from the start to the end of treatment.

As for safety, since it is an application, there were no major issues with it.

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**

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

This is our plan for the future. This is page 76.

In the US, this is prescribed under the brand name EndeavorRx. It is self-funded and reimbursed by insurance. We received approval from the FDA in June of last year, and we are currently implementing open labeling for the older age group of 13 to 17 years old.

In Japan, based on these results, we would like to proceed with the development of the drug by considering its positioning in consultation with PMDA and others.

Development area

S-770108

Idiopathic Pulmonary Fibrosis

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Next is page 77. S-770108 is an inhalation formulation of pirfenidone that is under development.

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 events5*

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.**

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* 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

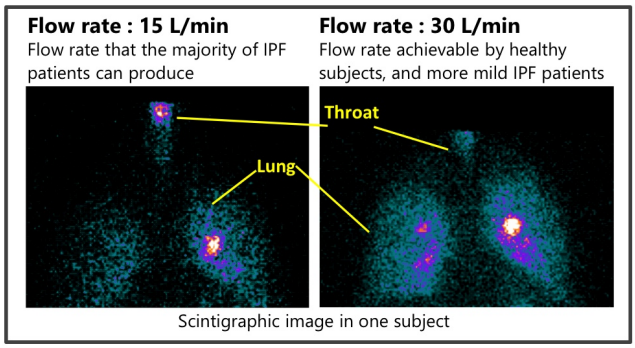
This is shown on page 78.

Pirespa and Ofeb are the standard therapies for IPF, but the current problem is the high frequency of side effects. According to our data, the incidence of photosensitivity is 14.4%, and the frequency of decreased appetite and nausea is also high. Due to these adverse reactions, in many patients, the recommended dosage cannot be reached. Also, about 20% of patients discontinue treatment due to adverse events.

We are planning to develop inhaled pirfenidone with the concept of overcoming this safety issue and aiming for higher efficacy. By delivering the drug directly into the lungs with an inhalation type significantly reduces systemic exposure. As a result, we believe that we can administer the drug for a long period of time, or rather for a period of time that can be expected to achieve the target efficacy, with a better safety profile and reduced side effects.

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*



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.

This is page 79.

We conducted a lung deposition study using this device. This was done in the UK. As you can see here in the photo, the flow rate is 15 or 30 liters per minute. This 30-liters-per-minute figure can be achieved by healthy people, but is unattainable by many IPF patients. In any case, deposition in the lungs has been confirmed.

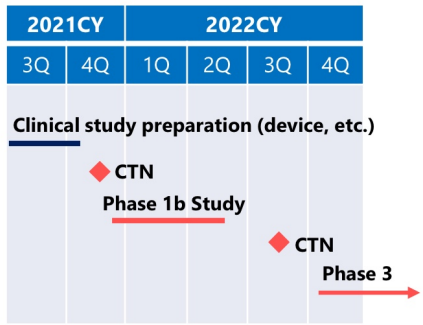
On the other hand, we are currently planning to develop a new device that will make it easier for patients with impaired respiratory function to take a drug.

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

As you can see on page 80, as a result of consultation with the regulatory authorities in Japan, we have decided to conduct a study to see how much the new device can actually improve the inhalation function of patients, and then to start Phase 3.

Therefore, as you can see on the right side of this page, we are planning to proceed with the development of S-770108. As I said, this will be an inhalant formulation of pirfenidone. The plan will be to first submit a notification of Phase 1b clinical trial during this fiscal year. We will then aim to implement Phase 3 in the next fiscal year.

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	

2021年度の開発品：主な進展予定 2/2

カテゴリー	パイプライン	適応	マイルストン	達成
その他品目	S-309309	肥満症	米国：Phase 1 試験開始	
	S-770108	特発性肺線維症	日本：Phase 1b 試験開始	
	SDT-001	ADHD患者における不注意症（小児）	日本：Phase 3 試験開始	
	ゾフルーザ®顆粒剤	インフルエンザウイルス感染症（小児、体重20kg未満）	日本：追加適応承認	
	S-649266［セフィデロコルトシル酸塩硫酸塩水和物］	各種感染症	日本：申請	

Next, on pages 82 and 83, I have summarized the milestones for our current development items.

This concludes the development part of the presentation.

Kyokawa: Thank you.

I would like to conclude with a summary from Dr. Teshirogi. Thank you.

Teshirogi: Thank you. This time, Dr. Kiyama and Mr. Iwasaki have done all the work, including Dr. Isou. They have achieved some good results in research and development at Shionogi. I believe that we have become much stronger, and in that sense, although perhaps everyone wouldn't agree, I believe that the past year and a half has been a very significant time for our research and development.

