SHIONOGI & CO., LTD.

SHIONOGI R&D Day 2022

October 12, 2022

Presentation

Kyokawa: My name is Kyokawa, Vice President, Corporate Communications Department of SHIONOGI CO., LTD. Thank you for taking the time out of your busy schedule to join us today.

SHIONOGI R&D Day 2022 is now called to order.

I would like to introduce today's speakers. Mr. Isao Teshirogi, PhD, President & CEO.

Teshirogi: Hello. This is Teshirogi. Thank you for joining us.

Kyokawa: Mr. John Keller, PhD, Senior Executive Officer, Senior Vice President, R&D Supervisory Unit.

Keller: Hello. This is Keller. Thank you.

Kyokawa: Mr. Yasuyoshi Isou, PhD, Senior Executive Officer, Senior Vice President, Research Division.

Isou: This is Isou. Thank you.

Kyokawa: Mr. Takeki Uehara, PhD, Senior Vice President, Drug Development and Regulatory Science Division.

Uehara: This is Uehara. Thank you.

Kyokawa: Mr. Yasunori Aoyama, PhD, Corporate Officer, Senior Vice President, Biopharmaceutical Research Division.

Aoyama: This is Aoyama. Thank you.

Kyokawa: These are the speakers today.

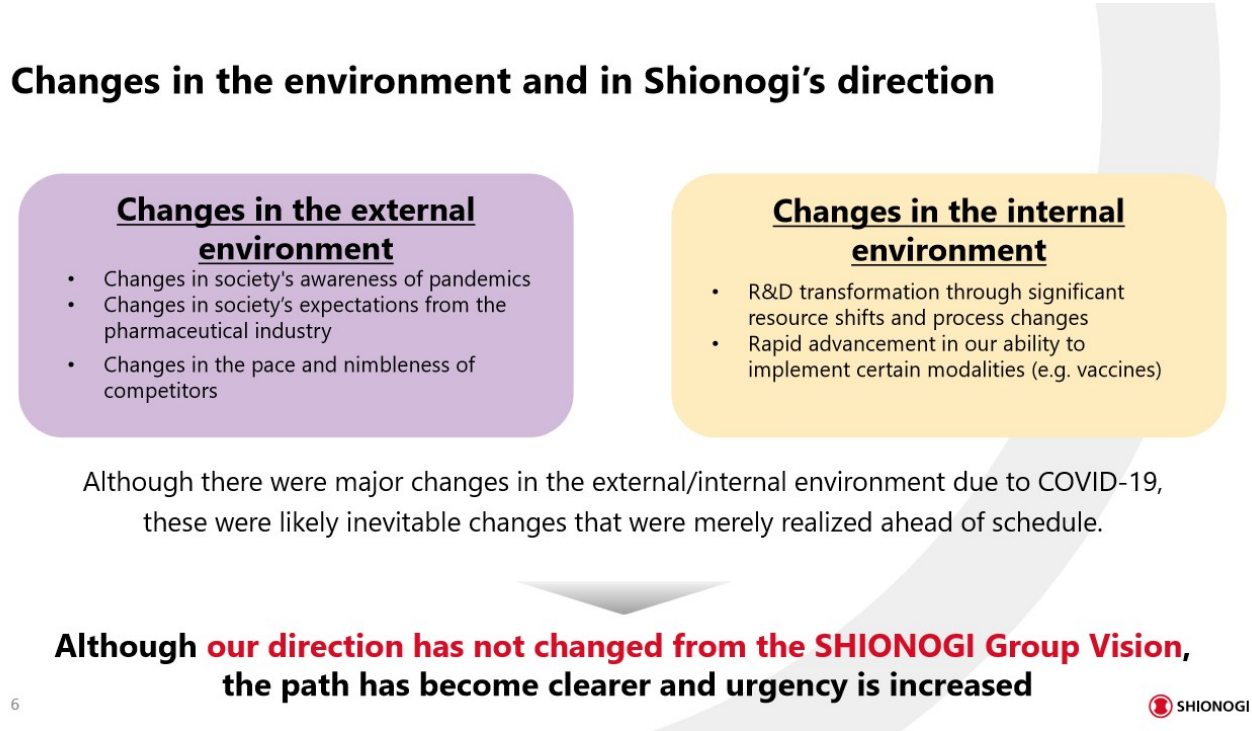
Simultaneous interpretation is available for today's briefing. If you wish to use a simultaneous interpretation service, please log in to Zoom and select a language from either Japanese or English by clicking the globe icon at the bottom of the screen. The operating procedure may vary slightly depending on your selection. Please confirm the operating procedure in the instruction manual that has been sent to you in advance.

Let me quickly introduce today's agenda. Mr. John Keller, R&D Director, will open the event by giving an overview of SHIONOGI's R&D strategy. Because this will be a presentation by Mr. Keller, if you would like to take an advantage of simultaneous interpretation, please select your language at this time.

Next, Mr. Uehara will discuss the progress of COVID-19-related projects. Following that, Mr. Isou and Mr. Aoyama will discuss the progress of the development, research, and vaccine business, respectively. Mr. Keller will then summarize the content of today's presentation, and Mr. Teshirogi will provide a summary, followed by a question-and-answer session.

We will be accepting questions from both on-site and virtual participants during the Q&A session. More details on the procedure will be provided at a later time. This event is scheduled to adjourn by noon. Extended hours are available up to 12:30 PM.

Now, let's begin. First, Mr. Keller will provide an overview. John, go ahead, please.



Keller: Thank you very much for your presence and for your attention. Very much appreciated.

To begin with, our slide six, COVID-19 as we all know, has changed our world and the way that we in society operate.

As an infectious-disease-committed company, it dramatically changed the focus of our efforts in R&D in the pharmaceutical industry.

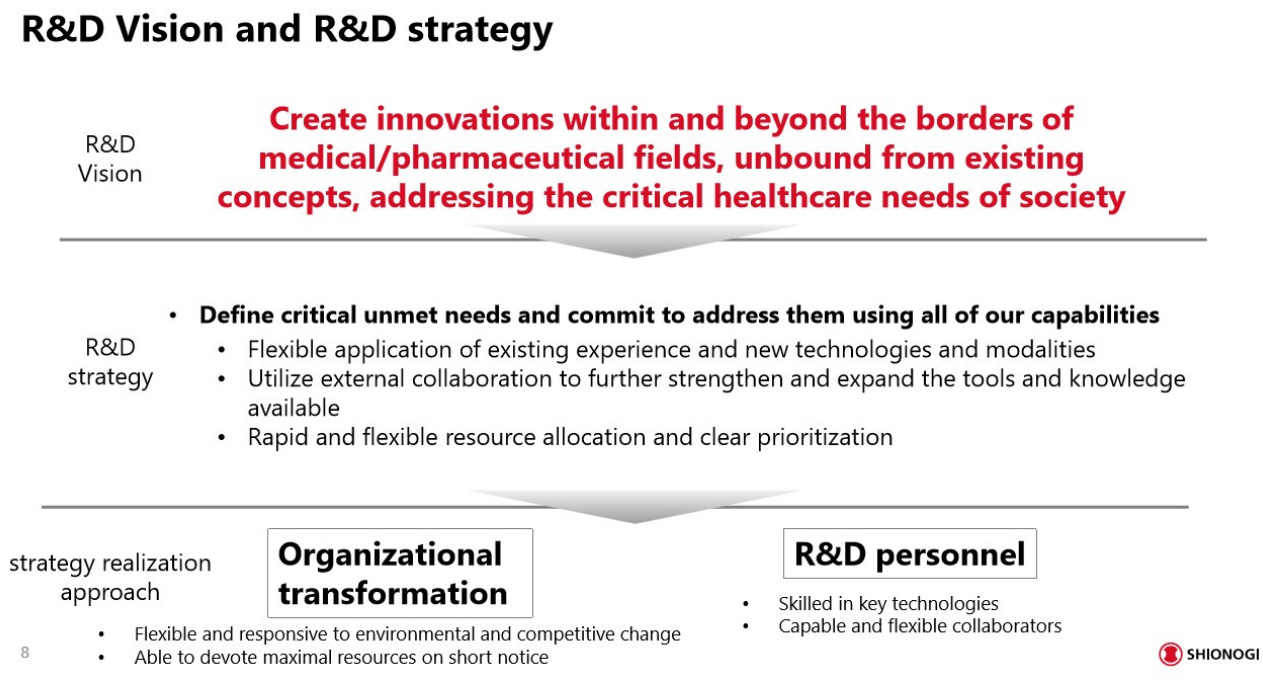
Now at the same time, we have always been committed to infectious diseases. The speed, nature, and resources required to compete in this environment are very different and needed most urgently to address the critical needs of society.

Within the R&D organization, it created a new approach to drive resources, intense focus, and rapid decision-making, around the progression of a certain number of key programs. That sense of urgency has become part of the DNA of our entire organization. So, we are bringing that spirit and the inspiration and the ability to move resources and energy around to all of our programs, of course, driven by priorities.

Now it also has told us that we need to be prepared to bring together whatever technologies and modalities needed to solve medical needs, and it has driven within our need to expand the range of technologies, modalities, and capabilities at our command, to meet the medical needs.

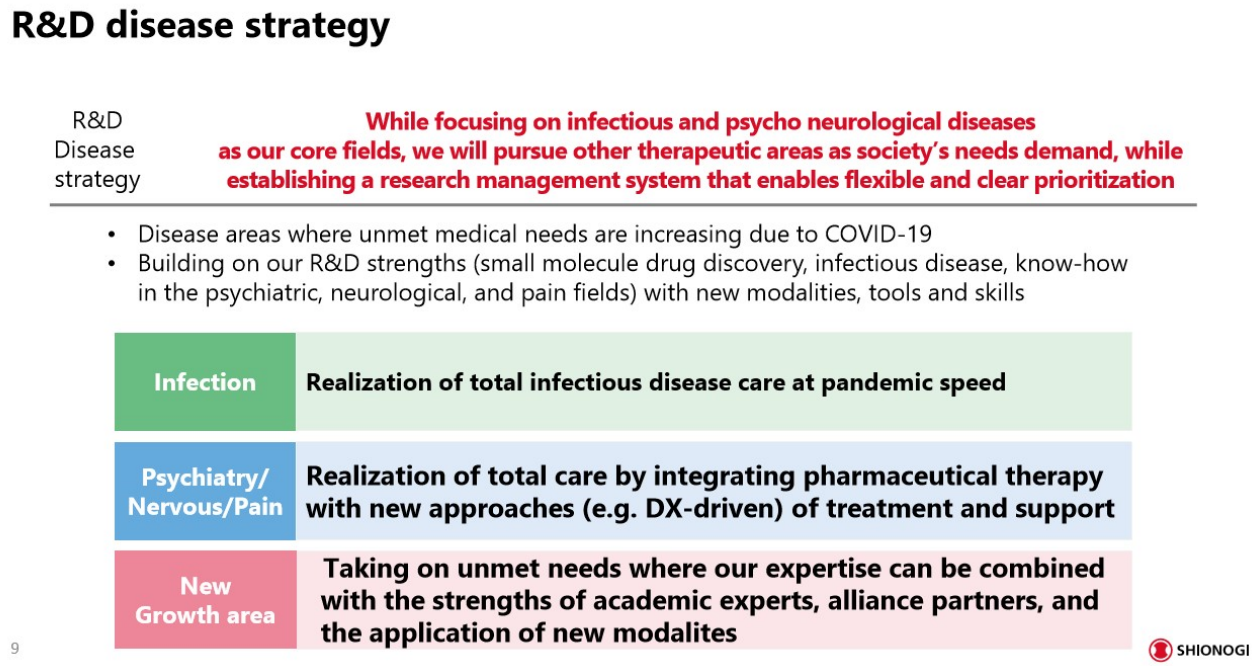
While our basic directions have not changed from our overall vision of the SHIONOGI Group point of purview, the way we approach it has shifted as the world has shifted.

The 2030 vision is “Building Innovation Platforms to Shape the Future of Healthcare”.



But how we do that is different, and how we create those innovations and how we source the technology to do it, both internally and externally, has shifted and become more urgent.

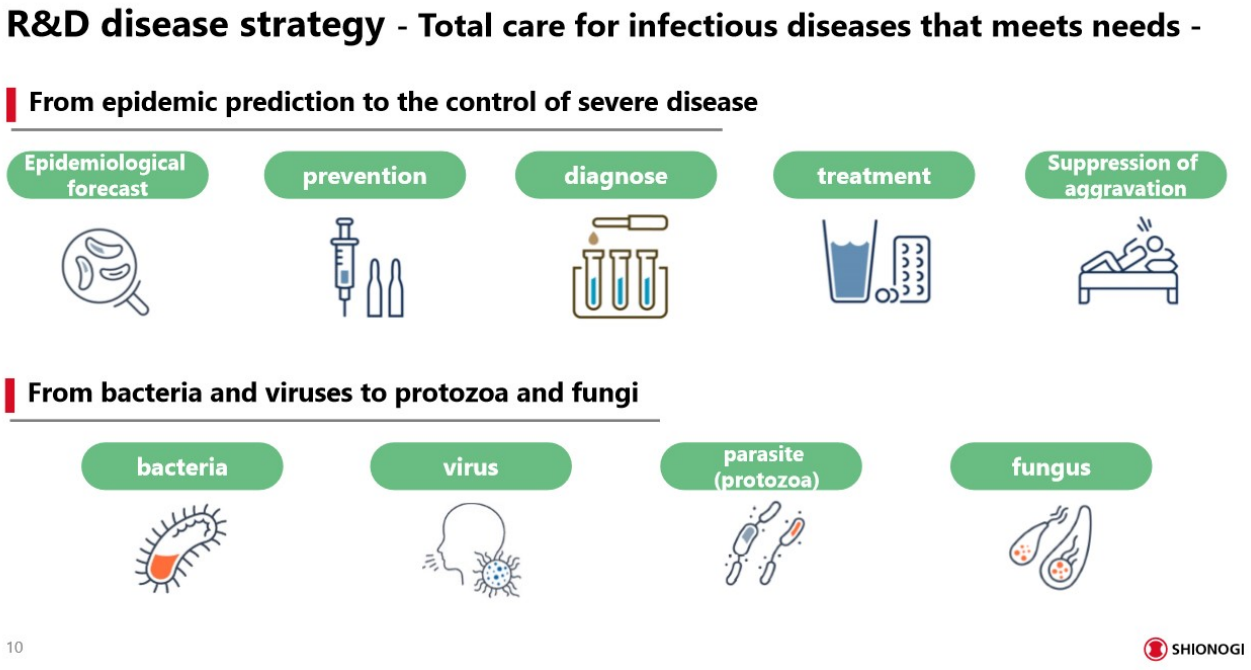
In parallel, we needed to expand the capability and the depth and specialization of R&D personnel that we bring to it. As you also see, technology, modality, and platform are increasingly important in how we approach, and we structure our discovery, research, and our work of development.



In terms of disease strategy, of course, we continue to be strongly committed to infectious diseases, but we are now taking a broader view of infectious diseases. As you see it is a comprehensive approach to the impact that infectious disease has on a patient and has on society.

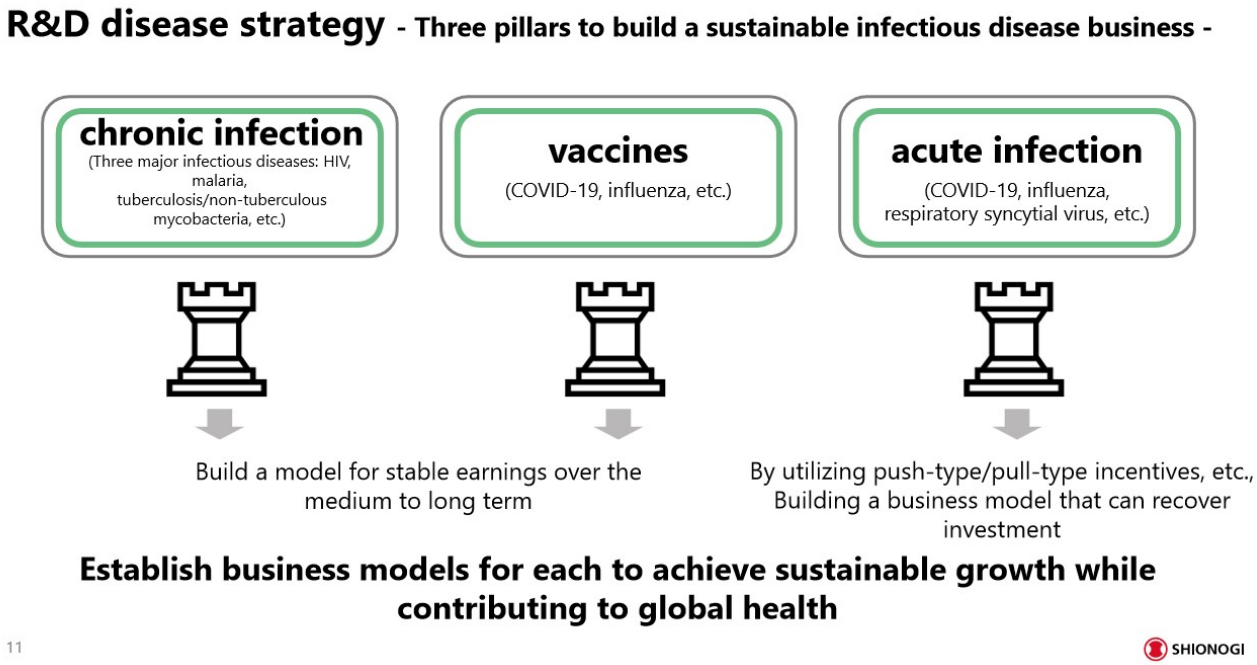
Psychiatric and neurological disorders and pain are also our commitments. But now, the broader range of technologies and capabilities comes inside to support the patients in more ways than just a drug itself. Because in these diseases, support for compliance and for care for other aspects of therapy is absolutely critical to achieving positive sustainable therapeutics itself.

And then finally, as always, we do retain some optimistic opportunities to chase new drugs and new modality areas for growth. Actually, the vaccine initiative is so critical for us now in the infectious disease area, which was, at a time, brand-new growth area for us. As we continue to look in on the outside and inside for new ideas that can bring us into new areas.



To recap infectious disease, we are now pursuing comprehensive issues; everything from epidemiology forecast to wastewater detection, for example. Prevention through vaccines and rapid diagnosis is just so critical to get the right therapy to the patient at the right time. Of course, appropriate treatments, and, if the infection isn't stopped in time, treatments to prevent the development of the severe disease for the suppression of exacerbation.

We want to provide solutions to the ever-broader range of pathogens, not only bacteria and viruses, but also protozoa and fungi.



We have three pillars.

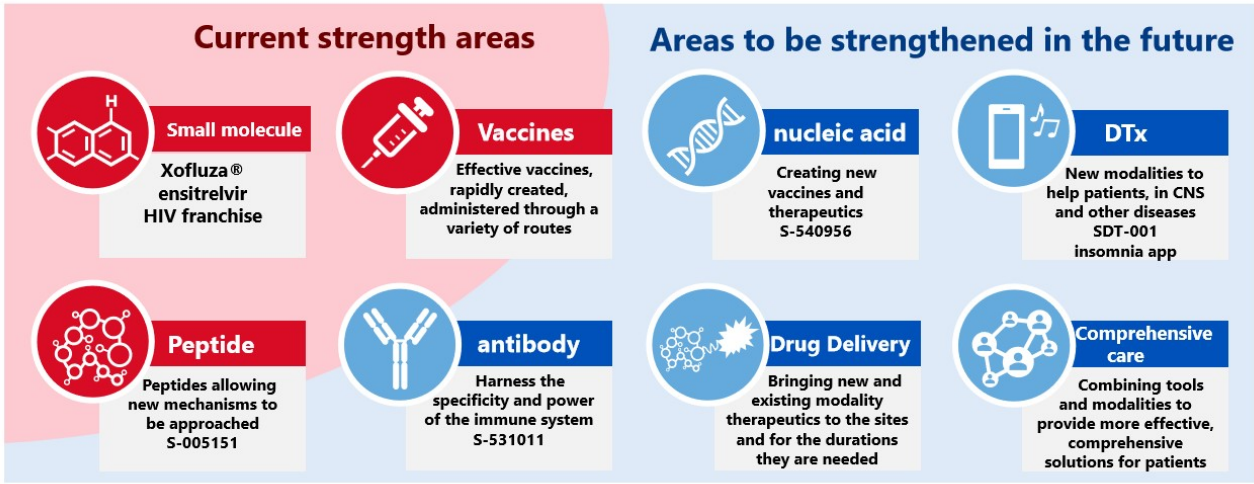
First, acute infections. Acute infections include COVID-19, influenza, bacterial, and other viral infections. These business models are quite different. This is because these acute infections are very unpredictable. So, it is very difficult to maintain a sustainable market. It is very difficult to achieve a stable market without an active government policy.

In terms of COVID-19, government stockpiles have stabilized, but in terms of antimicrobials like cefiderocol, there are models in place in some countries, but if you think globally, if you think about the global community, there is still a lot of work that needs to be done.

Then there are chronic infections. This is still a major problem in developing countries. Malaria, tuberculosis, these diseases do not have a huge impact on society as a whole, however, in developing countries, this is still a major problem. Therefore, we must control this as well. HIV is also still a problem as a chronic infectious disease.

Next, let's talk about vaccines. This is to control infection, but this is now a new platform, a new opportunity. In conducting a sustainable business, there are various types of products, some by patent, some not by patent.

Strengthen and expand modalities



Acquiring diverse modalities to discover new treatments addressing that meets diverse unmet medical needs

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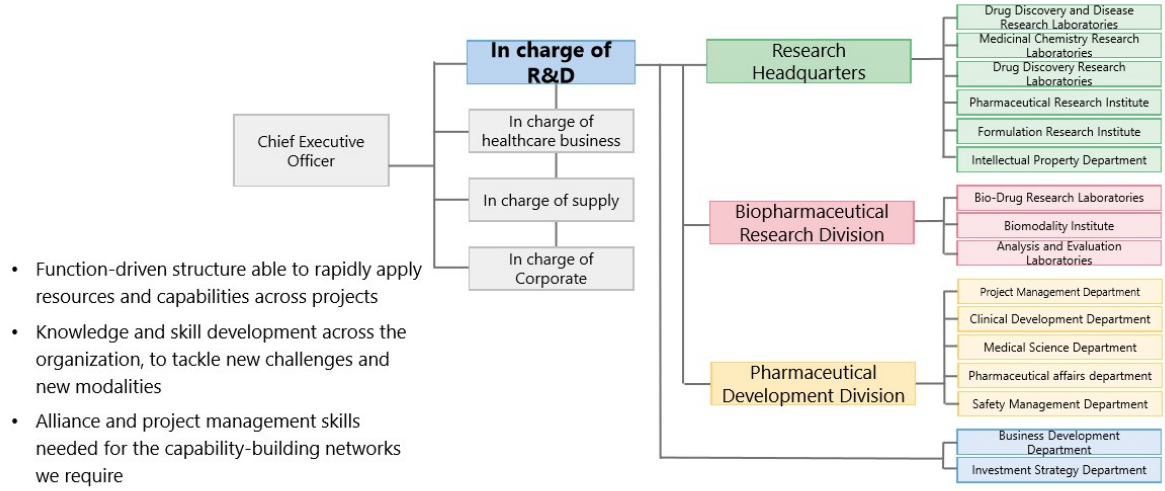
Next, let's look at the modalities.

We have a very long history of small molecules. Later, the business was expanded to include peptides and other products. There is now a vaccine available. However, these platforms alone are not enough. This is not enough to accomplish medical needs. Therefore, a new platform is needed. Not only mRNA, but also nucleic acids and other such things.

Also, new drug delivery techniques, digital approaches, as well as antibodies, are still new areas for SHIONOGI. We would like to utilize these various capabilities both internally and through the use of external networks.

Approach to Realizing R&D Strategy - Organizational reform -

New R&D system (from July 2022)



- Function-driven structure able to rapidly apply resources and capabilities across projects
- Knowledge and skill development across the organization, to tackle new challenges and new modalities
- Alliance and project management skills needed for the capability-building networks we require

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Here is the organization. We are trying to embody these ideas.

We have a biopharmaceutical drug discovery and new modality platform, as well as a pharmaceutical development division. Business development, and the investment strategy department, for example, investing in ventures and creating new entities, all under the same organization, now under R&D.

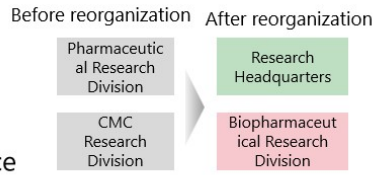
In this way, we would like to build a strong network of external contacts and networks, and then do all of these things: acquisitions, collaborations, and then innovation networks, and so on. It means that everything is under the jurisdiction of R&D.

So, our job is to utilize all the tools to achieve these unmet medical needs.

Approach to realizing R&D strategy - Organizational reform -

Outline of reorganization

- **Establishment of management**
  - Focus on decision-making quality and speed
  - Responsive resource deployment and prioritization
  - Seamless collaborations across divisions and functions
- **Pharmaceutical Research Division and CMC Research Division integrated for the two primary modalities, low-molecular-weight drugs and biopharmaceuticals (including vaccines)**
  - Integrating all steps from exploratory research to product and process development Building functional expertise and experience



- **Established the Investment Strategy Department and incorporated the Business Development Department, both within R&D**
  - All the capabilities to establish and nurture the technological development required to realize these healthcare solutions are under one organization

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In doing so, we will make decisions with quality and speed. Regarding decision-making, we would like to collaborate seamlessly, not only on a disease-by-disease basis, but also across organizations and functions. We will then adopt key needs and key priorities. Everything needed for these is currently in R&D.

Approach to realizing R&D strategy - Strengthening R&D human resources -

Capabilities to be strengthened in the future

Strengthen human resources with capabilities to meet unmet needs

- **World-class knowledge of new modalities including vaccines**
- **Ability to deeply understand unmet needs and focus on using every tool possible to address them**
- **Creation and maintenance of an expanded external network, including academic, SME, VC/investor, and mega-pharma, to rapidly access needed technologies, expertise, and infrastructure**

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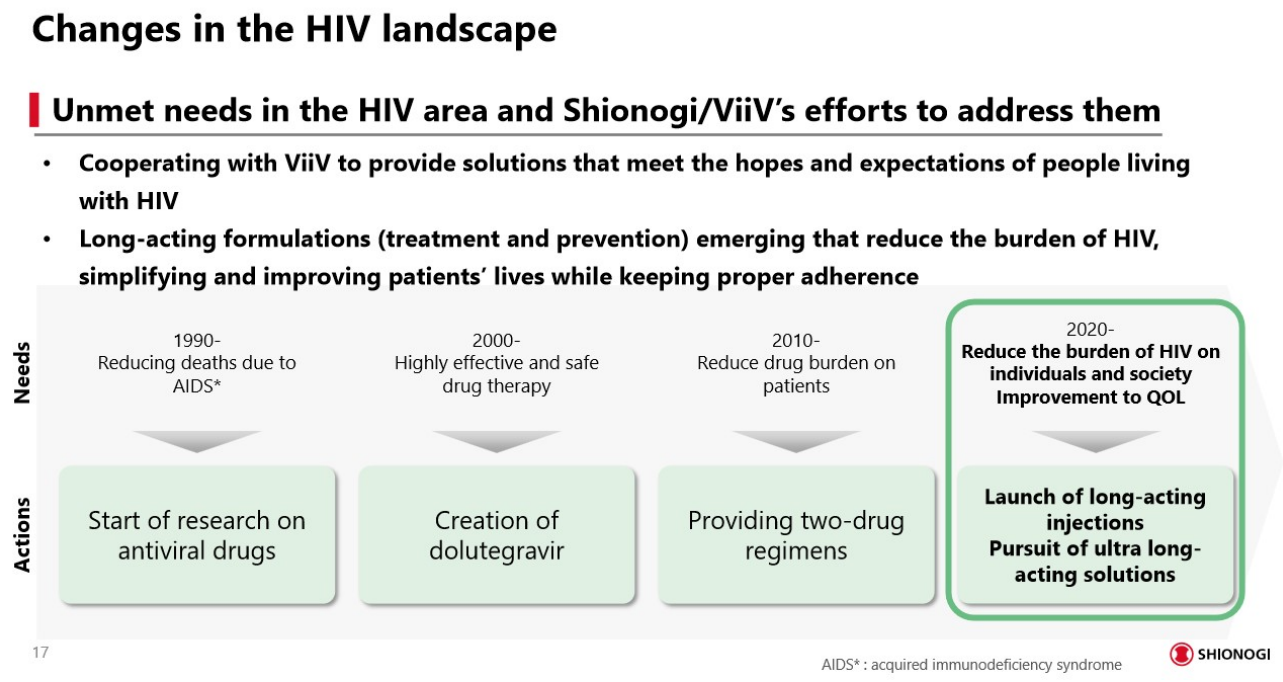
Next, I would like to discuss strengthening human resources.

We need to develop a solid understanding of the capability of internal resources. We need to identify what people are available, what technology is available, and then identify outside firms, new technologies, and work with them. These are to work as a broader SHIONOGI. We are committed to bringing innovation to the world and to meeting the needs of society.



Now I would like to talk about the next two slides, HIV.

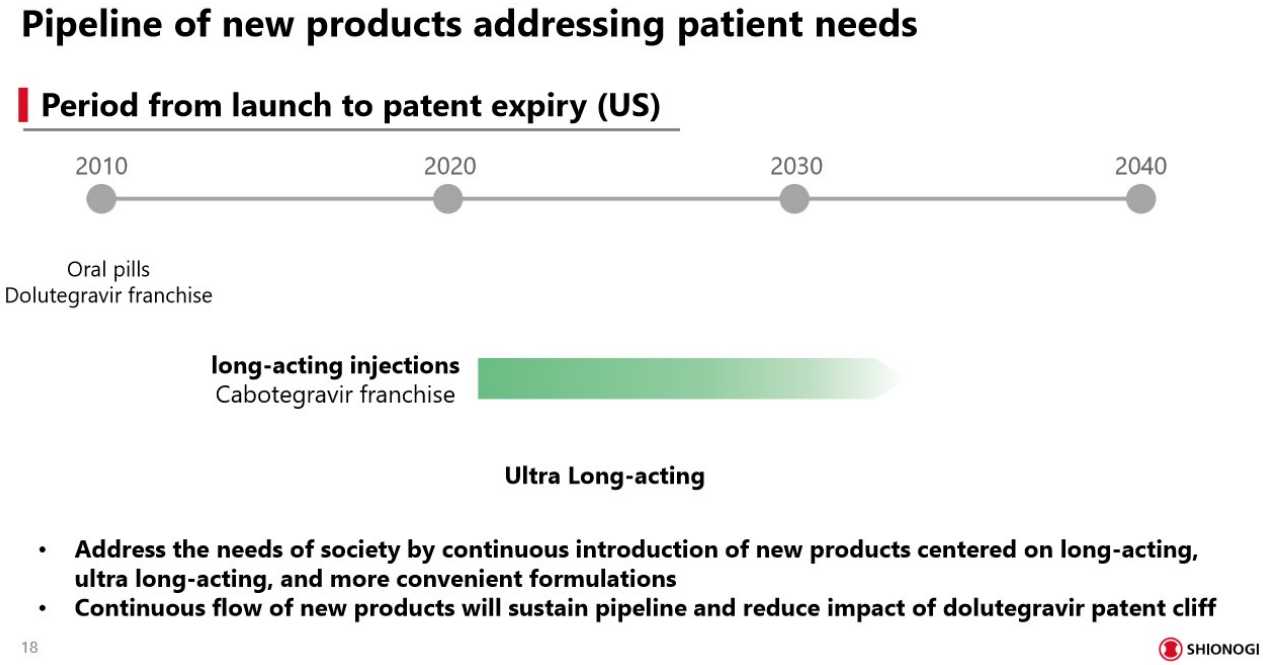
HIV, but as you all know, the area of HIV is seeing a great deal of growth. Therefore, we will continue our research.

