SHIONOGI & CO., LTD.

SHIONOGI R&D Day 2024

June 7, 2024

Presentation

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

I would like to introduce today's speakers. Dr. Isao Teshirogi, President, and Chief Executive Officer.

Teshirogi: I am Teshirogi. Thank you.

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

Keller: Hello, I'm Keller. Thank you.

Kyokawa: Dr. Yasuyoshi Isou, Senior Executive Officer, Senior Vice President, Drug Discovery Research Division.

Isou: My name is Isou. Thank you.

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

Uehara: I am Uehara. Thank you.

Here is a quick overview of today's agenda. As for today's agenda, Dr. Teshirogi will begin by discussing the future of the Infectious Disease Program which is part of the Corporate Vision 2030.

After that, Dr. John Keller, our R&D Director, will give a presentation on our R&D strategy. The presentation will be given in English, so if you would like simultaneous interpretation, please follow the procedure discussed later in the presentation.

Next, Dr. Uehara will discuss our R&D efforts in our focus areas. Finally, after Dr. Teshirogi provides the summary, we will have time for a question-and-answer session. This session is scheduled to conclude at approximately 1:00 PM.

As I mentioned earlier, simultaneous interpretation will be available at today's briefing, so if you would like to access it, please click on the globe icon at the bottom of the screen and select either Japanese or English, whichever language you prefer.

Now, let us begin the presentation. I would like to turn this session over to Dr. Teshirogi who will discuss the direction of the Infectious Disease Program.

Teshirogi: Once again, my name is Teshirogi. Thank you for joining us today.

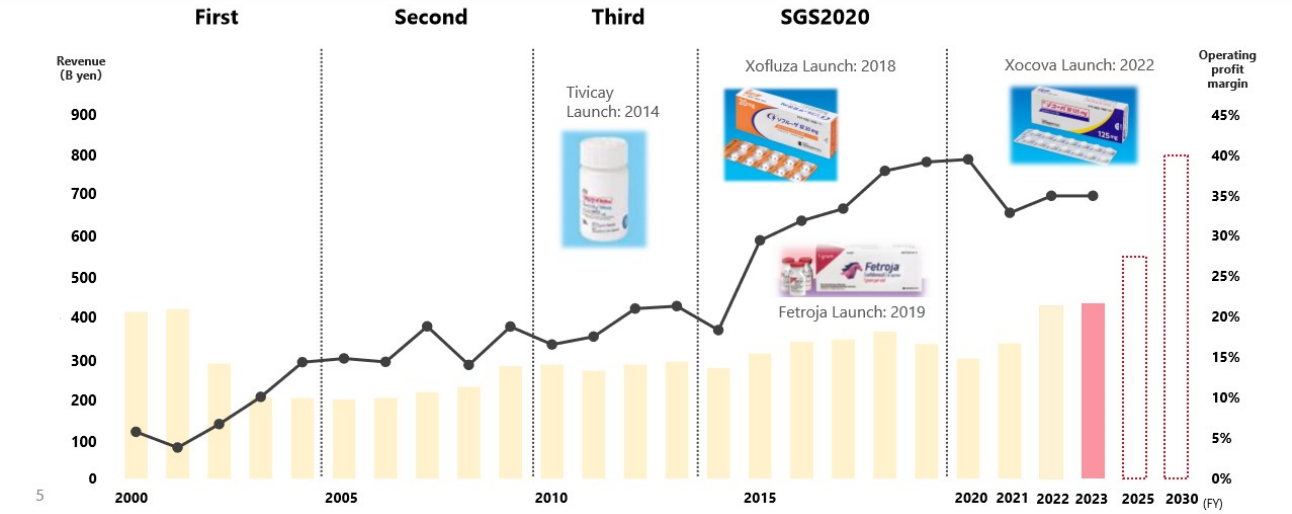
In March and April, I spoke with various investors, including those in the US and Europe, and after the closing of the fiscal year, I spoke with more investors.

At that time, many of them told me that while they understood that SHIONOGI has interesting pipelines, like S-309309, they believed that SHIONOGI had not fully conveyed the core principles it stands for.

As a business, of course, it includes a strategy to stabilize the HIV business, especially in terms of short-term revenue. It also includes AMR products such as cefiderocol, for acute infectious disease business. I was told that SHIONOGI has not yet done enough to thoroughly communicate how to stabilize these businesses, what interesting pipelines are on the horizon, and how the company assesses them. In some cases, I faced strong reprimands from certain shareholders, particularly those who hold significant shares in the company.

As such, while I did not initially plan to give an opening speech today because it is R&D Day, I would like to talk about our current approach as an introduction.

SHIONOGI's Growth Goes Hand in Hand with In-house Discovered Compounds



We have heard from so many shareholders on this topic. For example, a company that can deliver operating profits. Or a company who has tight control over expenses. There are not that many companies that constantly deliver at 10-year milestones without many ups and downs. Have we done enough to fully communicate that? On that topic, I would like to present this chart.

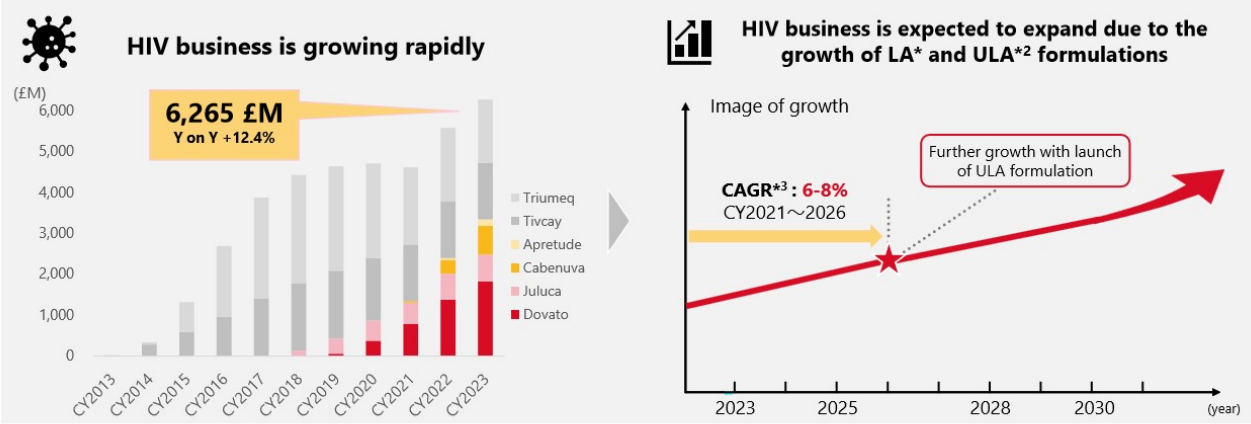
As for the operating margin, we are shifting gears slightly, as we are now in the phase of increasing sales while consistently producing an operating margin that is reasonably high in the industry, although of course well supported by royalties from Crestor, ViiV, and HIV Field.

How has the company grown from an earlier stage? I think this topic requires thorough communication. In this context, at least three or five years from now, the HIV business should remain solid. The infectious disease business is certainly growing. On top of that, what will be the next growth stage? Communication and discussion with you all on an occasion like this R&D Day, I think that is a crucial step.

That is why I decided to present this chart. With all due respect, we have done a lot of research on other companies in the same industry. Only a few companies are really stable, and the rest are quite bumpy. I thought that we need to be better understood as a company that offers peace of mind as one of our characteristics.

Growth Factors ①: HIV Business

HIV business continues to grow strongly and steadily



Last year, ViiV and GSK made their positions quite clear, and I think this is gradually being understood by everyone. If you look at the table on the left, you can see how ViiV has grown in the so-called Integrase family and the Integrase franchise, both in terms of percentage and value.

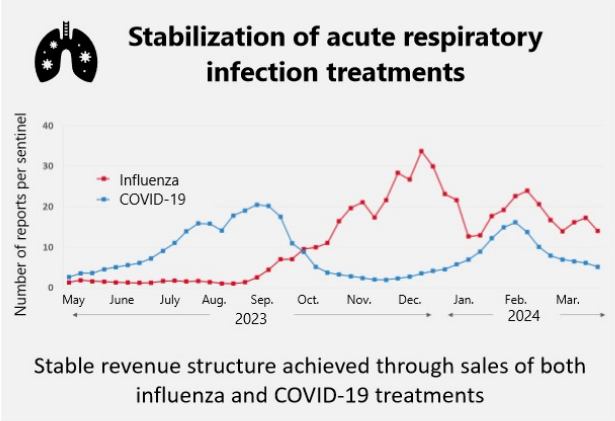
At this point, roughly calculated, 97% of ViiV's sales come from the Integrase family of companies, which means that ViiV is almost equal to the Integrase family of companies. We run a loyalty business that has grown to sales of GBP6.2 billion. The rate today is about JPY200, so equal to JPY1.2 trillion. The rate of dependence can be expressed as Integrase-Dependent. Since we are supporting this, of course, how will we develop and grow the injectable drug market in the future? This is still an important theme.

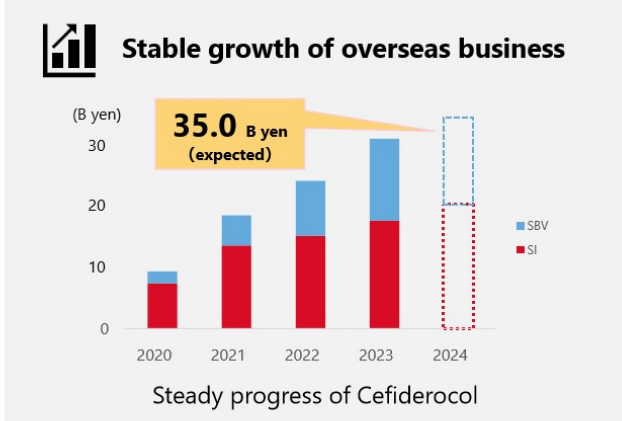
I hope today's event helps you understand how we, John and Isou, remain committed to HIV. I felt slightly shocked when people outside voiced their surprise to learn that SHIONOGI is involved in HIV.

Conversely, considering that we did not communicate this, I hope you understand how committed we are to the HIV field this time, especially in the small molecule area, and that it is looking in a bright direction.

Growth Factors ②
: Embracing the challenge of evolving our business model

Japan's acute respiratory infection business and overseas business are growing steadily





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Acute infection. AMR may also be a category of acute infection, though, given that it is administered for a maximum of two weeks. Solid growth of Cefiderocol in the US and Europe.

We did not say from the beginning that the market would reach JPY30 billion or JPY50 billion. In fact, I think, with all due respect, that probably none of the various analysis models, including ours, did not expect it to go this way.

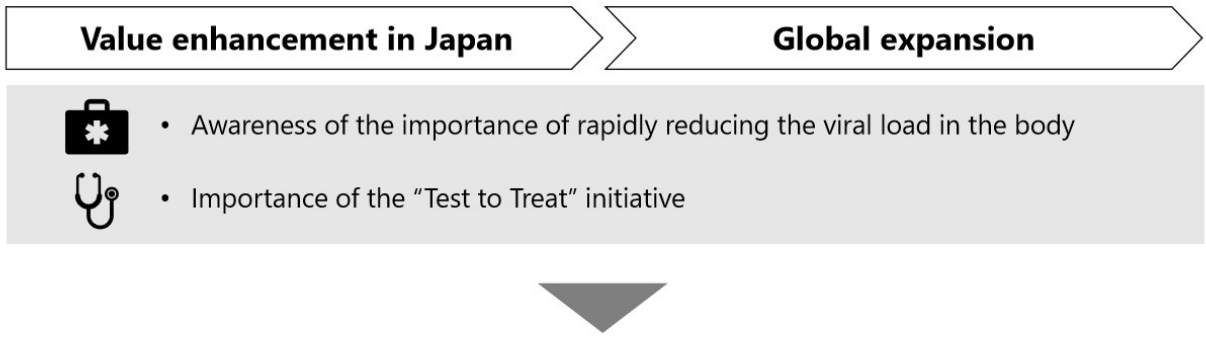
I am sure you will understand that we have been steadily expanding our business, including Xocova and Xofluza, starting with Japan, and I believe that we can achieve the level of business stability by having two or three drugs that cannot be achieved with a single drug. We believe that this is a phase in which we are gradually beginning to achieve it.

Although not the topic of today's discussion, Xocova's performance in the Japanese market in April, May, and June has been extremely strong. Xofluza (Baloxavir) have very strong antiviral activity against H5N2 and other viruses such as the one that appeared in Mexico today.

I am confident that SHIONOGI will be able to continue to do this kind of business and have peace of mind when various new products are introduced in the future. I hope you understand that we are gradually creating the foundation for growth through this process.

From Stability to Further Growth in Infectious Disease Business

The domestic sales growth and global expansion of Xocova are of utmost importance



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However, how to expand our business not only in Japan but also globally is a major issue for us. Dr. Uehara will address today, based on the SCORPIO-HR trial, negotiations with health authorities in various countries, especially with the FDA, have been going extremely well. It is our very important mission to expand globally, and we will be able to deliver the results of these meetings in a timely manner.

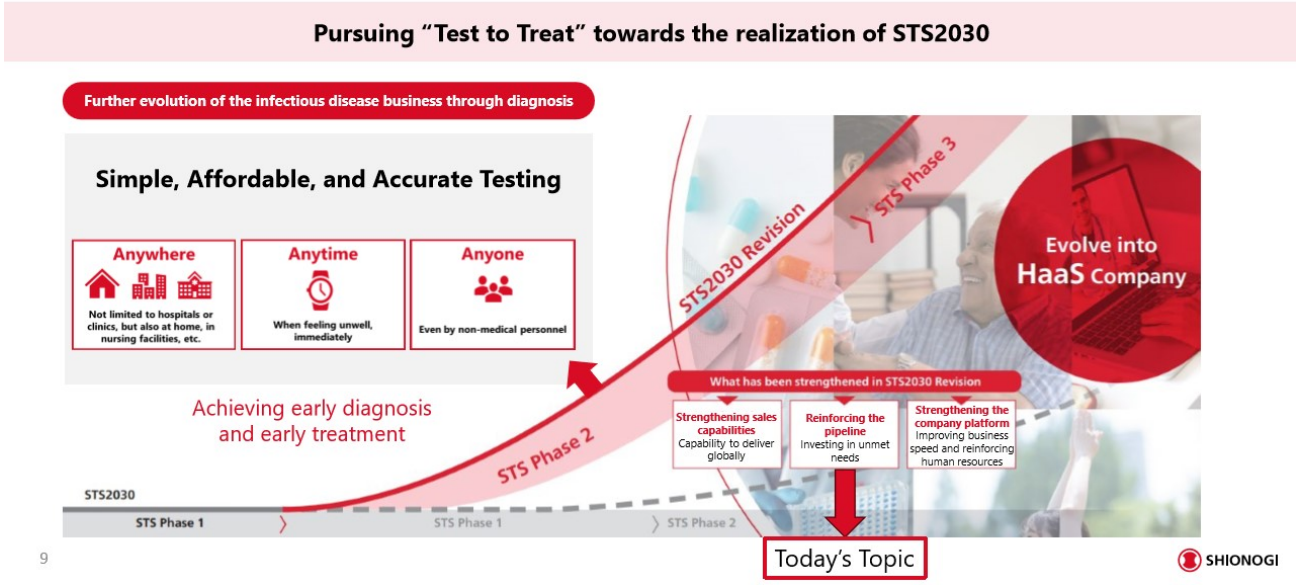
However, when we look at influenza drugs, their use in the US and Europe is not that advanced compared to Japan, and when we dig a little deeper, we find that diagnosis is still not advanced.

When the CDC recently released the news that FLiRT may be a little dominant in COVID-19 and that it smells somewhat bad, the comment below was that although they say so, they are not fully aware of the actual situation because people are not getting tested in the US. The CDC has said that it is a great concern for us that we do not know what is really going on.

In Japan, it is possible to check for both influenza and COVID-19 immediately with a nose swab, but in the US and Europe, this is not a common practice. We hypothesize that this is because inexpensive, accurate, and simple diagnostic agents are not widely available.

Even though President Biden addressed that people should access the Test-to-Treat initiative in order to better manage the disease, the testing part is still not widely activated. Without going one step further into diagnosis, we may not be able to maximize our Baloxavir and Ensitrelvir. We are currently concentrating on this area.

SHIONOGI is Working to Implement Test toTreat Globally



This is the last one.

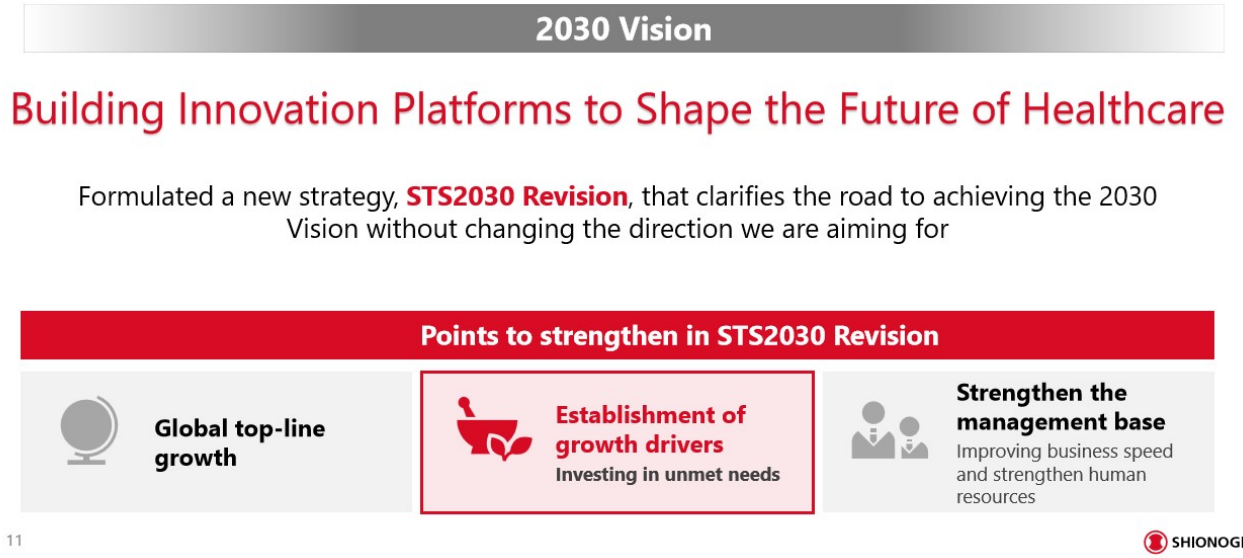
We have achieved solid growth in the past, mainly in infectious diseases, HIV, Ensitrelvir, Baloxavir, and AMR products. We believe that this will continue as a base or as an additional growth, but we would like to ask you at today's R&D Day to grasp a little about what has happened since then.

Not to reiterate or anything, but S-309309 is an important compound and we will continue to use it, but it is impossible for us to talk about the R&D of the company only in terms of single Phase II assets. I would like to hear from the three R&D top leaders today about what kind of interesting things are coming up next, and what we can expect from them.

I sincerely hope that the insights shared by our three speakers other than myself will resonate with you, as your genuine excitement would truly make all the effort in hosting this R&D Day event worthwhile. Thank you in advance for your attention.

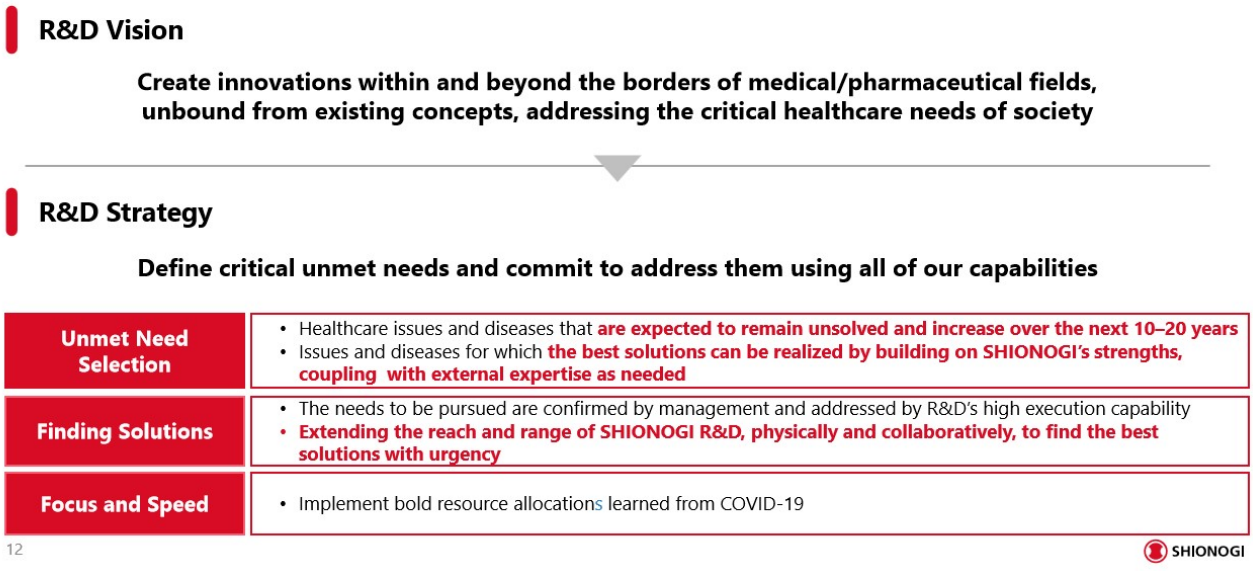
Kyokawa: Thank you very much. Dr. John Keller will now address our R&D strategy. Thank you.

2030 Vision and Medium-Term Business Plan STS2030 Revision



Keller*: Hello, I'm Keller. Thank you. I am pleased to be here today to talk with you about our R&D strategy and about our plans for the future. In the STS2030 Revision, we stated that we would create the future of healthcare on a new platform. Of course, our main focus was on establishing new growth drivers, especially on meeting unmet needs.

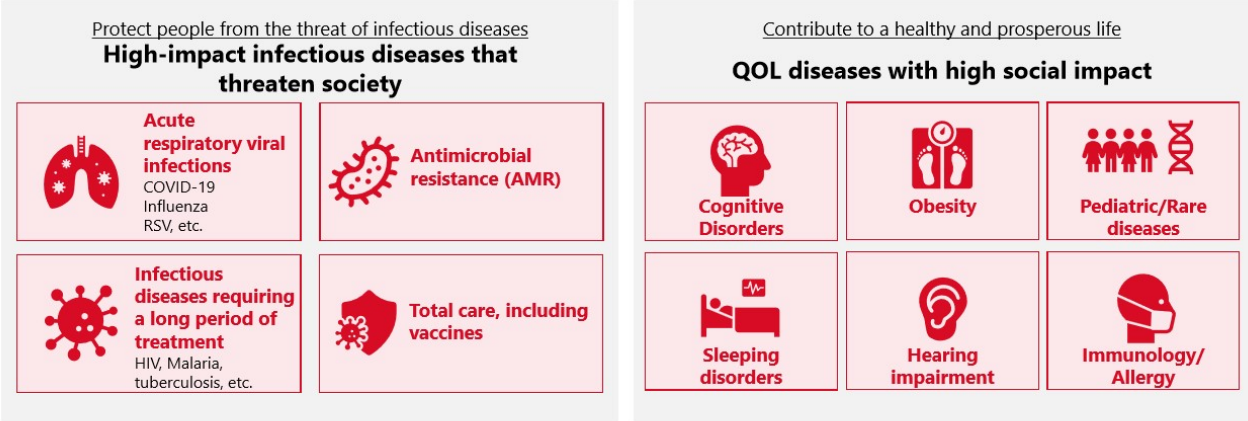
R&D Vision and R&D Strategy



In other words, unmet needs. There are various cascades depending on the disease, not just the unmet needs of the disease. There are various social impacts. And because they have not yet been solved, they will be a major challenge for society in the next 10 to 20 years. To address these new fields, we will continue to leverage our strong internal capabilities while also collaborating with external parties that possess unique expertise in these areas, thereby accelerating our ability to meet these needs.

R&D Disease Strategy: Focus Areas

Focus on areas where unmet needs exist and where SHIONOGI's strengths can be maximized



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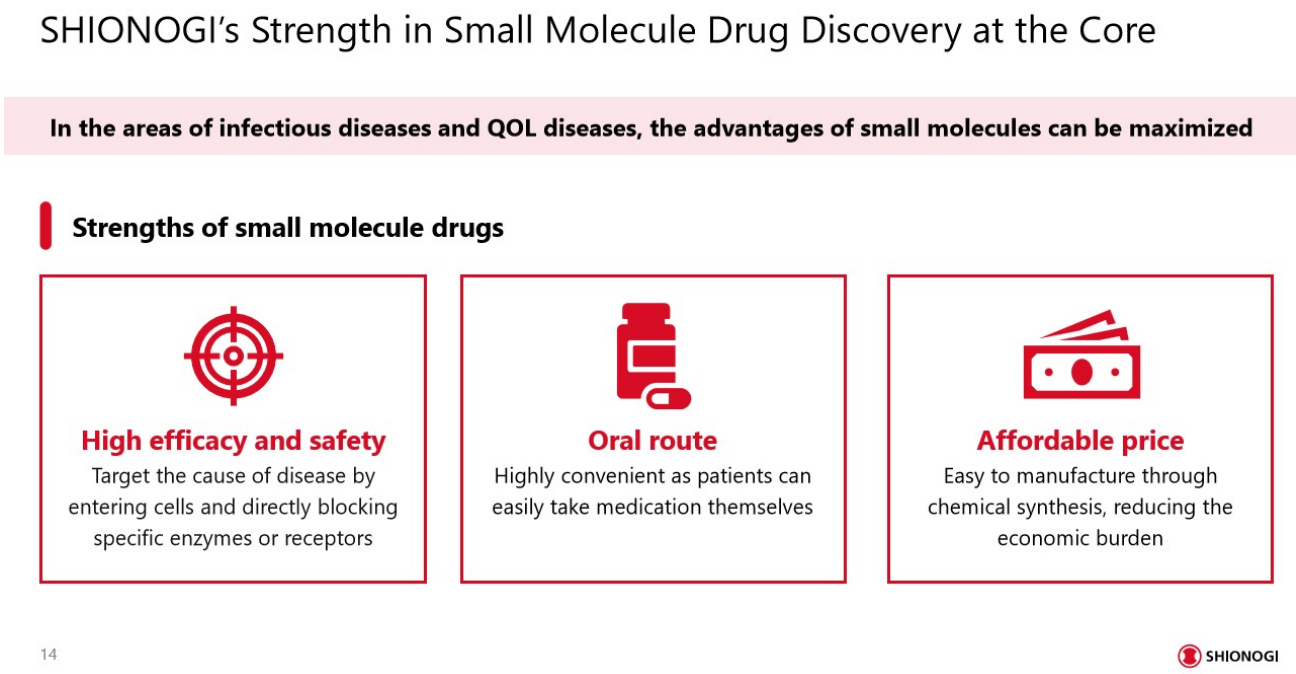
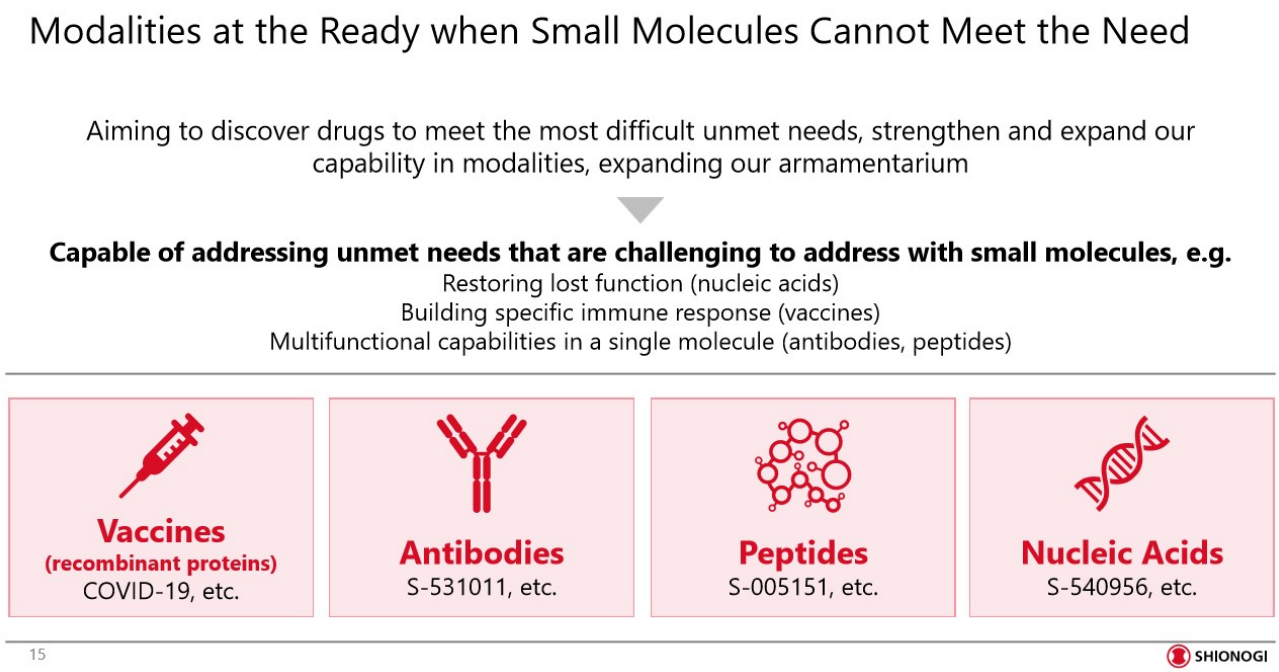
Regarding infectious diseases, as shown on the left half of the slide, we continue to focus on acute respiratory infections. This, of course, includes COVID-19, influenza, and now also RSV. Additionally, we are addressing AMR, which includes our pipeline from the acquisition of cefiderocol and QPEX. Although infections that require long-term treatment are present, HIV remains the most important among them; however, socially, diseases such as malaria and tuberculosis are also significant. And by total care for infectious diseases, we mean total care including vaccines, vaccines, and diagnosis, and test-to-treat is important to provide comprehensive solutions.