When it comes to COVID-19, I would like to say just 2 things. The first is that if you look at the timeline of the vaccine, we already have data for the first 35 days of the new formulation, which is 2 weeks after the second dose. In the end, the standard is to look at neutralizing antibodies after 50 days or after 2 weeks, so we did not provide data for 35 or 36 days this time. However, we believe that we have created a preparation that is comparable to any vaccine that is being developed in Japan.

We are very confident that we are 1 or 2 steps ahead of the domestic market in terms of mass production, and we will continue to work with the authorities to determine how quickly we can obtain approval. We are confident that we are getting close to our target profile, which is clearly different from the formulation we started with in December.

In addition, the news is changing all the time. We will have to consider whether 3 doses is good or not, and whether mRNA virus vectors and recombinant proteins are good or not. In light of the relationship with these vectors and recombinant proteins, including those from Sanofi and Novavax, we will proceed with how to obtain approval and supply them as products.

As for the therapeutic agent, Dr. Kiyama didn't mention it, but there was a similar candidate about 3 weeks before S-217622, and S-217622 seemed to be better, so we moved to that. We are a specialized manufacturer of small molecule compounds, so we are also providing products after S-217622. In this sense, I believe that we are quite competitive globally in terms of delivering a constant stream of good compounds to the world.

In fact, at this point in time, Mr. Iwasaki, Dr. Kiyama, and Dr. Isou are working day and night, looking also at manufacturing. On the headquarters side, there are several companies that have supply contracts with several countries or want to license this compound at any cost. I have been in discussions with these people for a long time, and the head office side has been busy in a different way, to the point where I can hardly sleep.

At any rate, starting with S-217622, as an oral antiviral drug, it will be of great benefit to those who are mildly ill or asymptomatic. Our goal, of course, is to conduct prevention trials, and we will be able to see how well the virus titer drops in patients with mild disease in October. The results will be out in October, so we will have to wait and see.

Of course, bacteria and viruses are not going to abide by human rules. As you may remember, the 0910 H1N1pdm suddenly became Tamiflu-resistant, which shook the world.

After that, it didn't appear for the next year or so. No one knows why. As Dr. Kiyama mentioned, there have been 3 coronavirus pandemics, and while this may be the end of all pandemics, it may not be. While we don't know much about it, there are probably not many companies in the world that have such a platform for infectious diseases, especially small molecules including oral treatments, and we would like to fully promote this platform.

Secondly, regarding HIV, there was one point that Dr. Kiyama may not quite have driven home enough. S-365598 is an idea that we have been working on as a backup for a long time.

Since S-648414 is a new mechanism, I was wondering if it could be combined with Cabotegravir to make it longer-acting. I want to go for at least 3 months. We thought that Cabotegravir itself could be managed for 3 months, even if it was just barely possible, so we thought of a second mechanism to match it.

The antiviral effect as an oral drug was as we had expected, but when it was made into a long-acting injection, it did not last very long. We had to give up on this compound, S-648414, because it would cause local irritation. However, we are still trying to find a way to use this mechanism to pair it up with integrase.

Naturally, the combination of Merck and Gilead, our rivals, has a great significance for us, but we believe that the base of treatment should continue to be integrase. We believe that there is no other product that has been so safe and reliable over such a long period of time.

It may be wonderful to see how long the safety and regeneration profile of the capsid can be guaranteed, but it will take 10 years to confirm it. Merck's products are based on nucleic acids, so even if they don't appear at first, long-term toxicity may occur, just like with Truvada or Descovy.

In light of this, the long-term safety of integrase is very reassuring, and I think that having an ultra-long-acting integrase at the base is very strong.

As Dr. Kiyama said, we are also looking at functional cures. Gilead has been doing a lot of work, but it is difficult to predict how much the functional cure itself will change, including the mRNAvaccines. If patients can gain peace of mind with injections every 6 months, which one is really more beneficial to them is yet to be seen.

In such a situation, we thought that we could be competitive enough to produce injectable drugs every 6 months, and we signed a contract with ViiV to work together on a project that we had been working on.

This is also a preclinical compound under normal circumstances. There is no way that we can receive such a high royalty rate, so in order to receive the same royalty rate as now, we have to take a certain amount of risk and share the development cost. We have signed this contract on the basis that we can continue to receive a very high royalty rate as a success fee.

As for the other items, S-812217, for example, was a very difficult area, but we think it was very encouraging that it met the primary endpoint so well. I have very high expectations for both SDT-001 and S-005151.