Dolutegravir, and then efficacy and safety, which is now the gold standard for oral drugs, so the question is how do we improve this, how do we improve once a day drugs? And the question is how this will be done to welcome the patent cliff. We must consider this.

By working together with ViiV, we are in a situation where we have to remind patients every day that they are HIV, because this alone is not comprehensive enough to meet their needs. There are still risks. There is a risk that they will find out that you have HIV because of family, friends, or because you are taking HIV medications. So, I'm feeling the burden of one treatment per day. But that is not enough.

The introduction of long-acting drugs reduces this burden. If you do your injections in a hospital, your friends and family will not find out. Bringing about this kind of treatment would also be more convenient.

You could go to the hospital every two months, three months, or maybe even longer. Preventive therapy, now once every two months, has shown efficacy. And full coverage against infection can be freed up from the time it takes to drink once a day for prevention, especially for those patients who do. We believe this is a new frontier. We believe this is the beginning of a new era of HIV treatment.



With that, there is a very big opportunity. This is an opportunity for this franchise, an opportunity to grow versus the future.

When we started this, how many patients were interested in bimonthly injections, roughly 15% of the middle and 20% of the patients were interested in that. But then it becomes once every three months, then once every six months, or even once a month, and they give injections at home.

In thinking about this, we have come to understand whether the HIV market will actually favor the long term. And we now know what the long-acting form of HIV sustainability will look like in the future. Thank you very much.

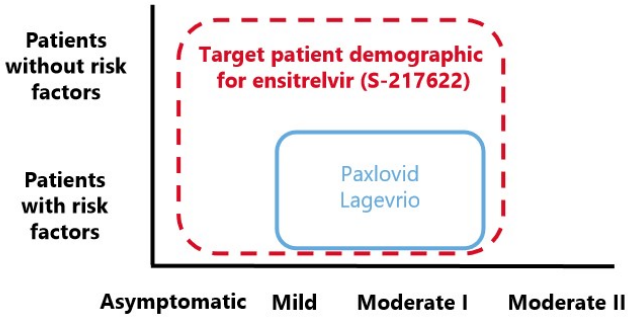
Let us now move on to the COVID-19 topic. Thank you.

Kyokawa: Next, Mr. Uehara will discuss the progress of COVID-19-related projects. Mr. Uehara, please go ahead.

Uehara: Thank you for the introduction. This is Uehara.

I would like to start by talking about COVID-19, two products, therapeutics and vaccines, and then I would like to continue with the discussion of our pipeline in the areas of infectious diseases, pain and neurology, and ultimately, future growth drivers.

Positioning of COVID-19 oral drugs



[Current status of existing oral drugs]

- Clinical trials were conducted in unvaccinated patients in the pre-omicron stages of the epidemic
- Patients without risk factors were not eligible

Severity	Oxygen saturation	Clinical condition
Mild	$SpO_2 \geq 96\%$	No respiratory symptoms or Cough only, no dyspnea
Moderate I	$93\% < SpO_2 < 96\%$	Dyspnea, pneumonia findings
Moderate II	$SpO_2 \leq 93\%$	Oxygen needed

COVID-19 Medical Treatment Guidelines Version 8.0 P.32 modified

- **Phase 2/3 trial of ensitrelvir was conducted during the Omicron stage of the epidemic and mainly in vaccinated patients (approximately 90%)**
- **Ensitrelvir studies cover a wide range of patients with and without risk factors**

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Now, please take a look at the slides. First, let me talk about therapeutic agents and oral agents.

S-217622, which is ensitrelvir, has already been approved as an oral drug for patients with risk factors, based on data from various clinical trials for the two prior oral drugs, PAXLOVID and LAGEVRIO.

However, in the real world, especially in the case of our products, the majority of patients are vaccinated, so there are many patients who truly need a COVID-19 therapeutic, whether they are vaccinated or not, and whether they have risk factors or not. In order to create and deliver a product that can be taken by as diverse people as possible, we are conducting a seamless single test for the second and third tiers for the segment that is circled by this red dotted line.

Ensitrelvir: Antiviral effect against mutant strains*

In vitro antiviral evaluation using VeroE6T cells

virus strain	Ancestor	alpha strain	beta strain	gamma strain	delta strain	omicron strain					
						BA.1	BA.1.1	BA.2	BA.2.75	BA.4	BA.5
EC_{50} (μM)	0.37	0.46	0.40	0.50	0.41	0.29	0.36	0.52	0.30	0.22	0.40

- **Ensitrelvir shows antiviral efficacy against a wide range of strains, including past prevalent strains and recent Omicron mutant strains (BA.4, BA.5, BA.2.75), whereas existing neutralizing antibody drugs have been reported to have reduced efficacy against Omicron mutant strains**.**
- **Ensitrelvir shows antiviral efficacy against existing drug-resistant viruses (no cross-resistance)**

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* Nakashima et al OPTIONS-XI P-205 Sep 2022 ** Efficacy of Antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2 | NEJM

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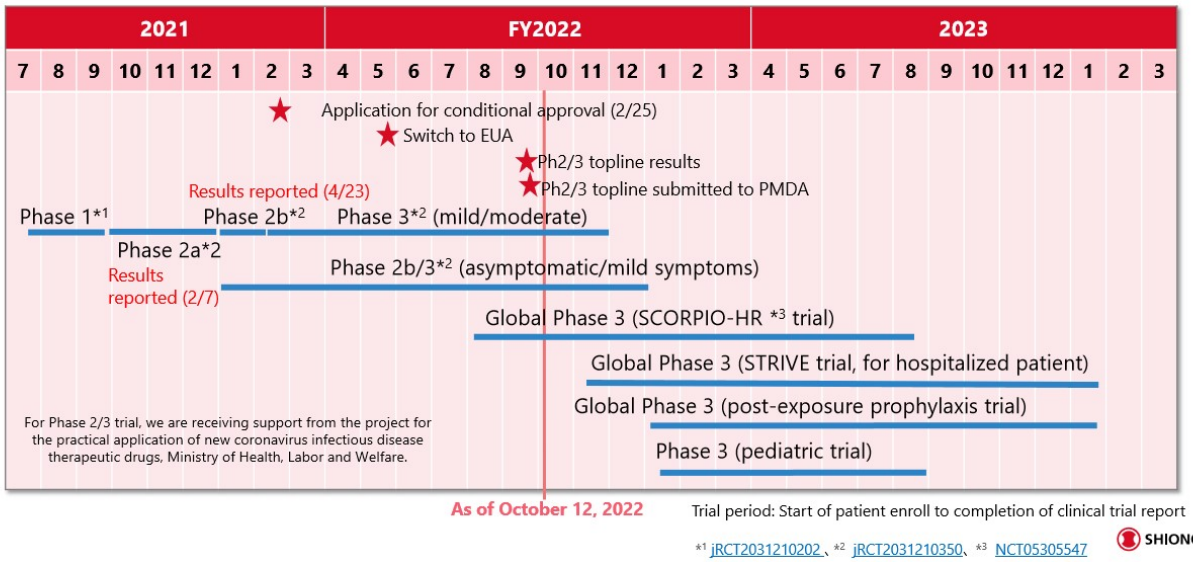
Under such circumstances, the antiviral effect is naturally very important. To achieve the antiviral effect that is effective against patients who are currently infected with the disease. From left to right, the original virus strain, then Alpha, Beta, Gamma, and Delta. These strains gradually mutated, and now the Omicron strain is the mainstream epidemic strain.

As shown in the table, the EC50 value is 0.3 to 0.4, and you can see that the values do not change significantly from left to right. Various therapeutics, especially neutralizing antibody drugs that target spike proteins on the cell surface, are highly effective but are ineffective against strains that repeatedly mutate. In contrast, our drug targets an enzyme in cells called 3CL protease, which has a wide range of activity, and is expected to be effective against viruses resistant to existing drugs.

Ensitrelvir: Progress summary



Here is the history of our drug development to date, and what kind of development we will be pursuing in the future.

First, we have initiated the Phase 1 trial, then Phase 1 and Phase 2, so that we have one seamless trial, the Phase 2/3 trial, for FY2021 to FY22.

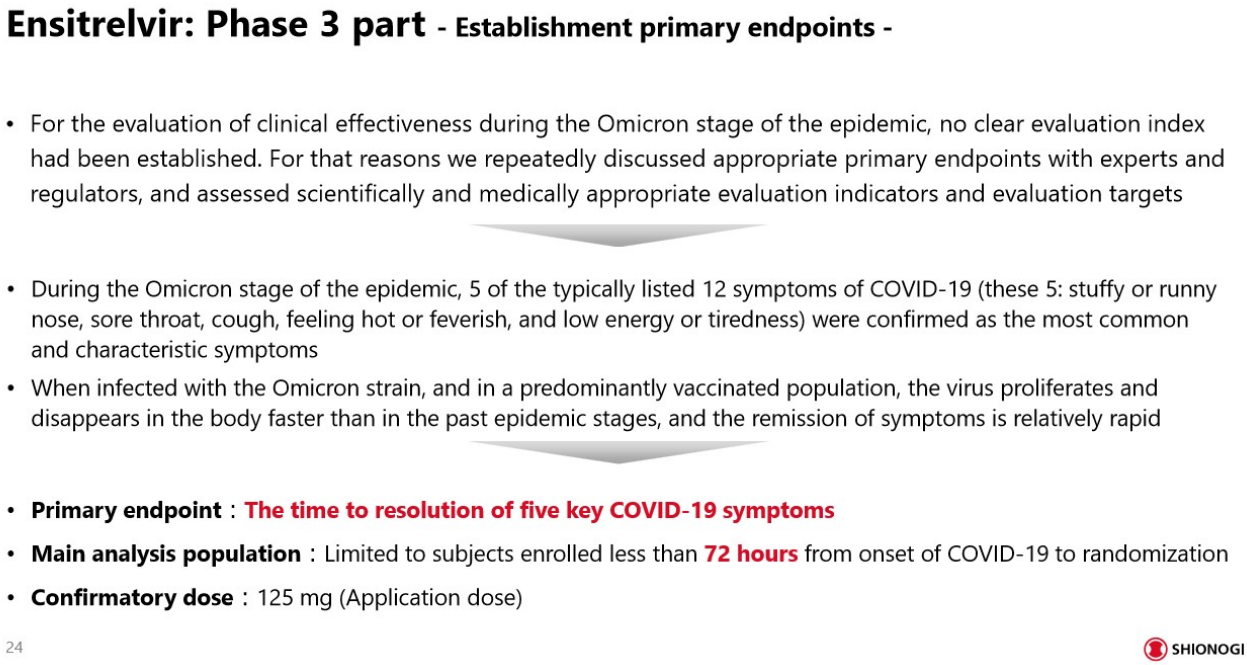
As you are well aware, based on the results of the Phase 2a and Phase 2b part, which are for symptomatic patients, we have switched to a new system of conditional and urgent applications for approval for consideration. Finally, the subcommittee and the subcommittee will hold a joint meeting to discuss the issue. At this time, we are continuing to discuss the issue in the form of a continuing deliberation.

Under these circumstances, the results of the Phase 3, and Phase 3 are now available. They are marked with an asterisk. I have obtained the topline report of the Phase 3 of the Phase 3II in September and have presented the results to PMDA.

Based on these results, we are now in the process of discussing the possibility of continuing the discussion based on the results of the third phase. Today, I would like to present some of the results of this Phase 3.

Also, the Phase 2b/3 on the bottom row. This one is a study with endpoints in the form of reduced incidence in patients who are asymptomatic, mainly asymptomatic, or only very mildly symptomatic. We are continuing to evaluate this project and will report back to you as soon as we get the results.

In the last part of my presentation, I will also give a brief overview of some of the trials, including the critical care trials, as well as the HR, global trials for high-risk patients, as well as prevention trials, and trials for pediatric patients.



Here is a summary of the primary endpoints of the Phase 2.

As I mentioned earlier, we held joint meetings with the pharmaceutical and food hygiene assessment group, subcommittee, and working groups. The Omicron strain was the main topic and accounted for the majority of vaccinations. Given that situation, we repeatedly discussed possible approaches to evaluate oral anti-coronavirus drugs, especially with a focus on scientifically and medically appropriate evaluation endpoints. I'm sure you are already aware of this.

Based on these discussions, and after further discussions with medical experts, relevant government bodies and agencies, as well as regulatory authorities in Japan and the US, we have summarized our final evaluation method for Omicron stock as follows.

The primary endpoints are the time to complete the resolution of the five main initial symptoms of nasal, throat, cough, fever, and fatigue, and two systemic symptoms, which are the most common symptoms in patients infected with Omicron. The primary endpoint was the time required for the complete disappearance of these five symptoms.

Then, with the Omicron strain, the virus gradually and progressively multiplies at a very rapid rate, and also disappears from the body at a rapid rate, and many patients recover from their symptoms relatively quickly. However, we have also seen some characteristics, such as gradual worsening within 72 hours in some patients. From this perspective, we conducted the primary evaluation on patients who had been on the drug for less than 72 hours in order to confirm the drug's efficacy relatively quickly.

In addition, we have continued to evaluate two capacities, low capacity and high capacity, since Phase 1a. As we have already confirmed that the maximum antiviral effect can be obtained at a low dose, as apparent from our low-dose application at the Phase 2b stage, we have set the dose of 125 mg as the verification dose.

Ensitrelvir: Phase 3 part - Summary patient background for registered cases -

Background information in the ITT* population

		125 mg N = 603	250 mg N = 595	Placebo N=600
Sex	Male	318	323	311
	Female	285	272	289
Mean of age		35.9	35.9	35.3
Vaccination of SARS-Cov-2		562 (93.2%)	551 (92.6%)	553 (92.2%)
Time from onset to randomization	< 72 hours	347	340	343
	≧ 72 hours	256	255	257

* Intention-to-treat (ITT) : All subjects who were randomly assigned to the trial intervention and had a SARS-Cov-2 infection based on RT-PCR. 1,798 subjects excluding 23 subjects that were PCR negative at baseline from 1,821 subjects

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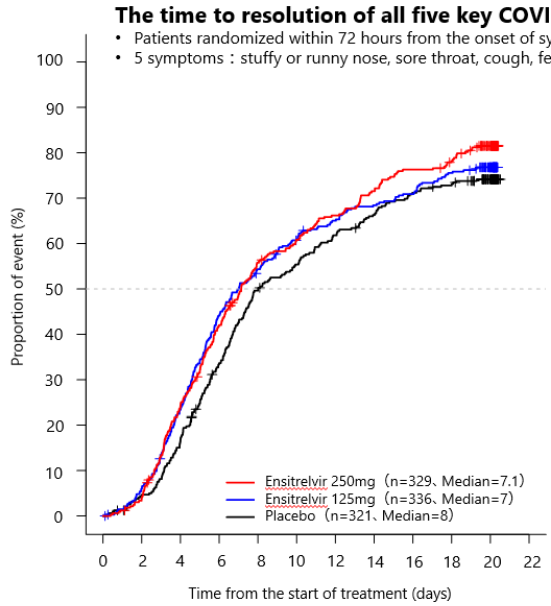
I would like to discuss the main patient backgrounds of the patients enrolled in the Phase 3. A total of more than 1,800 patients, approximately 600 in each group, were enrolled in the Phase 3 of the study.

As you can see, the average age for each age group was between 35 and 36 years, so the study was mainly conducted on fairly young adults, and patients from 12 years and older to 72 years old were enrolled in the study.

Below that, in terms of the number of people who were administered vaccines, the vaccination rate is 93% to 92%, and almost all patients have already been vaccinated. And as a feature of Phase 3, we have already evaluated the efficacy of the treatment in immunized patients in such a way that boosting is also being done in many of them.

The time from the onset of illness to the time of allocation and administration of medication is 120 hours from the onset of illness, or within five days. The overall evaluation week is within five days, but the primary evaluation is for patients within three days or less than 72 hours, or approximately 60% of eligible patients.

Ensitrelvir: Phase 3 part - The time to resolution of all five key COVID-19 symptoms (Primary endpoint) -



Target of primary endpoint

		125 mg N = 347	250 mg N = 340	Placebo N = 343
Median [95% CI]		167.9 [145.0, 197.6]	171.2 [150.8, 190.3]	192.2 [174.5, 238.3]
Difference in median vs. placebo [95% CI]		**-24.3** [-78.7, 11.7]	-21.0 [-73.8, 7.2]	---
Stratified Peto-Prentice's generalized Wilcoxon test vs. placebo [a]	P value	**0.0407**	0.0203	---

CI = Confidence Interval
[a] Adjusted by the following stratum (SARS-CoV-2 vaccination history [Yes or No])

Significant reduction in the time to resolution of 5 symptoms of COVID-19 characteristic of Omicron strain compared to placebo (primary endpoint achieved)

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Here are the results of the main evaluation.

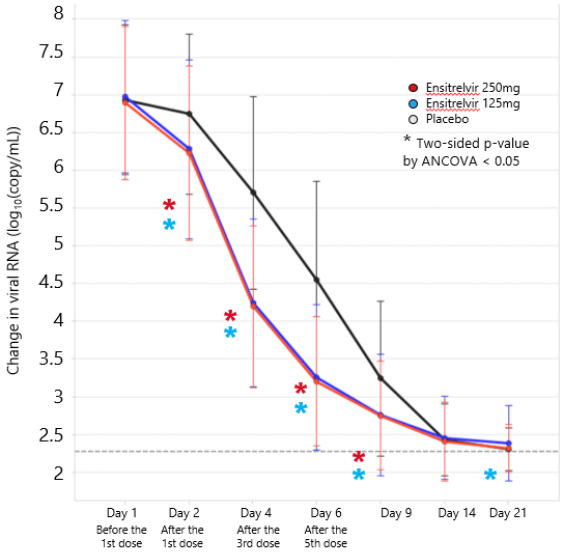
We have already disclosed the results in our press release, but we would like to discuss the results once again, along with Kaplan-Meier here.

If you check the Kaplan-Meier on the left, black is a placebo, and blue is a low dose, which is the applied dose, and red is the high double dose. As you can see, all symptoms recovered by the eighth day, which is a median of placebo.

You can see that the red and blue lines are closer together, compared to their distance from the black line. The difference among median values is about 24 hours, or about one day earlier; this means a reduction of one day in the time needed to eliminate all five symptoms compared to a placebo.

The primary efficacy endpoint was 125 mg, with a p-value of 0.04, which is a statistically significant reduction in the duration of the disease compared to the placebo.

Ensitrelvir: Phase 3 part - Change in viral RNA amount (Key secondary endpoint) -



【Population within 72 hours from the onset of symptoms】
Changes in viral RNA levels on day 4 of administration (after 3 doses)

		Target of key secondary endpoint 125 mg N = 347	250 mg N = 340	Placebo N = 343
Mean (SD)		-2.737 (1.085)	-2.690 (0.974)	-1.235 (1.528)
ANCOVA vs. placebo [a]	LS mean (SE)	-2.48 (0.08)	-2.49 (0.08)	-1.01 (0.08)
	Difference in LS mean (SE) [95% CI]	**-1.47 (0.08)** [-1.63, -1.31]	-1.48 (0.08) [-1.64, -1.32]	---
	P value	**<0.0001**	<0.0001	---

UNIT: log_{10} copies/mL
ANCOVA = Analysis of Covariance; SD = Standard Deviation; SE = Standard Error; LS = Least Squares; CI = Confidence Interval
Lower limit of quantification of viral RNA is 2.08 log_{10} copies/mL.
If viral RNA is negative and less than the lower limit of quantification, the viral RNA was imputed 2.27 and 2.08 log_{10} copies/mL, respectively.
[a] Covariate: SARS-CoV-2 viral RNA at baseline, SARS-CoV-2 vaccination history [Yes or No]

Ensitrelvir (125mg group) reduced viral RNA level to 1/300 compared to before administration on day 4 of administration (after the 3rd dose) (placebo decreased to 1/10)

Significantly reduced viral RNA levels on day 4 of administration (after 3 doses), confirming superior antiviral effects

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As the key secondary endpoint, we measured the antiviral effect, specifically the amount of viral RNA and viral genome in the nasal swab fluid, which was quantitatively measured by the PCR method.

The graph is shown on the left. You can see that both low and high dose show superior antiviral effects.

As you can see, we have set this day 4 point as the pre-specified key secondary endpoint, and as you can see from the two-sided p-value, it is 0.0001, which is a statistically significant difference.

The difference between low dose and the placebo is a reduction of 1.47 logs. To put this in plain language, the amount of virus in the actual drug group was reduced to 1/300 of that before the drug was administered on the day after 3 doses.

In contrast, the body's immune system will gradually and progressively reduce the virus without taking placebos. On placebo, it drops to 1 log, or one-tenth of a log. So, you can see that the effect is to lower the amount of virus by one-thirtieth.

This is the day 4 data, after 3rd dose of administration and the next day. As you can see, the results of day 2, the day after administration, and day 6, the day after 5th doses, all showed statistically significant differences in antiviral efficacy.

Ensitrelvir: Phase 3 part summary

Efficacy

- Population within 72 hours from the onset of symptoms
  - ➢ The median time to resolution of all five COVID-19 symptoms was significantly reduced in those treated with ensitrelvir (125mg group) . Achieved the primary endpoint in the Phase 3 part
    - ✓ The time to resolution of the 12 or 14 COVID-19 symptoms also showed a trend towards shortening for the 12 symptoms and a significant shortening for the 14 symptoms
    - ✓ Ensitrelvir also showed a significant reduction in viral RNA on day 4 (following the third dose) relative to placebo (greater than 1.4 log10 copies/mL vs. placebo change from baseline on day 4)
- Population within 120 hours from the onset of symptoms
  - ➢ Time to resolution of 5, 12 or 14 symptoms of COVID-19 showed a numerical reduction in the 125 mg group compared with placebo (all with p-values greater than 0.05)

Safety

- There were no serious adverse events or deaths in this trial.
- In the ensitrelvir 125mg group, the most common treatment-related adverse events were decreased high-density lipoprotein and increased blood triglycerides, as observed in previous trials

SHIONOGI

This is a summary of the results of the Phase 3.

First, as for efficacy, the time to the disappearance of the five symptoms was significantly shortened compared to the placebo. In addition, we have recorded all 12 symptoms, 12 including systemic symptoms, and 14 including taste and smell disorder.

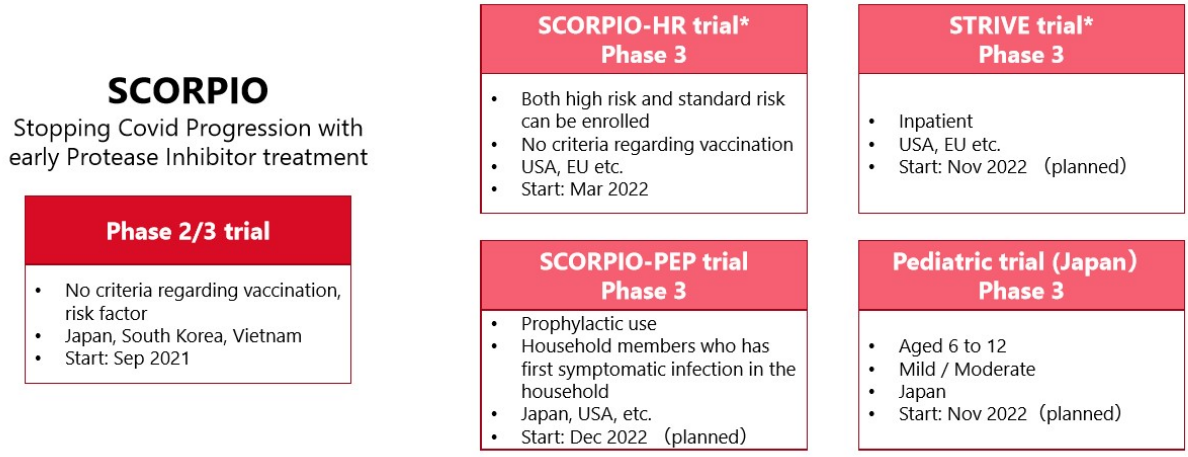
The results for the five primary symptoms are shown here, but the results for the 12 or 14 primary symptoms also showed a trend toward efficacy and a reduction in the duration of illness, or a reduction in the duration of illness, indicating a certain level of treatment efficacy regardless of the type of symptoms. Furthermore, I have just told you about the antiviral effect.

However, in the overall population within 120 hours of the onset of illness, there was a numerical trend toward the shortening of illness, and although shortening was observed, the p-value was 0.05 or greater in all cases.

Regarding safety, there have been no reports of serious side effects or deaths, and the drug has been confirmed to be well tolerated and safe, as in the Phase 2a and Phase 2b trials.

As for the main side effects, it was confirmed in the Phase 2 that a decrease in HDL cholesterol or an increase in blood triglycerides transiently occurred in the high frequency of observed side effects, and that the parameters returned to normal promptly after the medication was stopped without subjective symptoms. We interpret all of these as changes that are not problematic in terms of tolerability.

Ensitrelvir: Further clinical trials



Trial start：IND * NIH sponsored trial

SHIONOGI

Next, I'd like to talk about our forecast.

I have just spoken to you about the Phase 3 of the Phase 2/3 trial in the left-hand column. We conduct tests in Japan, South Korea, Vietnam, of Asia.

In contrast, written in the upper left corner on the right, in the form of the SCORPIO-HR trial. Here, the US NIH will fund the entire project and implement it in each country globally. Specifically, we have started a trial in which we plan to enroll patients with no risk factors as well as those with risk factors at approximately a 50-50 ratio. We have already started the trial.

In the right-hand column, we have written STRIVE trial. The NIH has fully funded this one as well, and they also conduct all of the testing themselves. We are now in the final stages of protocol development for a study to determine whether an add-on to existing therapy can be expected to improve the severity of illness and reduce the mortality rate in severely hospitalized patients, based on the antiviral effect of the drug. We are currently in the final stages of the protocol.

Moving on to the lower part of the page. PEP, post-exposure prophylaxis, is a prophylaxis test to prevent the onset of disease in infected family members who live near the infected person and who are taking the medication. We are preparing to launch this winter in Japan, the US etc.

The pediatric trial shown at the bottom right is also being conducted globally, but we would like to promote pediatric development in Japan ahead of other countries. Specifically, we are preparing to implement the program this winter for schoolchildren, patients between 6 and 12 years of age with minor illnesses and those who do not require hospitalization.

Ensitrelvir: The SCORPIO-HR trial design

Trial design	A multicenter, randomized, double-blind, placebo-controlled
Subject	Non-hospitalized participants with COVID-19 (HR: 50%, OwH: 50%)
Primary purpose	To evaluate the efficacy of ensitrelvir against placebo for non-hospitalized COVID-19 patients
Primary endpoint	Time to sustained symptom resolution through Day 29
Secondary endpoint	• Change From Baseline in Quantitative $\log_{10}$ SARS-CoV-2 RNA Levels by PCR at Day 4 • Hospitalization rate due to COVID-19, mortality rate due to all causes
Dosing group	ensitrelvir, placebo
Dosage	Oral administration once daily for 5 days
Target number of patients	1,490 cases

- HR: High-risk subjects (50% of all enrolled subjects)
  - Vaccinated and un-vaccinated
  - Age 65+
  - Age 18-65
  - Obesity (BMI >30)
  - Diabetes, hypertension, cardiovascular disease, chronic lung disease
- OwH: Otherwise-healthy subjects (50% of all enrolled subjects)
  - Vaccinated and un-vaccinated
  - Age 18-64 without high-risk factors

30

SHIONOGI

We will also be presenting each of the trials and some data. The first is the study design of the HR trial.

This is a global version of the Asian study, but the protocol is very similar.

For the primary endpoint, the time to resolution of symptoms, the secondary endpoint is the amount of change in viral RNA, or the rate of hospitalization or mortality. The study will collect approximately 1,500 cases globally and will evaluate the efficacy of the vaccine in high-risk patients and patients without risk factors, regardless of vaccination status.

Ensitrelvir: Pediatric development plan

- To seek approval using the Phase 2/3 trial data in adolescents (12 to <18) in JP/EU/US
- To conduct the clinical trial for 6 to <12 in JP with higher priority than EU&US
- To plan the separated clinical trial in 0 to <12 for Global

Pediatric population	Japan		Global	
	Clinical trial	Formulation	Clinical Trial	Formulation
12 to <18	Phase 2/3 trial (ongoing)	Tablets	Phase 2/3 trial (ongoing)	Tablets
6 to <12	Phase 3 pediatric trial (in preparation)	Tablets (under consideration)	Global Phase 3 pediatric trial (under discussion)	Granules (under consideration)
0 to <6	Global Phase 3 pediatric trial (under discussion)	Granules (under consideration)		

SHIONOGI

Pediatric development plan.

As I mentioned earlier, we have already included adolescents aged 12 years and older in the Phase 3 of the Phase 2/3 trial to incorporate the cases in the trial.

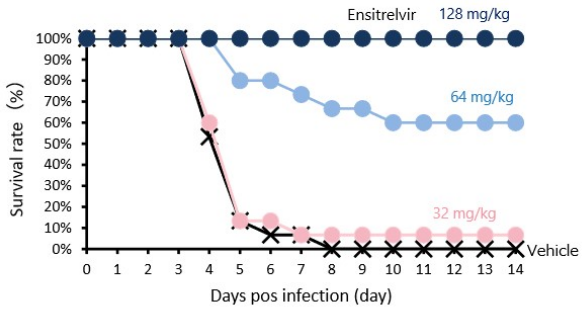
In Japan, we are preparing smaller pills for schoolchildren aged 6 to 12 years old, and we are preparing for a trial to confirm the efficacy and tolerability of this new tablets.