As for QOL diseases, which have a larger social impact, we are focusing on dementia, obesity, as well as pediatric diseases, rare diseases, and sleep disorders. The impact of these diseases is significant, and in

addition to these, hearing impairments, immunology, and allergies are also important factors.



As you know, SHIONOGI is particularly strong in small molecule drug discovery. And we intend to continue to develop this strength to the fullest. Excellent efficacy and high safety can be achieved with small molecules. And oral administration is more preferred. It also means affordable prices. This is also an important advantage for small molecules.



And some unmet needs cannot be addressed by small molecules alone. For example, if you have to use the immune response to regain a lost function, and when it comes to the multifunctionalization of a single molecule, that small molecule alone is not enough.

We would like to have this kind of modality in our hands. They are not only for their respective purposes but also because these are necessary to meet unmet needs. For example, vaccines. This will be the pillar of our future business. The same is true for antibodies, peptides, and nucleic acids.

Actions to Realize the R&D Strategy: Strengths of the New Organization

Drug Discovery Research Division
Specialize in research to integrate all modalities and create healthcare solutions to meet unmet needs

×

Pharmaceutical Technology Research Division
Pursue pharmaceutical technology from the perspectives of quality, speed, high functionality, and cost, and maximize the value of our products

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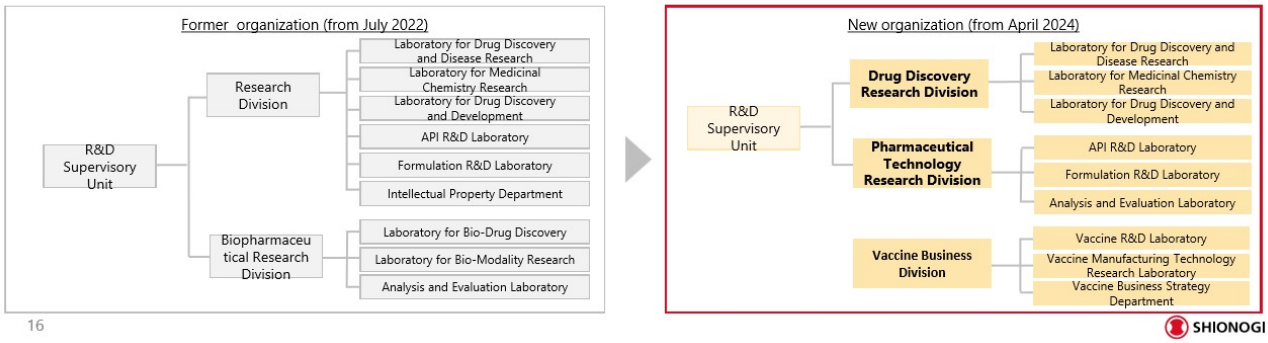
Vaccine Business Division
Build a system integrating everything from research to supply (accelerate the establishment of a foundational business)



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Our organization has been restructured to reflect this focus. Each group's objective is to provide solutions and to concentrate on delivering them in the best possible way.

The Drug Discovery Research Division integrates all modalities into one. The Pharmaceutical Technology Research Division applies technologies to develop drugs that are easier to use, more affordable, and more accessible, performing crucial functions across multiple modalities.

Regarding vaccines, because this is a unique and specialized business, we have established a dedicated division to create a seamless system from research to supply.

Current Status and Future Strengthening Points for Realizing the R&D Strategy

Further improve the quality and speed of R&D by maximizing our own strengths augmented through external collaboration

Current R&D status

While creating a highly profitable earnings structure through the creation of in-house growth drivers, build upon what we have achieved and the lessons we have learned

- The need to understand clinical patient needs ⇒ Products that are best-in-class as compounds but do not provide the best solution for patients
- Changing R&D processes and mindsets through competition with global megapharma companies amid COVID-19
- Rapid response to changes in global (especially US) regulations and the competitive environment

Future Strengthening Points

Thorough pursuit of unmet needs

Speed to win global competition

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Based on our long history of R&D, we have had many successes, but we have also learned some lessons.

From COVID-19, we learned that speed and a focus on resources are crucial. From past experiences, we also learned that focusing too much on science can cause us to lose sight of unmet needs, the competitive environment, and changes in opportunities for external collaboration.

Therefore, we aim to pursue thorough unmet needs by addressing patients' needs. We also want to ensure that we respond to changes in the competitive and regulatory environments, as well as business perspectives, with the same commitment and energy as we do with new science.

And we want to produce products that will be commercially successful. And we hope to meet the actual needs of our patients in a timely manner.

Now, in order to do that, we will be working to strengthen several elements. This is the strengthening of external collaboration.

First, from a physical standpoint, we will engage in external collaborations beyond Japan. QPEX, a company based in San Diego, has important and unique experience in antibiotic drug discovery. We will rebuild and expand their labs to facilitate not only technology transfer from SHIONOGI but also direct cooperation with major U.S. government and academic research institutions. This is crucial for responding to infectious diseases, particularly pandemics.

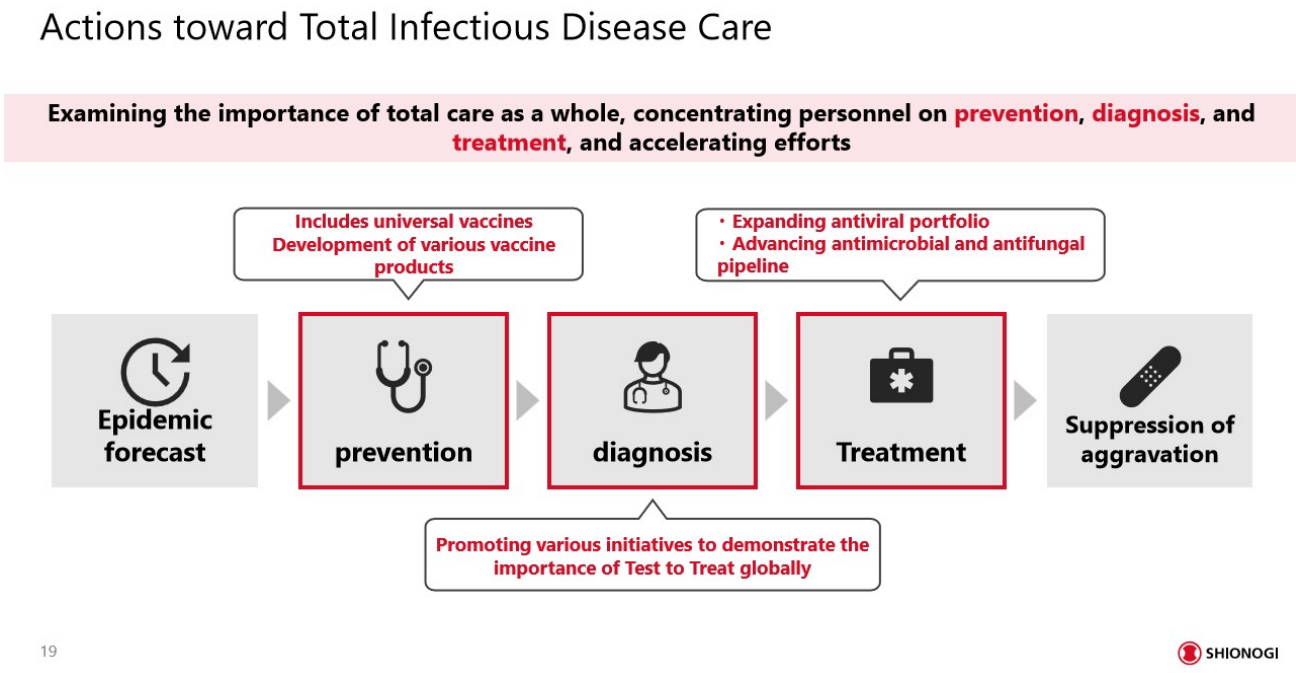
Next, in new therapeutic areas that require highly specialized clinical knowledge and patient insight, we will collaborate with the best experts in top fields. Companies like Apnimed and Cilcare are deeply connected with top experts and academic institutions, which accelerates the introduction of these new therapeutic areas and increases the likelihood of success compared to working alone. Collaboration with government agencies is essential from a business perspective for pandemic response and preparedness as an infectious disease company. To achieve this, we will especially work with the U.S. government. This will expand our relationships with organizations such as NIH, BARDA, the U.S. Department of Defense, the EU, and WHO, and allow for

cooperation in the U.S. and other countries based on existing relationships with these institutions. For example, QPEX has built an excellent relationship with BARDA, which is fully integrated into our relationship with SHIONOGI. Our collaboration with U.S. agencies involved in healthcare and human services as well as national defense is expanding.

Additionally, venture capital firms like LSP are also important. This is not just for investment but to connect with their networks. We collaborate to stay updated with information, test the latest technology trends, and explore new ideas. For instance, our relationship with LSP and the Dementia Fund allows us to work in real-time with CNS experts in Europe and the U.S., enabling rapid exchange of opinions on pipeline indications, biomarkers, and clinical trial designs.

Their network of experts will be able to use cutting-edge technology. We are in a position to contact them in real time. To be able to obtain information on clinical trials and other information in a timely manner through this EQT and other means, both in the US and in Europe. I don't agree with all of that. But to know where to look for new technology and where to track it. I believe this is nothing less than grasping the clinical needs of the patient.

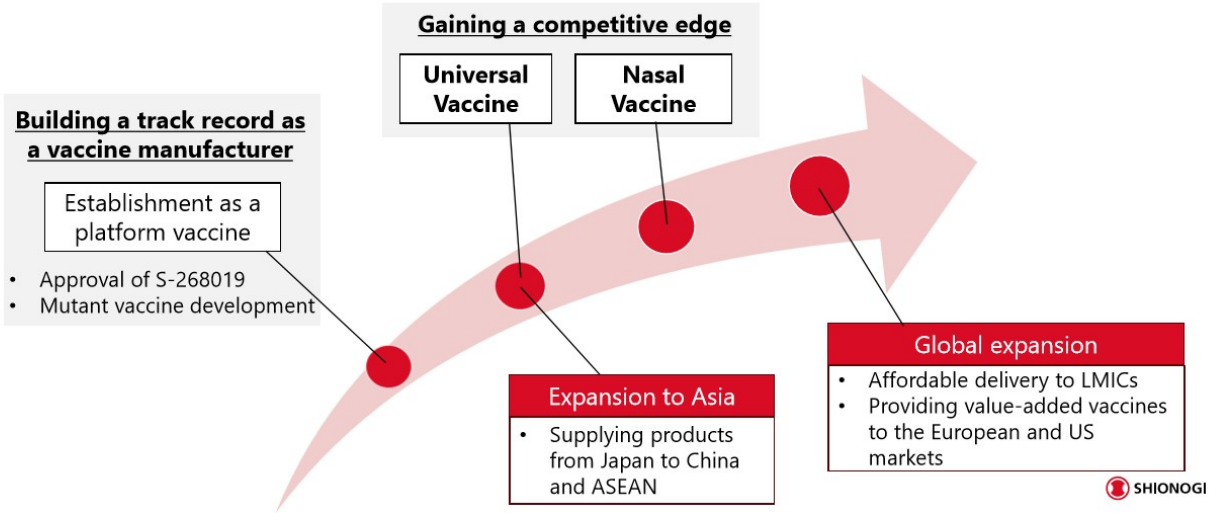
And it is a relationship with academia. For example, we are promoting vaccine research with Chiba University. And not only in Japan, but we are also promoting cooperation with various universities, especially with American universities, outside of Japan, where we have strong academia.



This commitment to total care for infectious diseases is not limited to treatment alone. Prevention and accurate diagnosis through the use of vaccines is the first step in this process. And it is thereby possible to prevent deterioration and to prevent serious illness.

Prevention: Vaccine Vision/Strategy

Continue research and development of vaccines against respiratory infections and expand vaccine supply globally



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Now, let's talk about prevention.

The strategy for the vaccine is as follows We started with COVID-19 and now we are launching a vaccine platform. We are in the process of establishing several platforms. By establishing this platform, we will be able to offer COVID-19 vaccines in Japan and Asia.

Diagnosis: SHIONOGI's Vision for Test to Treat

Realize an environment where patients can receive prompt diagnosis and treatment whenever they need it, anywhere, globally

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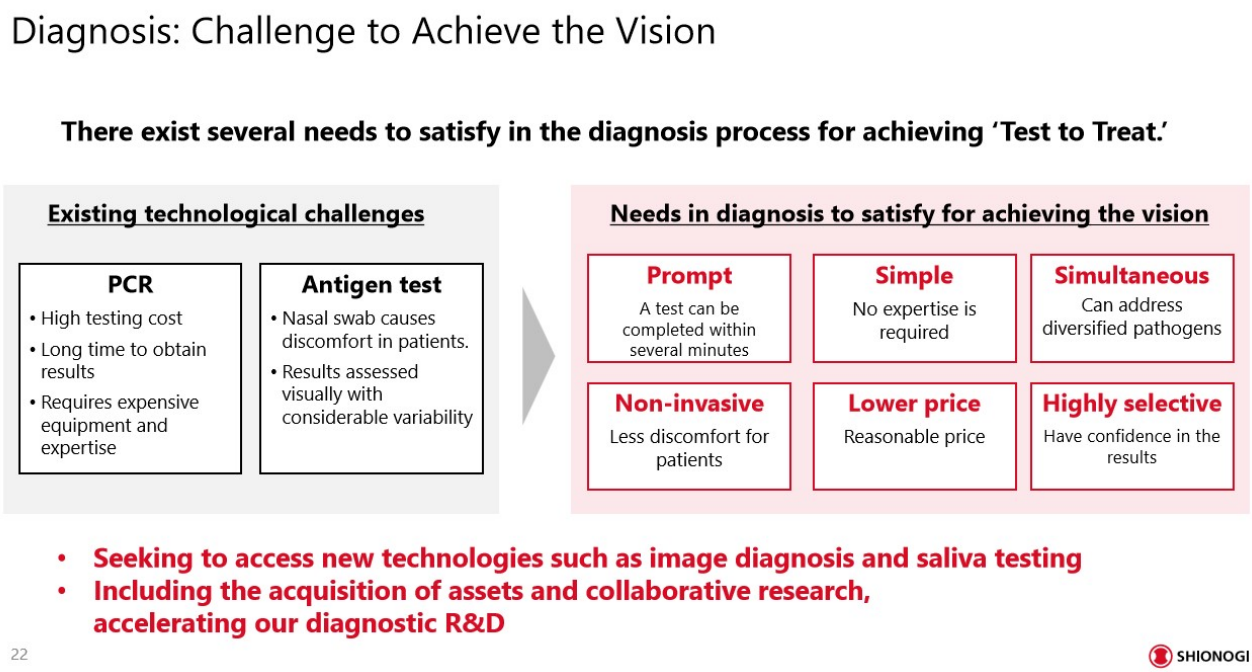
So what then is the need for the next generation of vaccines? I think it is a universal vaccine. And from COVID to universal, this is not just COVID, but new vaccines, intranasal vaccines, speed is important. This opens up global business potential.



With differentiation, we can differentiate ourselves on the global stage. I believe that the business of vaccines will launch us further into the long-term future.

What I mean by simple patient needs and diagnosis is to use nasal swabs in the doctor's office and to do an Immuno-Strip test. It's hard to decipher and understand it; it's just not good enough.

Therefore, the first step in therapy for coronavirus, influenza, RSV, and adenovirus is to know if the virus is present and, if so, what kind of virus it is, and to get the right therapy as soon as possible when you find out that you are not feeling well. The first thing to do is to get the right therapy as soon as possible. This is precisely what resonates with the outcome of the treatment. That is something that not only health care workers can provide but can do at home.

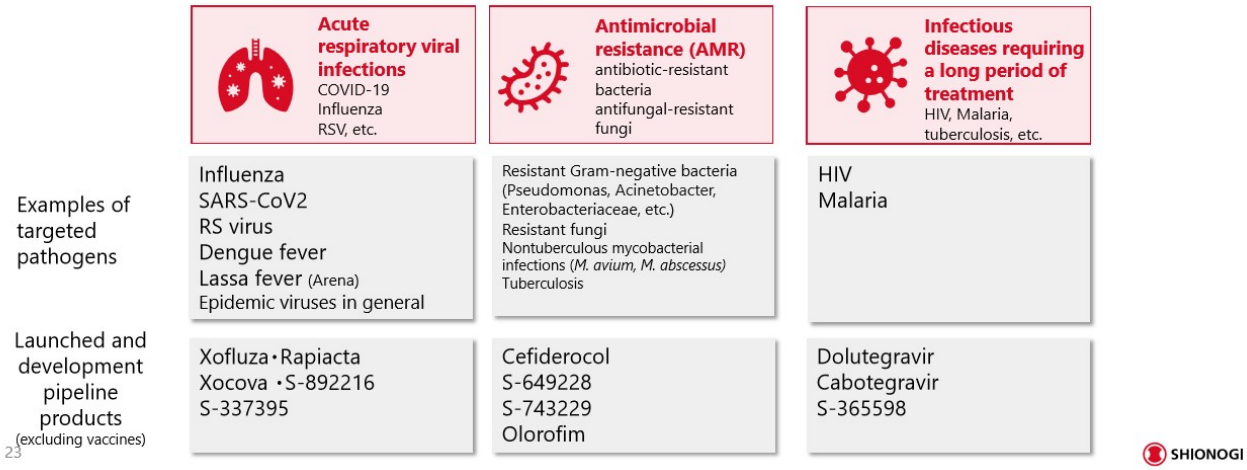
And to make this possible, the gold standard is accuracy. And the level of detection, equivalent to PCR. PCR is very expensive, time consuming, and difficult to do at home. Antigen testing requires testing that leads to discomfort, such as nasal swabs. And the judgment result is difficult.

Not so much more convenient, quicker, and faster than Immuno-Strips, and cost. Since it will be done at home, cost is also important. And connectivity. It is necessary that it be communicated immediately and clearly to the medical system.

And the most important thing when putting it into practice is that it can be done in the US and the EU. It means that proper virus treatment can be done not only in Japan but also in other countries.

Treatment: Focus areas in Infectious Diseases

While honing our strengths in infectious disease drug discovery, utilize external collaborations to satisfy global unmet medical needs



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That acute infectious disease, I mean, influenza and coronavirus will continue. And then again with RS virus, and then furthermore, for example, globally, there are infections that have started and are now spreading. In the US and Japan, for example, dengue fever is the first thing that comes to mind, and as an infectious disease company, we have to deal with such things.

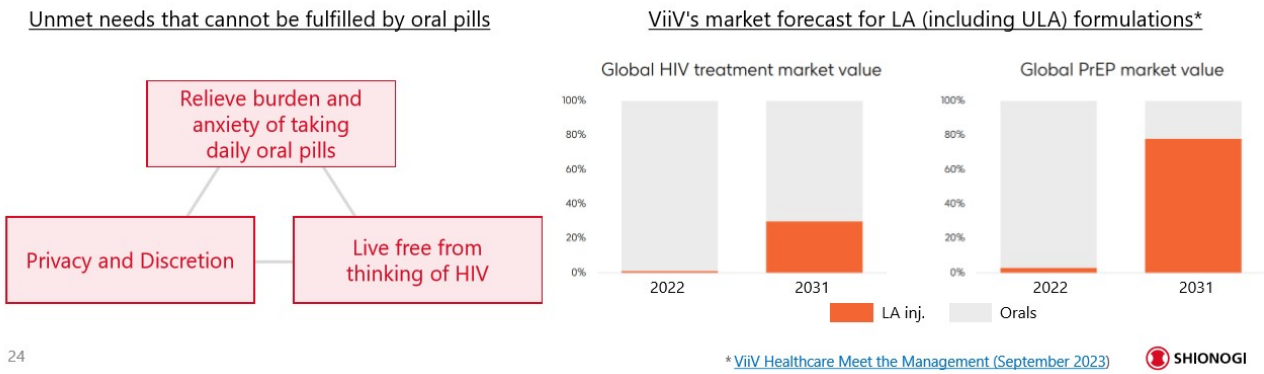
For AMR, the antifungal nature and the integration of S-743229 made it possible. This is a resistant fungus, and we are in the process of developing this as well.

And I will discuss about the long term. HIV, and malaria. Infections that require long-term treatment. This continues to be important.

HIV Franchise: ULAs Taking the Lead

The spread of ULA formulations will further accelerate the paradigm shift in HIV treatment and prevention

In parallel with ViiV's actions, SHIONOGI is committed to researching novel ULA candidates



And we are talking about very long-term HIV therapy.

This collaboration with ViiV has created a very strong market presence and impacted the quality of life of our patients.

However, anxiety about taking it every day is a characteristic of HIV, and the psychological aspect of not wanting others to know is a factor unique to HIV. So, it is important to erase HIV from your life, and that is what we are doing. And I think that 30% of the treatment, and again 70% of this pre-papering, in that sense, will shift to long acting in the future.

HIV Franchise: Creating the “Last in Class” ULA Therapy

To meet remaining unmet needs, ULA R&D competition among companies has intensified

Anti-HIV drug R&D trends among major pharmaceutical companies

Shift from once-daily oral to LA (oral and injectable)
- Competitors enter market led by ViiV and SHIONOGI

Focus on LA formulation of existing mechanisms
- Integrase inhibitors and NRTTI* with established long-term efficacy and safety, etc.

Percentage of LA preparations in major pharmaceutical companies' pipelines*2

* Calculation based on the pipelines of ViiV, Gilead, Merck, and J&J (based on each company's 1Q 2024 financial results) *2 Nucleoside reverse transcriptase translocation inhibitors

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This is an area where we are very much in the lead, and the integrase inhibitor, and the LA, ULA, and injectable treatments, which probably came from our Cabenuva, for example, and then Gilead and competitors came in, and it has been seven years since then.

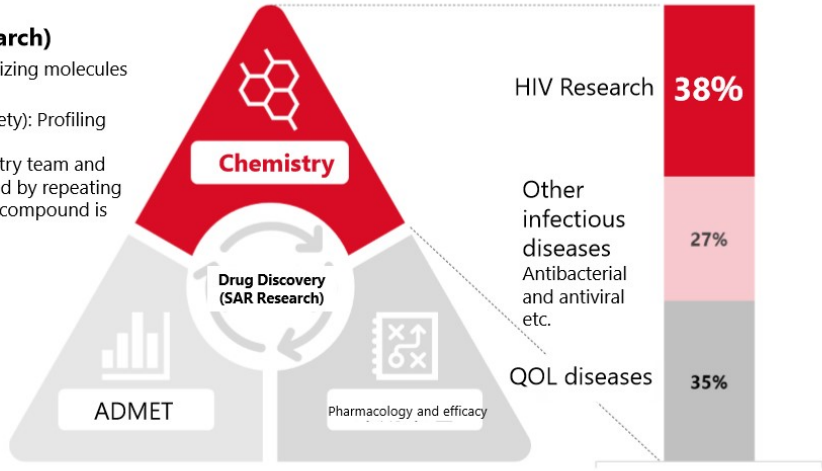
For seven years, not nothing, but the very best regimen, not that it was there all that time, but from one to another, for example, Gilead also came in with its own compounds. And long acting has come to account for 80% of the total, all by pharma.

Allocation of Human Resources in the Research Institute

Appropriate resource allocation: 38% of chemical resources, the starting point for manufacturing, are allocated to HIV research

Drug Discovery (SAR Research)

- Chemistry: Designing and synthesizing molecules
- Pharmacology and efficacy, ADMET(pharmacokinetics and safety): Profiling and evaluation of compounds
  Based on this information, chemistry team and synthesizes better compounds, and by repeating this cycle multiple times, the lead compound is turned into a drug



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But what happens next? Chemistry then become important. Forty percent of our drug discovery efforts are devoted to HIV research. And, after all, we want to stay on the front lines by doing so. This is the market we have created and the medical needs we are addressing. We do not want to lose this.

Research and Development Policy for Bacterial Infections (Antibiotics)

Established a new antimicrobial discovery laboratory in the US to utilize the experience base of Qpex and further build our US collaborative network

Opening of Qpex US Lab., a new drug discovery hub

- Activities taking advantage of the strengths of Qpex US Lab.
  - Based in San Diego, a significant biotech hub, build even stronger connections with US government, academia, and biotech
  - Maximize agility in research and development for AMR

In cooperation with public institutions such as NIH and BARDA, proactively work on research and development for difficult bacterial infections to prepare for future threats

SHIONOGI

In the US, a new US laboratory was established in San Diego. This is a very good location for a biotech company. And we have a lab where you can use QPEX knowledge.

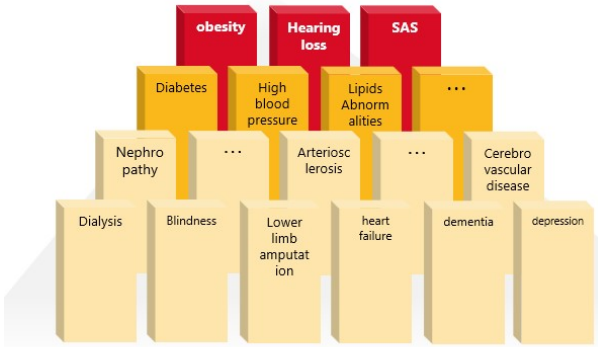
At this time, QPEX is not only promoting AMR research, but also has a network with the US government and US research institutes. For example, when we go to a certain ministry in the US for pandemic research, we have to cooperate with them on their soil. In this sense, I think it is fair to say that we now have this capability.

We can prepare for the next pandemic quickly and in an integrated manner. By using this resource, we are connected to academia and even to the government.

Significance of Addressing QOL Diseases that have a Significant Social Impact

Identify the root causes of diseases with cascading impact that shortens functional lifespan

Sequential chain of disease (image)



Before the onset of serious disease,there are multiple risk factors, which trigger further consequences like dominoes

Seeking to address the underlying diseases before their irreversible consequences take hold

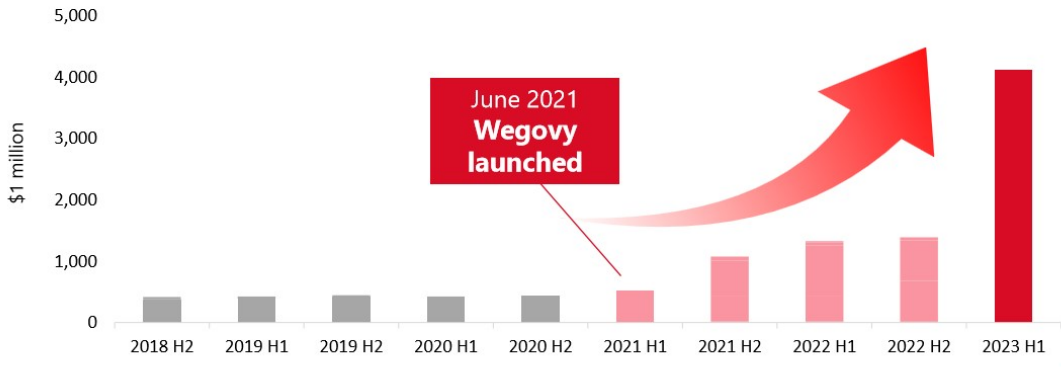
SHIONOGI

Now we turn to quality-of-life diseases. The key to these diseases is not only the medical need. Of course this is important, but it is the result that it brings. Social isolation, dementia, accidents, and various other life problems can trigger cardiovascular problems and dementia. We focus on quality of life, because while the disease itself is important, so are the results it produces.