In the case of S-600918, the placebo effect was very large, but we believe that there are many very good points. I think that the milestone is whether or not we can get agreement on the implementation of Phase 3, including the sub-analysis, at the meeting with the FDA. If we can get the FDA's agreement to proceed to Phase 3, I think we will be able to ensure sufficient competitiveness in our relationship with Bayer, and I believe that we will reach a peak with regard to S-600918 by the end of this year.

Last but not least, until this December, or possibly January or February, we will be concentrating our company's resources on S-217622 and vaccines until they are ready for use. In the next fiscal year, I would like to talk about how we will build on this base to develop research and development, and separately, I would like to talk about how Shionogi's research and development should be conducted.

I would be happy to answer any questions you may have. Thank you.

Kyokawa: Thank you.

Question & Answer

Kyokawa: Now, we will take your questions for about 45 minutes.

Kohtani: I am Kohtani of Nomura Securities. I would like to ask you just oneor two questions.

First of all, regarding the coronavirus drug stated on page 10, I think your company first developed coronavirus drugs, and then discontinued the development of one drug and redid it again.

When I asked about the coronavirus drugs at the last briefing, I think Ms. Sawada answered that you had tried both polymerase and protease and found that the protease worked better, so you proceed that.

This time, you say that the selection was made. In addition, you say you are developing it since the structure is known. How can we understand this? Had you intensively focused on the protease?

One of the strengths of your company is that you apply your technology to things whose structure is known, and in this point, looking at your track record, you are probably oen of the top companies in the world. I believe that dolutegravir and baloxavirprobably hadn’t been made by accident.

So, if you are selecting something whose structure is known, is it correct to say that your company is quite confident about S-217622? This is the first point.

Kiyama: The project introduced at the last R&D briefing is completely different from this one.

Since the spread of the COVID-19 started, we have had 4 or 5 projects running concurrently within the Company, and the project with the compound that we introduced last time had progressed most rapidly. This was actually a phenotypic drug discovery. However, we were unable to determine the mechanism until the end.

In the end, due to safety issues, we decided that we should not proceed with this project as Shionogi's policy, so we stopped it and shifted all our resources to the protease.

As Mr. Kohtani mentioned, we have a very long history in the field of structure-based drug design, and we are confident in our strengths. In the process of the protease drug discovery, S-217622, we were able to quickly clarify the X-ray structure of the first hit compound, and we were able to determine how we could improve the activity and where we could make changes to make the compound even better. Therefore, we have been able to achieve this speed.

Kohtani: I don't know if you can disclose this, but is it correct to understand that this has a similar structure that inhibits the amino acid core of the catalytic site of 3CL-protease, which is cysteine and histidine, like Pfizer?

Kiyama: We are working on the schedule for the disclosure of the structure, and we hope to disclose the structure at academic conferences soon, but its structure differs from that of the compound of Pfizer.

As a protease, it has an active center where the viral protein gets stuck in the groove and cuts it off at a certain point. It is the same in that the compound binds to the active center and competitively inhibits it. The only difference is that Pfizer's protease inhibitor is a traditional type that you see all the time, but the structure of ours is completely different and new.

Kohtani: I understand.

Secondly, when we look at the data of the evaluation of the coronavirus drug efficacy in mice on page 13, virus titers show a roughly up to 2 to 3 log reduction after 48 hours, and about 4 log reduction after 72 hours.

I'm very aware that we can't really make an apples-to-apples comparison with other research papers, but looking at the papers that are available right now, molnupiravir similarly shows a roughly 2 log reduction after 48 hours. Even Pfizer's 1 shows an about 2 log reduction after 4 days.

We only have mouse evaluations at this point, but can we assume that the efficacy of the drug is roughly the same as that of Pfizer or molnupiravir?

Kiyama: We think that Merck's compound is also showing a 3 log reduction. Based on our non-clinical results, we believe that the effect will be almost the same.

Kohtani: Of course, there is the advantage of once a day, and no booster is needed, but even so, if the effect is the same, we have to proceed very quickly. I have a feeling that you will be able to release the product on the same schedule as Pfizer in Japan, but the problem is global development planas mentioned on page 18.

If you start discussions in 3Q of 2021, Phase 3 will start in 4Q at the earliest. If so, as Pfizer took more than 6 months, it looks like the launch will be the end of next year.

What do you think about the possibility of acceleration while using Japanese data to obtain the EUA first, for example?