Furthermore, also many patients cannot take pills. We are also preparing granules formulation for patients under 6 years old, and as soon as such granules are ready, we plan to conduct a pediatric indication study using the granule formulation in each of the global countries.

Ensitrelvir: Estimation of prophylactic effectiveness in humans

Prophylactic Effect of ensitrelvir against Lethal Infection with SARS-CoV-2 in Mice

Condition：subcutaneously administrated 24 h post infection



A single subcutaneous dosing of 64 (Plasma concentration is 2.99 μg/mL at the time of infection) or more significantly prolonged survival time compared to vehicle treatment.

Prophylactic administration of ensitrelvir improved survival of SARS-CoV-2 infected mice

Stop virus increasing/spreading, contribute to people getting back to normal life quickly

SHIONOGI

These are the results of non-clinical, animal experiments. This is non-clinical data to verify whether or not the antiviral effect can be used to prevent infection.

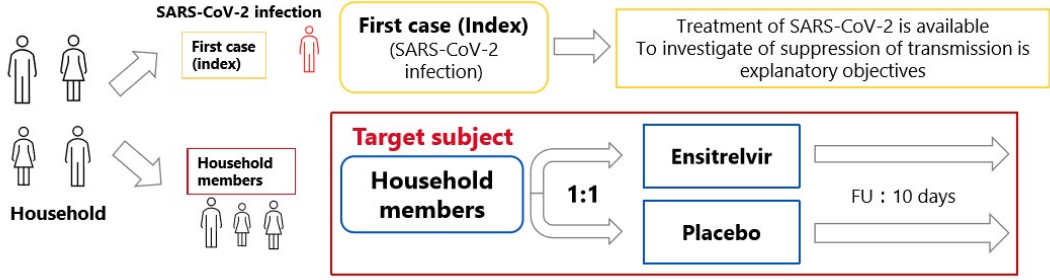
The drug is administered subcutaneously as a single dose to mice. The reason why we used subcutaneous drugs is that we used a form of administration that is sustained in the bloodstream, and we evaluated whether the subcutaneously implanted drug, while at a low concentration, would show a constant concentration in the bloodstream, thereby preventing the virus from taking root, increasing in number, and causing death in the animals. This is a test to evaluate how well it can inhibit the virus from taking root, increasing in number, and causing lethality in the animals.

The upper circle is ensitrelvir, 128 mg/kg administered in the pre-clinical setting, and 100% survival rate has been confirmed. For the lower crosses, we have the placebo and vehicle treatment groups.

Since the dose-dependent lethal inhibition effect has been confirmed, the results of the preclinical animal model suggest that administration of the drug may inhibit the growth of the virus, leading to suppression of disease onset in patients who have been in close contact with the drug.

Ensitrelvir: Post exposure prophylaxis trial (PEP) design

Primary objective	To compare ensitrelvir with placebo in the prevention of symptomatic SARS-CoV-2 infection in participants at Day10 after the first administration
Target population	Participants who are household members of SARS-CoV-2-infected patients
Design	Randomized, double-blind, multicenter, parallel-group, placebo controlled
Sample size／Location	2,040 participants (2 arms) Japan, USA, other several countries



Target 2Q FY2023 for completion of enrollment, trial preparation on-going

SHIONOGI

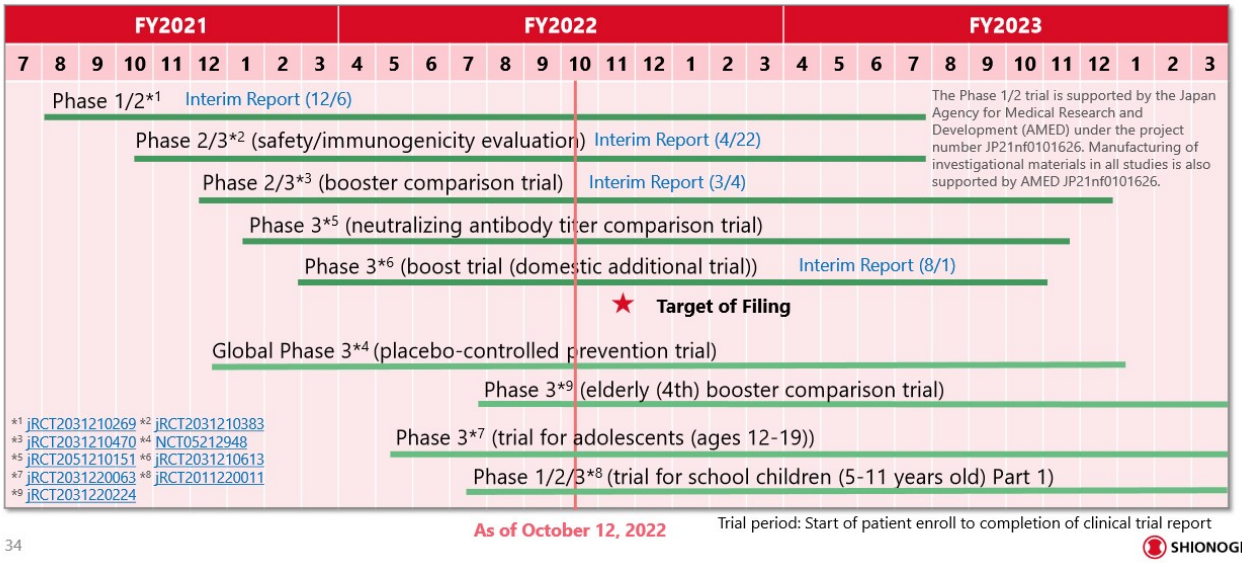
The next step is to design a clinical trial.

The line art of people on the left represents a family who lives under one roof. For those patients who were infected for the first time, there are a variety of medications available, and they should take them. The family members living together are the subject of this project. We are planning to evaluate the efficacy of this drug against a placebo in preventing the onset of disease in various countries around the world by having parents and family members who were brought to the hospital together take a placebo or ensitrelvir.

This is a very challenging test. However, there are high expectations for its antiviral effect, and therefore, there is a great need for this study. Therefore, we would like to actively conduct clinical trials where there is a need and consider the possibility of utilizing this drug.

This wraps up on oral drugs.

S-268019 (recombinant protein vaccine): Progress summary



In the next segment, I would like to discuss recombinant protein vaccines.

Here is a summary with a list of various trials and their progress.

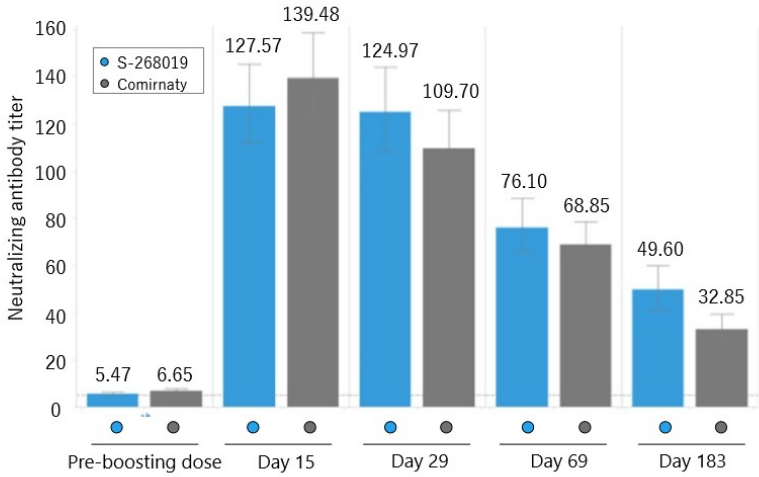
As you are aware, the Phase 1/2 trial was initiated, and today we have the results of the Phase 2/3 trial, which evaluated the safety and immunogenicity of 3,000 participants, as well as the boosting dose, a comparative study of immunogenicity in the third dose, and the neutralizing antibody titer. The results of the main application package studies are now available, such as the comparison of the efficacy parameters of the vaccine with existing vaccines.

I would like to present some of those results today. We are preparing to apply for approval based on these results this year.

In terms of prevention of disease onset, we are conducting a variety of trials, including a placebo-controlled prevention trial in Vietnam, a trial on adolescents, a trial on schoolchildren, and a study on the elderly in Japan. We will consider such data in the form of additional applications as soon as the results are available.

S-268019: Phase 2/3 booster comparison trial
- Neutralizing antibody titer after vaccination -

Purpose	Verification of non-inferiority of immunogenicity to intramuscular injection of S-268019 when boosted with Comirnaty
Subjects	Adults aged 20 years or older who have received two doses of Comirnaty intramuscular injection 6 months earlier or longer
Dosing Regimen	1 booster dose of S-268019 or Comirnaty Intramuscularly
Target Number of Participants	204 cases



Long-lasting neutralizing antibody titer was shown in booster dosing after Comirnaty priming

SHIONOGI

Let me introduce some of the data. First, let's look at the results of the boosting. This is the same copy of the previously introduced report.

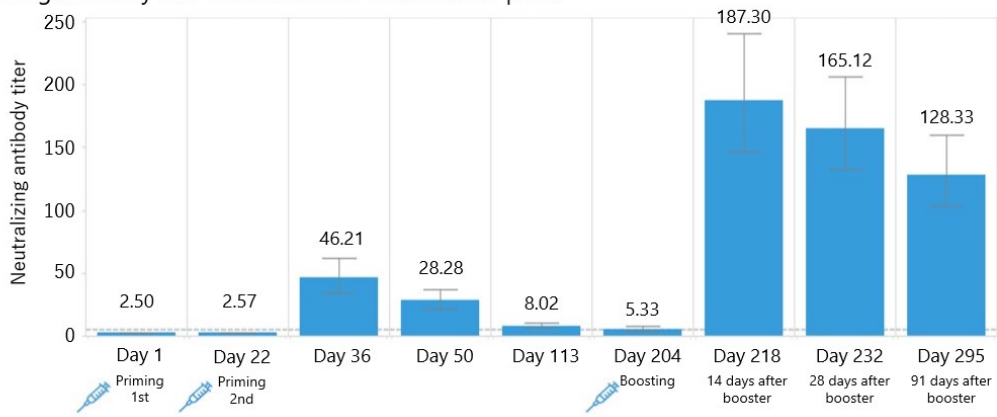
The study evaluated how neutralizing antibody titers could be induced by the third dose in participants who had received two doses of COMIRNATY intramuscular injection at least six months after the first dose, and in adults 20 years of age and older.

On the left of the bar graph is the baseline of S-268019-arm and COMIRNATY-arm before the additional immunization, represented by blue and gray bars respectively. Both are low and aligned. We administered booster shots for 204 of these participants, each approximately 100 cases. We were able to confirm the induction of neutralizing antibody titer of the vaccine by boosting over time from Day 15, Day 29, Day 69, and Day 183, and also, a notable feature is that the decrease in blue titer seems to have slowed down a little. In addition, a notable feature is that the decrease in blue titers seems to be slowing down a little.

This is not a pre-defined endpoint from a statistical point of view as a direct comparison, but it is data that suggests that, as a characteristic of recombinant protein vaccines, neutralizing antibody titers may be expected to have a profile that lasts for a long time.

S-268019: Phase 1/2 trial
- Neutralizing antibody titer after priming and boosting vaccination -

Trial Outline: Adults aged 20 years and over were vaccinated with S-268019 twice at 3-week intervals as the priming immunization, and then, after 6 months, were vaccinated with one dose of S-268019 as a booster. The neutralizing antibody titer was measured at each time point



Priming and boosting of S-268019 vaccination showed long-lasting and high neutralizing antibody titer

SHIONOGI

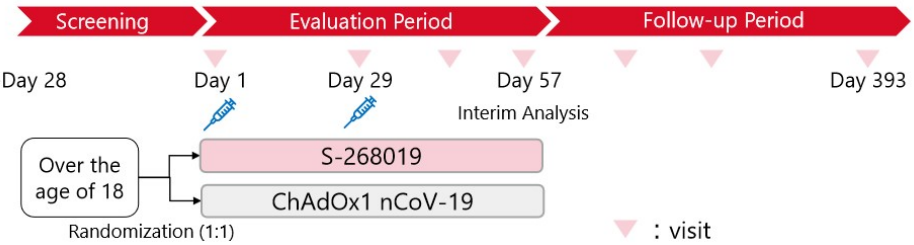
One more page, please go to the next slide. This page summarizes the neutralizing antibody titers for initial and additional immunizations.

First, although the values are very low at the initial immunization stage, after the first dose and then the second dose, a certain level of neutralizing antibody titer induction could be confirmed at Day 36 and Day 50. Then, with additional immunization, the third dose, in the form of 187, is shown here, Day 218, roughly 14 days later, then 28 days later, then 91 days later, and so on, and the changes over time are shown.

We believe that we have been able to indicate a vaccine profile that is satisfactory to a certain degree, as we have been able to confirm high induction and persistence of immunity here as well.

S-268019: Phase 3 neutralizing antibody titer comparison trial
- Trial design -

Purpose	To assess the superiority of S-268019 over ChAdOx1 nCoV-19 intramuscular after 2 intramuscular injections
Primary	GMT of SARS-CoV-2 neutralizing antibody titer at 28 days following the 2nd vaccination
Key Secondary	Seroconversion rate for SARS-CoV-2 neutralizing antibody titer at 28 days following the 2nd vaccination
Trial Design	Active-controlled, parallel-group, observer-blind, multicenter
Subjects	Naïve men and women over the age of 18
Target Number of Participants	1,000 cases (500 cases: ChAdOx1 nCoV-19 intramuscular injection, 500 cases: S-268019)
Dosing	2 doses (Day 1, Day 29)



SHIONOGI

The results were compared with those of existing vaccines in a comparative study of neutralizing antibody titers.

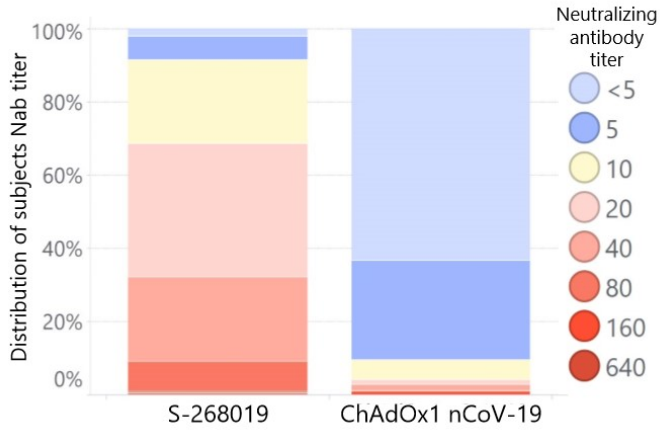
Specifically, we conducted this trial to evaluate how immunogenic the drug is under the conditions of first and second dosing, and to verify its superiority over ChAdOx1 nCoV-19. The study is a comparative study of approximately 1,000 cases. 500 and 500 adult participants, male and female, 18 years of age and older, who have not yet been immunized.

S-268019: Design of neutralizing antibody titer comparison trial
- Neutralizing antibody titer at 28 days following the second vaccination -

Planed Statics	S-268019	ChAdOx1 nCoV-19
Number	497	514
Geometric mean antibody titer (GMT)	19.92	-
95% confidence interval	(18.68, 21.23)	-
P-value*	<0.0001	-

* Trial result of GMT ratio of S-268019 group to ChAdOx1 nCoV-19 group

It was assessed that the neutralizing antibody titer in the S-268019 group was statistically significantly higher than that in the ChAdOx1 nCoV-19 group.



SHIONOGI

This is the result. You can see the percentages of this neutralizing antibody titer in the distribution on the right. As for the neutralizing antibody value 28 days after the second administration, the right side shows the result of ChAdOx1 nCoV-19, and the left side shows S-268019.

The colors are arranged in order from blue to dark, from warm to warm to dark, as you can see that the redder the color is, the higher the induction of neutralizing antibody titers. As you can see, the results of the Phase 3 trial showed that the vaccine administered twice induced very high neutralizing antibody titers, which is superior to existing vaccines. The results of the Phase 3 trial have also been disclosed.

S-268019: Development status

Adult: Filing preparation

- **Preconsultation completed**
  - Nonclinical Part: Pharmacology & Toxicology
- **Preconsultation in Progress**
  - Clinical Part: Ph1/2 trial, Ph2/3 trial, Booster comparison trial
- **CTD preparation**
  - CMC Part, Clinical Part: Neutralizing antibody titer comparison trial, Boost trial (domestic additional trial)

Filing Planned by the end of 2022

Pediatric: Clinical studies on-going

- Started investigation in adolescents and is currently conducting dose finding trial in school children

Action to new variants

- **Confirmed increase of neutralizing antibody titers against various variants in S-268019 clinical trial specimens**
  - Neutralizing antibody titer at booster is similar to neutralizing antibody titer at booster by community
- **Preparation of new variant antigen production**
  - Investigation of the antigen production process based on the genetic information of the Omicron variant is in the final stage
  - Mice booster immunogenicity test confirmed increasing of neutralizing antibody titer against new variants

SHIONOGI

Let me address the final page which summarizes the development progress.

As I mentioned earlier, we are proceeding with various consultations and pre-application consultations for adults now that these application packages are available.

We are currently preparing to complete the submission of all manufacturing data, including the CMC part, and plan to apply by the end of this year. We are also working to explore dose for pediatric patients.

In addition, as for the response to mutant strains, existing mRNA vaccines are bivalent, and vaccines that are also compatible with omicron are in widespread use. Although S-268019 has been designed the antigen for the wild-type strain, we have already confirmed that it has a certain level of neutralizing antibody activity against the Omicron strain.

Nevertheless, we continue to adjust antigens for various mutant strains in order to enhance the immunogenicity of these ever-changing strains. Although at the animal experiment level, we were able to confirm an increase in neutralizing antibody titer against the mutant strain, and we are now in the process of preparing a new antigen.

This is a brief discussion of the two COVID-19-related projects.

Development area

Disease area	Project	Target disease	Stage	Posted page
Infection	**olorofim (F901318)**	Invasive aspergillosis	Global: Phase 3	P.43-45
Psychiatry/Nervous/Pain	**resiniferatoxin**	Pain associated with osteoarthritis	Global: Phase 3	P.46-48
	sivopixant (S-600918)	Intractable/Chronic with unknown cause cough	Global: Phase 2	P.49-50
	zatolmilast (BPN14770)	(1) Fragile X Syndrome (2) Alzheimer's dementia	(1) United States: Phase 2/3 (2) United States: Phase 2, Japan: Phase 2	P.51-53
	zulanolone (S-812217)	depression/depression	Japan: Phase 3	P.54-60
New growth area	**redasemtide (S-005151)**	(1) Dystrophic epidermolysis bullosa (2) Acute cerebral infarction (3) Knee osteoarthritis (4) Chronic liver disease (5) Cardiomyopathy	(1) Japan: Preparing for additional studies (2) Global: Preparing for Phase 3 trial (3)(4) Japan: Physician-initiated clinical trials underway (5) Japan: Preparing for incestigator-initiated clinical trial	P.61-67
	S-309309	Obesity	United States: Phase 1	P.68-71
	S-531011	solid cancer	Japan/United States: Phase 1b/2	P.72-75
	S-770108	idiopathic pulmonary fibrosis	Japan: Phase 1	P.76-78

SHIONOGI

I have one more topic to discuss today regarding infectious diseases, which is olorofim. I would like to briefly discuss the current status of the compound newly licensed from F2G for the treatment of invasive aspergillosis.

I will then talk about the various pipelines regarding psychiatry, neurology, and pain. I will also give you an update on several projects we have for the new and growing areas.

Olorofim [F901318]: Profile

Indication

- Invasive fungal infections with limited treatment options

Product Characteristics

- Oral antifungal drug with novel mechanism of action different from existing drugs

Market

- Number of symptomatic patients: Tens of thousands are estimated as diagnosed invasive aspergillosis patients in Europe and China
- 90-day mortality of azole antifungal therapy is 20-30%* and resistance is widespread

Unmet Needs

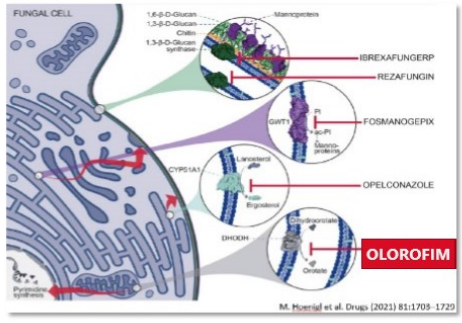
- Oral drug with a new MoA for invasive aspergillosis, where treatment options are limited due to resistance and tolerability issues
- A new treatment option for patients with rare fungal infections

Current Status

- Global Ph2b trial, Global Ph3 trial: On-going

Mechanism of Action

- Fungal dihydroorotate dehydrogenase inhibitor
- Fungicidal activity by inhibiting the pyrimidine synthesis pathway essential for fungal growth



SHIONOGI

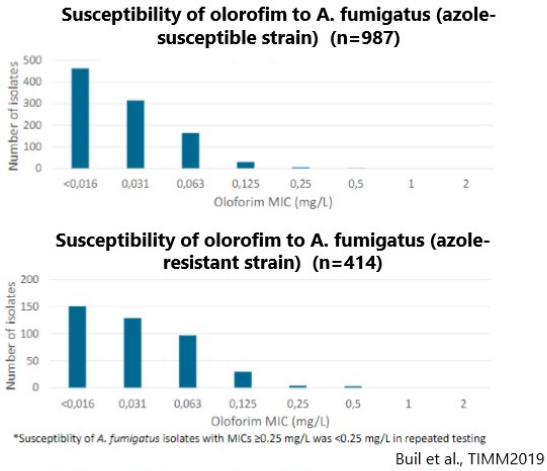
* Lancet. 2016;387:760–769, N Engl J Med 2002; 347:408-415, Clin. Infect. Dis. 2010; 50:1091–1100

Now, let's talk about olorofim.

The lower right-hand corner of this page shows a detailed picture of the mechanism of olorofim. At the end of the arrow is the mitochondria. The enzymes in the mitochondrial membrane, specifically dihydroorotate dehydrogenase and the enzyme that synthesizes orotic acid. By inhibiting the enzyme, it inhibits the orotic acid and pyrimidine synthesis pathways, and thus has fungicidal activity. Specifically, we have confirmed that this enzyme has a specific inhibition of filamentous fungi, so we can expect to see strong antifungal activity against filamentous fungi.

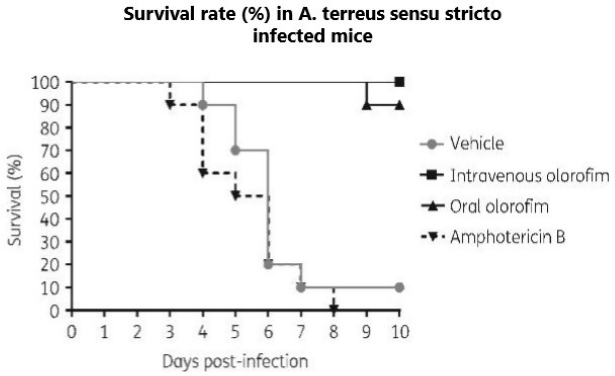
There are various antifungal agents in the market today, but they have a very unique mode of action, and there are still many unmet medical needs, including patients who have efficacy problems with existing antifungal agents, patients who cannot use them due to resistance problems, and patients who cannot use them due to safety concerns. We are currently developing a new treatment option for these patients.

Olorofim: Activity against *Aspergillus*



Buil et al., TIMM2019

High antifungal activity regardless of azole resistance



Lackner et al., https://doi.org/10.1093/jac/dky329

Olorofim showed high survival rate in infected mouse model

SHIONOGI

I would like to briefly introduce you to some non-clinical data.

The left side shows in vitro data. The olorofim-susceptible strain is Aspergillus fumigatus. These graphs show the azole-susceptible strain vs the azole-resistant strain, both in vitro.

As you can see from the graph, both the sensitive and resistant strains maintain very high antifungal activity. It is a new treatment option that maintains activity independent of resistant strains.

The results of in vivo evaluation of sensitivity to amphotericin B are also presented, showing the inhibition of lethality that cannot be improved by placebo or amphotericin B administration, either orally or intravenously.

Non-clinical results show that oral olorofim has shown a mortality improvement of nearly 100%.

Olorofim: Summary of on-going studies

FORMULA-OLS (Phase 2b trial)

Salvage trial in patients without treatment options

- Official Title: Phase IIb Trial of F901318 as Treatment of Invasive Fungal Infections Due to Lomentospora Prolificans, Scedosporium Spp., Aspergillus Spp., and Other Resistant Fungi in Patients Lacking Suitable Alternative Treatment Options (NCT03583164)
- Target Number of Subjects: 200
- Trial Countries: US, Europe, APAC

OASIS (Phase 3 trial)

RCT in invasive Aspergillosis when azole is difficult to use

- Official Title: Phase III, Adjudicator-blinded, Randomised Trial to Evaluate Efficacy and Safety of Treatment With Olorofim Versus Treatment With AmBisome® Followed by Standard of Care in Patients With Invasive Fungal Disease Caused by Aspergillus Species (NCT05101187)
- Target Number of Subjects: 225
- Trial Countries: North & South America, Europe, APAC

Joint development with F2G as a treatment for invasive fungal infections with limited treatment options

SHIONOGI

Based on these preclinical data, we are now moving on to clinical development, starting with the Phase 2b trials, specifically salvage. The study is being conducted globally with a target of 200 patients with various resistant strains, albeit at an open trial, as a last-resort treatment for patients who have no existing treatment options.

The interim data also showed very encouraging results, and we have started the Phase 3 of the trial. We're preparing things for the anticipated accumulating case studies in Japan.

In a global, blinded, multicenter study, the treatment of switching to standard therapy is the standard of care. This is a blinded study to compare the efficacy of olorofim in these patients.

In collaboration with F2G, we are developing the Phase 2b and Phase 3 studies globally to provide new treatment options in Asian countries, including Japan.

Resiniferatoxin: Profile

Indication

- Osteoarthritis of the knee

⇒ Moderate to severe pain associated with knee osteoarthritis in patients who have failed one or more prior therapies

Special characteristics

- An injection that can reduce pain and improve functionality by injecting into the knee joint once every six months on average

Market

- Number of symptomatic people : 25 million (Japan)
- Market size : Over 70 B yen (Japan)

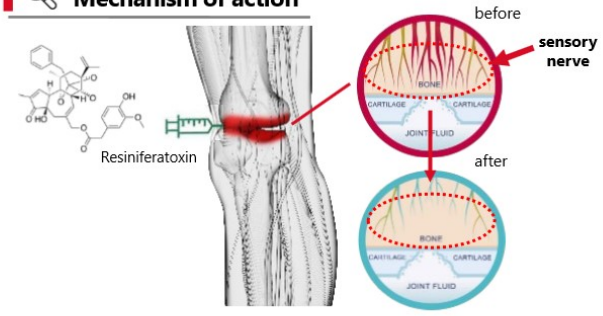
Unmet needs

- Insufficient efficacy or short duration of effect is a problem with existing drugs, and there is a need for drugs that can control pain for a long time
- Drugs with strong analgesic effects are required as adjuvants for exercise therapy

Current status and future plans

- Global Phase 3 trials initiated in US and Europe, preparing for start in Japan later this year

Mechanism of action



1. Resiniferatoxin acts on TRPV1* on sensory nerves projecting into the knee surface
2. Causes strong desensitization and retraction of sensory nerves from the knee (pain is suppressed)

* Transient Receptor Potential Vanilloid 1

SHIONOGI

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Continuing on, here is another new asset.

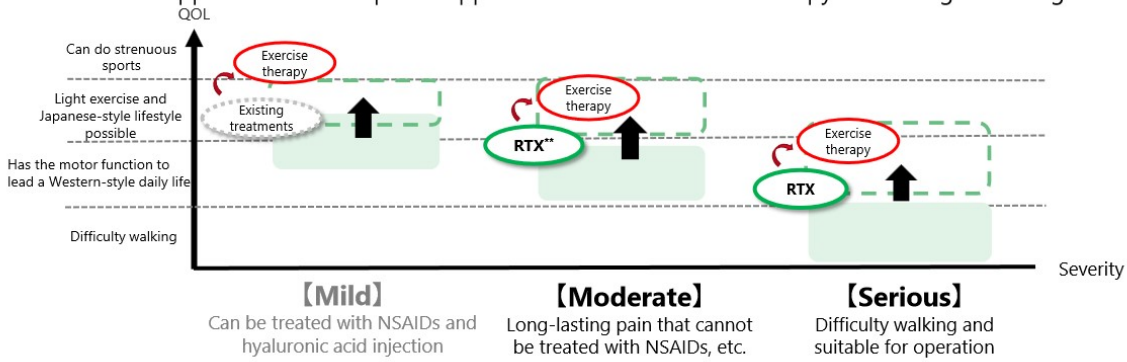
Which has already been released. Resiniferatoxin is a new compound. I will briefly discuss its mode of action and other details.

This is osteoarthritis of the knee. It is a very common chronic disease that afflicts a large number of patients. There are very high unmet medical needs due to pain. Many patients have ongoing pain that existing NSAIDs, or hyaluronic acid, or such things do not remove.

You can see the picture of a syringe being inserted into the knee of such a patient. Administration of resiniferatoxin into the joint cavity. The reason why it works is that it is a compound that desensitizes the sensory nerve TRPV1. So, we desensitize, numb, and take away the pain in a situation where the pain nerves are treated. The data to date indicate that this effect can be sustained over a long period of time with a once-every-six-month administration, and we are developing this therapeutic as a potential new therapeutic agent for the knee.

Resiniferatoxin: Role in therapy

- Providing a new analgesic option for patients who have an inadequate response to existing treatments
- Improving patient QOL* by reducing pain and improving functionality with injection once every 6 months on average
- Pain relief supports other therapeutic approaches such as exercise therapy and strength training



【Mild】 Can be treated with NSAIDs and hyaluronic acid injection

【Moderate】 Long-lasting pain that cannot be treated with NSAIDs, etc.

【Serious】 Difficulty walking and suitable for operation

Contributes to reducing pain, improving functionality and QOL and increasing activity levels in patients with moderate to severe disease

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* Quality of Life ** RTX : Resiniferatoxin

SHIONOGI

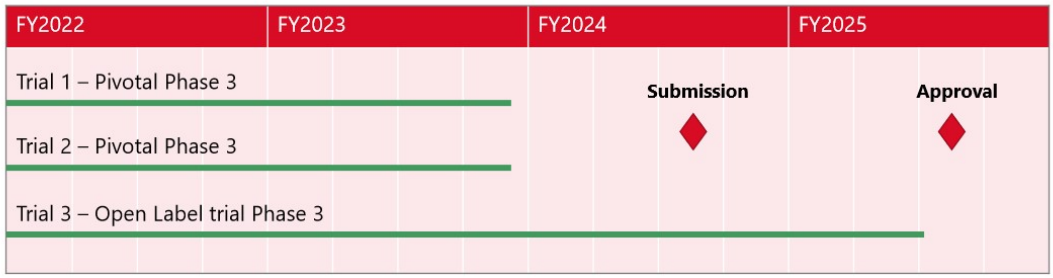
I have put together slides as to the value we can provide.

