Shionogi & Co., Ltd.

R&D Day

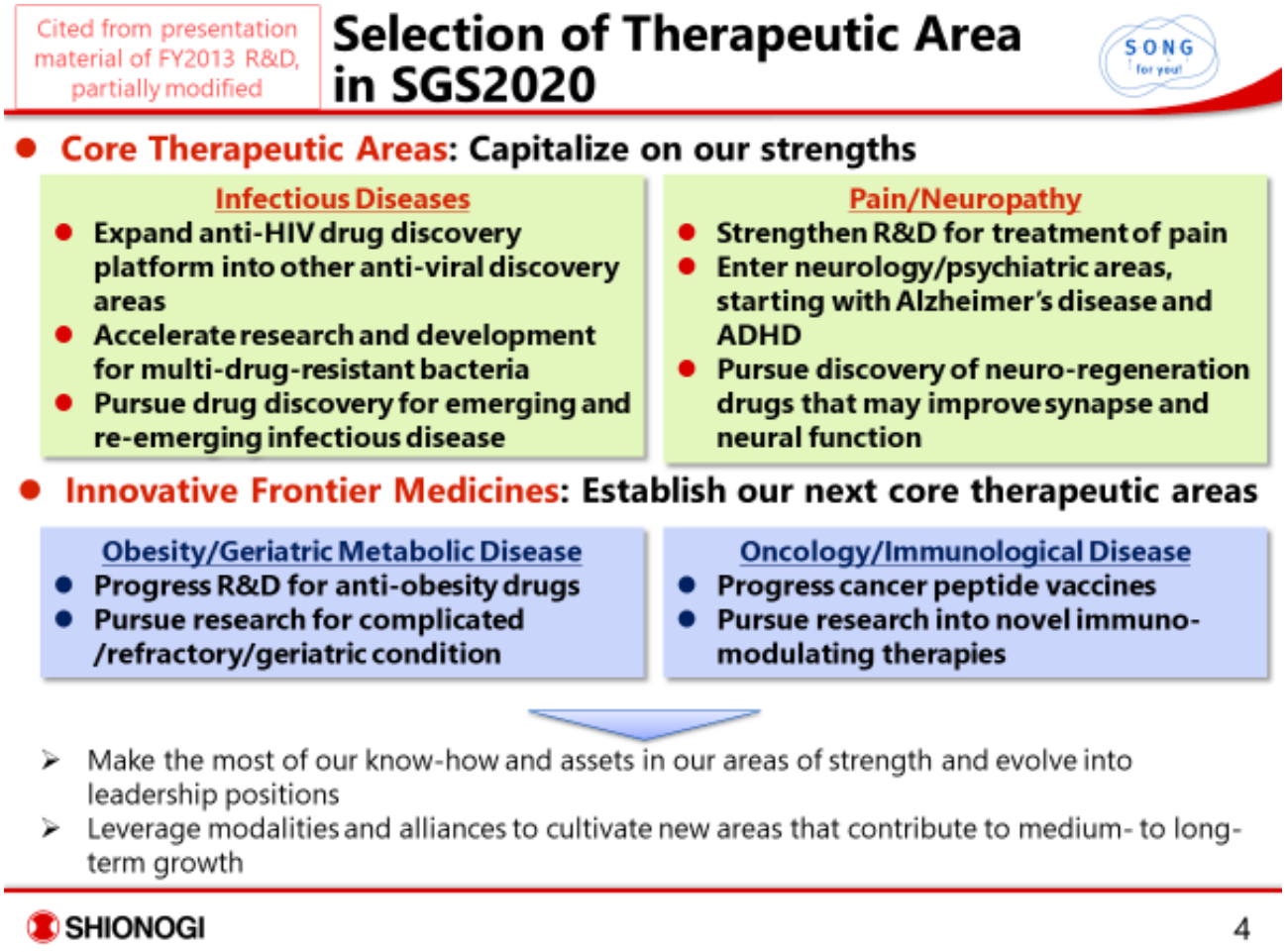
March 19, 2020

Agenda

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

Kyokawa: Right, I'll start by explaining today's agenda. This is the agenda, and after Teshirogi has made some introductory remarks, we're going to tell you about our sustainable growth drivers in the order or Research, Development, and CMC. After that, Teshirogi will provide a summary, and then we'll move on to the Q&A session.

Teshirogi: Once again, good morning. I'd like to express my gratitude to you for being here today.



I'd like to start by talking about the Shionogi Growth Strategy, or SGS2020, which is our medium-term corporate plan, and which we began implementing in FY2014. This is an illustration of the direction for R&D that we want to take.

As you can see, we are maintaining infectious disease, and also pain/CNS as our core therapeutic areas, while also retaining open, completely free research, though it only forms part of our research base.

We have not been focusing solely on these two core therapeutic areas, and we want to maintain a certain level of freedom for our researchers, who are incredibly passionate and want to continue pursuing good research. And from their work, we have chosen as future growth areas obesity and geriatric metabolic disease, for example, and looking forward to 2030 or 2040, with the world's population growing older, we have been continuing with research based on the idea that we might be able to come up with some drugs that could be useful in that area.

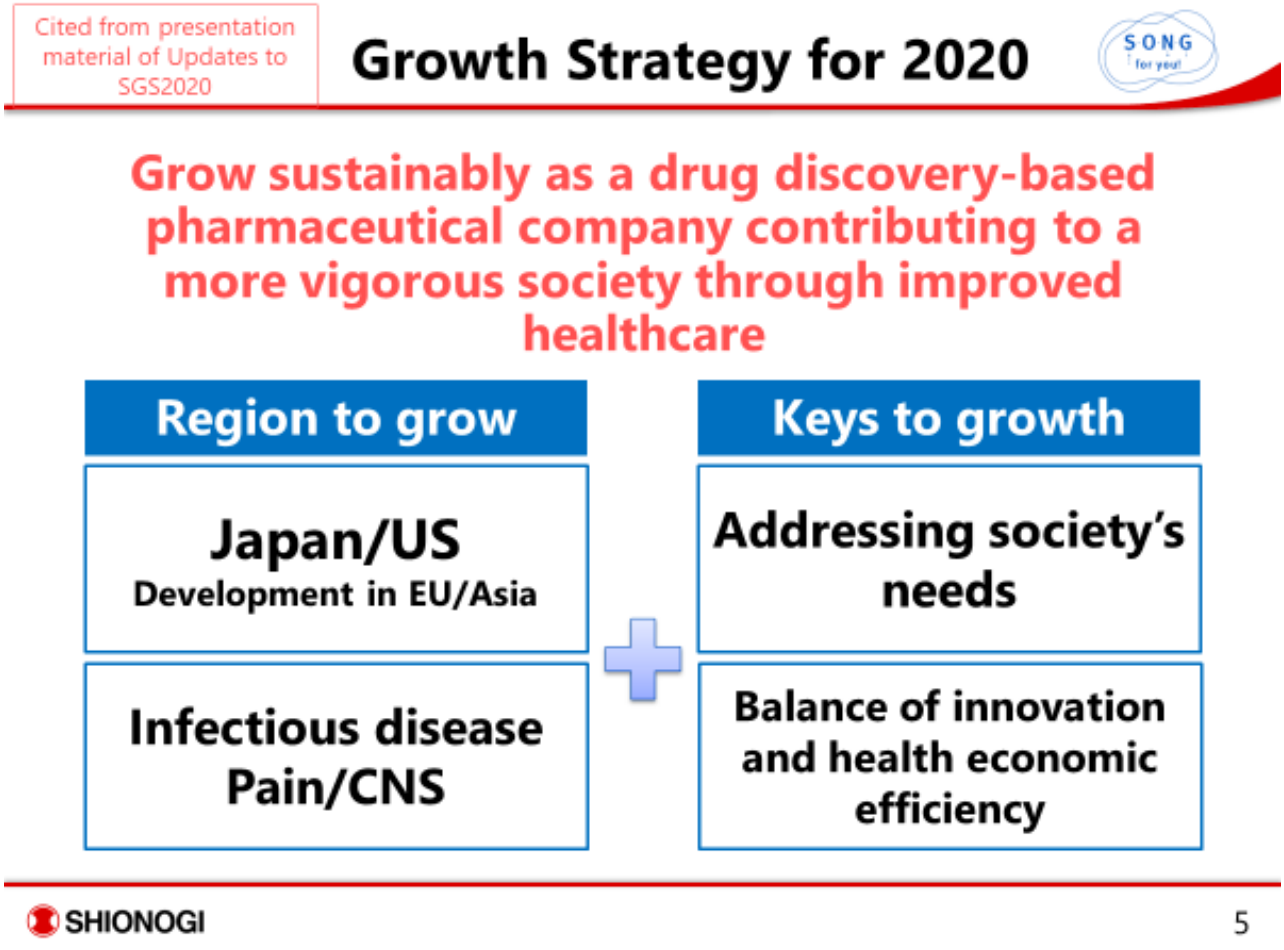
We have been aiming to challenge new modalities, particularly with regard to antibodies and nucleic acid, and because we have been tackling oncology and immunological disease for a comparatively long time, we have continued in the belief that if we stick with such research we will be able to produce something interesting in these therapeutic areas.

In line with this policy, we have been working on the pipeline, and as for the HIV product patent cliff, that would arrive in around 2028, considerable changes are expected. I think that not only ourselves, but all companies that sell HIV oral drugs, will face the same problem, and with that timing in mind, the question is what sort of pipeline we should build. We recognize that in the next

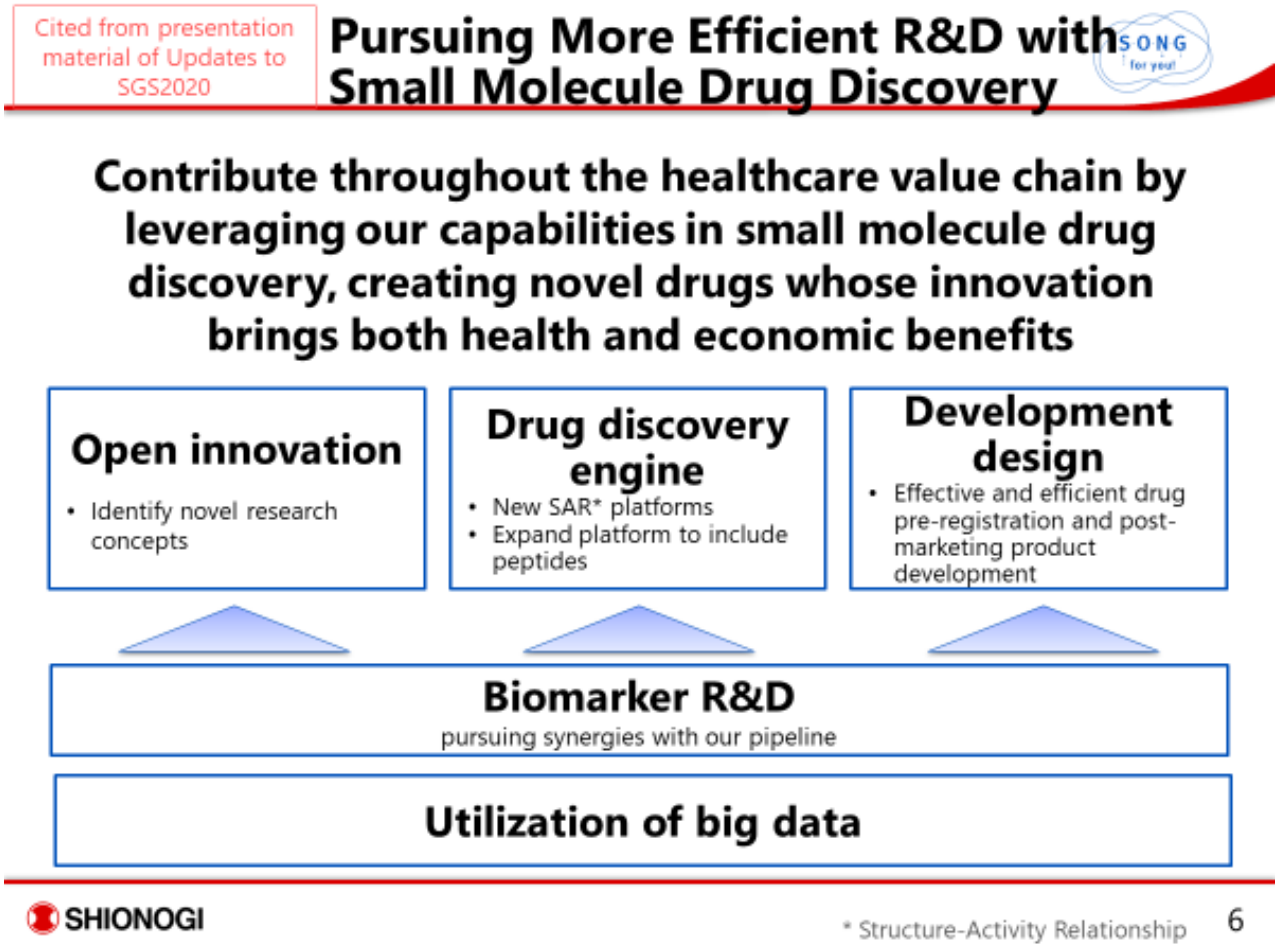
several years, in the two or three years from 2020, unless our next core therapeutic area becomes clear, our earnings structure will find itself in a considerably severe situation.

So with that also in mind, during this R&D Day, we'll be talking mainly about drugs that will go into clinical entry or are achieving progress in the clinical phase during FY2020. After that, we'll be discussing the one exception, an anti-cancer drug, which will not be going into clinical entry until FY2021, but from our point of view, it has really interesting attributes, and the adjuvant it's expected to be used with the cancer drug will be in the clinical phase during, so we're going to be offering the pair as a set.

Looking ahead to FY2021, exactly one year later, we'll be talking about pipeline that will go into clinical entry from FY2021.

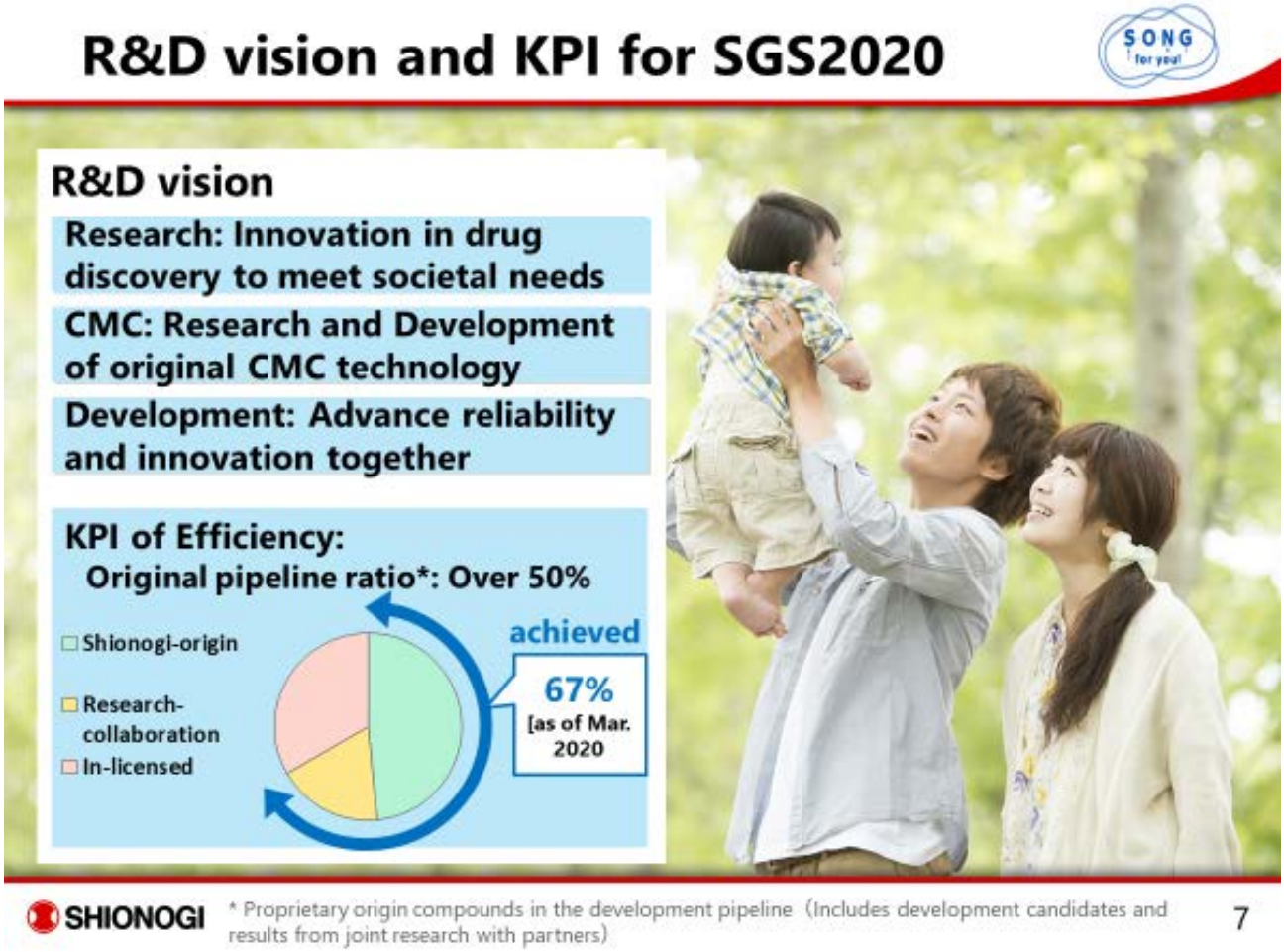


So as I mentioned earlier, we're going to focus on the U.S. and Japan and maintain the core therapeutic areas of infectious disease and pain/CNS as a base, while articulating what we're going to be offering in the next phase. Especially, we have positioned the aging society as an important theme..



Regarding our R&D in the field of small-molecule drug discovery, I believe that we have strengths at an extremely high level of in the world even now. However, when I talk to the researchers, when considering to approach the new targets, such as enzymes, proteins, or membranes, it gradually becomes difficult to approach only with small molecule drug discovery. So we'd like to expand the scope of modalities a little.

For about five years, we've actually possessed antibodies and nucleic acid drug discovery technology, so we've been conducting a number of ongoing studies on whether they can be translated into drug discovery. Today we're planning to talk about anti-cancer drugs and adjuvants, and we have been gradually building a technical foundation not only for small molecules but also for larger molecules, and I'd like you all to realize that.

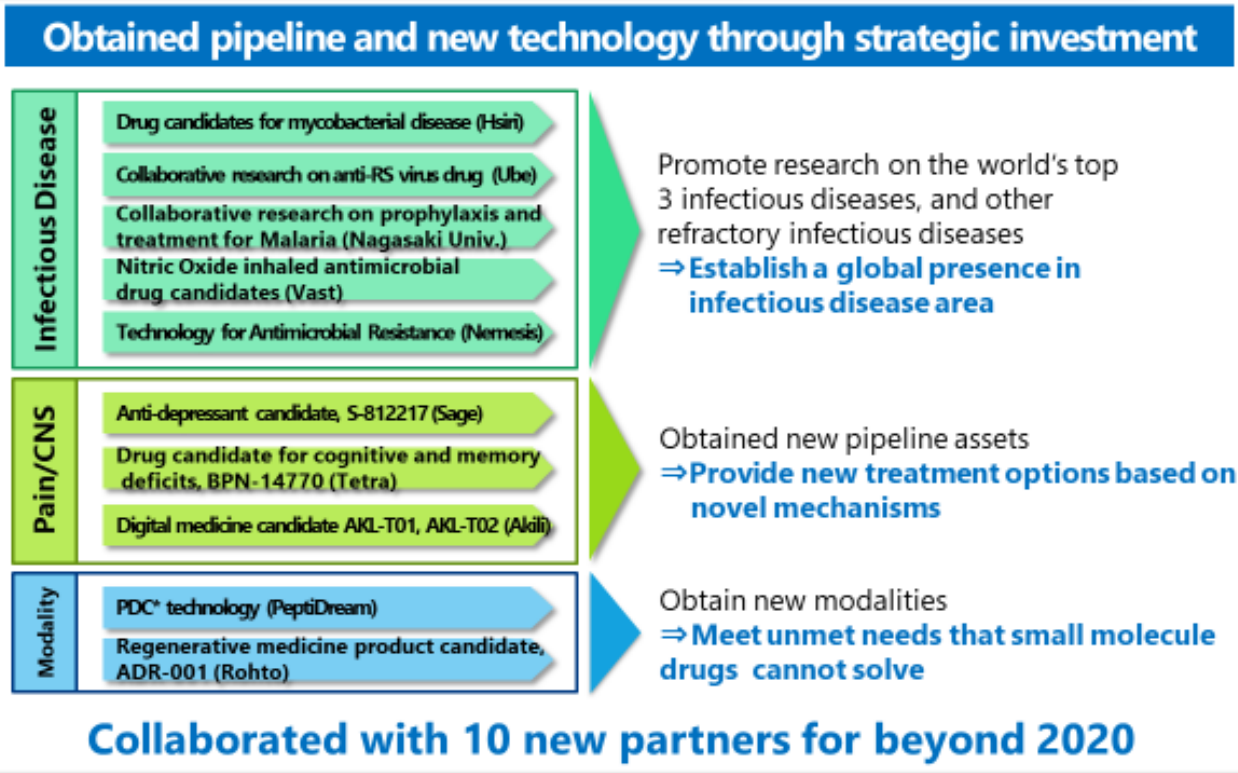


So our research has always focused on these sorts of KPIs. Not everything is developed in house, and when we work with startups, for example, we start with joint research. During this joint research, we find out whether our researchers and the researchers at the company can generate synergy effects. By collaborating, we confirm that 1+1 equals 3 or 4, and if we are able to confirm that, we move to further expand the relationship.

We include all that, but we still have achieved an original pipeline ratio of over two-thirds, and in our next medium-term plan, which will be looking ahead to 2030, this is going to continue to be an extremely major approach and direction for us.

Cited from presentation material of FY2018 Financial Results

Strategic Investment in FY2018



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* Peptide drug conjugates

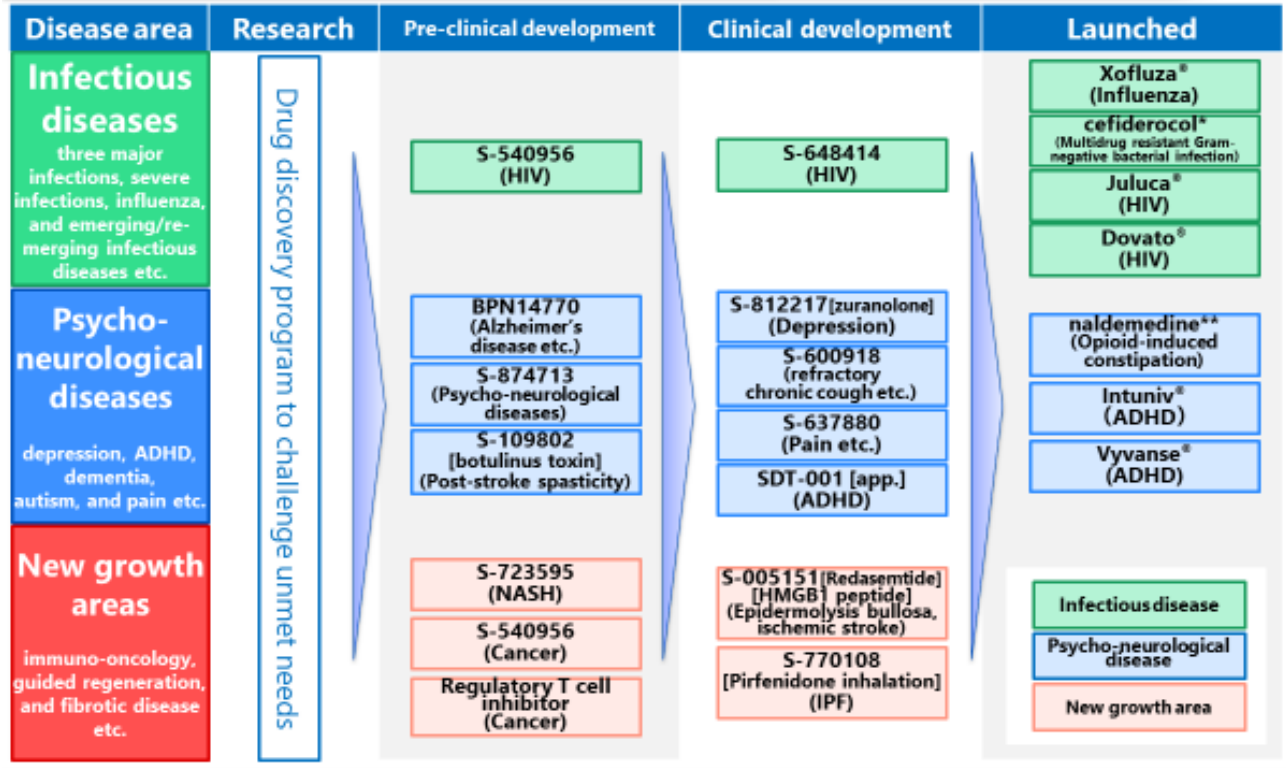
This shows our strategic investments in FY2018, so one year ago, and some of them are have been blossoming, but we've made a wide variety of investments. Of course, one approach would be to acquire capabilities through M&A deals costing 100 billion, 200 billion, or 500 billion yen, but we want to maintain strong R&D capabilities that are based on our own research, I think that continuing to conduct investment on that scale is vital for our company.

Enhance Assets and Maximize Value Through Alliances

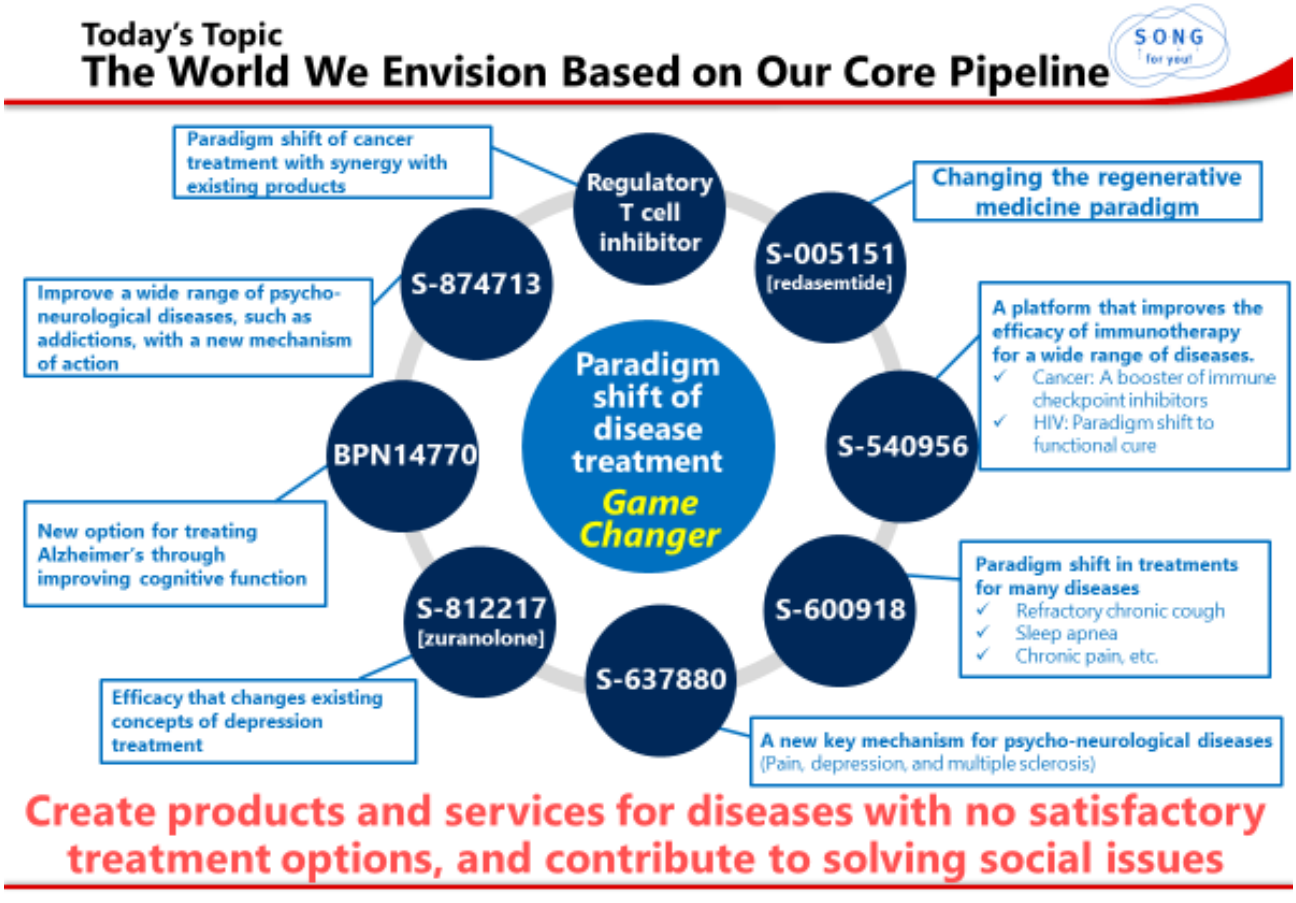
So we're somehow managing all these alliances, but when considering healthcare as an increasingly important platform as we move toward 2030, a key issue will be how to establish partnerships with players outside the pharmaceutical industry, so we will need to continue to polish our collaborative capabilities and alliance capabilities going forward.

Right now, we're working with all these various companies/organizations, and I think that further enhancing these sorts of capabilities is probably desirable for a next-generation pharmaceutical company.

Growth Drivers Discovered/Acquired in SGS2020



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



Regarding page 10, it shows drugs produced in 2020 under SGS2020, and I won't mention them all, but these are today's themes. From 2020, as I mentioned earlier, we're going to see a drop in revenue, and profits, from HIV products, particularly oral drugs, as their patents expire, and regarding what sort of answer we're going to come up with to make up for this drop, this is our solution at the present time.

Anti-cancer drugs are at the top, and the division heads of Research, Development, and CMC are going to be explaining them all later, so moving clockwise, these anti-cancer drugs and S-005151, and the adjuvant have a potential to create a new paradigm. And S-600918 and S-637880 are small molecules, and can treat pain, CNS disorders, and new diseases. S-812217 and BPN14770 target the CNS. And S-874713 is our original pipeline. So we believe that we have come up with products that are have strong marketability potential.

I'm proud to say that naldemedine and mulpleta are extremely good products, and when I said that it is our drug-discovery capabilities that enable us to provide products to the world, I'm still not entirely satisfied with the amount of market share we can capture, so in light of that, we intend to push forward aggressively with these promising pipeline while remaining conscious of marketability.