Sawada: As for EUA, the FDA's primary endpoint for approval of EUA is prevention of severe disease or death. From that point of view, the Phase 2/3 that we are trying to implement in Japan will actually be more like a normal FDA package, so as a trial for the EUA, we still need to conduct a trial for the prevention of severe disease.

However, we are also receiving a lot of interest overseas, including from the NIH. We have already received the FDA's opinion through the NIH and other organizations, although the discussion with the FDA itself will be postponed until October. The framework of the protocol is already in place, so we hope to start clinical trials in the 3rd quarter.

Kohtani: Lastly, I badly want to ask about sivopixant on page 50.

None of the doses met the primary endpoint. However, if we look at page 53, in the subgroup analysis, efficacy was seen with 300 mg for patients with severe disease, or those who did not have chronic cough. However, looking at page 52, with a 300 mg dose, 33% of patients have taste disorder.

In the Phase 2b of Merck's gefapixant, I think about 50% of patients had taste disorder, and about 16% dropped out, at the dose that you just tested in Phase 3.

In your company, the discontinuation rate is probably less than 5%, which means that although there are some adverse events, they are not so severe, but it doesn't seem like a big difference. I think your product will be launched later, and the commercial potential will be limited. How do you think about it? This is the last question.

Iwasaki: With regard to taste abnormalities, in the PoC, the rate was about 10%, in the single digits. We need to do more market research to see if this 33% rate is acceptable. However, we would like to go with this 300 mg, as MSD is also going forward with 50%.

Bayer also already has the results. Bayer's drug also probably has the same change in coughing frequency at lower doses as our 150 mg, and the results of taste abnormalities are also the same. We will proceed with 300 mg due to efficacy. However, we need to discuss the design of the adoption meeting with the FDA first. We also have to consider the acceptability from the market side in parallel, so we are not able to give a clear answer as to whether the rate of taste abnormalities is acceptable or not at the moment.

Kohtani: I understand. Thank you very much.

Kyokawa: Mr. Ueda, please.

Ueda: I am Ueda from Goldman Sachs Japan.

I would also like to ask you about the therapeutic agent for COVID-19 and its antiviral effect that you show on page 11. First of all, regarding 3CL-protease mutations, can you tell us if there are any mutations other than K90R that we should be concerned about, and also if there will be any viruses that mutate against your drug, if you know of any? In that case, I would also like to know how effective it is against such mutated viruses, if you know.

In addition, last year, you showed us a comparison with remdesivir in a chart. If there are any comparisons with other drugs in the preclinical stage, including those of Pfizer, Merck, Roche, etc., could you please let us know?

Kiyama: First of all, I would like to talk about the protease mutant strains. There are a huge number of new coronavirus strains registered in databases around the world, but only a very small number of them have protease mutations.

Currently, we have not fully investigated whether our compounds are effective or not against the mutated strains, but we believe that there is almost no need to worry about it.

This is because all spontaneous mutant strains

have mutations that are outside the active center, so they do not come into contact with the compound in the simulation. Therefore, I believe that there is no need to worry at all about the spontaneous mutations that are currently known and are not subject to so-called drug resistance pressure.

I think the next question is about drug-resistant mutations. This is the fate of antiviral drugs. Viruses always mutate to become resistant to mutation pressure. However, at present, it is actually very difficult to test for the isolation of mutant resistance. The results of the experiment will vary depending on the virus strain, cell strain, and the concentration of therapeutic agent, so we have to proceed with caution. However, we predict that mutations will occur near the main active sites.

Ueda: Thank you very much. Do you have any suggestion about the resistance to drugs? For example, Is there a way to get faster drug resistance results, such as by performing a special culture?

Kiyama: Currently, we are conducting tests under GLP, the reliability standards, so I would like to refrain from making any comments today.

Ueda: I understand. Thank you very much.

Secondly, I would like to know about the COVID-19 vaccine. If you have any information on the current profile of adverse reactions, especially fever, I would like to hear from you.

At the same time, although today's discussion focused on COVID-19, I would like to know about the future strategy of your company, including the possibility of applying your technology to RS virus, influenza, etc., and whether or not a combination vaccine will be developed.

Iwasaki: Adverse reactions include pain and systemic symptoms such as fever and fatigue. 20% of patients have fever and other symptoms. We are now making an accurate comparison, but I think it is about the same level compared to other recombinant vaccines.

Compared to the RNA vaccine, I have the impression that the degree of fever and pain may be lower, based on their grading.

Kiyama: I think you are talking about expanding to other diseases. First of all, the technology we have now is BEVS, which is an expression system for baculovirus. The recombinant protein vaccine will function most effectively in respiratory vaccines, so what we would like to promote at present is a combined vaccine with influenza vaccine.