InnovationInnovation in Consequential QOL Diseases Drive Major Market Opportunities

The anti-obesity drug market has expanded dramatically with the emergence of GLP-1 agonists

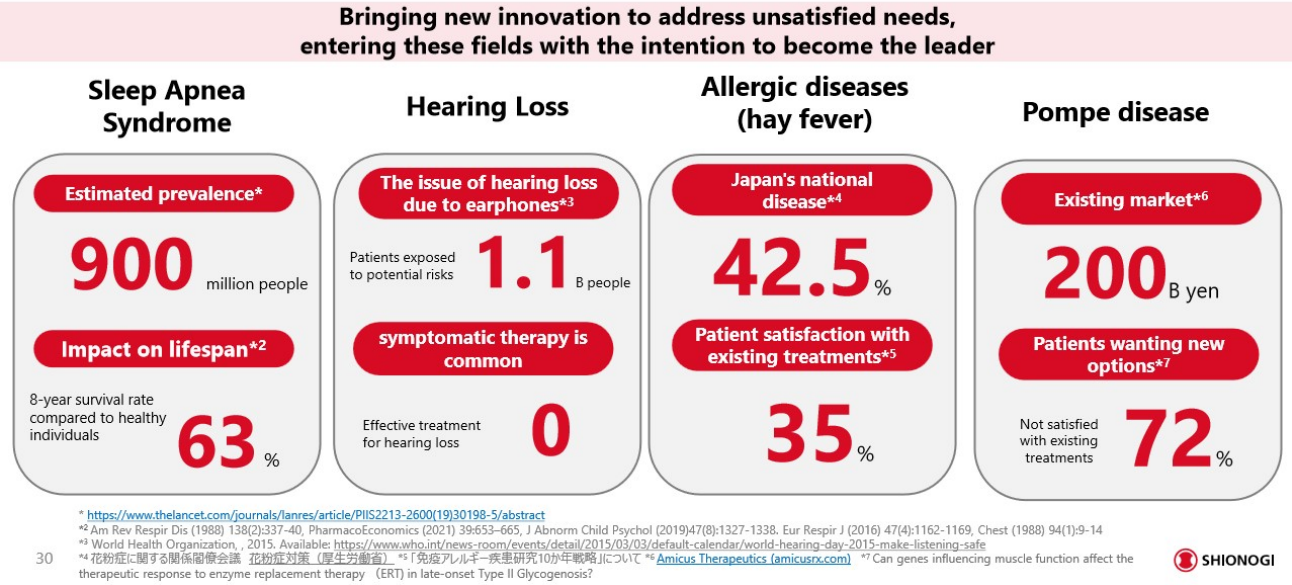
US Anti-obesity drug market



SHIONOGI

Now, as for the obesity market, I think this illustrates it well. This is not only the obesity market itself, but the various consequences of it. We are looking at the results of the study. Liver disease, and 40% of apnea is due to obesity. These results are key in diseases of quality of life, and we have chosen these diseases for good reason.

Unmet Needs of QOL Diseases with a High Social Impact that SHIONOGI is Addressing



* https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30198-5/abstract
*2 Am Rev Respir Dis (1988) 138(2):337-40, PharmacoEconomics (2021) 39:653–665, J Abnorm Child Psychol (2019)47(8):1327-1338. Eur Respir J (2016) 47(4):1162-1169, Chest (1988) 94(1):9-14
*3 World Health Organization, , 2015. Available: https://www.who.int/news-room/events/detail/2015/03/03/default-calendar/world-hearing-day-2015-make-listening-safe
*4 花粉症に関する関係閣僚会議 花粉症対策（厚生労働省） *5「免疫アレルギー疾患研究10か年戦略」について *6 Amicus Therapeutics (amicusrx.com) *7 Can genes influencing muscle function affect the therapeutic response to enzyme replacement therapy （ERT) in late-onset Type II Glycogenosis?

SHIONOGI

Sleep apnea affects 900 million people. And the impact on life expectancy is a 60% survival rate after 8 years.

Hearing loss, however, is a problem with the earphones. Among the various noises from earphones, earphone noise affects 1.1 billion people.

And allergies. This is a particularly important issue in Japan. The prevalence rate is 42.5%, and 35% are satisfied with their current treatment.

And Pompe disease. We can use our knowledge of small molecules to address these rare diseases. For example, in the case of Pompe disease, it is expected to lead to a business worth JPY200 billion. And 72% of patients want new options.

QOL Diseases with High Social Impact: Develop New Focus Areas - SAS -

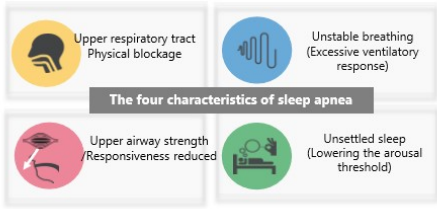
Addressing the complex pathology and causes of OSA and providing the right therapies to the right patients

Global market for hearing loss*2

CAGR from 2024 to 2030	6.5 %
Market forecast for 2030	About 1,200 B yen

Unmet medical needs

- Highly effective and safe therapeutic drugs other than devices and surgical treatments
- Treatment options for patients with nasal continuous positive airway pressure (CPAP) resistance or intolerance
- The pathophysiology of SAS is mainly formed by the complex interplay of the following four factors, making treatment difficult (only 40% of SAS patients with obesity)



31 * Sleep Apnea Syndrome
*2 Sleep Apnea Devices Market by Type, Therapeutic (PAP Facial Interfaces, Oral Appliances, Accessories), Diagnostic, End User & Region - Global Forecast to 2028

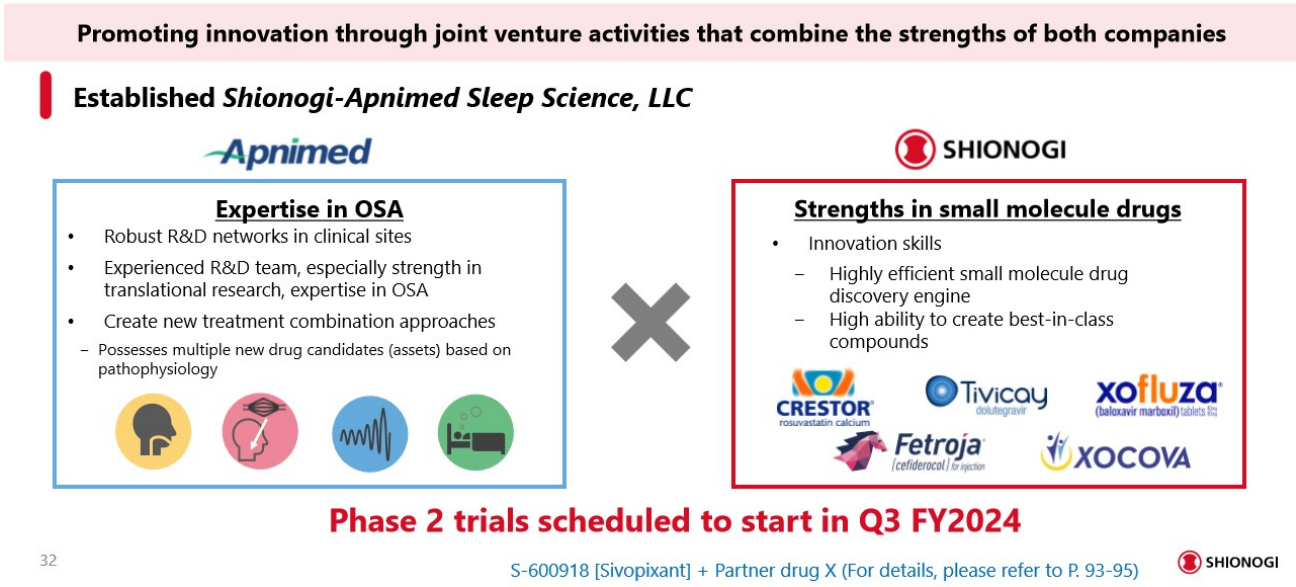
SHIONOGI

So, the market forecast for 2030 and quality-of-life diseases is JPY1.2 trillion. There are four causes of apnea. There is a physical blockage. There is also decreased upper airway capacity and responsiveness, unstable breathing, and unstable sleep, the levels of which vary from patient to patient.

And you must first know your patients. Without knowing enough about what patient groups we are treating; we cannot provide appropriate treatment.

With regard to CPAP, there are very few people who are fully satisfied with it. And CPAP has become a treatment option for refractory/unresponsive patients.

QOL Diseases with High Social Impact: Develop New Focus Areas - SAS -



Apnimed is a company that specializes in the field of apnea. 80% of the management team are clinical scientists. We are also connected to the most prestigious academics in the field.

It is the study of what is the cause of the disease, with respect to a particular patient, how to diagnose it, and how to treat it with the appropriate solution. Various combinations and combination therapies will be important.

So, we will also combine this with our strength in small molecule drug discovery. There are drugs that we have. I believe that combinations with new drug discovery in new targets will also emerge.

QOL Diseases with High Social Impact: Development of New Focus Areas
- Hearing Loss -

Plans to introduce early treatment drugs providing new breakthrough options in the expanding hearing loss market

Global market for hearing loss*

CAGR from 2024 to 2030 | **5.3** %

Market forecast for 2030 | About **1,800** B yen

Unmet medical needs

- There are no effective treatments, and **symptomatic therapy is common**
- Hearing loss occurs gradually, making it difficult to self-diagnose, leading to **a low diagnosis rate**
  - For example, the prevalence of hearing loss in diabetic patients is about 30%, but the diagnosis rate is only about 10%
- Hearing impairment is the biggest issue in communication with others, and it has a negative impact on both work and private life

* Hearing Loss Disease Treatment Market Size, Share & Trends Analysis Report By Product (Devices, Drugs), By Disease Type (Conductive, Sensorineural), By End-user (Hospitals, Otology Clinics), By Region, And Segment Forecasts, 2024 - 2030

The average annual growth rate for hearing loss is 5.3%. And the market forecast for 2030 is JPY1.8 trillion. We may see more and more of them in the future.

Symptomatic treatment, devices, and easy-to-use solutions are also important. Since this kind of hearing loss occurs gradually, it is difficult to be aware of, making diagnosis important. It also leads to social isolation. This can lead to dementia.

QOL Diseases with High Social Impact: Development of New Focus Areas
- Hearing Loss -

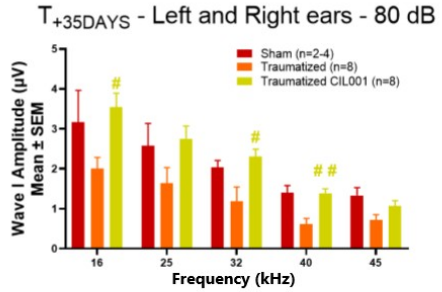
Acquired the option rights to a very promising low molecular compound (CIL001) from Cilcar

Obtained the option rights for a candidate hearing loss treatment drug

- Exclusive license for the development, manufacturing, and commercial science of CIL001 and CIL003 compounds worldwide
- CIL001 confirmed auditory nerve protective effects in preclinical trials
  - Enhanced gene expression necessary for synaptic recovery
  - Confirmed an increase in the number of synapses
  - Improved the first wave of ABR* correlated with hearing loss

cilcare
MAKING HEARING A PRIORITY

The effects of CIL001 (in preclinical trials with a mouse noise trauma model)



Improved the ABR Wave I amplitude across a wide range of frequencies

Phase 2a clinical trial will start in FY2025*2

34 *2 Auditory brainstem response (ABR) Wave I:
The first electrical signal generated by cochlear nerve cells in response to an auditory stimulus, believed to reflect the function of the cochlear synapse" *2 Cilcare will conduct

SHIONOGI

Cilcare is a very specific company. It is a company that provides the hearing loss community with a pipeline of drugs, and pre-clinical or clinical research tools. The firm is highly specialized with preclinical and clinical research targeting hearing loss. They also have a very important pipeline.

Here, in our major compounds, they are looking at compounds that regain lost synapses. This compound is the result of a mouse model of noise-induced hearing loss. Though it is not necessarily an earphone, the red color in this mouse noise model is Sham. And orange is the placebo, and green is the results for the group treated with CIL001.

This pre-clinical model, and this will be moved to clinical in 2025. These models are what we do every day. Cilcare specializes in these areas. The company has great strengths in clinical trials and commercialization potential.

QOL Diseases with High Social Impact: Development of New Focus Areas
- Immunology and Allergies -

Aiming to provide innovative solutions for hay fever, a condition referred to as the national affliction in Japan and a global social issue

Global market for allergic rhinitis*

CAGR from 2024 to 2030 | **4.8** %

Market forecast for 2030 | About **1,000** B yen

Allergic rhinitis (including hay fever) market in Japan

Market in 2019 | **170** B yen*2

Unmet needs

- Patient satisfaction with antihistamines for cedar pollen allergy is only 35%
  - Dissatisfied with the effectiveness and drowsiness

* Allergic Rhinitis Drugs Market by Route of Administration (Intranasal, Intraocular, Oral), Class of Drugs (Antihistamines, Immunotherapies, Intranasal Corticosteroids), Application - Global Forecast 2024-2030

*2 花粉症に関する関係閣僚会議 花粉症対策（厚生労働省）より

SHIONOGI

And immune allergies. Seasonal hay fever, allergic rhinitis of various kinds, the overall market is as shown here. Many people in Japan have allergic rhinitis and are not satisfied with the current treatment.

QOL Diseases with High Social Impact: Development of New Focus Areas
- Immunology and Allergies -

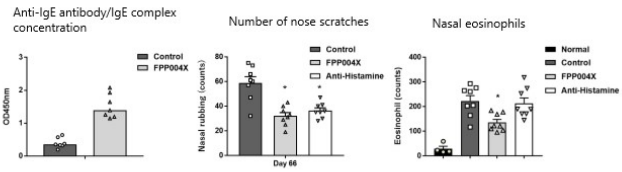
Acquired the option rights for a promising hay fever vaccine candidate (FPP004X) from Funpep

Obtained the option rights for an anti-IgE antibody induction vaccine

- Exclusive research, development, and commercialization rights for FPP004X worldwide
- Expect to have sustained effects against allergies
  - Stimulate IgE antibody production in immune cells for a specific period
  - The anti-allergic effects resulting from the reduction of IgE are also attracting attention from other companies

Efficacy of FPP004X (Preclinical trials in an allergic rhinitis model*)

- FPP004X demonstrated efficient induction of anti-IgE antibody
- Confirmed suppression of allergic reactions
  - A reduction in the frequency of nasal scratching and eosinophils



Phase 1 clinical trial will start in 4Q FY2024*2

* Nonclinical trial conducted using humanized mice with IgE/FcεR1 *2 Funpep will conduct

SHIONOGI

And together with Funpep, we have a new arrangement with this company. We are developing a vaccine. It produces anti-IgE antibodies in immune cells for a certain period of time and is expected to have a lasting effect on allergies. It can knock down IgE. And it also has a protective role.

It is now considered very important that various types of damage occur due to allergies. As shown on the right, this is a preclinical model, but if we can knock it down in humans, we can address seasonal hay fever. And we believe we can accommodate a variety of other allergies.

This means targeting IgE. If the compound proves to be successful, we believe we will be able to make further progress.

QOL Diseases with High Social Impact: Development of New Focus Areas
- Pompe Disease -

Aiming for early introduction of therapeutic drugs that can break through the current situation in the high unmet needs Pompe disease market

Global Market for Pompe Disease*

The market is expected to expand further with the launch of S-606001

CAGR of 2024-2030	**4.3** %
Estimated market of 2030	**300** B yen

Unmet needs

- The only existing treatment is intravenous enzyme replacement therapy (ERT)
  - Over **72%** of patients currently undergoing treatment want to further slow the progression of their disease
  - Over **82%** of people want to reduce the burden of visiting hospitals and avoid injections

Features of S-606001

- Further improvement effects when used in combination with ERT
- The only oral small molecule drug in development

Phase 2 clinical trial will start in FY2024

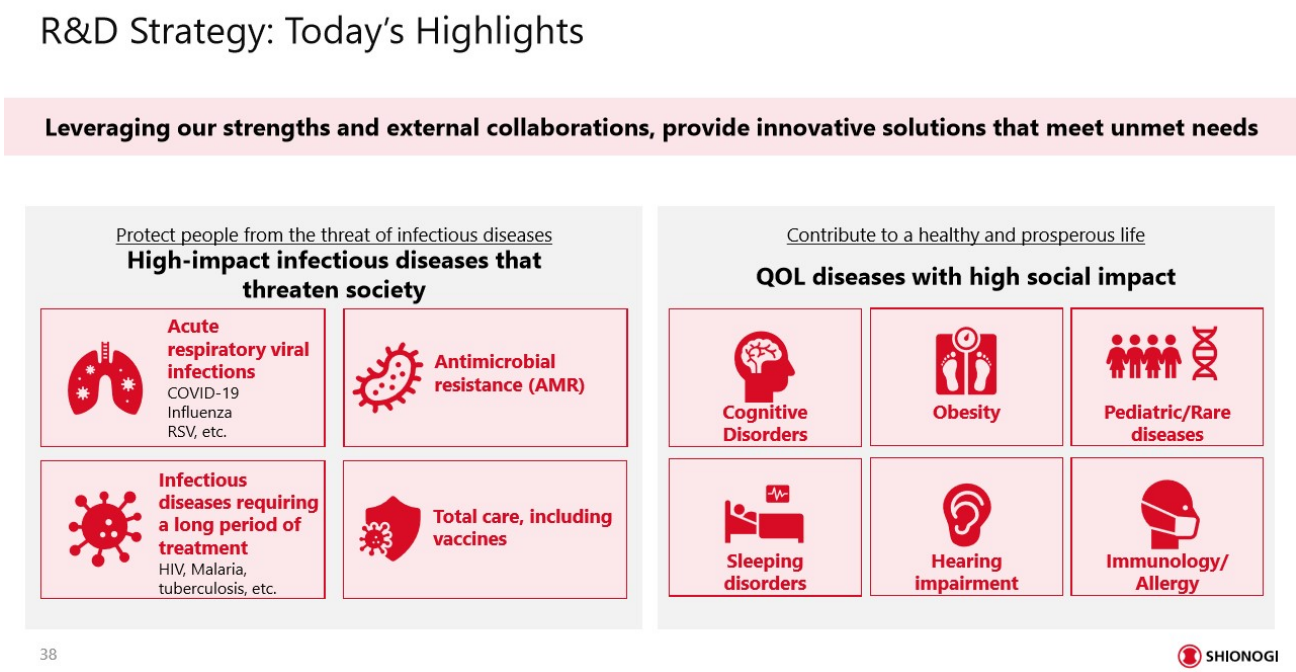
* Global Pompe Disease Therapeutics Market - 2023-2030

S-606001 (For details, please refer to P. 84-86)

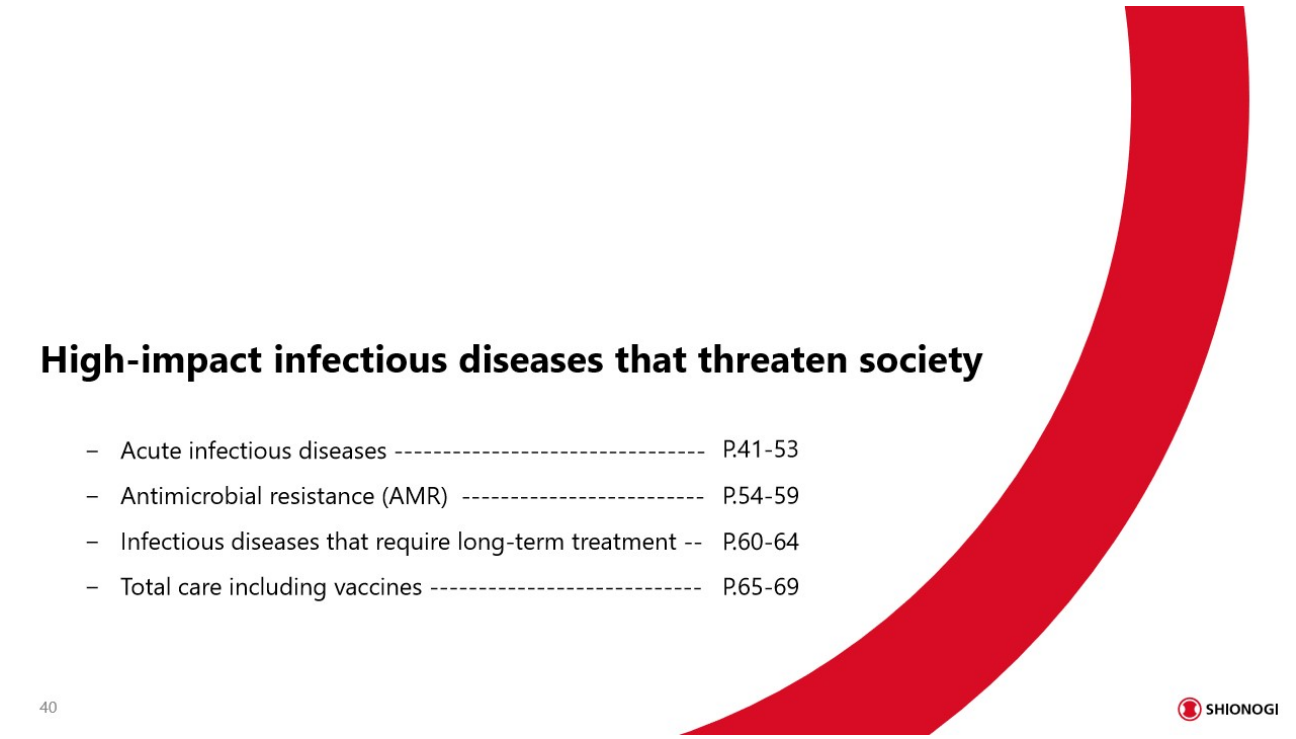
SHIONOGI

And as for the rare diseases, we have first of all Pompe disease. This will be entered with a small molecule. Many patients are currently receiving ERT and enzyme replacement therapy. Every few weeks the patients must take a long drip infusion. It is painful and a terror for children. And the effectiveness can decrease. And more than 82% are unsatisfied with their current treatment, which means they want to avoid injections.

Therefore, we are considering licensing from Maze and responding to this with small molecules. We are starting a new approach not only with ERT but also with small molecules in addition to it. Phase II trials are scheduled to begin in FY2024.



So, that is the summary. We will now have a more in-depth explanation.



Uehara: Hello. I would appreciate your attention. The first half of the presentation is about infectious diseases, which is the foundation of our company, and then I will talk about quality-of-life diseases and various areas of focus.

We have many pipelines. Since time does not allow us to introduce all of them, I tried to keep the list as compact as possible, focusing on the most important items that have received major updates. Still, there is lot to go through.

Threat of acute viral infections (respiratory)

As a leading company in infectious diseases,
Creating diagnostic technologies and therapeutic drugs to address society's needs

A pandemic caused by a new viral infection

Responding to the ever-changing mutations of the virus

- Ensitrelvir: Development and approval of a drug for treating COVID-19
- S-892216: Development of the next generation of COVID-19 treatments
- S-337395: Development of treatment for respiratory syncytial virus
- Pandemic drug discovery: Creating broad-spectrum antiviral drugs

Borderless society leads to rapid spread of infection

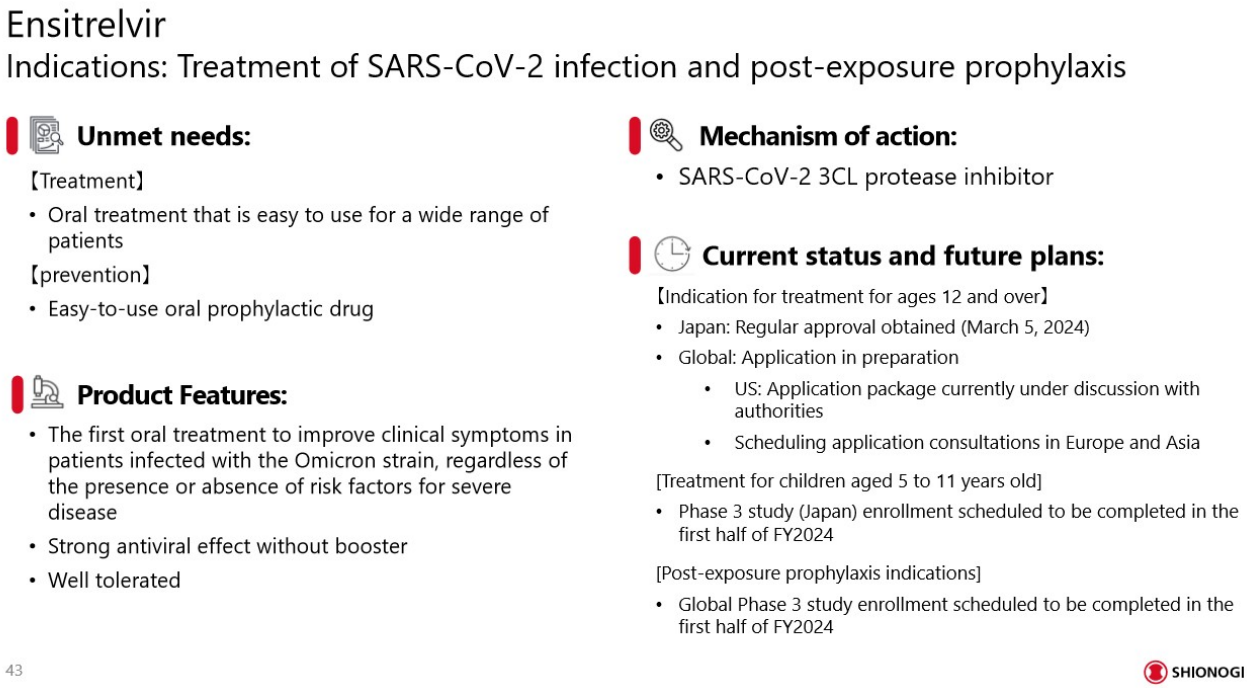
- Ensitrelvir: Clinical trials to obtain post-exposure prophylaxis
- Baloxavir: Verification study to confirm its effect in suppressing transmission

SHIONOGI

The first is acute viral infections.

As you all know, our company has a drug called Xofluza that treats Influenza. We have also developed many good products such as Xocova, RS virus, and what we call the "three respiratory brothers".

I would like to talk about the progress of such items, as well as the perspectives on how to strengthen them in future drug discovery, especially in lowering viruses. We are confident in our ability to deliver compounds that are finished to a high degree of antiviral efficacy. Prevention, not just treatment, and from a public health standpoint, not spreading the virus around. We are working on a variety of new ways to use these drugs as therapeutic agents, and I would like to talk a little about them.



Now, about Xocova, Ensitrelvir.

As you are aware, we have received approval in Japan. Following that, we were able to conduct a global Phase III trial with a further application for global approval. As shown in the following slide, the primary endpoint was not met, but the results showed good safety and good antiviral efficacy.

We have confirmed the results in the global environment, and in the same analysis method for the primary endpoint as in Japan, the p-value was also below 0.05. We are now discussing with the global authorities in other countries prior to the application. We are in the process of discussing this very thing, so we will update you on this when the time is right.

Ensitrelvir: Summary of Results of the SCORPIO-HR trial

Obtained the results of the SCORPIO-HR trial and proceeding with preparations for regulatory approval in the United States and globally

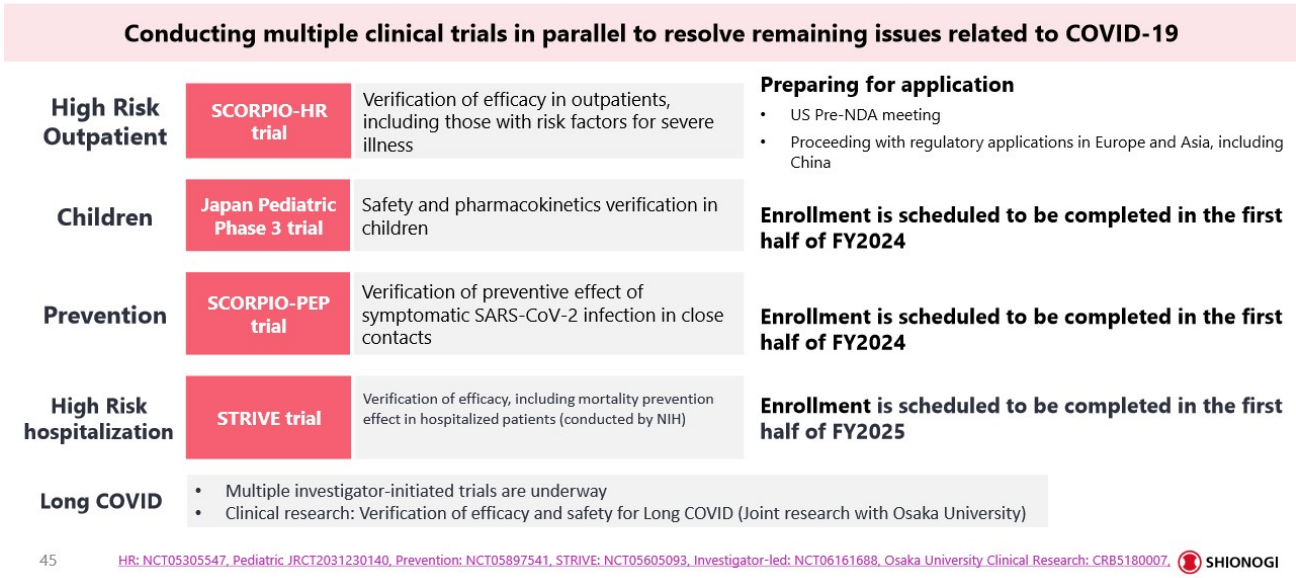
Primary endpoint	**Symptom improvement effect**	• Although ensitrelvir demonstrated a numerical reduction in the time to symptom resolution compared to placebo among participants treated within 3 days of symptom onset, the difference was not statistically significant. → A pre-defined supportive analysis of resolution of six symptoms for one day-using a statistical method similar to that used in the SCORPIO-SR Study (Phase 3 part of the Phase 2/3 study of ensitrelvir conducted in Asia) yielded a significant difference ($p<0.05$) in the time to resolution of symptoms
Secondary endpoints	**Effect for Long COVID**	• Ensitrelvir did not demonstrate a statistically significant reduction in the proportion of participants with post COVID-19 symptoms (Long COVID) at three months, but there was a tendency for a higher proportion of participants to report "having returned to pre-COVID health" and "felt no fatigue" compared to placebo. → Further detailed analysis is planned, including additional follow-up at six months.
	Antiviral effects	• Ensitrelvir demonstrated a potent antiviral effect for both viral RNA and culture, compared to placebo. • Symptomatic viral rebound was not observed in this study, supporting previous findings from SCORPIO-SR.
	Hospitalization and death prevention	• No deaths were observed in either group up to Day 29 of follow up, and very few cases of COVID-19 related hospitalization were observed in either arm.
Safety		• No new safety concerns were identified. • Ensitrelvir had similar tolerability to placebo and there were no reports of taste disturbance.