Transpiring around 2028

Overcoming the "HIV Product Patent Cliff" for Sustainable Growth

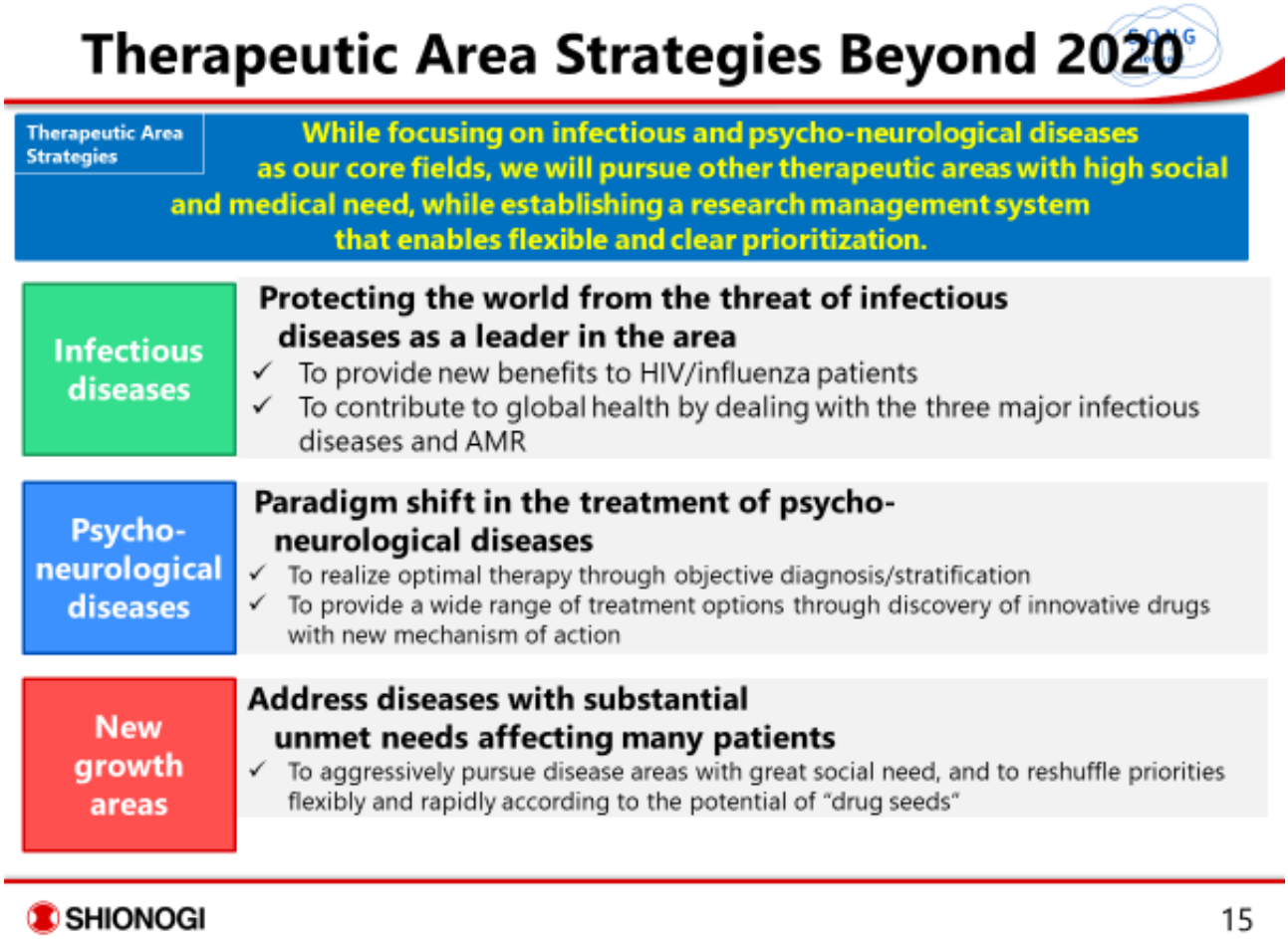
The main theme can be summed up with this phrase. How can we overcome the HIV-product patent cliff to achieve sustainable growth? Of course, because we're a pharmaceutical company, our business is based on pharmaceuticals, but we want to create a new Shionogi in the future, including by establishing other business models. I believe that the most important core element for that is the R&D strategy we're telling you about here today.

Today, after taking your questions and hearing your opinions, we intend to continue to evolve, so thank you for today.

Kyokawa: Moving on, Dr. Kiyama is going to discuss the research field.

Kiyama: I'm going to tell you about the progress we're making in the field of research.

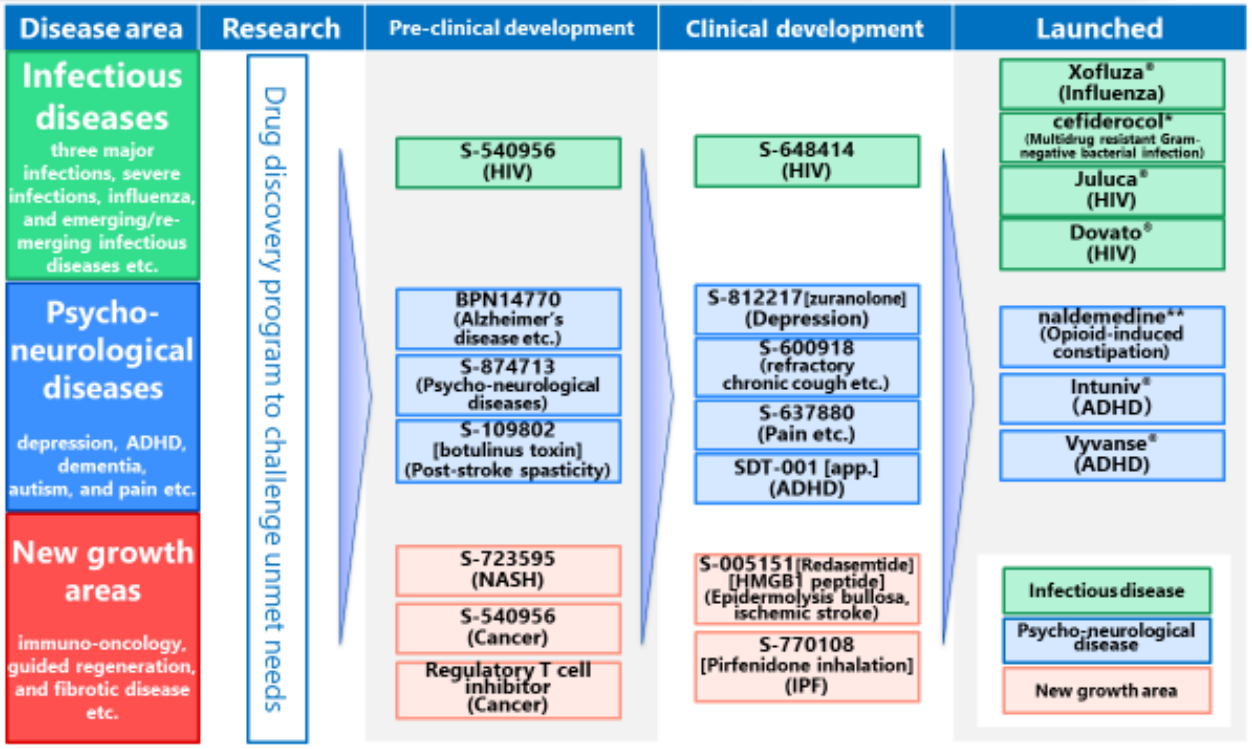
This is our R&D vision, Beyond2020. The key components are expanded modalities, collaboration with a wide range of business partners, and realizing high-level business operations, and as Teshirogi mentioned earlier, we are going to be expanding into new modalities while further augmenting our strength in small-molecule drug discovery. As we announced in February, we have launched two new research centers: an advanced pharmaceutical research center and an innovative medicine research center. By revamping our organization, we have clarified where responsibilities lie.



As for therapeutic area strategies, we are going to maintain infectious disease and psycho-neurological disease at the core, and when something promising emerges from other therapeutic areas, we will, as I have continued to state in the past, reshuffle priorities flexibly and rapidly.

Re-appeared

Growth Drivers Discovered/Acquired in SGS2020



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

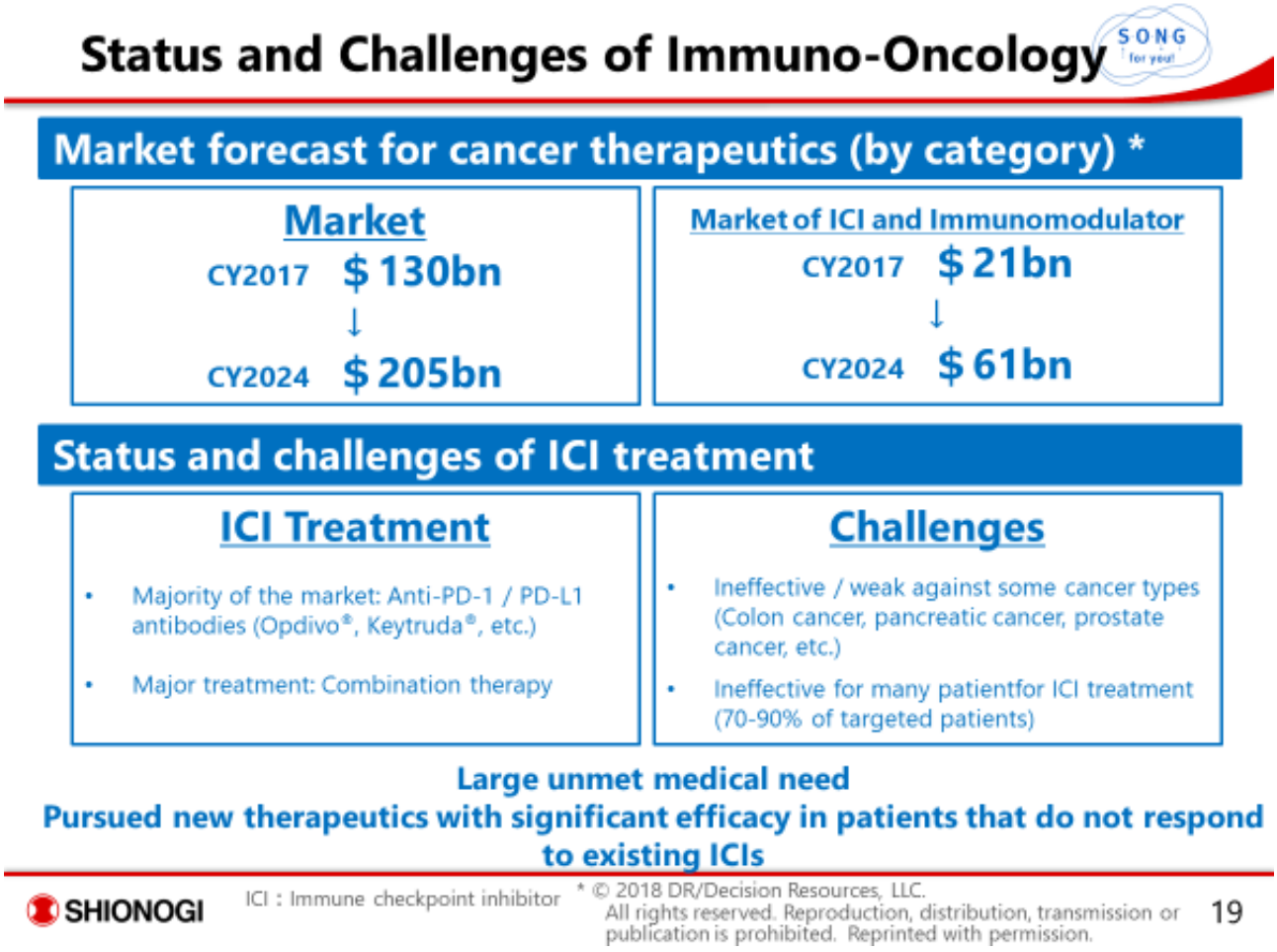
This was displayed earlier, so I'll skip it.

Research

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

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

Today I'm planning to talk about seven projects, and I believe that the parts highlighted in red represent core pipelines that could lead to paradigm shifts in disease treatment.

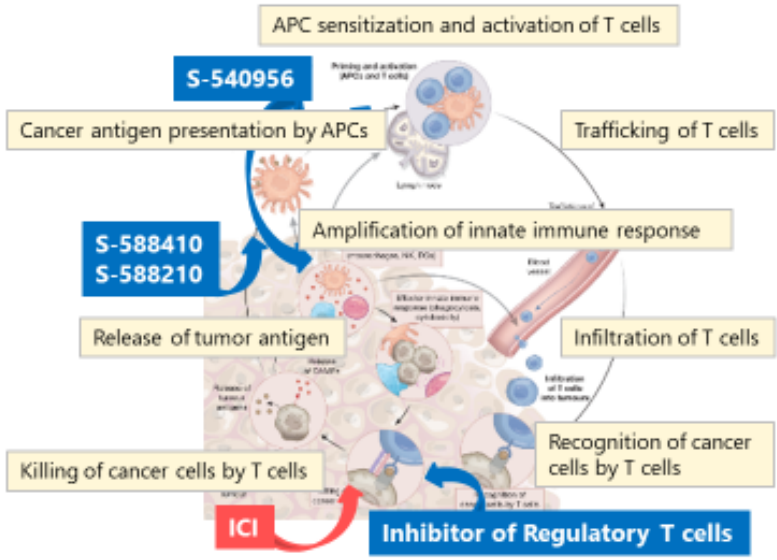


I'll begin with cancer. As you all know, the cancer market continues to expand, and the market size for ICI and immunomodulators, in particular, are going to keep increasing. However, the main players in the immuno-oncology market are Opdivo and Keytruda, which are anti-PD-1/PDL1 antibodies, and obviously, there are cancers for which these are ineffective or only mildly effective, and patients for which these treatments don't work account for between 70 and 90 percent of the total, so I believe the immuno-oncology market will continue to grow.

Unique Immuno-Oncology Assets Innovated by SHIONOGI

Diverse modalities with different mechanisms

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



Building a cancer platform that enables various treatment approaches

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

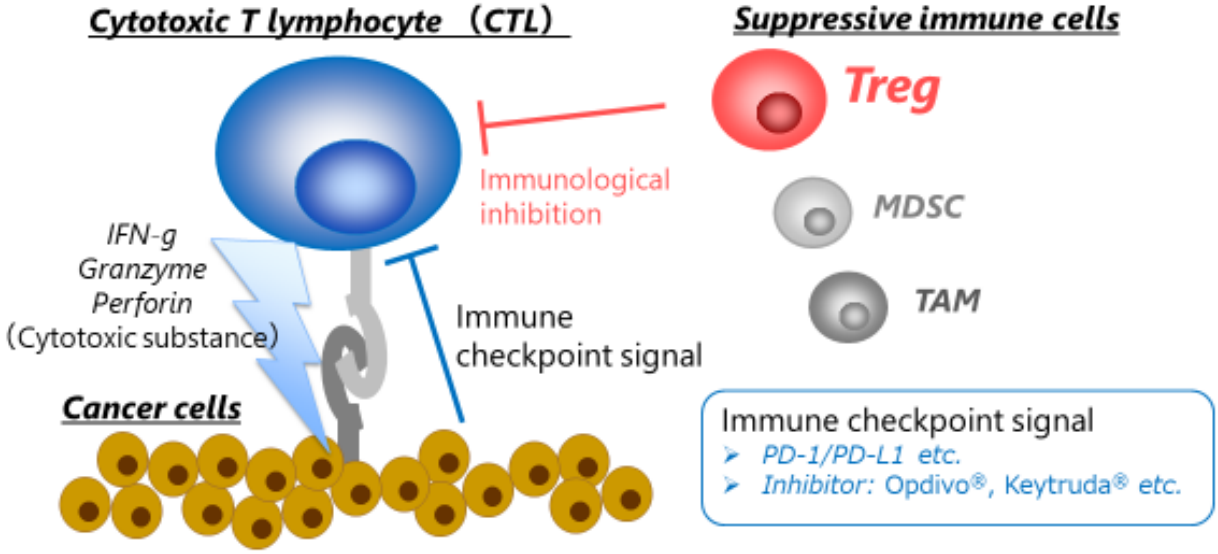
図：Nature. 2019 Oct;574(7776):45-56 より

APC：Antigen presenting cells ICI：Immune Checkpoint Inhibitor

Regarding unique immuno-oncology assets that Shionogi possesses, for some time we have been working on the development of a cancer peptide vaccine, and in addition to this there is a nucleic acid adjuvant, a TLR9 agonist, which we announced last year, and an anti-CCR8 antibody, which I will discuss today. These are described on the right, and as you can see they work against various targets of the cancer-immunity cycle, so a variety of treatment approaches are possible.

Collaboration Research on CoMIT with Osaka University

Tumor immune-related cells in the intra-tumoral microenvironment



Search for treatments selectively inhibiting Treg in the tumor microenvironment

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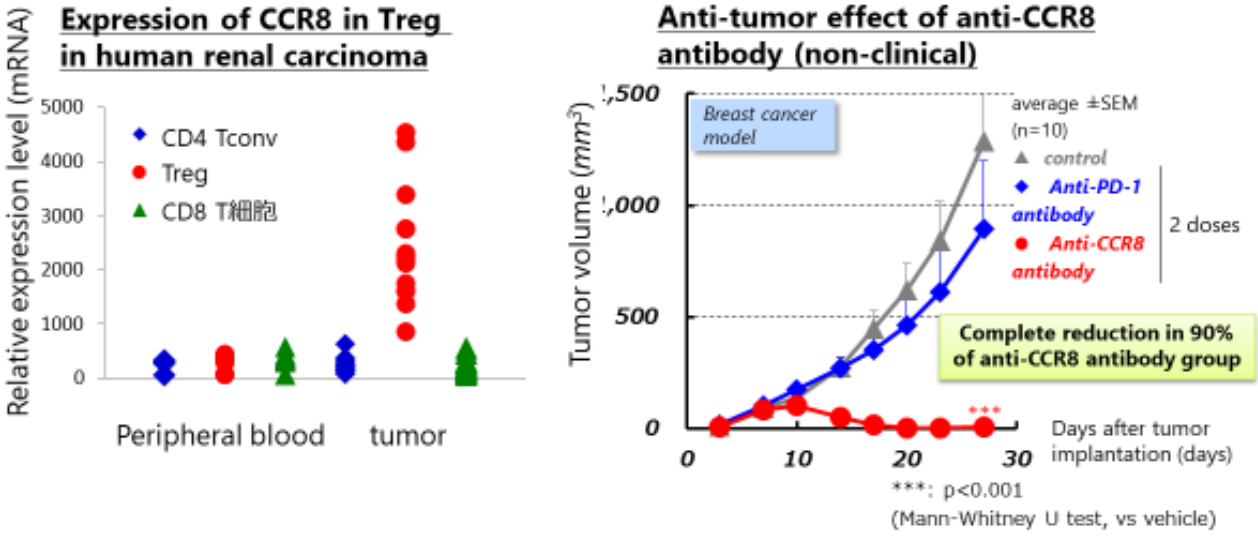
CoMIT: Center of medical innovation and translational research
MDSC: Myeloid-derived suppressor cells
Treg: Regulatory T cells
TAM: Tumor associated macrophages

Let's move on to page 21. Regarding tumor immune-related cells in the intra-tumoral microenvironment, we have focused on regulatory T cells (Treg). As you know, cancer cells emit an immune checkpoint signal, which prevents attack by cytotoxic T lymphocytes (CTL), but there are also other suppressive immune cells with this immunological inhibition. Among them, we have focused on Treg, which plays a major role. This research is being conducted jointly with Osaka University's Center of Medical Innovation and Translational Research (CoMIT).

Discovery of Regulatory T-cell Inhibitor

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



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

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

This is page 22. We identified CCR8 as an anti-tumor target selectively overexpressed in tumor Treg. The graph on the left shows what kind of cells CCR8, which are indicated as red circles, are expressed in, and we found that in peripheral blood, they are expressed in hardly any cells, and that they are highly expressed only in cells that have penetrated tumors.

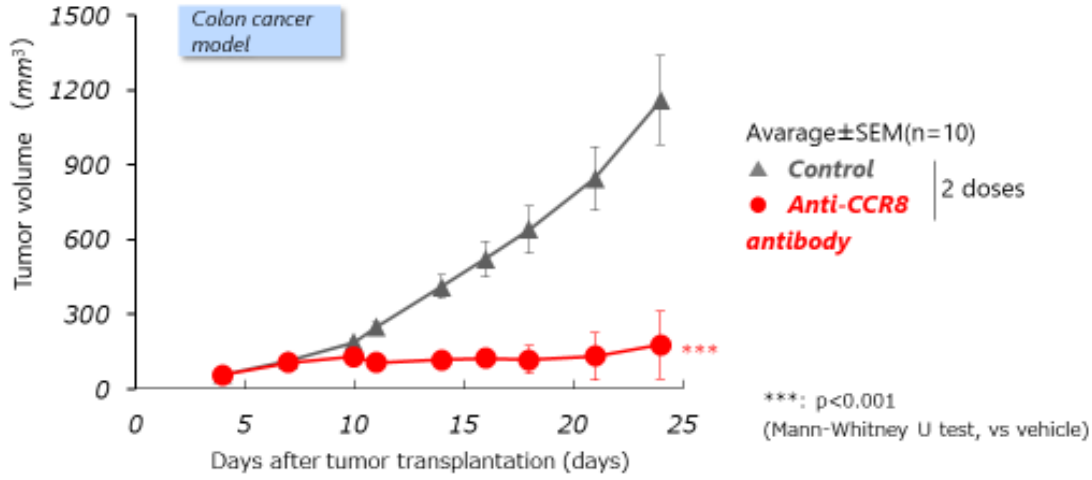
Furthermore, they are not expressed in the effector $CD4^+$ T cells and $CD8^+$ T cells, and only expressed in Treg, which acts suppressively, so I believe we have identified an extremely interesting target.

Described on the right is the anti-tumor effect of the anti-CCR8 antibody. We used a breast cancer model for mice, and even in the case of cancers for which PD-1 antibodies are ineffective or only moderately effective, the anti-CCR8 antibody is shown to be extremely effective. In this experiment, there was a complete reduction, meaning that the cancer had completely disappeared, in 90 percent of the group. And even after a long period of continued observation, the cancer did not reappear, demonstrating an excellent level of treatment effectiveness.

Discovery of Regulatory T-cell Inhibitor

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

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



Accelerating research to achieve early clinical entry

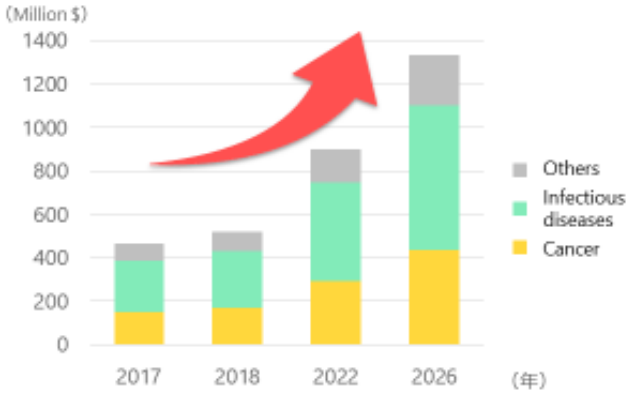
Let's move on to page 23. In the previous experiment we gave mouse antibodies to mice, but here we see the effect of a development candidate antibody to CCR8-humanized mice. We used a colon cancer model, but just as was seen with the previous experiment, the anti-CCR8 antibody demonstrated a high level of anti-cancer effectiveness. We are now accelerating research to achieve early clinical entry.

Status and Challenges of Vaccine Adjuvants

Market and vaccine adjuvants competitors

Forecast of vaccine adjuvants

Growth markets, infectious diseases and cancer



Major Launched Vaccine Adjuvants and Indications

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

Issues of products on the market

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

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

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* Global Vaccine Adjuvants Market Outlook (2017-2026)

Let’s move on to page 24. This shows the current status of vaccine adjuvants. The graph on the left shows our forecasts for the vaccine adjuvant market, and as you can see, the adjuvant market is expanding in both the infectious-disease and cancer fields.

The graph on the right shows vaccine adjuvants that are already on the market, as well as their indicators. So various adjuvants are already available, but there are issues with them, including side effects such as inflammation. These adjuvants induce humoral immunity but they have a weak point of weak induction of cellular immunity. We therefore believe that a safe adjuvant that induces cellular immunity is required.

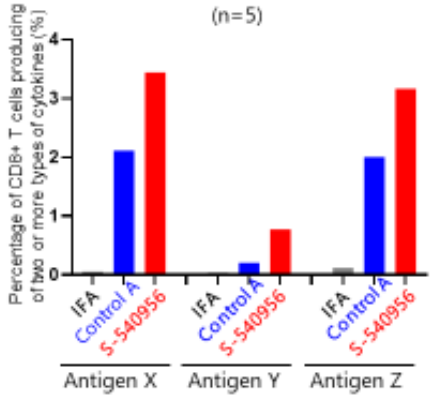
S-540956, Nucleic Acid TLR9 Agonist

Features of S-540956 (non-clinical)

Excellent immune enhancement

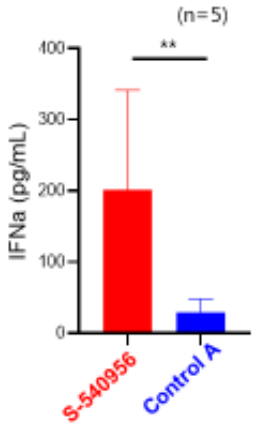
Evaluation of functional CTL induction

(Cytokine evaluated: IFNγ/IL-2/TNFα)



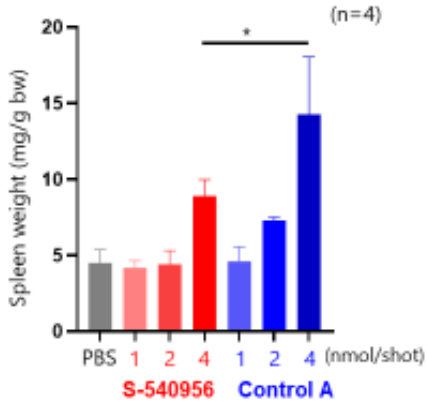
High IFNα induction

In vitro evaluation of human PBMC



Low safety concerns

Effects on the spleen



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

Day0, 2, 4: Intramuscular injection
Day7: Mesurement

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

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

Let's go on to page 25. Last fiscal year we told you about the TLR9 agonist S-540956, and here we see its characteristics.

The graph on the left of page 25 shows that typical adjuvants such as Montanide do not induce CTL at all with respect to various antibodies, while our S-540956 exhibits extremely powerful CTL inducibility. It also exhibits superiority over existing adjuvants.

The graph in the middle shows productive induction of IFNα in vitro with human PBMC.

The graph in the right shows that spleen enlargement is suppressed to an extremely high degree compared with existing products, and indicates that there are few safety concerns.

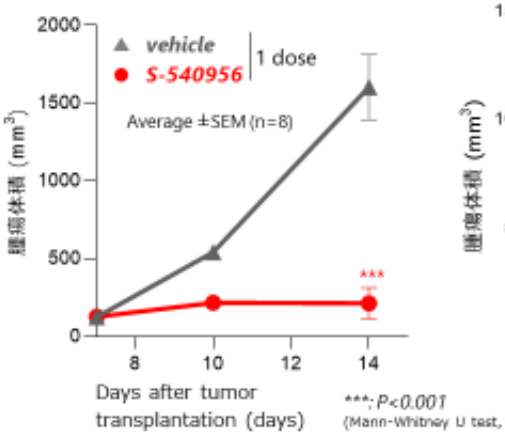
Antitumor Effect of S-540956 (Sole Administration)

Showing efficacy by intratumoral and subcutaneous administration

Lymphoma model

Antitumor effect of intratumoral administration

(Effective at 1/10 dose than subcutaneous administration)

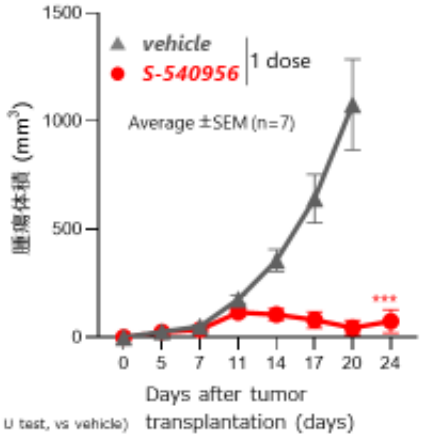


***: P<0.001
(Mann-Whitney U test, vs vehicle)

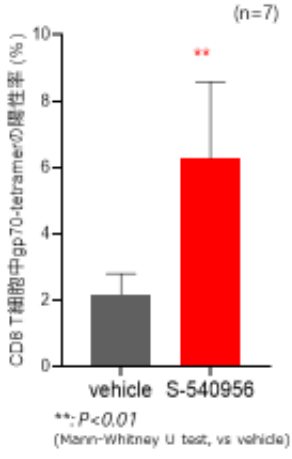
Colon cancer model

Subcutaneous administration distal from the tumor

Antitumor effect



CTL inducibility



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

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

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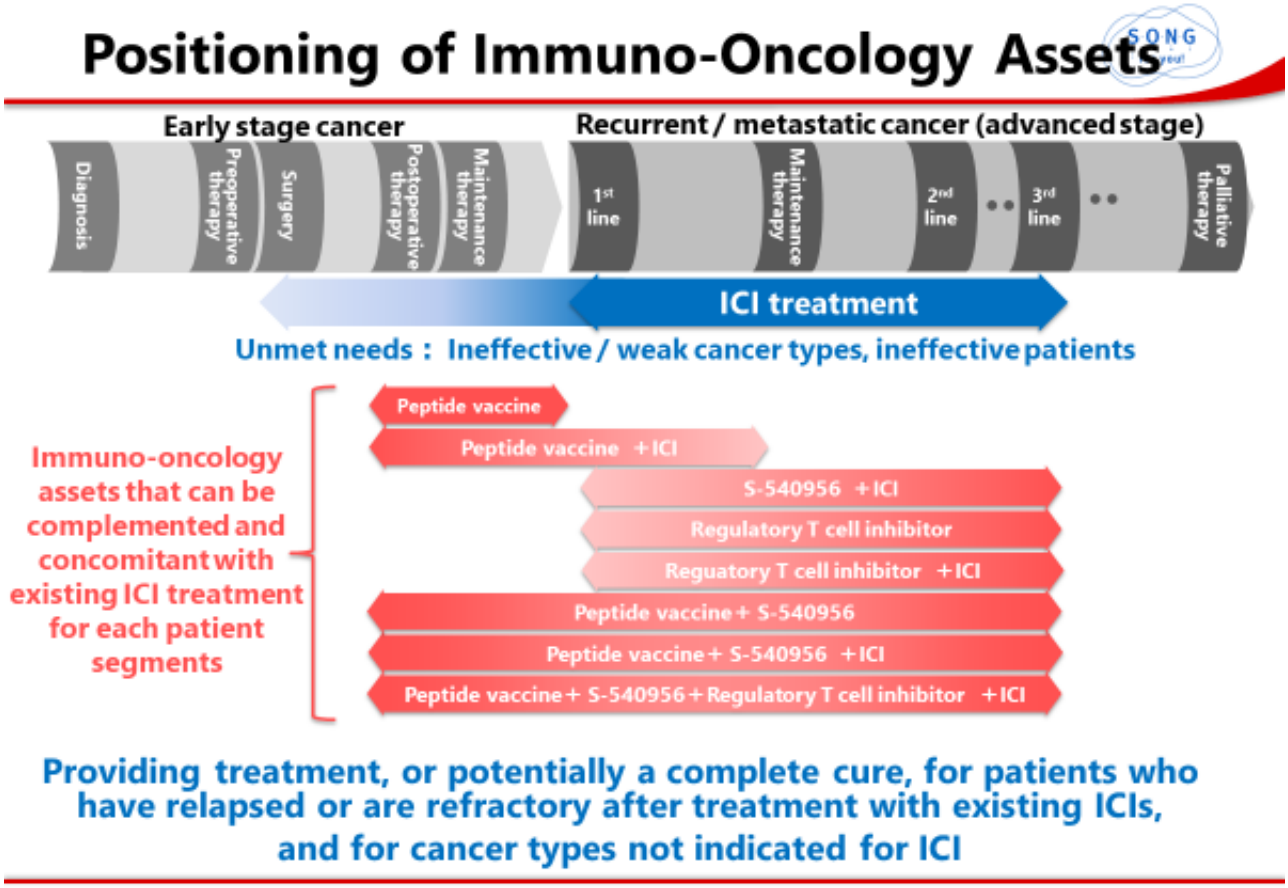
CTL: Cytotoxic T cells

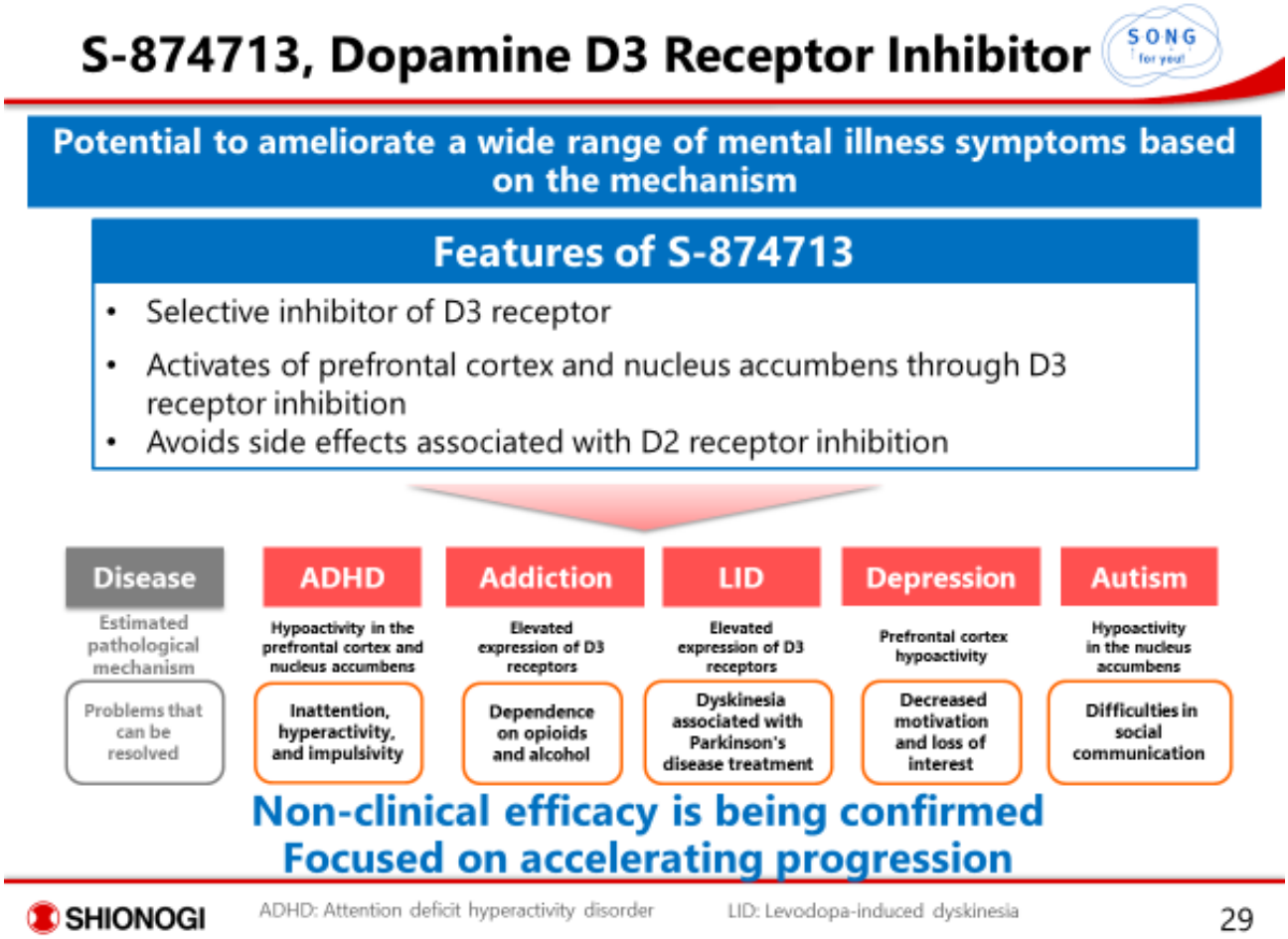
Let's move on to page 26. This shows that when S-540956 is administered alone, even when only the adjuvant is administered, there is still an anti-tumor effect, but the graph on the right shows the results of an experiment where the adjuvant was administered directly into a lymphoma, and as there is powerful suppression of the tumor.