Ueda: I understand. Thank you very much. That's all.

Kyokawa: Mr. Hashiguchi, please.

Hashiguchi: I am Hashiguchi from Daiwa Securities. Thank you very much.

The first is about the safety of S-217622. Mr. Iwasaki mentioned earlier that it has a very good safety profile. Did you mean that, like with Xofluza, there is still a possibility of safety, like a placebo, or did you mean that the expected efficacy is so high that there will not be a big problem in the balance with the benefits? I know you only have a limited amount of data, but can you tell us what you feel at this point?

Iwasaki: I believe that the frequency and extent is very low. It is difficult to say how great Xofluza is, but there have been no cases of discontinuation or fever, so from that perspective, the profile itself is very clean.

In addition, even if there are fluctuations in the clinical laboratory test values, etc., the dosing period is only 5 days. Therefore, unlike long-term drugs, even if side effects occur or abnormal laboratory values are found, you can recover from then. We believe that this will be the profile.

Teshirogi: As a company policy, no matter how short it is, we stop when it comes to fatalistic side effects on heart, kidney, liver, and so on. So, we try to conduct those clinical laboratory tests as soon as possible, and we have not seen such effects at all.

Hashiguchi: Thank you very much.

Regarding the vaccine development plan, I would like to know the criteria and timing of the decision on whether or not to conduct the trials mentioned at the bottom of page 24.

I understand that there is no particular need to do this in order to get approval or to fulfill the minimum mission. However, I understand that in order to contribute more to society and to pursue more returns as a company, you are considering conducting this study. Is that correct? In order to do so, I understand you are trying to see how much efficacy and safety of S-268019 can be obtained in the Phase 1/2 study. Or, are you also assessing other aspects of the world environment that your company cannot control? Can you tell us about the criteria and the timing for making such a decision?

Teshirogi: There is a lot of discussion about getting approval in ICMRA, and if we cannot get approval unless we conduct onset prevention trials for all new types of vaccines in the future, there is also the question of how to use placebo, so there is some debate about that.

However, I think that the results of the onset prevention study are very important for the global recommendation of the WHO to use this vaccine or not.

I'm sorry to say an emotional thing, but the fact that none of the COVID-19 vaccines from Japan have been tested for the prevention of onset of disease on a global scale is also a problem. Therefore, we would like to do this while talking with the government and other organizations.

In order to obtain approval, for commercial purposes, and since a number of people are waiting in Japan, we would like to go ahead with this. If we don't conduct onset prevention trials, it will be difficult for the vaccine to gain citizenship beyond the last step.

The timing and decisions are as described here, and we haven't decided everything yet. As far as we're concerned, if we don't do it, it means that when the next new pandemic comes out, people might say that Japan can't even do Phase 3. So we are looking into the possibility of doing this, especially in Asia.

Hashiguchi: Is it correct to say that there is a high possibility that you will conduct a placebo controlled trial because you think it is likely that you can secure a certain number of people who will cooperate in terms of such as money?

Teshirogi: Basically, I think your understanding is correct, and we also have issued press releases about the placebo. In Vietnam, for example, the government is willing to at least consider participating in placebo-controlled trials if we can help them with manufacturing facilities so that they can prepare for the next step.

In the past, most of the countries that participated in Phase 3 were provided with the vaccine itself as soon as it was approved, but in the future, not only the vaccine but also the technology transfer will be very important items. If there are more than a certain number of countries that are willing to participate, we would be very happy to conduct.

Hashiguchi: Thank you very much. That's all.

Kyokawa: Last from the audience, Sakai-san.

Sakai: I am Sakai from Credit Suisse Securities. Actually, I would like to ask you about the commerciality of your pipeline, but since this is an R&D Day, I will refrain from that.

You mentioned that 80% of your company's R&D human resources were invested. I was a little surprised by this. I would like to know to what extent management would be committed to COVID-19 in the future. Naturally, I understand that you are trying to avoid delays in other projects, but at the same time, we are starting to see the end of the pandemic. In such a situation, how do you balance the management? This is 1 of the first things I would like to ask you.

Also, as an extension of this, I'll talk about vaccines later. First, I would like to ask you about this question.

Teshirogi: You are right, and we can't just keep doing this without an end, so we have 2 points in mind.

First, we set a time limit. As I mentioned earlier, we are planning to run the project until December, but after that, we will probably not continue with this project structure, unless even worse mutant strains than the delta strain emerge. We will anyway commercialize S-217622 and S-268019 as the main products and think of an internal system we can provide them to the world.