As I told you, we can deal with mild symptoms can be treated with NSAIDs or hyaluronic acid. We are providing therapeutic agents and painkillers for knee joints in such a way that patients can actually recover by using existing therapies and adding exercise therapy when their quality of life has improved.

In the lower stage, when a patient who has difficulty in walking or sending daily mobility is treated with intra-articular knee resiniferatoxin once every six months, he or she can actually perform light exercise or has daily mobility, and the one-stage condition is improved. We believe that this drug has the potential to provide a new value of treatment by allowing patients to exercise even a little, improving their quality of life, and also improving their physical condition through movement.

Resiniferatoxin: Future development plan

- Aligned with the development of S-005151 for osteoarthritis of the knee, to create a portfolio addressing both pain and cartilage regeneration
- Projected launch in launch in Japan in 2025



Trial period: Start of patient enroll to completion of clinical trial report

Expected to contribute to domestic sales expansion after 2025 and drives top-line growth

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As a drug with such potential, our future development plans include trial 1, trial 2, and trial 3, two double-blind global Phase 3 trial of pivotal, and three open-label extension studies. Based on these data, we are planning to launch the product in Japan in 2025.

Sivopixant [S-600918]: Profile

Indication

- Refractory / unexplained chronic cough (RCC/UCC)

Product property

- Well-tolerated and peripherally acting antitussive

Market

- Chronic cough: 5%-10% of adult population
  RCC/UCC: 20%-40% of patients with chronic cough (estimated)

Unmet medical needs

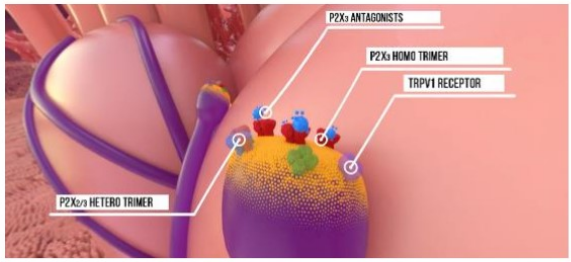
- There is no approved drug for RCC/UCC (other than Japan*)
- Long-lasting use of central antitussives is not recommended due to safety concerns
  → Efficacious and safe drug is needed

Current status and future plans

- Regulatory meetings were held after Phase 2b completion
- In preparation for Phase 3 studies

Mechanism of action

- P2X3 receptor antagonist
  (Purinergic receptor subtype P2X3)



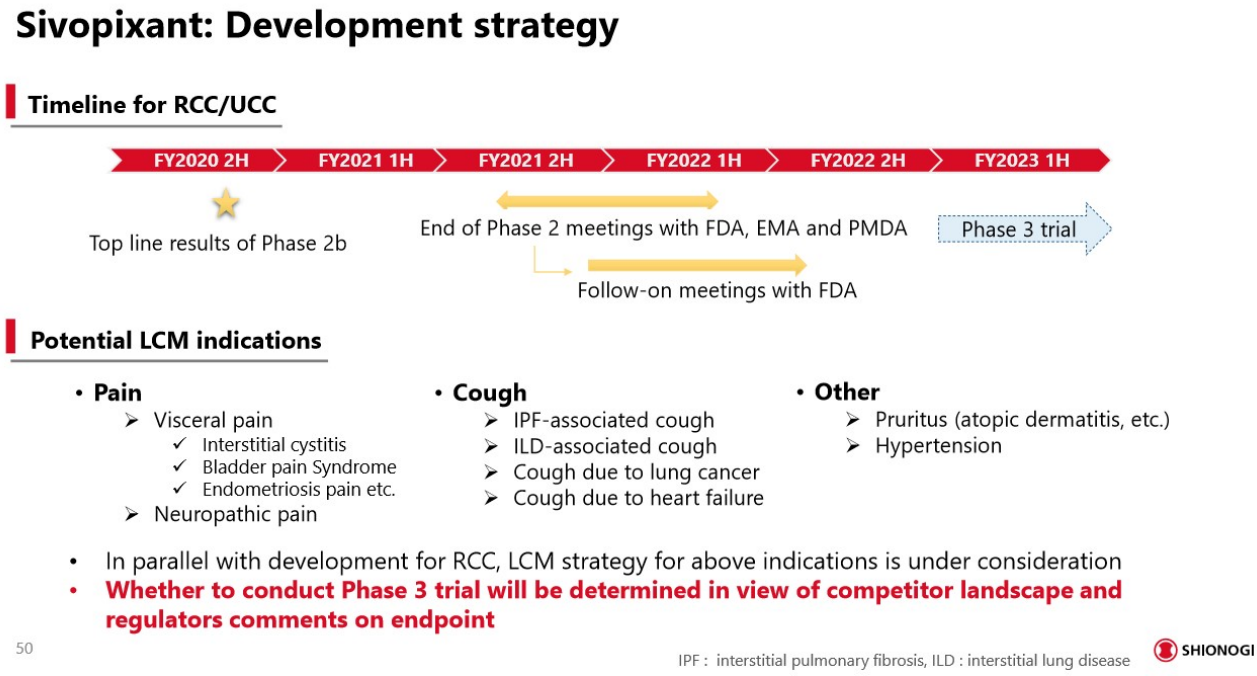
* In 2022, gefapixant was approved in Japan

SHIONOGI

This is S-600918, Sivopixant.

This drug is being developed for the treatment of refractory chronic cough of unknown cause. As you are already well aware, the mechanism of action is antagonism of the P2X3 receptor. P2X3 is an ATP-dependent receptor. The heterotrimer on the left side on figure , and P2X2 and 3 hetero-HETERO are receptors related to taste. Sivopixant has a higher affinity for monotrimer, a single receptor, P2X3, than for P2X2 and 3 hetero.. We are developing this drug as a new treatment option to reduce the risk of taste disorders, stop cough signals, and stop the pain.

Phase 2b trial has been completed, and we are currently conducting interviews with the authorities.



I will briefly discuss the timeline.

In the top row, the timeline for chronic cough, as you know, we have talked about the results of the Phase 2b trial in the last issue. Based on the results of the Phase 2b trial, we are discussing with the global authorities. Specifically, we are in the process of continuing discussions with the FDA, and we would like to make a final decision on the implementation of the Phase 3 trial based on the status of these discussions.

This is the target for chronic cough, but there is also the possibility of expanding this drug to various indications, including pain, cough, itching, hypertension, and various other cough-causing conditions. We are now in a situation where we are trying to determine the potential of this drug in various applications.

Zatolmilast [BPN14770]: Profile

Indication

- Fragile X Syndrome (FXS*1) / Alzheimer's disease (AD*2)

Product Characteristics

- Enhanced cognitive function, especially memory formation
- Well tolerated without notable GI side effects

Market (FXS)

- Prevalence：About 1 in 10,000 have been diagnosed with FXS
- Market Size：$187MM (US, Male, ≥18 years old)

Unmet Needs (FXS)

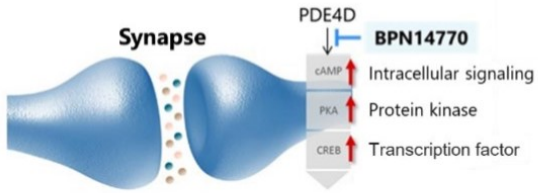
- No approved treatments for FXS
- Treatment for severe behavioral symptoms (e.g., anxiety), cognition and communication disabilities

Current Status and future plans

- FXS: US Phase 2/3 studies ongoing
- AD: Future development plan under consideration

Mechanism of Action

- PDE4D*3 allosteric inhibitor
  (phosphodiesterase subtype that hydrolyzes cAMP*4)



1. Increase the cAMP signaling, and gene expression in neuron, resulting that the neuronal / synaptic function is enhanced
2. Improve the cognitive impairment / behavioral abnormality

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*1 Fragile X Syndrome *2 Alzheimer's disease *3 Phosphodiesterase 4D *4 cyclic adenosine 3,5-monophosphate

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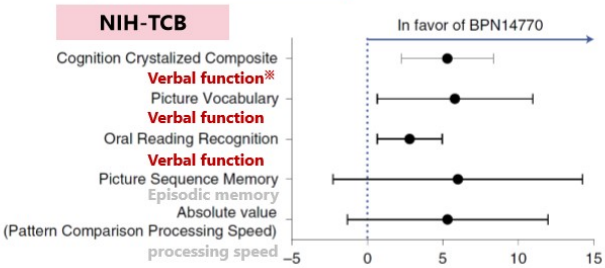
Continuing onto BPN14770.

The zatolmilast mechanism is the PDE4D allosteric inhibitor. zatolmilast is currently being developed for two applications: Fragile X syndrome and Alzheimer's type dementia.

Because the mechanism of action of BPN14770 is to inhibit PDE4D, it actually increases cAMP and protein kinase, transcription factors in the cells, which in turn regulates gene expression related to actual nerve function. We are developing this for Fragile X or Alzheimer's disease, as a new treatment option for patients suffering from cognitive dysfunction.

Zatolmilast: US FXS Phase2 trial (conducted by Tetra)

Target population	Male adult with Fragile X Syndrome (18~45 years old)
Key efficacy endpoint	NIH Toolbox cognitive battery (NIH-TCB, cognitive function)
Trial design	Single site, randomized, double-blind, cross-over (no washout period)
No. of subject	30 subjects
Arms / Treatment period	BPN14770 25 mg BID, Placebo / 12 weeks



At 25mg BID for 12 weeks, significant effect in NIH-TCB* (verbal function) and caregiver VAS (assessment of language and daily function) , BPN14770 has efficacy on verbal function and daily function in FXS patients.**

US Phase 2b/3 studies with primary endpoint if NIH-TCB CCC (verbal function) being conducted (US NDA: ~2024).

Berry-Kravis EM. et al., *Nat Med.* 2021 May;27 (5) : 862-870
※Composite score calculated by Cognitive Crystalized Composite: Oral Reading Recognition、Picture Vocabulary

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* National Institutes of Health Toolbox Cognitive Battery ** Visual Analogue Scale

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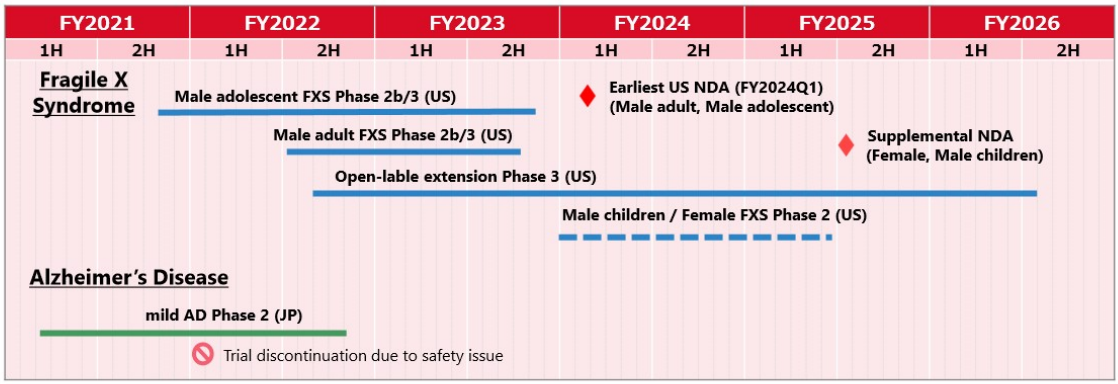
Let's talk about Fragile X.

This was a very promising trial for a genetic disease for which there are limited and no approved drugs.

The Phase 2 trial, conducted by Tetra, was a trial of 30 adult male Fragile X patients between the ages of 18 and 45. The sample size was merely 30 in total. As you can see, the NIH-TCB endpoints for language and other functions showed significant improvement over placebo in cognitive and language functions.

Although we have not shown a significant improvement in the VAS of caregivers, we can see a trend of efficacy in episodic memory and processing speed, and we have confirmed that it can be the only new treatment option based on these data. Based on these data, we are now proceeding with global development in the Phase 2b/3 trial, mainly in the United States.

Zatolmilast: Development schedule



Trial period: Start of patient enroll to completion of clinical study report

Fragile X Syndrome (FXS)

- Conducting the male adolescent FXS Phase 2/3 trial, male adult FXS Phase 2/3 trial for US NDA
- Preparing for Phase 2 studies in male children / female

Alzheimer's Disease (AD)

- Analysis of JP AD Phase 2 trial results for continuation of AD development

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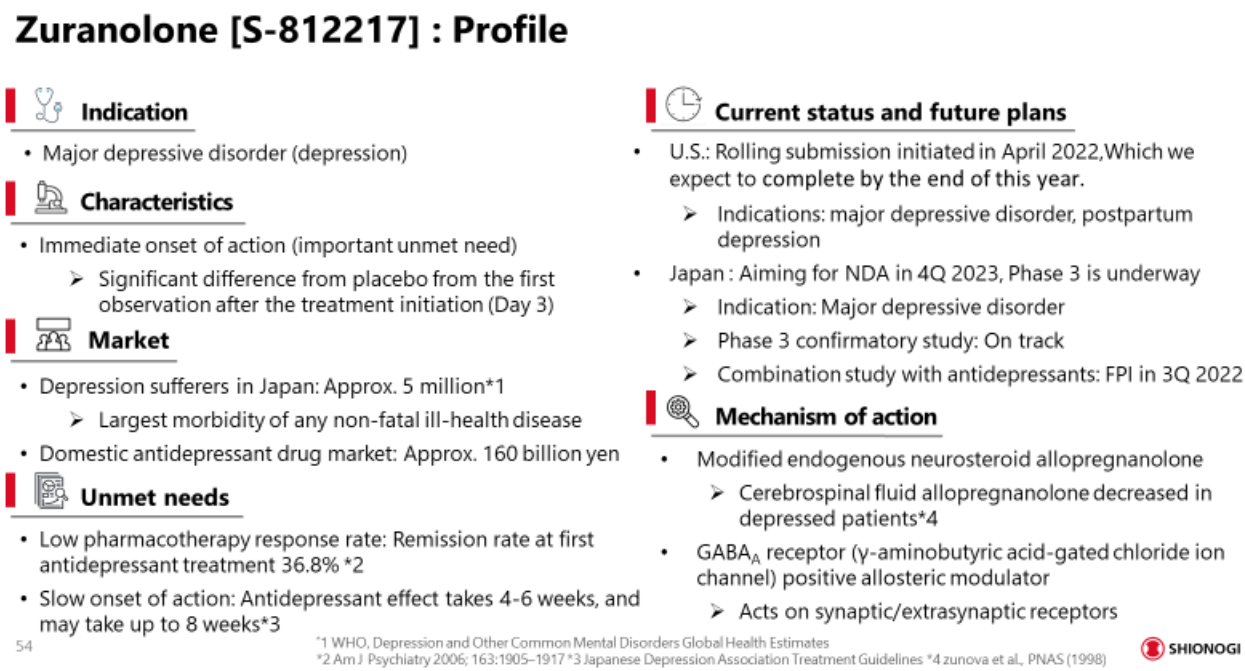
In that timeline, the top row is Fragile X and the bottom row is Alzheimer's.

First, Fragile X, we are now in the process of implementing the Phase 2b/3 trial in the US, as well as the Phase 3II trial for adults. From there we are also planning the Open-label extension Phase 3 trial. Based on these data, the timing for the fastest NDA in the US is FY2024, and we will first apply the NDA to adult and adolescent males. We will continue to obtain data on pediatric and female patients and aim to expand the application of the NDA.

On the other hand, we also conducted a test for mild Alzheimer's disease. The Phase 2 trial was conducted in Japan, but as reported here, the trial was terminated due to safety concerns. We are currently analyzing how to proceed with the development of Alzheimer's disease based on the data.



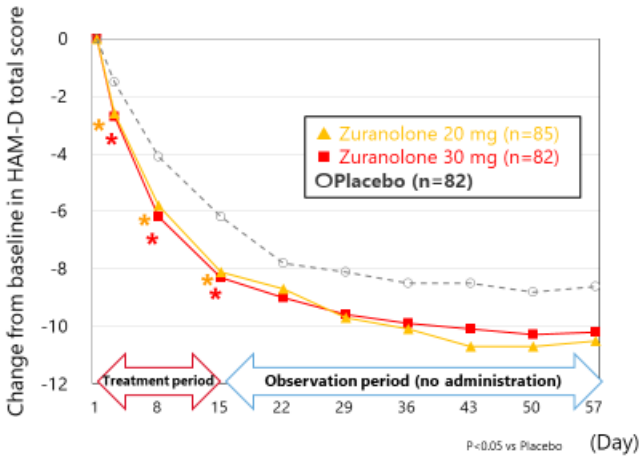
S-812217, zuranolone. This is a drug for depression introduced by Sage.

As you already know, this is an allosteric modulator of the $GABA_A$ receptor. With this mechanism of action, we believe that this drug may have an effect on the treatment of depression that is not seen in existing drugs for depression, and that it may have an extremely rapid effect.

Current status and future plans, we have written in the upper right corner. First, the US development of the major depressive disorder and postpartum depression, for which we will present data later. The plan is to complete the application in the form of these two applications by the end of 2022.

In contrast, domestic development is currently underway or planned for major depressive disorder, either as existing monotherapy or in combination with existing depression. I would like to talk today about this situation.

Zuranolone : Phase 2 study in Japan



Efficacy

- **Both 20 and 30mg achieved primary endpoints**
  - Significant improvement in change from baseline in HAM-D* total score versus placebo at 20mg and 30mg from Day 3 (initial observation) to Day 15 (treatment completion)
  - Response rate** significantly improved over placebo on Days 8 and 15

⇒ Confirm the "immediate onset of action"

  - During the observation period from Day 15 to Day 57, there was no significant difference from the placebo, but a tendency for the treatment effect to persist was shown.

Safety

- **No safety concern**
  - All adverse events were mild or moderate and no new concern was raised

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* HAM-D: Hamilton Depression Rating Scale ** Percentage of cases with ≥50% improvement in HAM-D total score from baseline

SHIONOGI

This data is previously released. These are the evaluation results of the Phase 2 trial of zuranolone in Japan.

The characteristics of this drug include rapid improvement in symptoms even with monotherapy. This is indicated by plotting the HAM-D, the Hamilton Depression Rating Scale, the amount of change from the baseline on a graph. You will see that there is a significant difference on day eight of the first two weeks of drinking, and even earlier, for both the 20 mm and 30 mm doses.

You can see that the improvement in symptoms is immediate, and that the difference between the placebo and the placebo is maintained in parallel after two weeks of oral administration. Based on the results of the Phase 2 trial, we are proceeding with the Phase 3 trial of this drug, including the confirmation of safety and tolerability.

Zuranolone : Characteristics and Development Strategy

Strengths: Immediate onset of action (important unmet need)

- **Achieving efficacy in 2 weeks that required 6 to 8 weeks of treatment with existing antidepressants**
- Early improvement after the treatment initiation indicates a favorable outcome*, and may be of great clinical significance.

Ease of use: 2-week administration only when treatment is needed contributes to convenience

- No need to adjust dosage, potential for effectiveness in as little as 2 weeks, high adherence is expected

Development strategy: Goal to achieve a "leading drug for acute treatment of MDD"**

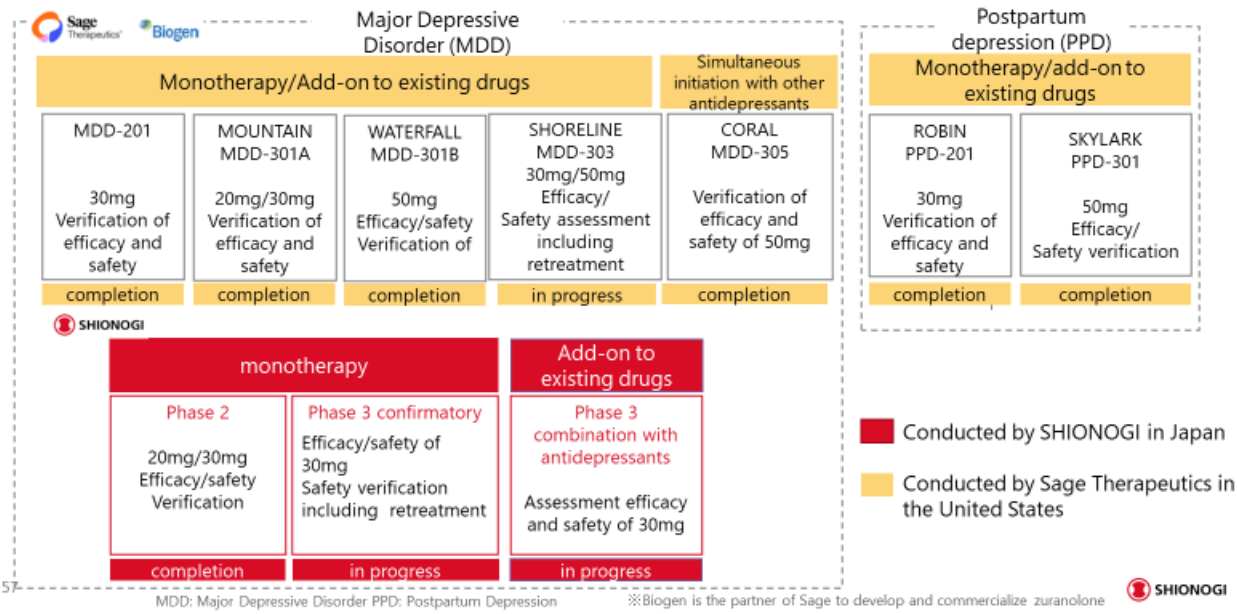
- Treatment concept: Improving depressive symptoms and leading to remission in a short period of time for patients with depression who require therapeutic intervention regardless of initial, relapse, or recurrence
- This drug covers a wide range of antidepressant treatment
  - ➢ Conduct clinical trials to evaluate efficacy and safety under the following conditions
    - ✓ Monotherapy for Naive Depressed Patients
    - ✓ Combined treatment with antidepressants for patients who unresolved episodes of depression by antidepressant monotherapy

*J Clin Psychiatry 2009;70(3):344-353
** Acute phase of depression: From the treatment initiation after diagnosis of depression to remission (disappearance of depressive symptoms)
(Source: Depression Treatment Guidelines, Key Points of Depression Treatment-10)

56 SHIONOGI

The characteristics of this drug are Immediate effect. Existing drugs require 6 or 8 weeks of treatment, but it can be achieved in 2 weeks, and the effects can be seen quickly.. And with no need for dose adjustment, high adherence may be expected. We are also developing this new treatment option for acute care.

Zuranolone : Clinical Trial Program



57 MDD: Major Depressive Disorder PPD: Postpartum Depression ※Biogen is the partner of Sage to develop and commercialize zuranolone SHIONOGI

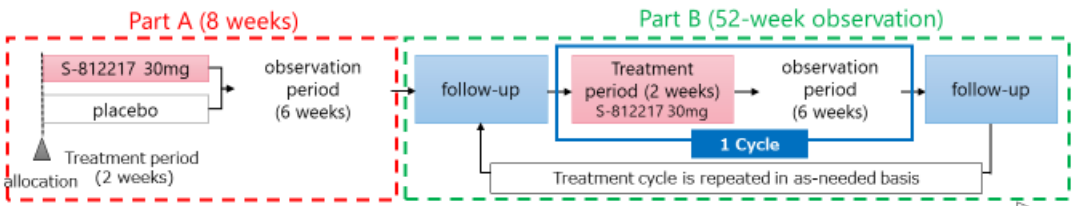
The above is a little busy, but it shows the characteristics of the tests conducted by various Sage companies, shown in yellow in the upper row, and those conducted by our company, SHIONOGI in the lower row.

Sage is conducting trials for patients with major depressive disorder, or MDD, and postpartum depression in various forms, including monotherapy, add-on therapy, and concurrent administration, and has completed Phase 3 trial.

Based on these results, we are currently conducting monotherapy and add-on therapy trials for patients with MDD. We will show its test design in the lower part of this page.

Zuranolone : Overview of Phase 3 study in Japan

	Ph3 confirmatory study	Ph3 Add-on study
subject	Patients with moderate to severe major depressive disorder	Patients with major depressive disorder on other antidepressants
Purpose	[Part A] Examination of superiority of Zuranolone over placebo [Part B] Examination of safety and tolerability of re-administration when necessary	Consider the following when adding Zuranolone to other antidepressants: [Part A] Efficacy vs placebo [Part B] Safety and tolerability of re-administration when needed
clinical trial design	[Part A] A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial [Part B] Multicenter, open label	
Dosing group	Zuranolone 30mg group, placebo group	
Sample size	200 in each group, 400 in total	50 in each group, 100 in total
Dose administration	Oral administration once a day for 14 days after dinner	



SHIONOGI

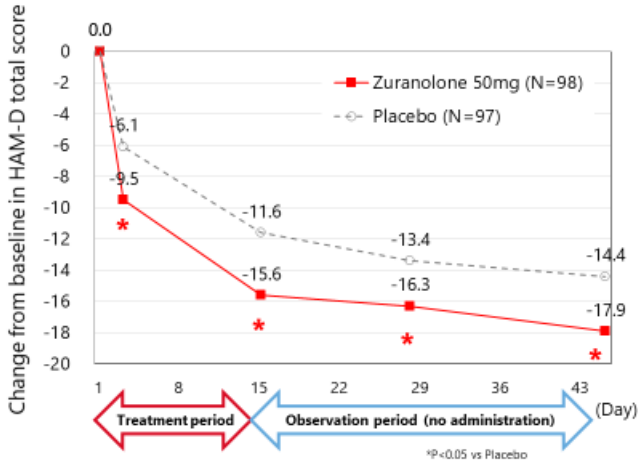
On the left is the Phase 3 validation trial, which is a monotherapy. The Phase 3 add-on trial is shown on the right.

The left side confirms the superiority of single-agent treatment effects over placebo. This is the same study design as the Phase 2 study that I mentioned earlier. The trial is to confirm the reduction in HAM-D scores of symptoms after two weeks of treatment versus placebo.

The red dotted line is part A, which is eight weeks per cycle. Patients will be monitored once, and if their symptoms worsen again, a second dose will be administered, and then a third dose will be administered. The trial design is to administer the drug repeatedly.

A total of 400 cases, 200 in each group, will be tested in the trial. In contrast, the Phase 3 add-on trial is not intended to statistically verify superiority, but since there are patients who are using existing drugs, we are conducting the trial to obtain data on the efficacy and safety of the add-on administration of this drug to patients who are using existing drugs.

Zuranolone : US Postpartum Depression Phase 3 Trial (SKYLARK, PPD-301)



Effectiveness

- **Met primary and secondary endpoints**
  - Significant improvement over placebo in change from baseline in HAM-D total score from Day 3 (initial observation) to Day 45 (4 weeks after the end of administration)
  - Achieved the primary endpoint at Day 15
    - ✓ **Confirmed "immediate onset of action" and "durable effect"**
- Significant improvement in clinical global severity (CGI-S*) compared to placebo on Day 15 (treatment completion)

Safety

- **No safety concern**
  - The 50mg dose was well tolerated with no new concerns

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* CGI-S : Clinical Global Impression – Severity

SHIONOGI

The trial I mentioned earlier was for MDD or major depression, and this trial was conducted by Sage for patients with postpartum depression, although the doses were different.

The results were the same as in the Phase 2 trial, i.e., a rapid decrease in symptoms during the treatment phase, with improvement maintained during the observation period without administering this drug.

I'm sure that there are many patients with mental illnesses and depression due to this kind of pandemic. Since this is my first experience with postpartum depression, it is possible that a single drug will be effective immediately, and that it will be possible to provide a new life, including childcare

In the US, postpartum depression is a separate indication category, so Sage's strategy is to submit applications for both major depression and postpartum depression. In Japan, however, the drug is included in a single package, so we are proceeding with development to provide a new option for patients with postpartum depression, a drug that is effective and fast-acting even as a new monotherapy.

Zuranolone : Creation Evidence and Indications

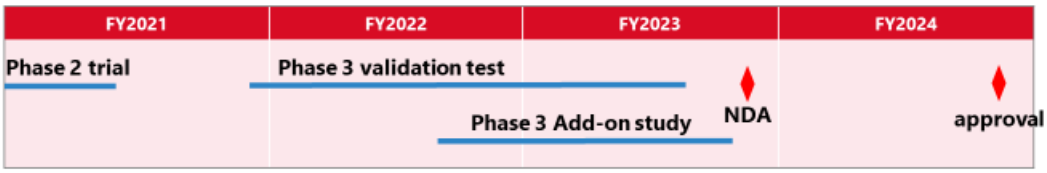
evidence

- **major depressive disorder**
  - Broad acquisition of data on monotherapy and combination therapy
- **postpartum depression**
  - Clear efficacy confirmed in clinical trials (immediate onset of action, durable effect)

indication

- **US (Sage): Major depressive disorder, postpartum depression**
  - Following ZULRESSO (brexanolone*) injective CIV, which is the only indication for postpartum depression, Sage aims to obtain indications for postpartum depression for this oral drug
- **Japan (SHIONOGI): Depression**
  - Broad coverage of depression including postpartum depression

Japan development schedule



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*Brexanolone is chemically identical to endogenous allopregnanolone

SHIONOGI

Regarding major depression and postpartum depression, we are currently conducting a Phase 3 validation part and an add-on trial and are preparing to submit for approval at the end of FY2023.

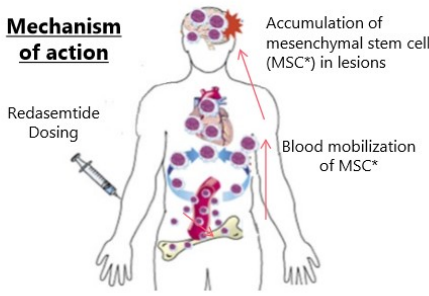
These are the results for zuranolone, S-812217.

Redasemtide [S-005151]: Challenges and developmental significance for regenerative medicine

Conventional regenerative medicine (transplantation, regenerative medicine products, etc.)	
cost	High
therapeutic opportunity	Limited accessibility • To medical institutions, doctors • To early transplantation treatment
others	Difficult to manage cell quality

Regeneration-inducing drug (Redasemtide)
Low
Easy accessibility • To medical institutions, doctors (No special equipment required)
Easy to manage the quality because of a chemically synthesized product

Mechanism of action



Reproduction

- **Acute Ischemic Stroke**
- **Epidermolysis Bullosa**
- **Chronic Liver Disease**
- **Knee Osteoarthritis**
- Cardiomyopathy etc.