Our S-540956 is superior to previous products in that it has high transferability, in that it travels into the lymph node when injected subcutaneously, and as you can see from the middle graph, even when it is subcutaneously injected far away from the tumor, it exhibits anti-tumor efficacy.

The graph on the right shows CTL inducibility.



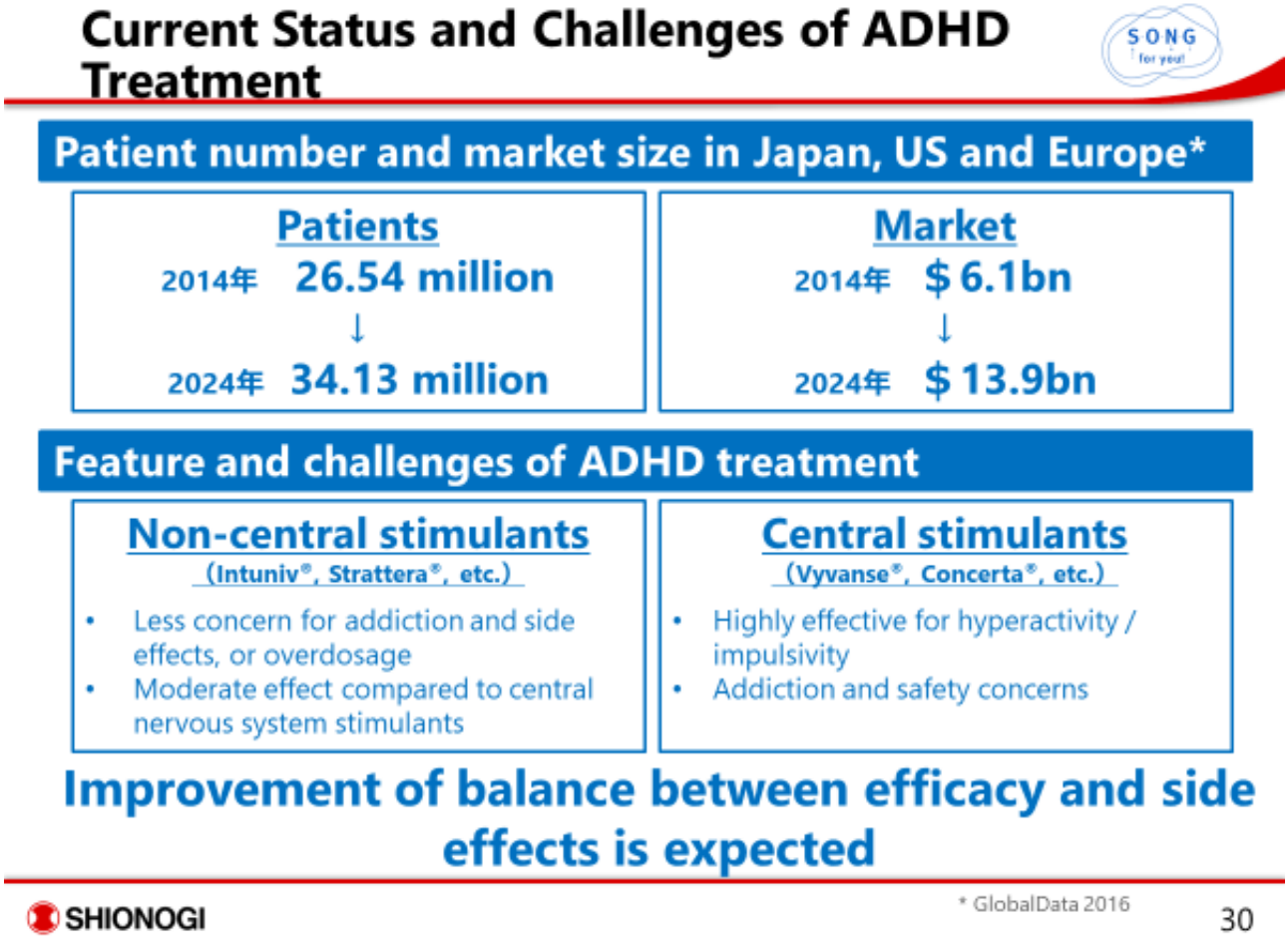
Let’s turn to page 27. As you can see, at present, treatment involving immune checkpoint inhibitors is mainly used with advanced-stage cancers, and considerable efforts are being made to expand its application to early-stage cancers, but in the case of patients for which it is ineffective, by combining our assets in this way, we hope that we will be able to achieve broad application, and ultimately, to provide treatment methods that can be expected to cure the disease completely.



Next I'll discuss psycho-neurological diseases. It's on page 29. Recently, our in-house research has led to the discovery of a compound called S-874713 that is a selective inhibitor of the dopamine D3 receptor to an extremely high degree. The characteristic feature of this compound is that it is a strong inhibitor of the D3 receptor. Compared to other nucleic receptors, it is over 5,000 times more powerful. And it is also exhibits more than 4,000 times the selectivity toward D2, through this D3 receptor inhibition, prefrontal cortex and nucleus accumbens are activated.

With respect to D2, it has, as I mentioned earlier, over 4,000 times the selectivity, tso this compound can also prevent side-effects caused by D2.

Regarding future disease applications, it is expected to be applicable to huge number of psycho-neurological diseases, including ADHD, addiction, dyskinesia, depression, and autism, and we are currently in the process of formulating a strategy concerning which indications to address first.

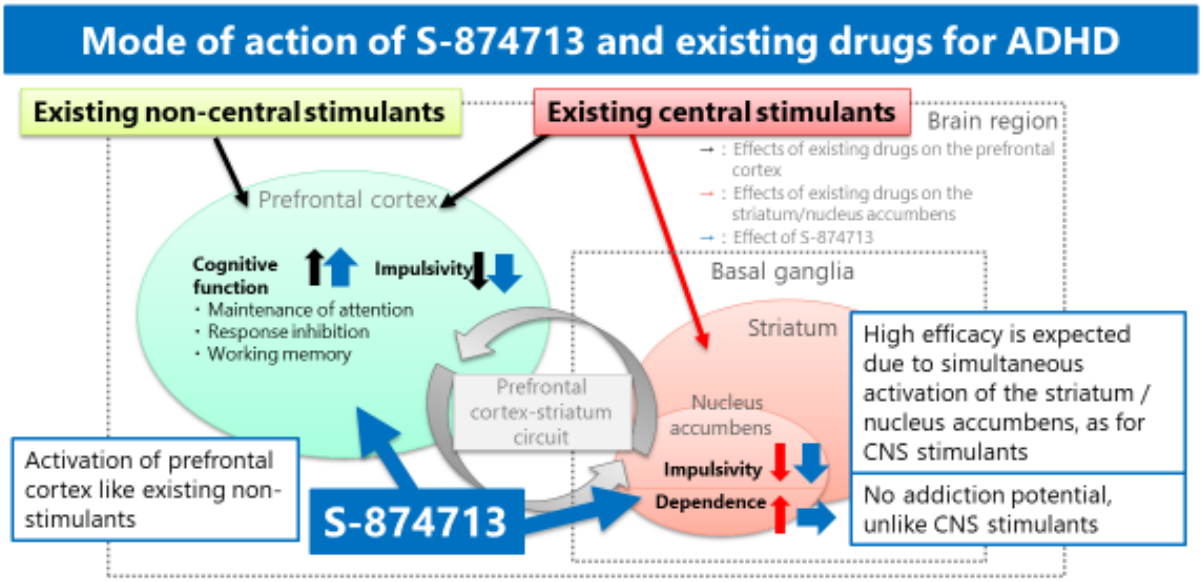


An example of this is shown on page 30. I'd like to show you some data regarding ADHD, a disease that we already offer products for.

As you all know, ADHD drugs comprise non-stimulants and stimulants. With non-stimulant drugs, such as our product, Intuniv, there is little concern about addiction or side-effects. And while Intuniv is effective for inattention, the effect is slightly weaker than that of stimulants.

Stimulants, which are shown on the right, are highly effective for hyperactivity and impulsivity, but there is a slight risk of addiction or safety, so going forward, a balance needs to be struck between effectiveness and side-effects.

Mode of Action of S-874713



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

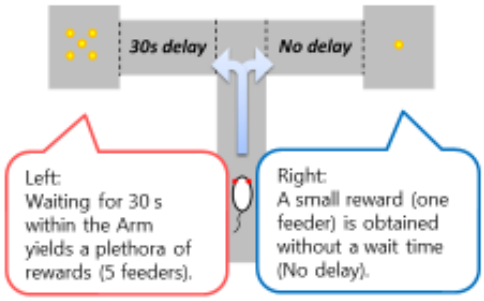
Let's go on to page 31. The non-stimulants I referred to earlier are indicated by the black lines at the top left, and they act upon the prefrontal cortex, improving cognitive function and reducing impulsivity. Stimulants, on the other hand, act not only on the prefrontal cortex, but also on the striatum and the nucleus accumbens of the basal ganglia, which means that they are more powerful, as they further reduce impulsivity. However, addiction may occur.

D3 antagonists act on both, so they are almost as effective as stimulants, while not resulting in addiction. They therefore have extremely superior characteristics.

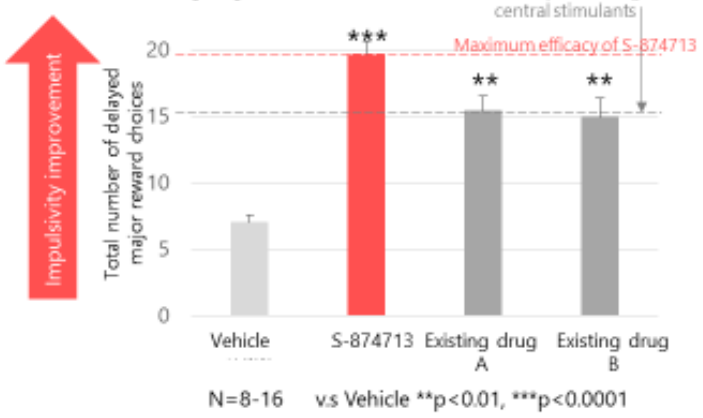
Pharmacological Action of S-874713

Potential for greater efficacy than existing non-stimulants

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



Impulsiveness evaluation (non-clinical)



N=8-16 v.s Vehicle **p<0.01, ***p<0.0001

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

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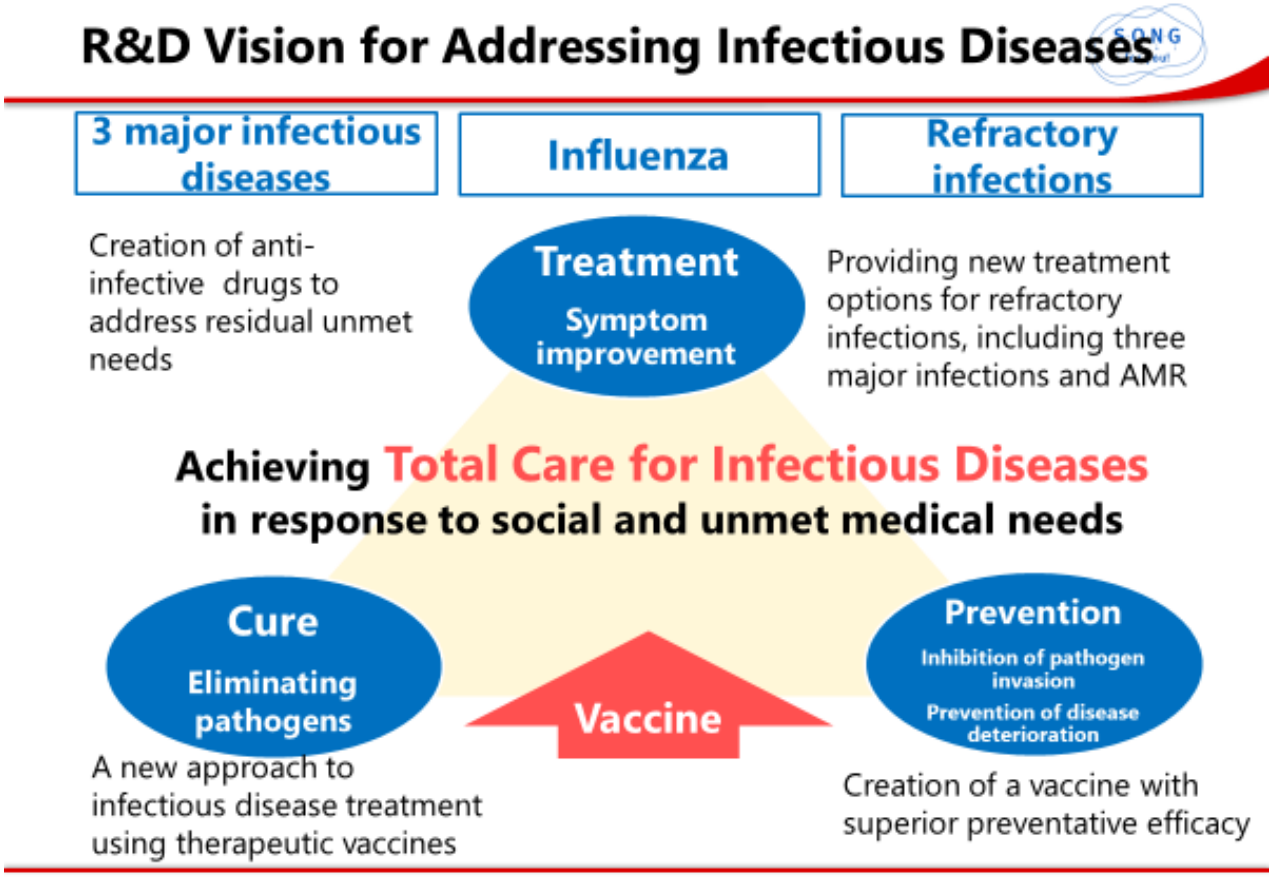
The results of a T-maze test are shown here on page 32. With this experimental model, a mouse was placed in this maze, and if it turned right, it would immediately receive one piece of food, whereas if it went left, the door wouldn't open for 30 seconds, after which it would receive a lot of food, though it would have to wait 30 seconds to get it.

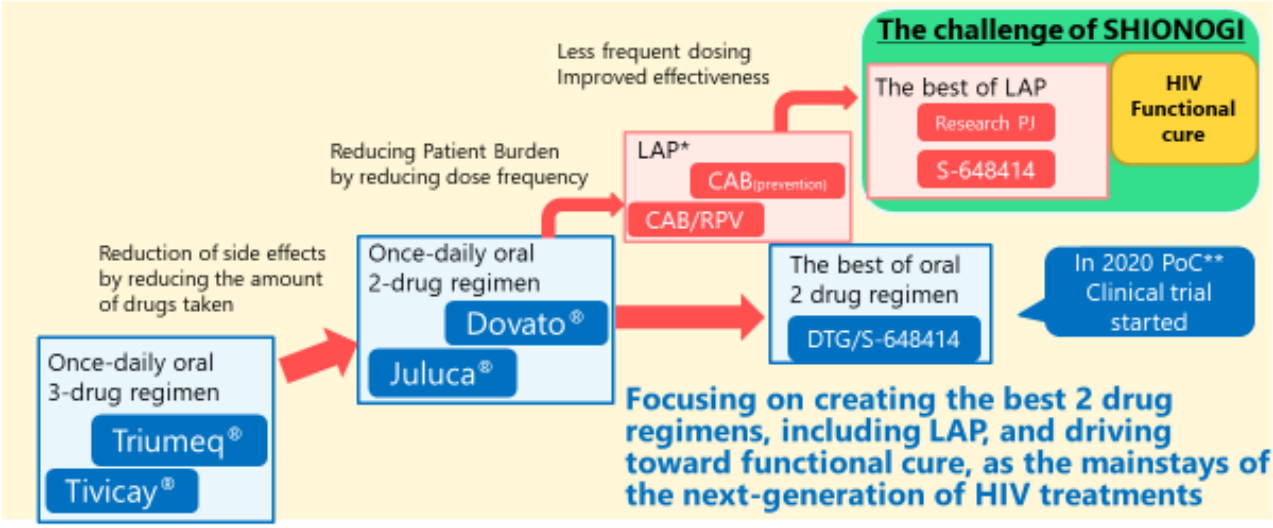
The experiment was repeated 50 times, and here we see the number of times that the mouse turned left. In comparison, the results were like this. With existing drugs A and B, the mouse went left 15 times out of 50. With S-874713, however, it went left 20 times, indicating greater efficacy than current non-stimulants in terms of controlling impulsiveness.



Continuing on, I'd like to discuss our progress in the field of infectious diseases. This is page 34. Until now we have focused on the three major infectious diseases, influenza, and refractory infections, and our R&D has primarily targeted the alleviation of symptoms. But now we're adding vaccines to the mix so we can get involved in prevention. We also want to try employing treatment vaccines to cure diseases.

Challenges for Developing Anti-HIV Drugs

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



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

Page 35 shows our challenges going forward in the realm of anti-HIV drugs. We want to employ S-648414, which we told you about last fiscal year, and create the best two-drug regimen.

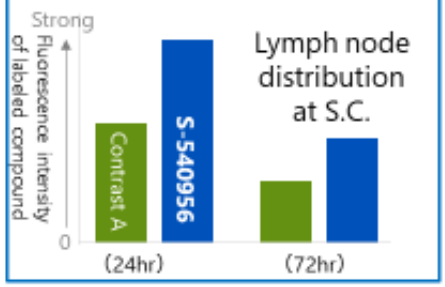
Having said that, the GE market, centered on dolutegravir, is expected to expand from 2028, and for the purpose of meeting needs that aren't met by once-daily oral pill regimens, namely the burden and stress felt by patients due to having to take their medicines every day, means that are long-lasting medicine that can be injected will likely become necessary in the future.

Furthermore, in addition to the drugs we're currently developing, we want to make an ideal long-lasting injectable regimen that contains S-648414, and after that we want to achieve a functional cure for a HIV, so we're currently pressing ahead with research to that end.

Efforts to Discover HIV Functional Cure

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

Lymph node transfer of S-540956



"Kick & Kill"

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

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

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

Regarding a functional cure, as I mentioned in my previous discussion of tumor immunity, we're conducting research using S-540956. S-540956 exhibits extremely high transferability to the lymph node. Because the HIV virus lies dormant inside lymph nodes, a "kick and kill" approach could perhaps be applied to wake up the dormant HIV virus, which could then be eliminated using drugs and the immune system, so we're currently pursing research in that area.

Entry into Vaccine Business

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

UMN Pharma

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

Characteristics of platform technology (BEVS) of UMNs

Four "S" enables stable supplies

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

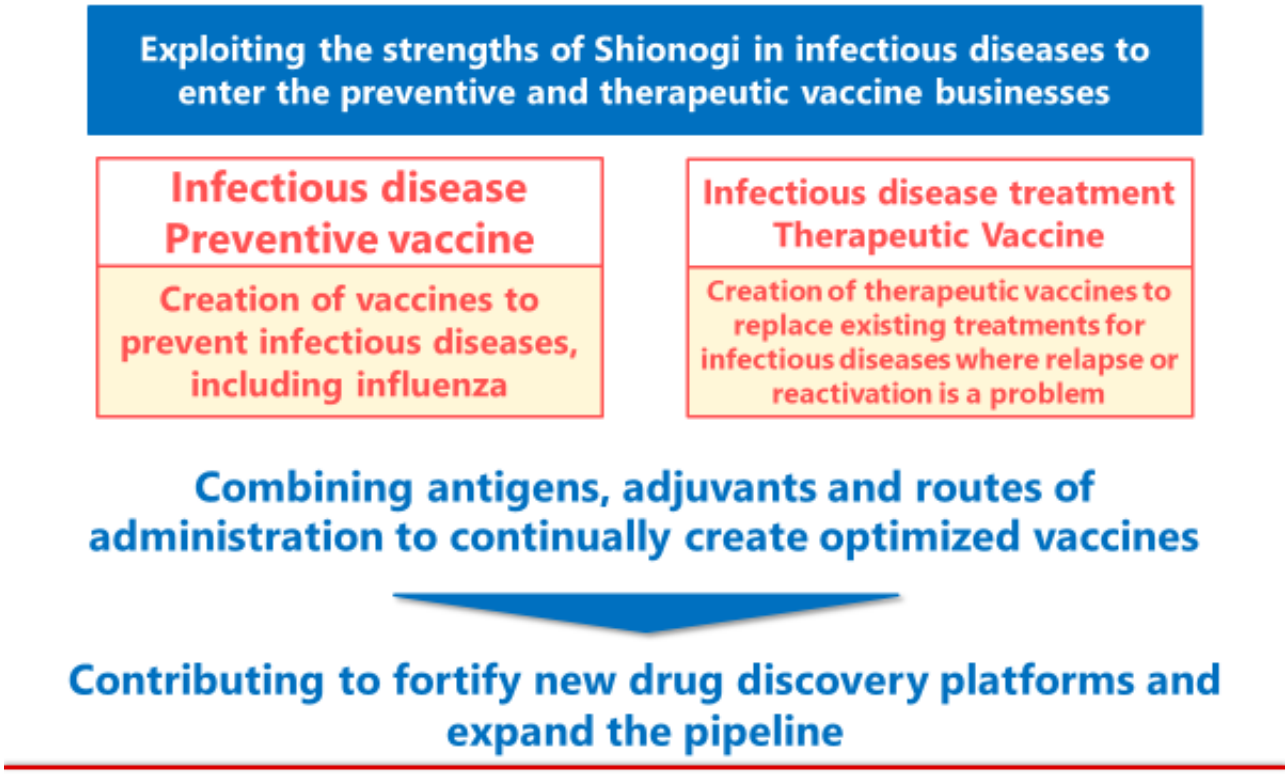
Starting with a **preventive influenza vaccine**

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

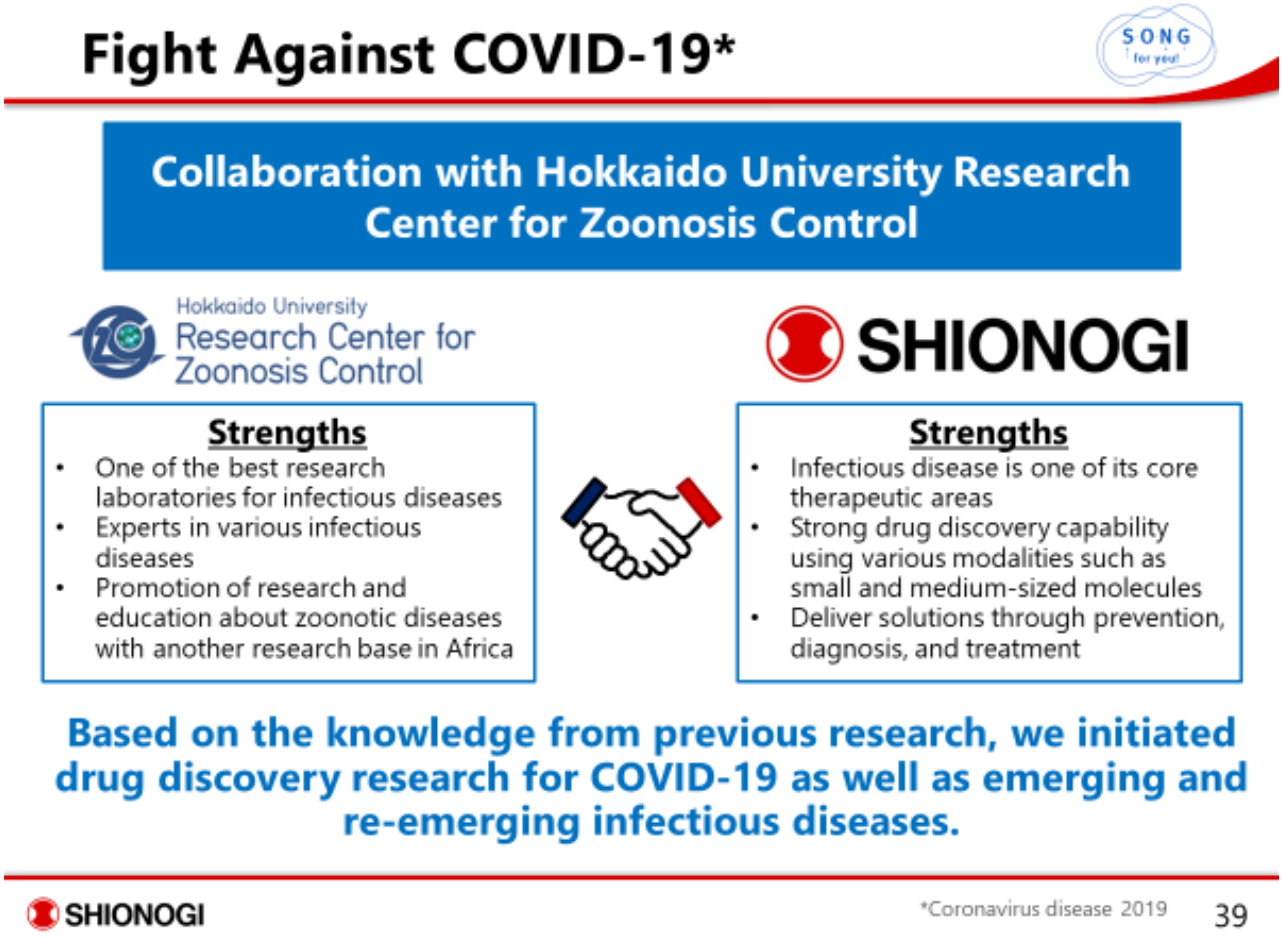
Regarding the vaccine business, you will be aware that we have acquired UMN Pharma, and yesterday, March 18, it became a wholly-owned subsidiary. So finally, the Shionogi Group is in the vaccine business, and we will be pushing forward with vaccine R&D by fully utilizing UMN Pharma's BEVS platform.

We're starting by working on a vaccine for preventing influenza, but we're currently thinking about second and third R&D themes to follow that.

Future Development of Vaccine Business



In the vaccine business going forward, we intend to work not only on vaccines for disease prevention, but also on vaccines that could treat or cure new-emerging or re-emerging infectious diseases.



I'd now like to talk a bit about what we're doing to tackle the novel coronavirus, which is currently causing unease and posing a threat all around the world.

We have had a research center at Hokkaido University for some time, and we have been collaborating with the University's Research Center for Zoonosis Control for many years. Even before this novel coronavirus emerged, we had actually been conducting research on new drugs for treating coronaviruses. So by combining the respective strengths of Hokkaido University and Shionogi, we have begun drug-discovery research using the novel coronavirus.

Exploratory Data About the Novel Coronavirus (flash report)

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

(EC_{50} : μM)

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

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

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

We moved quickly to use a sample of the novel coronavirus supplied by the National Institute of Infectious Diseases to build an assay of the virus, and at the end of last week were finally able to produce a reliable assay method, and from this week we have started applying compounds.

As you know, we have been conducting R&D on anti-viral drugs such as Dolutegravir and Xofluza, so we possess an incredibly varied library. From this library, our researchers have selected promising ones based on their own experience, and we have currently started assaying, but, for example, we have found that this compound, shown here as Compound-1, exhibits an extremely powerful action of 0.1 μM against the novel coronavirus.