SHIONOGI

And this is the result.

The point is that we were able to confirm the effectiveness of the symptom improvement, and for the long COVID, we just finished all six months of follow-up just this month. So, as originally planned, we have completed all the follow-ups, and we plan to summarize how the administration of Ensitrelvir suppresses the occurrence of long COVID and present the results at the conference in the future.

Ensitrelvir



In this context, we are preparing to apply for a global trial that includes and targets high-risk outpatients, and pre-NDA consultation, as I mentioned earlier. We are developing a small tablet or granule formulation for children and for the global market.

First, we decided to conduct the trial in Japan ahead of the rest of the world. We are now conducting the trial for children in order to complete the registration by the first half of this fiscal year. We have obtained a definite effect of antiviral prophylaxis. It is prevention. If someone in your family contracts the disease and if you believe you are in close contact, you can take this drug to prevent infection. In this way, people can avoid contracting disease. We hope that the drug can be applied that way. Currently, no drug has this type of application.

We aim to deliver global indication once we succeed in conducting the world's first trial for post-exposure prophylaxis. We are now in the final phase. In H1 2024, we want to complete registration and from there we will be moving along with the process of confirming the results.

We are also conducting trials around the world on how to improve mortality rates in critically ill hospitalized patients and how to improve their return to work immediately after hospitalization. Furthermore, in Japan, we are working with Osaka University to verify the effectiveness of reducing the long-term COVID symptoms in actual clinical use, which means that in many aspects we continue our work in developing Ensitrelvir.

S-892216

Indications: Treatment and prophylaxis of infections caused by SARS-CoV-2

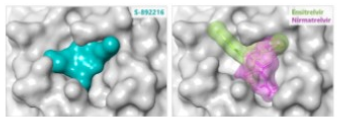
Global Phase 2 trials will begin in the first half of FY2024, with the aim of conducting Global Phase 3 trials in the first half of FY2025

Mechanism of action:

- SARS-CoV-2 3CL protease inhibition

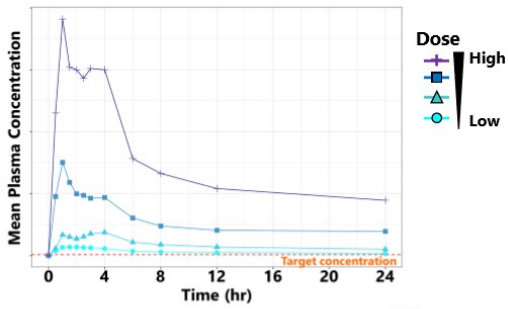
Product Features:

- Fewer drug interactions
- Strong antiviral effects
- No contraindications for pregnant women (no teratogenic effects observed in non-clinical studies)
- Different binding mode from other 3CL protease inhibitors, resulting in a distinct drug resistance profile



Result of Phase 1 trial

- Favorable pharmacokinetics, safety and tolerability
- No risk of CYP3A inhibition



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This research and development is supported by AMED under Grant Number 22fk0108522

SHIONOGI

Furthermore, the following compounds of Ensitrelvir. Ensitrelvir is something we quickly developed within the limited time during the pandemic. The only regret I have is the DDI perspective and drug interactions. In terms of teratogenicity, there is a restriction against taking the product in pregnant women, just to be safe, even though the data is based on animal studies.

We believe that we can create better medicines, so we are developing new items.

You see this colored, fuzzy thing on the bottom here, and the pink color in the area shown on the right is the active agent with Paxlovid, Nilmatrelvir. The green color hiding behind it is the Ensitrelvir, our Xocova. The form is different, in essence, how to inactivate the enzyme by binding it to the active center with a small molecule. The main part of the active center is the same, but if the form is different, various mutations can occur, various activities are different, and the effect can be maintained even in resistant strains.

This time, it is the blue figure on the left. You can see that it branches out in a different way. Therefore, while there is no particular strain that is resistant to Xocova at this point in time, it is expected that changing the binding mode will provide a new reserve for the new strains. And compounds without various drug interactions that can be taken by pregnant women.

Now that we have confirmed the efficacy of the drug in humans, we will be conducting a global Phase II study. We are preparing the next generation of Xocova as a new compound to replace the previous generation of Xocova.

RSV Infection

Even with widespread use of preventive vaccines, treatments for RSV infection is needed as a new option

Market :

- Pediatric* (Under 5 years old, Global) : 33.1 million people
- Elderly people*2 (Over 60 years old, in developed counties) : 5.2 million people

Current situation

Multiple drugs have been approved and launched for pediatric and elderly populations

However, all of them are preventive drugs

Patients who are expected to require treatment

High risk patients

- Pediatric with high risk factors, elderly, breakthrough infections

Not vaccinated

- US: Vaccination for elderly is not uniformly administered; it involves shared clinical decision making*3

* *Lancet*. 2022;399 (10340):2047-2064. *2 Influenza Other Respir Viruses. 2023;17(1):e13031
*3 Not universally recommended for administration to all individuals in a group; proposals are made based on physician judgment, and agreement is reached between the physician and the patient

SHIONOGI

In this context, since there is currently no cure for RS virus, various neutralizing antibody drugs can be used to prevent RS virus in infants and young children. However, even if there is a vaccine, there is no guarantee that a therapeutic drug will be necessary. Since the virus cannot be eradicated, some people will develop the disease even if they are vaccinated, and there are many people who are not vaccinated, so we are creating a treatment that can be delivered to such people.

S-337395
Indications: RSV Infection

Mechanism of action:

- By inhibiting the RNA-dependent RNA polymerase activity of the L protein, which is essential for viral replication, it inhibits the replication and transcription of the viral genome, thereby suppressing viral proliferation.

Product Features:

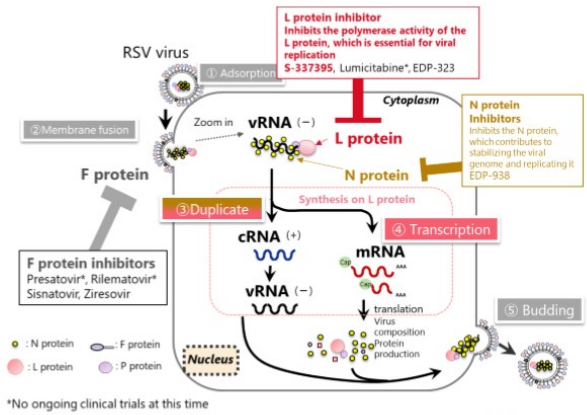
- Antiviral drug with a new mechanism of action (L protein inhibitor)
  - Compound discovered through joint research with UBE
- Easy to use oral medication
- Potent antiviral effect

Current status and future plans:

- RSV human challenge study (UK) ongoing
- Patient trials to begin in FY2025

RS virus replication process and site of action:

- Competitor products (small molecule drugs)
  Features of each mechanism of action:



*No ongoing clinical trials at this time

SHIONOGI

I have summarized the mechanism of action here.

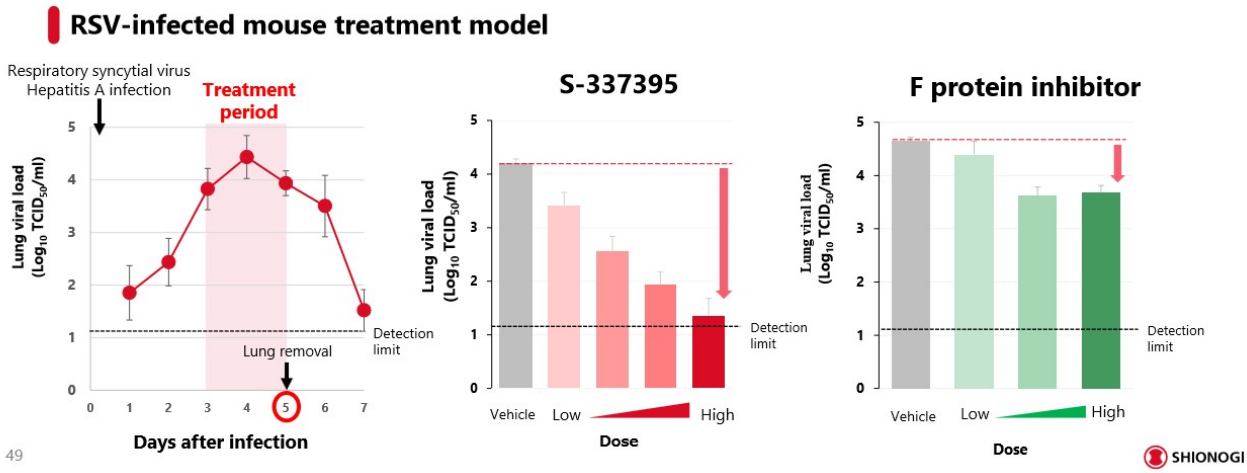
In the life cycle of a virus, the virus flops onto the cell in the upper left corner, and from there, it is adsorbed and goes inside. The process is called fusion protein, and it is this fusion process that Pfizer and others are targeting.

Our company, after all, wants to stop the increase inside. The mechanism of action differs depending on the virus, but for this virus, we are targeting the L-protein, which is marked in pink, as the best point to attack.

Stopping here inactivates the polymerase and thus stops the replication process in that cell. If we stop polymerase, there may be some people who are concerned about safety. We have properly designed the virus to stick to virus-specific points. We are now in the process of developing an antiviral drug with a low risk of side effects that could be delivered for RS.

S-337395: Non-clinical data

Compared to F protein inhibitors, this drug shows a clear virus reduction effect even when administered near the peak of viral replication



How superior is this mechanism of action? The data is still at the animal level, though.

The figure on the left shows an acute viral infection in which the virus is seeded into the mouse, from which the virus gradually and progressively increases, and from which the virus gradually drops from the peak by natural immunity.

The timing of when human patients actually develop the disease and take the medication is usually about the time when the symptoms appear, which is shown here in red, has risen, and the treatment is based on how quickly the virus can be lowered. That is the condition. You can see that our compound, S-337395, when taken at this timing, just as it is imitated in humans, the virus is neatly and dose-dependently brought down significantly.

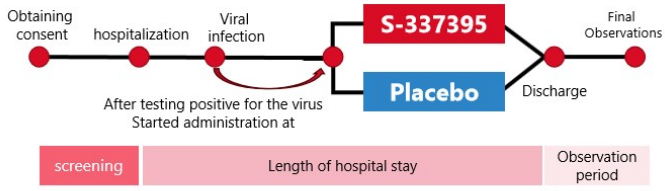
We have confirmed the power of the drug to stop the growth of viruses, and since the effect of the drug is limited in the fusion process, we are currently developing this drug with the hope that it will be a game changer in this sense.

S-337395: Clinical Development Plan

Confirm drug potential in RS virus human challenge study, accelerate development globally

Human challenge trial (UK, ongoing)

- Healthy adults are inoculated with the virus, and after confirming viral infection, they are administered S-337395 or placebo
  - Confirm efficacy against RSV
- So far, no adverse events have occurred



Adult development

- Dose setting in human challenge trial
- Verification trial will start in FY2025

Pediatric development

- Observational trials (Japan, USA):
  - Understanding the pathology in children (viruses, symptom progression)
- Based on the findings from the observational trial, a trial plan will be drawn up and a patient trial will be conducted in FY2025

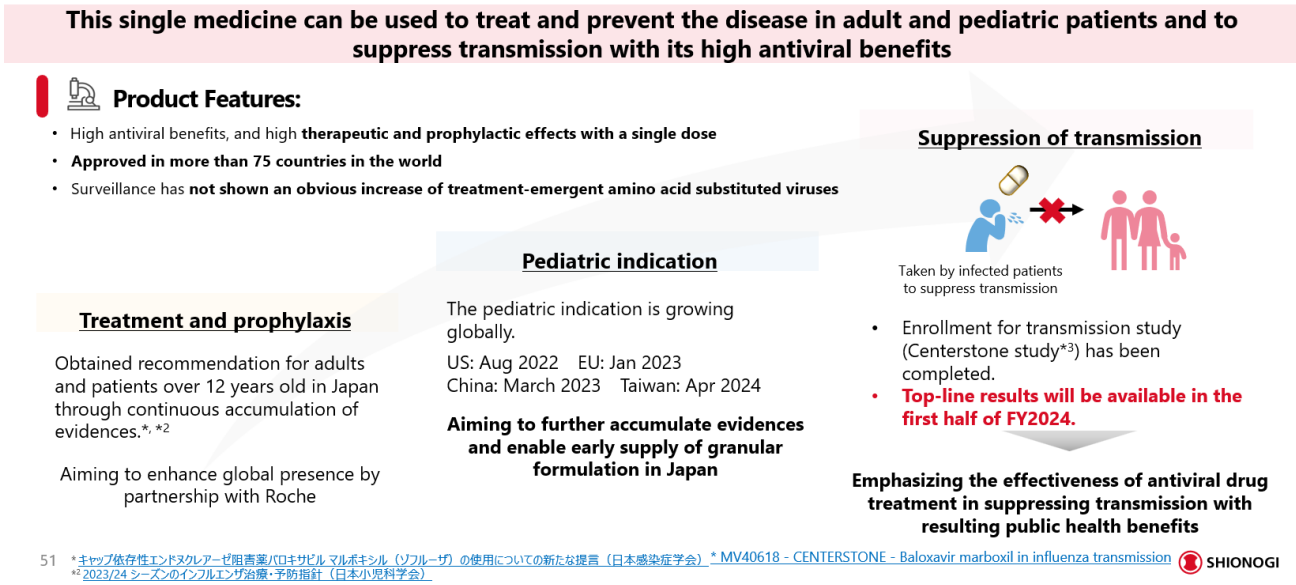
SHIONOGI

Phase I has already been completed, and we are currently conducting a study to confirm the antiviral effect in healthy adults who have actually been seeded with the virus and infected with the virus in a safe, albeit artificial, environment in the UK.

After confirming the level of viral resistance in the experimental environment, we plan to proceed with Phase II and Phase III of treatment for adults and children, respectively. We are now in the process of global development with plans to proceed with the necessary Phase II and Phase III for each arm.

Xofluza

Indications: Treatment and prophylaxis of Influenza A or B viral infection



Now, Xofluza is a medication for influenza.

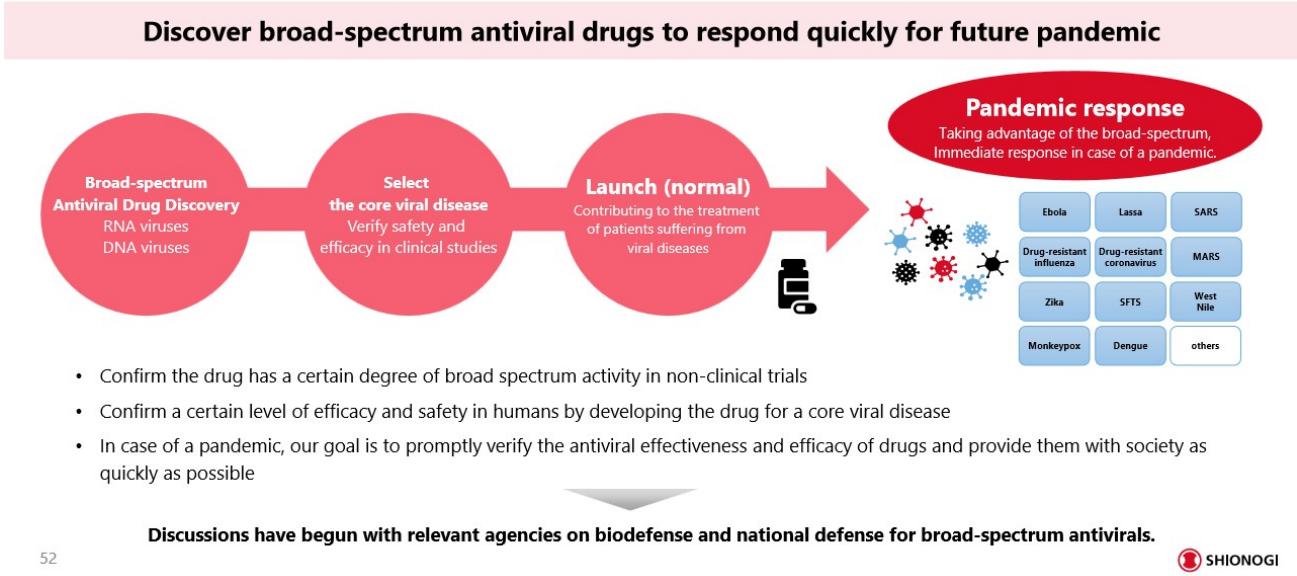
After obtaining indications in Japan and the US, we handed over the global rights to Roche, and they are proceeding with development around the world. The handout mentions more than 75, but actually, we reached 80 worldwide. It is now available in 80 countries. Just one does is enough to powerfully lower the virus. This will improve the symptoms.

In particular, this update is about the control of the spread of the virus, which I mentioned at the beginning of this article, and I believe that the treatment effect of your drug will not only improve your symptoms, but also lower the spread of the virus around you. The scientific hope is that this will reduce the spread of the virus to your family and surroundings.

In the experimental environment, a lot of such conceptual data has been collected. However, we have been wondering whether this can be verified in actual clinical use on humans, and this has been an issue for a long time, so Roche and we have been conducting tests around the world on inhibiting the spread of the disease. We have collected data from over 2,000 patients worldwide for the final 2,000 cases, and we will report back on these results, which we hope to be able to publish again in the summer.

Therefore, in terms of treatment, we are trying to deliver the maximum effect possible with drugs for each viral infection, such as diagnosis, medication, and prevention of spreading the virus to others.

SHIONOGI's Drug Discovery Strategy for Furure Pandemics ("Disease X")



In this way, we were able to respond to each viral infection one by one, but we still had to be prepared for pandemics and what would happen next. If you respond after it happens, you still have a limited amount of time. It inevitably takes time.

The next strategy is to have a certain number of drugs that are effective against various viruses, and if these drugs are approved once for a particular indication, they can be used to respond to a pandemic when a different virus becomes prevalent again. In the midst of this concept, we have received requests from Japan and around the world to work with us in the biodefense field, based on our strengths and achievements to date. Therefore, we are already working on the development of the next infectious disease treatment that will respond to this pandemic or the next pandemic.

Drug Discovery Research aimed at Creating Broad-spectrum Antiviral Drugs

In anticipation of mobilizing in times of emergency,
we are advancing drug discovery for broad-spectrum antivirals

	RNA Viruses**														
Compounds	**Influenza virus A (H5N1)***	**SARS-CoV-2**	**Entero virus (A71)**	**Dengue virus-2***	**Zika virus***	**Yellow Fever virus***	**JEV**	**CHIKV***	**La Crosse virus**	**RVF***	**SFTSV**	**TMPV**	**Tula virus**	**RS virus**	**Rabies virus**
Compound X	W	M	M	S	S	S	S	S	S	S	S	S	S	NT	W
Remdesivir	W	S	S	M	M	W	S	W	W	W	W	NT	NT	S	W
Ribavirin	W	W	W	W	W	W	M	W	S	M	M	NT	NT	M	M
Favipiravir	W	W	NT	W	W	W	W	W	M	S	M	NT	NT	NT	W

	DNA Viruses					
Compounds	**HSV-2**	**VZV**	**HCMV**	**HHV-6**	**EBV**	**AdV3**
Compound Y	S	S	S	S	S	S
Compound Z	S	S	S	S	S	S

In vitro antiviral activity: **S** M W — S: strong, M: moderate, W: weak

NT = Not tested

*Designated high pandemic potential viruses (Economic Incentives and Strategies for Pandemic Preparedness from U.S. Government Accountability Office)
** Collaborative research with Hokkaido University

Japanese encephalitis virus (JEV), chikungunya virus (CHIKV), rift valley fever virus (RVF), severe fever with thrombocytopenia syndrome virus (SFTSV), thottopalayam thottimvirus (TMPV), Herpes simplex virus type-2 (HSV-2), varicella-zoster virus (VZV), human cytomegalovirus (HCMV), human Herpesvirus 6 (HHV-6), epstein-barr virus (EBV), adenovirus serotype 3 (Adv3)

SHIONOGI

This is just the current progress, but I have written Compounds X, Y, and Z. On the right-hand side, I listed the viruses. For the H5N1 flu virus, I would recommend using Xofluza. For other viruses, the RNA virus is on the top, and the DNA virus is on the bottom.

Agents that can cover many virus strains with a single drug, and that maintain antiviral activity, have already been found. They can take many forms, like oral, intravenous, and chemo-type. Therefore, we are vigorously promoting the development of new drugs to prepare for possible outbreaks of Rift Valley fever or other diseases that may occur in the future.

Efforts towards Antimicrobial Resistance (AMR)

Bacterial infections due to AMR are steadily increasing and are threatening humanity as a "silent pandemic" that is expanding unnoticed

Cefiderocol:

A new option for AMR infections caused by gram-negative bacteria

- Launched in Japan, the U.S., Europe, etc.
- In partnership with GARDP and CHAI to expand access to 135 countries (about 70% of the world)

S-649228 (Cefiderocol+Xeruborbactam):

A preparation for more advanced drug-resistant bacteria
Preparing treatment options for highly drug-resistant bacteria that may emerge in the future

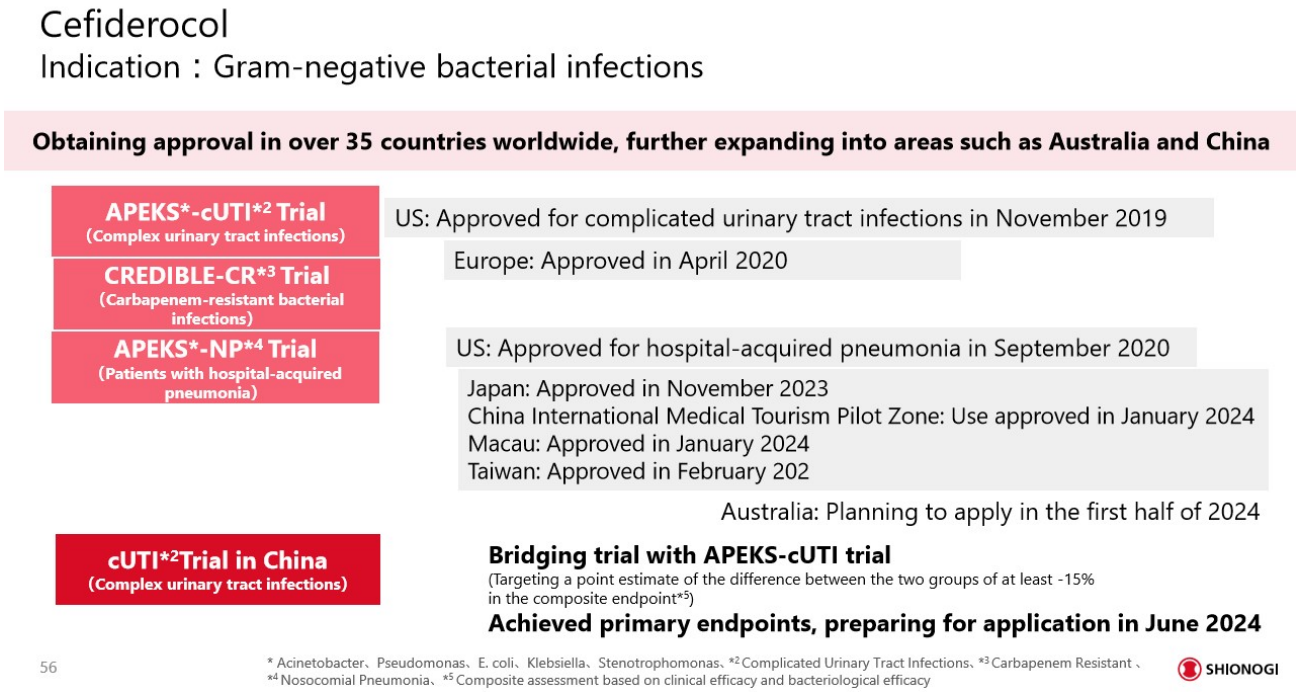
S-743229 (Ceftibuten+Xeruborbactam):

Providing a new AMR treatment option of oral medication
Achieving improved patient QOL and reducing the burden on healthcare workers

SHIONOGI

Now, the AMR perspective is the next bacteria.

With cefiderocol as the core, we have worked with QPEX to acquire a drug called xeruborbactam. We are now in the process of starting clinical trials for a fixed-dose combination with xeruborbactam. I will discuss the status of each of the three items.



First of all, cefiderocol.

It has already been approved in more than 35 countries around the world, including the United States, Europe, and Japan. In addition to expanding to various countries in this context, a major update is at the bottom of the page. We met the primary endpoint of the complex urinary tract infection trial, Phase III trial, which was conducted in China. In response to this, and once again, we would like to make cefiderocol accessible in the Chinese market.

S-649228 (Cefiderocol+Xeruborbactam Injection)

Indication：Gram-negative bacterial infection

Market：

- Market size of drug-resistant gram-negative bacteria (2023)*: $819.1 million

Unmet needs：

- New treatment for expanding carbapenem-resistant gram-negative bacteria
- Future treatment options for the emergence of further resistant bacteria

Product Characteristics：

- Injectable drug useful for treating various infections caused by multi-drug resistant gram-negative bacteria

Current Status：

- Start of Phase 1 trial in 2Q 2024

Mechanism of Action：

- Cell wall synthesis inhibition
- Improved power of cefiderocol with concomitant use of novel beta-lactamase inhibitor Xeruborbactam

Confirmed good antibacterial activity against a special collection of strains consisting only of cefiderocol low-susceptibility strains*2

			Cefiderocol	Cefiderocol + XER (4 μg/ml)
Enterobacterales	Cefiderocol MIC>2 (N=52)	MIC_{50}	4	0.25
		MIC_{90}	64	1
Acinetobacter spp.	Cefiderocol MIC>1 (N=124)	MIC_{50}	>64	0.25
		MIC_{90}	>64	1
Pseudomonas aeruginosa	Cefiderocol MIC>1 (N=31)	MIC_{50}	2	2
		MIC_{90}	8	4

XER: xeruborbactam
All MIC units are in μg/mL

* Total sales of the following products in the major seven countries (USA, UK, Italy, Germany, Spain, France, Japan)：CEFIDEROCOL, AVIBACTAM-CEFTAZIDIME, CEFTOLOZANE-TAZOBACTAM, CILASTATIN-IMIPENEM-RELEBACTAM, COLISTIN, DURLOBACTAM-SULBACTAM, ERAVACYCLINE, MEROPENEM-VABORBACTAM, POLYMYXIN B, TIGECYCLINE

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*2 Reference: Olga Lomovskaya, IDWeek2023

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As for cefiderocol, there are no particularly resistant strains prevalent at this time. However, bacteria are smart. These cephem-based drugs are designed to produce beta-lactamase, which is a mechanism that breaks down the drug. They are readily available, and when they were isolated and assayed experimentally, the activity of cefiderocol was revived again in combination with xeruborbactam.

Therefore, by having this drug ready in case of an outbreak of resistant bacteria in the future, we can once again benefit from the efficacy of cefiderocol. We are discussing with various authorities in order to proceed with Phase I this fiscal year. This is making steady progress.

S-743229 (Ceftibuten+Xeruborbactam Oral)

Indication：Complex urinary tract infections

Market ：

- Complex urinary tract infections Annual incidence: 2.8 million people (US)*1
  - Many of the causative bacteria of complex urinary tract infections are Enterobacteriaceae*2
  - Annual medical expenses total: more than $6 billion (US) *1

Unmet needs ：

- A new oral treatment for complex urinary tract infections that do not respond to existing oral antibiotics

Product Characteristics ：

- Oral antibiotics that can be used to treat complex urinary tract infections caused by resistant bacteria

Current Status ：

- Currently conducting Phase 1 clinical trials
- Aiming to enter Phase 3 trials by 2026

Mechanism of Action ：

- Cell wall synthesis inhibition by ceftibuten, a cephalosporin antibiotic
- Improved efficacy of cefdibuten by concomitant use with novel β-lactamase inhibitor Xeruborbactam

Confirmed good activity against various β-lactamase-producing Enterobacteriales*3

Phenotype	Number of isolates		Ceftibuten	Ceftibuten + XER (4 μg/mL)
ESBL	(N=154)	MIC_{50}	8	≤0.03
		MIC_{90}	>64	0.125
KPC	(N=76)	MIC_{50}	16	0.125
		MIC_{90}	64	0.25
OXA-48-like	(N=91)	MIC_{50}	32	0.25
		MIC_{90}	>64	0.5
Metallo	(N=79)	MIC_{50}	>64	2
		MIC_{90}	>64	64

XER: xeruborbactam, ESBL KPC: Klebsiella pneumoniae Carbapenemase, OXA: OXA β-lactamase，Metallo: All units of metallo-β-lactamase MIC are in μg/mL.