Disease under development

The development of this drug is of great significance as a next-generation drug that can induce regenerative ability stably at a lower cost.

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* Mesenchymal stem cells

SHIONOGI

I would like to move on to the next one, S-005151, redasemtide.

As an introduction, I would like to summarize the issues related to regenerative medicine and the potential value that our company's redasemtide can deliver to address these issues.

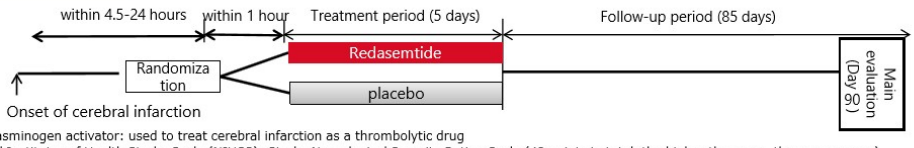
As you know, there are various transplants and regenerative medicines. However, the cost is inevitably high. And because we prepare for symptoms after they develop, it is difficult to provide early treatment. There are various issues such as such concerns and cell quality control.

In contrast, our redasemtide can be chemically synthesized and supplied at a relatively low cost compared to existing regenerative medicine. In such a situation, stem cells administered with redasemtide are derived from bone marrow, and mesenchymal cells are mobilized into the bloodstream and delivered to where they are needed to promote regeneration, and the drug has such a mechanism of action.

The right side of the page lists acute ischemic stroke, epidermolysis bullosa, chronic liver disease, and knee osteoarthritis. I mentioned earlier about resiniferatoxin being administered into the joint cavity of the knee. We are developing various pipelines to regenerate and relieve pain in various knee diseases. Today, I would like to discuss the current status of these diseases.

Redasemtide: Acute Ischemic Stroke Phase 2 Trial Overview

Clinical trial design	Multicenter, randomized, placebo-controlled, double-blind
Main purpose	Efficacy and safety of redasemtide in patients with acute ischemic stroke
Target patient	• Can be administered within 4.5-25 hours from the onset of symptoms at age 60-84 older • Presymptomatic mRS 0 or 1 (no symptoms, symptoms but no obvious disability) • Intravascular recanalization therapy (t-PA* treatment, endovascular treatment) cannot be performed
Administration group/ number of cases	• Redasemtide (1.5 mg/kg) group : 75 cases • Placebo group : 75 cases total 150 cases
Dosing method/duration	Intravenous administration once daily for 90 minutes for 5 days
Primary endpoint	**Modified Rankin Scale (mRS) after 90 days of administration**
Secondary endpoint	Presence or absence and frequency of adverse events, NIHSS**, Barthel Index (BI)***, mRS (Day365), days to discharge, QOL assessment
Country	Japan
Period	April 2019 - December 2021



* tissue plasminogen activator: used to treat cerebral infarction as a thrombolytic drug
** National Institutes of Health Stroke Scale (NIHSS): Stroke Neurological Severity Rating Scale (42 points in total, the higher the score, the more severe)
*** Barthel Index (BI) : Evaluation scale for activities of daily living such as eating, bathing, and toileting (total 100 points, the higher the score, the more independent the person is, and the guideline for complete independence is 95 points)

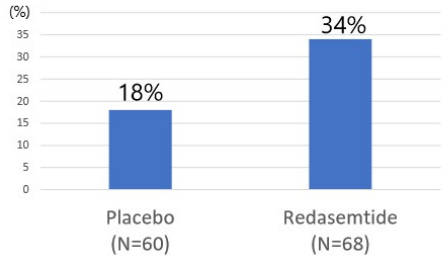
First, let me give you an overview of the Phase 2 trial of acute cerebral infarction.

We have already presented the results in the press release, and now we would like to share some of the results with you. The trial is designed for elderly patients with cerebral infarction who cannot be treated with intravascular recanalization therapy, intravascular thrombosis therapy., and can be administered within 4.5 to 25 hours of onset of stroke.

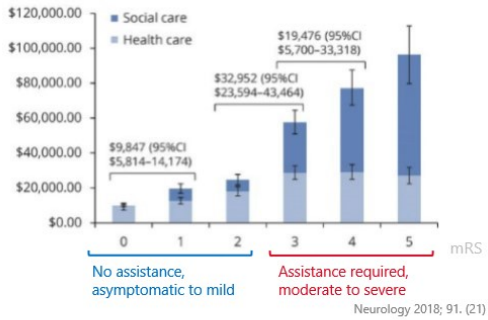
This is a study in which intravenous administration for 5 days evaluated the prognostic evaluation index called the modified Rankin Scale 90 days after administration during the follow-up period.

Redasemtide: Acute ischemic stroke Phase 2 trial results

Percentage of patients requiring care after 6 days of administration who became care-free (mRS*≤2) after 90 days



mRS at 3 months after ischemic stroke and 5-year social and medical costs (per person)



Neurology 2018; 91. (21)

※Reference
- **Prevalence(number) : 1.65 million**
- **(estimate for Japan, the US, and Europe in 2021)**
- **Market size: 735MM USD**
- **(estimate for Japan, the US and Europe in 2021)**

- **The percentage of patients requiring long-term care who improved to a socially independent level that required no assistance increased compared to the placebo group.**
- **The deterioration of mRS due to ischemic stroke has a large impact on the increase in social and medical costs, and the improvement of mRS using this drug is of great social significance.**

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* Modified Rankin Scale (mRS) : General prognostic rating scale (degree of social reintegration) ``Score 0 (no symptoms) to score 6 (death)'' in 7 grades

SHIONOGI

Here are the results we have posted. Placebo on the left and redasemtide on the right.

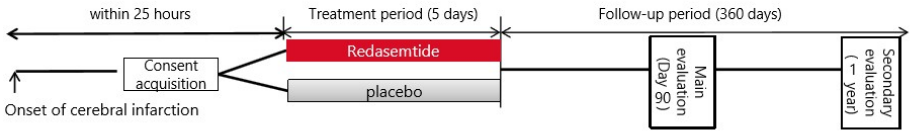
In the modified Rankin Scale, the following two are particularly important indicators. As to why two, on the right side, I have indicated a summary of social and medical cost data for stroke data. In the modified Rankin Scale, 0, 1, 2, 3, 4, 5, and up to 6, with 6 being deaths, the major categories in red are 3, 4, and 5, which are moderate to severe and have a poor prognosis and require assistance.

The bar graph shows medical costs in the light blue area, social care costs in the dark blue area. Since assistance is absolutely necessary, medical costs, such as medical care and assistance, are very high. The aim of this drug is to reduce the number of such patients by treating them promptly after the onset of cerebral infarction.

As you can see on the left side, 34% of the patients who took or received redasemtide compared to placebo, which is a proof of concept trial that is expected to promote recovery in a higher percentage of patients compared to placebo.

Redasemtide: Acute Ischemic Stroke Global Phase 3 Trial Overview (Draft)

clinical trial design	Multicenter, randomized, placebo-controlled, double-blind
main purpose	**Verification of efficacy of redasemtide in patients with acute ischemic stroke**
Target patient	• Can be administered within 25 hours from the onset of symptoms at age 18 or older • Presymptomatic mRS 0 or 1 (no symptoms, symptoms but no obvious disability) • Intravascular recanalization therapy (t-PA treatment, endovascular treatment) cannot be performed
Administration group/ number of cases	• Redasemtide (1.5 mg/kg) group : 678 cases • Placebo group : 678 cases total 1356 cases
Dosing method/duration	Intravenous administration once daily for 90 minutes for 5 days
Primary endpoint	**Modified Rankin Scale (mRS) after 90 days of administration**
Secondary endpoint	NIHSS, Barthel Index (BI), mRS (Day365), days to discharge, QOL assessment
country	Japan, Europe, North America, China, etc.



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SHIONOGI

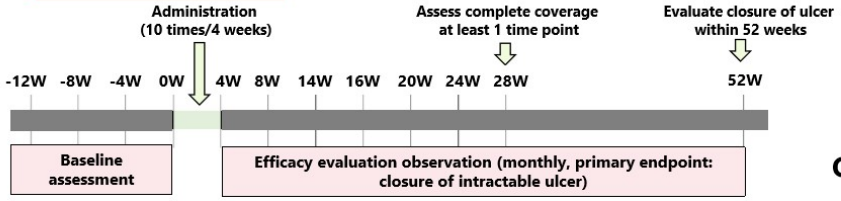
Based on these results, we are currently communicating with authorities in various countries around the world.

Please be advised that this is only a draft for the design of the test, and this one can change. Based on the design of such a trial, we would like to conduct the Phase 3 trial after reaching an agreement with the global bureaus. We are preparing to conduct a trial design that is relatively similar to the proof of concept trial mentioned earlier.

Naturally, we are planning to conduct a very large the Phase 3 trial with 678 cases in each group, in order to achieve a clear and statistically significant difference.

Redasemtide: Dystrophic epidermolysis bullosa additional Phase 2 trial (domestic) started

Clinical trial design	Multicenter, open-label, uncontrolled
Main purpose	Evaluation of efficacy and safety of redasemtide in patients with dystrophic epidermolysis bullosa with intractable ulcers
Administration group/ number of cases	Redasemtide (1.0 mg/kg) group: ≥3 subjects
Dosing method/ duration	Intravenous administration once daily for 30 minutes, 10 times/4 weeks [First week of administration: 4 days, Weeks 2-4 of administration: 2 days/week (once every 3-4 days)]
Primary endpoint	Closure of intractable ulcer*



July 2022: Clinical trial notification submitted

Q4 2022 (FY) : FPI scheduled

* At least one time point of complete coverage within 28 weeks of administration and closure of intractable ulcer within 52 weeks of administration
Definition of closure: Complete coverage of the ulcer surface by the epidermis continues at 2 time points separated by 2 weeks or more

SHIONOGI

Continuing on, we have epidermolysis bullosa.

We have already conducted the Phase 2 trial and found that seven out of nine patients showed skin regeneration, making this a very promising new regeneration tool.

Although it is a small-scale trial to see if the refractory ulcer can be completely closed in patients with additional refractory ulcers, we are conducting additional very small-scale trials with 3 or more patients. Based on these data, we are proceeding with development with the aim of submitting an application for approval in Japan.

Redasemtide: LCM vision

Investigator-initiated studies are underway based on evidence accumulated in non-clinical research in academia

Chronic liver disease

- Investigator-initiated Phase 2 trial (final observation in November 2022)
- Improvement of liver function by suppressing liver fibrosis in chronic hepatitis
- Providing new treatment opportunities for patients for whom there are no effective treatments

Knee osteoarthritis

- Investigator-initiated Phase 2 trial (final observation in December 2022)
- Improvement of Morphological/joint function in knee osteoarthritis
- Providing new treatment opportunities that can contribute to improving QOL in an aging society

An investigator-initiated trial for cardiomyopathy is being planned to maximize the value of this drug as a regeneration-inducing drug

Cardiomyopathy

- Improvement of cardiac function by suppressing cardiac fibrosis
- Considering targeting patients with ischemic cardiomyopathy with symptoms of heart failure

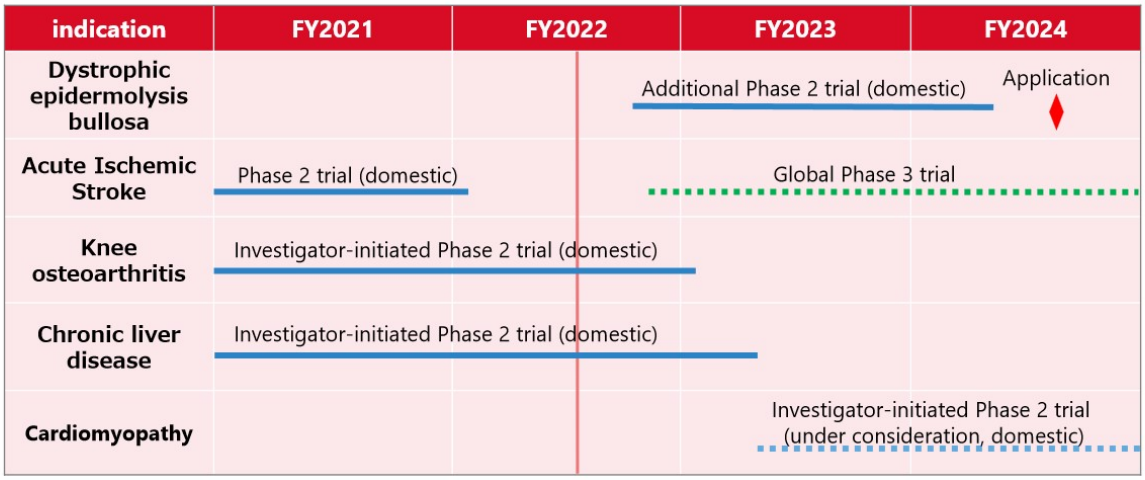
SHIONOGI

Finally, this is the vision of LCM.

Chronic liver disease, we are conducting a physician-initiated the Phase 2 trial here. We are approaching November 2022, the final observation. The same situation applies to knee osteoarthritis, which is also approaching its final observation date. Based on the results of these Phase 2 investigator-initiated clinical trials, we are in the process of developing further development packages.

In addition, a new investigator-initiated clinical trial for cardiomyopathy is currently being planned.

Redasemtide: Development schedule



As of October 12, 2022

Trial period: Start of patient registration to completion of summary report

SHIONOGI

The schedule of development, the one started in 2021 on the left side, shows the current stage.

Phase 2 trial has been completed and the Phase 3 trial is indicated by the dotted line. For knee osteoarthritis and chronic liver disease, depending on the results, we will consider global development in the future, and for cardiomyopathy, we are planning physician-led clinical trials in Japan.

S-309309: Profile

Indication

- Obesity

Product characteristics

- Best-in-class efficacy among existing oral drugs (weight loss of 10% or more per year) with no safety concern
- Lower economic burden compared to GLP-1[*1] injectables

Market

- Obese patients[*1]: 245 million (7MM[*2]), 125 million (U.S.)
- Market size[*3]: $ 1,692 MM (2021) (including 93% in the US)

Unmet needs

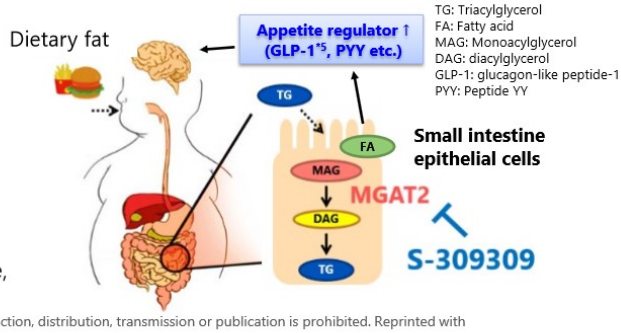
- There is a demand for a drug that has no safety concerns, shows a sufficient weight loss effect over a long period of time, and has a low out-of-pocket cost.

Current status and future plans

- Phase 1 trial ongoing in the US
- Planning Phase 2 PoC trial

Mechanism of action

- Monoacylglyceroltransferase 2 (MGAT2[*5]) inhibitor



*1 glucagon-like peptide-1 *2

*3 7 major markets: US, France, Germany, Italy, Spain, UK and Japan *4 *5 monoacylglycerol acyltransferase 2

SHIONOGI

I would like to move on to S-309309, the next item.

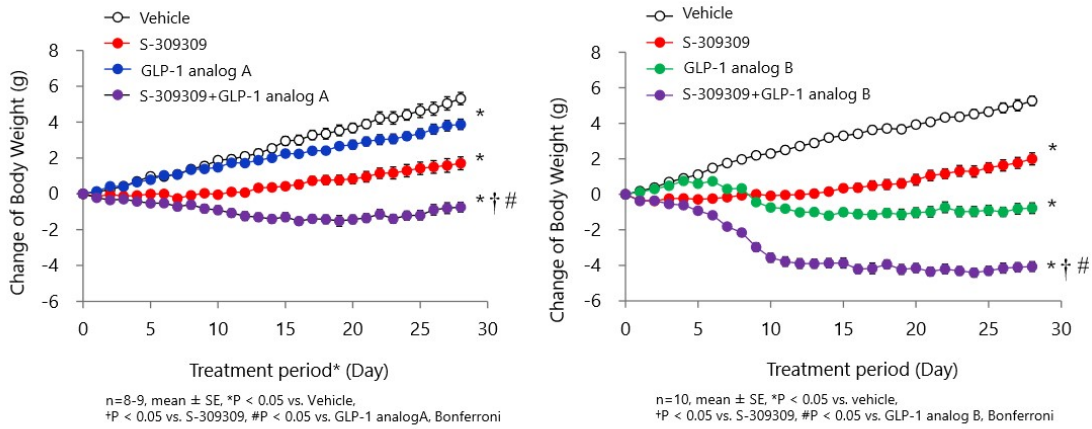
At this point in time, there is probably no other company with this mode of action in its development pipeline for anti-obesity drug. Mechanism of action is Very interesting and unique mechanism of action.

A schematic diagram is shown on the right. In the process of absorbing various dietary lipids from the gastrointestinal tract, triglycerides are absorbed in gastrointestinal epithelial cells and decomposed into monoacylglycerol and fatty acid. Once again, MGAT2 converts lipids into triglycerides and absorbs them into the body, which is the absorption process of lipids in the gastrointestinal epithelium.

S-309309 inhibits this MGAT2, monoacylglycerol transferase, so fatty acid accumulates in the cells, and that fatty acid is then released into the lumen of the digestive tract. Therefore, it actually modulates the balance of various hormones such as GLP-1 and peptide YY, which are appetite regulators, thereby causing food suppression. This is a very unique anti-obesity agent with a novel mechanism.

As you already know, GLP-1, an injectable formulation, is noticeably expensive. S-309309 is an oral drug that can be chemically synthesized, and based on preclinical data, it is expected to have a reasonable level of efficacy. We are now in the process of developing this product globally in the hope that it will also become a new treatment option.

S-309309: Combination effect with GLP-1 analog



S-309309 showed a combination effect on weight reduction with GLP-1 analogs

* Administered for 4wks in high fat diet induced obesity mice

SHIONOGI

These are the results of animal experiments.

As I mentioned earlier, it can also be used in combination with GLP-1 analogs. This is a comparison of the results of three arms of a high-fat diet in obese mice: S-309309 as a single agent, a GLP-1 formulation, and a combination of the two.

You can see that the weight is gradually increasing in white circles. In contrast, you will notice that S-309309, red, suppresses weight gain. And we have shown the results of organism A and organism B, respectively, that the combination with GLP-1 analogs can confirm the additive effect of weight loss.

With such preclinical data, we have started Phase 1 trial to develop the drug globally.

S-309309: Phase1 SAD/MAD trial status

Part 1 Single dose trial

- AUC increased in dose-proportional manner between 1 – 300 mg.
- There are no significant food effect on the PK

Part 2 Repeated dose trial

- Ongoing

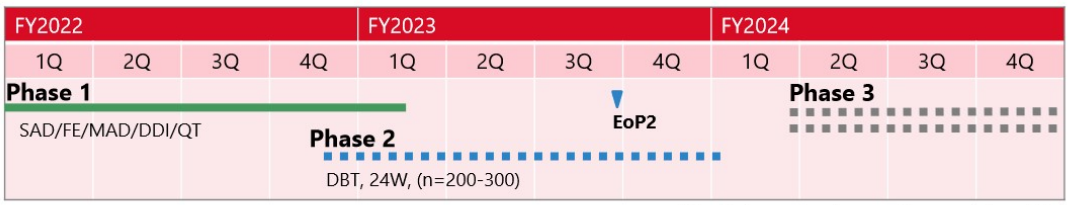
Country	U.S.
Trial design	Phase 1 (single/multiple), single-center, randomized, double-blind, placebo-controlled trial • Part 1: Single dose (1-300 mg/person): Healthy adults • Part 2: Multiple doses (50, 100 mg/person, 14 days): Healthy adults and obese but otherwise healthy adults
Evaluation content	• Safety and tolerability with single and multiple doses • PK after single and multiple doses • Food effect, QT analysis, Drug-drug interaction (midazolam)
Trial period	January 2022 (FPI) to October 2022 (LPO)

SHIONOGI

This is a Phase 1 SAD/MAD trial being conducted in the United States.

We performed dose-escalation from 1 to 300 and found that the AUC increased with increasing volume, confirming the expected PK profile. And since there is no dietary influence, we are in the process of implementing the repeated dose stage at this time.

S-309309: Upcoming schedule



Trial period: Start of patient enroll to completion of clinical trial report

Phase 2 trial design (draft)

- **Primary objective**
  - Examination of weight loss effect of S-309309
- **Trial design**
  - Multicenter, randomized, placebo-controlled, double-blind
- **Primary endpoint**
  - The percent change from baseline in body weight at Week 24
- **Key inclusion criteria**
  - Adults with BMI = 30 or greater
  - Adults with BMI to 27 or greater with the presence of dyslipidemia or hypertension

  (excluding patients with diabetes, secondary obesity, and obesity drug treatment)

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SHIONOGI

This is the schedule for the future.

We are now preparing to conduct a Phase 2 trial in the US this year as soon as this Phase 1 trial is completed. We are preparing to start the Phase 3 in FY2024, after conducting a proof of concept studytrial to see how much weight loss from baseline can be achieved in 200 to 300 patients with BMI of 30 or more, or those with an underlying disease of 27 or more.

S-531011: Profile

Indication Disease

- Solid tumors

Product Properties

- A humanized anti-human CCR8* monoclonal antibody
- Strong anti-tumor effect with no major safety concerns
  - ➢ CCR8 is expressed in tumor-infiltrating regulatory T cells (Treg) in a wide variety of cancer types regardless of staging.

Unmet Needs

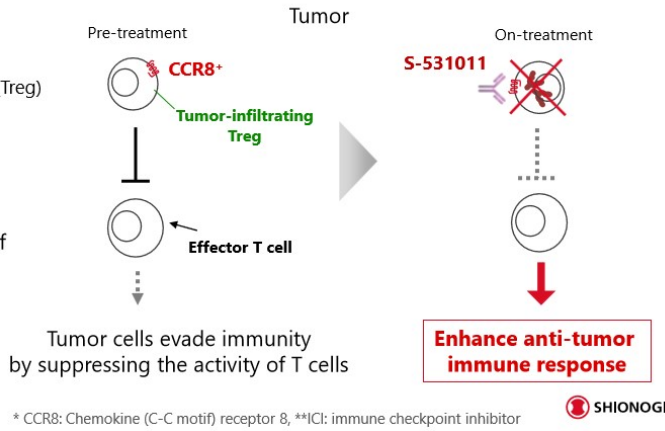
- High unmet medical needs for advanced cancer patients who have no approved ICI** therapy or limited efficacy of ICI

Current status and future plan

- Phase 1b/2 trial is ongoing for 12 solid tumors

Mechanism of Action

- Selective depletion of tumor-infiltrating Tregs by S-531011 is anticipated to restore antitumor immunity without inducing autoimmunity.



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* CCR8: Chemokine (C-C motif) receptor 8, **ICI: immune checkpoint inhibitor

SHIONOGI

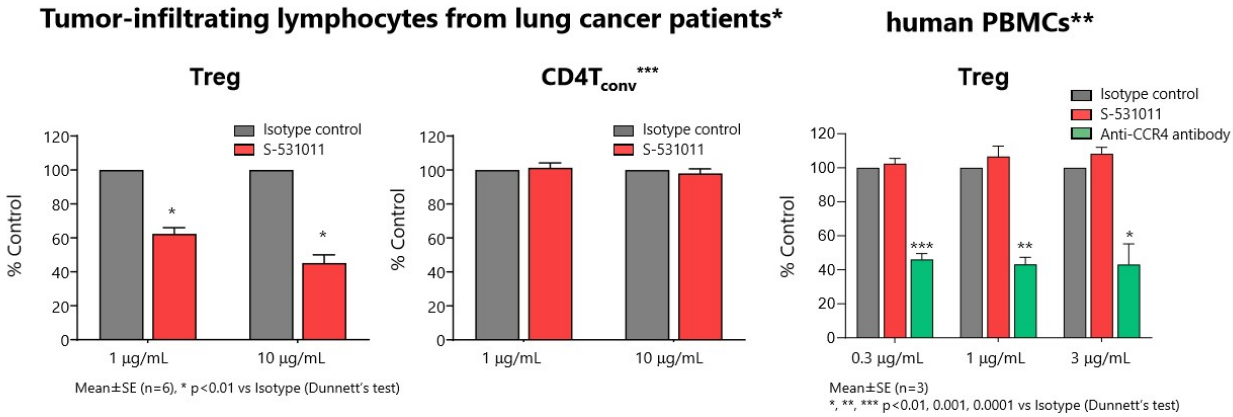
In addition to these anti-obesity agents, I would like to talk about our pipeline of anti-cancer agents, S-531011.

This is a monoclonal anti-CCR8 antibody for solid tumors. A schematic diagram of the mechanism of action is shown on the right. In fact, the body's lymphocytes, or T cells, attack tumors and shrink them, and the body is inherently immune to such actions.

Tregs, or regulatory T cells, infiltrating the tumor act to suppress the body's immunity. Therefore, by depleting T cells that act as brake cells with CCR8 antibody, the brake is suppressed, and the gas pedal state is maintained, specifically, the anti-tumor immune response is enhanced, and the body's immune system is able to reduce the size of the tumor.

We are currently developing the drug in the hope that it may be used as a monotherapy or in combination with existing anti-PD-1 antibodies, as it has shown considerably sharp tumor effects in preclinical studies.

S-531011: Antibody-dependent cellular cytotoxicity activity using human samples



S-531011 is anticipated to selectively deplete tumor-infiltrating Tregs but not other effector T cells or peripheral Tregs

* Calculated percentage of Tregs or CD4 Tconv in CD45+ cells ** Calculated percentage of Tregs in CD4T cells ***CD4T cells other than Tregs

SHIONOGI

This one, as a proof of actual action, is a trial using human lung cancer lung cancer cells on the left side, and in the cells within the lung cancer, the regulatory Tregs that are infiltrating the cancer, are specifically lowered. In contrast, congenital CD4-positive T lymphocytes, which are depleted without depletion. We are lowering things unique to regulatory T cells.

And of special note is the peripheral blood. The right side of the image shows that the drug does not act on T cells or Tregs contained in mononuclear cells in the peripheral blood, and we believe that its characteristic is that it specifically depletes regulatory T cells that suppress the tumor at its original location.

S-531011: Development plan and positioning

The purpose of the Phase 1b/2 trial is to evaluate the safety, tolerability and efficacy of S-531011 monotherapy and in combination with an anti-PD-1 antibody

Monotherapy	Evaluate the safety and antitumor activity as monotherapy targeted on patients that have limited therapeutic option
Combination with ICI	Evaluate the safety and antitumor activity in combination with an anti PD-1 antibody expecting the possibility of using S-531011 with current standard therapies

S-531011 could be a promising new antitumor drug candidate for patients who are refractory or insufficiently treated with ICIs, either monotherapy or in combination with ICIs.

SHIONOGI

Under these circumstances, we are proceeding with the Phase 3 trial.

We are now preparing to administer the drug in combination with a checkpoint inhibitor after first confirming the safety and tolerability of the single-agent treatment.

S-531011: Phase 1b/2 trial progress and upcoming schedule

Safety

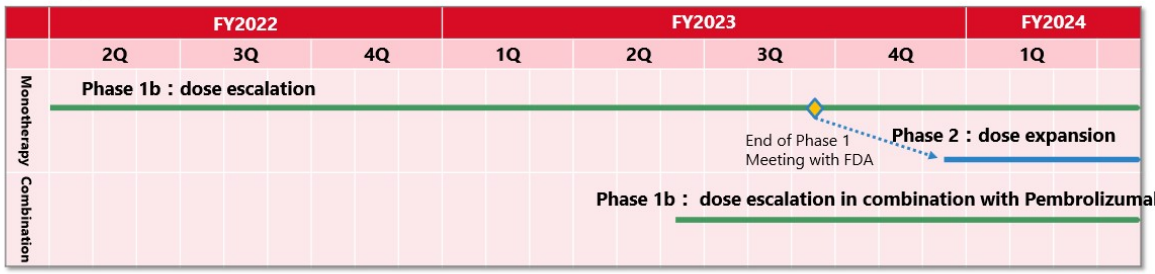
- No Dose Limiting Toxicity (DLT) occurred to date

Pharmacokinetics

- Drug concentration and other parameters are confirmed and similar to prediction by animal scale up

Pharmacodynamics and proof of mechanism

- Change in the proportion of tumor-infiltrating CCR8-positive Tregs using pre- and post-treatment biopsy samples; ongoing



Trial period: Start of patient enroll to completion of clinical study report

SHIONOGI

I have summarized on the next slide.

At this point, we are proceeding with dose escalation and have not observed any dose-limiting toxicities or problematic adverse events.

Based on these samples, we are currently confirming pharmacokinetics and PoM markers. Based on such data, we are preparing to start combination studies with checkpoint inhibitors in FY2023.

S-770108: Profile

Indication
- Idiopathic Pulmonary Fibrosis (IPF)
- PF-ILD* also under consideration

Characteristics
- Dry-powder, inhaled formulation of Pirfenidone
- Greatly reduced dose, and systemic exposure compared to oral pirfenidone, reducing side effects (photosensitivity, gastrointestinal symptoms)

Market
- Prevalence：89,000 (US, JP, EU5 no. of diagnosed patients)
- Market Size：＄4.2 B (JP, US, EU5, 2021)

Unmet Needs
- Existing treatments only slow down speed of lung function decline
- Combination therapy leading to improved treatment effect predicted to be the next phase in treatment of IPF

Project Status and future plans
- Phase 1 Lung deposition trial - Complete（UK）
- Phase 1b IPF patient trial - Complete（JP）
- Phase 2 trial – Under preparation（Global）

Mechanism of Action
- Anti-fibrotic

* Idiopathic pulmonary fibrosis ** Progressive Fibrosing Interstitial Lung Disease

SHIONOGI

We will continue with the last slide. S-770108, an inhaled formulation of pirfenidone.

As you know, pirfenidone is an orally administered drug that is currently available in Japan for patients with idiopathic pulmonary fibrosis, but there are patients who cannot take or continue taking it due to potential side effects such as photosensitivity or gastrointestinal disorders. Therefore, we need to reduce the systemic exposure and increase the local concentration in the lungs. By delivering such a new formulation, we can increase the number of patients who can use this pirfenidone. We are developing an oral inhalation formulation with the possibility of delivering it to those who want to use it but cannot continue to do so.