Because throughput is still poor, I can't show you any results today, but, for example, Compound-2 and Compound-3, which have a completely different structure to our Compound-1, are somewhat effective against existing coronaviruses. If you compare the Compound-1 data for the novel coronavirus with that for a previous coronavirus, you will see that Compound-2 and Compound-3 could also be promising.

Regarding targets, we've also included data here on Remdesvir and Favipiravir, which are currently undergoing clinical trials, but we want to show that even compared with drugs like those, Shionogi possesses compounds that are by no means inferior.

Fight Against COVID-19*

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

Difficulties in the current diagnosis

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

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

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

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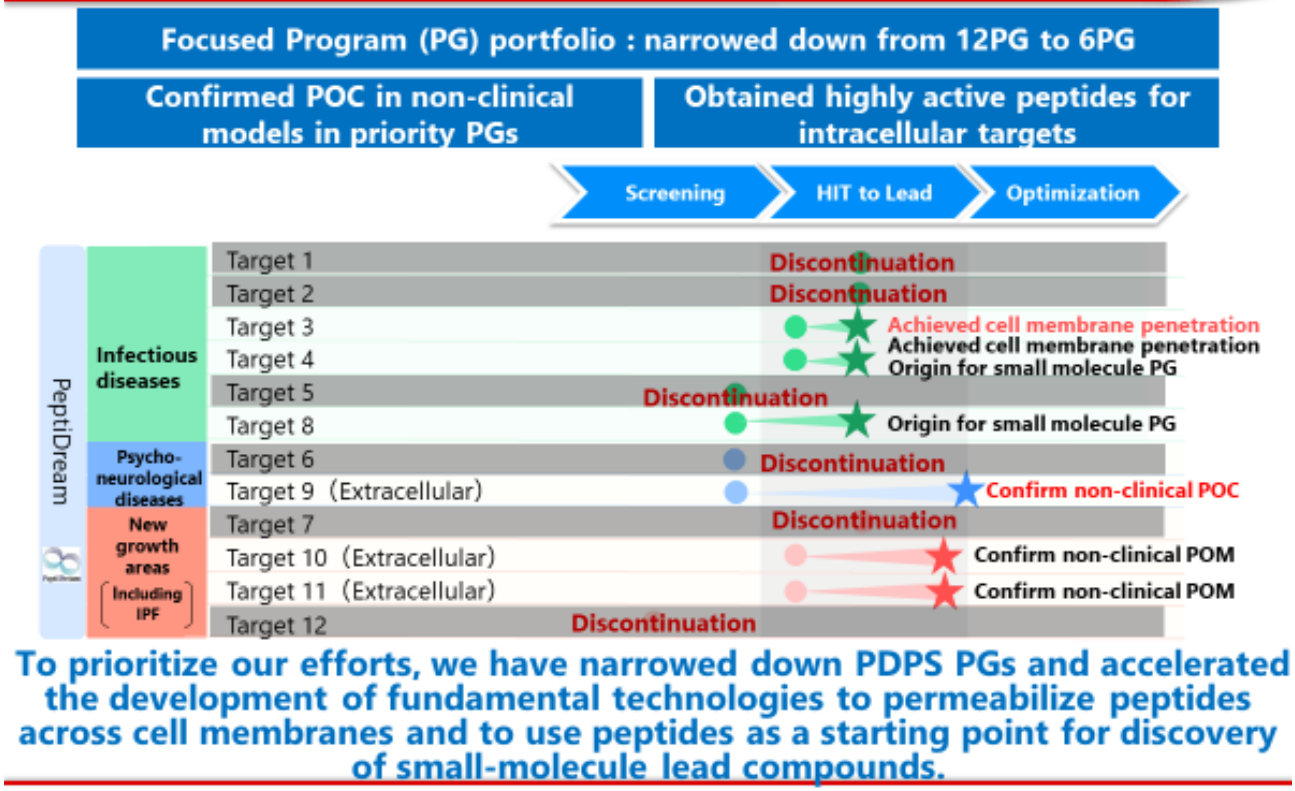
*Coronavirus disease 2019

This concerns diagnostic drugs. This week, we've issued a press release about this, but we have started working with Micro Blood Science to introduce a test kit that simultaneously measures both IgG and IgM antibodies, and produces test results in ten minutes with just one drop of blood from a finger.

Obviously, the PCR test, which is administered by the national government, is an essential test method for identifying patients. However, throughput remains poor, and the test method we are planning to offer would not replace the PCR method. Rather, the respective advantages of both methods could be put to use in different situations, which we hope would help to relieve the current turmoil in society.

Progress in Peptide Drug Discovery



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

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As of Mar. 2020
As of Mar. 2021

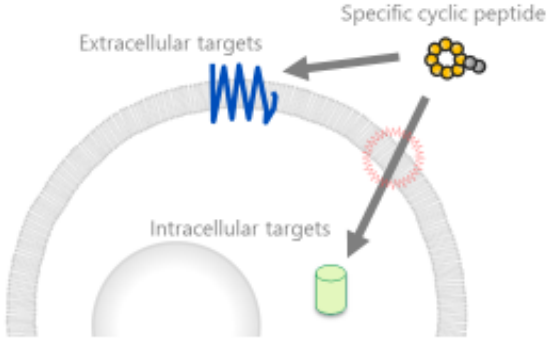
PDPS: Peptide Discovery Platform System
IPF: Idiopathic Pulmonary Fibrosis
POC: Proof of Concept
POM: Proof of Mechanism

Finally, I'd like to talk a little about our progress with peptide drug discovery. We have deployed a PDPS, making us able to obtain good peptide seeds and hits for various targets extremely rapidly.

We have declared that we are to begin non-clinical development during this fiscal year, and we have already confirmed non-clinical PoC for extracellular Target 9. And based on a strategy of select and focus, we are pouring resources into this theme.

Expectations and Challenges for Peptide Drug Discovery

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



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

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

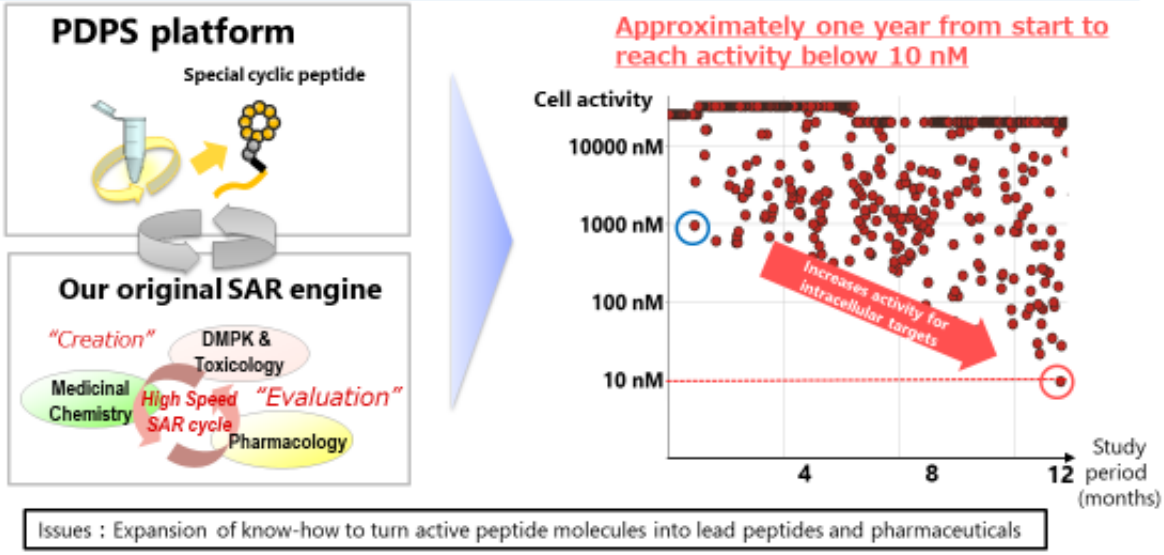
Combine our small molecule drug discovery capabilities with PDPS technology to establish a unique peptide drug discovery platform for highly difficult drug discovery targets

On the other hand, during this process we have also become aware of various problems. This is on page 44. Regarding extracellular targets, good ones can be obtained relatively rapidly, but with intracellular targets, drug discovery involves suppressing the intracellular target by getting the peptide through the cell membrane into the cell, but this is extremely difficult. The same is true worldwide, and every company is struggling.

In view of this, want to have a platform for peptide membrane permeation technology, and because we have confidence in small-molecule drug discovery, we are moving forward in two directions to building a platform for technology for converting peptides into small molecules as well as peptide membrane permeation.

Establishment of Technology for Cell Membrane-Permeable Peptides

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



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

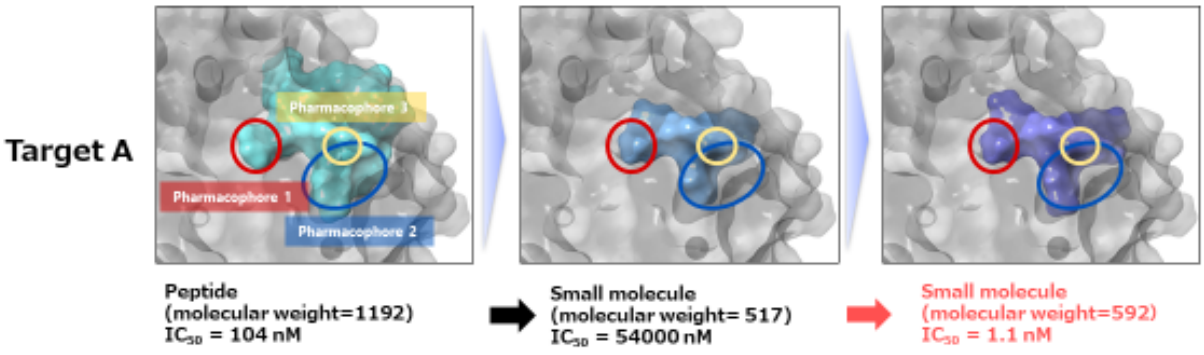
Structural optimization of intracellular target-directed PDPS hit peptides to obtain lead peptides

Page 45 concerns membrane-permeable peptides. If you look at the graph on the right, you'll see that all the drugs here are compounds that are known to be active by enzyme assay. With cells, they are not active. In other words, they do not permeate the cell membrane, but we have increased membrane permeability by 100 times in about a year, and become able to identify compounds that also work on cells.

At first glance, it may look as though we've just picked up ones we can make at random, but that isn't the case. We have now accumulated knowledge about what sorts of compounds they are, and what sorts of peptides can pass through membranes. Going forward, I believe that we may, conversely, be able to identify which membrane-permeable peptides in our library will be hit compounds.

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

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



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

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

This is page 46. This concerns small-molecularization technology, and our future goal with peptides is to cure disease with protein interactions, so it won't be adversely affected by factors such as conventional high-throughput screening.

These are images of the bonding of peptide hits with a target. It shows IC50 at the 0.1 micro level, and the molecular weight is 1,200. It can't get through the cell membrane. In contrast, these red, yellow, and blue pharmacophores are identified, and when a small molecule with such properties is designed and bonded, the molecular weight drops to half but activity also disappears.

With regard to these, if we leverage the SAR engine of small molecules we have already cultivated, in just a short period of time, actually about three or four months, we have increased activity by 50,000 times without increasing molecular weight. We're proud to say that this is technology that other companies have difficulty emulating.

Research

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

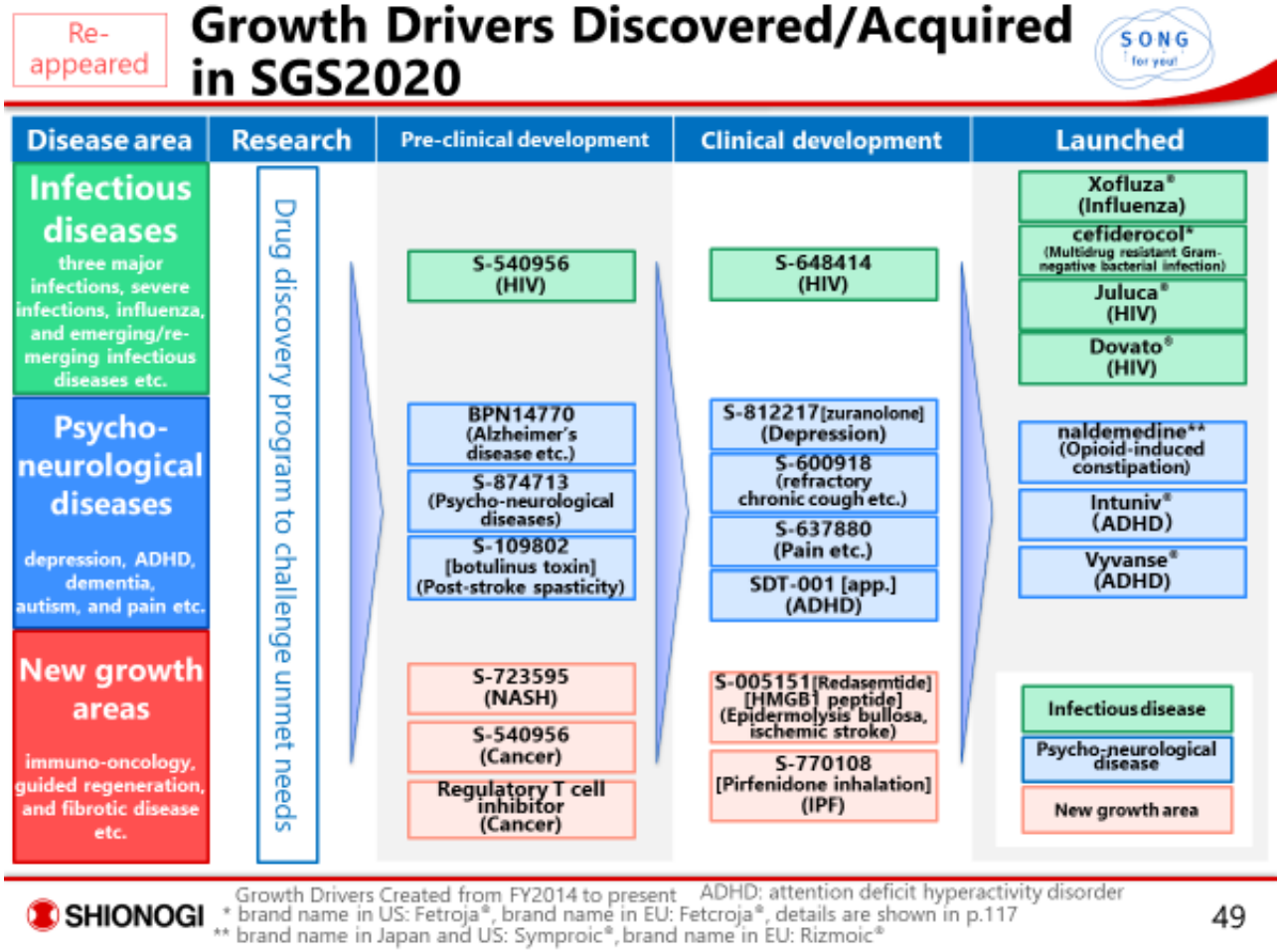
Progress research activities for core pipeline assets to initiate clinical development and continuously create new growth drivers

It was a bit hurried, but regarding the compounds I've told you about today, the Treg inhibitor will see the initiation of clinical study in FY2021, while in the case of the others, I believe clinical study can be initiated in FY2020, so during the next fiscal year.

As for a vaccine to prevent influenza, we have already finished selecting candidates, and are currently gearing up for GLP testing, so clinical study will probably be initiated in FY2021, and I hope you will look forward to it.

Thank you very much for your attention.

Kyokawa: Now let's move on to Iwasaki, who's going to talk about development.



Iwasaki: I am Iwasaki. I will explain about the development part.

Page 49 shows the growth drivers we have discovered and acquired in the SGS2020. This table classifies the growth drivers in disease areas of infectious diseases, psychoneurological diseases, and new growth areas, and shows the items in pre-clinical development stage, in clinical development stage, and launched items.

Development

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

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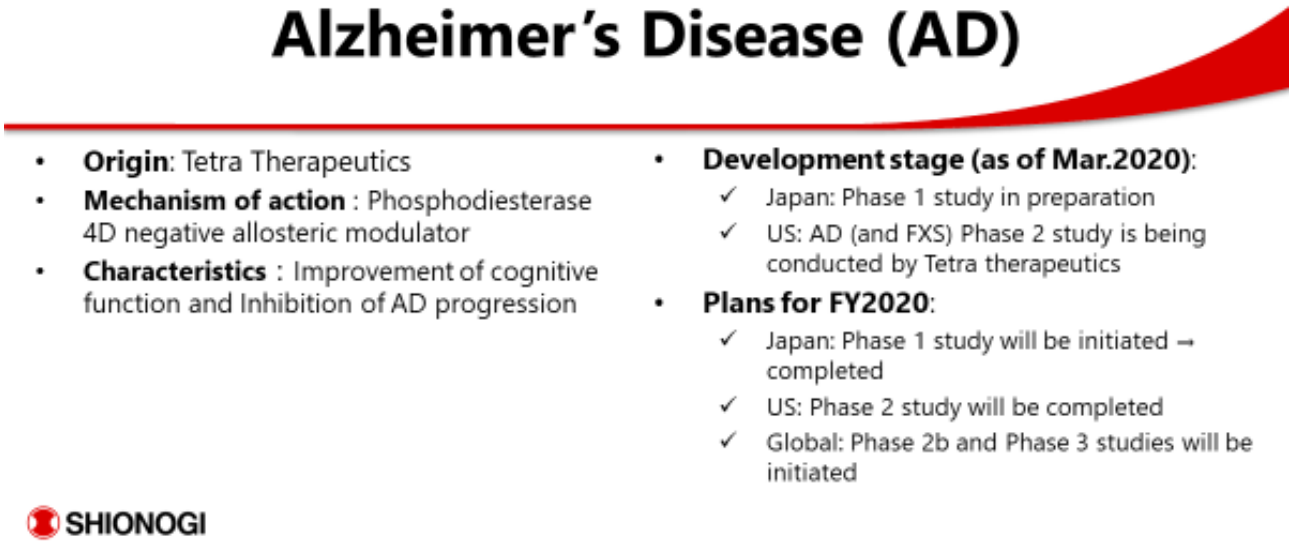
Projects in red are core pipelines with which we desire paradigm shift of disease treatment

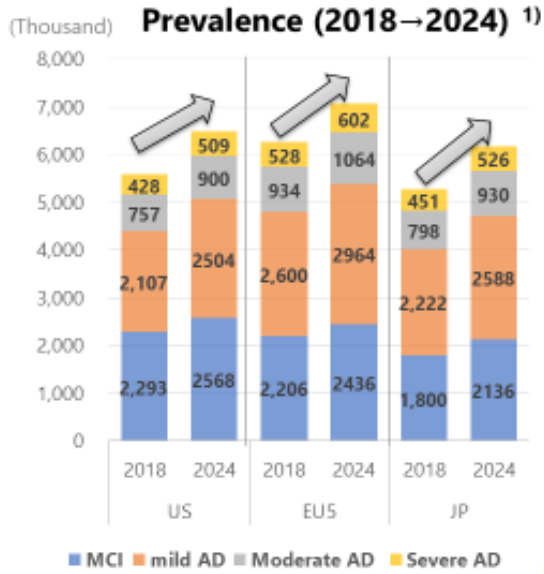
* S-812217: Phase 3 studies are being conducted by Sage

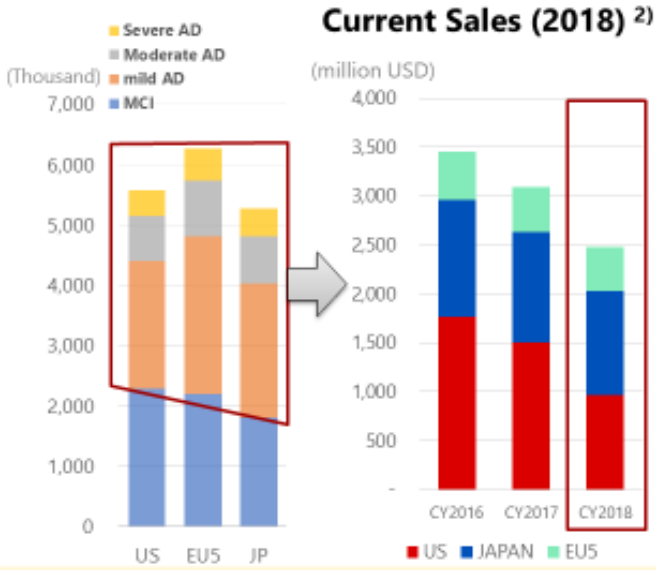
Page 50 shows the current stages of our development projects as a whole. Today, I would like to explain mainly about the items written in red, which are the items that we as the Development Headquarters should particularly focus on.



Next, page 51. BPN14770 is a drug introduced from Tetra Therapeutics. Its mechanism of action is phosphodiesterase 4D negative allosteric modulator. The development stage in Japan is Phase 1 study in preparation. In the US, Phase 2 study is being conducted targeting Alzheimer's disease.

Sales forecast in AD





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

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

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

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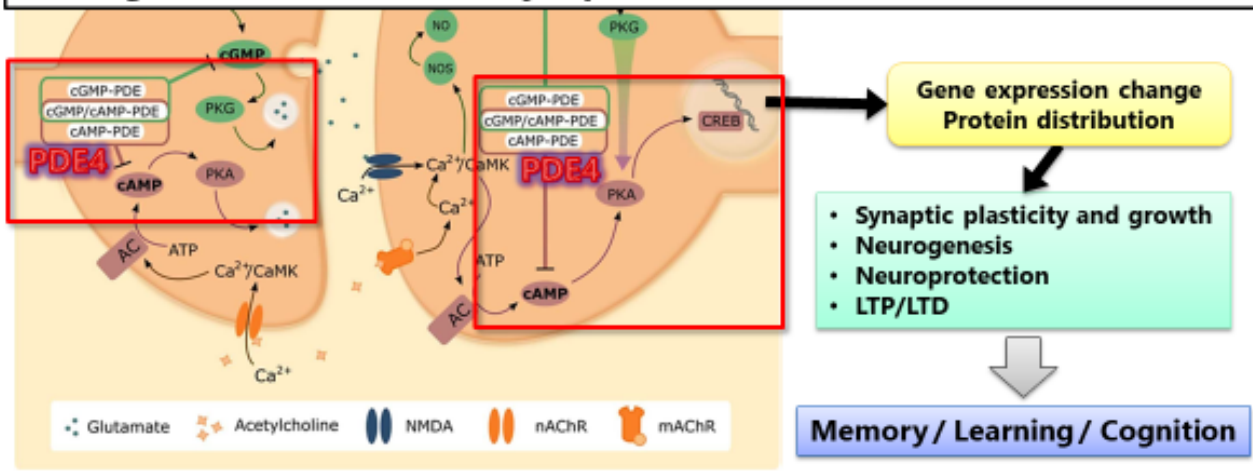
1) Decision Resources Group Landscape & Forecast Alzheimer's Disease June . 2019 2) IQVIA Analytics Link
3) Mild Cognitive Impairment 軽度認知機能障害 4) Alzheimer's disease アルツハイマー型認知症

Page 52 shows sales forecast in AD. The number of AD patients, including mild cognitive impairment (MCI) patients are expected to be very large in all of Japan, US, and Europe. At present, the scale of sales of existing drugs has been shrinking year after year partly due to GE. But as I mentioned, this area still has potential to expand because drugs with new mechanisms of action can expand the target market to include MCI patients.

Characteristics of BPN14770

Phosphodiesterase (PDE) reduces cAMP in neurons

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



Gene expression change
Protein distribution

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

Memory / Learning / Cognition

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

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

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

Page 53 shows characteristics of BPN 14770. Phosphodiesterase, or PDE, decomposes cAMP and reduces cAMP in neurons. An increase in cAMP activates these PKA and CREB, causing gene expression change, which results in the enhancement of so-called synaptic or neuronal functions, as well as the enhancement of cognitive function.

As described here, this BPN14770 enhances cAMP signals by interfering with PDE4, thereby improving and maintaining cognitive function. This is our intended mechanism.

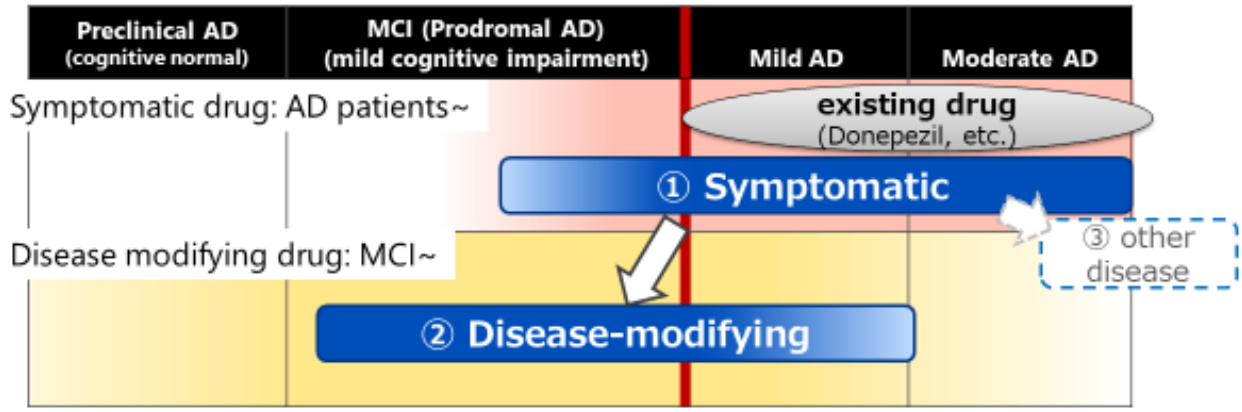
Position of BPN14770 in AD treatment

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

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

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

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



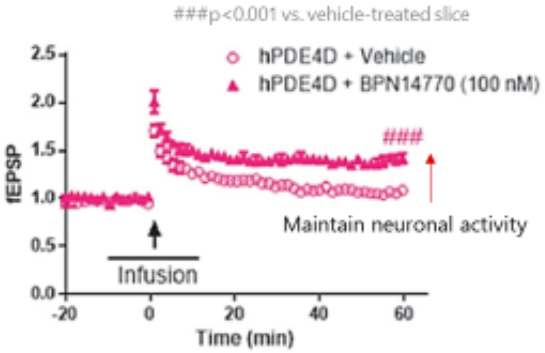
Page 54. Based on this mechanism, our position is, as shown here, to first aim at symptomatic improvement of mild or moderate AD patients with existing drug. Another aim is the disease-modifying effect for MCI or prodromal AD patients. We are expecting these two effects.

Non-Clinical Study: Symptomatic Effects

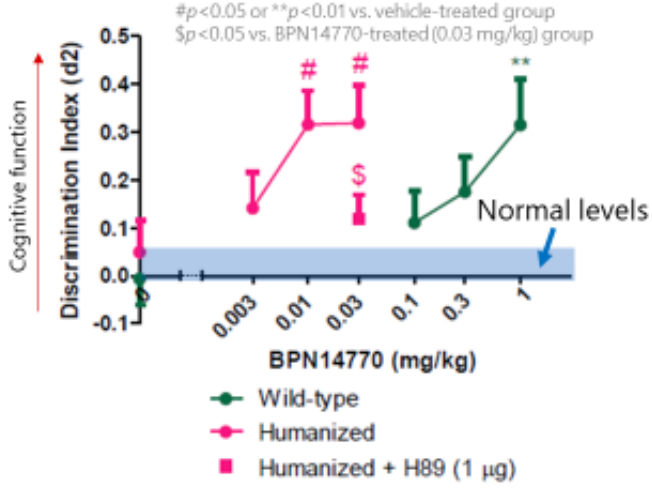
Effects on cognitive function (symptomatic)

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

Neuronal plasticity (synaptic LTP)



Cognitive function (novel object recognition test)



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

I would like to explain evidence for these aims on the next page, Page 55. First is the effect of improving the cognitive function. The graph on the left shows potential difference along the ordinate. This red curve above is the group to which BPN14770 was administered. The lower curve is the control group.

When electrically stimulated, the control group recovers over time as shown here, while the group with BPN14770 does not recover but maintains the neural activity. This indicates that neurons remain activated, and the status of being activated results in the improvement of memory function.

The graph on the right is data obtained by using mice. Mice recognize everything as new thing. So first we put mice in cage with an object. One day later, put the same object or a different thing. The test sees whether the mice recognize an object after a day, to figure out how BPN14770 works to help retain memory.

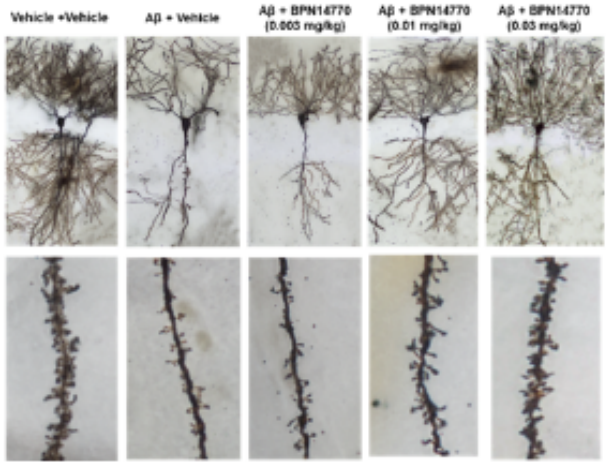
The graph shows cognitive function on the ordinate and concentration of BPN14770 on the abscissa. As you can see, mice with BPN14770 show the improvement in cognitive function in a dose-dependent manner. Based on these data, we have concluded that BPN14770 can help symptomatic improvement of cognitive function.