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*1 Carreno, Joseph J., et al. Open Forum Infectious Diseases. Vol. 6. No. 11. US: Oxford University Press, 2019.
*2 Nicolle LE. Urinary tract infection. Crit Care Clin. 29:699–715, 2013. *3 Reference: Olga Lomovskaya, ESCMID Global (2024)

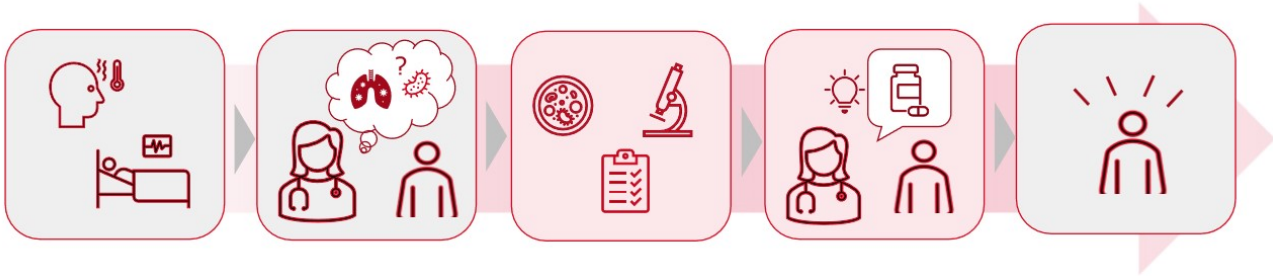
SHIONOGI

In oral drugs, ceftibuten, which is our third-generation cephem drug. We have also developed an oral drug that is effective against resistant strains by combining it with an oral prodrug of xeruborbactam. This one, Phase I, has already started globally.

If there is an oral drug that can provide such AMR protection, it is not necessarily necessary to prescribe it in the inpatient setting, because it is not necessary. This new drug is expected to be used in various ways, such as to control hospitalization costs by switching to this type of oral drug when serious conditions can be avoided to some extent.

Concurrent efforts for the development of antibiotics and corresponding antimicrobial susceptibility testing (AST)

Establishing a diagnostic system to ensure appropriate treatment



Patient develops infectious disease	Conducting examinations, collecting lesion samples, implementing empirical treatment	• Identifying pathogens within lesion samples • **Performing Antimicrobial Susceptibility Testing (AST)**	**Switching to appropriate antibiotic treatment based on the results of the AST**	Treatment is effective and patient recovers

Promoting collaboration with AST device manufacturers around the world to ensure the availability of diagnostic devices by the time the antibiotic is launched

AST: antimicrobial susceptibility testing

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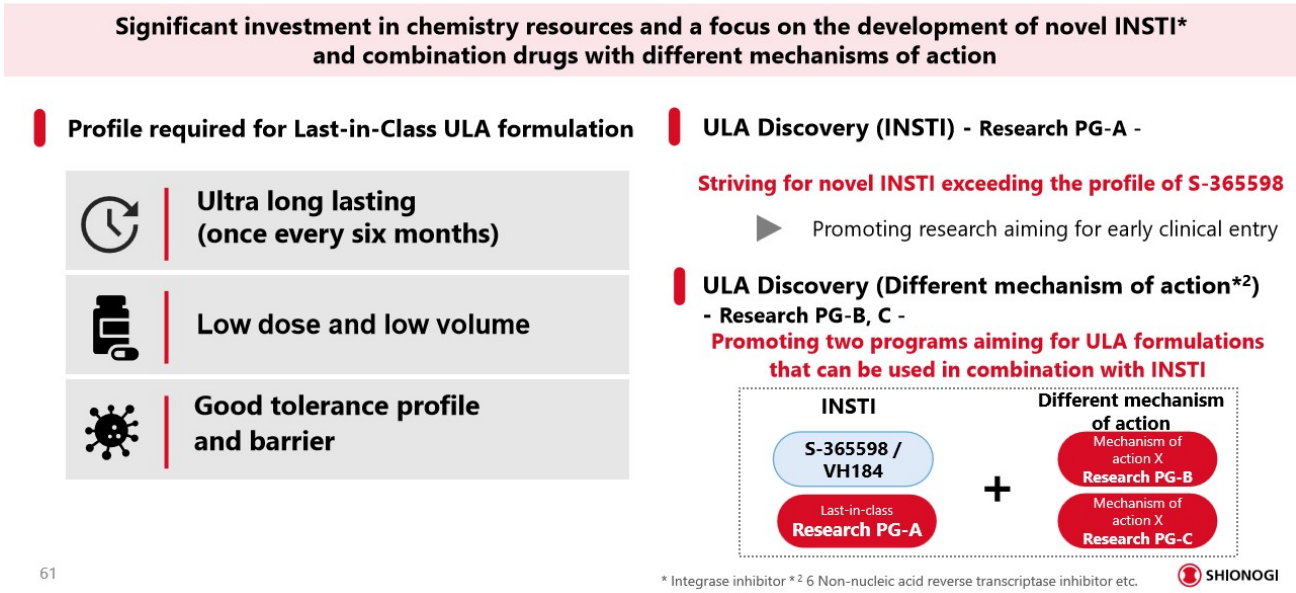
Now, in order for you to use antimicrobials in these circumstances, we need to know if our drugs remain effective against antimicrobials. We need a device that can easily evaluate such things and an evaluation method for susceptibility.

There are various device manufacturers all over the world, and we are working in parallel to develop a method for measuring sensitivity so that these devices can be used as diagnostic agents promptly in accordance with the timing of the launch of these products.

HIV Drug Discovery: Aiming for the Development of Last-in-Class ULA Formulation



Now, I would like to talk a little bit about chronic infectious diseases, HIV, malaria.

We have also introduced dolutegravir for its antiviral effect on HIV, and later we licensed out S-365598, a next-generation integrase inhibitor, to ViiV.

However, there is still much need to create drugs with longer durations, lower doses, higher tolerance profiles, and higher barriers. Therefore, we have concentrated our chemist's resources to develop a long-acting integrase inhibitor program, which we call "Integrase Inhibitor Program A," to enable once-every-six-months delivery.

The programs with different mechanisms of action, which I am writing in the form of A, B, and C, are also LAP, long-acting, and ultra-long-acting. With the establishment of such a two-drug combination program, we are now developing a last-in-class LAP formulation that can be easily administered once every six months or once every six months to control the disease.

Research on Concomitant Drug Candidates for HIV ULA Treatment

Currently identifying lead series expected to have ultra long acting sustainability and conducting structural optimization

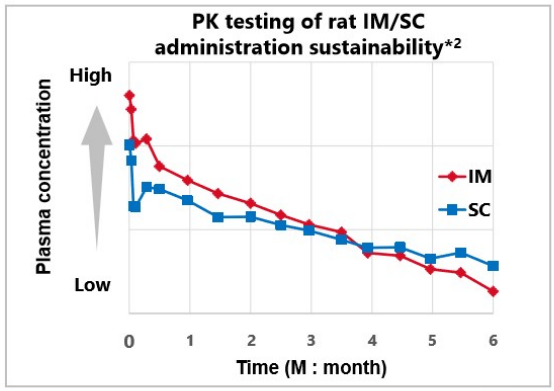
Search for concomitant drug partners for integrase inhibitor

ULA* regimen

INSTI + Concomitant medication

- To develop concomitant ULA drug with integrase inhibitor, we are conducting research programs with multiple mechanisms of action
- In the top runner program, we obtained a lead compound with a potential to last six months in rats administered with IM/SC.
- We identified promising lead series and are currently conducting higher-order selection evaluation to progress into nonclinical studies

Evaluation of ULA potential of lead compounds

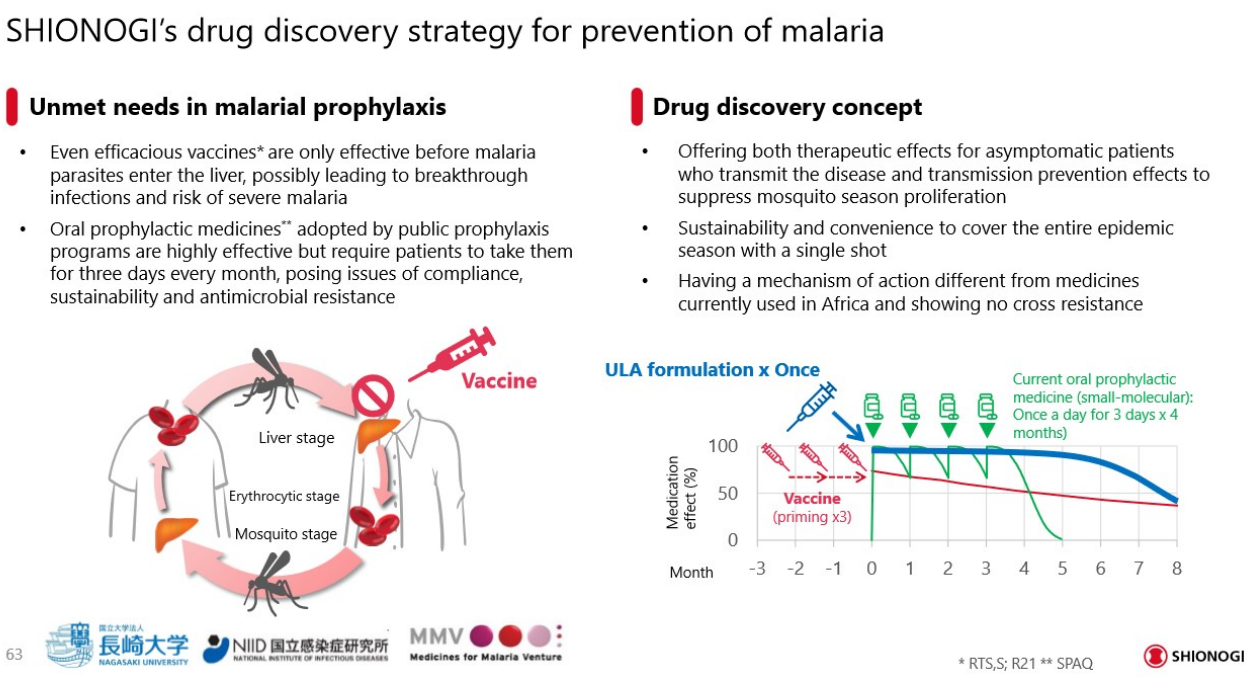


*ULA: Ultra long acting *2 Exploratory study with QA (Audit according to the reliability standards by the Reliability Assurance Department) not implemented yet, dose: 30 mg/head; SC: Subcutaneous, IM: Intramuscular

SHIONOGI

We have already found good lead compounds.

This combination drug is shown on the right. As you can see, IM, whether administered intramuscularly or subcutaneously, can remain in the bloodstream for a very long period of time, in excess of six months under any of the administration conditions. By hastening the development of such drugs, we believe that we are likely to be able to deliver the next more controlled and simplified HIV drug product.



Now, I would also like to talk a little bit about our efforts with malaria.

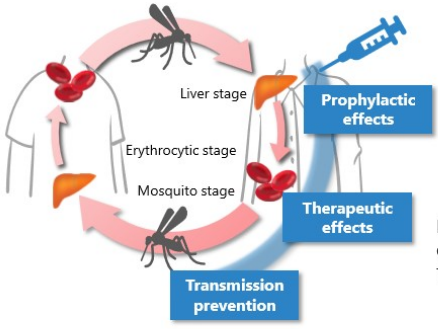
Malaria is a mosquito-borne infectious disease that will never disappear in Africa and elsewhere. The malaria parasite is processed through mosquitoes and then enters the red blood cells and travels through the blood. Vaccines are available, but they are not reaching all the people.

There are actually prophylactic drugs that are taken prophylactically, with an approach of multiple doses per month of a prophylactic drug. However, people still die from malaria, especially in developing countries, due to the lack of adherence with medication and the lack of regular implementation of such measures.

Our Ultra Long Acting malaria prophylaxis is given once and it lasts for several months. Complete prophylaxis exactly in time for the malaria mosquito epidemic. Our concept is to create new products with high adherence.

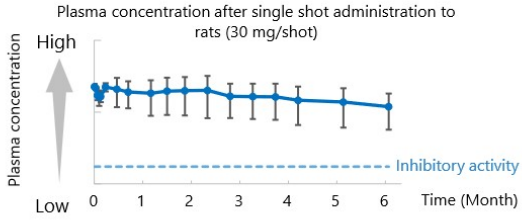
Discovery of ULA medicines effective against malaria parasites in multiple stages

We are promoting drug discovery studies for ULA formulations with superior prophylactic, therapeutic, and transmission prevention effects



Stage	EC_{50} (nM)
Liver stage	1.5
Erythrocytic stage	8.3
Mosquito stage	6.3

Lead compound A shows equivalent inhibitory activity in all the stages.*



Lead compound B shows ultra long acting sustainability in rats.*

Currently identifying compound groups expected to attain the both and conducting research on structural optimization

長崎大学 NAGASAKI UNIVERSITY　NIID 国立感染症研究所　MMV Medicines for Malaria Venture

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This study has been supported by the GHIT Fund since April 2024.

SHIONOGI

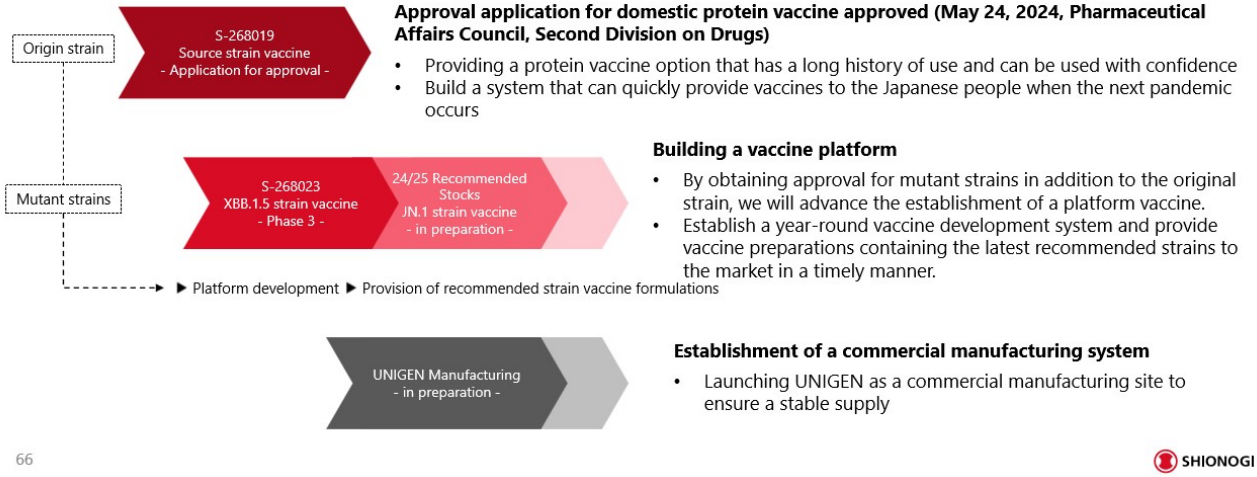
This preventive effect, though, is also unique.

If it is administered to humans and the required amount can be maintained in blood levels, it can be maintained in the bloodstream and in the bodies of mosquitoes that have sucked it. So, since the drug will be effective throughout its life cycle, it is expected to lower the overall prevalence of malaria, including mosquitoes, rather than its own preventive effect. The lead compound is already in the process of being finished, as such a concept is expected.

This is also actual data. This new drug, which can maintain high exposure for a certain period of time, is expected to have a very good prophylactic effect and is under development.

COVID-19 Vaccine Platform

Establishing a vaccine platform and aiming for timely market supply of vaccine formulations containing recommended strains



Approval application for domestic protein vaccine approved (May 24, 2024, Pharmaceutical Affairs Council, Second Division on Drugs)

- Providing a protein vaccine option that has a long history of use and can be used with confidence
- Build a system that can quickly provide vaccines to the Japanese people when the next pandemic occurs

Building a vaccine platform

- By obtaining approval for mutant strains in addition to the original strain, we will advance the establishment of a platform vaccine.
- Establish a year-round vaccine development system and provide vaccine preparations containing the latest recommended strains to the market in a timely manner.

Establishment of a commercial manufacturing system

- Launching UNIGEN as a commercial manufacturing site to ensure a stable supply

SHIONOGI

Now, I would like to talk a little bit about vaccines next.

As you are already well aware, approval for our first recombinant protein vaccine for S-268019, Wuhan strain, have been granted. We would like to establish such a platform in Japan to prepare for the next pandemic, rather than the current pandemic, by using recombinant proteins, which have been used for a long time as a vaccine with established safety on a different platform from messenger RNA and others. We are in the process of receiving the first of these approvals.

In actual clinical practice, the Omicron strain, BA.5, XBB, and JN.1 have already changed, and we are developing another vaccine against these recombinant strains. As soon as these data are obtained, and once the indication for the mutant strain is approved, we believe that an environment will be created in which these vaccines can be used in Japan.

At the same time, we are also working on the establishment of large-scale production in parallel.

S-567123: Universal vaccine

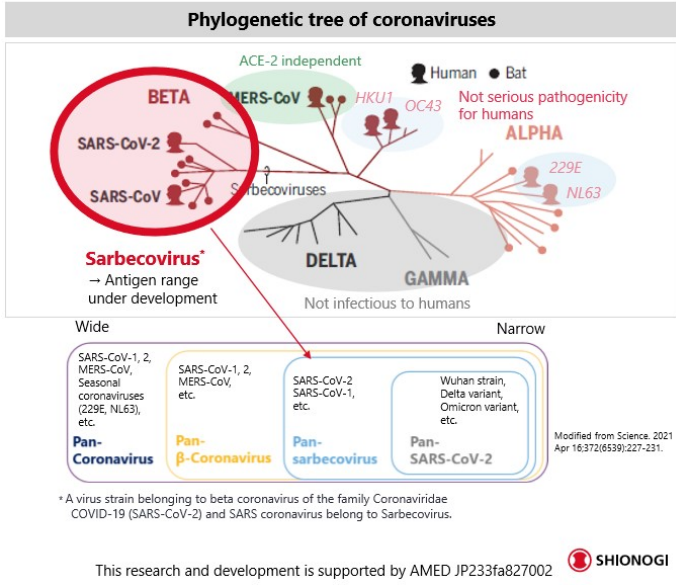
The World we enbision with universal vaccines

- Vaccination in the early stages of a pandemic will save many human lives.
  - Life-saving measures that were not possible in the recent COVID-19 pandemic
- A seasonal vaccine in ordinary times will induce strong immunity and contribute to prevention of severe disease.
  - Preventing new pandemics

Targeted vaccine concept

- Can be used as a prophylactic SARS-CoV-2 vaccine in ordinary times
- Can be used for outbreak of SARS-CoV-1 or other sarbecovirus infections
- Better safety than existing vaccines

KOTAI NIID 国立感染症研究所 NATIONAL INSTITUTE OF INFECTIOUS DISEASES



This research and development is supported by AMED JP233fa827002

SHIONOGI

In this environment, the coronavirus is changing rapidly, and the recommended strains for this year are constantly being created and changed. We have no other choice but to do so for now, but we are forced to do so, but the concept of universalism.

If there is a certain number of antigens that can maintain immunity even if they are changed, then it is okay not to change them. We are developing a next-generation vaccine, a universal vaccine for coronavirus, in the hope that we can deliver such a vaccine.

S-567123: Advantages of S-567123

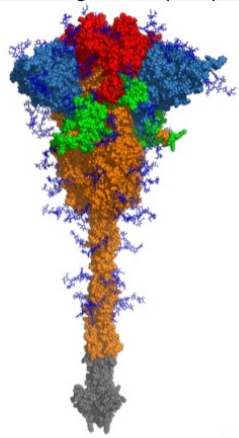
Antibody induction to conserved regions of Sarbecovirus with coverage that competitors' vaccines cannot provide

Characteristics of antigen design technology and antigens

- Building an antigen design technology that induces antibodies against preserved regions, not in regions where mutations can easily occur
- Collaborating with KOTAI Co., Ltd. to on this antigen design technology
  - Overview of antigen design technology
  - ① Induction of antibody production to conserved regions by glycan control
  - ② Introduction of epitopes preserved between different viruses and strains
  - ③ Increased immunogenicity by control of protein structure and dynamics

Creating a universal antigen that selectively induces antibodies across the entire family of Sarbecoviruses

Schematic diagram of spike protein



This research and development is supported by AMED JP233fa827002

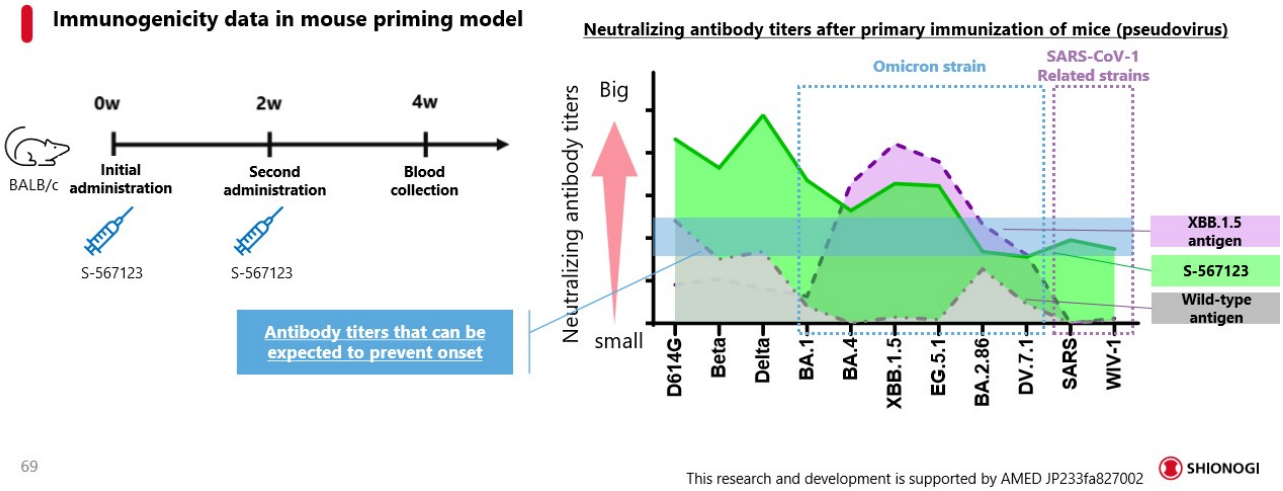
SHIONOGI

The schematic diagram of the spike protein is shown on the right, and some parts of it change frequently while others do not. Therefore, we designed a recombinant protein by designing a protein that would not change and creating a hybrid of such proteins.

If we can create a universal vaccine that can induce antibodies that bind to various sites, we will be able to deliver vaccines that do not need to be constantly changed every year, as I have been talking about earlier.

S-567123: Progress and Data

Development antigen selection completed, Preparing for clinical trial entry within FY2024



This research and development is supported by AMED JP233fa827002

SHIONOGI

In fact, the antigen has already been created. The gray area is the Wuhan strain, the vaccine derived from the original strain of origin, the left side is the Wuhan strain, and in the middle is Omicron. Then there are SARS-CoV-1, SARS, and MARS, strains that seem to have been prevalent in the past. The Wuhan strain compatible vaccine is still the Wuhan strain.

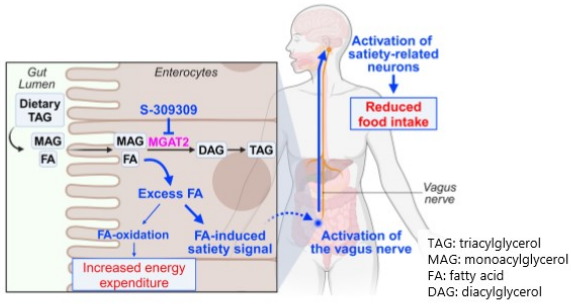
The one in the middle in pink is for BA and Omicron stocks, and our new universal is shown here in green. We have confirmed that it is effective against both the Wuhan and Omicron strains, and also induces neutralizing antibodies against SARS-CoV-1, a different strain that may be prevalent in the future, even though it is an animal model. Based on this data, we will conduct clinical trials this fiscal year and develop new modalities that can be delivered worldwide.

S-309309
Indication: Obesity

Phase 1* trials confirm mechanism of action in humans

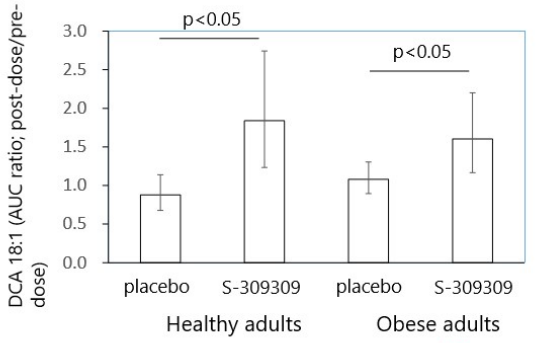
Monoacylglycerol acyltransferase 2 (MGAT2) Inhibitors

- Inhibits the resynthesis of triglycerides, inhibits the absorption process of triglycerides (TAG) from the small intestine, and causes accumulation of dietary fatty acids in the small intestinal epithelium
- Food intake is suppressed via the vagus nerve



Plasma DCA 18:1 measurement results

- DCA18:1 (oleic acid oxide): produced by oxidation of dietary fatty acids accumulated in the small intestinal epithelium, etc.



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* US program: NCT05247970

SHIONOGI

Now, following on from the infectious diseases, I would like to discuss one by one the remaining QOL diseases with high social impact.

Obesity. Let me briefly remind you of the mechanism: triglycerides, or triglycerides in the diet. It is broken down and absorbed through the small intestinal epithelium, and this MGAT2 is the enzyme that resynthesizes fat particle into triglycerides one more time.

So, by interception at this point here, fatty acids will accumulate in the small intestinal cells. As fatty acids accumulate in the cells, food suppression signals go out, as if saying, given the condition you don't need any more food.

Therefore, it is not a drug that inhibits lipid absorption in the gastrointestinal tract. We are often asked if it causes diarrhea, but the mechanism of action is not intended to cause diarrhea.

In Phase I, DCA in plasma, which is a new biomarker, was found in subjects who took the drug, supporting the mechanism of action. Therefore, we have confirmed in Phase I that the proof-of-mechanism of the fatty acid accumulation in the small intestinal cells is probably occurring with this drug, and we have moved to Phase II.

S-309309: Topline Result of Phase 2 Clinical Trial

Favorable safety profile confirmed, suggesting potential as a new option for obesity treatment

Overview*

Country	US
subject	Adults with a BMI of 30 or more
Study design	Multicenter, randomized, double-blind, dose-finding, Placebo-controlled
Dietary restrictions	Daily calorie intake is calculated by subtracting 500 kcal from the total energy expenditure calculated based on age and sex. (Complies with the Anti-Obesity Drug Development Guidelines)
Dosage and Administration Number of cases	• Once daily orally for 24 weeks • No dose escalation, no food restrictions when taking medication • S-309309: 3 doses, placebo, 80 cases per group (total 320 cases)
Primary endpoint	Weight change from baseline (24 weeks after administration)

Preliminary results (under analysis)

- Good tolerability was confirmed. The incidence of gastrointestinal symptoms, known to occur with GLP-1*2 preparations, was similar to that in the placebo group, and there were no concerns about tolerability.
- The rate of weight loss from baseline (group average), which was set as the standard for determining whether or not to develop a single agent, did not exceed 5%.
- A tendency towards weight loss in humans with this mechanism of action was confirmed

Consider a new development strategy based on the "unmet needs of existing treatments" rather than a development strategy based on S-309309 alone

*1 ClinicalTrials.gov: NCT05925114 *2 Glucagon-like peptide-1

SHIONOGI

We have conducted a Phase II study in the US.

We are actually conducting a clinical trial for adults with a BMI of 30 or higher, and we are conducting a standard fat Phase II trial, specifically, we are having them take this drug after eating a slightly lower calorie intake that is restricted in their diet. We conducted the trial to see how it can be effective to lose weight.

One of the things we expected to confirm is safety. There was a heightened concern for diarrhea but none was confirmed. The fact that the drug was well tolerated compared to placebo was a very significant gain.