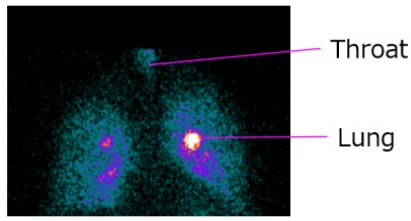
At this point, we have completed the Phase 1 trial and are preparing to conduct the Phase 2 trials in various countries around the world. I would like to show some of the data.

S-770108: Formulation development concept

Formulation

- Capsule-based dry-powder formulation
- Convenient to use
- Particle size suited to delivery to lung periphery
- Confirmed transferability to the lungs in lung deposition trial

Lung Deposition



- By dosing pirfenidone directly to the lungs by inhalation, systemic exposure is greatly reduced (1%-2% of that seen with oral pirfenidone)
- Large reduction of oral pirfenidone associated side effects (photosensitivity, gastrointestinal symptoms) . Drug efficacy expected with sufficient lung concentration and good adherence
- IPF treatment is expected to move from mono- to combination-therapy in the near future, and as such inhaled pirfenidone is expected to have a good efficacy and safety profile, enabling use as both monotherapy, and in combined therapy with other approved agents.

SHIONOGI

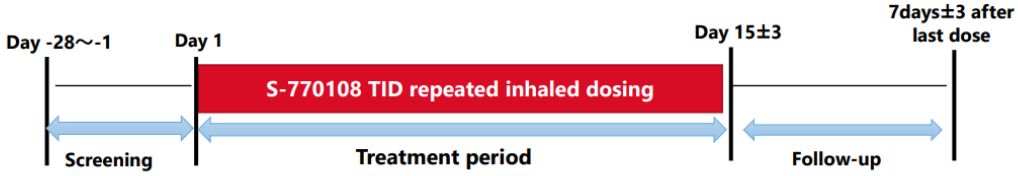
The capsule-filled dry powder formulation is shown on the right in the actual pulmonary deposition rate test, and I think it has the potential to suppress local lung disease and fibrosis by scattering the powder in the lungs when inhaled. We are now ready to deliver a new inhalation formulation for local delivery.

Based on such data, the following slide shows the actual situation of inhalation in patients with IPF.

S-770108: IPF patient Japan Phase1b trial results

Trial Design

25 IPF patients treated with S-770108 TID for 2 weeks (Feb-Jun 2022)



Trial Results

- A cough was reported directly following dosing, but was transient and mild in all cases.
- 1 participants discontinued treatment due to an adverse event, but was deemed related to a concomitant medication, not to S-770108
- All participants achieved the target flow rate of 30* L/min using the inhaler device

* Based on in vitro, and clinical lung deposition trial data, flow rates of 30 L/min and above、were deemed to be sufficient to ensure adequate lung deposition of pirfenidone for efficacy

All IPF patients in the trial achieved the target flow rates, and tolerability of S-770108 was confirmed. A Phase 2 trial is under preparation

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SHIONOGI

We have conducted a Phase 1b trial in IPF patients in Japan.

We checked to see if a patient with IPF could inhale, and if they could cough, which is highly difficult to continue.

The target intake volume was confirmed. Furthermore, coughing occurs a little because it is an inhalant, of course, but it does not cause coughing that cannot be continued. Based on these data, we are now moving forward with Phase 2 trials on a global basis.

And that was the quick, high-level overview of our projects in the pipeline.

Kyokawa: Thank you very much. Mr. Isou will now discuss the projects in research phase. Mr. Isou, please go ahead.

Research part

Disease areas	Projects to be introduced today	Target disease	Posted page
Infection	**COVID-19 therapeutic drugs**	COVID-19	P.84-88
	HIV Franchise (S-365598)	HIV infections	P.89
	S-337395	RSV infections	P.90-93
Psychiatry/Nervous/Pain	**Pain Medicine (S-151128)**	Chronic pain	P.94-96

SHIONOGI

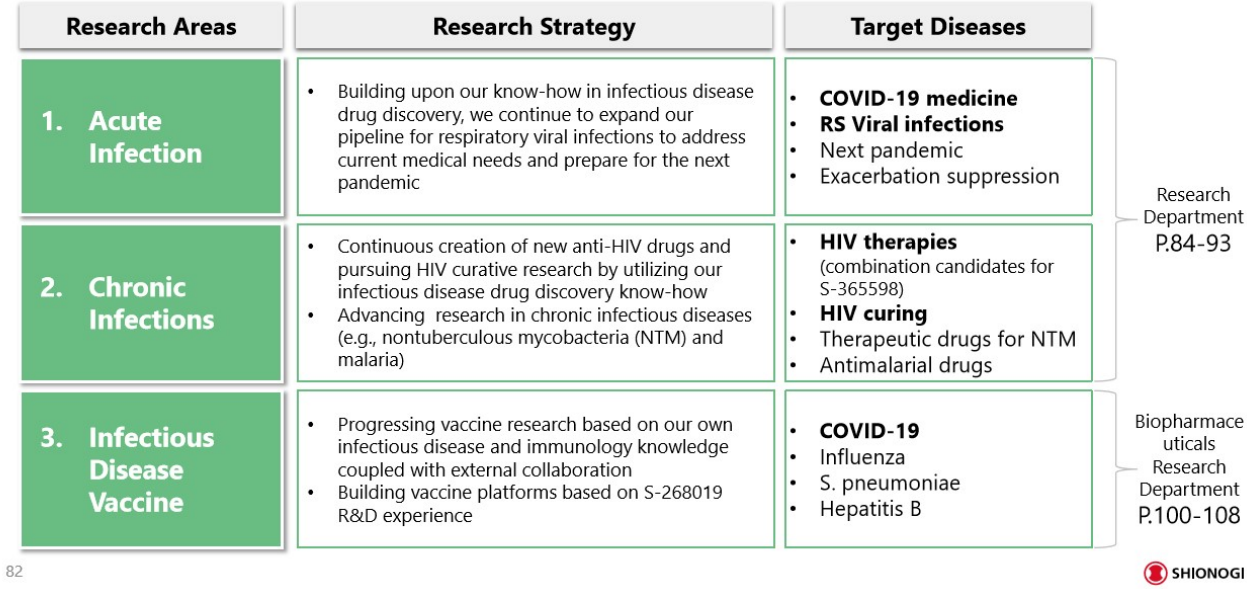
Isou: Thank you for the introduction.

First, please turn to page 81. This is an agenda of my presentation for research projects.

Our main focus is infectious diseases, which include COVID-19 therapeutic agents and the HIV franchise, mainly S-365598. Then, new therapeutics for the treatment of RS virus infection, S-337395. Also, a pain medication therapeutic for pain and nerve areas. For this one I would like to introduce a new mechanism, the S-151128.

The relevant page numbers are shown on the right of the chart.

Actions in the area of infectious diseases

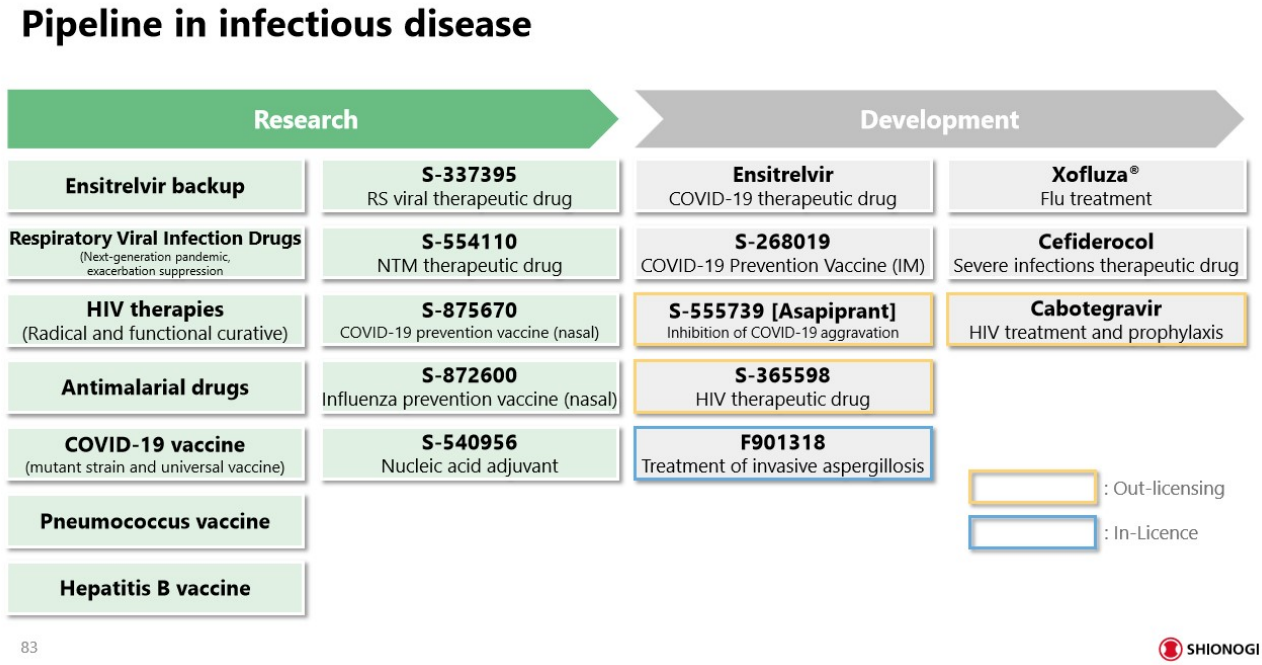


Now, please turn to page 82. This is a summary of our efforts in the field of infectious diseases, focusing on our policies regarding the research.

It is divided into three parts: acute infections, chronic infections, and vaccines.

As for acute infectious diseases, the target disease is COVID-19, which was just introduced. The other main disease is RS virus infection, which I will introduce in the next section. Then, for chronic infections, we have HIV therapeutic agents, and this is the candidate therapeutic for S-365598 in combination with HIV therapeutics. We are also working diligently on a candidate for a curing for HIV, which I will not introduce today.

Vaccines will be introduced later in the bio part from Aoyama.



Page 83. The pipeline regarding infectious diseases. To the right are the compounds that have reached the market. The one on the far left will be the compound under trial.

Although there is no strict classification for research and development, I believe that the S-compounds and the ensitrelvir, which Uehara introduced, are the pipeline items that are currently under development and are attracting attention.

1. Acute infection

COVID-19 therapeutic drugs: Actions overview

Small molecule	**Initial candidate compound**	Fastest provision of COVID-19 specific therapeutic drug ⇒ Discontinued
	Ensitrelvir	Applicable to a wide range of patients therapeutically and prophylactically
	Ensitrelvir backup	Creation of oral therapeutic drugs that meet future needs
Peptide	**S-880008**	Broad-spectrum therapeutic drug with a more potent effect by using inhaled formulations, whth one day dosing ⇒ Discontinued

SHIONOGI

Page 84. Among these, I would like to introduce some of the history, particularly with regard to the overview of the COVID-19 therapeutic agents initiative.

There were three small molecule candidate compounds.

The initial candidate compound was introduced on a televised program called *Dawn of Gaia* on TV TOKYO network. We developed it to serve as a silver bullet for COVID-19; however, due to the safety concerns that emerged during the process, we had no choice but to abort the development plan.

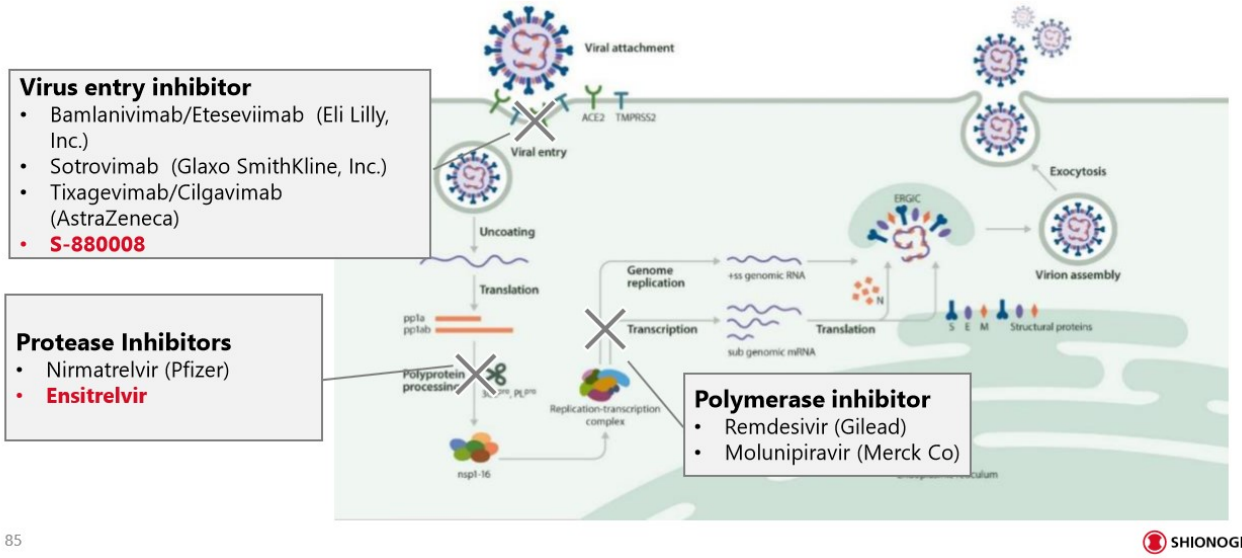
Following this, we were strengthening our second and third arrows. The second arrow is this ensitrelvir. This one is currently under development as a possible drug that can be used in a wide range of patients, which is already essential to prevent the spread of foot infections.

We are also developing a third arrow, the ensitrelvir backup. We are currently in clinical development to create an oral treatment that will meet the needs of the future.

Also, unfortunately, we dropped this one along the way, but Our peptide drug discovery has produced very unique compounds S-880008. The administration route here is an inhalation formulation, and by directly approaching the respiratory tract, it is very convenient as a therapeutic agent with a strong effect that can be completed in one day and a broad spectrum, and variations for future resistant strains. It was a promising therapeutic drug. I will introduce this later.

1. Acute infection

COVID-19 therapeutic drugs: Drug discovery targets for SARS-CoV-2

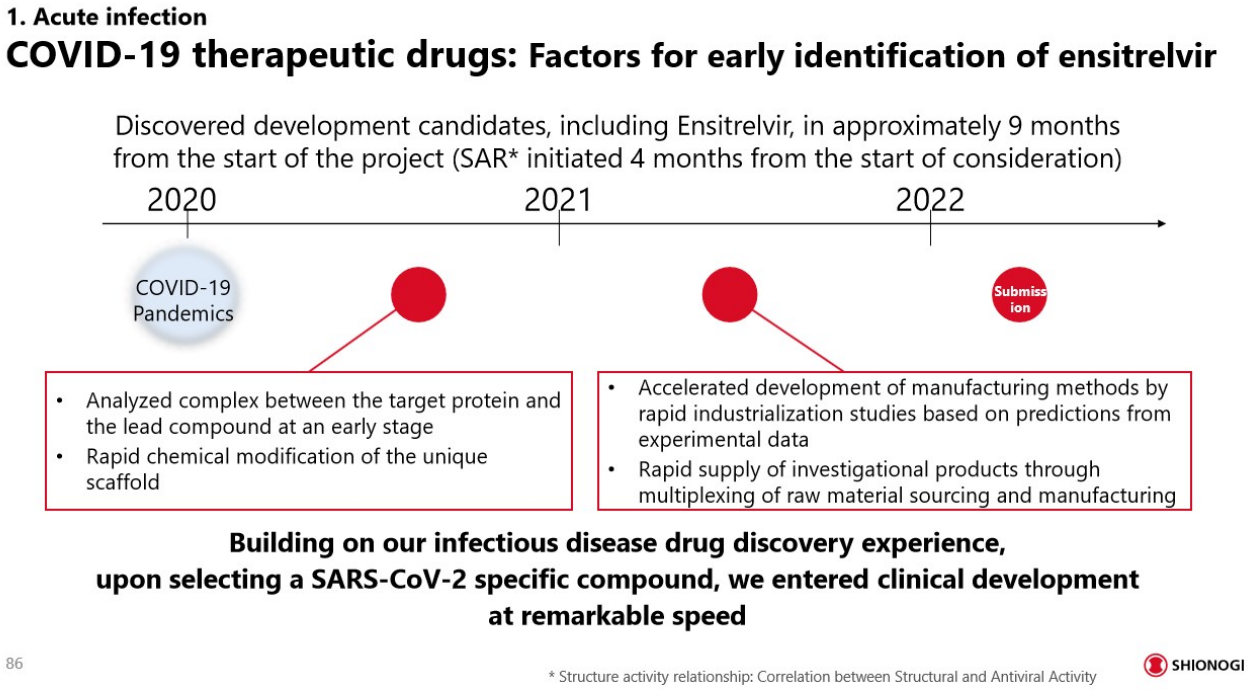


85

SHIONOGI

Page 85. This is the therapeutic target for each compound developed for COVID-19 therapeutics.

As mentioned in the introduction, ensitrelvir is an inhibitor of 3CL protease, which is the same as nirmatrelvir. Other drugs such as remdesivir and molnupiravir are also polymerase inhibitors, but the one I mentioned earlier as being slightly unique is this S-880008. This is a viral invasion inhibitor that acts on the ACE2 receptor in humans and has very strong inhibitory activity in blocking the invasion part.



Page 86.

This is one of the factors that contributed to the early submission of the ensitrelvir application, and we believe that we were able to shorten the time from the start of the project to the submission for approval to an unprecedented extent.

The first factor here is the discovery part. I think the fact that we were able to obtain a complex of an early-stage target protein and a lead compound is significant.

Then, based on that lead compound, a bold chemical modification of the unique skeleton. This is what is called SAR research, and it has a very effective influence here. Our know-how and experience have been extremely useful, and we have been able to speed up the process.

In addition, in the CMC area on the right, we made maximum use of predictions based on experimental data, which enabled us to quickly study industrialization and manufacturing methods. This time has been significantly reduced this time.

The risk was very high because it was a prediction, but this time we dared to take the risk and shortened the time through risk mitigation.

We have also been able to achieve top-class therapeutic discovery speed as a specific compound for the treatment candidate of COVID-19 by double and triple hedging risks through the rapid supply of the investigational therapeutic by double and triple procurement and production of raw materials.

1. Acute infection

COVID-19 therapeutic drugs: S-880008 (peptide)

Concept

More effective therapeutic drugs delivered directly to target organs
(upper and lower respiratory tracts, and lung)

Inhalation formulation ✖ **Novel mechanism expected to have high potency and broad spectrum**

Discovered Non RBD* binding peptide S-880008 (SARS-CoV-2 incursion inhibitors) in a short period of time utilizing our peptide-drug discovery capabilities

* Receptor Binding Domain: SARS-CoV-2 with human ACE2 receptors

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As I mentioned earlier, I introduced a peptide with a somewhat unique mechanism, the concept of which, as I mentioned earlier, is aimed at effective therapeutic agents that directly approach the respiratory tract, especially the upper and lower respiratory tracts and lungs.

The benefits of the drug include its convenient inhalation formulation and a novel mechanism that aims for potent and broad-spectrum effects. We have been able to apply the power of peptide drug discovery following small molecules to this SARS-CoV-2 invasion inhibitor and have discovered a non-RBD binding peptide, S-880008, in a short period of time.

1. Acute infection

S-880008: Reasons for discontinuing development

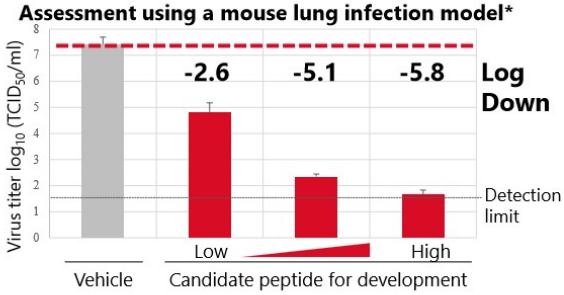
Although we were able to confirm potent in vivo efficacy, including against BA.1 strain, however, activity against a BA.2 strain with multiple amino acid mutations is reduced

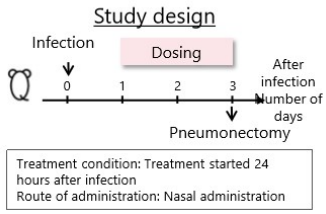
Discontinued preclinical development because broad coverage cannot be assured for newly emerging variants

In vitro efficacy

Viral strains	EC_{50} (nM)
Conventional strains	4.2
Alpha strain	8.5
Beta strain	2.2
Gamma strain	6.4
Delta strain	7.8
Omicron BA.1 shares	6.4

In vivo potency
Assessment using a mouse lung infection model*





This research is supported by AMED under Grant Number JP20fk0108509

* SARS-CoV-2(WK-521 line) using virus acclimated in murine lung tissue

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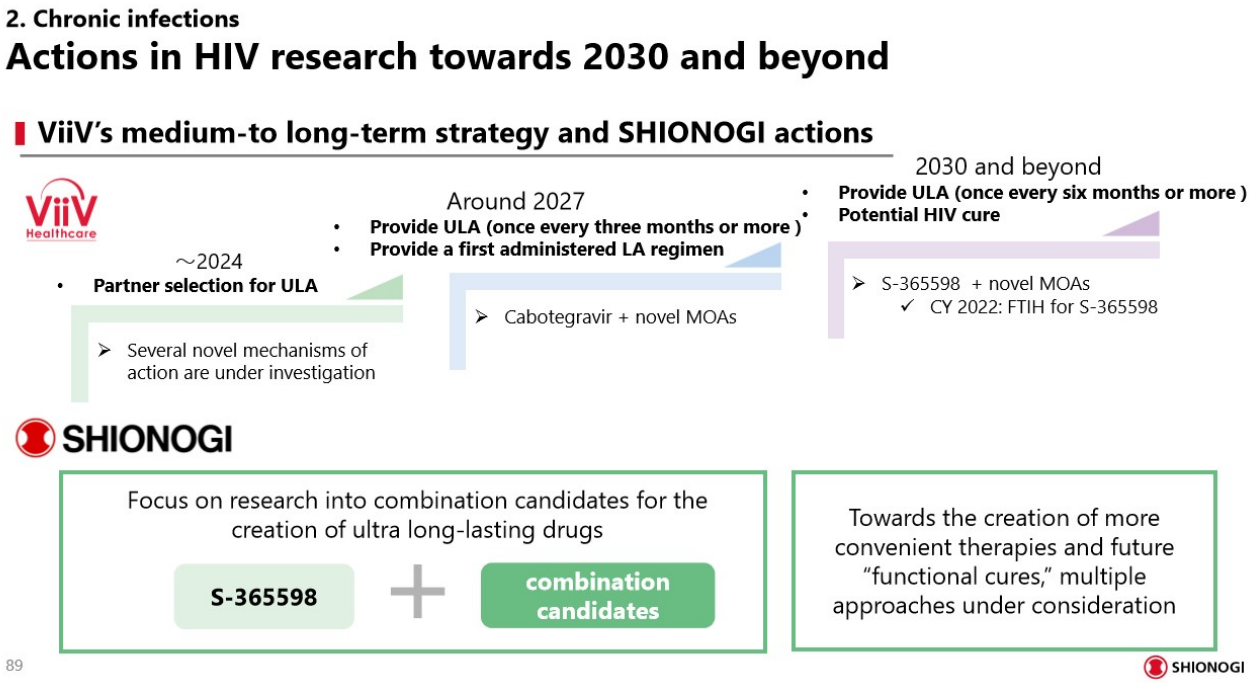
Unfortunately, however, this has been discontinued.

As shown here, we were able to confirm broad-spectrum activity up to BA.1 strains and strong in vivo drug activity. The table on the left is for vitro activity and the graph on the right for vivo activity.

For the BA.2 strain, which has a large number of amino acid mutations, however, a slight decrease in activity was observed. This decrease in activity overshadowed our concept of broad-spectrum activity, and we were unable to guarantee broad-spectrum activity for newly emerging mutant strains. Therefore, we have suspended the preclinical development.

Unfortunately, our prediction for the wide range of the peptide drug discovery was a little off, but there were some lessons learned from this peptide drug discovery, and we would like to further enhance this modality and apply it to our research in the future.



Page 89. In the context of HIV research efforts for 2030 and beyond, I would like to talk a little bit about HIV, although it will be on one slide here.

In terms of ViiV's mid- to long-term strategy and SHIONOGI's initiatives, ViiV is selecting combination drugs for ultra-long-acting formulations by 2024. We are currently investigating several new mechanisms of action, and S-365598 is the one that falls into this category. We are currently focusing on the research of combination drug candidates with the goal of creating an ultra-long-acting formulation by 2024.

The following year, around 2027, we will offer an ultra-long-acting formulation, which will be administered once every three months or longer. Then the goal is to provide self-administered regimens. We hope to accomplish this based on Cabotegravir, plus a combination drug with a novel mechanism of action.

Furthermore, for 2030 and beyond, we aim to provide an ultra-long-acting formulation, plus a curative treatment for HIV. In order to realize a cure for HIV, we are currently conducting research using the "kick and kill" mechanism and considering various modalities, and we are beginning to see positive results.

The first-in-human study of S-365598 is expected to be initiated within 2022.

1. Acute infection

S-337395: What is respiratory syncytial virus infection?

Disease overview

- A respiratory viral infection with an infection rate of 100%* by age 2
- RSV infection can cause severe symptoms, mainly inflammation of the lower respiratory tract, especially in the first few weeks to months of life*
- It induces cold-like upper respiratory tract inflammation, and when it leads to lower respiratory tract inflammation, it causes severe bronchiolitis, pneumonia, recurrent wheezing, etc.

There is no effective antiviral drug against RSV,
and RSV infection is one of the diseases with extremely high unmet medical needs

* World Health Organization.(2017).WHO Preferred Product Characteristics for Respiratory Syncytial Virus (RSV) Vaccines.

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Page 90. Next, I would like to introduce S-337395, a therapeutic for the treatment of RS virus infection.

First, an overview of the disease. As many of you may know, RS virus infection is one of the respiratory viral infections, and the infection rate is 100% in children, especially infants and toddlers up to two years old.

RS virus infection is a disease that can cause severe symptoms, mainly inflammation of the lower respiratory tract, in the first few weeks to months of life, and it is not uncommon for the disease to lead to death. It induces a cold-like upper respiratory tract infection, and when it reaches the lower respiratory tract, it causes severe bronchitis, pneumonia, and recurrent wheezing.

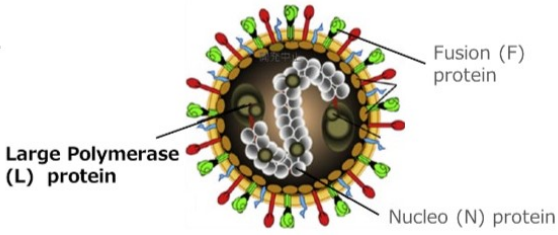
There is currently no effective antiviral drug against this RS virus. Therefore, we believe that this is one of the diseases with very high unmet medical needs.

1. Acute infection

S-337395: Concept and developmental status of competitors

Concept and major development competitors*

- F protein inhibitor antibodies on the surface of virus was launched only
- There are multiple developments centered on F protein targets
- By targeting the inhibition of the L protein, which is essential for viral propagation, wide-spectrum and potent antiviral effect on A and B types is expected



Microbes and Infection Volume 15, Issue 3, March 2013, Pages 230-242

Phase 1	Phase 2	Phase 3	Application and approval	Launch
BC-0335 Shandong	**EDP-938** Enanta	**MK-1654** Merck	**Nirsevimab** AstraZeneca	**Palivizumab** AstraZeneca
RSV-N Pfizer	**Sisunatovir** Pfizer	**Rilematovir** Janssen, Inc.	**Ziresovir** Ark Biosciences	
EDP-323 Enanta				

: F protein inhibitor : N protein inhibitor : Others
: L protein inhibitor : antibody

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* As of October 12, 2022

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Page 91. In this disease background, this is the development status and concept of a competing product that will compete with S-337395 as a therapeutic agent.

The main products and concepts under development are shown on this slide. The only product on the market is an antibody that inhibits F protein on the virus surface.

Then there are several developments targeting the F protein. By targeting the inhibition of L protein, which is essential for viral growth, we have created S-337395 with the expectation of broad-spectrum and potent antiviral effects against type A and type B viruses.

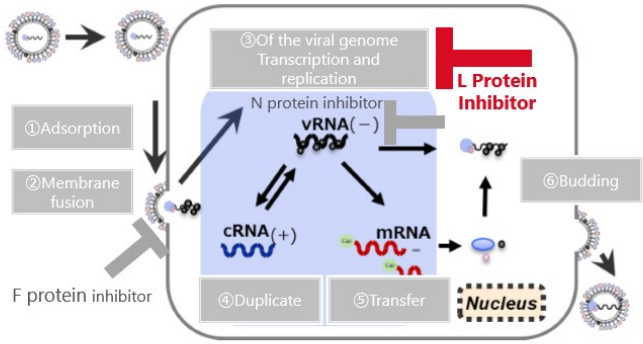
Below is the status of the development that is currently competing with us. We believe that targeting L protein is very unique.

1. Acute infection

S-337395: Compound summary

RS viral replication processes and mechanisms of action

Synthesis of mRNA by RdRp* activity of L protein, the first step essential for RS virus replication, is suppressed by inhibiting the function of L protein



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* RNA-dependent RNA polymerase

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Page 92. Here is an overview of the S-337395 compound, which shows the replication process and mechanism of RS virus.

This concept is based on the hypothesis that by inhibiting the RdRp activity of the L protein, which is an essential first step in RS virus replication, the mRNA synthesis of both type A and type B viruses will be suppressed, thereby achieving strong antiviral activity.

1. Acute infection

S-337395: Non-clinical data

In vitro activity*

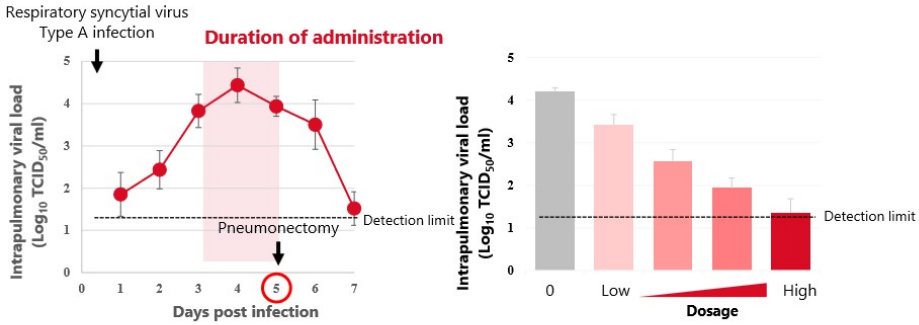
- For types A and B, strong antiviral activity was confirmed

Antiviral activity (EC_{50}; nM)	
A type	B type
0.35	0.76

In vivo drug efficacy* (murine)

- Viral growth is suppressed even when administered at a therapeutic timing around the peak of viral growth

⇒ Strong efficacy according to the dose was confirmed under conditions close to actual clinical conditions.