Non-Clinical Study: Inhibition of AD Progression

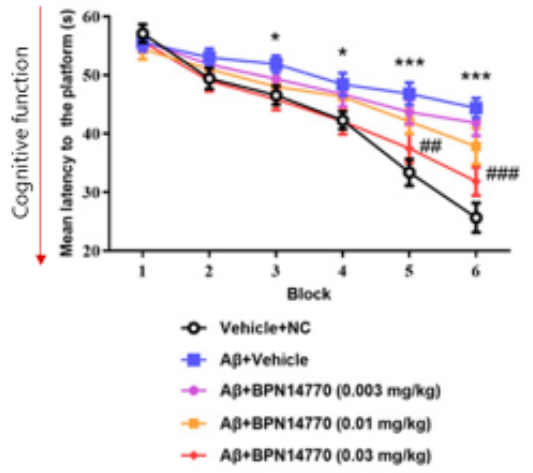
Effects on neuronal impairment (inhibition of AD progression) in hippocampus β-amyloid (Aβ) infusion models

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

Neuronal impairment
(Golgi staining, CA1 in hippocampus)



Cognition (Morris Water Maze test)



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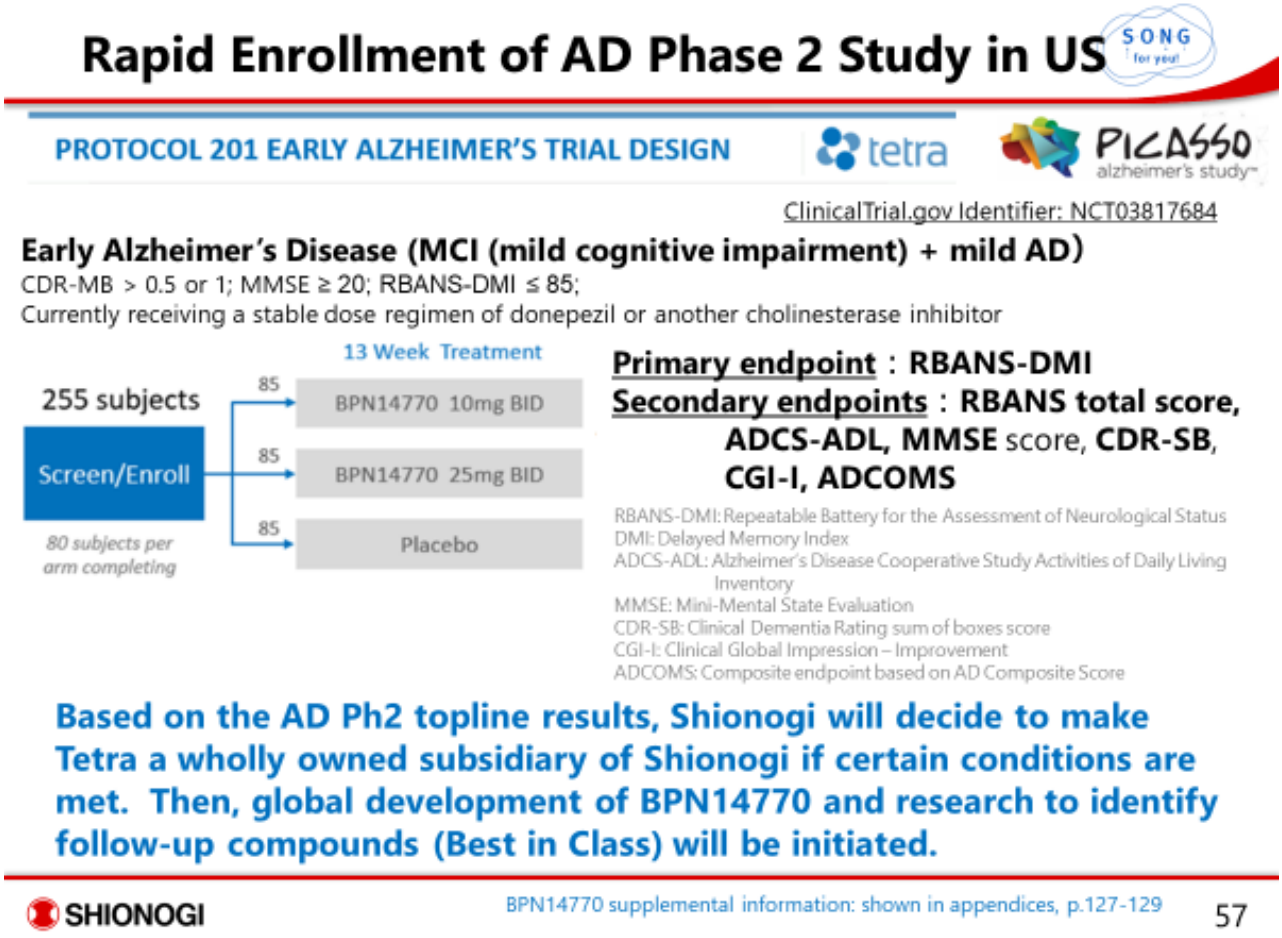
Cui SY et al., J Pharmacol Exp Ther. 2019;371:250-259

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

As for the effect of inhibition of progression, please take a look at the data here on page 56. The figure on the left shows neuronal impairment due to β amyloid. When neuronal impairment occurs, dendrites shrink like this string, and as shown in the figure below, spines decrease.

By administering BPN14770, such reduction of dendrites and spines could be controlled. Based on these data, we expect BPN14770 has the effect of inhibiting progression.

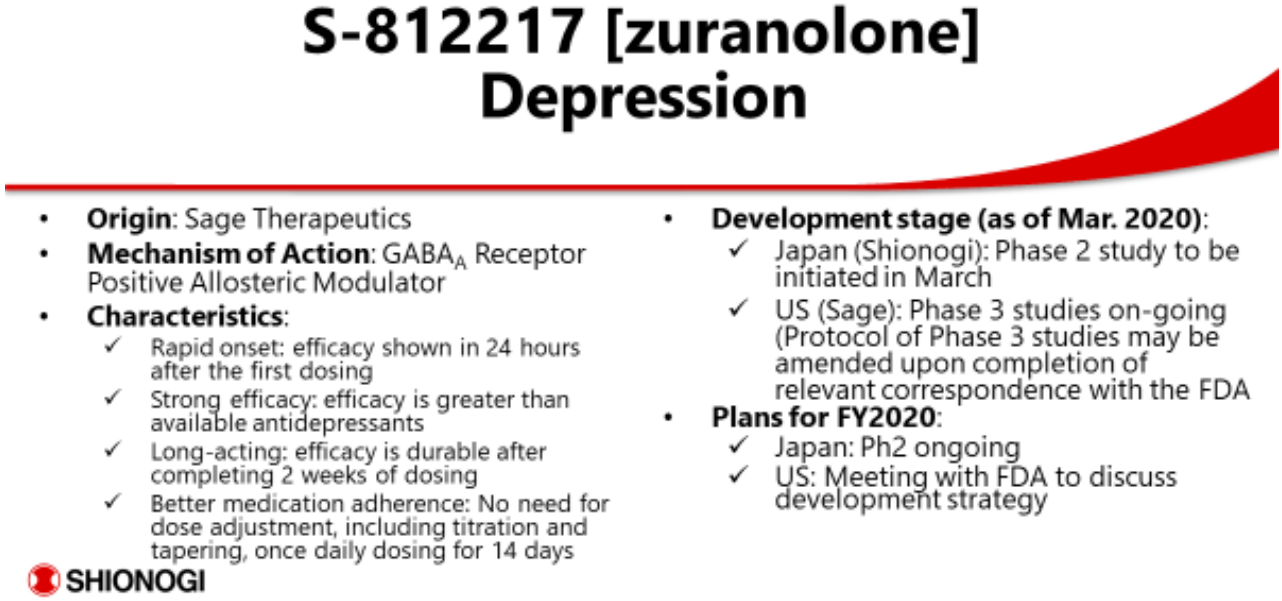


Based on these data, Tetra Therapeutics is currently conducting Phase 2 study. The progress is faster than we expected. This indicates great expectations for this drug. Based on non-clinical data or Phase 1, the study is now on 10 mg, 25 mg and placebo groups.

This PDE4 is said to have many side effects, such as gastrointestinal problems and nausea, and that is why other companies have dropped out of the development. However, in this profile, no such side effects have been observed in Phase 1. To further ensure safety, the study set this 25 mg group.

Primary endpoint is RBANS, which is used in trials for MCI, etc., and also MMSE, which is normally used in such AD development.

The results will soon come out. As soon as the results come out, since we are ready for Phase 1 and if the results are positive as expected by the public, we will promptly join the global study they are planning.



Let us move on to the next page. S-812217 (zuranolone), introduced from Sage Therapeutics. This has the mechanism of working as positive allosteric modulator for GABA$_A$ receptor.

Social impact of Depression in Japan

Antidepressant market & work productivity loss due to depression

5M Patients

- Ca. **5M patients** with depression in Japan[1)]
  - The most prevalent non-fatal diseases
- Current antidepressant market in Japan : Ca. **160 B yen**: Cymbalta® maintains top-share

160 B yen Market

40M days/year & 400 B yen losses

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

Major unmet medical needs with current therapies

Insufficient Efficacy

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

Slow Onset

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

Complicated regimen

- Dose adjustment is necessary to mitigate adverse events

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

Page 59 shows the social impact of depression in Japan. As you may know well, three major unmet needs with current antidepressants are shown here.

First, efficacy is insufficient. Our goal of drug treatment is to increase remission rate. But the remission rate after the first SSRI treatment did not reach 40%.

Second is slow onset. Normally, two to eight weeks are needed for onset of efficacy. Though some improvement is seen, prolonged debilitation and increased risks of deterioration or suicide are concerned during this period. Drugs with rapid onset of efficacy are desired by clinical doctors.

Also, because current drugs have adverse side effects on digestive system, complicated dose adjustment is necessary. Thus, development of drugs that satisfy these three unmet needs is strongly demanded.

Target Product Image

Novel antidepressant with breakthrough profile

<First-line antidepressant >

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

Unmet needs in depression treatment

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

zuranolone

Resolve unmet needs

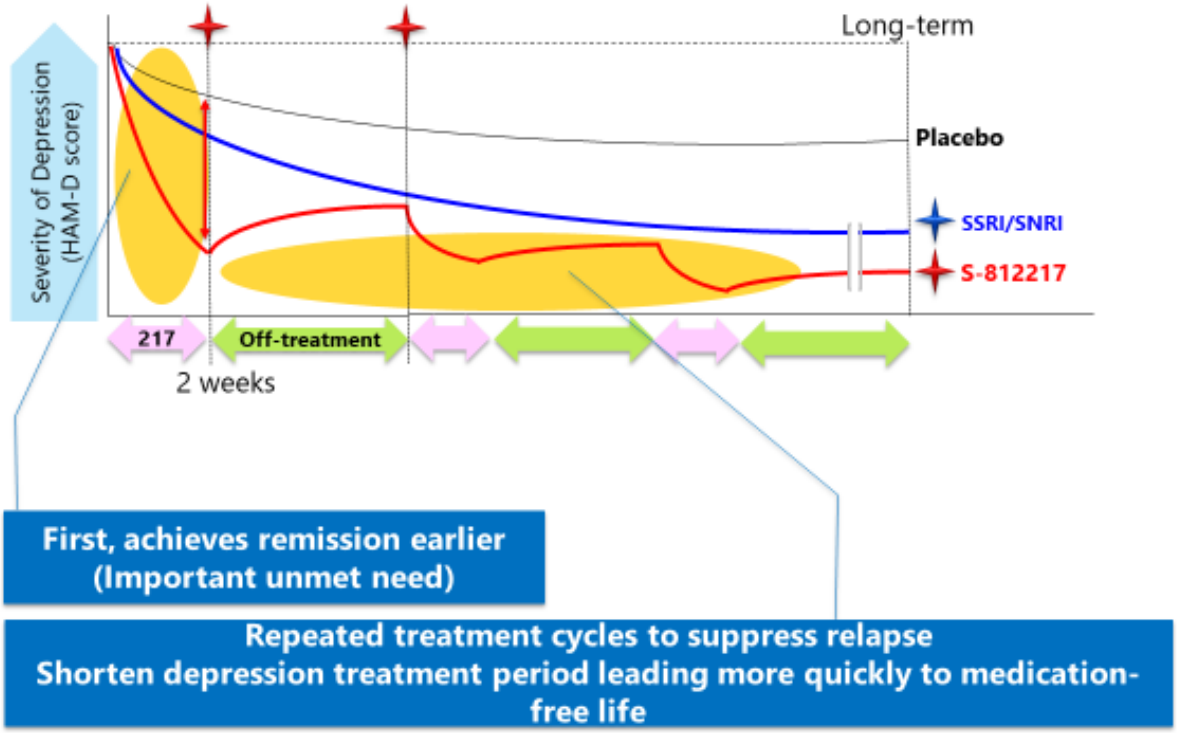
Values of S-812217

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

Potential to be effective across a broader range of depressant symptoms

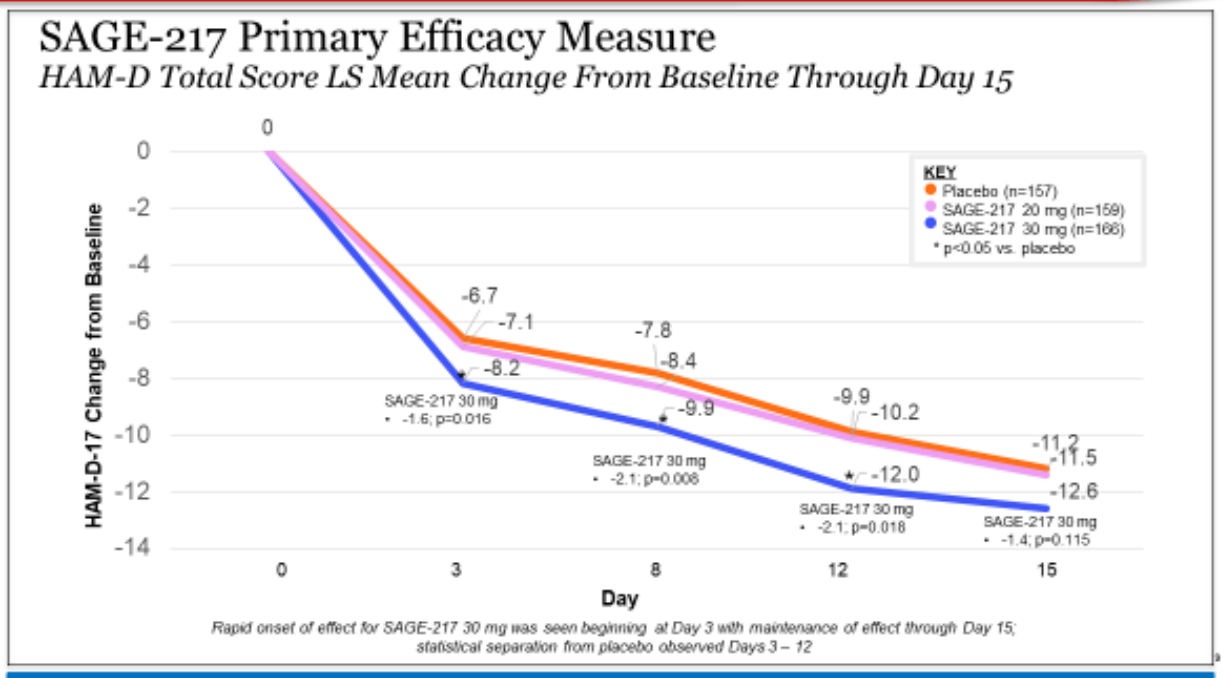
Page 60. With this S-812217 introduced from Sage, to satisfy these unmet needs first, we are currently planning Phase 2, aiming at three profiles: rapid onset, greater antidepression efficacy, and durable effect after two weeks of drug treatment.

Depression Improvement by S-812217



As shown here, existing antidepressant works slowly and maintains the efficacy. Zuranolone, which is administered for two weeks, works quickly within the two weeks. After some off-medication period comes the administration for two weeks. By repeating this cycle, rapid onset of greater efficacy, as well as reduced risk of side effects due to the off-medication period, can be expected. We are aiming at these profiles.

US Phase 3 Pivotal: Topline Results



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

SHIONOGI MDD-301 study, referring to the announcement on Dec 5, 2019 by Sage 62

As you know, it was revealed that data of Phase 3 conducted by Sage did not meet the primary endpoint. We have already discussed with Sage on this issue.

Our conclusion is that we will not change our profiles. This is the data in question. The 301 trial conducted by Sage measured the primary endpoint on Day 15.

But the values on Day 3, Day 8, and Day 12 are statistically significant and the HAM-D shows rapid onset of efficacy on Day 3. We therefore think that the data still shows the rapid onset and greater efficacy we are aiming at.

Next Step

zuranolone efficacy

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

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

We have experienced antidepressant studies with Duloxetine, etc. We have experienced failures in some of them. In the area of depression, where the placebo effect is often great, test results often include both failure and success, which we have experienced several times. Even though primary endpoint was not met just once, we think this data sufficiently reproduces the profiles we aim at. We will therefore conduct Phase 2 as planned and promptly advance to Phase 3.

Page 63 is a summary of what I said. We will thus continue on our development plans as usual.

S-600918
Refractory Chronic Cough etc.

- **Origin**: in-house
- **Indication**: Refractory chronic cough, Sleep apnea syndrome, Neuropathic low back pain
- **Mechanism of action**: $P2X_3$ receptor antagonist
- **Characteristics**:
  - ✓ Once-daily, oral
  - ✓ Well-tolerated safety profile

- **Development stage (as of Mar. 2020)**:
  - ✓ Global: Phase 2b dose finding study for refractory chronic cough is ongoing
  - ✓ Japan: PoC study for sleep apnea syndrome will start
- **Plans for FY2020**:
  - ✓ Preparation for other LCM indications

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Next is about our in-house origin S-600918. This is for refractory chronic cough. Mechanism of action is as : $P2X_3$ receptor antagonist.

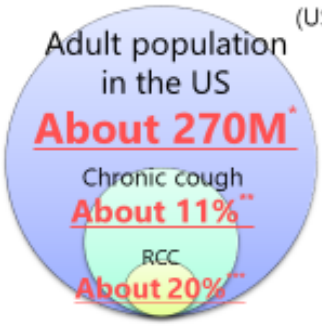
Development stage is Phase 2b globally, in Japan, US and Europe. In Japan, we are planning to start PoC for sleep apnea syndrome.

Contributions to Societal Needs

Refractory Chronic Cough (RCC)

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

Estimated number of RCC patients



About 6 million patients are suffering from RCC in the US

There are no approved drugs

Centrally-acting antitussives have CNS side effect concerns

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

GERD: Gastroesophageal Reflux Disease
* United Nations Population Database、** Song WJ et al.、2015、*** Levine BM et al.、2008

Refractory chronic cough, or RCC, is cough that lasts at least eight weeks caused mainly by asthma, sinobronchial syndrome, or GERD, or gastroesophageal reflux disease. This long-lasting cough makes patients feel reluctant to go out in public, worsening their QoL.

In the US, where the population is 270 million, there are no drugs for this disease, and therefore there are many unmet needs in this field. So we are conducting studies on this disease.

Presentation of PoC Study at ERS2019

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

Primary Endpoint: Cough Frequency in Daytime

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

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

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

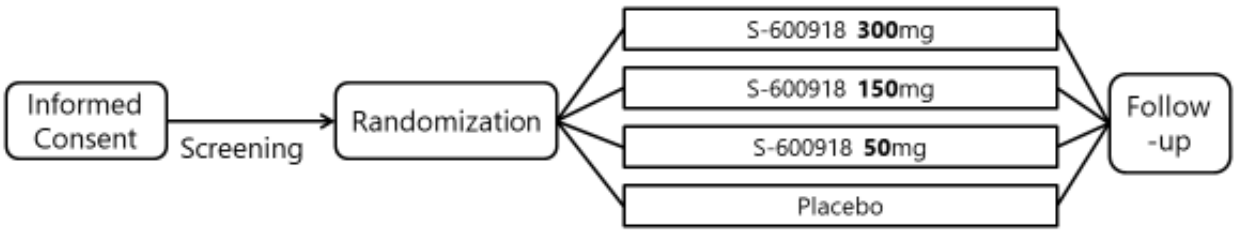
【Safety】
No significant difference in the incidence of AEs. Taste-related AEs, reported in similar drugs, was observed in 2/31 (6.5%) during S-600918 treatment.

This shows the results of the PoC study, which we presented a little last year. This was adopted at the European Respiratory Society International Congress held in September last year. We think this indicates the great expectations on this drug.

The primary endpoint for efficacy was set to be the cough frequency in daytime. The rate of change was 31.6%. For safety, no significant difference was observed in the incidence of adverse events. Taste disorder, which is reported in similar existing drugs with a very high incidence, was observed in this study with a very low incidence of 2 out of 31 cases. We therefore expect this drug can be sufficiently differentiated from others.

Study Design of Phase 2b Dose Finding Study

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



【Current status】
FPI: Achieved in Feb. 2020

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

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FPI: First Patient In, LPI: Last Patient In 67

An outline of the Phase 2b study is as follows. We set three groups of 50, 150 and 300 mg and a placebo in Japan, US and Europe, and complete First Patient In in February, and Last Patient In by the end of this year.

For this study, we set the hourly cough frequency in 24 hours as primary endpoint. Not only daytime coughing, cough at night time is also associated with serious unmet medical needs as patients cannot sleep well. We therefore changed the primary endpoint to cough frequency in 24 hours after consulting specialist doctors.

Potential roles of $P2X_3$ in Disease

Characteristics of S-600918

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

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

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

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

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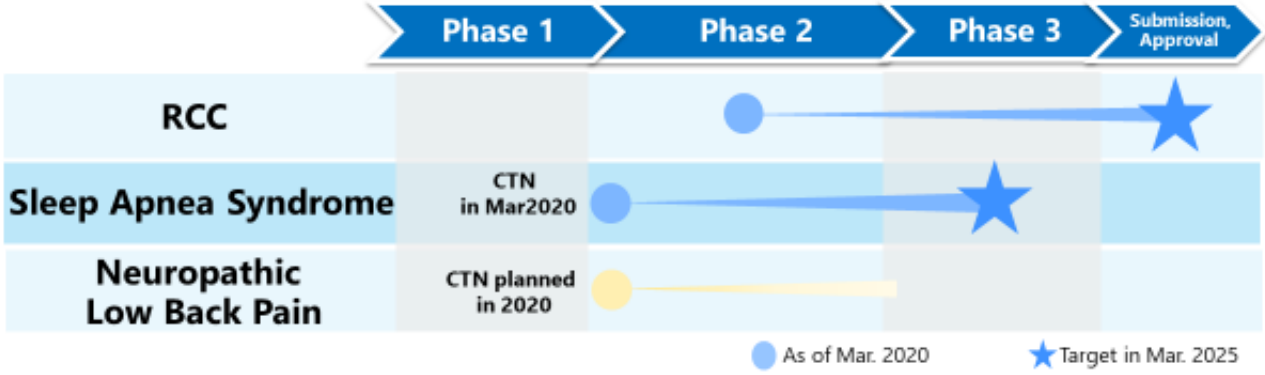
S-600918 supplemental information: shown in appendices, p.130-132

$P2X_3$ exists in many peripheral nerves. Therefore, besides cough, S-600918 is expected to be applied also to pain, sleep apnea syndrome, itch and hypertension. Among them, we focus first on sleep apnea, using a machine called CPAP. In response to heightened expectations for drug therapy, we will conduct PoC study on sleep apnea first in Japan.

LCM Development Plan



Sleep Apnea Syndrome

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

Drug treatment contributes to patients' usability

Neuropathic Low Back Pain

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

High unmet medical need for effective and safe treatment

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

For this, we are now almost ready to submit clinical trial notification. Preparations are also under way for neuropathic low back pain.

S-637880
Neuropathic pain

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

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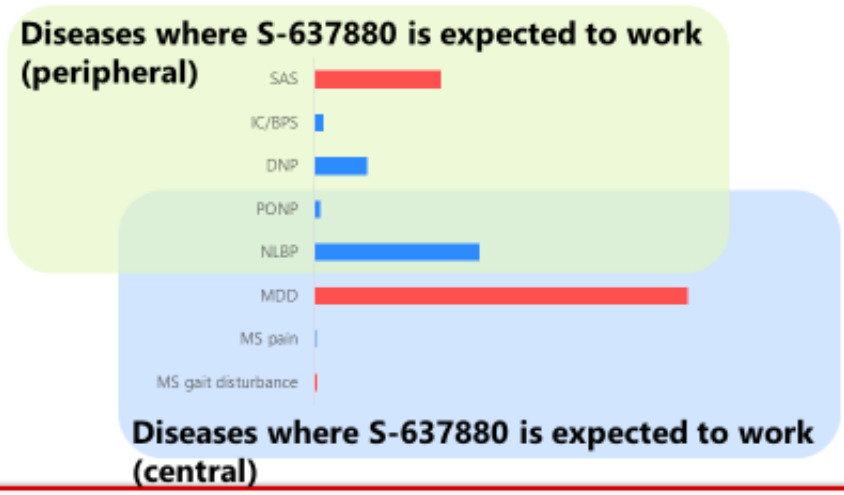
Next is S-637880.

New Opportunity in Pain Area

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



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

Pain Others
Bars show market potential (patient number)

Please turn to page 71. One of Shionogi's current targets is the pain market, mainly Cymbalta and the Oxycontin family. As a compound that follows these drugs, we intend to develop S-600918, which I mentioned earlier, and S-637880, which is expected to be effective in central neuropathic pain, for back pains.

Since the mechanism of back pains are extremely complex, which include focal and central neuropathic, we will develop back pain drugs flexibly by determining which drug is more effective, or whether both drugs will be used for development.

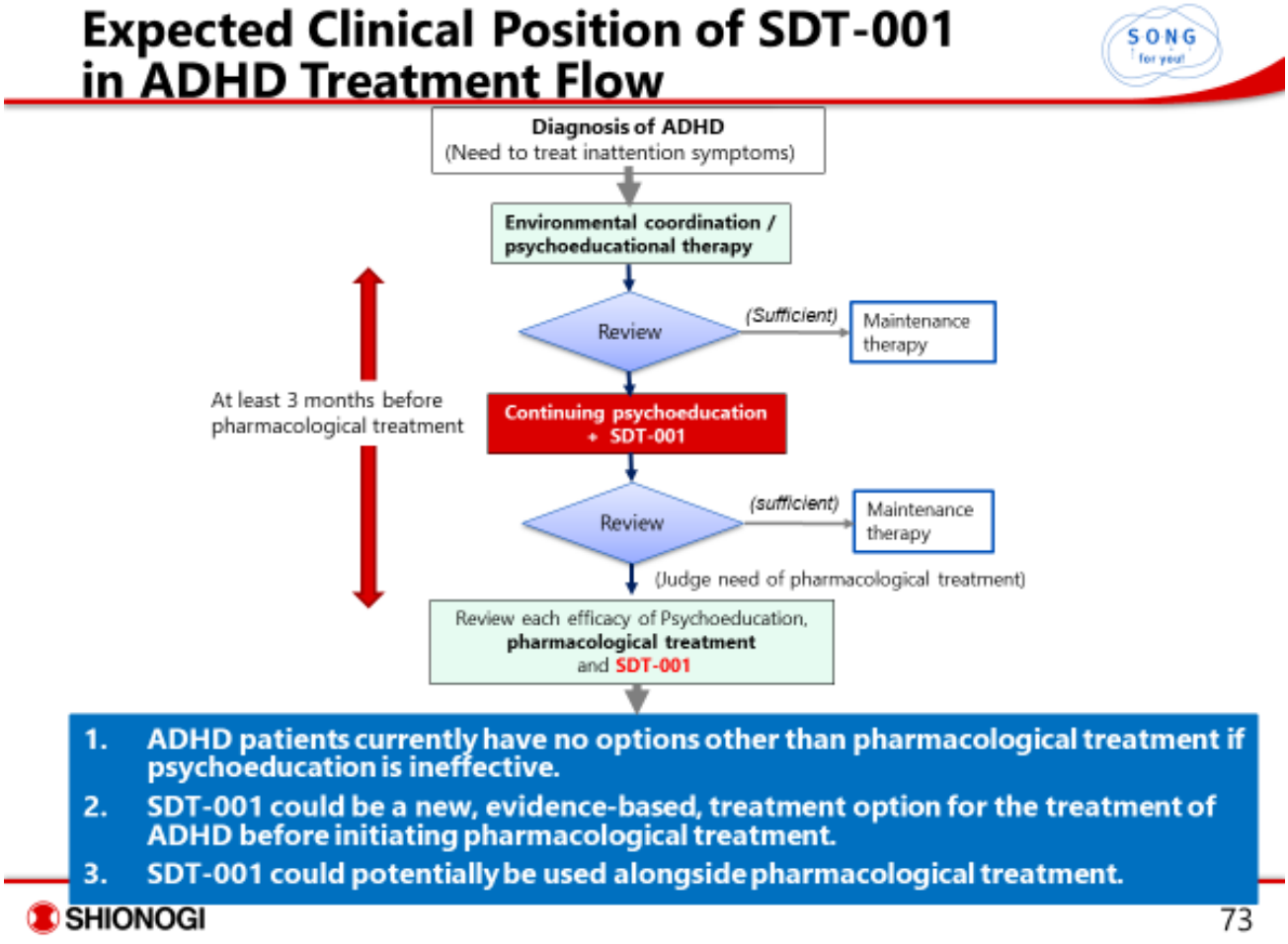
Furthermore, in terms of the mechanism of S-637880, we are thinking that the drug could be effective for depression or MS gait disturbance and will consider selecting the next LCM while we accumulate evidence, including non-clinical tests.

SDT-001
Inattention symptoms of pediatric ADHD patients

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

SHIONOGI

Next is SDT-001. This is a digital app that we have introduced from Akili.



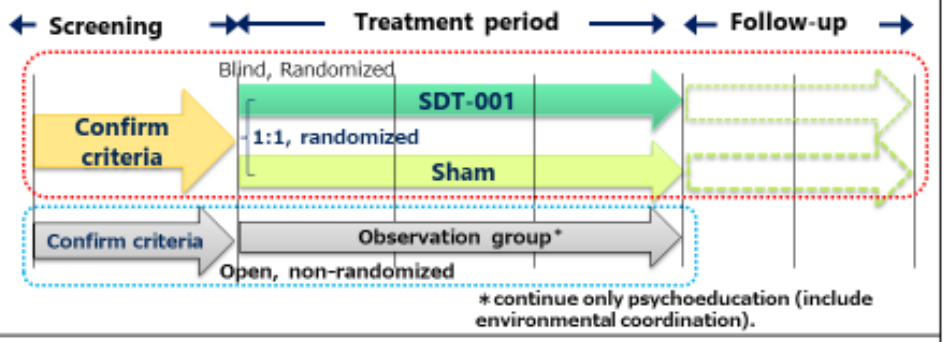
Please turn to page 73. Shown here is the treatment algorithm of ADHD. After a diagnosis is finalized, improvement is sought through efforts such as environmental coordination, psychoeducational therapy, counseling, and group camping. If those are ineffective, then pharmacological treatment is initiated. That is the process.

Therefore, we have positioned this digital app as an alternative or adjunction to environmental coordination and psychoeducational therapy, and are currently planning testing against these patients.

Obviously, there are parents and patients who do not prefer to use pharmaceuticals since some of the pharmacological treatment are addictive. We intend to apply this digital app to such patients in the hope that it will be effective for them, and to other phases as well in the future.