The other thing is that the supply system and how to commercialize the product is different from what we have seen in the past. We would like to see the extent to which we can incorporate such things as government commitment and stockpiling into our business model.

If the world or government is not receptive to such things, we are faced with the same problem when the next pandemic occurs. we have many shareholders and will be faced with the question of whether or not it is really good to continue with infectious diseases business.

For us, in order to continue with the base of infectious diseases, it is very difficult to do so unless there is a framework in which society, including the governments of each country, can support it to a certain degree. In the short term, if S-217622 is successful, it will be purchased by a variety of countries, so it may sell very well for 1, 2, or 3 years. However, we also should consider if it will be applied as a business model in the future.

Sawada as the main person in charge is discussing the possibility of making such purchases and subscriptions in Japan, just as we are doing in Europe with cefiderocol. Otherwise, I don't think there is any point in us even applying for approval in Japan.

We would like to think about the future of resource management by assessing those 2 things: the fact that there is a time limit and whether we can take a few steps into new business models.

Sakai: Ronapreve, and the Novavax vaccine Takeda being produced by Takeda in Japan will be probably purchased by the government. you believe and expects that the government will adopt a similar approach in the end, and it is a very natural trend?

Teshirogi: In fact, we have been talking about this, so I think the reality is extremely high.

Sakai: Thank you very much.

I learned a lot from the table on page 11. I think this is a table that is also shared by vaccine and therapeutic agent staff at other companies. I think the game will be decided in part by how well you control the spike protein.

In this context, mRNA vaccines are now the mainstream in the world. I don't understand to what extent your recombinant vaccine will be able to demonstrate its superiority in this situation.

Earlier, Mr. Iwasaki mentioned that it would be good for the respiratory system. I would be very grateful if you could explain the whole picture.

Teshirogi: No one knows how safety of mRNA and Viral vector vaccines will turn out in the long term. On the other hand, the safety of recombinant proteins and inactivated vaccines over a period of 5 or 10 years can be supposed based on experience with other viruses.

In terms of efficacy, especially in the case of such a large pandemic, and how quickly it can be brought to an end, I recognize that it will be efficacy-driven, and that it will work on a balance where the benefits clearly outweigh the risks for a certain level of safety.

In a situation where everyone has some immunity and is vaccinated every year, like the influenza, I think it is not acceptable to have a fever of 39 degrees every year.

In this sense, I believe that in the phase where safety shifts to a dominant position, there will be more opportunities for medium- to long-term use of vaccines such as ours.

Sakai: I understand very well. Thank you very much.

Kyokawa: Thank you very much.

We will now take questions from participants by phone.

Please follow the instructions of the operator.

Operator: Our first question comes from Mr. Yamaguchi of Citigroup Global Markets Japan.

Yamaguchi: This is Yamaguchi from Citigroup. Thank you very much.

The first question is about S-217622, Phase 2/3 in Japan, where I believe there are 2,000 recruits. I think you plan to do it within a month or 2. I feel that the number of subjects of the trial is quite large, regardless of whether the infection number is large or not.

I understand that your company is doing everything in its power, but can you tell us what the system is in Japan to make this early enrollment possible?

Iwasaki: Although the number of patients is decreasing rapidly, we would like to accelerate clinical trials in hotels with the cooperation of local governments, although I cannot tell you the names of the prefectures.

If patients enter the hotel for recuperation, we can enroll them intensively with a small number of staff. We are now thinking of accelerating the clinical trial by implementing it intensively in hotels, especially in municipalities with a large number of patients.

Yamaguchi: I understand. Is there a possibility that there will be a need to take measures such as increasing the number of municipalities if the number of patients decreases?

Iwasaki: Rather than increasing the number of municipalities, it would be better to increase the number of hotels. I believe that municipalities with a large number of patients are limited, so rather than increasing the number of municipalities, we should increase the number of hotels in municipalities with a large number of patients. Or, we would like to increase the number of home clinical trials.

Since this is a home-based clinical trial, we will need to dispatch clinical trial doctors and nurses, and since we are currently seeing a shortage of medical staff, we would like to do this in a centralized city.

Yamaguchi: I understand.

Also, the primary endpoint is the time to symptom recovery for patients with mild disease and the symptom onset rate for asymptomatic patients. Are the numbers of each patient group fixed and compared with each placebo group? It seems to be difficult to compare with placebo when they are grouped together. Is there a fixed ratio of patients with mild disease and asymptomatic patients?