* Exploratory studies that have not yet performed QA(QC completed)
QA: Quality Assurance
QC: Quality Control

SHIONOGI

Page 93. Here are the non-clinical data that have been tested based on the hypothesis.

As for the in vitro activity on the left side, we were able to successfully confirm strong antiviral activity against both type A and type B, as we had expected.

In the in vivo efficacy study using mice, viral proliferation was reliably suppressed even when administered at the timing of treatment near the peak of viral proliferation, which means that the strong efficacy of the drug was confirmed under conditions similar to those in actual clinical use.

Page 94 please. I would like to introduce a new budding therapeutic for pain treatment. The compound is known as S-151128.

I would like to introduce the unmet needs and current status of pain treatment. The unmet needs for pain medications are drugs that provide analgesic effects for any type of pain. Furthermore, the analgesic effect must be sharp and free from side effects and tolerance. At present, such drugs are hard to find. Currently, opioid therapeutics are considered the most powerful in terms of analgesic efficacy, but as you are aware, abuse and dependence problems due to inappropriate use have become apparent in the United States.

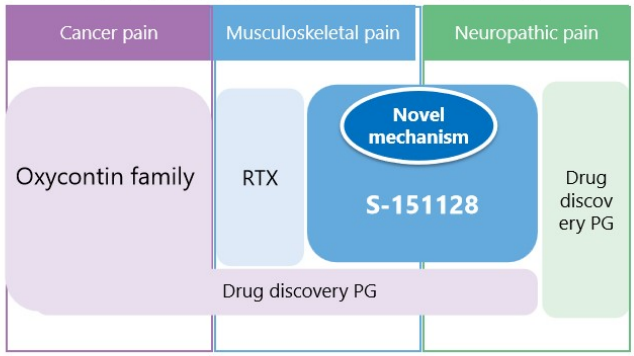
Under these circumstances, prescriptions for opioid medications have declined significantly. Moreover, the situation still remains one of unnecessary suffering due to excessive prescription restrictions and weight loss, which is a challenge.

There are of course existing non-opioid therapeutics, but the level of satisfaction with these therapeutics is not high, and there is a need for new therapeutic agents and analgesics that reduce anxiety about moderate to severe pain care, psychodependent effects, and abuse risk.

S-151128: Actions in the pain area

SHIONOGI strategy for pain treatment

Provides treatment options from a pipeline of diverse mechanisms, freeing patients from the burden of pain



RTX: Resiniferatoxin

SHIONOGI

Page 95.

S-151128 aims to position itself in this area of pain treatment, which is SHIONOGI's goal in this context.

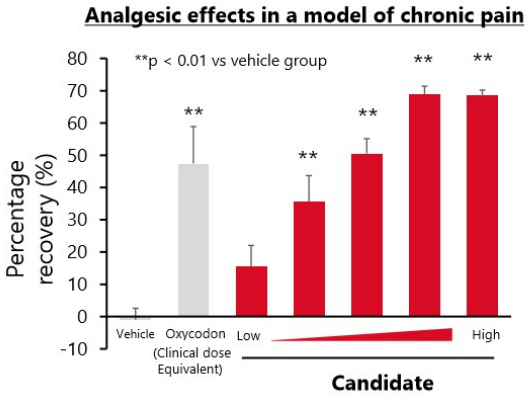
SHIONOGI seeks to free patients from the various hassles associated with pain by offering treatment options in a pipeline of diverse mechanisms, but there are three main categories of pain: cancer pain, musculoskeletal pain, and neuropathic pain areas. In this context, we intend to cover a wide range of pain, especially across musculoskeletal and neuropathic pain, with this candidate compound with a novel mechanism.

Within musculoskeletal pain, resiniferatoxin, which we introduced earlier in the development part. It is a compound under development for osteoarthritis of the knee. And we are running a separate drug discovery program for neuropathic pain.

We are also working diligently on a drug discovery program that would cover the cancer pain area and be effective for a wider range of pain.

S-151128: Analgesic with a novel mechanism

In vivo potency (rat)



Characteristics of S-151128

- Mechanisms of action that are yet to be marketed, such as ion-channels, GPCR*2, and PPI*3, which are highly challenging to discover
- High selectivity to other subtypes is more than 1000-fold
- High analgesic efficacy in multiple pain models

S-151128 is expected to have an analgesic effect equal to or better than that of opioids without the damaging side effects

* Exploratory studies that have not yet performed QA *2 G protein-coupled receptor:G Protein-Coupled Receptors
*3 Protein-protein interaction: Protein-protein interactions

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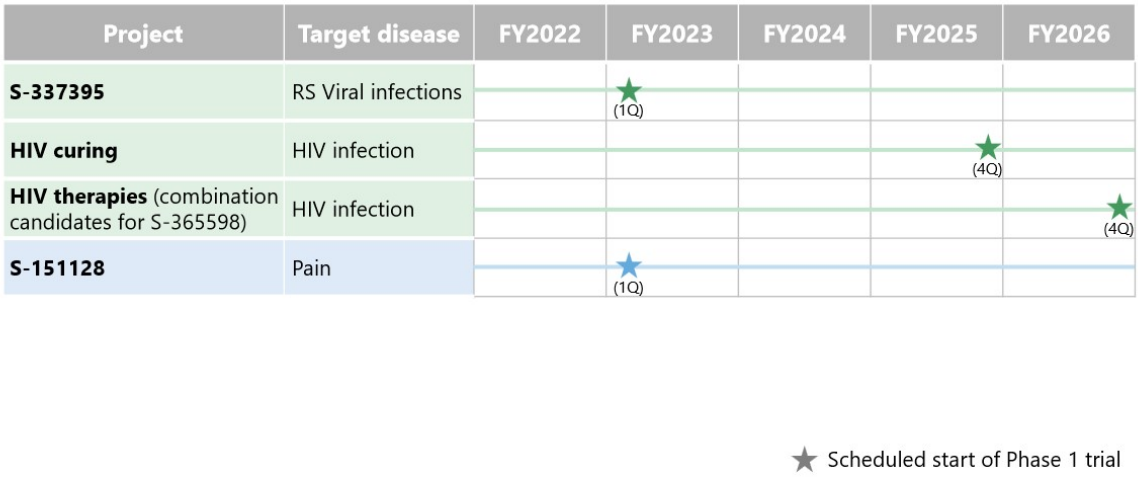
Page 96. Here is an introduction to the medicinal properties of S-151128 analgesic.

The in vivo efficacy on the left side shows that the recovery rate of the oxycodone model used as a reference is less than 50%, but the animal model shows that the efficacy of this candidate is higher than that of oxycodone while having dose dependence.

S-151128 has a mechanism of action that is difficult to discover and has not yet been marketed, like ion channels, GPCRs, and PPIs, but its selectivity for other subtypes is more than 1,000-fold, so it is a compound with considerably fewer side effects and has shown high analgesic efficacy in multiple pain models. It has shown high analgesic efficacy in several pain models.

For these reasons, we believe that the drug can be expected to have a strong analgesic effect equivalent or superior to that of opioids, without the side effects observed with existing drugs and other medications.

Timeline until the start of Phase 1 trial



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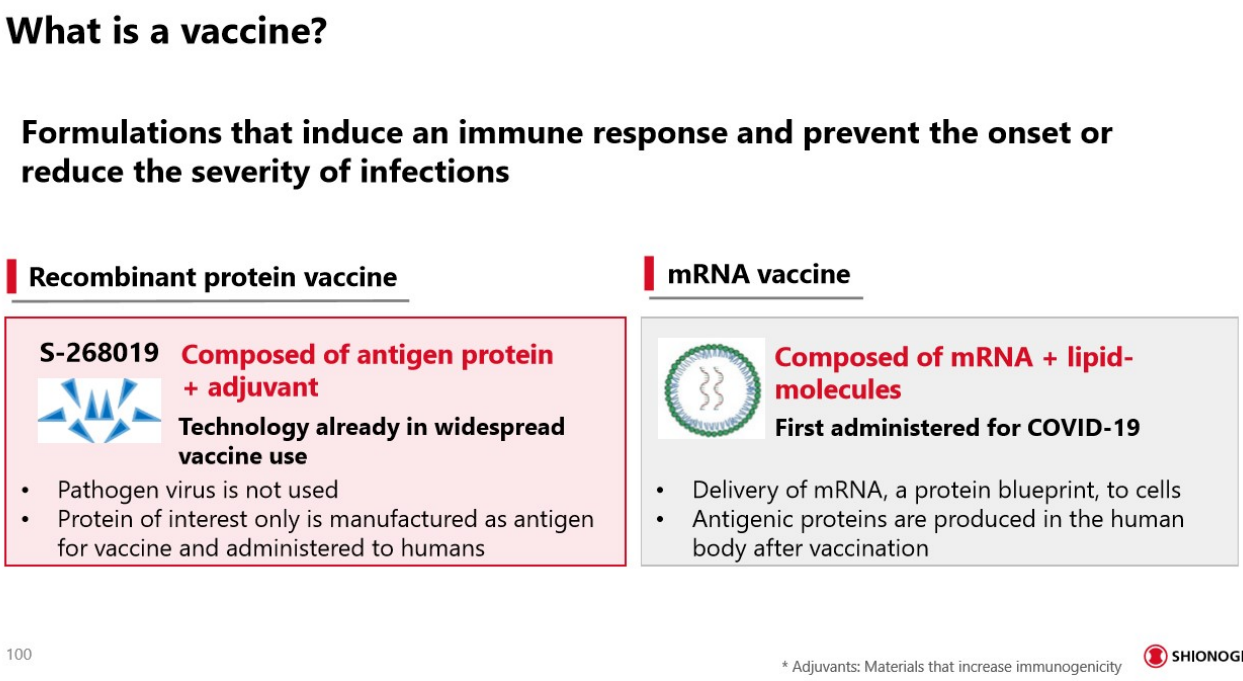
The next slide will be the last. Page 97. This is the timeline up to the start of the Phase 1 trials for the compounds and others we have just introduced.

This compound, S-337395 for the treatment of RS virus infection, in Q1 of the next fiscal year. And then there is HIV curing, and this is the Q4 of FY2025. Then for the HIV therapeutics, S-365598 combination candidate, the Q4 of FY2026. As for S-1511128, the last therapeutics I introduced for the treatment of pain, we are now working hard to develop this therapeutic with the hope of starting the Phase 1 in Q1 FY2023.

That's all from me.

Kyokawa: Thank you very much.

Mr. Aoyama will now discuss the vaccine business. Thank you.



Aoyama: Now, I would like to talk about the vaccine business.

Page 100, please. This is an introduction to vaccines and a brief introduction to vaccines.

As mentioned above, a vaccine is a preparation that is administered in advance to induce an immune response and prevent the onset or severity of an infectious disease.

There are various types of vaccines such as inactivated vaccines in the past, but I would like to briefly introduce the recombinant protein vaccine we are currently using in S-268019 and the mRNA vaccine that has been the focus of much attention since COVID-19. I would like to briefly introduce these two vaccines.

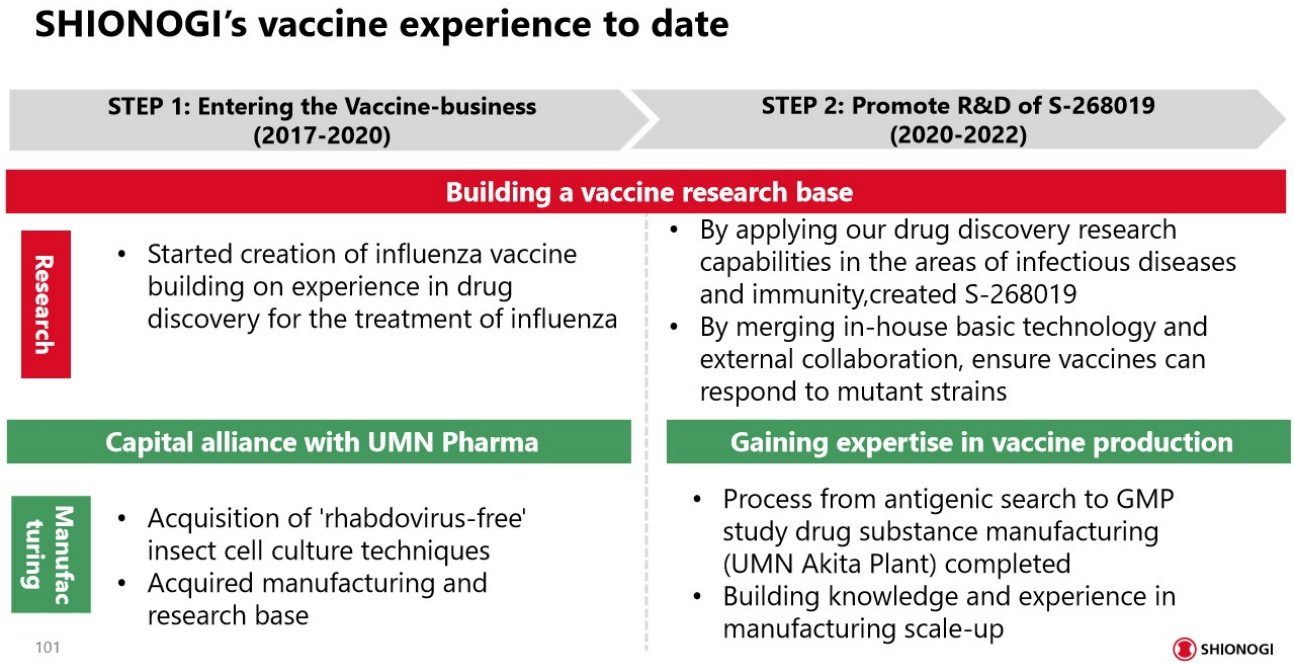
First, recombinant protein vaccines. Basically, it consists of two components: an antigen protein and an adjuvant to boost the immune antigen. The antigenic proteins are produced biologically, using a variety of cells.

In this case, we are using insect cells. There are cell lines in the world that may contain pathogens or viruses. We are conducting our manufacturing activities using cell lines that do not contain such risks.

Basically, the recombinant protein vaccine is characterized by the fact that only the target protein is manufactured as the vaccine antigen and administered to humans.

Next is the mRNA vaccine. mRNA vaccines differ slightly from recombinant protein vaccines. The active ingredient is mRNA, the blueprint of the protein, which is delivered to the cell. Lipid molecules are needed for delivery to these cells.

After the vaccine is administered, a blueprint is sent to the body. Based on this blueprint, the protein that will become the antigen is created in the human body. This is the major difference between recombinant protein vaccines and mRNA vaccines.



Page 101 will introduce SHIONOGI's past vaccine efforts on two axes: before COVID-19 and after COVID-19.

First, I would like to discuss how we started working on this kind of vaccine.

Around 2017, based on our experience in the discovery of influenza therapeutics, we began the creation of an influenza vaccine. Specifically, through the capital and business alliance with UMN Pharma, we were able to acquire safe insect cell culture technology that is rhabdovirus-free, as well as API manufacturing and research bases owned by UMN Pharma.

Then, while the flu vaccine was being studied, the COVID pandemic occurred. Since then, we have been focusing on COVID. Subsequently, we have applied our drug discovery research capabilities in the areas of infectious diseases and immunology to discover S-268019.

In addition, as you all know, mutant strains are appearing one after another. Initially, we did not have an evaluation function, but we are now able to evaluate mutants in a timely manner by integrating our own basic technologies and external collaborations.

Regarding the manufacturing process, we are now able to perform everything from antigen discovery to GMP investigational new drug antigen production, which is performed at UMN's Akita Plant. We are also in the process of acquiring biopharmaceutical manufacturing experience and knowledge through this experience.

Newly acquired research ability through the creation of S-268019

Profile of S-268019	
Antigen	Recombinant antigen S-910823 of the full-length spike protein prepared in UMN Pharma's "rhabdovirus-free" insect cell culture
Adjuvant	Optimaize response to A-910823 for increased neutralizing antibody titer

Acquired new capabilities and technologies through our effors

Adjuvant selection

- Rapid selection of the adjuvant
- Ability to change the adjuvant with flexibility

Neutralizing antibody titer assessment

- Rapid response to the emergence of mutant viruses

Antigen production

- Stable production and supply of investigational products

SHIONOGI

Page 102 is a brief introduction to the newly acquired research capabilities through S-268019 creation.

S-268019, as I mentioned earlier, as a recombinant protein vaccine, the components are antigen and adjuvant. The antigen is a full-length spike protein recombinant antigen prepared from UMN Pharma's rhabdovirus-free insect cell culture.

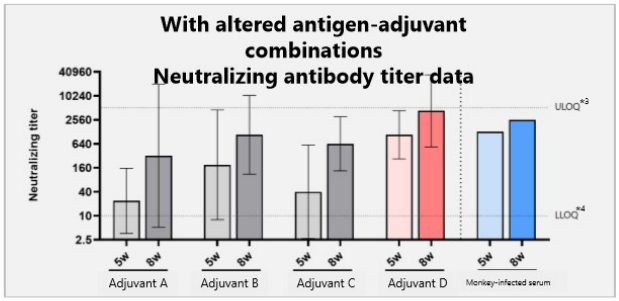
As for the adjuvant, we have selected the most suitable adjuvant to increase the antibody titer against this antigen. We are in the process of acquiring new strengths and technologies through the creation of domestically produced vaccines with superior efficacy and safety.

First, regarding adjuvant selection, we have actually included two adjuvants in our clinical trials. This will be discussed on the next page.

Also, neutralizing antibody titer evaluation, which is also very important. At present, we are able to respond quickly to the emergence of mutant viruses. In addition, we have achieved antigen production, stable manufacturing and supply of investigational drugs.

Adjuvant studies essential for the creation of S-268019

Previous adjuvant research	1st adjuvant selection in S-268019	Clinical studies with 1st adjuvant 2nd adjuvant selection	Decided to change adjuvant
Accumulated knowledge of adjuvants including by S-540956 creation	Selection of adjuvants based on VDE*1 risk and Th1*2 selectivity risk	Explored multiple combinations of antigens and adjuvants in parallel with Phase 1 trial	Higher neutralizing antibody titer induction



Approximately 4 months from the decision to change adjuvant to the start of the second Phase 1 trial

Appropriate adjuvant selection was achieved

*1 Vaccine induced Disease Enhancement *2 helper T1 cells *3 Upper limit of quantification *4 lower limit of quantification

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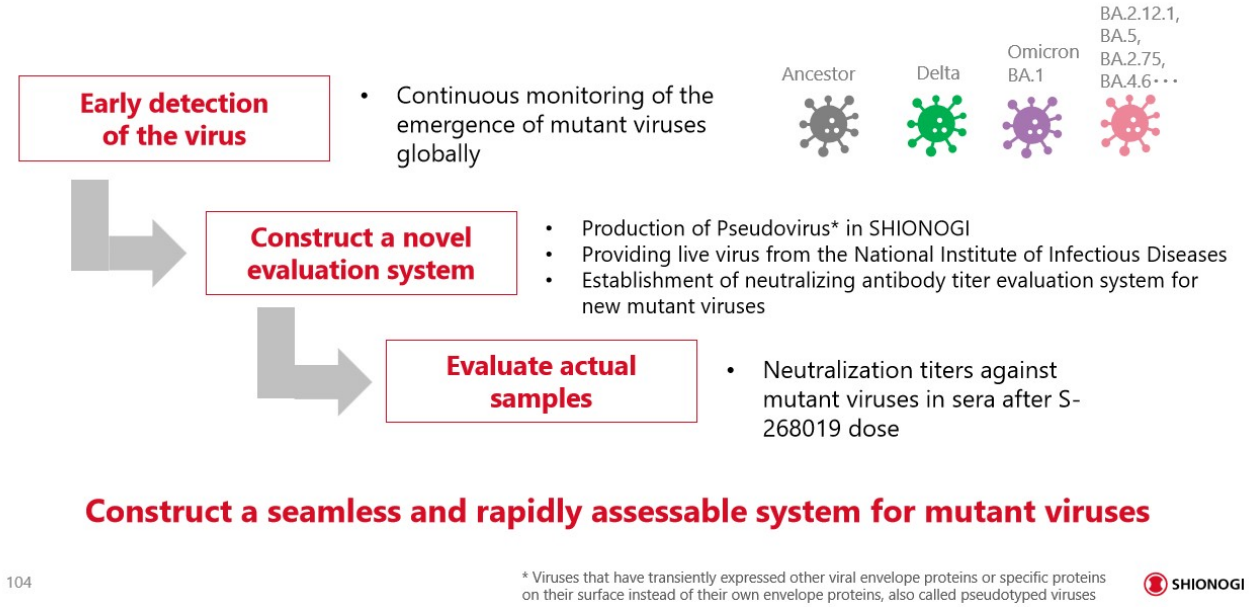
On page 103, we will introduce the adjuvant research essential for the creation of S-268019 and how the adjuvants currently available have been discovered.

We have been accumulating knowledge on adjuvant research through the creation of S-540956. The COVID-19 occurred at that time. First, in the selection of the first adjuvant for S-268019, we selected the first adjuvant based on the following considerations: VDE, disease enhancement by vaccine administration, and helper T cell selectivity. We selected the first adjuvant.

We were conducting clinical trials, but the neutralizing antibody titers were not rising fully, so we were screening for a second adjuvant in parallel with the clinical trials.

The figure there is the result of a non-clinical study. We have conducted various evaluations. Non-clinical results were seen that the adjuvant D described here resulted in a very good neutralizing antibody titer increase. As a result, we immediately decided to make the change and began a second Phase 1 study. This period naturally included the production of a new adjuvant, which was accomplished in four months.

We believe that through the accumulation of adjuvant research to date, we have been able to select appropriate adjuvants for our antigens and change them flexibly.



As I mentioned earlier, mutant viruses are emerging, so it is very important to establish this evaluation system. The diagram shown here illustrates the current situation at our company. This was built in a short period of time.

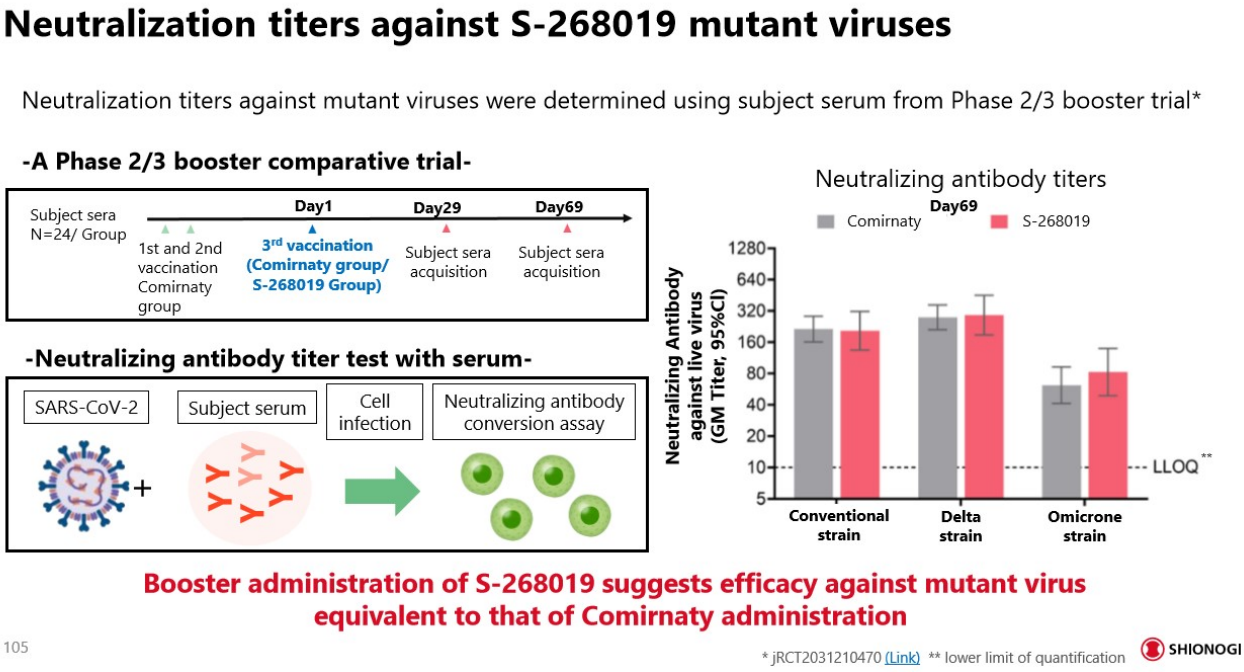
Currently, when new viruses are discovered, we monitor the emergence of mutant viruses on a global basis, and as soon as we see such a virus, we immediately start working to establish an evaluation system.

Currently, we are constructing two major evaluation systems. We have two production systems, one using pseudovirus and the other using live viruses. This pseudovirus is not a live virus itself, but a virus that resembles a live virus. The reason why this is good is that it can be constructed in a timely manner and in a very short period of time, and we are first constructing an evaluation system using pseudovirus, where speed is very important.

In addition, the National Institute of Infectious Diseases, or NIID, will provide us with live viruses, and we will also have an evaluation system using these viruses, so that both parties can confirm the results.

The actual specimens are then evaluated, for example, in the measurement of neutralizing antibody titers against mutations and mutant viruses in serum after administration of S-268019.

In this way, we have established a system that enables seamless and speedy evaluation of mutant viruses.

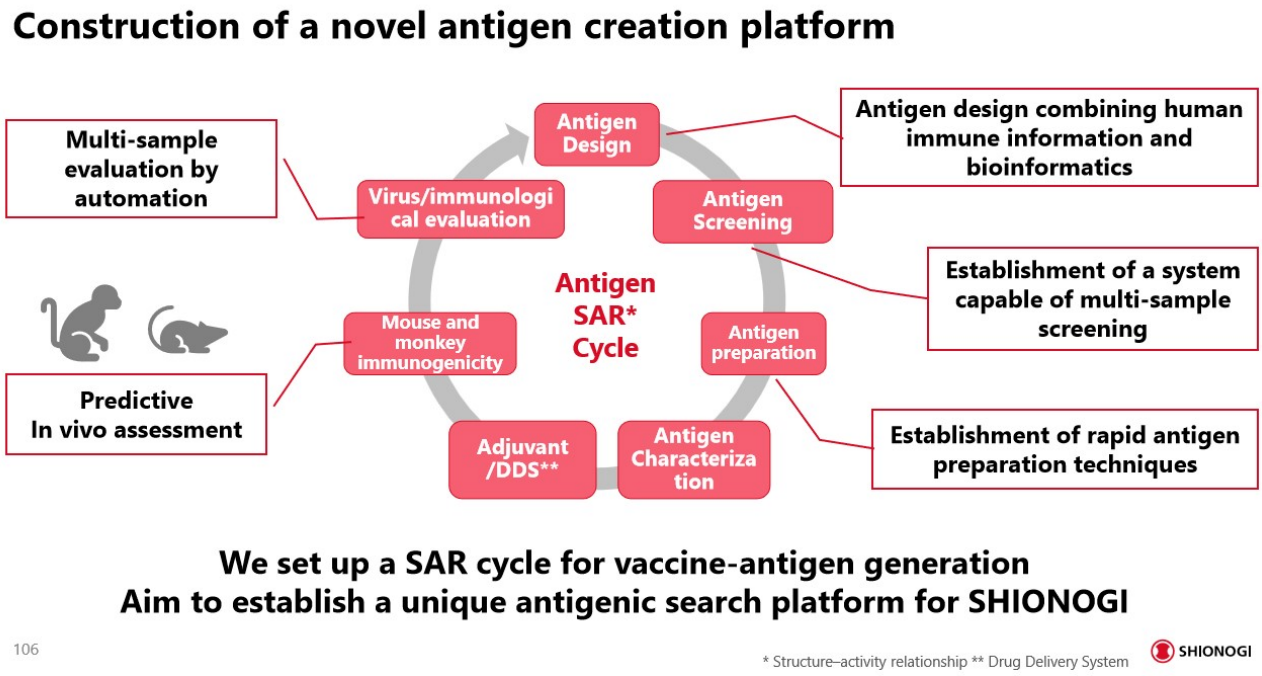


Page 105 is about neutralization titers against the S-268019 mutant virus, and how we are measuring neutralization antibody titers using the evaluation system I presented on the previous slide.

As mentioned in the previous development part, using the subject sera from the Phase 3 additional immuno-comparative trial, we are checking the neutralizing antibody titers against the Delta and Omicron strains through human sera, as I mentioned earlier about the neutralizing antibody titers against the conventional strains.

Specifically, neutralizing antibody titers were measured in the COMIRNATY group and the S-268019 group in the third time, respectively, after COMIRNATY administration for the first and second time. That is the figure on the right.

The gray is COMIRNATY. The red will be S-268019. The vertical axis of the results for the conventional, Delta, and Omicron strains shows neutralization titers, and the results are similar, suggesting that the efficacy against mutant viruses is equivalent to that of the COMIRNATY administration.



Page 106 is about the construction of a new foundation for antigen creation, which we intend to create as our strength.

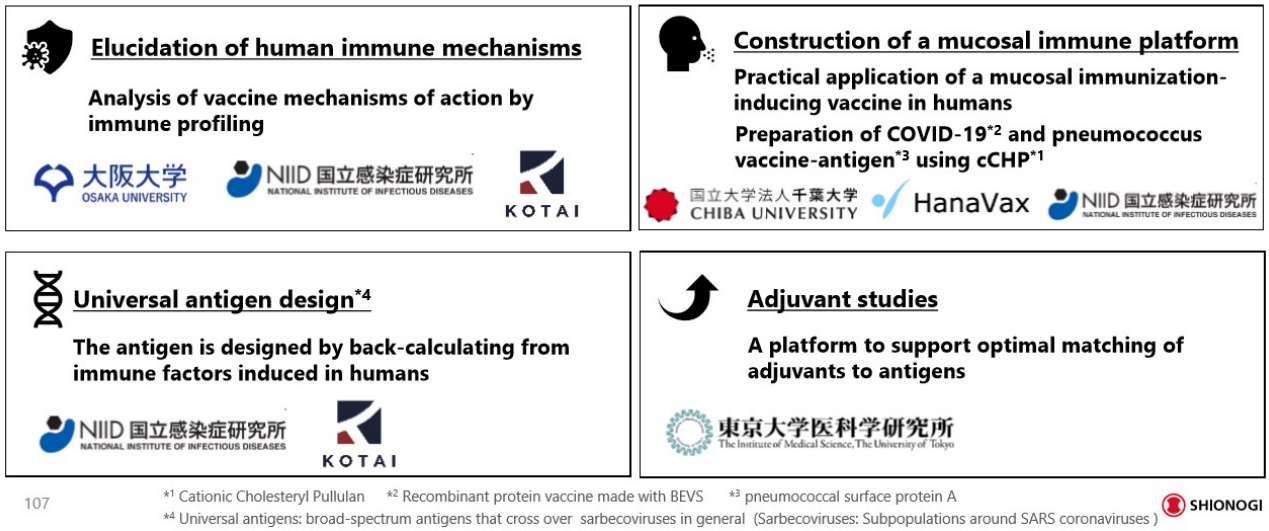
Regarding small molecules, we have a drug discovery platform for the speedy development of such small molecule drugs with our small molecule drug discovery engine. We will apply this drug discovery platform to the vaccine business.