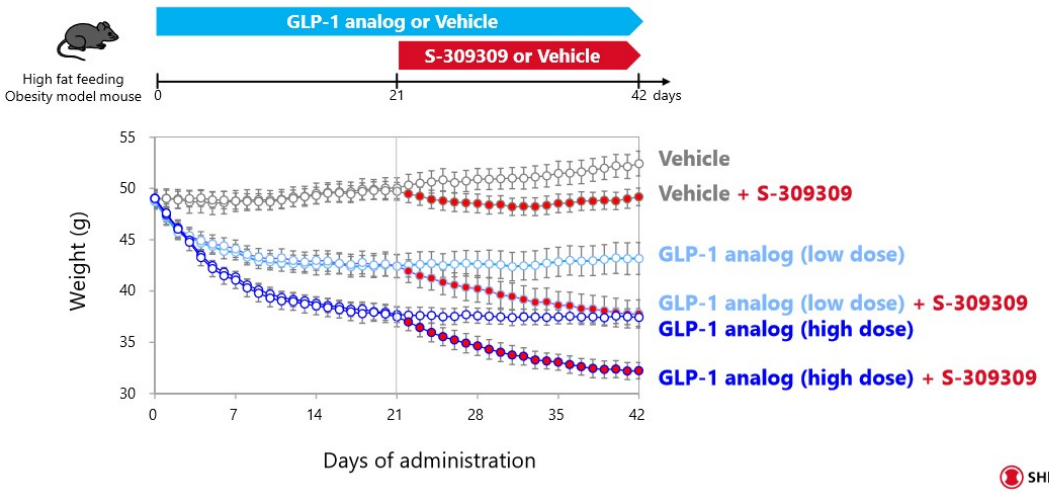
As you are already well aware and have seen in the second line, this is our internal standard for weight. We had set a criterion of 8% or 10% if possible, and as far as the GLP-1 data was concerned, we had set a criterion of at least 5% in order to fight with a single agent. Unfortunately, that criterion has not been reached.

Nevertheless, the mechanism of action has been confirmed and the effect of weight loss has been confirmed. So, we have confirmed that it is a drug that shows weight loss by suppressing appetite through a new mechanism of action.

Therefore, we believe that we will not be able to proceed with Phase III as a single agent based on the current data, so we are currently conducting various studies to determine what kind of unmet needs we can satisfy.

S-309309: Non-clinical Trial Results - Add-on Effect

S-309309, as an add-on, exerts an additive or greater effect on the weight-reducing effect of GLP-1 analog



SHIONOGI

This is new data, non-clinical data that we were already allowed to take.

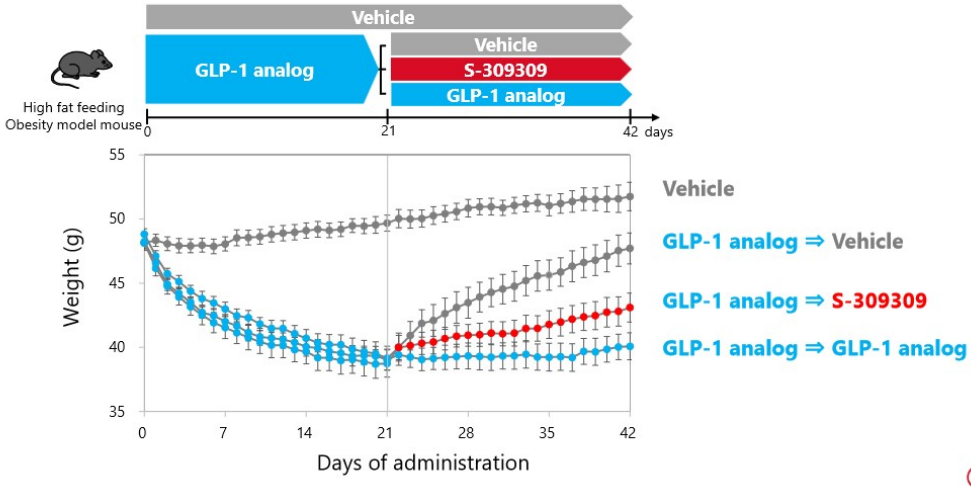
When taken in GLP-1, weight loss can happen. As you know, some patients may have difficulty escalating doses during the tightening process, and the cost of the drug is very high.

If the same level of efficacy can be achieved with as low a dose of GLP-1 as possible in a place where it is difficult to create a API, this could be a place where the small molecule S-309309 can be used to its fullest potential. This is non-clinical data on looking at such a concept.

The patient who started GLP-1, the animal, but at the midpoint, the red point, S-309309 is put on. Since the effect of S-309309 was apparently more than additive in those who used GLP-1, we can expect a higher effect by using two drugs. The nonclinical data are such that one might expect that adding on S-309309 to a smaller dose than going with GLP-1 alone might provide the same amount of benefit.

S-309309: Non-clinical Trial Results - Efficacy Maintenance effect

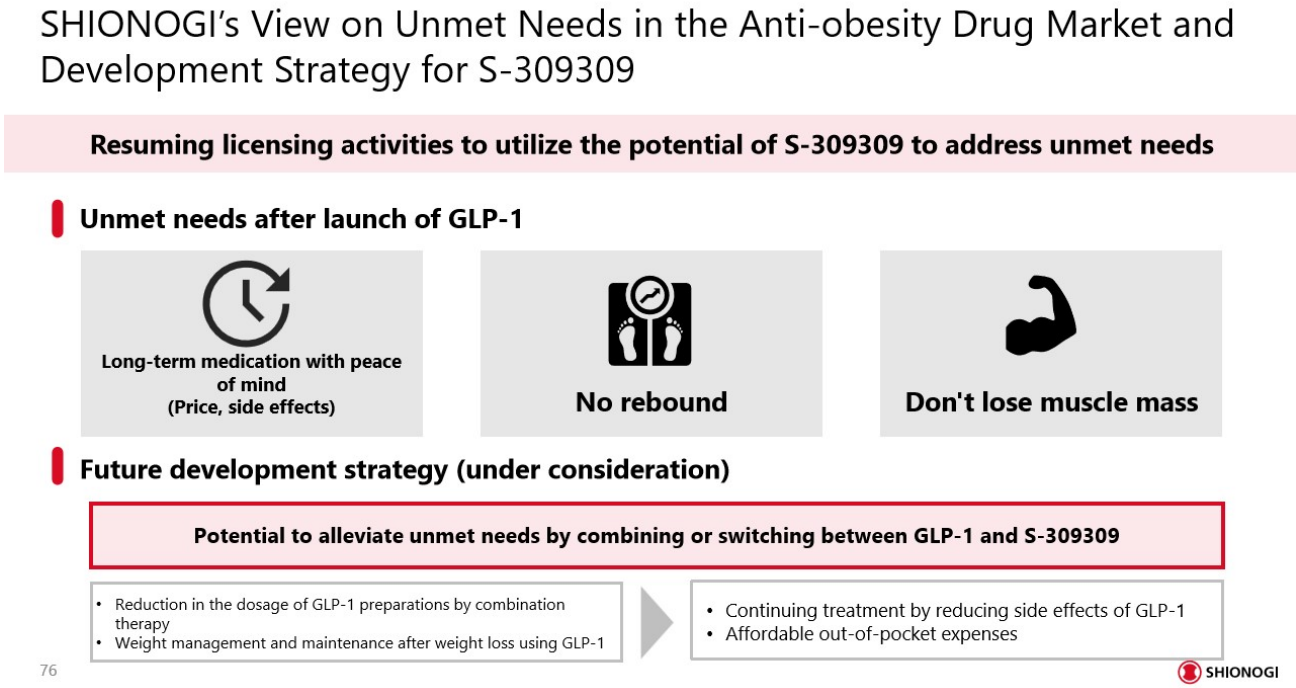
Switching to S-309309 after GLP-1 analog treatment reduced weight rebound compared to the vehicle group



SHIONOGI

This is a different use. There are also those who stop using GLP-1 because their weight has dropped to some extent, and those who stop because they cannot tolerate the side effects. There are also many people who quit due to cost considerations.

Rebounding has become a real social problem, and if S-309309 can be used to control that rebound, it could be used to maintain weight loss while gently controlling weight. So, of course, we were willing to use a single agent, but we were also conducting various pre-clinical verifications in parallel to see if such usage was also possible.



Interesting data has emerged. Including these nonclinical data, we can also expect that the product can be used safely over the long term, without rebounding, and in some cases, without losing muscle mass. This is a licensing activity that we are resuming in order to consider new formulations that will allow us to offer these affordable prices in the future, aiming at the possibility of resolving new unmet needs.

I would like to reiterate our future development strategy, including various data in this context.

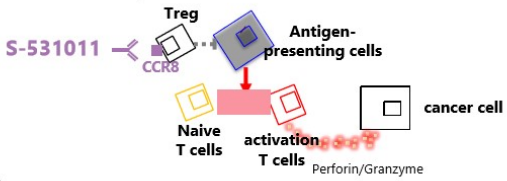
S-531011
Indications: Solid Cancer

Product Features :

- Anti-CCR8* humanized monoclonal antibody
- Excellent safety and strong efficacy expected by activating tumor immunity
- Potential for use in a variety of cancer types
  - ➢ CCR8 is expressed in tumor-infiltrating Tregs in various cancer types and stages.

Mechanism:

1. The antibody binds to CCR8, which is selectively highly expressed on regulatory T cells (Treg) in tumors, and removes the cells to relieve immune suppression.
2. Tumor immunity is restored and antitumor effects are achieved



Development history

2014
Joint research course established with Osaka University*2
- Search for molecules other than PD-1 involved in tumor immune evasion

2018
Discovery of CCR8
- Patent application (Granted)

2022
Started Phase1b/2 in Japan and the US
- Phase 2 part in preparation

Delivering new cancer treatments from Japan to the world

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* CCR8: Chemokine (C-C motif) receptor 8 *2Department of Clinical and Basic Tumor Immunology, Center for Innovative Medical Innovation (CoMIT), Osaka University

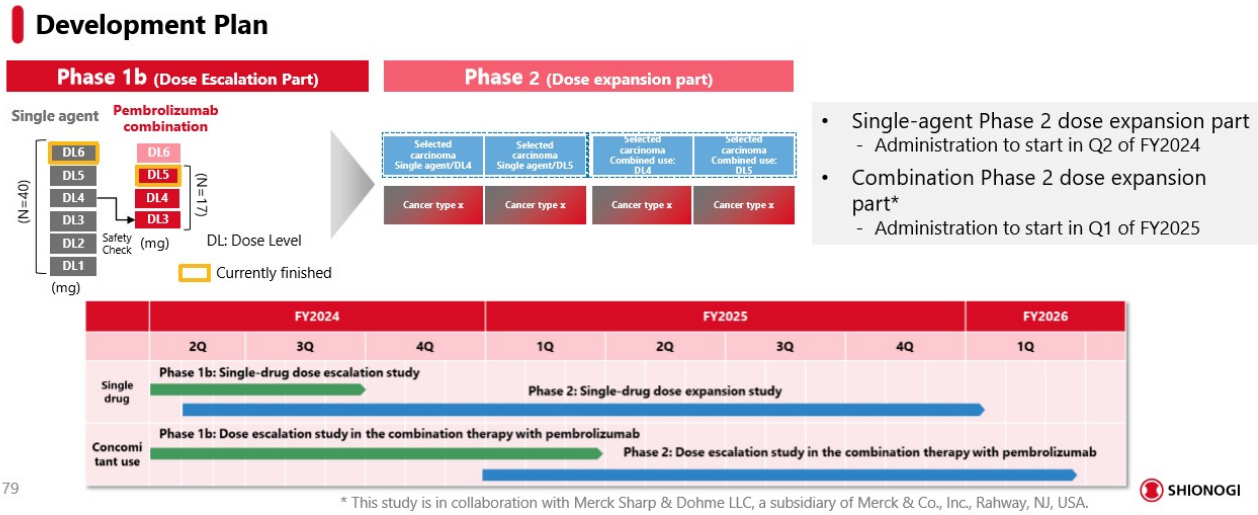
SHIONOGI

Now, let me tell you a little about cancer. We have patented the CCR8 antibody against Tregs worldwide. This is a molecule that we discovered together with Osaka University, and its role is to stop the brake signal of activated lymphocytes by suppressing this molecule. The antibody actually accelerates the attack of activated lymphocytes on cancer cells.

We have been collecting various data on what we can expect from the use of this product, and I would like to talk a little about the progress of the clinical trials.

S-531011: Progress of Phase 1b/2 Study in Japan and the US

At present, there are no safety concerns regarding either the single agent or the combination



We are now implementing the development plan, Phase Ib, worldwide.

Good safety has been confirmed with a single agent. This has been administered in actual cancer patients. Dose escalation but be patient. We are also in the process of confirming the tolerability of Merck's pembrolizumab in combination with the drug.

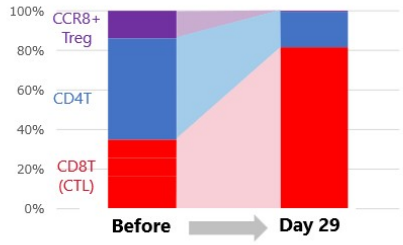
In such a situation, it is the Phase II part, the dose expansion part. This is a design for evaluation based on a slightly expanded number of cases of eight cancer types and conditions selected in the protocol. Among them, we have already progressed to the dose expansion part. I am sorry, but I would like to withhold which conditions for which cancer types.

S-531011: Pharmacodynamic Analysis (Single-Agent Dose Escalation Part)

It has been confirmed that the administration of CCR8 leads to a reduction in suppressive Tregs and an increase in CD8 T cells within the tumor

Decreased CCR8+ Tregs and increased CD8 T cells in tumor tissue (percentage of T cells)

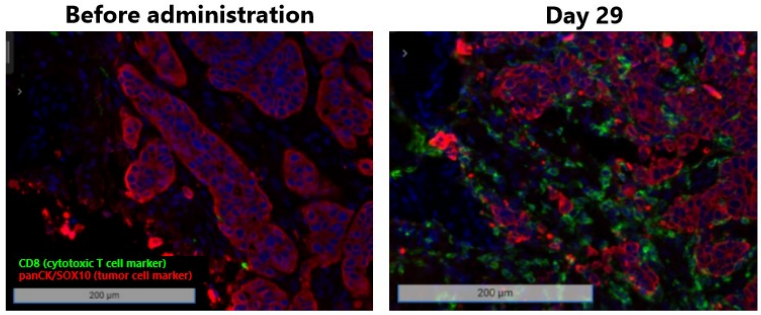
(Flow cytometry analysis)



CCR8+Treg: Decreased from 14% to 0%
CD8 T cells: increased from 34% to 81%

CD8 T cells in tumor tissues are observed
(multiplex immunohistochemical staining)

Before administration **Day 29**



The administration of S-531011 results in an increase in CD8 T cells

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SHIONOGI

We have some interesting data that shows some promise.

In the middle photo, this is the patient before administration, and the red glowing striped area is the tumor cells. It is increasing in nodules and in fullness, but if you look to the right, the green color is increasing. These dots are activated lymphocytes. CTL.

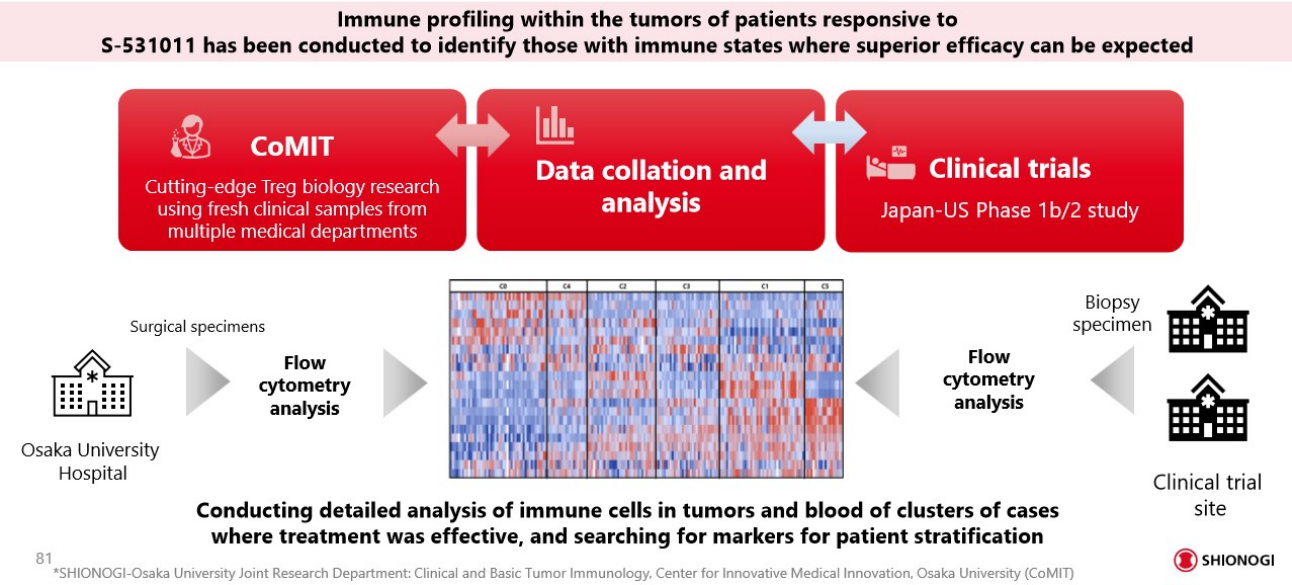
You can see that the red tumor cells seem to have collapsed slightly. So, the activated lymphocytes are attacking the tumor, and the tumor is getting a little smaller. This is a fluorescence microscopic image of such a tissue photograph.

As to why this is happening, this flow site, looking at the same sample before and after administration, shows that the red ones are lymphocytes. So, the number of attacking lymphocytes is increasing exactly, even when counted with a flow cytometer.

The purple color at the top is Treg. We have been able to confirm a proof-of-mechanism in which lowering Treg with our CCR8 antibody, which is regulatory, increases activated lymphocytes to attack the tumor.

We are including this condition as an accelerator to move forward with certain cancer types, and I am sure we will have many discussions about this as more data becomes available.

S-531011: Collaboration with Osaka University CoMIT* Joint Research



In these circumstances, a drug that works for all patients would be optimal. However, we would like to find patients with cancer types, conditions, and characteristics that will allow us to use the product well. This is why we are also doing this in cancer from the perspective of biomarkers and test-to-treat.

We are collating various data to identify cancer types and patients who will benefit from the drug and are working with companion diagnostics to develop this drug for delivery.

S-531011: Strategies That Can Be Implemented Given Safety Profile

Simple and low-burden treatment with potential application to childhood cancer

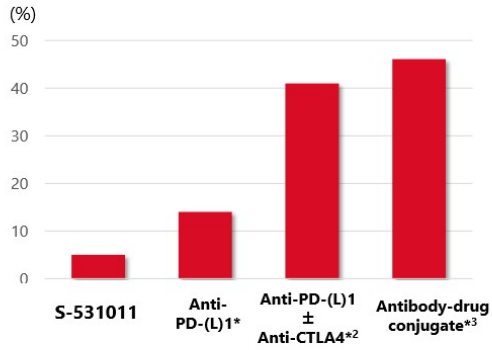
Anticancer drug options free from side effects

- **Safe to use**
  - Minimize the impact on your daily life (grade 3 or higher)
- **Anyone can use it**
  - Even if you are physically weak

High level of safety allows for various indications and approaches

- Combination therapy with various anticancer drugs
- Pediatric cancer drugs
- Subcutaneous formulation

Adverse events causally related to the study drug



* Wang et al., 2019, JAMA, 5(7):1008, *2 Gu, et al., 2019, BMC Cancer, 19:559 *3 Zhu et al., 2023, Cancer, 129 (2):283

SHIONOGI

Once again, this is a characteristic of this drug.

Safety is quite high. Unlike the old chemotherapeutic agents, and unlike chemotherapeutic agents attached to antibodies, our drug lowers tumor-specific Tregs. We are proud of the fact that this is a new antibody that has the potential to be used safely in various types of cancer patients, and we will continue to develop it so that we can deliver it as soon as possible.

Introduction of S-606001【MZE001】, a New Therapeutic Drug Candidate for Pompe Disease

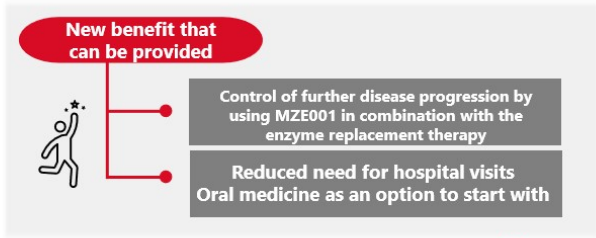
Aiming for a paradigm shift in Pompe disease treatment with a new oral treatment with a novel mechanism of action

What is Pompe disease?

- A genetic disorder characterized by dysfunction of acid α-glucosidase
  - It causes an accumulation of glycogen in cells due to a deficiency in glycolysis
  - Symptoms include motor dysfunctions, respiratory disorders, and cardiac dysfunctions
- Enzyme replacement therapy (intravenous drip) is the only existing therapy
  - Disease progression occurs in many patients even under ERT (transition to artificial respiration, wheelchair)

Characteristics of MZE001

- Introduced from Maze Therapeutics in May 2024
- Novel oral GYS1* inhibitor
  - It inhibits the synthesis of glycogen, which is the cause of accumulation in cells
- The only small molecular drug in the clinical development stage



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* Glycogen synthase1 *2 Can genes influencing muscle function affect the therapeutic response to enzyme replacement therapy (ERT) in late-onset Type II Glycogenosis? *3 Questionnaire survey on home enzyme replace therapy for lysosomal storage disease patients (N = 23, 2020)

SHIONOGI

Now, I would like to change the subject slightly and talk about the remaining diseases.

In terms of rare diseases, we focus on Pompe disease, Fragile X, and various other diseases.

As John mentioned earlier, Pompe disease is an inherited disease that causes glycogen buildup in the muscles. If it accumulates, we can use enzymes to get the glycogen out. However, patients would need to receive an IV, once every two weeks, for a long period of time.

Even if such intravenous infusions are given, autoantibodies to the enzymes may develop, and from the standpoint of safety, such practice is not sustainable. The disease progresses slowly and progressively no matter what. It is a genetic disease with an extremely severe prognosis after contraction. This S-606001, Pompe disease, introduced by Maze, is a small molecule.

If this glycogen buildup is bad, why not inhibit the buildup? The mechanism of action itself is very clear, so we have teamed up to deliver a new therapeutic drug that can be used affordably, such as by reducing the frequency of intravenous infusions as much as possible.

S-606001
Indication: Pompe disease

Market:

- Prevalence: About 50,000 people (Globally, estimate)
- Market size: US$160 million

Unmet Needs:

- **Oral medicine that can reduce burden on the body due to injections and reduce burden caused by outpatient visits** (ERT requires intravenous injection once per 2 weeks.)
- **Disease progression can be stopped.**

Product Property:

- Easy-to-use oral drug
- Since it has a mechanism of action different from ERT, enhanced effects can be expected when used in combination.

Current Status :

- Q2 FY2024: Additional domestic Phase 1 study (BA/FE study for new formulation)
- Within FY2024: Phase 2 study will be started.

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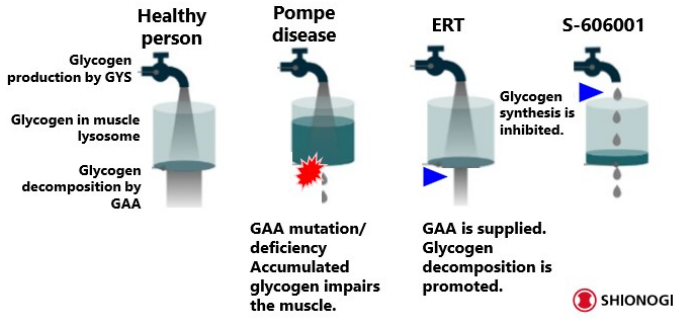
Mechanism of Action:

- Pompe disease is a condition that glycogen abnormally accumulates in muscle lysosome due to mutation (decreased activity) of glycogenolytic enzyme (GAA) in muscle lysosome and muscular tissues are destroyed.
- S-606001 reduces accumulation of glycogen in muscle lysosome by inhibiting muscle-specific glycogen synthase (GYS1), thus suppressing destruction of muscles.

Treatment concept using this drug



The picture on the right is the schematic of the mechanism of action that I have just discussed orally.

The water supply is like glycogen, and the part that goes out underneath where the glycogen accumulates is the enzyme. In patients with Pompe disease who do not have that enzyme, it is not released downward, so more and more glycogen accumulates.

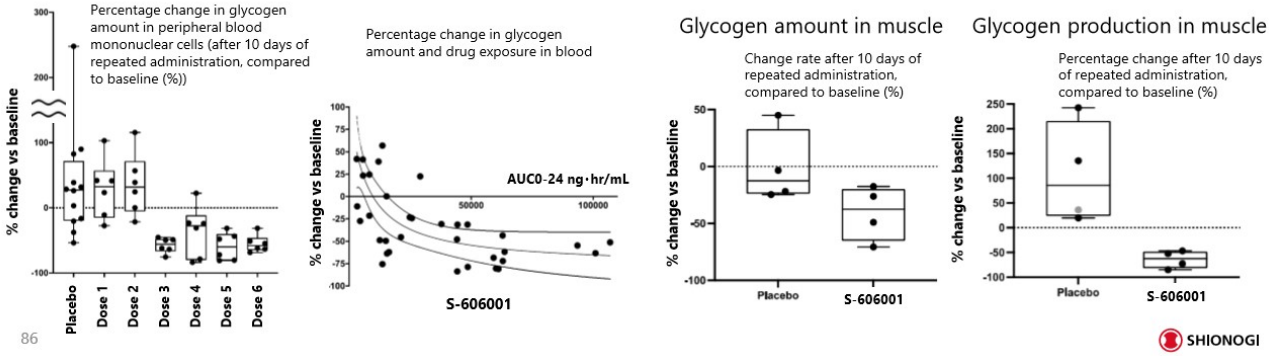
It destroys muscle cells. If that is the case, then this S-606001, let's shut off the upper water supply. If it doesn't flow, then there's no need to add on top. Therefore, rather than a symptomatic treatment, we are implementing a curative treatment, or rather, a treatment that will definitely bring gospel by stopping the root cause of the disease with a low-molecular weight. Phase I data is already available.

S-606001 : Clinical Data

Confirmation of good safety and Proof of Mechanism

Healthy human Ph1 trial in the US

- Good safety and tolerance
- Peripheral blood monocyte glycogen levels suppressed in an exposure-dependent manner
- Significant suppression of glycogen amount and glycogen production in muscle



SHIONOGI

Our company, including the fact that we have very promising data, so we have indicated our willingness to do this. The safety of the product has already been confirmed in Phase I. The left picture shows the amount of glycogen in PBMC. Those who took the medicine were confirmed to have reduced glycogen.

In addition, muscle biopsy results showed that glycogen levels in the muscles of those who took the medication were also lower.

And right, We are measuring the amount of glycogen synthesis with the labeled substance, and this is also going down. So, we have clearly identified a proof-of-mechanism.

Of course, since they are healthy patients, they may have different potential than sick patients, but I am sure that this mechanism of action will lower glycogen in the muscles. Therefore, it is strongly expected that this drug will be effective when used in patients with Pompe disease.

We already have such a formulation, so we have created a new formulation, and we are now in the process of starting an additional Phase I. And global Phase II clinical trial will be started as soon as possible.

Zatolmilast [BPN14770]
Indication: Fragile X syndrome (FXS)

Fragile X Syndrome (FXS) :

- rare disease caused by the extension of a 3-base (CGG) sequence of the X chromosome FMR1 gene
- Main symptoms : Developmental delays and intellectual disabilities, behavioral abnormalities (autism, ADHD), and physical abnormalities

Market:

- Prevalence: About 1 in 10,000 people
- Market size: 20 billion JPY or more (on male at 18 years old or over in the US)

Unmet needs:

- No medicines have been approved for fragile X syndrome.
- High needs exist for relief from anxiety and improvement of cognitive functions, and medicines to improve communications between patients and caregivers (family) are needed.

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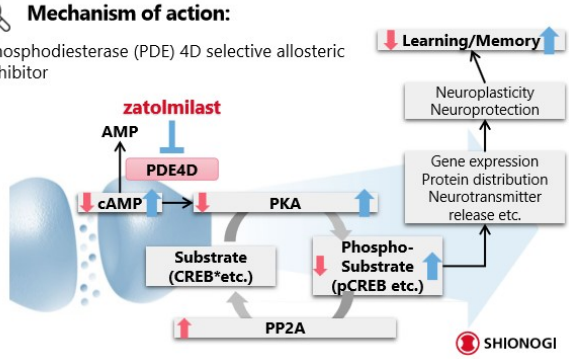
Designated as an Orphan/Fast track by FDA and EMA:

FDA
- Orphan Designation (April 2018)
- Designated for Rare Pediatric Diseases (September 2023)
- Fast Track Designation (March 2024)

EMA
- Orphan Designation (March 2024)

Mechanism of action:

Phosphodiesterase (PDE) 4D selective allosteric inhibitor



Now, Zatolmilast. This is an item that we are working on together with Tetra, which we acquired. Fragile X, which is also a rare disease in children, is a highly anticipated drug with orphan, rare disease, and fast track designations from both the FDA and the EMA.

The mechanism of action itself is a specific and selective inhibitor of phosphodiesterase, PDE4D. Simply put, it is a drug that activates cognitive functions through nerve signals. By stopping the degradation of cyclic AMP, the drug's mechanism of action is to turn the signal around and activate the CREB pathway, causing the learned signal to stick tightly to the brain.