Iwasaki: Mainly, we want to collect data from patients with symptoms. From the standpoint of safety, we want from asymptomatic patients as well. We knew that it would be very difficult to collect data only from symptomatic patients, so we have been collecting from asymptomatic patients as well, with the purpose of increasing the safety package.

As for the number of cases, we are currently considering 500 cases and 500 cases. These are symptomatic patients. We are considering low dose and high dose. We are hoping to collect about 1,000 cases of so-called symptomatic patients in total.

Yamaguchi: Is it basically based on collecting patients who are mildly ill rather than asymptomatic?

Iwasaki: That's right. Patients with symptoms. However, when I talked with the primary doctors, said that if a patient comes in as a close contact and tests positive by PCR, a treatment at an early stage is necessary in Japan.

Considering this, we would like to collect data on asymptomatic patients as well.

Yamaguchi: I understand. When you analyze data, you look at them separately. There is no way to see them all together.

Iwasaki: Yes, that's right.

Yamaguchi: I understand.

There is 1 more thing that I would like to mention briefly. Although it is not related to R&D, the production volume of oral drugs and vaccines have been reported in the media.

In the current situation, especially in the case of oral drugs, the figures of 1.2 million and 10 million have come out. Could you tell us once more the credibility of these figures, or what the best-case scenario is at the moment?

Teshirogi: I'm going to be straightforward, because the people here are really experts. Normally, for example, it takes 1 year for Phase 3, and then another 8 months or 1 year for the review of the application for approval. So normally, once Phase 3 starts, we have about 2 years to prepare for production.

This time, we only have about 4 months from Phase 2 to supply the products by the end of this year, so the supply chain has been working hard since June to find out what we can do during that time. We also think that we can manage about 1.2 million in a fiscal year.

The figure of 10 million is impossible unless we collaborate with other companies. In that sense, as I mentioned earlier, our John Keller is being chased around so much that he can hardly sleep.

1 of the major conditions for a license is how much we can produce. We would like to think about how much more we need to produce, and which 1 of us will produce more.

Our current estimate by Mr. Isou is that we can expect a solid 5 million per year in the next fiscal year, starting in April. However, this depends on the dosage, so if the dosage has doubled or tripled, the number will decrease. If the dosage is what we expect, I think we will be able to produce 5 million.

If we were asked to create 30 million globally, it would be difficult for us to do it alone, so we would have to negotiate with our partners.

Yamaguchi: I understand. Just to confirm, 1.2 million and 5 million are possible for your company, and if you want to produce 10 million, you need a partner, is that right?

Teshirogi: Yes, you're right.

Yamaguchi: Thank you very much.

Operator: Our next question comes from Mr. Wakao of JPMorgan Securities Japan.

Wakao: This is Wakao from JPMorgan. Thank you. I would like ask about the treatment for coronavirus.

First of all, with regard to the domestic market, I would like to know how your product will be positioned if everything goes well, including the other 3 products from Merck, Pfizer, and Roche. As your product is once a day administration and the speed of development is rapid, I think that the target patients would be asymptomatic or mildly ill patients regardless of their risk factors.

In your answer to Mr. Yamaguchi about asymptomatic and mild disease, you mentioned that mild disease will be the main focus, so should we not expect the treatment for asymptomatic disease at first? Should we understand that when the first supply starts, the main focus will be on the mild cases?

Teshirogi: In terms of supply, it is unlikely that we will be able to get approval and distribute to wholesalers in the beginning, so we will probably have to go through the goverment for distribution in the first year.

In this situation, I think it is difficult for us to have any influence on how the needs of the medical community are met and how they are allocated. Of course, in terms of medical needs, I think the first priority should be on mild to moderate illnesses, so that the overwhelmed medical system can be improved as soon as possible.

Naturally, there are many asymptomatic people who have unfortunately passed away at home, as reported by the media, etc. So, how to allocate it to such people is something we cannot determine, especially in the first year, when we have a limited supply of about 1.2 million by March.

Wakao: I understand. Then, considering that the first year will be based on government purchases, should we assume that the product profiles of the companies will not have much impact?

It will depend on the timing of launch and the timing for the government to intervene, but basically, don't we need to think about whether the profile has an impact on the government purchase or the allocation, or not?

Teshirogi: I think that at least for the first year, all companies will be either short of or on the verge of being short.

We won't be able to see how sharply our product will lower the virus until October, but we think there is still a possibility. So, I think that differentiating factors will probably be much clearer.

Wakao: I understand very well. You mean that you may be able to differentiate your product in terms of the sharpness of lowering the virus after the second year rather than the first year, or when the profile affects the market share a little more.