Summary of Phase 2 Study

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

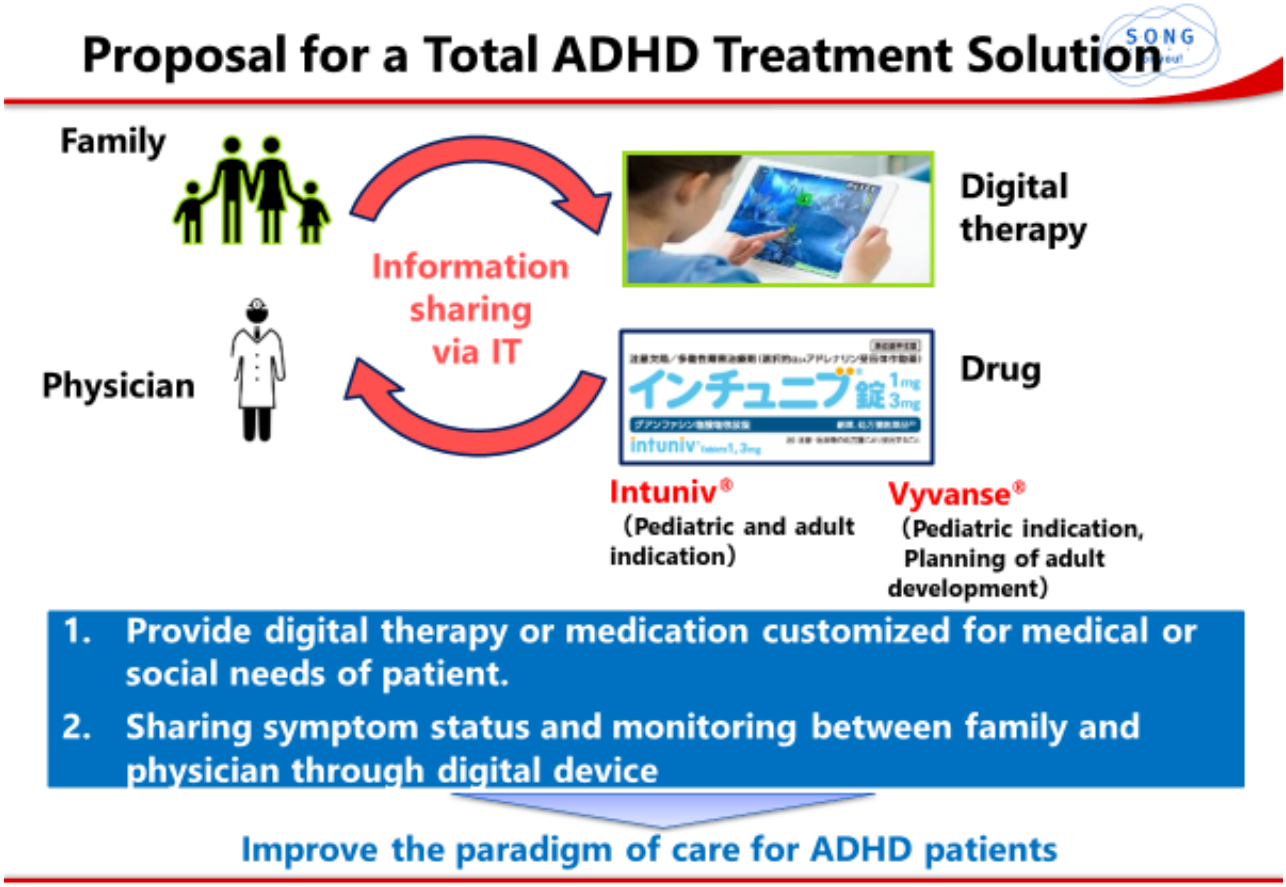
Objective	● To initially assess the efficacy/safety of SDT-001 compared to sham (exclude core mechanism of SDT-001). ● Collect reference data from psychoeducation-only group (include environmental coordination).
Study design	
Treatment method	SDT-001 or sham everyday for 6 weeks.
Efficacy endpoint	●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

With regard to the summary of this Phase 2 study, we use the so-called digital app device and Sham, which is an app that excludes the program that controls ADHD's inattention symptoms and is equivalent to a placebo in pharmaceuticals.

Furthermore, as I mentioned in the beginning, we also want to see how it compares with cognitive therapy and social environmental therapy, so we have set up that observation group.

The treatment method is to use this app once a day for about 30 minutes for one week and continue this for six weeks.

With regard to efficacy endpoints, we evaluate the app's efficacy and especially the degree of improvement of ADHD's inattention symptoms from the so-called ADHD-RS, the normally used scores, and an objective indicator called TOVA.



By applying this app, a digital treatment, in addition to pharmaceuticals such as Intuniv and Vyvanse, which are a stimulant and non-stimulant drug that we currently market, we hope to improve the treatment paradigm for ADHD.

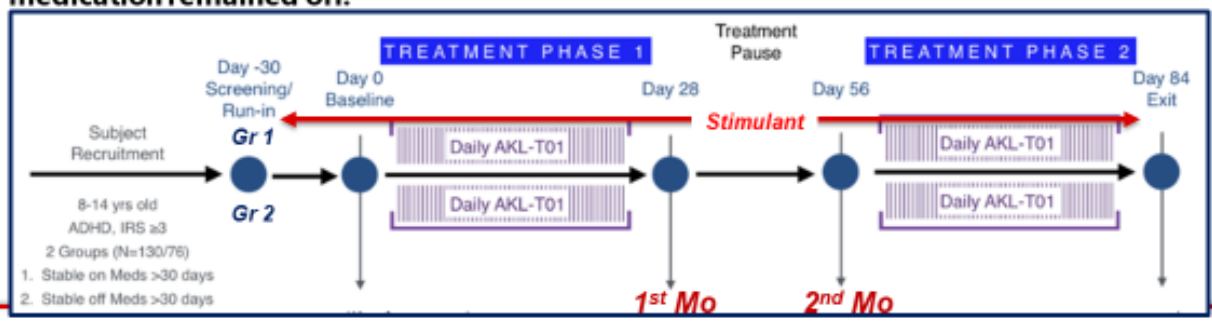
AKL-T01 Adjunctive Study (US, Akili)

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

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

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

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



SHIONOGI

I would like to report on Akili's situation in the U.S.. Akili is currently carrying out efficacy evaluation of cases where a stimulant medication, Concerta, is combined and cases where it is not combined. I will write down the test design.

Interim Report of Adjunctive Study：Efficacy

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

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

On page 77 is an interim report of a two-month period. Significant improvement has been demonstrated in the baseline of major efficacy endpoints at first month and second month.

Additionally, ADHD-RS, which is combined with clinical conditions, and CGI, which indicates the degree of overall improvement, both showed an improving trend.

While a direct comparison with the drug cannot be made since it is still an open test, this digital app by Akili has demonstrated a similar improvement in both the on-stimulant and off-stimulant cohorts. Improvement was also shown after the first month and the second month, which indicates that there was an effect.

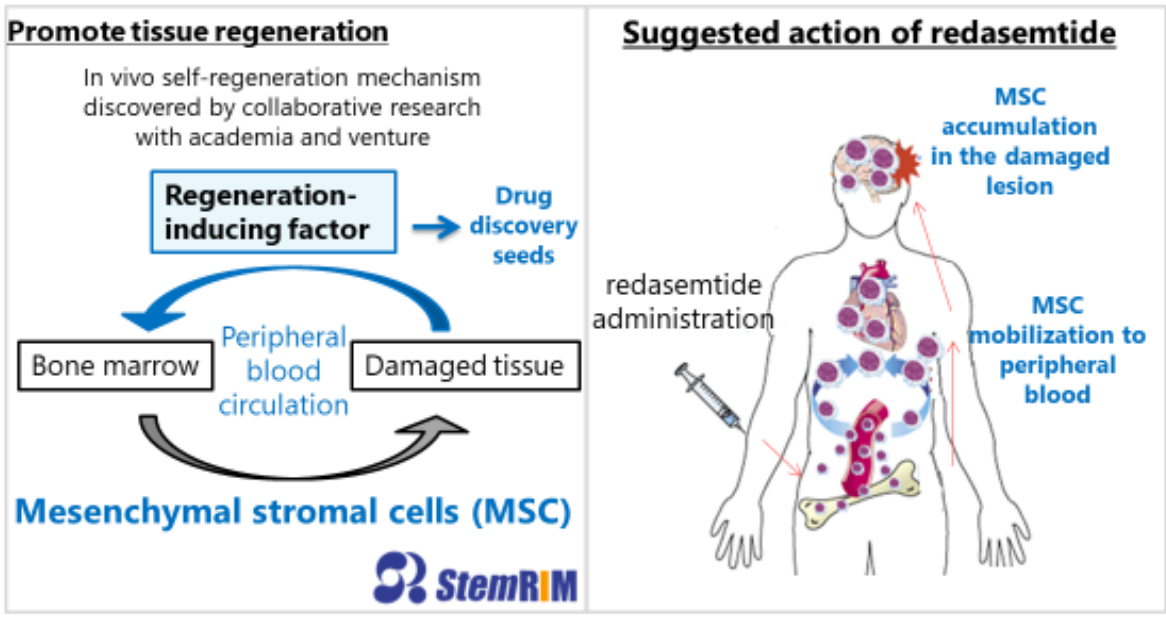
S-005151 [redasemtide] Dystrophic Epidermolysis Bullosa, Acute Ischemic Stroke etc.

- **Origin**: Stemrim
- **Mechanism of action**: Mobilization of mesenchymal stem cells (MSCs) to peripheral blood
- **Characteristics:**
  - ✓ Drip intravenous infusion
  - ✓ Induction of regeneration by mobilized MSCs
- **Development stage (as of Mar. 2020)** :
  - ✓ Dystrophic Epidermolysis bullosa (DEB): Follow up study after Investigator-initiated Phase 2 study (Japan)
  - ✓ Acute ischemic stroke (AIS): Phase 2 study (Japan)
- **Plans for FY2020:**
  - ✓ DEB: Completion of follow up study, PMDA meeting (Japan)
  - ✓ AIS: Conduct Phase 2 study (Japan)

SHIONOGI

Please turn to page 78. I would now like to explain about S-005151, or redasemtide, which we introduced from Stemrim.

Mechanism of Action



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

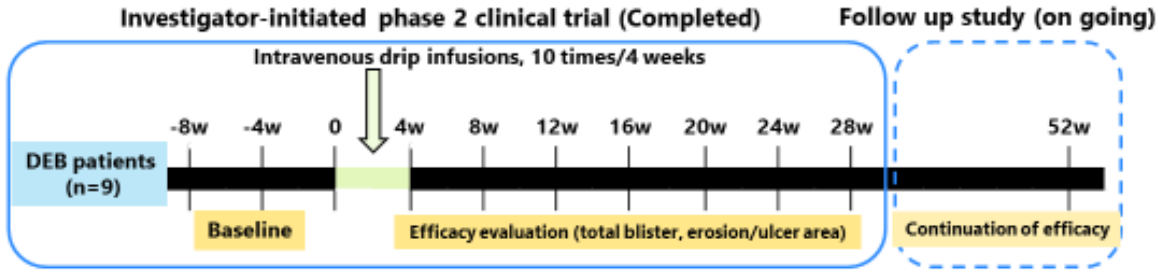
Please turn to page 79. I would first like to go over the mechanism of action. As shown at the left-hand side, the administration of peptide with regeneration-inducing effects mobilizes mesenchymal stromal cells (MSC) from the bone marrow, and MSC moves to the damaged tissue. This MSC cures the tissue damage.

This redasemtide was introduced from Stemrim, a start-up originating from Osaka University.

Study Result of DEB Clinical Study (Flash Result)

Study Design

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



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

SHIONOGI

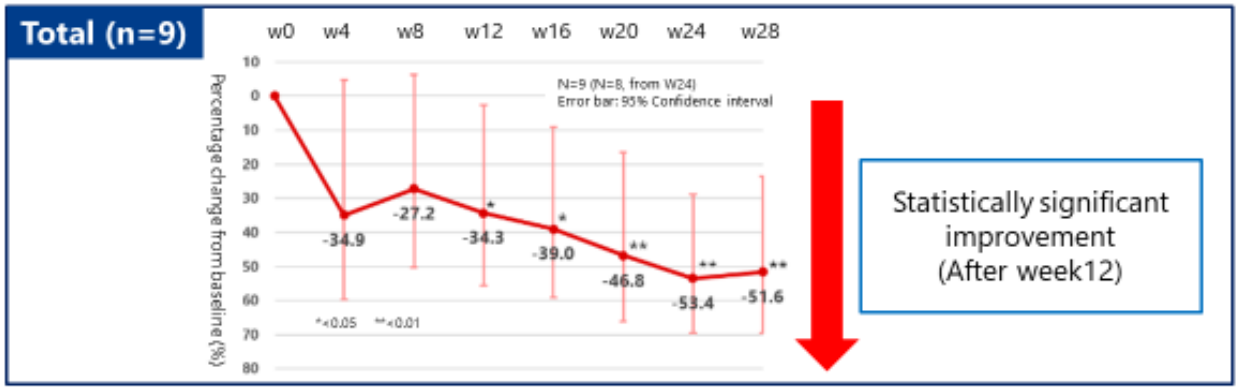
*This clinical trial was supported by AMED (AMED Study No. JP19lm0203018, Representative: Katsuto Tamai, Site: Oosaka University).

Let me present a summary. The subjects are nine patients of epidermolysis bullosa at Osaka University, Toho University, and Keio University.

Administration is 10 times over four weeks, and the primary endpoint is the change from the baseline, the areas of blisters and erosions/ulcers on the whole body.

We have completed 28 weeks, and in order to see how these effects have been maintained or not after the 28 weeks, we are carrying out a follow up study at Shionogi as a clinical trial. Today, I would like to introduce the results of the 28-week investigator-initiated trial.

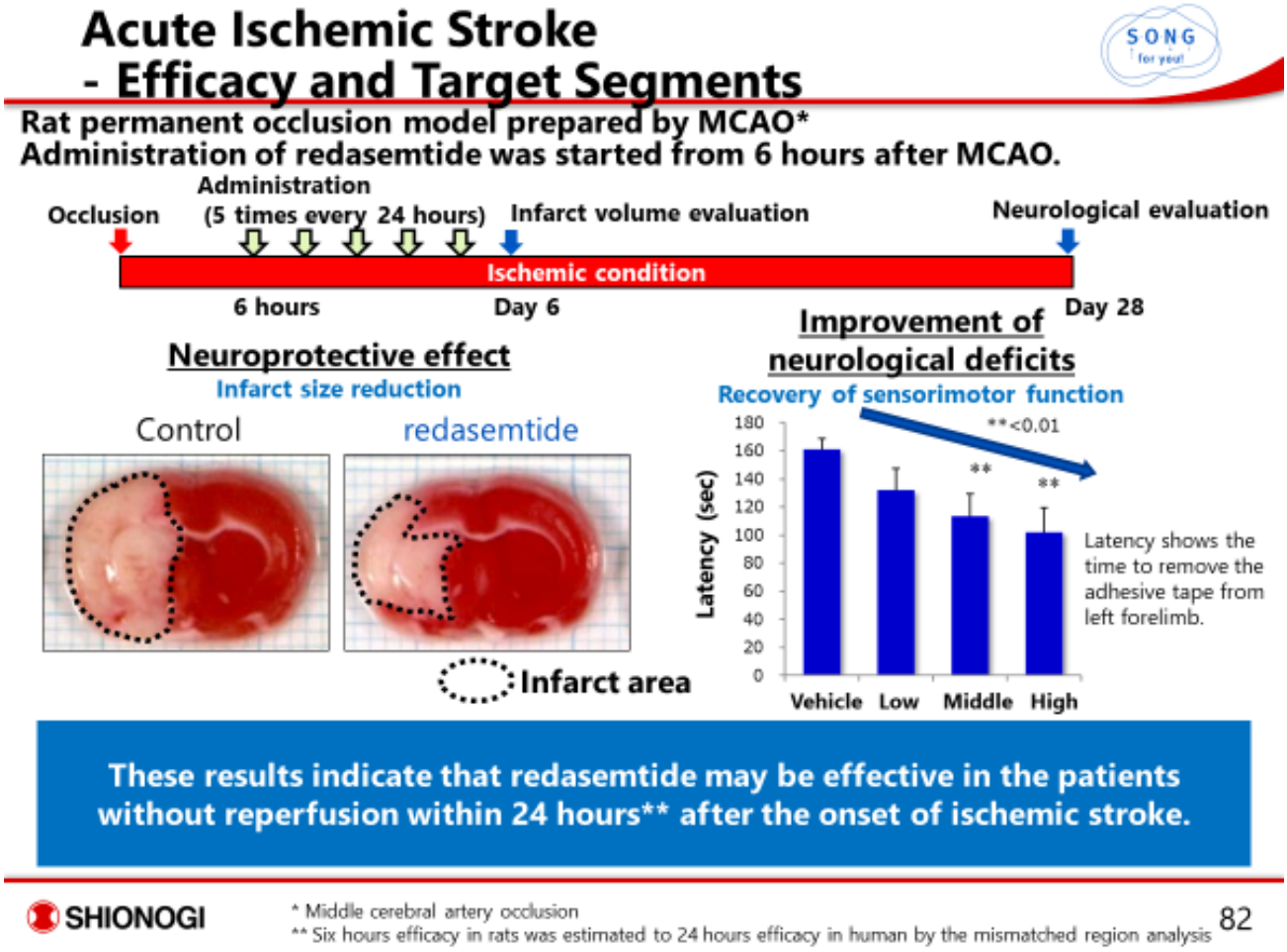
Percent Change from Baseline in the Total Area of Blisters, Erosions/Ulcers on the Whole Body (Flash Result)



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

Please turn to page 81. The vertical scale is the change from the baseline and the average value after 28 weeks. As it says in the slide, the chart shows a statistically significant improvement.

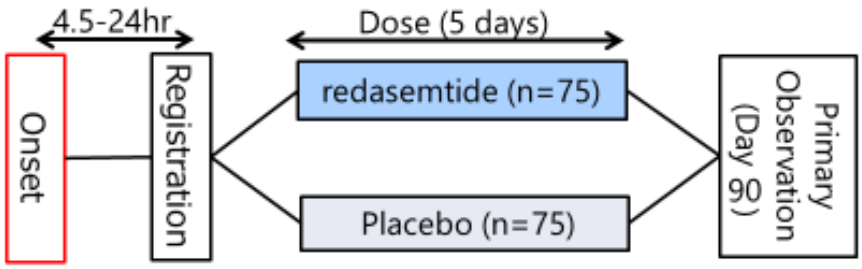
We believe that redasemtide might be effective in lesions on the entire body, differing from conventional regenerative medicines whose efficacy is limited to the site of administration. Therefore, we are currently carrying out the next LCMs after epidermolysis bullosa.



One of them is shown here on page 82. It is acute ischemic stroke. The chart is based on non-clinical data and shows how the infarct has changed by administering redasemtide six hours after the infarction, using a rat permanent occlusion model. As you can see, the redasemtide cohort shows a contraction of the infarct, which is the area that is lighter, compared to control, indicating that redasemtide is effective in a dose-dependent manner even in an animal model of a recovery of sensorimotor function of a rat.

Study Design:
Acute Ischemic Stroke Phase 2 Study

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

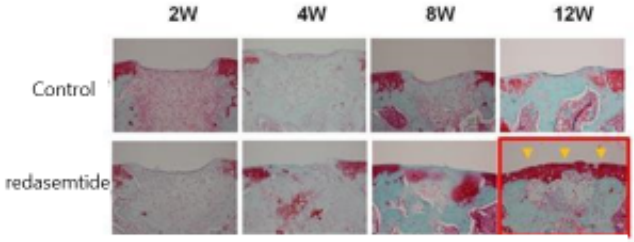


Nov, 2019: First Patient In **Sep, 2021: Last Patient Out**

Based on this data, we are currently carrying out Phase 2 POC studies against 150 cases in Japan. This is the table. Dosage is once daily for five days and we registered the first patient in last November, with the observation scheduled to end in September next year. Enrollment is currently progressing steadily.

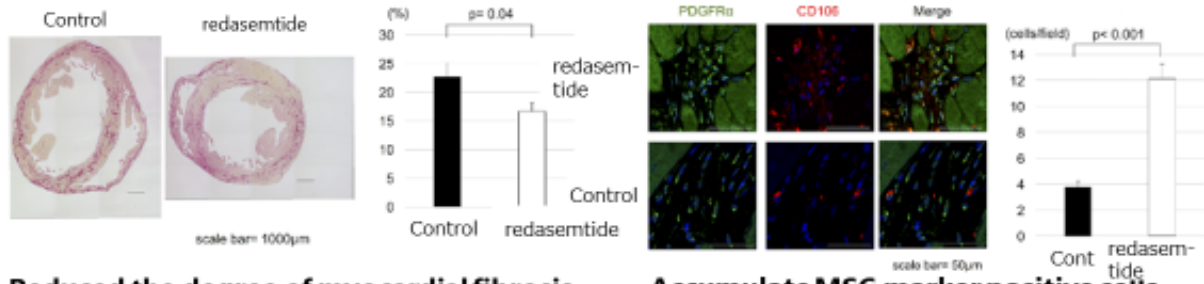
Non Clinical Study Report

Cartilage regeneration in rat joints



(collaborative research by Osaka University and STEMRIM)

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



Reduced the degree of myocardial fibrosis

(collaborative research by Osaka University and STEMRIM)

Accumulate MSC marker positive cells in myocardium

Furthermore, this is the joint study by Osaka University and Stemrim. It is the efficacy check in cartilage regeneration in rat joints and in a hamster model of dilated cardiomyopathy. As you can below, here on page 84, the degree of myocardial fibrosis has been reduced and MSC markers have accumulated in myocardium, and we expect redasemtide can be applied to various diseases based on the mechanism of this drug.

LCM Plan

Cirrhosis of the liver

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

Knee osteoarthritis

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

Cardiomyopathy

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

Licensed exclusive development, manufacturing and marketing rights worldwide from STEMRIM

Plan to start physician initiated clinical study based on the nonclinical evidence
Maximize the value of S-005151 as a regeneration-inducing drug with strong collaboration with academia

As I have explained, Stemrim has started a joint study with Osaka University and is applying the drug to various diseases. Since we have the technology that can fully supply this peptide drug development, we intend to synergize the strengths of Stemrim and Shionogi, and will promptly carry out development for multiple diseases.

S-770108
Idiopathic Pulmonary Fibrosis

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

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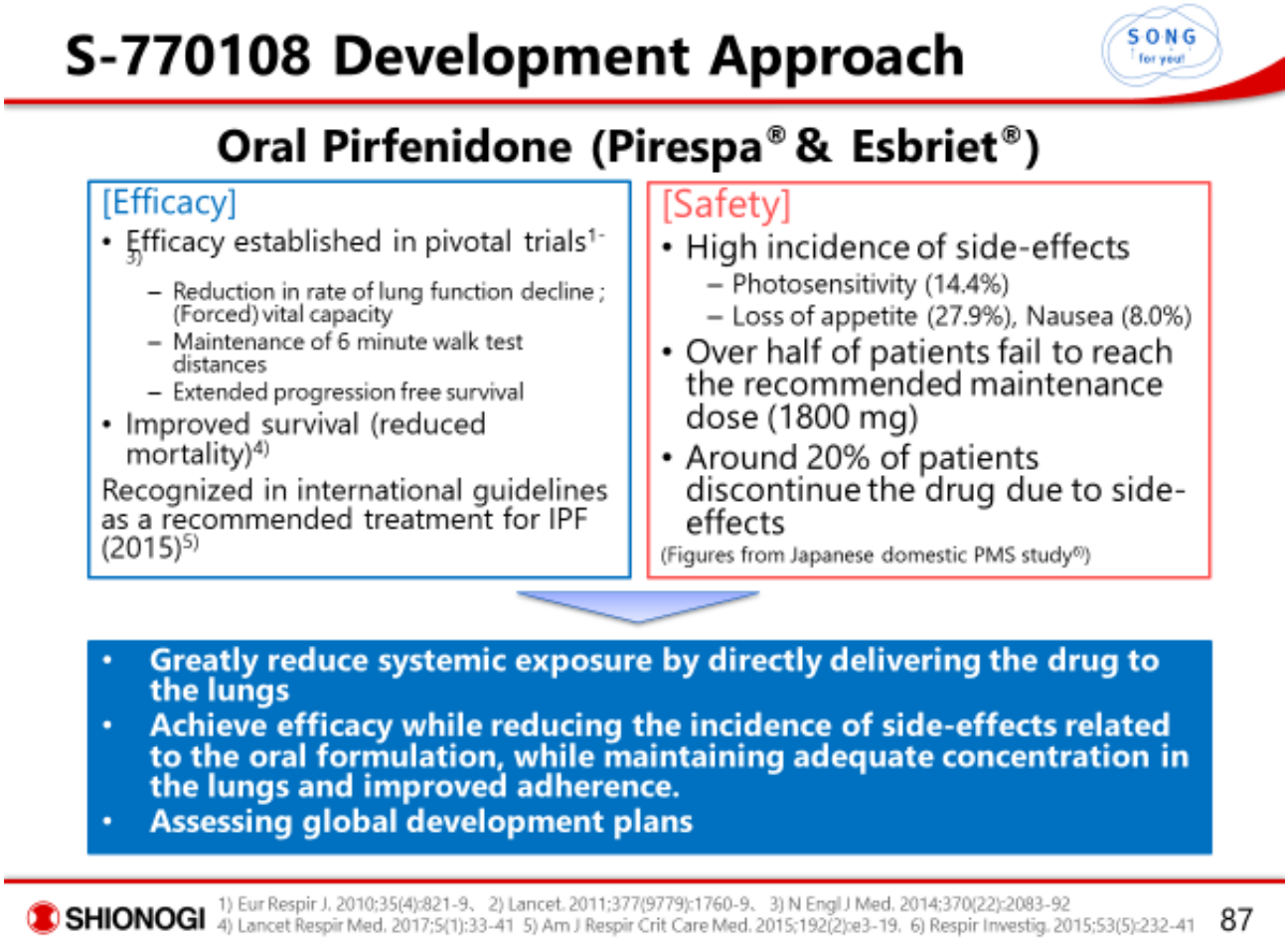
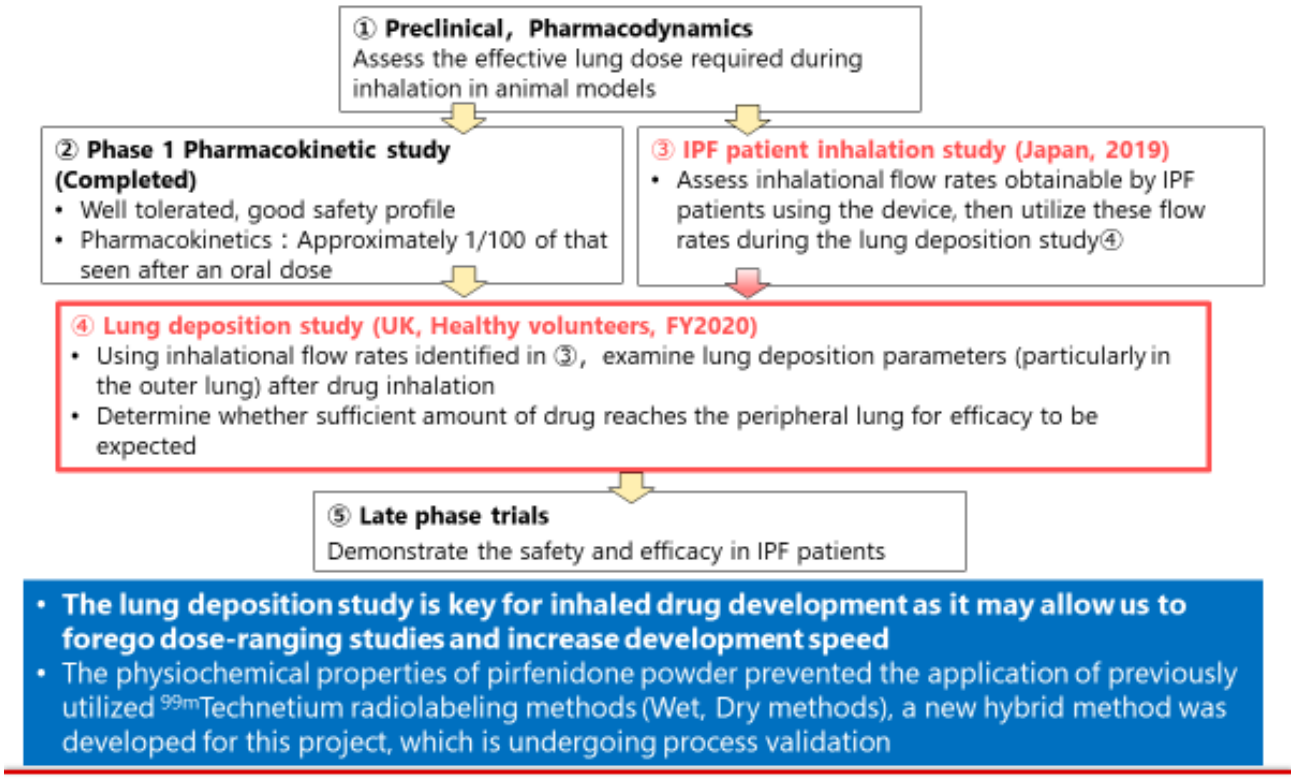
Next is S-770108. This is a so-called inhaled formulation of pirfenidone.



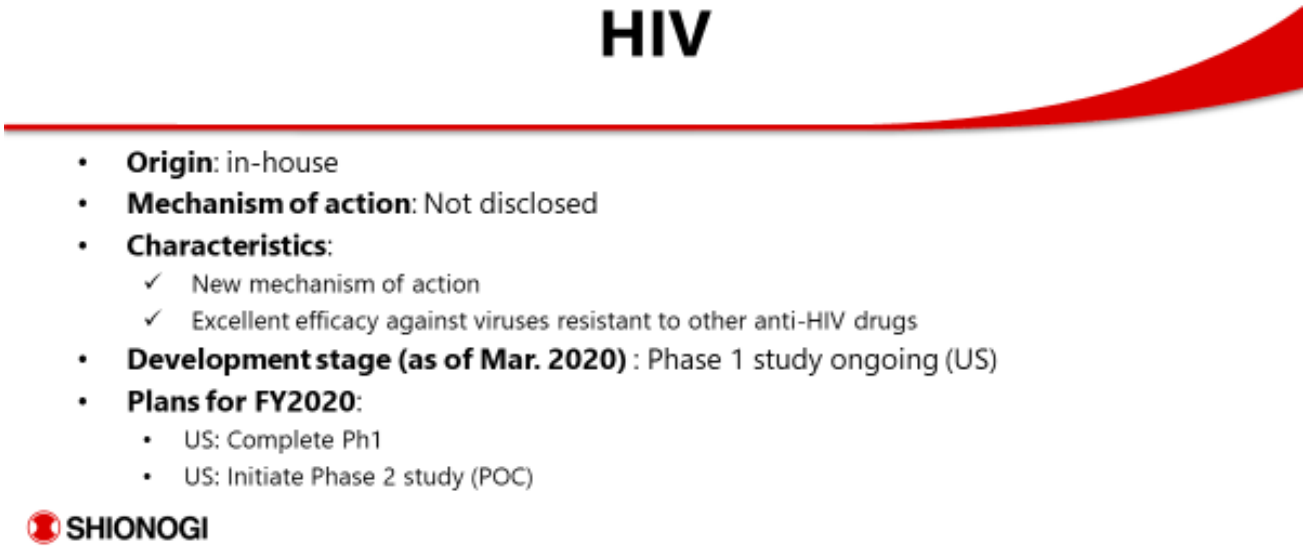
Please turn to page 87. Oral pirfenidone is currently the golden standard of treatment drugs, but its issues include side effects, especially photosensitivity and digestive symptoms such as loss of appetite and nausea.

However, we are currently developing an inhaled drug since we consider there will still be needs, as an inhaled drug will significantly reduce so-called systemic exposure as well as the incidence of side effects as a result.

S-770108 Overall Development Strategy



Following the end of Phase 1, we consulted with Japan's regulatory authorities, who pointed out that we should proceed to clinical testing after checking the lung deposition parameters. Therefore, we are currently planning studying the amount of lung deposition after inhaling this radiolabeled pirfenidone. After this study is completed, we will smoothly move onto Phase 3 tests.



Next is S-648414, HIV.

I will skip page 90 since Kiyama has explained this earlier.