Zatolmilast: Progress in development for fragile X syndrome

Currently conducting clinical trials in the US with the cooperation of FXS support groups*, aiming to submit for approval by 3Q FY2025

US PoC Testing*2

- Conducting a Phase 2 study with support from FRAXA*
- Significant improvement in language function and daily life function

US late-stage clinical trials

- Ph2/3 study for young males (ages 9-17)
- Phase 2/3 study for adult males (18-45 years old)
- Open-label extension study

tetra THERAPEUTICS SHIONOGI Group Company × FRAXA Research Foundation

SHIONOGI

NATIONAL FRAGILE X FOUNDATION

Global development including Europe, and expansion of indications to pediatric males (under 9 years old) and females under consideration

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* FRAXA: FRAXA Research Foundation, NFXF: National Fragile X Foundation *2 Berry-Kravis EM. et al., Nat Med. 2021 May;27 (5) : 862-870

SHIONOGI

In fact, we have received very enthusiastic support from the Fragile X patient group.

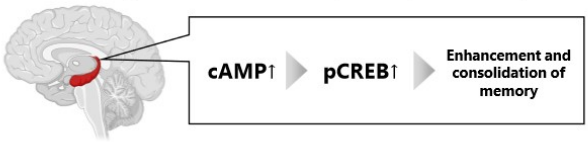
So, the background is that we have confirmed proof-of-concept, and also there is no drug, no cure. Therefore, we would like to get this drug on the market as soon as possible, and with your full cooperation, we are now conducting a pivotal trial in the US. in the form of Phase II/III. As soon as these results are completed, we will apply for approval.

Drug Discovery Aimed at Improving Symptoms of Dementia

Drug discovery concept

A compound that selectively inhibits PDE4D* within neuronal cells

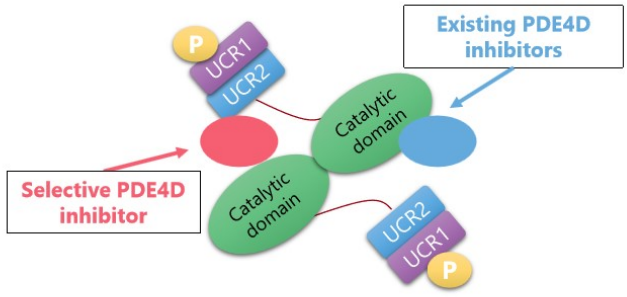
- Enhancing and maintaining the expression of genes related to neural function through the augmentation of the cAMP-CREB pathway*2
- Boosting neural and synaptic function, thereby improving cognitive functions including learning and memory



Creating an effective and user-friendly PDE4D inhibitor by selectively and appropriately regulating activity through the allosteric effect of PDE4D inhibition at low doses over a long period, tailored to the phenotype of symptom improvement in a wide range of age-related cognitive disorders, including Alzheimer's disease

Mechanism

- Unlike existing PDE4 inhibitors, the UCR2*3 site is involved in binding
- The involvement of the UCR2 site in binding allows for the selective inhibition of PDE4D
- As a result, it is expected to avoid side effects such as vomiting and improve cognitive functions, including learning and memory



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* PDE4D: Phosphodiesterase 4D *3 UCR2: Upstream Conserved Region 2
*2 cAMP: cyclic adenosine 3,5-monophosphate, CREB: cAMP response element binding protein

SHIONOGI

Now, in this situation, the mechanism of action is the same, but it is a compound for dementia, and I am wondering if we can increase its activity and selectivity with the same mechanism of action. We have many chemists under the supervision of Dr. Isou, so we thought that our excellent chemists could create a better drug, and this is what we created.

In order to make the drug work in patients with dementia, we are motivated to make it more active and more effective, thereby improving symptoms and memory learning.

This is a drug that achieves selective inhibition of PDE4D, thereby reducing the potential risk of side effects and increasing selectivity.

S-898270 : Preclinical study

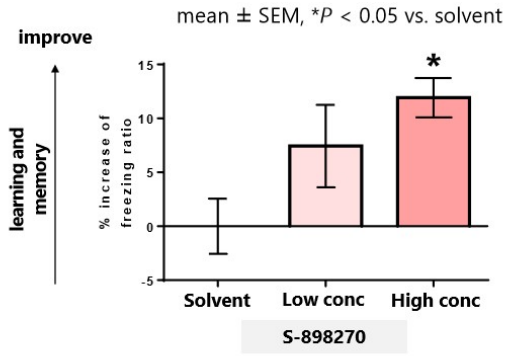
Aiming for Phase 1 entry by the first half of 2025
for a wide range of patients suffering from cognitive decline, including memory loss

In vivo efficacy (improving learning and memory)

Train mice to associate a specific stimulus with a testing environment

After a set period, present the testing environment without the stimulus

Verify if the mice remember the association between the testing environment and the stimulus



Administration of S-898270 improves learning and memory

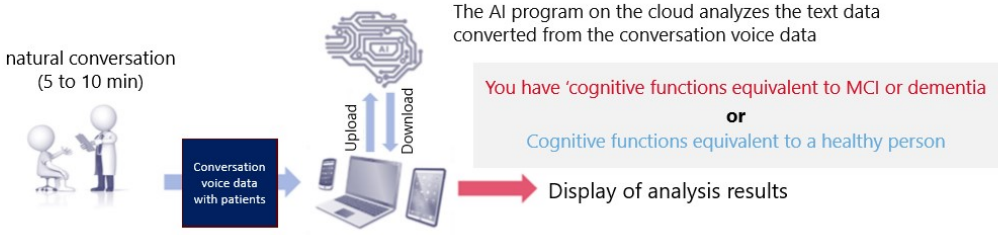
Exploratory testing not yet conducted (QC already implemented)

SHIONOGI

Although this is animal data, we have actually seen activation of memory learning and brain signals in animals, and the memory learning effect has actually been confirmed in an experimental mouse model. Under these circumstances, we are now proceeding with the final GLP study, etc., with the aim of conducting the Phase I study in the first half of FY2025.

SDS-881 (SaMD diagnostic support)
Conversational Dementia Diagnosis Support AI Program (Collaboration with FRONTEO)

Aiming to start by the third quarter of fiscal year 2024, preparations are underway for domestic validation trials



- **Diagnosis based on natural conversation between patient and medical staff of about 5 to 10 minutes**
- Differences from existing neuropsychological tests (MMSE, etc.)
  - No specialist knowledge or experience required
  - Reduces the time and psychological burden on patients and examiners
  - No accustomization effect, so repeated (regular) tests are possible

Promoting referrals and collaboration from non-specialists to specialists to achieve early treatment

91 MMSE (Mini-Mental State Examination): A test to evaluate cognitive function including orientation, memory, calculation, language, and graphic ability, with a maximum score of 30 [11 questions in total]
Hasegawa-style assessment: Cognitive functions such as orientation, memory, and calculation are evaluated on a scale of 30 [9 questions in total]
Announcement of the Strategic Business Partnership Agreement for Diagnosis Support AI Program in Dementia and Depression between FRONTEO and Shionogi | SHIONOGI

SHIONOGI

In this context, I wanted to think a little about test-to-treat in dementia as well. I am sure you have experienced this when you have actually talked with dementia patients, that people can sense that they may have dementia if they communicate with them.

If we can use machine learning to select people suspected of having dementia based on data from conversations, we can have such people go to the hospital, receive a definitive diagnosis, and take the medication. We are also working with FRONTEO to develop such tools that will allow for early treatment and access to medical care as soon as possible, without the need for diagnostic procedures that can only be performed by specialists.

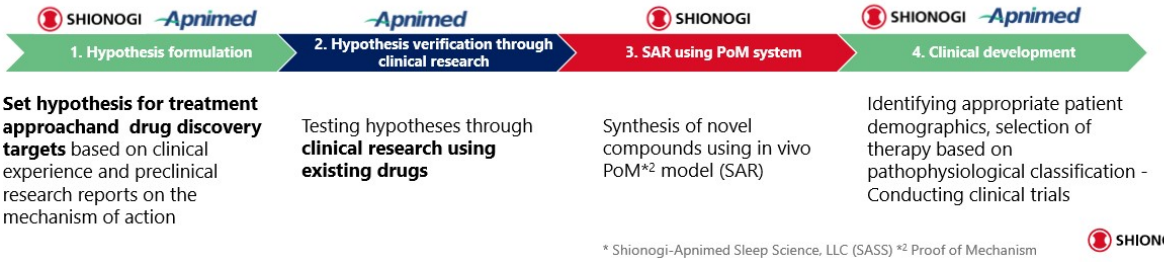
Expertise in Sleep DisordersEstablished a joint venture * with Apnimed, a company with outstanding expertise in sleep disorders

Multiple programs are underway to address sleep disorders by addressing multiple mechanisms

Apnimed's Strengths

- High scientific expertise and development track record in the treatment of sleep apnea and other sleep disorders, as well as a global network for clinical research
- Multiple pipelines assets for sleep apnea syndrome

Drug discovery based on hypotheses and drug target setting based on clinical evidence



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* Shionogi-Apnimed Sleep Science, LLC (SASS) *2 Proof of Mechanism

SHIONOGI

Next, Sleep disorders.

We are also working with Apnimed, a company that is an expert in sleep disorders. When we came up with a concept that might work if it worked here and here, we conducted a clinical study. If it is effective in a clinical study, we modified our existing items. Two companies collaborated while providing products, and we are now in the process of establishing such a system.

As we worked on conceptual level and produced numerous drugs, we are already preparing for clinical trials.

Market and Unmet Needs of Sleep Apnea Syndrome

Market:

- Number of affected people: Approximately 900 M people

  Among the above, the target group is patients with increasingly unstable breathing

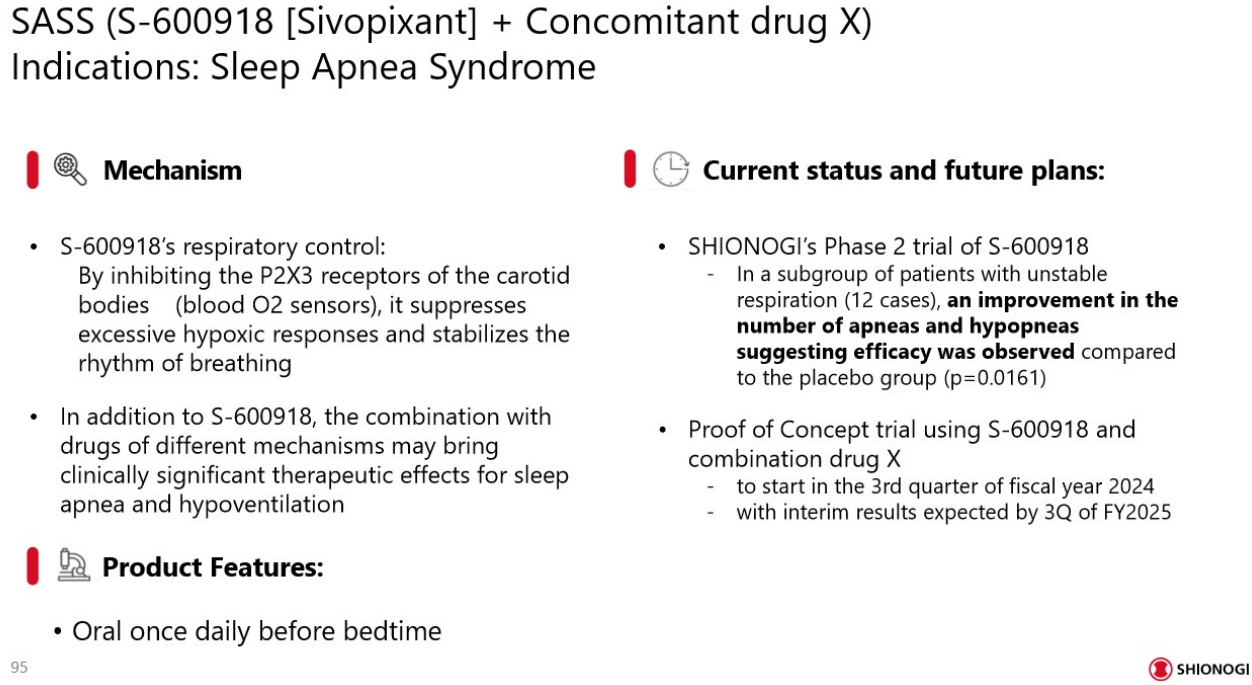
Unmet needs:

- Highly effective and safe therapeutic drugs as alternatives to devices and surgical treatments
- Treatment options for patients with nasal continuous positive airway pressure (CPAP) resistance or intolerance

SHIONOGI

It is difficult to use CPAP to open the airway for obese patients with obstructed airways, as you well know, and it is difficult to manage such obstructed airways with medication. If the patient is obese, then there are many ways to control weight, but there are also many ways to control apnea from the central nervous system's perspective. There are many things that can cause heart disease.

The main concept is to control apnea syndrome by using oral medication for those who cannot use CPAP, even in the mildest of cases. Such is the concept of the drug. In particular, we are working on the concept of somehow getting the drug to act on this upper right blue area, the unstable breathing area.



We are actually working on this S-600918, Sivopixant, which you may remember was done up to Chronic Cough, Phase IIb. In fact, we have been able to confirm that Chronic Cough lowers cough. There is no doubt as to the mechanism of action.

In parallel, we were conducting a Phase II study on sleep apnea as a Phase II study. Although the primary endpoint has not been met in total, we have discussed this mechanism of action with members of Apnimed, who specialize in this field, and we have found that the P2X3 receptor is present in the O2 center of the blood.

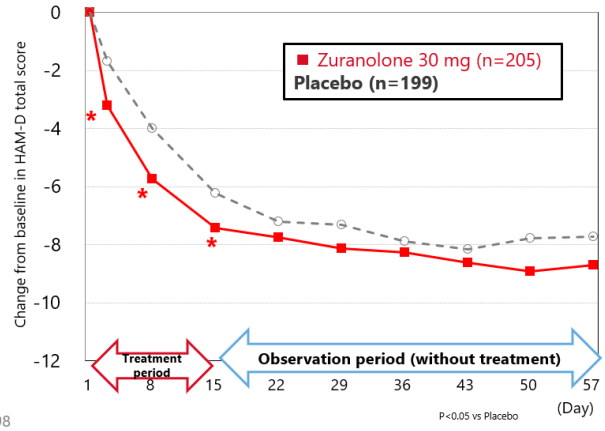
The mechanism of action, the one that we believe this drug will be effective for is high-loop gain, which is a person who has a large breathing rhythm. If you take a big breath while sleeping, you can sort of understand the feeling of one satisfied breath and then apnea for a while. If it was a small breath, keep going and going. So, I thought the S-600918 could be used to signal that side of the market to suppress that big wave. Such is the concept.

Let me call this, drug X. By combining the two, by stopping the different parts, by lowering this large loop gain, we could contribute sleep apnea treatment. With these expectations in mind, we are preparing to start Phase II of this, mainly in the US. We are in a position to confirm first-in-human early this fall.

Zuranolone: Phase 3 Study Results in Japan

Demonstrated rapid improvements in depression symptoms, application for approval scheduled for 1Q FY2024

Phase 3 validation study in Japan: Change from baseline in HAM-D total score



Efficacy

- **Domestic Phase 3 verification study: Primary endpoint achieved**
  - Significant improvement in change from baseline in HAM-D* total score versus placebo at Day 3(initial observation), Day 8 and Day15(end of treatment) at 20 mg and 30 mg
  - During the observation period from Day 15 to Day 57, the treatment effect was confirmed to be sustained
- **Phase 3 Add-on Study**
  - The added effect of zuranolone on other antidepressants could not be confirmed (possibly due to the small number of subjects)

Safety

- Consistent tolerability profile across studies; adverse events were generally mild to moderate in severity
- No subjects reported dependence on the drug

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* HAM-D: Hamilton Depression Rating Scale

SHIONOGI

These are the Phase III results for the primary endpoint.

The reason why we have not been able to release the results until now is that we have been successful, but we have met our commitments by closing the trial properly without any placebo effect after the final follow-up was properly completed and the results were disclosed.

As you can see, it is still in effect from the leftmost point, and you can see that it has a star. Once you take it, you will feel the effects immediately. That is the point where we see the overall characteristics of the drug being effective exactly during the two-week dosing period, and not rebounding afterwards, but rather sustained.

We also had another Phase III trial, an add-on trial, to take data from when the drug was given as an additional dose to an existing depressant. We have confirmed that this product is safe and that there are no problems, but it is very difficult to test for depression to see if it will improve symptoms further. The result is that with a very limited sample size, it was indeed not possible to show add-ons to the standard of care with the effect of add-ons in the add-ons that were made.

Nevertheless, the safety of the product has been confirmed, and we are now in the process of finalizing the process to apply for approval based on this data.

SDT-001
Indications: Attention Deficit Hyperactivity Disorder (ADHD) in Childhood

Market :

- Approximately 260,000 pediatric ADHD patients diagnosed (domestic)

Unmet needs :

- Convenient treatment options other than medication

(Due to a shortage of human resources in medical institutions, few can provide psychosocial treatments).

Product Features :

- Digital therapeutic application
- Daily training for about 25 minutes using the application

Current status and future plans :

- Approval application in progress (domestic, February 2024)
- Approval obtained, insurance coverage (within 2025)

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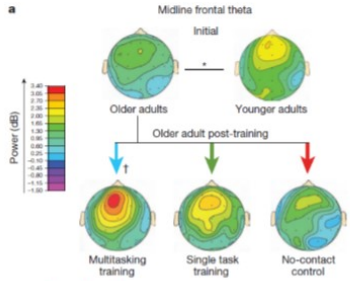
Mechanism :

- By performing dual tasks adjusted for difficulty for each patient, the application activates the prefrontal cortex functions (which are diminished in ADHD patients) and improves symptoms of inattention and hyperactivity/impulsivity

Dual task execution (Steering tapping)

Activation of brain function through difficulty-adjusted dual tasks*



Dual task > Single task > Control
Training increases brainwaves (theta waves)

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

SHIONOGI

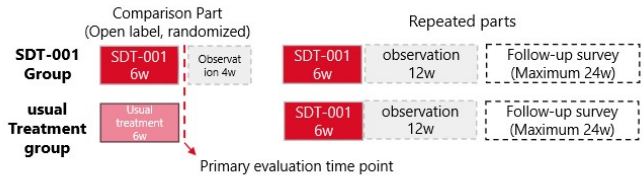
Another ADHD, this is a digital therapeutic application.

The picture in the middle is from the iPad mini. This is the real thing. The images are quite realistic, glittering, and you can control it, it's kind of like a driving game. You can tap to dodge. You can tap the left and right controllers at the same time. The brain cortex is activated by the picture you see on the right. For patients with ADHD symptoms such as inattention and hyperactivity, this is a new digital therapeutic application that activates brain functions and shows therapeutic effects by forcing them to play these games for a certain period of time.

SDT-001: Phase 3 Study in Japan for Pediatric ADHD Patients

Primary and key secondary endpoints achieved

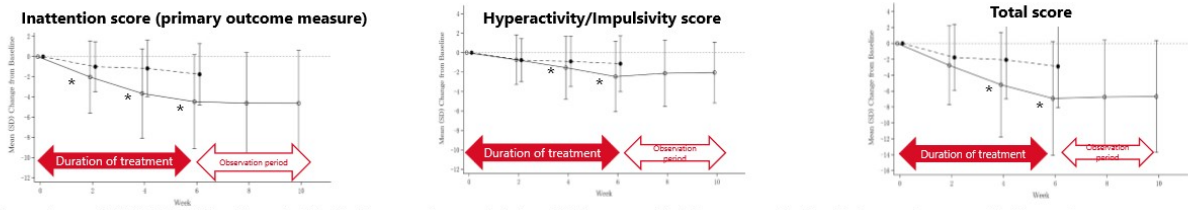
Subject	Children with ADHD (ADHD-RS inattention score of 15 or more*)
Primary endpoints	Change from baseline in ADHD-RS-IV (clinician-rated) inattention score
Secondary endpoints	Efficacy, safety and tolerability of SDT-001 when used repeatedly



Study results (comparison part): Change from baseline in ADHD-RS-IV (physician-assessed) scores

SDT-001 / TAU

TAU = treatment as usual *: p < 0.05 (MMRM analysis)



- Comparison part: ADHD-RS-IV (physician-rated) inattention score, hyperactivity/impulsivity score, and total score were significantly improved compared to the usual care group
- Repeated Part: ADHD-RS-IV scores were reduced even after two cycles of SDT-001 use. Improved ADHD-RS-IV scores were maintained for at least 12 weeks after discontinuation of use

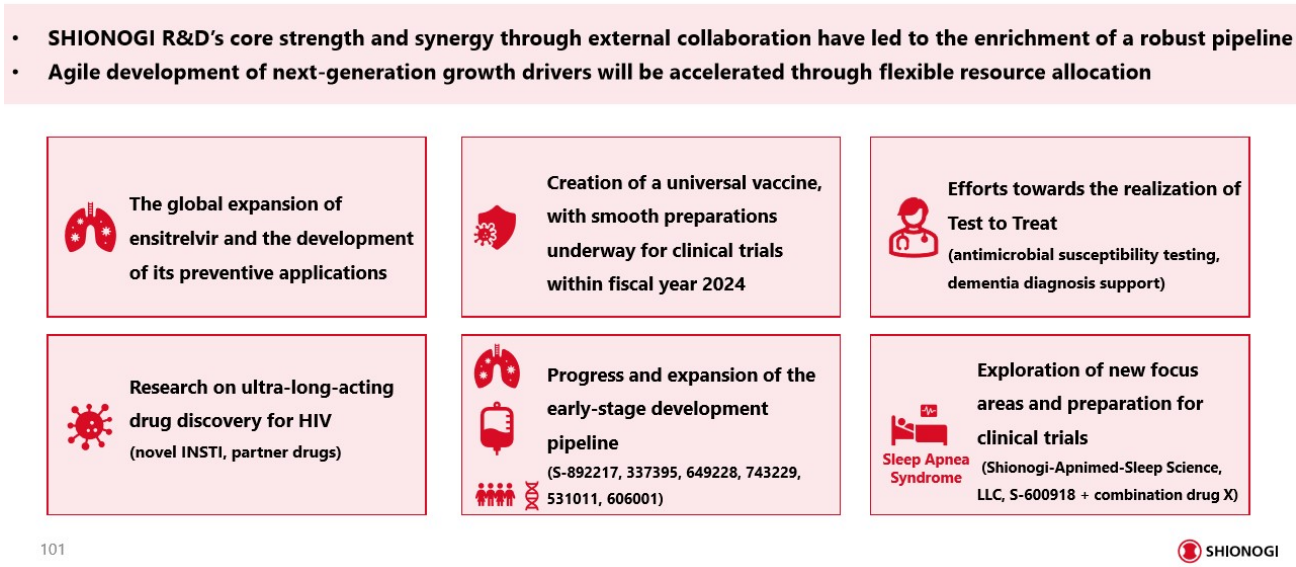
SHIONOGI

This is the result of Phase III.

The primary endpoint, the inattention score, is nicely lower at the bottom left than the standard of care. There is also a significant difference in the hyperactivity score, and the overall total score has also dropped nicely and significantly.

It is not a sure bet that ADHD can be completely cured with these digital tools alone. However, there is a need to delay medication as long as possible before it is taken by patients with ADHD. Some patients do not need medication as their intelligence develops, so we ask them to manage a little period of time with SDT-001.

The Phase III results were very clean, giving us hope that we could delay medication or create patients who would eventually not need medication. So, we have already proceeded with the application for approval. Approval, I believe that in Japan we will soon be able to deliver.



Now, the highlight of the day.

I think it is evident that we have the basic strength for R&D, and that we have the basic strength to be partnered with a wide range of companies. In fact, we built a network with partnering firms who want to work with us. We have many new pipelines with such synergies.

In this situation, however, we are a small Japanese company, so we are trying to deliver these important growth drivers to the world as quickly as possible with resource allocation, and this means developing in an agile manner, including resource allocation, which we learned at COVID. We are currently developing the various pipelines I have described here in a rush to deliver them as quickly as possible.

That is all from me.

Kyokawa: Thank you very much. Now, I would like to ask for a few more minutes for Dr. Teshirogi to provide you with a summary.

Progress of Major Development Products - Infection diseases -

※The bar starts from FPI and ends at CSR, Topline results: It is the timing of acquisition, and the timing of disclosure will be considered separately

	Pipeline	Indication	Current stage	FY2024	FY2025
COVID-19 Family	S-268019	COVID-19 (Vaccine)	Consent for Approval*		
	Ensitrelvir	COVID-19	Submission・Phase 3 Phase 3 (Pediatric)	Phase 3 topline results (FY24 4Q)	
	Ensitrelvir	COVID-19 (prevention)	Phase 3 † Data analysis in progress	Phase 3 topline results (FY24 3Q)	
	S-268023	COVID-19 (XBB1.5,Vaccine)	Phase 3		
	S-892216	COVID-19	Phase 1	Phase 2 start (FY24 2Q) topline results (FY24 4Q)	
	S-567123	COVID-19 (Universal Vaccine)	Preclinical	Phase 1/2 start (FY24 4Q) topline results (FY25 2Q)	
Infection diseases	Olorofim	Invasive aspergillosis	Phase 3		
	S-337395	RSV infections	Phase 2		
	S-743229	AMR (Complex urinary tract infection)	Phase 1	Phase1 (combined use) topline (FY24 3Q)	
	S-649228	AMR (Gram-negative bacteria infection)	Preclinical	Phase1 (combined use) start (FY24 2Q) topline results (FY24 3Q)	

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* Consent for approval was given at the Second Committee on Drugs held on May 24, 2024

SHIONOGI

Progress of Major Development Products - QOL Diseases with High Social Impact -

※The bar starts from FPI and ends at CSR, Topline results: It is the timing of acquisition, and the timing of disclosure will be considered separately

Disease area	Pipeline	Indication	Current stage	FY2024	FY2025
QOL Diseases with High Social Impact	SDT-001	ADHD	Submission	Approval (FY24 4Q)	
	Zuranolone	Depression	Preparation for application	Submission (FY24 1Q)	Approval (FY25 1Q)
	Resiniferatoxin	Pain associated with knee osteoarthritis	Phase 3		Submission (FY25 3Q)
	Zatolmilast	Fragile X Syndrome	Phase 2/3	Phase 2/3 topline (FY25 1Q)	Submission (FY25 3Q)
	Redasemtide	Acute ischemic stroke	Phase 2b		
		Dystrophic epidermolysis bullosa	Phase 2		
	S-309309	Obesity	Phase 2	Phase 2 topline (FY24 1Q) Considering future development strategies	
	S-531011	Solid tumor	Phase 1b/2	Phase 2 part start (FY24 2Q)	
	S-600918＋Drug X	Sleep apnea syndrome	Phase 2	Phase 2 start (FY24 3Q)	Phase 2 topline (FY25 3Q)
	S-606001	Pompe	Phase1		Phase 2 start (FY25 1Q)
	S-151128	Chronic pain	Phase 1	Phase 1b topline (FY24 2Q)	

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SHIONOGI

Teshirogi: Once again, thank you very much for your time. Some people may say that they do not need to hear that, but I have tried to cover a fairly broad range of topics.

However, some of the phases are on-going and have not changed that much over the last year, so I have written a list and an appendix at the back of the list.

Olorofim, or S-005151, or S-151128, or Resiniferatoxin. All of this is very interesting to us as a compound, but it is not something that new data will come out with the change of phases.

Clinical trials for Olorofim or S-005151, for example, for cerebral infarction, inevitably take quite a long time. Dr. Uehara didn't cover it this time because there was no change. But I hope you will understand that we were not in that phase, not that we are not doing it or do not expect to do it.

This expression may be strange, but I think we are in the operational phase to grow sales for total R&D. We have talked about a medium-term management plan of JPY550 billion and a final plan of JPY800 billion. I believe that we are moving straight toward that goal at this point.

Nevertheless, it is impossible to achieve such growth with the current R&D personnel and R&D budget. We would like to proceed with research and development, including a certain amount of upfront investment.

We believe that the budget for this fiscal year, JPY120 billion. However, this is our usual pattern, which is to put the compounds in order of priority and stop when they reach JPY120 billion. We will continue to consider how to allocate resources in a way that does not affect operating income, etc., but I think we are close to the limit.

For example, there are not enough people doing biology under the direction of Dr. Isou, nor are there enough medicinal chemists as it is now. So, can we hire new personnel immediately? Unfortunately, the answer is no. The current situation is that there is a global shortage of skilled workers.

This time, I have teamed up with John to create a new research institute in the antimicrobial area based on QPEX in San Diego. We were surprised to receive quite a few applications from people who had wanted to do antibacterial and anti-infective work in the US but had given up because there was no place to do it, and they were willing to open there. In fact, QPEX overall has grown considerably in number since we purchased it.

This has the effect of attracting people who want to work in fields such as biology or chemistry, if there is a field where they are allowed to work. As John mentioned, we would like to increase the number of research personnel and expertise as we increase the number of research and development projects, including those linked to government and other organizations.