The cycle is described there. In vaccines, especially for proteins, antigen design, or sequencing, is very important. We are now working to design antigens by combining human immunological information and bioinformatics and hope to make this our strength.

After that, we are currently studying the possibility of constructing a system that will enable us to screen in a timely and speedy manner whether the designed product can actually be produced as a real product, whether the cells can properly produce the protein, whether the produced protein is really safe in terms of physical properties, and whether the neutralizing antibody titer actually rises. We are currently studying the possibility of establishing a system that would allow us to conduct these screening processes in a timely and speedy manner. We are aiming to establish SHIONOGI's own antigen discovery platform in this area.

External cooperation

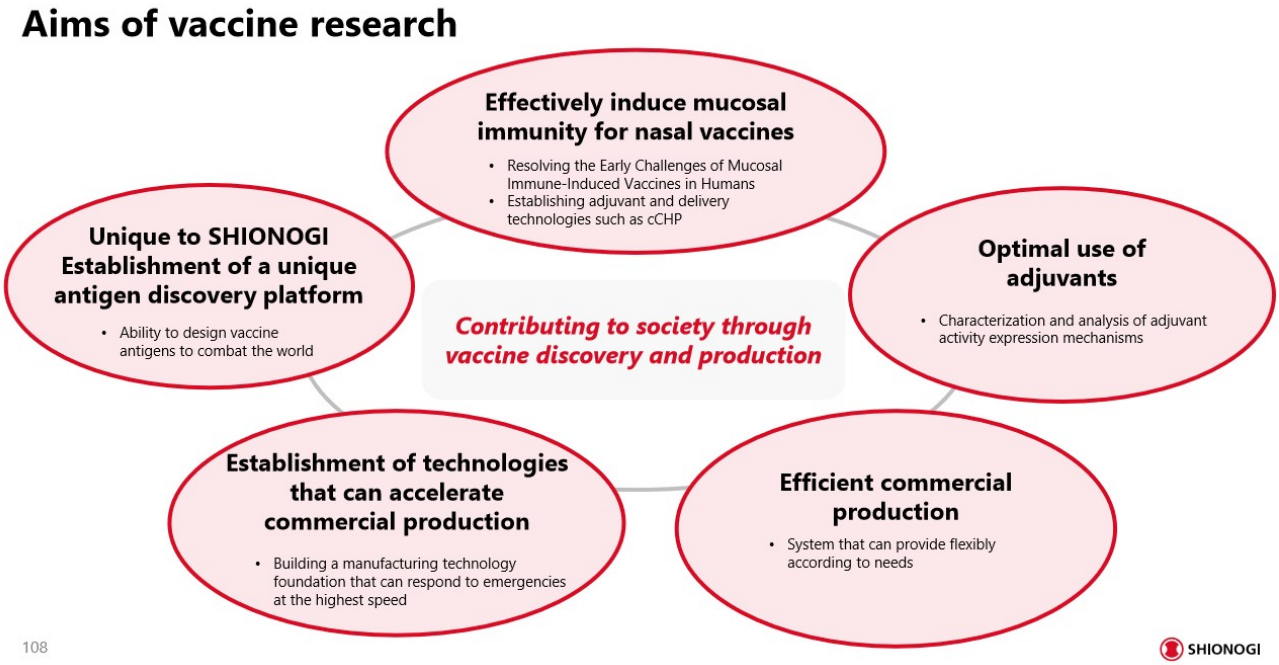
Collaborating with world-leading research institutes and companies to build technical infrastructure and create new vaccines



*1 Cationic Cholesteryl Pullulan *2 Recombinant protein vaccine made with BEVS *3 pneumococcal surface protein A
*4 Universal antigens: broad-spectrum antigens that cross over sarbecoviruses in general (Sarbecoviruses: Subpopulations around SARS coronaviruses)

This is where we work with outside companies.

We are working with world-class research institutions and companies to build a technological foundation and create new vaccines in order to build on our various strengths and establish a foundation. We have shown some examples of this here.



Page 108. This is the figure we are aiming for in vaccine research.

The five main points are listed here. The platform for antigen discovery, which I have just introduced to you. The creation of a vaccine that can effectively induce mucosal immunity, which I will not discuss at this time due to time constraints. This applies to intranasal vaccines. Or how to speedily establish manufacturing methods and analysis for important adjuvants for recombinant proteins, or antigen preparations, and how to actually bring them to commercial formulations.

By firmly establishing such a platform, we aim to contribute to society through vaccine creation and become a company that is indispensable to the world.

That's all from me.

Kyokawa: Thank you very much.

John Keller will continue with a summary. John, will you?

Keller: Thank you. Please take a look at page 111.

Based on the experience through COVID-19 and toward the completion of our STS 2030, we will continue to focus our resources and capabilities to address unmet medical needs in a timely manner.

As we go forward, we would like to do this while creating new drugs and developing new platforms and health solutions to the fullest extent of our modality in the future. Based on these transformations, we hope to achieve our future goals.

Upcoming pipeline events 1/2

As of Oct. 12, 2022 Not all plans are listed

Pipeline	Indication	Stage	FY2022 3Q-4Q	FY2023	FY2024
olorofim（F901318）	Invasive Aspergillosis	Phase 2b、Phase 3	Ph2b Interim report (3Q)		Ph3 Completion of case registration (4Q)
S-337395	RSV infection	Preclinical		Ph1 start (1Q)	
S-365598 (HIV franchise, out license)	HIV infection	Preclinical	Ph1 start (3Q)		
resiniferatoxin	Pain associated with knee osteoarthritis	Phase 3			Ph3 topline results (2Q) Submission (3Q)
zatolmilast（BPN14770）	①Fragile X Syndrome ②Alzheimer's disease	①Phase 2/3 ②Phase 2	①		Ph2b3 topline results (4Q)
zulanolone（S-812217）	Depression	Phase 3		Ph3 topline results (3Q)	Submission (4Q)
S-151128	Chronic pain	Preclinical	Ph1 start (4Q)		

● Timing of trial start ★ Timing of topline results ◆ timing of submission

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These two slides show what events are coming up. In particular, I would like to draw your attention to the seven programs on this slide, six of which are related to alliances or acquisitions. The last one, S-151128, which is about pain, there was talk of a new mechanism.

S-365598 is a ultra long-acting, and it is also based on our innovation. If you look at the other compounds, some are related to regional in-licensing, and then there are some related to acquisitions and in-licensing.

So, our commitment is always to do this through internal innovation. And not only that, we would like to leverage the capabilities of our partners, and for Japan, and globally, and also to expand our pipeline and utilize various things as a toolkit. We hope to accomplish this with our new R&D organization.

Data from the Phase 2b and then Phase 3 will be available in the future. The Phase 1 of S-337395 will begin in FY2023. Then the Phase 1 of S-365598 will begin this year. Resiniferatoxin will have a top-line report in FY2024, and zatolmilast, and others like it, in FY2023. Then we will begin the Phase 1 of S-151128 this year.

Upcoming pipeline events 2/2

As of Oct. 12, 2022 Not all plans are listed

Pipeline	Indication	Stage	FY2022 3Q-4Q	FY2023	FY2024
redasemtide (S-005151)	①Epidermolysis bullosa ②Acute ischemic stroke ③Knee osteoarthritis ④Chronic liver disease ⑤Cardiomyopathy	①Preparing for additional clinical trial ②Preparing for Phase 3 trial ③④Investigator initiated clinical trial（Phase 2 trial) in progress ⑤Preparing for Investigator initiated clinical trial	① Submission (3Q) ② Ph3 start (4Q) ⑤ Ph2 start (2Q)		
S-309309	Obesity	Phase 1	Ph1 topline results (3Q)	Ph2 start (4Q)	Ph2 topline results (3Q)
S-531011	Solid tumor	Phase 1b/2		Ph2 start (4Q)	
S-770108	Idiopathic pulmonary	Phase 1		Ph2 start (1Q)	

● Timing of trial start ★ Timing of topline results ◆ timing of submission

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S-005151, redasemtide, but we are also aiming to file for nutritionally impaired epidermolysis bullosa, FY2024 for this as well. And global Phase Ⅲ for stroke will start FY2022, and plans are currently being made for a physician-led program.

The results of the Phase 1 will be available this year for the S-309309, and the results of the PoC will be available next year.

S-531011, solid tumors, for which Phase 2 will begin in FY2023. This is after the selection of the dose escalation.

S-770108, IPF, for which The Phase 2 will begin in FY2023.

Thank you very much.

Kyokawa: At this time, Mr. Teshirogi will provide an executive summary. President Teshirogi, thank you.

Teshirogi: Hi, I'm Teshirogi. Thank you all for your time and attention today.

The event is running a little long. What I would like to share with you today is our new R&D organization structure. Since July, we have been operating under a drastically different governance structure of the executive teams.

Before July, all the general managers representing 10 or 11 divisions had attended the meetings under the name of the Management Committee and, during the past several years of monitoring, I started wondering if the number of speakers during these meetings was balanced, or if the key decisions were truly coming from a mutual agreement of all the representatives. And so, I applied four major frameworks to reshape the organization: R&D, production & supply, sales & marketing, and corporate. The people who represent these frameworks are called supervisory unit, within this framework, we

are quite conscious of speeding up the executive actions supported by fairly rapid review by the four divisional directors, plus two executive officers, we have multiple auditors, effectively, a total of six.

For this R&D presentation today, for example, John and three other officers exercised their autonomy to build the presentation deck. You may have noticed that the R&D meeting presenters are different from two years ago. I would like to keep this new scheme of four for the time being.

Since BD has continued to operate under John, we are trying to speed up the decision-making process by integrating BD, research, and development into a single operation that can be directly linked to the Management Committee. Our goal is to achieve the growth that we envision for society after COVID-19, between 2023 and 2024.

Of course, we would like to finish ensitrelvir and 019 accordingly. Ensitrelvir is still under review, which makes it difficult to disclose everything we know; however, we believe that it relates to standard risk in a true sense all over the world. In other words, a therapeutic drug candidate that is not limited to high-risk patients and therefore is highly challenging for any organization to tackle. In this situation we achieved one milestone.

We will continue to grow these projects from here in an LCM-like approach, but it does not mean that we will continue to talk only ensitrelvir and 019, these are a part of what John and the three directors decided to share today in terms of what is in the pipeline as of now regarding infectious diseases, pain, and neurology.

Please use the remaining time of today's meeting to ask your questions that you may have. I may or may not intervene in answering some of them but otherwise, I would like to let these four executives to take your questions directly.

I look forward to your continuous support.

Kyokawa: Thank you very much, Mr. Teshirogi.

Question & Answer

Kyokawa : Okay, I will now take your questions.

How about Mr. Kohtani.

Kohtani : I am Kohtani from Nomura Securities. Thank you for your presentation.

As for ensitrelvir, I was looking at the data this time, and I thought that it worked for less than 72 hours, but if it was within 120 hours, p was not achieved. And Kaplan-Meier, right, this page 26. If you look at a long period of time, it will inevitably see a cross or coming close. A way of interpreting the results is that it may have a difference if it in a short period of time but if it's longer, there are differences by individual depends on immunity of each person.

What I would like to ask is, what will happen to Japan in the end. I am not sure about this current process, but I think that if SCORPIO-HR works out in the end, everything will work out well. The duration of symptom resolution is four days or more, which is probably different from Japan. Based on the current data, first of all, is SCORPIO-HR, within 72 hours? And can you please tell me how this probability of success changes when it is more than four days? This is my first question.

Keller : Thank you. Now look at page 26.

It is a little difficult to see, but the blue and black lines do not cross each other, although they are quite close. Then the second point, which must be considered in all of this, is the duration of the antiviral. This is an antivirus, so if you look at the strongest one, the most, if you look at the RNA slide, it's at the beginning of that. 72 hours.

If you look here, you will see that there is a very large difference between before and after 72 hours. Changes in the amount of RNA is big different. So, this kind of effect is very important in the first 72 hours, and this is the role of antiviral drugs.

For standard-risk patients, symptom resolution is like this on the 16th and 18th day. And then, regarding high-risk patients, SCORPIO-HR, I think it can alleviate symptoms, regarding the profile of high-risk patients.

This may have to do with personal immunity, since the design of this study is supposed to be 120. However, it may be necessary to interpret the standard risk, and then the high-risk part, in a different way of thinking.

Uehara : This is Uehara.

I would like to add one more point: the endpoint we have set for the second half of Kaplan-Meier is the time until all symptoms have completely disappeared.

The nose, cough, throat, and fatigue are all symptoms that make it difficult for even a normal person to fully recover from the disease. Furthermore, during the winter season and early spring, for example,

there comes seasonal allergy, and the nose can get stuffy or runny. This is really a sensitive endpoint as an endpoint.

Kaplan-Meier often shows that there are people who have died in the form of cancer drug indicators, but this time it is basically a curable disease, so it will all stick together in the end.

Therefore, the Phase 3 part of this evaluation is focused on increasing the number of patients who receive treatment as soon as possible and recover from the symptoms at the earliest possible time.

Kohtani : I understand, that in essence, this means that SCORPIO-HR is administered within 120 hours, not 72. Moreover, in the Japanese trial this time, as I recall, it is only required that the symptoms disappear for at least one day. In the US, this had to be for four days in a row.

What you are saying is that it is true that high-risk patients have quite a lot of symptoms, so I understand that the recovery of those symptoms will be quite different. What is the probability of success for the standard risk of SCORPIO-HR, and how should we think about it in the normal way? Can you please suggest us something?

Uehara : Regarding the definition of the endpoint of symptom resolution, in the Phase 3 part of the trial that we conducted in Japan, if the symptoms are disappear for 24 hours, we define it as symptom resolution. On the other hand, in global trials, if a longer period of time is set, such as 96 hours, or if the symptoms disappear completely for a long period of time, of course, this will cause a lot of noise, so there is probably no global standard on how many hours is good.

In fact, we have been communicating with the FDA, and since the FDA recently came up with a different figure of 48 hours, we are now asking if the SCORPIO-HR trial can be changed to 48-hour duration.

Based on the data we have obtained, including the duration of symptom resolution and sustained resolution within the trial conducted our Asia area, we will discuss the design of the SCORPIO-HR trial with the FDA and other global authorities.

In particular, as key takeaways, symptoms were improved by lowering the virus in patients who had the virus. It is a matter of course, but this study confirmed this in this patient.

So, if a patient has persistent viral shedding, we believe that there is more than enough room for symptoms to improve by lowering the virus beyond 72 hours, as a matter of course.

These are the results in Japan and Asia in the current immunological situation and the current epidemic strains. Therefore, I would like to ask for more time to interpret the data and discuss the design in terms of the probability of success on a global scale as well as if it is having to be strictly within 72 hours.

Kohtani : I understand.

Also, regarding the commercial potential of ensitrelvir, this is of course a matter for the authorities to decide, but if we look at it in a normal way, these five symptoms are more like omicron, more than COVID-19. So, I was concerned that it might be more Omicron medicine than COVID-19.

As shown on page 28, the 14 symptoms showed a statistically significant reduction, so am I correct in understanding that this can probably work for the entire COVID-19?

Also, looking at the DDI, the CYP3A inhibition interaction is the same as PAXLOVID, according to the current review report, etc. I feel that it may be somewhat difficult to use for pregnant women. How do you see a commercial potential?

Keller : Regarding the Omicron Phase 1 is still most similar to influenza. Improvements of this type have been observed in oral influenza medications.

The most important goal is for society, and individuals, to return to normal life as it was. I think the only demonstration we found out from this demonstration is that we were able to demonstrate its effectiveness in an omicron context. Oral med and easy to use, this are exactly what we are targeting.

And as for the antiviral properties, if the pandemic were to return, I believe that the effectiveness to this virulence would be recognized. But the key points are still eased to use and targeting standard-risk patients.

Teshirogi : As for whether it only works for Omicron or not, it just so happens that Phase 2a is 100% Delta data, and everything from Phase 2b to Phase 3 is Omicron.

Naturally, we are taking data from Phase 2a to see how much the virus goes down and what the symptoms were, although the number of cases is small. So, our interpretation is that it just happened to be Omicron, and we don't see any reason not to cover all viruses withing COVID-19 extension, so there I think it should work fine.

As for new variants that will come out in the future, unless the virus has a very strange resistance to 3CL protease or something like that, I believe it should cover them.

As for commercial potential, as you mentioned earlier, we have to work on DDI one by one thoroughly at this point, but we believe that the first starting point is at the same level as PAXLOVID. Then, as for pregnant woman, it is still rather similar in level to LAGEVRIO.

However, potential target patients are for those of standard risks. In the case of high-risk patients, the older age group is also a high-risk group, and many of these patients are taking a considerable amount of concomitant or medication.

In this case, we were in the Phase 3 part with Omicron, 35 years old, and many of the patients were quite young, and most of them had very few regular medications, or so-called chronic medications. In that sense, the populace subject to DDI itself is totally different between high risk and standard risk.

From the point of view of actual Japanese clinicians, if it is allowed to prescribe to standard risk patients, there is no DDI for their patients who come to their clinics. In fact, the potential is very great because there is no need to check the GFR that applies to PAXLOVID such as renal dysfunction and prescribe smoothly.

The price will depend on how much it is. Since government purchase is not only option for standard risk and commercialization including price setting for each country is still under discussion at this point.

Kohtani : I understand.

Last but not least, I personally think that S-531011 is the biggest hidden gem of SHIONOGI. Of course, we don't know yet, I would like to know the background, where it came from. Tregs in cancer tissue are highly expressed in single cell analysis and not in Tregs of other tissues. I think it is very interesting that the target was chosen because it is not expressed on normal CD4/CD8 T cells.

This is next year's PoM, but will there be data on changes in CCR8 positive Tregs in the tumor, which is sort of a given already, so what I wanted to see the most is whether T cells are activated by removing Tregs. If this is activated, then pembrolizumab will also work, and we can see some commercial potential.

So, I would like to ask you, if that were to happen, would you go so far as to cut the central nervous system and invest in cancer? This is the last.

Teshirogi : Uehara will answer in term of the protocol.

Uehara : Thank you for your question.

As you mentioned, as PoM, for example, we look to see if the number of Tregs infiltrating the tumor is decreasing, but we will also examine various markers from different perspectives. Of course, we will not only look at Tregs and molecular markers, and we will also look at whether the tumor is shrinking or not. We can also take such parameters as whether it is progressing or not, so we plan to determine its potential compliantly based on data from various patients, first as a single agent, and then in combination with pembrolizumab.

Teshirogi : That question is very difficult to answer, and I think it depends on how many multiples of combination therapy you have to consider. Considering the current state of cancer treatment, it is not likely that everything can be settled with a single agent. Realistically, considering how smoothly a partner drug can be selected, I think that it would be a realistic solution to work with a partner who is currently engaged in a wide range of anticancer drugs.

Kohtani : Thank you very much.

Kyokawa : Mr. Yamaguchi from Citi, go ahead.

Yamaguchi : I am Yamaguchi from Citigroup.

The first question is about enshitrelvir. I think you are saying that you have presented data for both 125mg and 250mg at Kaplan-Meier and that it has not been verified, I am a little confused as to how to look at this 250mg data from a non-professional view.

The usability of this 250mg, as red seems to be subtly a little less. Maybe you are not developing it now, but how will you develop this 250mg in the future? Also, could you first tell me how to look at the first Kaplan-Meier data?

Uehara : Thank you for your question.

As to which has a stronger antiviral effect, 125mg or 250mg, I interpret this data to be the same for both. Many experts have also evaluated the antiviral max effect at low doses, and the same trend was observed in Phase 2b, which was also confirmed in Phase 3. Antiviral efficacy has already reached max at low doses.

As for the significance of the high dosage, one of the most significant values is that we were able to confirm that there were no safety issues even when double-dose was used.

Specifically, because it is an antiviral drug, there is of course the view that if it is safe, the higher dosage is better. However, considering the risk of DDI and various other factors, it is a risk to raise the dosage carelessly. Low doses are sufficient for the current epidemic strain and the current immune situation. However, we do not know how the virus will change in the future.

Perhaps, as Teshirogi mentioned at the beginning, we may see a virus that looks like an altered 3CL protease. In such a case, it is very significant that the safety can be assured by administering double the dose as a contingency option. This is the reason we kept evaluating the high dosage variety to the last.

Yamaguchi : You have not verified 250mg on the Kaplan-Meier, but 0.02 looks good from a numerical point of view, which is fine because it has not been verified, but can you say that this was working properly?

Uehara : In terms of significant differences in the validation study, only the low dose was significant, but as you can see, the p-value was less than 0.05.

Yamaguchi : So, it does not mean that the small dose works but the high dose doesn't. The small dose works, and the high dose also works, although you didn't say that because you didn't analyze the data, but the data shows that it worked, is that what you mean?

Uehara : You are right.

Yamaguchi : I understand.

Secondly, and this is a bit off topic, but S-309309. Not that I'm asking because I'm fat, but there has been talk of anti-obesity drugs, and it seems to me that this is an area that is suddenly gaining momentum, just as oral GLP-1 has recently begun to be developed.

I have a feeling that it would be very druggable if the concept were to decrease by 10% or more a year, as it is written here. Looking at it from this mechanistic point of view, it seems like it might cause gastrointestinal symptoms, but so far, the balance between potential side effects and effectiveness. Especially in the case of oral drugs, there are various possibilities such as difficulty in taking, ease of taking, nausea, etc. How are you looking at that at the moment?

Uehara :

The extremely high tolerability of the drug has been confirmed in nonclinical animal studies, and in Phase 1 of clinical trials, no side effects of concern have been observed even after escalation.

Yamaguchi : If anything, this goes into appetite suppression rather than digestive symptoms. Amount of eating is reduced.

Uehara : You are right. The mechanism of action is not in the form of inhibition of absorption of lipase and such, which results in lipid stools and diarrhea. It is not an inhibitor absorption, although it does act in a similar process to the absorption of triglycerides.

Yamaguchi : I understand. Thank you very much.

Teshirogi : Also, in my experience with NPYY5, I still think that weight reduction, including appetite, is difficult because when one mechanism stands, another one compensates. Appetite is essential for human, so if we suppress it too much, other things will kick in. I was wondering if there is a dual mechanism, perhaps including a combination with GLP-1, in terms of long-lasting effects.

We were wondering if it is possible that if you keep doing that, it will gradually become ineffective. In that sense, I thought it would be very good for people to have a mechanism, something different. I would like to see this somehow.

Yamaguchi : While we are on this topic, since there are only a few GLP-1 groups, do you think it would be better to work with them? Is this your company's way of trying to establish a franchise in a certain way? How about that?

Teshirogi : I often talk about this with John.

We commercialized Xofluza but not Xocova this time, I think we can probably finish the development by ourselves but when it comes to commercialization, I think we will need a partner in the primary care field.

Anti-obesity drugs do need primary care as well as fairly strong sales and marketing. Even if the development is successful, we are probably not selling them all on our own, so at some stage we will need to think to have a realistic partnership.

However, in order to increase our value split, we would like to develop as much as possible until the end of the project.

Yamaguchi : Thank you very much.

Kyokawa : Ueda-san, go ahead.

Ueda : My name is Ueda from Goldman Sachs Securities.

I would like to ask you about ensitrelvir, as well. In light of this data, is there anything that needs to be done in the areas of distribution or testing in order to make effective use of this very fine drug? Also, I think that long COVID-19 is a very serious problem, so I would like to know what your company is doing to address this issue.

Teshirogi : The develop team will answer the question about long COVID-19, etc., but as Mr. Ueda said, as to how to market it, I think it is very important how to develop it on a global scale to facilitate proper diagnosis.

In Japan, we have been selling dual antigen test kits for influenza and COVID-19 since this October in cooperation with Towns. We are seriously discussing within the Company that unless we have our own diagnostic agent capability for acute infectious diseases, we may not be able to maximize the global market in mid- to long-term basis.

Once we had a diagnostics department, which has continued only quite sparsely, and it is called the biomarker R&D. When we do this acute to chronic infectious disease, we need to have diagnostic capabilities.

We have heard this story at cefiderocol, and we have experienced that the delay of diagnostic reagents has slowed down the spread of the disease globally, so we believe that diagnostic capability is necessary for the treatment of infectious diseases.

Although there is the question of whether to do it by ourselves or to work with a very premier partner, I have experienced that not having this network in our hands has been quite detrimental to the maximization of drugs, so this is a priority for us right now. We are considering this matter with a high priority.

Uehara : Regarding long COVID-19, we are collecting data on the presence or absence of post-COVID symptoms at each of the follow-up digits in the Phase 2b and Phase 3 studies that we are conducting, which are three months, six months, and one year, respectively.

Naturally, we cannot collect data from all patients, but there are many patients who voluntarily submit data, so we will analyze such data to see if we can meet the expectation that taking this drug will reduce the risk of developing long COVID-19.

Specifically, the long COVID-19, which has not been very visible, is apparently more likely to be persistently infected with the virus. We are gradually accumulating various evidence that something like reservoir cells is lurking in the body, or that inflammatory responses such as spike proteins or antigens are circulating thinly in the blood, and that such inflammatory responses are continuing all the time.

First of all, what do we define as long COVID-19, including defining what is long COVID-19, as a biomarker in the blood and as a symptom? We would like to analyze the data we have collected this time with this in mind.

Keller : We are currently talking with US government scientists, regulators, and then epidemiologists to discuss what endpoints should be set. We are still examining what long COVID-19 is and whether it differs from common COVID-19 symptoms or whether it has some more complex, neurological manifestation.

Ueda :

Secondly, I would like to ask about S-309309. You have told us that Phase 2 will be done as a single agent or in combination, also comparison with the GLP injection, but what is the impact on the development of your S-309309 as the development of the oral form is underway?

Uehara : First of all, we are planning Phase 2 study, which will be developed as a monotherapy. Naturally, since this is a proof of concept, we would like to achieve 10% weight reduction with a single

agent alone. After achieving the goal with single agent, then we would like to consider maximizing the value potential including combination.

Teshirogi : Since we are really just getting started with the oral GLP-1, we are not yet able to read what level of weight reduction we will achieve in Phase 3.

Maybe I am inflexible, but we had been going through bitter experiences with single mechanism for long time, so I think it is very difficult to keep delivering with only one mechanism. I think human homeostasis is quite effective. In that sense, I think it would not be a bad idea to have both with GLP-1.

I am not sure how widespread the use of GLP-1 injections will really be among the Japanese, but there are many people who say that it is more painful than expensive. Some said that the injections were so painful that Asians would have a hard time keeping such things up for a long time, and that an oral anti-obesity drug would still be good for a long time usage. In that sense, I think it is an advantage to have several mechanisms.

Ueda : Thank you very much. That is all.

Kyokawa : Mr. Sakai, please ask the last questions.

Sakai : My name is Sakai from Credit Suisse.

This may be more of a personal comment than a question, but at this meeting your company has achieved a great deal in terms of S-268019 and ensitrelvir. I think the results are very important.

However, with regard to some of the development products you introduced, for example chronic cough, and zatolmilast, zuranolone, and redasemtide, all of which were introduced in last year's R&D, I see little progress from them. You have explained the details, but I do not see any clinical progress.

This is probably because, as Teshirogi-san mentioned at the beginning, or rather last year, nearly 80% of the R&D team's manpower has been focused on COVID-19. I have a sense of crisis that this is going to be a very difficult time for R&D next year, but I would like to ask Teshirogi-san whether we can share that sense of crisis and, in a sense, expectations? Please.

Teshirogi : Of course it is fundamental for us to continue to innovate on our own, but we also need to go a little further and license in our products, and we are very concerned about what we can actually bring to market in the 2023 to 2025 years.

We have some interesting compounds, interesting things, such as resiniferatoxin or zuranolone. In this way, as Mr. Kohtani mentioned earlier, S-531011 is interesting and we think anti-pain drugs are also interesting, but we have a very big sense of urgency about what we will deliver to the market in 2023 to 2025.

Regarding R&D activities, I believe that the research area in particular is very healthy, but the next part of the growth story, rolling out the development projects, is very important for us in the 2023 to 2025.

Because of the result for COVID-19, the R&D Day was held a little later this year, in October, but next year's R&D Day will be held at the timing a little closer to that of previous years. We would need to deliver how much progress has been made except for COVID-19 project. You may say that you are aware of the ensitrelvir and S-531011, but nothing else. As I mentioned earlier, we have made significant changes to our corporate structure from the standpoint of governance since July, which I believe you can interpret as an expression of our sense of crisis.

Sakai : Thank you very much.

Operator : Okay, Mitsubishi UFJ Morgan Stanley Securities, Mr. Kumagai, please ask your questions.

Kumagai : I'm Kumagai.

The first question is about ensitrelvir. Regarding to early application oversea in Phase 3II, I think I heard you say before that the US is asking for trial, but that you may be able to submit an application with the data, depending on the data, in Europe. Do you have any updates for us? This is the first one.

Keller : Scientific advice meetings are held with EMA and MHRA. Specific advice is still under discussion.

Kumagai : Secondly, S-600918. It has been quite some time since Phase 2b was completed, and it seems that discussions with the FDA have been ongoing, but I would like to know more about what the main issues are and what will be resolved to move forward.

Uehara : As for S-600918, it is a matter of negotiation with the authorities, so I will refrain from disclosing specific details, but as with other companies, we are in progress of how the endpoints and coughing will be evaluated. We are still discussing with the FDA on how to obtain approval for the application.

Teshirogi : And the other thing is, to put it straight, if you do two of these Phase 3s, which are a combination of three or four items with the same mechanism, it's a pretty big amount of money. Therefore, we have to make a cool judgement and analyze to see if it will be on pay line or not, if it is commercialized. To be honest, I am not sure how much content is in Merck's CRL.

It seems that Bellus went into this project with an at-risk attitude, but we need to recalculate on a global basis how much we can sell, at what price and to what patients. Since the cost at Phase 3 is huge, we need to see if it will get on a pay line as we also invest in R&D from business perspective which is also taking a long time to be honest.

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

Kyokawa : I would like to close now.

Thank you very much for SHIONOGI R&D Day 2022.