Single Oral Dose Study Results and Future Development

Phase 1 single oral dose study (preliminary results)

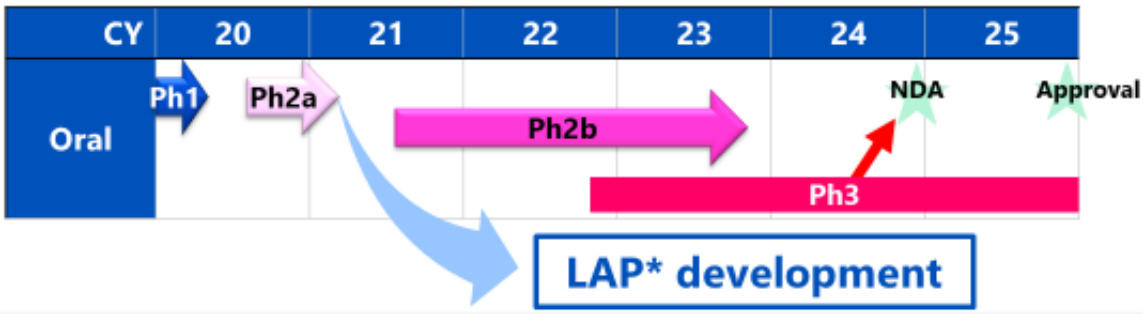
- Safety : No major concern
- PK : Achieved a target drug concentration for efficacy at low dose

Excellent safety and efficacy profile expected

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

Deliver the best 2 drug treatment with DTG

- Next step, development of LAP



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

Please turn to page 91. We have currently finished single oral dose. There was no major concern in safety. Since we have achieved a more than anticipated exposure at low dose in terms of PK, we are currently carrying out multiple dose tests and will initiate PoC study once we have confirmed safety and tolerability at multiple doses. We hope to carry out early submission under this schedule. At the same time, we are also considering long acting parenteral administration.

Xofluza®
Influenza Virus Infection

- **Origin**: in-house
- **Mechanism of action**: Cap-dependent endonuclease inhibition
- **Characteristics**:
  - ✓ Single oral dose
  - ✓ Potent antiviral activity against seasonal influenza (type A and B viruses) and virus with potential pandemic risk including highly pathogenic avian viruses
  - ✓ Confirmed safety/tolerability

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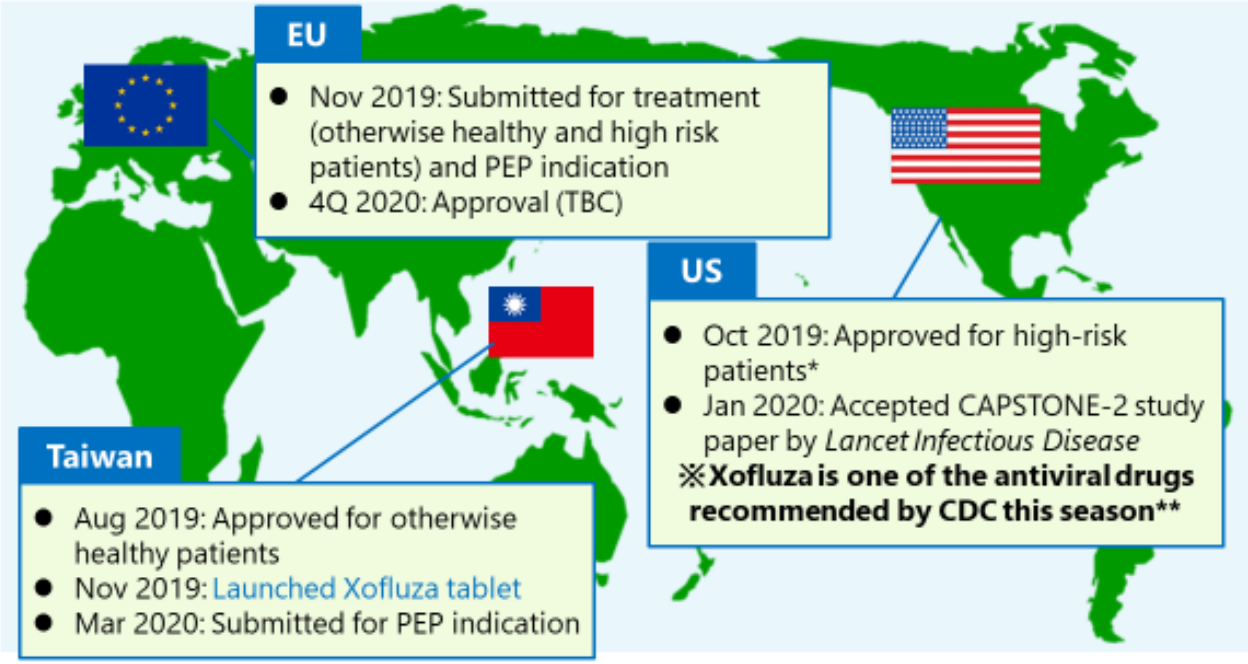
- **Development stage (as of Mar. 2020)** :
  - ✓ Japan: Submitted post-exposure prophylaxis indication (Oct 2019), Completed patients enrollment in Japan high-dose pediatric study
  - ✓ Taiwan: Launched Xofluza tablet (Nov 2019), Submission for post-exposure prophylaxis (Mar 2020)
  - ✓ US: Approved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

This is the last product—Xofluza.

Outside Japan: Smooth Development Progress to Support its Full Potential



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

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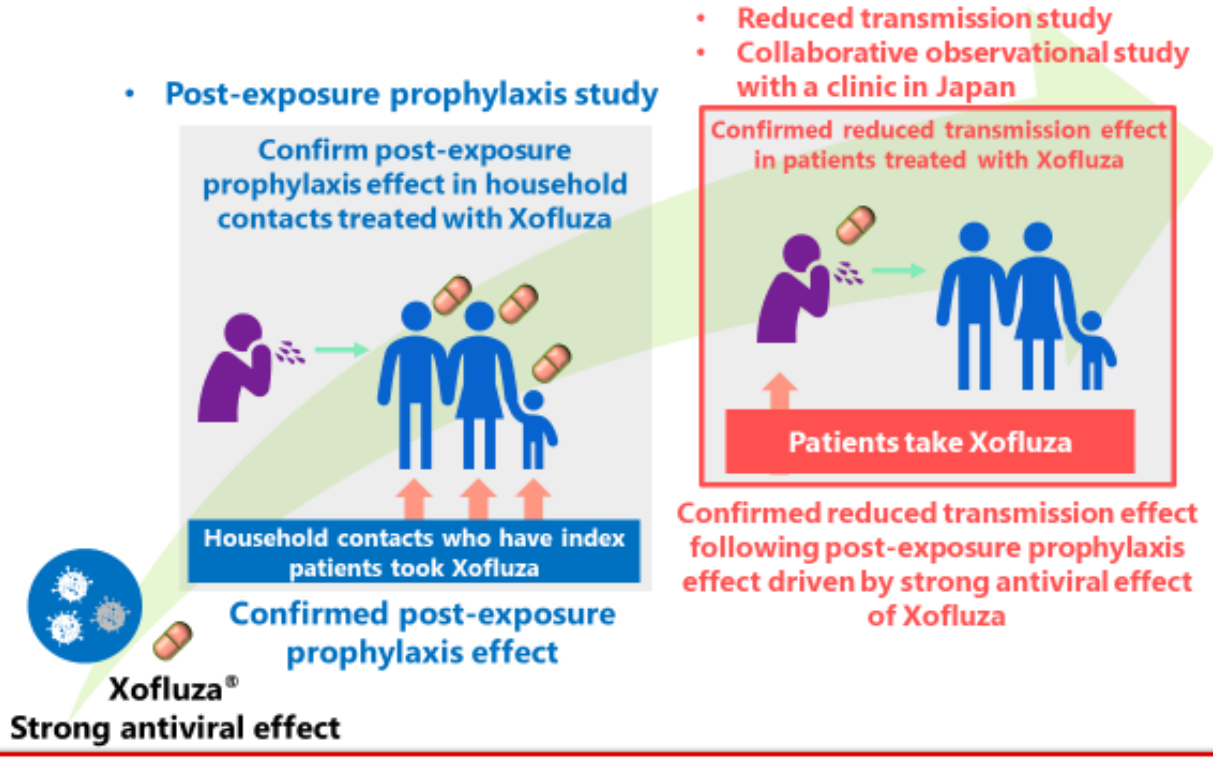
*high-risk patients : patients at high risk of flu complications PEP : Post-exposure prophylaxis

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

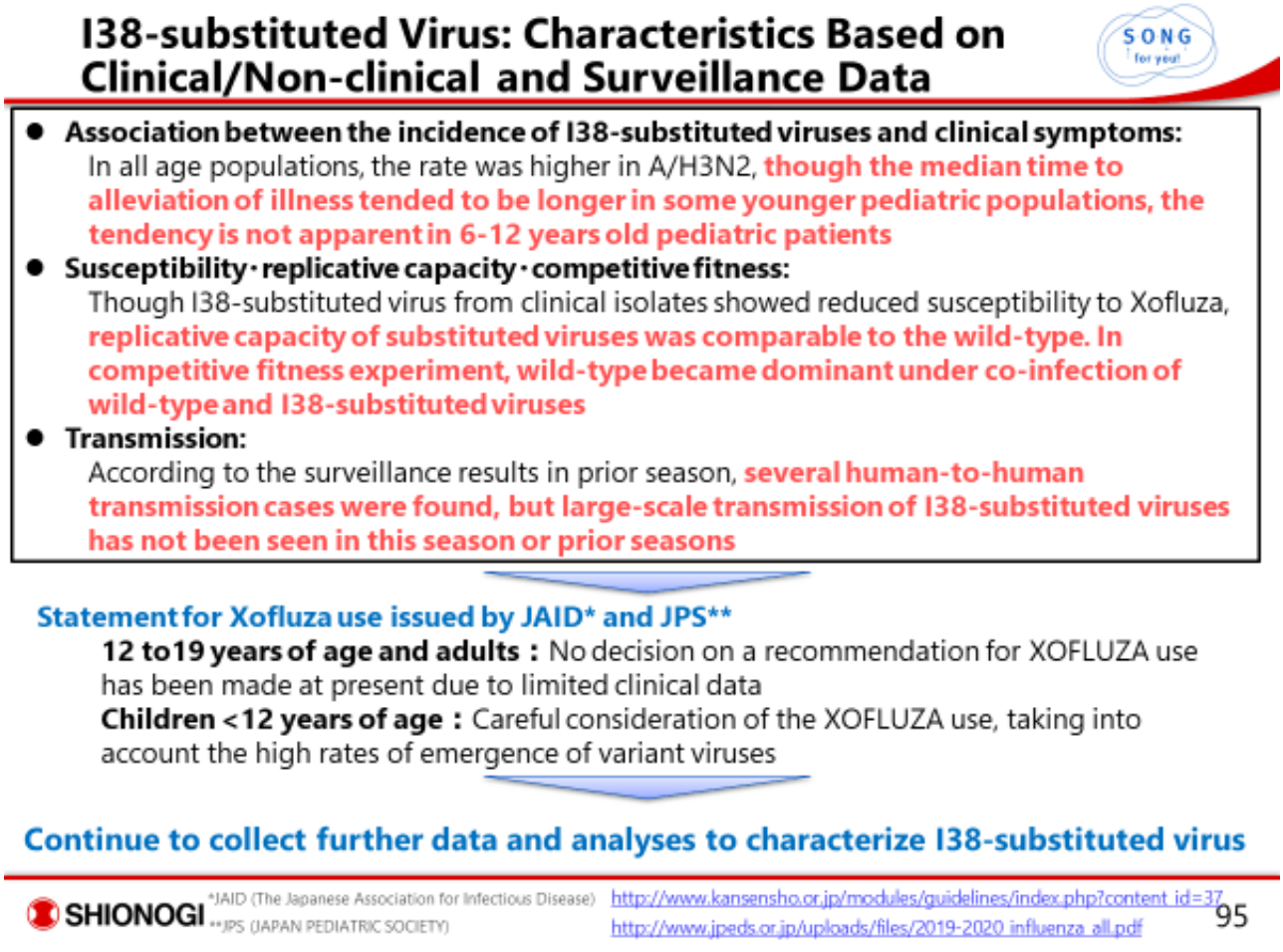
Please turn to page 93. We have made submissions and were approved in Europe, the U.S., and Taiwan, after Japan.

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



Please turn to page 94. The characteristic of Xofluza is its strong antiviral effect. We are currently carrying out prophylaxis study and transmission study. Since we have achieved excellent results from the prophylaxis study, we have made a submission.

As you are aware, the issue especially in Japan is the I38-substituted virus. I would like to review the characteristics we have learned so far.



Please turn to page 95. According to last year's data, the incidence of I38-substituted viruses was higher in H3. In particular, the median time to alleviation of illness tended to be longer in some younger pediatric populations under the age of five. On the other hand, the tendency was not apparent in 6–12 years old pediatric patients.

The replicative capacity was comparable to the wild-type. In a competitive fitness experiment the wild-type became dominant under co-infection of wild-type and I38-substituted viruses.

Thirdly, with regard to transmission, several human-to-human transmission cases were found, but large-scale transmission of I38-substituted viruses has not been seen in this season or prior seasons. We have shown you these data previously.

I did show you these data, but since we did not have enough evidence about whether these were actually a clinical problem, we were told by medical societies that they could not make a decision on a recommendation for Xofluza use on adults or that they would carefully consider the use of Xofluza on children. Therefore, we have been collecting more data on the I38-substituted virus.

I38-substituted virus: Actions for Surveillance

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

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

▶ **Drug use result survey: Niigata university** -> **Surveillance results uploaded in Shionogi website* twice a month**
Number of samples: 100 strains/year
Period: 6 seasons from 2018/19 season

▶ **Domestic surveillance (JPA surveillance)**
Number of patients: 300 patients/season
Period: 2-3 seasons from 2019/20 season

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

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

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

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

Our initiatives are shown on page 96. One is post-marketing surveillance, which we have outsourced to Niigata University. Other current initiatives include domestic surveillance by the JPA and a global surveillance by Roche.

Detection of I38-Substituted Viruses in This Season

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

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

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

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

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

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

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

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

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

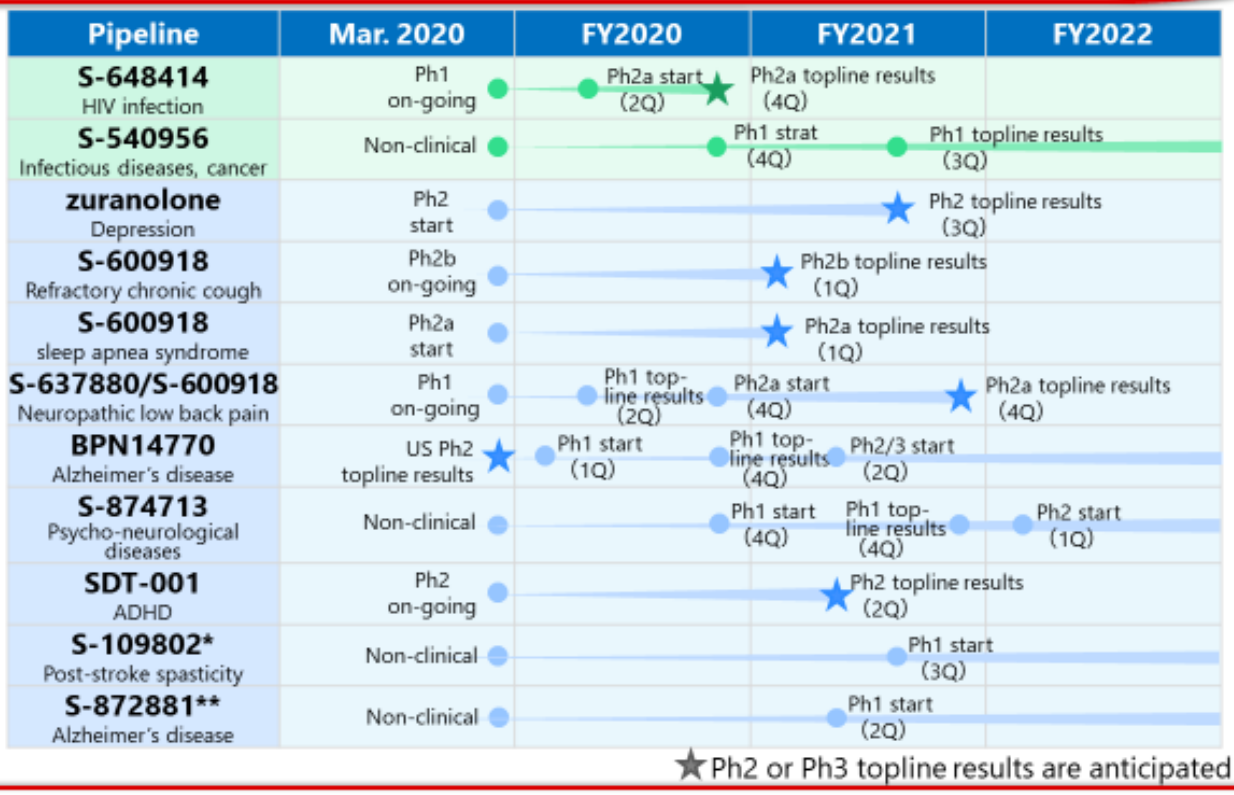
Page 97 shows the latest results. With regard to the surveillance by NIID, the number of antiviral drug-resistant viruses detected during the current season was 1 in H1 out of 515 samples tested and zero in H3 and type-B out of 36 and 15 samples tested, respectively.

In the drug use result survey, only 1 was detected in H1 out of 48 and none detected in H3 this season.

As you can see, though the drug resistance of I38 became a big issue or the risk of transmission was much talked about last season, in this year's data we have not observed a great amount of so-called drug-resistant viruses and no clinical problems have occurred either.

We intend to consult with the medical societies about evidence once again based on these facts and data so that the product could be used.

Key Events for Major Pipeline Compounds



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* S-109802: Profiles are shown in appendices, p.137-139
** S-872881: Profiles are shown in appendices, p.140, 141

Please turn to page 99. Our development timelines are presented on page 100. To be honest, there are few milestones in fiscal 2020, but we will advance our development in multiple items in fiscal 2021 based on these results of Phase 1 and Phase 2.

Key Events for Major Pipeline Compounds

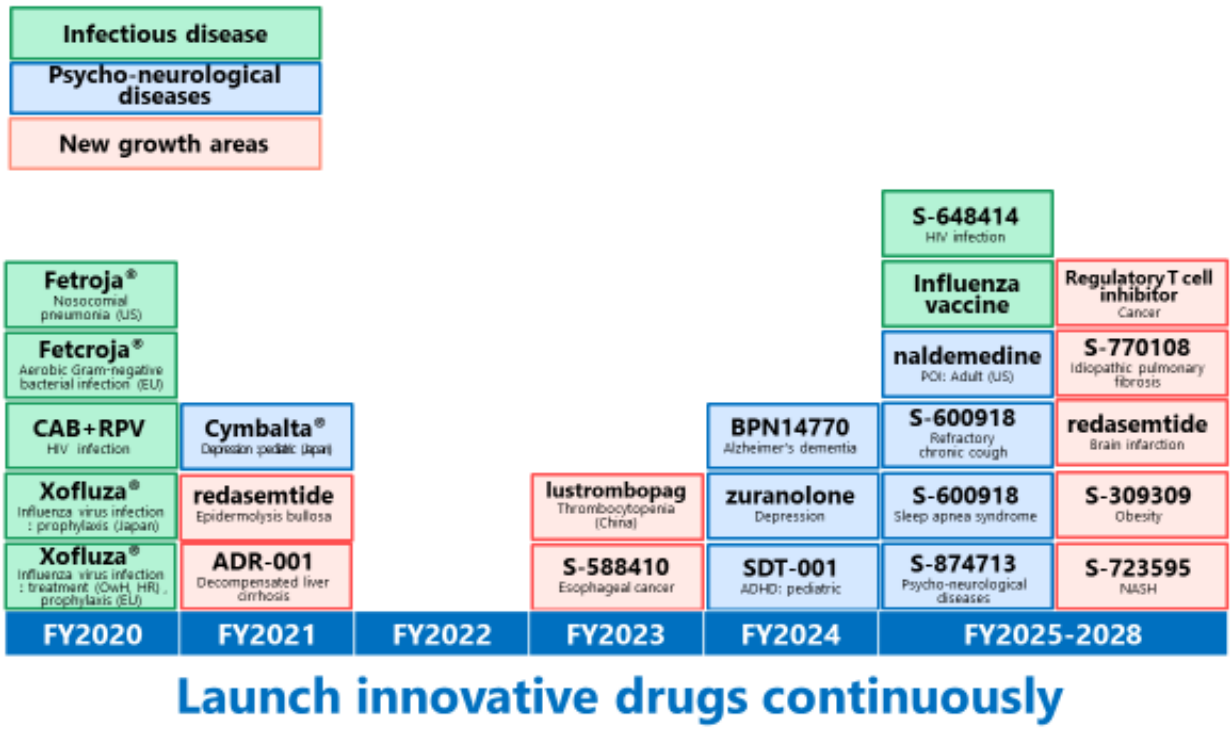
Pipeline	Mar. 2020	FY2020	FY2021	FY2022
redasemtide Epidermolysis bullosa	sponsor investigator top-line results ★		Launch	
redasemtide ischemic stroke	Ph2 on-going		★ Ph2 topline results (3Q)	
Regulatory T cell inhibitor Cancer	Non-clinical		Ph1 start (2Q)	
S-588410 Esophagus cancer	Ph3 on-going	★ Ph3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

★ Ph2 or Ph3 top-line results are anticipated

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

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

Launch/sNDA Approval Target



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

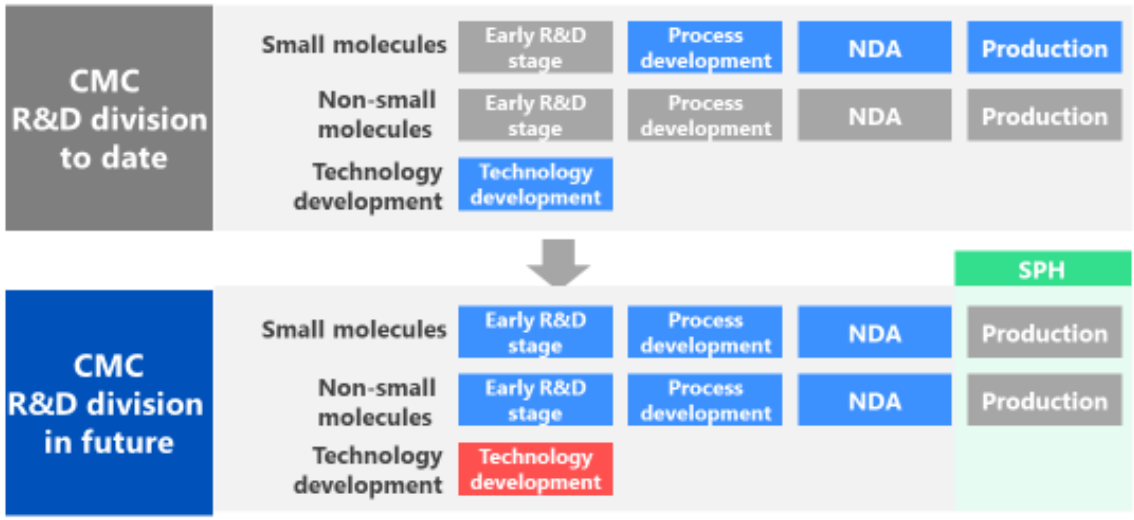
CAB: cabotegravir, RPV: rilpivirine

I will skip page 100. Please turn to page 101. We will launch innovative drugs continuously for the items listed here.

This concludes my explanation.

Kyokawa: Thank you. Since we are slightly behind schedule, I would like to proceed swiftly from here. Isou will explain about CMC.

Changes in the Role of CMC R&D Division



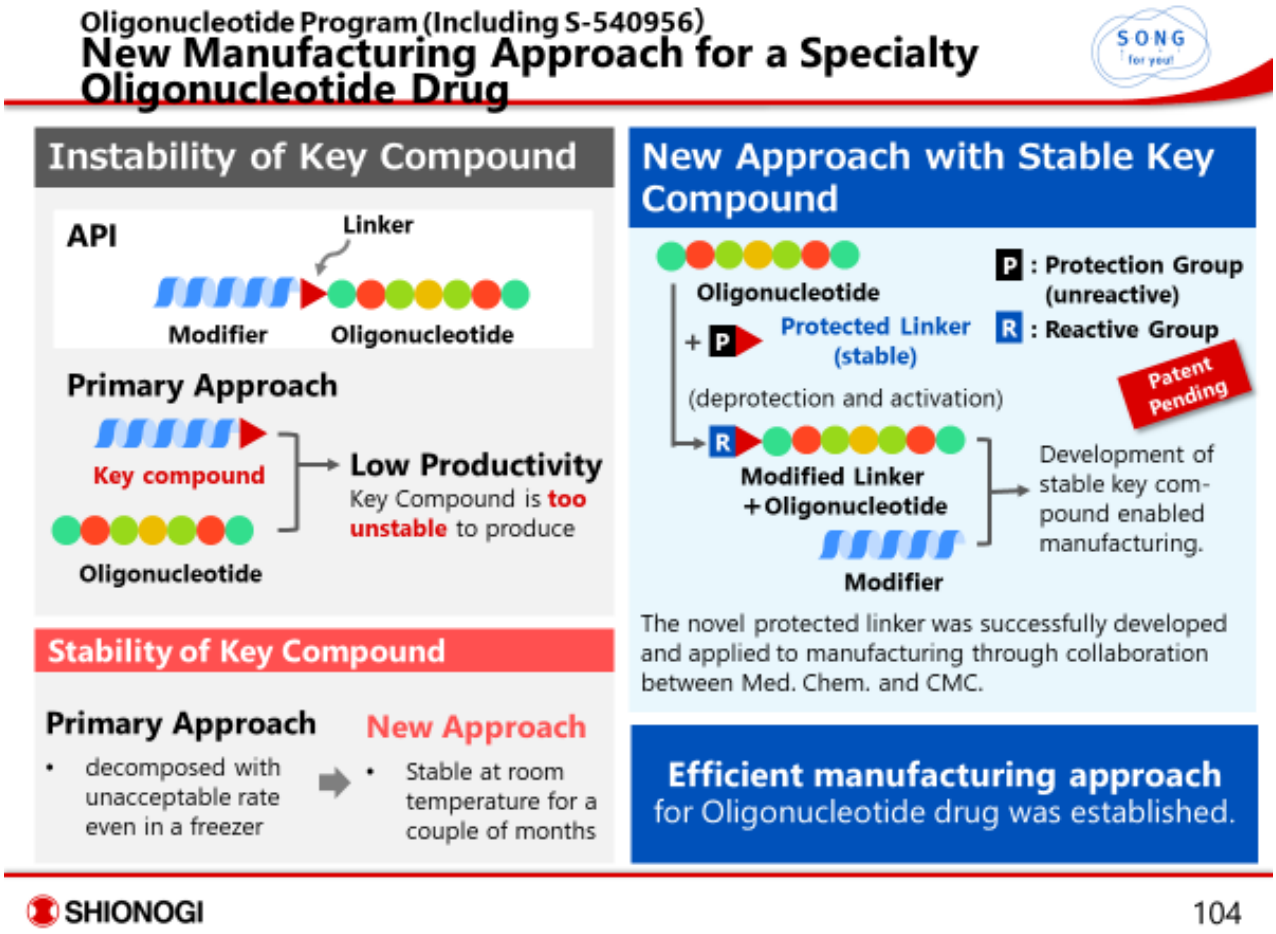
- Manufacturing function is unified into Shionogi Pharma (SPH)
  ➡ **Optimization of overall group companies**
- Expanding the scope of modalities beyond **small molecules to non-small molecules**
  - Application of legacy technologies/knowhow acquired through small molecule experience
- To further strengthen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

Isou: I would like to start with CMC research & development.

Please turn to page 103. As the outline of Shionogi's CMC, I would first like to explain the changes in the role of the CMC R&D Division.

The CMC R&D Division to date had focused mainly on small molecules, as is written here. As you know, we have decided to optimize our group by unifying all of our manufacturing functions into a group company called Shionogi Pharma. Therefore, CMC will focus on new technology development as well as expanding its scope of modalities beyond small molecules to non-small molecules in the future.

I will explain this again later, but in this technology development, we intend to focus on the following three pillars: 1) to improve the probability of new drug discovery, in other words, the probability of exploratory studies; 2) to seek improvement of product value by thoroughly concentrating on commercialization research; and 3) to improve industrial productivity.



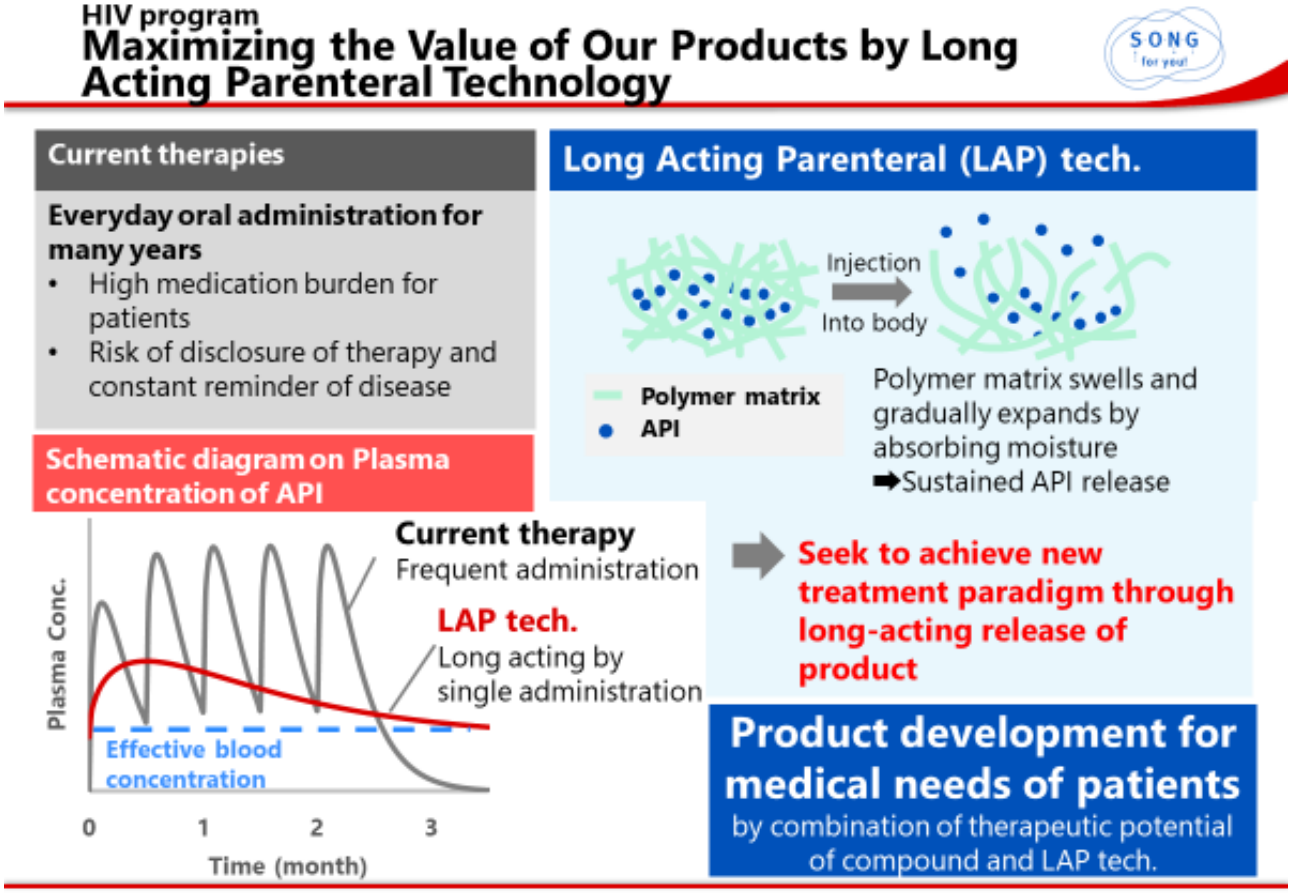
Please turn to page 104. Iwasaki has explained about clinical development, but in the following slides I would like to explain about CMC's actual technologies of what kind of value to add to clinical development and how to improve the product value.