Development, in fact, Dr. Uehara, pharmaceutical affairs is more of a Japanese pharmaceutical affairs, US pharmaceutical affairs. We were doing development globally, but we were also doing pharmaceutical affairs rather locally, and this would not be enough to make it in time. In the end, we had an American come in, but we have shifted to a new system that unifies all global pharmaceutical affairs and oversees all development in one place, and of course we need more people and expertise.

As for R&D, we would like to bring the next compound to the next stage and deliver it to patients as soon as possible, while increasing both the number of employees and the quality of new employees, rather than maintaining the current level.

Basically, we are discussing internally how to structure the pipeline for the fund of JPY800 billion minus royalties, including the risks involved, and if we can advance the pipeline at a certain yield rate, we should be able to reach that point. I am sure we will be able to reach that point if we can proceed with a certain level of yield. We would like to move forward toward that goal.

I anticipate an inevitable influx of questions about S-309309 today. From our point of view, we would love to address your various questions on how all of the ongoing pipelines are moving along, including the bariatrics, as it suggests that we made good communication with you all by hosting this R&D Day.

Question & Answer

Kyokawa : Thank you very much. I will now move on to the question & answer session.

Mr. Ueda, please.

Ueda : My name is Ueda from Goldman Sachs. First of all, I would like to ask about S-309309. With the recent development of new GLP-1 and various combination drugs, how important is the additional effect of S-309309, as shown in this presentation?

Since you mentioned about having partnerships, I was wondering if you could tell us about any data that you have obtained that would support S-309309 to be chosen as the drug of choice, given that there are many more candidates for combination drugs.

Keller : Thank you. We would like to move forward with pre-clinical packages, add-ons, and maintenance profiles. GLP-1 had great uptake, so there are many more problems. Complex titrations and gastrointestinal side effects are also observed with oral agents. And it is the kind of problem that has a sudden rebound.

These problems are clear. They are clear to leaders in the field and newcomers. So, I think the strongest pre-clinical data is particularly important, by covering the various pre-clinical models in these two profiles. I believe that discussions with various players will be necessary.

Ueda : Secondly, I would like to ask about HIV. With Gilead and Merck acquiring new data recently, and your acquisition of new ULA candidates, has there been any change in your view of the therapeutic landscape centered on integrase inhibitors? In light of your company's situation, could you comment on how you evaluate your positioning?

Keller : I think we are still in the lead position in the Integrase landscape. But there are many developments. I have not yet seen enough data, even for Gilead.

In other words, we have not seen an integrase profile that we would consider truly remarkable. But we cannot ignore what is happening. I think we need to find out the backbones of the new formulation.

Also, it should be easy for patients to use as much as possible. We must also consider making one injection instead of two injections of those two components in the future, not only smaller injections but also longer ones. I think another component is whether once every six months is sufficient.

So, I do not mean to share rumors, but I have not heard any rumors about which company has the better integrase. We believe we are best-in-class, and I believe we have to be best-in-class.

Teshirogi : In fact, the strength of cabotegravir and dolutegravir lies in their safety and the robust foundational data supporting them.

When we release a new compound, such as S-365598 or the next integrase inhibitor, we will, of course, try to create something wonderful, but because it is an NCE, we are always afraid as an apothecary that we do not know what will happen when we use the compound.

Therefore, it is incorrect for doctors to tell patients that a new integrase inhibitor is safe to use just because it is an integrase inhibitor. The safety specific to the compound cannot be determined solely from animal toxicity tests. It is essential for patients to use the compound gradually and properly, monitoring its safety

step by step. Forgetting this cautious approach would be extremely dangerous for the future of pharmaceutical companies.

I feel very comfortable with cabotegravir. It is administered every four months. Actually, it means that the oral drug is to be taken every month or every two months. The number of patients using it is increasing, and there are a few structural changes with dolutegravir. The fact that we are building up real data on the safety of cabotegravir as a drug is very reassuring for me. As a pharmacy, we should not underestimate its significance.

We do not want to say, nor do we want our competitors to say, "it's a new integrase, so it's totally safe," when new products are introduced by various companies in the future. So, I believe that the superiority of cabotegravir represents very important data for patients.

Ueda : Thank you very much. I would like to follow up on one point regarding safety. In the area of new ULA formulations, you mentioned resistance barriers. I think it is also important to diversify the tolerance profile, but I wonder if you can tell me if it is something that can contribute to this as well.

Isou : Thank you for your question. I, Isou, Senior Vice President of the Drug Discovery Research Division, will answer to your question.

In the slide that is just in front of you now, Research Program B for different mechanisms of action. This is a different mechanism of action from integrase, and naturally, in that sense, the tolerance barrier is also different from integrase.

In addition, it is very powerful in its new mechanism. I believe it has a wide range of uses, can be used in low doses, and has long-acting effects. I believe it could be used in various ways, not only as a six-month RAP but also as a four-month RAP with a reduced dosage to one shot. Doing so could address various unmet medical needs.

We have just started production but have found some exceptionally good compounds, so we are raising our expectations in various ways.

Ueda : Thank you very much. That is all from me.

Kyokawa : Mr. Hashiguchi.

Hashiguchi : My name is Hashiguchi from Daiwa Securities. Thank you very much. I have two questions.

The first question is about acute respiratory infections. From the slides on pages eight and nine, I understand that it is very important to develop R&D for testing and diagnostics quickly and effectively to forecast sales of drugs for the treatment of influenza, COVID-19, and RSV.

On the other hand, from what you have described on page 22, especially in red on this page, I have the impression that your company does not have much in the way of deliverables yet. If that is the case, could you tell us a little more about the time frame and how much you think you can or would like to achieve in the future?

Teshirogi : Thank you very much. We have seeds, rather, some products that are going to be in clinical trials. What we are concerned about most is when we think about products that are inexpensive and easy to use, it is small and convenient but expensive, even one piece of measurement equipment or machine, for example. I think that conceptually, we are getting better and better.

Let’s say that when we try to make an OTC product that you can buy at a pharmacy in the US for USD10 or USD5, for example, we should make some improvements on the machine that diagnoses. As Dr. Uehara mentioned, a nasal swab is not possible in the US and Europe for us, so other medium.

Perhaps saliva, swabbing the mucous membranes, or imaging, as NODOCA is doing, could be included in the list. At any rate, the question is how far we can go to make it non-invasive, as simple, accurate, and inexpensive as possible.

We can't do it alone, so we are tying up with a number of venture companies that are doing this on a global scale. We have a venture fund that is very good at this type of investment, so we are working together with them to introduce venture companies to us.

For our part, if all goes well, we hope to be able to deliver ensitrelvir globally in the next fiscal year or so. I'm not sure if we'll be ready for that, but we're getting to the point where the seeds are there. There's nothing completely wild about it, and with a timeframe of about two or three years, we'll manage to get there in time.

Hashiguchi : Thank you very much. Another point is what is the goal of HIV research.

I think you mentioned two key points at the last R&D briefing. One was the ultra-long-acting, and the other was the functional cure. I think you spoke with a lot of emphasis on the former this time, but is this some kind of change in policy, goals, or what you are trying to achieve? Could you please reiterate your thoughts on this?

Keller : For the ultra-long-acting, I think this is a clear direction in the market. And it is clear that this is also the direction for gaining market share among patients. We gather a lot of information through market research. There is a certain level of convenience with long-acting formulations, and beyond that level, no one really wants oral pills. From the patient’s perspective, there are voices expressing that they don’t want to visit the hospital more than 2-3 times a year. Strengthening our position in this area is of utmost importance.

A cure is a wonderful thing. As an HIV company, we are very interested in this scientifically and emotionally, but what it means to the patient is a different question. Given the current state of the cure, we need a kick drag, kill drag, and maintenance procedure.

Kick drugs can be a bit obnoxious, with side effects like intense fatigue. As for kill drugs, they might be similar to existing medications, but when it comes to maintenance drugs, no one really knows what will happen.

Ultra-long-acting allows patients to visit the doctor only three times a year, and they can effectively manage HIV with this schedule. On the other hand, for a cure, patients need to visit every two weeks, potentially experiencing intense fatigue each time. Over a continuous two-year period, there may be a 30% chance of success.

In any case, patients have to take a test once every six months. According to the KOL doctors, PrEP must be administered even if cured. So, I suggest that it would be better to have ULA two or three times a year.

Teshirogi : In short, nothing has changed, however we think the timeline will be delayed. With everyone, including the competition, looking at the long-acting and trying to do better, it is realistic within our limited resources to go that way if we are going to invest resources at this point. After the board meeting, both ViiV and we were saying, "at the end of the day, the cure is on the way." I always try to remember what we need to do in response to that.

As he said, kick drugs are quite, I mean, at the moment, as you all know, you have to make all the viruses that are lurking in your body come out to be cured. So, like an earthquake, you have to shake them up to see how you can make the virus come out.

We can kill the viruses that come out, but it is difficult to kill the ones lurking inside the body. Additionally, we cannot determine whether all the viruses inside have been flushed out. So, we have to shake them up quite a bit, figuring out how to make them all come out. It is quite hard on the body, but it is absolutely necessary. It is such a phase.

Hashiguchi : Thank you very much. That is all.

Kyokawa : Thank you very much. Mr. Wakao, please.

Wakao : Thank you very much. JP Morgan, Wakao. I would like to ask you about obesity, but before I do, I would like to ask about cancer.

S-531011, I think it has been quite a while in Phase Ib. You have shown us on the 80th slide in terms of the efficacy this time, but has the anti-tumor effect been confirmed in humans?

I do not feel it is behind schedule, but I think Phase Ib has been underway for a long time. I would like to know what is taking so long and what the next data point is. Could you please tell us about it?

Uehara : Thank you for your question. The tumor has gotten tiny. Please rest assured. Not that it's just a picture, but this patient's tumor has gotten tiny.

We will present the overall aggregate figures and other scientific information at another time.

In order to ensure the drug's safe use, we are still going through a process of dose escalation and confirmation. If the safety is confirmed, we will proceed to the next step. We are confirming this with actual cancer patients, and since it is an antibody, the cycle is long.

We cannot just inject it and see if it’s safe for a couple of days before moving on to the next step. We have to carefully examine the entire cycle and ensure it is safe. If the safety is further confirmed, then the process is to start with the lower dose in combination with pembrolizumab this time and again confirm the safety. As per protocol, this is a time-consuming study.

In the next decision point, within this Phase 1 process, there are patients with various cancer types and conditions whose tumors have become smaller. Therefore, in such cases, we are currently conducting an expansion phase to explore what can be expected. It is anticipated that this expansion phase will occur around the timeline of FY2025. Within this context, we will be able to discuss results for a certain number of cases.

Wakao : Thank you very much. Regarding obesity, I would like to know about S-309309. I think there were three doses in Phase 2 study, but I would like to know if the dose-dependent effect has been confirmed, and from the way it is written, should I understand that it is below 5% in all groups? I would like to know. Also, what about the placebo?

Furthermore, I am sorry, but I think it is important. You originally targeted 8% to 10%, and I thought you were confident in your target. How do you analyze the reasons why you did not reach 8% to 10% this time? Since you mentioned 8% to 10% based on the non-clinical results, there may be a problem with the extrapolation or the simulation, which is not a good way to put it, but there may be other problems. Please let us know about that as well.

Uehara : First of all, in terms of dose dependence, yes, there is. It's higher doses than the lowest dose, but I cannot say if it has a clean dose dependency.

I am writing about the results in the form of a preliminary report, but it is really a top-line report. We had finished following up with all of them, and from there, we were able to see a month of further follow-up. So,

it was really only about the end of last month that we locked the database and got the results. I received the blood level data this morning.

There are a few people who did not take but in the real world it is taken by many people, so I think the test conditions were good enough for evaluation. However, to be honest, I have not yet been able to dig deep enough to be certain. We are still in the process of thoroughly confirming the best dosage conditions, considering individual responses to exposure, other factors at the individual level, and drug compliance.

Nevertheless, overall, the trend shows that the results are a bit better in the middle dose and above than in the low doses.

Now, you mentioned about the placebo weight loss. The same is true for other drugs, but as I mentioned before regarding the protocol, patients are on a restricted diet. The patients are given dietary guidance only, so they do not always eat a certain food because we are in actual clinical practice.

So, I am sure that some patients do not adhere to it, while others follow the medication instructions properly. We are able to evaluate such a heterogeneous group, and overall, there are some people who show a tremendous increase on placebo, while on average, the placebo group drops a little bit. This is not solely due to the placebo effect; rather, dietary guidance is included, which is why it goes down. The method of evaluating anti-obesity drugs is how much it can be lowered from there.

You are right about less than 5% in all doses, but I would say that the estimates were not good enough. The difference between actual clinical conditions and animal conditions lies in the drug's control. In animals, the drug works in an environment where they are always in a high-fat state, eating and growing, whereas in humans, weight is further lowered under restricted conditions.

We had a goal of aiming for 8%, considering the mechanism of action, but we were also aware of the possibility that we might not reach that target. Therefore, we also considered combinations and switching in non-clinical studies.

Wakao : I understand that it was difficult to estimate the results for humans because they were obtained in an animal environment. If that is the case, I wonder if the animal data shown on pages 74 and 75 of this report should be discounted. How should we think about using and maintaining this data in the future?

Uehara : You are correct. This model is capable of producing S-309309 potential under these same conditions. There are a few different non-clinical obesity models, which are not many. We would like to adjust the experimental conditions to see how effective it is if we start with a low dose of GLP-1 and add S-309309 in an environment as similar to that of humans. Based on such experimental conditions, we now want to consider future strategies.

Wakao : I understand. This chart is the model before adjusting.

Uehara : Yes.

Wakao : Thank you, I understand very well. That is all.

Kyokawa : Mr. Mamegano.

Mamegano : My name is Mamegano, and I am from BofA Securities. Thank you for taking my questions. I know I seem to be persistent, but please tell me about the obesity drug.

This time, the weight loss was less than 5%. Although it is similar to the previous question, I would like to know what you think the reason was. Is it a limitation of the mechanism of action, or is it a problem with this

compound? Based on the data alone, you may not be able to comment in this area yet, but I am a little concerned about whether this mechanism of action can really meet the unmet needs of obesity.

There was talk about challenges with GLP-1, such as the complexity of titration and rebounding. Still, it is used in the market and evaluated well. Amid this, the result was under 5%. I wonder if this mechanism of action will work. I would appreciate your comments. Thank you.

Uehara : We only have one compound in our pipeline, so naturally, we do not know if this mechanism of action is absolutely useless forever, no matter which company does it. Nevertheless, based on the assessment of nonclinical data, we have reached the experimental conditions under which this effect is likely to occur. Based on the blood levels I reviewed this morning and considering that the patients have been taking the medication, this action is being effectively carried out within the body.

As you know, appetite is a fundamental part of life, and many different signals are involved. One of them indirectly acts on the gastrointestinal epithelium, where there are GLP-1 signals and other signals as well. The concept of this drug is to control diet by influencing a diverse range of hormones.

Therefore, the mechanism of action must be milder than strongly inducing GLP-1 signaling to produce its effects.

Under such circumstances, we believe that offering a combination of multiple drugs may be of some value since the current data indicate that it would be somewhat difficult to control with only S-309309, at least.

Teshirogi : Originally, I thought there were two problems. As I was talking with Uehara and John today, I realized that oral drugs in the real world are probably not being taken as prescribed, which I have to accept. Therefore, I think it would be difficult to accurately measure the potential of this drug without analyzing those who have taken the drug exactly as prescribed and how the other parameters are moving.

As far as that is concerned, we believe that this mechanism is as valid as we think it is. I promised that I would deliver an update on this R&D Day, but, as I mentioned, the blood levels report just came in this morning, and we do not have all the data from the various biochemistries, so we will not know the true potential until we start analyzing the data.

As I said before, we have to consider how people take drugs in the real world. Some people take them as prescribed, while others do not. We must accept this reality. We accept the fact that we did not reach 5%, but that does not mean that this drug does not have potential or that this mechanism does not work. I do not think that this is the case at all, and we will keep working on it.

Mamegano : Okay, thank you. One more question about HIV. Your company is quite ahead of the curve in terms of the long-acting effect, and I think you have an advantage. According to what President Teshirogi said earlier, safety is also very important, and I think you have an advantage in that matter.

I understand that it is quite difficult to produce, but Gilead is currently conducting tests on GS-6212. I believe your company has an advantage in terms of safety. Do you have any thoughts on this, specifically regarding the safety advantage since they came out later? Are you not too worried because you have an advantage, or are you surprised that they were able to produce? I would appreciate it if you could comment on that area.

Keller : Regarding the last question, I believe Gilead has switched their focused points to long-acting. Apart from its importance, I don’t have much data on their compounds. I don't have much data on their compound, So I can only comment based on rumors. I do not know if they have a long-acting compound that can be administered once every 4 months or 3 months like ours.

However, they seem to have some compounds, so of course, we must not relax. Even if everything goes well for them, their compounds will likely not be on the market until 2028 at the earliest, I think.

Of course, there is also the time for review, like a year for approval packages. I think it would be a bit difficult to compete with Cabenuva in terms of long-term efficacy and safety.

But they are pursuing it very aggressively. So, although the program will be early, we would like to have something that is even better than theirs in the pipeline so that when they catch up, we will be ready to compete with them.

Kyokawa : Another one from the audience. Ms. Haruta.

Haruta : UBS Securities, this is Haruta. I would like to know more about the approach or the winning strategy in the area of QOL disease.

I understand that your company has strength in drug discovery in the area of small molecules, but I wonder if this kind of disease requires collaboration with other companies and total solutions, as you are currently doing.

The market is large, but when considering the revenue model, you mentioned that you are in the phase of increasing sales, similar to a subscription model. What is your approach to the revenue part?

Teshirogi : It depends on the area. Of course, there is relatively clear foresight in the area of rare diseases in children, so I think the revenue model is pretty clear. In that sense, John and Isou are very committed now to addressing hearing loss and sleep apnea, though there are considerations to be made on how to view these areas.

Unfortunately, we do not believe that hearing loss or sleep apnea is a disease that can be completely cured, even though medication can alleviate symptoms or make the quality of life better. If it is used for a lifestyle-related disease, and people feel its effectiveness, they will continue using it. Therefore, we do not want to charge a very high price. Instead, we aim to set a price comparable to treatments for hypertension or hyperlipidemia or perhaps slightly higher. Our goal is to ensure that a large number of patients can continue using the drug.

On the other hand, in the case of hearing loss, for example, it is clear that the problem is caused by the deterioration of the inner ear hairs. Therefore, we need to explore approaches to regenerate the inner ear hairs, and we will pursue this course of action.

That is more like a complete cure. When that happens, what kind of pricing model should be used? We want to avoid a situation like Harvoni, which sold with a bang and then did not sell afterward. It may require a subscription, as you suggested earlier, something that would be paid over a number of years.

At this point, the compound we are trying to introduce into clinical practice is almost like a symptom-relieving drug. So, I think patients will be given it on a fairly continuous basis.

Haruta : Okay. Thank you very much. On the second point, John-san mentioned earlier that people don't want to use oral drugs and that they all use injectables. I think there is going to be a reform of Medicare Part D in the IRA in the US, and there will be a co-pay cap there. How should we look at the oral drug and whether it will be easier to use? Please let me know if there is any possibility that the shift to injectable drugs will be a bit more gradual.

Keller : Thank you. Of course, at ViiV, we look at the impact of IRAs. IRAs are very careful when it comes to HIV. Although different from the IRA, the effort within the government is to bring comprehensive coverage to PrEP. It has not been covered until now.

PrEP is covered now, and injectables are covered. There is a strong commitment and recognition, especially in the Biden administration, that it is important for people with HIV to have access to the best medicines.

And injectable drugs are the key to HIV control, according to the data. This is true in the poorest countries or among the poorest people.

One important site in San Francisco is conducting a study of the homeless population. And these are people and areas where HIV is not controlled at all. This means they have an unstable lifestyle or do not have Ainsurance. They are such people. The government collects people by providing food and controlling HIV through injections.

Our stance may change with elections, but our key objective now is to provide the best possible treatment to HIV patients.

Kyokawa :

One more from the audience, Mr. Wada.

Wada : Thank you very much. I also have questions about the anti-obesity drugs and the anti-cancer drugs. I would like to ask you about your positioning in relation to the competition,

First of all, regarding anti-obesity drugs, BMS developed MGAT2 inhibitors in 2019. The paper shows data from Phase 1b, where weight loss and appetite suppression are visible. They already developed the drug, but in response to this, where did you see the S-309309's potential for success in its development? I would like to ask you, first of all, what you think in terms of the profile of the compound.

I think they are developing this now with NASH. So, I would like to know your company's thoughts on whether there is any direction for development in terms of NASH or other areas.

Regarding anti-cancer drugs and anti-CCR8 antibodies, I have been inquiring about anti-CCR8 antibodies for some time now. I am looking at anti--CCR4 antibody mogamulizumab and wondering if Poteligeo, which is being developed by Kyowa Kirin, has a very similar mechanism of action. The mechanism of action was to increase $CD8^+$ T cell by Tregs depletion, which would then allow the anti-tumor effect to be observed.

I think they had high expectations and focused on solid cancers, but it did not work well. The problem is that at higher doses, Tregs are depleted, but $CD8^+$ T cells are also depleted. So, the anti-tumor effect is only visible at a certain dose. Therefore, they shifted to blood cancer since it is difficult to use for solid tumors.

In this area, I would like to ask if you can see where your anti-CCR8 antibody dose-dependently decreases Tregs without reducing $CD8^+$ T cell.

Isou : Thank you for your questions. Regarding MGAT2, as you mentioned, it is important how we maximize it in the future. As Uehara mentioned earlier, there are not many validated non-clinical models, but we have been able to find a certain direction. We are currently working on the following two areas**:** combination with GLP-1 or maintenance therapy. We are trying to focus on how to maintain GLP-1 once it is stopped.

As you questioned, we might have overestimated the model. Therefore, we will review the model system in the non-clinical setting to ensure it reflects changes more realistically and monitor these changes strictly in the non-clinical model.

Therefore, we would like to aim and combine with the GLP-1 as part of our new positioning.

Teshirogi : S-309309 has shown almost no safety concerns even in animal testing, and we are currently examining biochemically from various angles to see what effects can be achieved by inhibiting MGAT2 to a certain extent.We have no idea if dosage of S-309309 is the ceiling or not. So, there is a possibility that the dosage could be increased in the future. The safety of the drug, including the side effects on the human digestive system, has been very good, and almost nothing has been found. So, perhaps the dosage could be increased, or the method of administration could be changed, including combinations, after looking at the toxicity a little more carefully, as Isou mentioned.

I really don't think we are in a phase to discuss this compound in one piece in these first two phases.

Uehara : Another perspective on NASH, again, we have not seen all the results yet. We will collect data on liver lipid content in this trial, and if we can expand in that direction, we will actively consider it.

As Teshirogi answered, the biggest advantage of S-309309 is its excellent safety features. Therefore, we believe that there are still plenty of ways to use it.

Regarding S-531011, Mogamulizumab is the positive part of CCR4. It is used to treat tumor cells and blood cancers by lowering antibodies directly in the bloodstream, which is called direct acting.

Our anti-CCR8 antibody has various functions in Tregs, and CCR8 infiltrates tumors. There are cancer types that are specifically infiltrated by CCR8, and by targeting that, there is a clinical database study that suggests it will apparently have a clinical effect. We confirmed the concept in non-clinical studies and have been taking pure antibodies and selective antibodies, so it is different from the target perspective. When we say Treg, it has various different functions.

The other feature is that we want to lower Treg as tumor specific as possible. So, if we unnecessarily lower Treg throughout the body, we will see a variety of side effects. Therefore, we developed a method to lower tumor specific Tregs without reducing them throughout the body.

Therefore, it is highly safe and clear. I'd like you to be able to look at slide 80, the picture of the flow cytometry.. As you can see, Treg has completely decreased in purple, on the right bar graph after administration. It may depend on the conditions, since the CTL is increasing properly in red where Treg is gone. Not all of them are cleanly dose responsive.

In such a situation, there is no doubt that there are patients who can use the drug. Lowering Tregs does not mean that all lymphocytes will be unnecessarily decreased, but rather that the tumor will become smaller because the CTLs remain in place.

Wada : Thank you very much.

Kyokawa : Mr. Sogi of Alliance Bernstein Japan, please.

Sogi : Thank you for taking my questions. I would like to ask you a few questions.

Regarding Xocova, you commented that negotiations with the FDA are going well after the readout of the global Phase III primary endpoint. Of course, I understand that it has just started, but what is the baseline for alignment with the FDA?

Uehara : I will answer your question. The discussions are progressing smoothly, and since this is an active study, we have received commitments from a wide range of experts in the field of antiviral medicine at the FDA, doctors at the NIH, ACTG, and academia at universities.

We are now preparing for a pre-NDA discussion where all of these professors will gather together for an online discussion.

Sogi : Okay, thank you very much. I have a question about S-309309. You mentioned this drug does not cause muscle loss. What data supports this claim?

In this Phase II, will there be any results regarding this point?

Uehara : Thank you. Saying that data is available would be an oversimplification. We can separately measure muscle mass, lipid volume, and body fluid volume.

It will be a little difficult to interpret because there is a lot of noise, and I have not yet reviewed it thoroughly.

So, in this situation, I think that the actual mechanism of muscle loss with GLP-1 is not clearly understood. Naturally, when people stop eating, they lose fat, but often muscles atrophy first. If you suddenly control your weight, reduce your appetite, and stop eating protein, the muscles will break down first. When you stop the medication, only your appetite returns, leading you to eat mostly oil and carbohydrate. That is the mechanism I am thinking of, where muscles first lose and then gain weight back again.

Preferably, we may not want to lower the weight too gently, among other considerations, and we aim to delve deeper into the data from now on.

Sogi : I understand. You are right, and I was wondering if that was the mechanism too. So, I was curious if, in the broader concept of weight loss, there is no reason why only your drug would not reduce muscle mass, but rather because the weight loss is gradual.

Is it correct to say that the MGAT2 mechanism does not have any specific effect on the muscles?

Uehara: It does not directly inhibit lipid absorption, but it does store fatty acids and lipid components in the epithelium of the gastrointestinal tract, so its mechanism of action is rather to lower lipids.

Since it is a drug that lowers appetite but also aims to lower fat, which is the opposite of muscle mass, we are hoping that it will have a positive impact.

Sogi : I understand. One last question regarding future developments. Of course, you are going to analyze the data, but you mentioned that monotherapy is probably not a possibility in the future.

I believe the add-ons and maintenance development plan you have indicated will be the general direction. I would like to confirm if my understanding is correct.

Is this something your company will do alone when moving in that direction, or will you already be looking for a partner? If so, what is your timeline for moving in this new direction, considering deal time?

Keller : Thank you. As you said, we have just received this data and will be analyzing it, but we need to look at the non-clinical model as a whole. As for the timing, I cannot say right now. However, we already have some analysis done on the pre-clinical model, and I think we can provide more information in about six to nine months if we proceed seriously.

Kyokawa : Thank you very much. This will be the last question. Mr. Tsuzuki from the venue to close, please.

Tsuzuki : Thank you for choosing me. My name is Tsuzuki of Mizuho Securities.

The first question I would like to ask is whether the antiviral activity against RSV has been confirmed in the footprints, since you have provided us with data on the antiviral activity of the type A virus and the in vitro data that included type B virus. I would like to know if this has been confirmed in the current situation.

I would appreciate hearing your answer to whether this challenge test is a PoC and the timeline for announcing the results.

Uehara : Thank you for your question. We are currently acquiring data on typical B-type strains. Although B strains require a slightly higher concentration than A strains, they are not that far apart.

We are currently collecting data from around the world on many strains, including type A and type B strains that have been isolated in recent years. Therefore, considering all these factors, including the ineffective strain of type B, we will conduct the challenge test with type A to match the blood concentration level in humans, which is expected to be effective. The blood concentration of type A is multiplied by the blood concentration of type B, or it is like jack it up.

There are a variety of influenza A and B strains, and we have adopted such a strategy. We have selected a sufficiently effective blood concentration, so we are in the middle of this challenge test. First lots, second lots, and third lots are all artificially created, so it is not possible to collect them all at the same time.

However, since it is an acute infection, it will not take that long. I believe the results will be available sometime this fiscal year, allowing us to determine the next course of action.

Tsuzuki : I understand. One more point**:** you presented the external collaboration in a visible form this time regarding S-600918 in the sleep area. I believe you brought it back as a combination drug after its suspension. I understand that this return is associated with Apnimed. However, I have also heard that recruiting seems to be difficult.

I would be happy to hear your level of confidence in this area as the last question.

Keller : Thank you. As for recruiting, it is not easy with a defined population. However, Apnimed's Head of Medical, Chief Scientific Officer, is connected to the best clinical research centers. This is regarding patient identification and recruitment.

And in the apnea study, which they are doing as part of a joint venture, they are very competent, so I think we can do it.

For S-600918, we are working with the team to dig deeper into the data and examine specific patient populations. This was a previously unidentified population, but due to our lack of knowledge about the disease at the time, we relied on their expertise to identify patients with apnea syndrome who were diagnosed with S-600918.

Kyokawa : It is time for us to conclude SHIONOGI R&D Day 2024.

Thank you all for your participation today.

[END]