Teshirogi: That's right. Also, our product has a safety profile of once-daily administration, while other products are twice daily, and the dosage is quite high. I think the key to success will be how much the profile can be backed up by data in the next few months.

Wakao: I understand. Thank you very much.

Secondly, I think the development of this drug overseas, especially in the US, has changed a lot since your last presentation, so I would like you to clarify this again.

The last time you spoke to us, you had to apply for an IND in the US by September and finish Phase 3 by the end of March next year to get the emergency use permit. You mentioned that you were aiming for the US government to purchase your products. But as you explained today, collaboration with the NIH also came up, and I think your development plans in the US have changed considerably. Are you aiming for the EUA or not? Please tell us about that again.

Sawada: As mentioned earlier, we have not yet discussed this with the FDA. There is a question of whether or not we will surely be able to obtain an EUA, but we will inevitably aim for an EUA.

However, for the EUA, as I mentioned earlier, we look at the impact on serious illness or death in a relatively short period of time, 1 month. This is the recommendation for the endpoint.

However, on the other hand, since long COVID is now a very serious problem, I think that the clinical trial line itself will probably have to be prolonged considerably. I think the future discussion will be about what form of submissions are acceptable during the course of the project. In that sense, the major policy has not changed.

Wakao: In your previous explanation, you mentioned you would submit IND by September, didn't you? You mentioned that you would apply for an IND by September, get an EUA by March, and if you could provide 500,000 course, there would be a buyout. I thought this is now difficult in terms of timeline, but is this still what you are aiming for?

Sawada: We are aiming for it. It depends on FDA's intention and preference. It's still a matter of how many cases we can collect.

Wakao: I understand. By the way, you mentioned that you would apply for an IND by September. Have you already applied for this?

Sawada: We are planning to.

Wakao: I understand very well. Thank you very much. That's all.

Operator: The next question will be the last.

Ms. Kumagai from Mitsubishi UFJ Morgan Stanley Securities, please.

Kumagai: Good afternoon. I'm Kumagai from Mitsubishi UFJ Morgan Stanley.

Is there any possibility that you submit S-217622 with interim analysis? Also, on the slide, you say that you will submit by the end of this year, but will you submit only after the supply is ready?

Iwasaki: We are no longer planning to do an interim analysis. We will collect data all at once, and finally submit for with clinical evaluation and viral reduction. However, the timing of the submission will depend on negotiations with the authorities, since it takes time for viral evaluation to be measured, but we will submit when the clinical data is available or at the timing of key open, and then provide additional data sequentially during the review. We are thinking of negotiating a rolling submission.

Kumagai: I understand. In that case, is it correct to understand that the timing of the submission has nothing to do with the supply system?

Teshirogi: Yes. Anyway, we've already ordered all the things we need to make. We are now in the phase where we need to produce like a workhorse, so we will do that.

However, as Iwasaki just mentioned, of course, stability, for example, has to be a rolling submission. As of December, we probably only have about 3 months-plus of stability, so we need to consider how we proceed with the rolling submission.

As for the product, structurally, looking at Kiyama's department, there will be no problems in stability. However, physically, we have to deliver the product while we only have 3 or 4 months of data, so I think the question is how to run it.

Kumagai: I understand very well.

Regarding S-600918, if the placebo effect is well controlled, will 150 mg be possible, or will you proceed with 300 mg, which has shown taste abnormalities? Can you tell us how to balance the efficacy and safety of the product?

Iwasaki: This is a very difficult question, so I don't know how to answer it.

I think that even 150 mg is possible, but based on the results so far, I think that it should be 300 mm. However, if the FDA points out that we need to look at the dose-response properly, we will have to consider the 150 mg option in the future.

However, 33% for 300 mg is certainly high. We are aiming for at least single digits, so from that point of view, although it depends on the negotiations with the FDA, we have not yet planned for 150 mg.

Kumagai: I understand.

Lastly, as for S-600918, I think you mentioned that pruritus and hypertension would be considered in the future in the 2030 vision. Are there any updates?

Iwasaki: With regard to S-600918, we are currently examining our portfolio and other factors to determine which disease we should focus on next. We are also working on non-clinical studies, so for the time being, we would like to develop multiple LCMs and run multiple PoCs with chronic cough, apnea syndrome which there are needs for, and with a view to new diseases including pain in the future. At this stage, we have not been able to identify the specific name of the disease.

Kumagai: I understand very well. Thank you very much.

Kyokawa: Thank you very much.

This concludes the Shionogi R&D Day 2021. Thank you very much.

Teshirogi: Thank you.

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