I would first like to talk about the oligonucleotide program. This is partly aimed at S-540956 and is meant to solve the manufacturing issues of these specialty oligonucleotides or modifiers with a new manufacturing approach.

The conventional manufacturing approach was to apply these modifiers to oligonucleotide, mainly the phosphate ester section, by activating the side chain unit in this manner.

However, this approach leads to extreme instability and low productivity since activating reduces stability. The new approach replaces this with a protected linker unit, after which protection and activation are carried out. This step-wise approach enables these modifiers to be applied to the backbone of the oligonucleotide smoothly and with high yield, and leads to the establishment of very efficient manufacturing. We have applied for a patent.

In short, while the primary approach resulted in instability and low yield or quality, this approach achieves high purity and yield, contributing to accelerated development.



Please turn to page 105. These are initiatives in formulation. It is the improvement of product value by formulation technologies such as the long acting parenteral, or LAP, technology of the HIV program—mainly S-648414.

S-648414 is extremely soluble in water and LAP is generally very difficult with these drugs. However, we thoroughly focused on this matrix, the polymer matrix, which swells and very gradually expands by absorbing moisture, releasing small molecule API. This is what the LAP technology is based on.

This illustration here describes that in a diagram. Where frequent administration is necessary, we intend to apply a new approach with this kind of PK profile and mainly with the sustained parental solution, especially this polymer matrix, which I have explained.

To develop a product that meets the medical needs of patients, we are developing a formulation that guarantees a sufficient plasma level with two administrations of parenteral injections per month or a single administration every three months.

Peptide Program

Feasible Peptide Drug Manufacturing Methods

1: Peptide Drug

Typically High-cost

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

2: Productivity Improvement with Micro Wave (MW) Irradiation

MW irradiation improves the productivity of SPPS

- Acceleration of reaction time

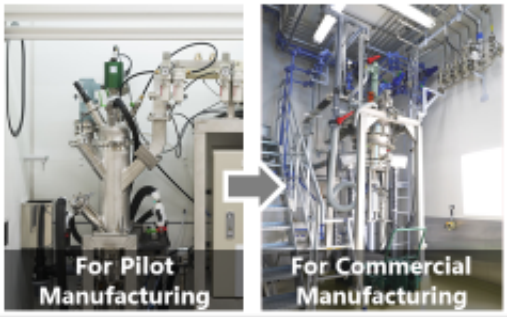
40hrs ➡ 1h

Announced at the 2017 R&D briefing meeting

3: From Lab. to Mfg.

Introduction of MW equipment in Commercial Mfg.

- Substantial lead-time required to implement special equipment.



4: Implementation in Mfg. Facility

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

PeptiStar

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

SHIONOGI Photos provided by PeptiStar Inc.

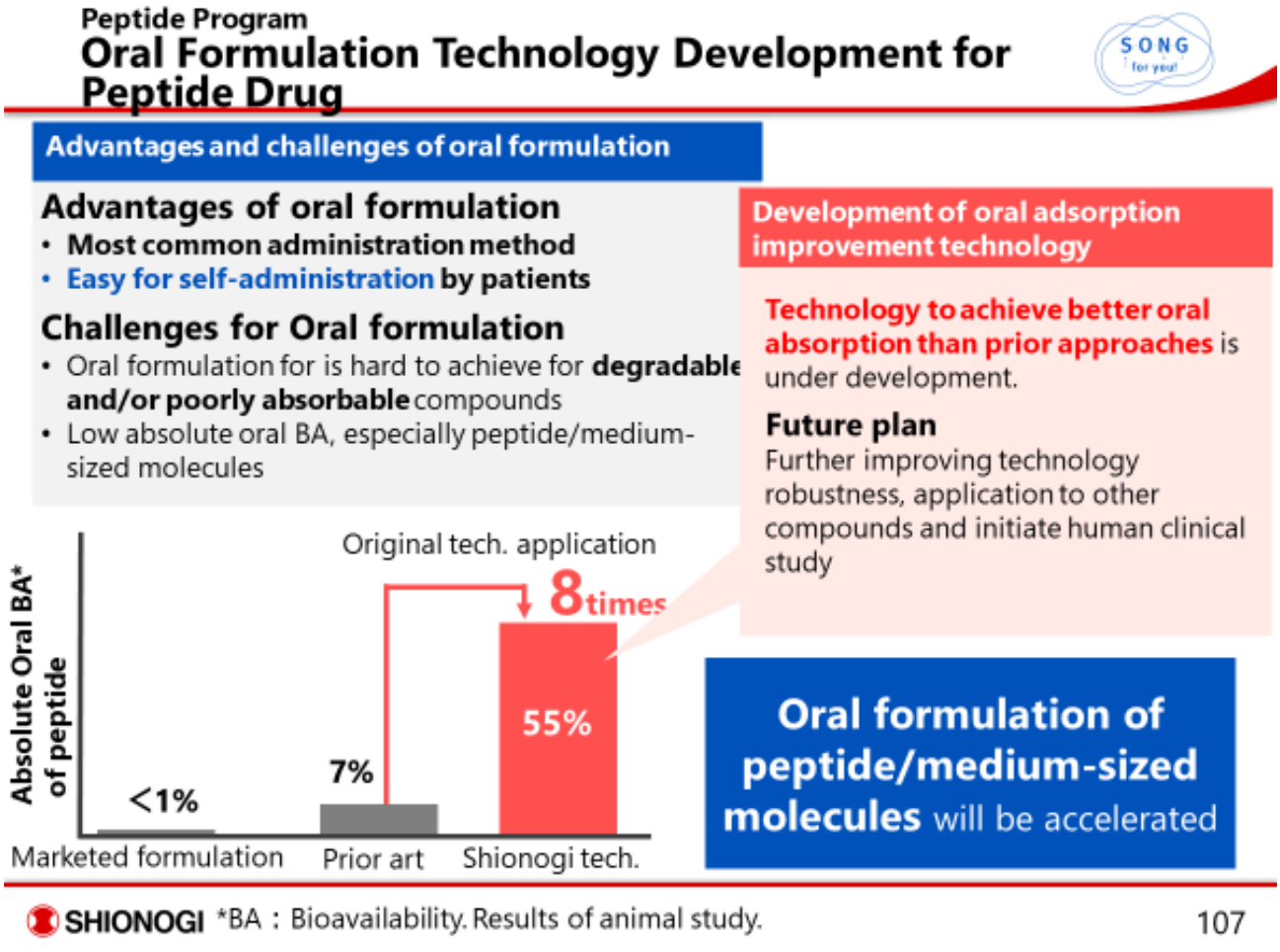
Please turn to page 106. This is the peptide program. As we have introduced earlier, many peptide drug candidate compounds are scheduled in the future. Amid this situation, improving the efficiency of peptide drug manufacturing will become an urgent issue.

Peptide is traditionally manufactured through solid phase peptide synthesis, but its reactivity is a big problem. There has been insight that micro wave is extremely effective in improving reactivity.

Micro wave, which is generally known for micro wave ovens, is very effective in attaching such inactive amino acid.

Also, the reaction time, which used to be about 40 hours, can be reduced to one hour. The reaction efficiency can also be greatly advanced by using this approach.

This technology innovation was difficult to be converted to manufacturing, and it was indeed difficult to apply to actual manufacturing, but we have achieved smooth introduction through a technical alliance with PeptiStar Inc. We intend to improve productivity by promptly inputting this technological innovation using micro wave into the peptide manufacturing system.



Now please look at page 107. We would like to touch upon oral drug formulation technique regarding the Peptide Program. As Mr. Kiyama has said, peptides with high oral absorbability come up from the SAR Research Group. However, one of the characteristics of peptides is low oral absorbability. With oral formulation technology to overcome such disadvantage, we are now working on development of formulation with improved oral absorbability.

In general, peptides are freely soluble in water. If they remain their water solubility and go to the intestines, they flow smoothly onto the mesenteries and are excreted. Therefore, we focused on adhesion. By securing adhesion, so-called retentivity, interaction between the mesenteries, we came up with the idea to use middle molecular peptides via paracellular route among the intestinal absorption routes. This is the origin of this technology.

By applying this unique technology, we have acquired oral bioavailability of peptides about eight times higher than that of competitors. By further utilizing such technology, we plan to improve oral absorption of peptides coming up from the Drug Discovery Group.

S-600918

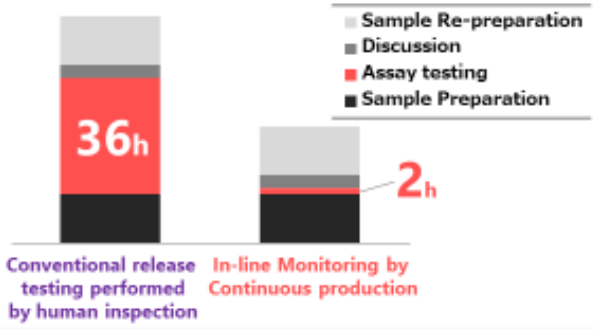
Drug Product Manufacturing Productivity Improvement with Continuous Production

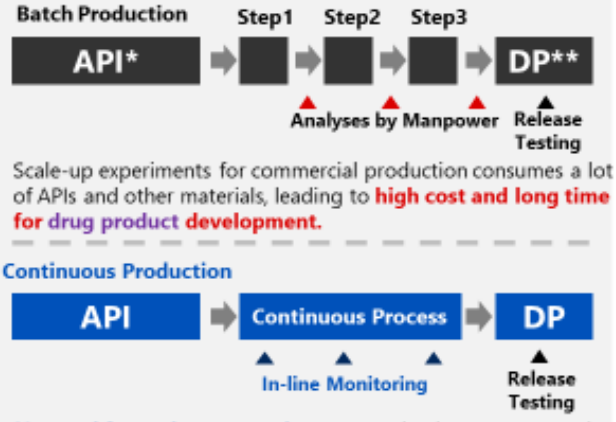
Continuous Production/ Monitoring Technology

Batch to Continuous Production

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

API Assay Evaluation Time for Each Batch





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

Continuous Production

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

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

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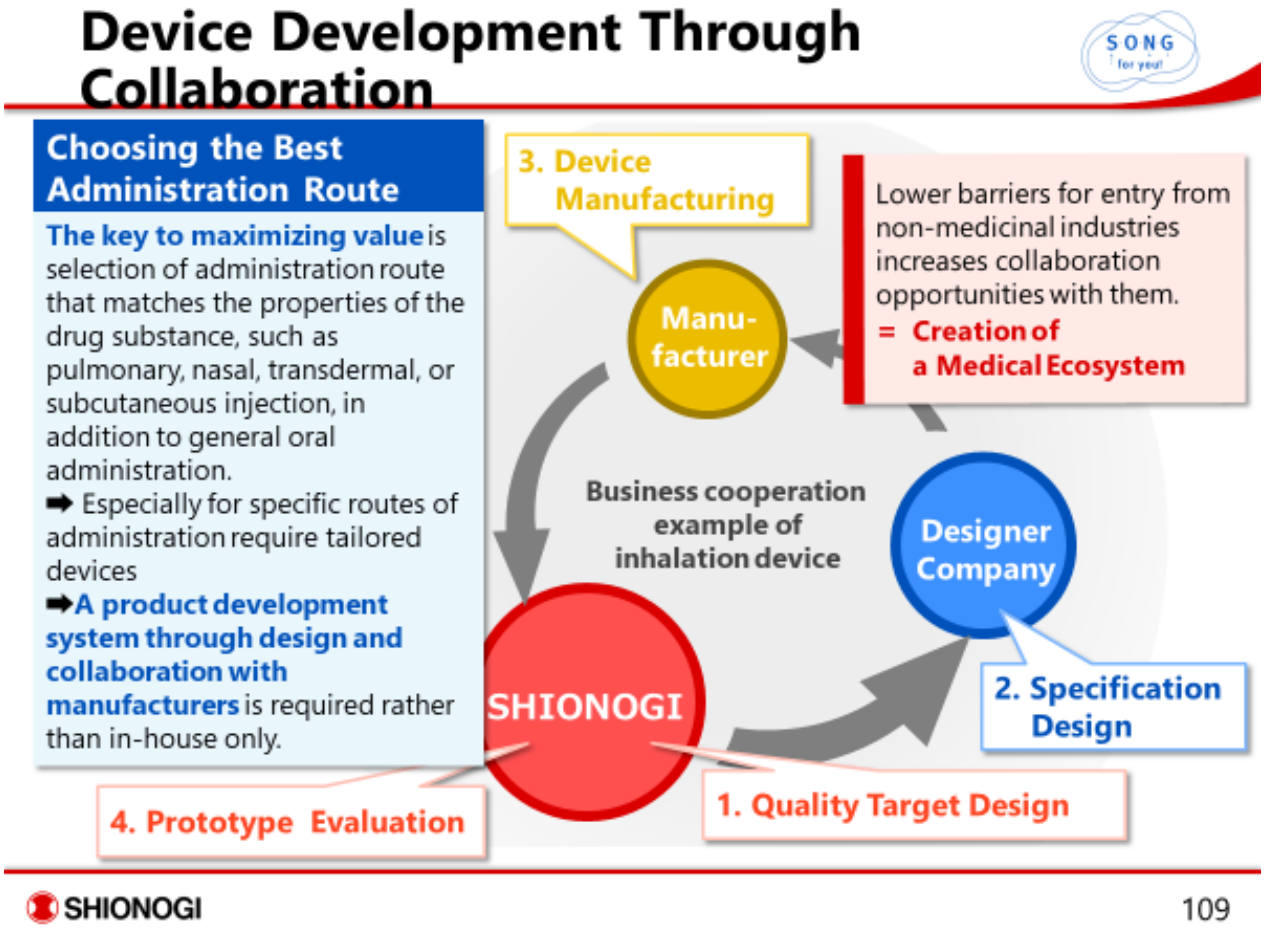
*API: Active Pharmaceutical Ingredients
** DP: Drug Product

Let me move on to page 108. This slide shows improved industry productivity by continuous production of S-600918. In general, continuous production has already used in the field of pharmaceutical production. However, the greatest issue is Process Analytical Technology, so called PAT.

At present, the greatest problem is how to secure the quality in the continuous production and how to make an analysis.

Facing that issue, we have decided to use an in-line monitoring technology, which is a new spectroscopic technique and is a joint research. Using such highly advanced technology, we will proceed with analyses of in-line continuous production.

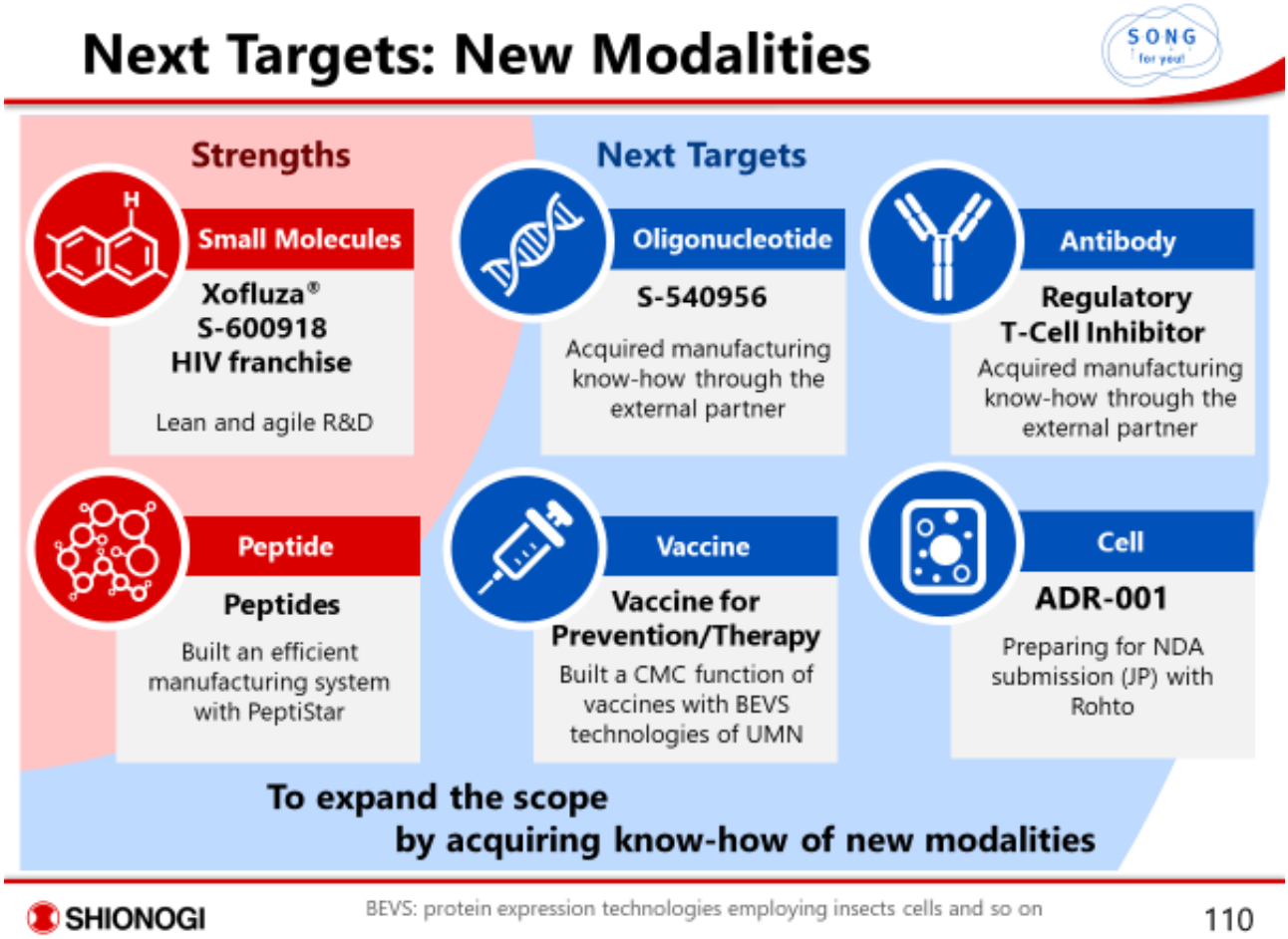


On page 109, I would like to talk about device development through collaboration with other companies. I think that highly diversified drug administration routes will be selected in the future. This trend will certainly be relevant to improvement of the product value. In that case, we have to choose best manufactures for producing such devices.

I often hear that manufactures with advanced technology find it difficult entering into the field of medication development, feeling barriers of regulations on pharmaceutical products.

Because our company has a rich stock of know-how and expertise on that matter, we would like to establish a framework to discover and develop the best novel products with the best partners by extending the opportunities for collaboration with companies which have had difficulty entering into the medical field and lowering the barriers so that the medical ecosystem can be established.

We have already built up the framework and collaborated with some partners in developing an inhalant device and a transdermal absorption device.



Please look at page 110. As we have discussed the area to be enhanced in the future as well as technology acquisition and application of modality, we consider that Shionogi has a great strength in small molecule preparations. In addition, regarding peptides, I consider we are approaching the realm of strength through collaboration with PeptiStar Inc. and the technology that we have touched upon in the presentation.

In addition, regarding the area to be enhanced in the future, mainly on biopharmaceuticals, we are glad that UMN Pharma Inc. has become one of our group companies in the field of vaccines. Their technology is basically related to biopharmaceuticals, and it can be converted to development of antibodies and cells.

Currently, technology transfer or technology application has been much discussed in the field of biological medicines. We hope that we will actively work on antibodies, cells or gene therapy based on such technology application. This slide shows that we aim at moving into the area to be enhanced by acquiring novel modality technology.

Strengths of Shionogi CMC

Provide solutions for research and development with high probability of success

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

Creation of completely new added value through product research

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

Improve industrial productivity

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

Create unexpected value from Shionogi's production technology

This is the last slide. As I have mentioned a little, regarding the strength of Shionogi's CMC, we will actively work on application of CMC technology to provide solutions in the early phase for raising success rates of drug discovery.

Then, we will research how to commercialize our products to meet product needs and market needs in a thorough manner so that we can attain drug discovery with completely novel added values.

And finally, in terms of further improvement of industry productivity, we hope to contribute to cost reduction and productivity enhancement through technology development such as continuous production.

Our motto for the future is to lead Shionogi's manufacturing strength by creating values that we have not seen.

That's all from the CMC Group.

Kyokawa: Thank you very much. Now, Dr. Teshirogi would like to sum up the presentation.

Teshirogi: Because we are running behind schedule, I will not touch upon what is written in the presentation material. But let me add a few things. One is that we would like to proceed with the R&D operation by these members, Sawada, Kiyama, Iwasaki and Iso for a while. If it doesn't work with these members, it can't be helped. In this sense, these people may feel considerable pressure, but I hope they will be thrilled with it and go ahead.

Another subject is about the novel coronavirus. Some people criticize that Shionogi is too quiet about this matter and seems to do nothing even the company is a manufacturer of anti-infectious disease medications. However, we would like to convey highly reliable information when publishing a news release because we are a company specialized in infectious diseases. This is our in-house basic concept.

As Kiyama mentioned, we have started a project on coronavirus including the new type since December. As you have seen, chemical compounds with the size of 100 nanometers or double-digit nanometers have been found. If we commit ourselves to this task including how we proceed with it, we would like to pursue chemical compounds steadily and appropriately so that they will be good drugs in the world. We proceed with it at top speed.

Concerning influenza test kits currently much talked about, we, as a company, would like to confirm the positioning of the PCR test in society. We have experience in testing ordinary types of influenzae, and we know that the accuracy differs depending on from which part the sample is collected, that is, from the nose, throat or the oral cavity. Taking this into consideration, there may be space that we can contribute to society with a kit to test blood samples as a quick scan which we think it useful for testing much more patients, although the PCR test should be used for the final confirmation.

Because we have committed ourselves to the field of infectious diseases, we hope we continue offering information what we can do from our perspectives based on our experience and expertise.

I'm going to finish soon, but there is one more thing I would like to point out. I consider that all pharmaceutical companies including Shionogi should pay special attention to how the novel coronavirus will affect clinical studies currently underway in the world.

At present, Global Development Division is investigating how the novel coronavirus will have impact in detail, especially on doctors who are experts of infectious diseases or respiratory diseases and how the virus has affected hospitals in which clinical studies have been stopped because of the shutdown. I'm sure the Division stays on top of the status of clinical studies which are ongoing without delay, comparable to other pharmaceutical companies. I hope to keep communicating with you about how the current situation is going to affect clinical studies from the perspective of the entire pharmaceutical industry by continued close observation.

Key Events for Major Pipeline Compounds

Pipeline	Mar. 2020	FY2020	FY2021	FY2022
S-648414 HIV infection	Ph1 on-going	Ph2a start (2Q)	Ph2a topline results (4Q)	
S-540956 Infectious diseases, cancer	Non-clinical		Ph1 strat (4Q)	Ph1 topline results (3Q)
zuranolone Depression	Ph2 start		Ph2 topline results (3Q)	
S-600918 Refractory chronic cough	Ph2b on-going		Ph2b topline results (1Q)	
S-600918 sleep apnea syndrome	Ph2a start		Ph2a topline results (1Q)	
S-637880/S-600918 Neuropathic low back pain	Ph1 on-going	Ph1 top-line results (2Q)	Ph2a start (4Q)	Ph2a topline results (4Q)
BPN14770 Alzheimer's disease	US Ph2 topline results	Ph1 start (1Q)	Ph1 top-line results (4Q) / Ph2/3 start (2Q)	
S-874713 Psycho-neurological diseases	Non-clinical		Ph1 start (4Q) / Ph1 top-line results (4Q)	Ph2 start (1Q)
SDT-001 ADHD	Ph2 on-going		Ph2 topline results (2Q)	
S-109802* Post-stroke spasticity	Non-clinical			Ph1 start (3Q)
S-872881** Alzheimer's disease	Non-clinical			Ph1 start (2Q)

★Ph2 or Ph3 topline results are anticipated

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* S-109802: Profiles are shown in appendices, p.137-139
** S-872881: Profiles are shown in appendices, p.140, 141

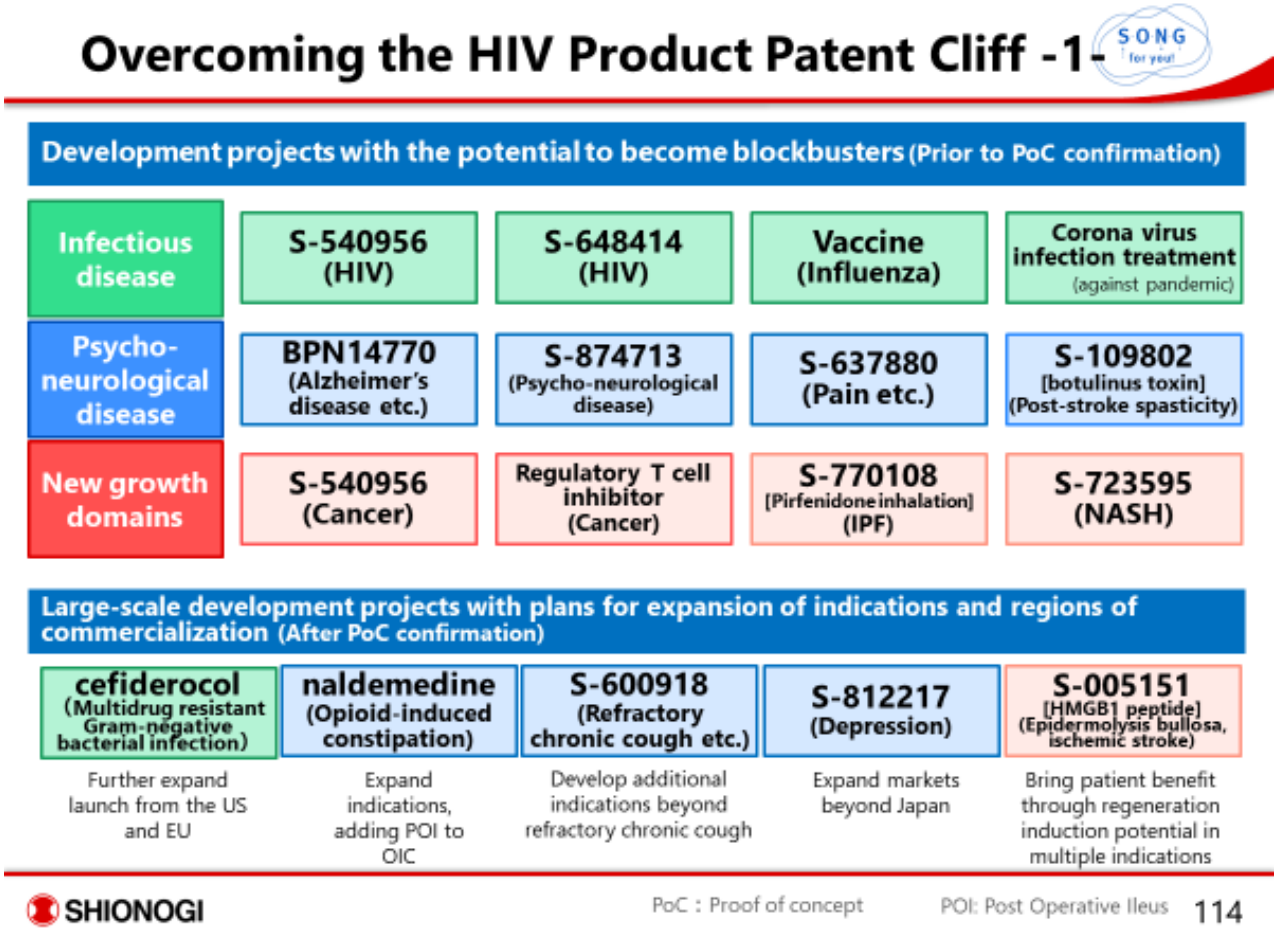
Key Events for Major Pipeline Compounds

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

★ Ph2 or Ph3 top-line results are anticipated

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

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



What I would suggest you follow up are pages 99, and 100 where Iwasaki discussed the events from 2020 to 2021 as well as my part on page 114 . We have discussed how we should overcome the patent cliff of HIV products, how much sales volumes are there, and how many patients we can make contribution to. Taking these into consideration, these three years will be extremely important for the future of Shionogi. We kindly ask for your understanding.

Activities to Fight Infectious Diseases

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

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

* Patients with no or limited treatment options

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

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

SHIONOGI

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

Before concluding the presentation, let me talk about one more thing. Please look at page 118. In fact there are not so many companies seriously working on the AMR issue. But, Shionogi would like to take the comprehensive initiative including cefiderocol on infectious diseases including the AMR issue all the way.

Fortunately, many people in the world have come to recognize the company name, Shionogi and our serious commitment to infectious diseases perhaps because of the ESG ratings. We would like to continue our efforts on this field.

I'm afraid I may have talked a bit too long. I would like to end the wrap up. Now, let us proceed into a question and answer session. Thank you very much.

Q&A

Kyokawa: Now, we have just 20 minutes or little more. So please ask questions briefly, and please give your name and affiliation.

Yamaguchi: I'm Yamaguchi from Citi.

First, I would like to ask a little bit about coronavirus. After checking the activity of Product 1, you said something like high-throughput, and blah-blah-blah. It's obscure whether or not you will proceed with it. Please explain first about how fast you can advance this Product 1 or 2 in a best-case scenario.

Kiyama: As everyone knows, any development of a drug does not progress so easily. Currently, we are only examining the efficient activation of these substances in vitro. To make them pharmaceutical products, we also have to confirm their safety as a matter of course. Given the scope of normal drug discovery research, I don't think that these compounds will meet the current corona crisis.

In the bottom we have remdesivir and favipiravir. They are very broad-spectrum compounds that have been designed to be effective for a variety of viruses. When considering the future pandemic, we think we need to prepare such products, too. We also believe that in the selection of compounds, we should choose ones that are effective for various viruses to some extent, including coronavirus.

Yamaguchi: Second, I found the functional cure of HIV in the first part of the presentation. I think that you are aiming at functional cure with S-540956, S-648414 and one more research project. Do you mean that currently your company already has all of the 3 compounds including the research project and will try to achieve the functional cure by combining the 3 compounds?

There are too many pages for the figures of HIV, so I don't remember it, sorry.

Teshirogi: In the "kick & kill" concept, the kick part will be done with S-540956 and we consider that it will give interesting results to some extent. With regard to how to handle the kill part, if a sustained-release injectable is actually available with few adverse reactions, we may be able to take the control to some extent. Considering this, we think we can use cabotegravir as a single entity administered about once every 6 months with devices of the drug formulation.

However, if considering up to the combination therapy with 2 drugs, or combination product, we may need more time including the S-648414. However, for the kick part, as the characteristics of S-540956 are very excellent compared with other drugs, it depends on the kill part, how much we achieve it using a sustained-release approach. We have almost all the materials. So, we are considering how to develop with them.

Yamaguchi: Thank you very much.

Kotani: I'm Kotani from Nomura Securities, I have two brief questions.

The first question, this presentation includes cancer, sorry, I have not been looking at your company so long time. But It seems that cancer was excluded once during some process and this time it is included again.

Most Japanese pharmaceutical companies are tackling cancer and central nervous system. But I feel that each company has totally different concepts and I also feel why they do not get into a fight about this. The reason is that, from the view point of person in the area of cancer, the procedure for the study on the central nervous system always uses very clear molecular mechanisms, for example, why does the study proceed with such data? In the case of your company, particularly, well, when it comes to infections and the central nervous system, to be honest with infections, you can see the viruses dead on the petri dish. As for HIV, it probably needs only the verification of safety.

On the other hand, for the central nervous system, you mentioned such as striatal circuits. But I am a little suspicious about whether you really understand the chemistry.

What I want to ask is why you did not tackle cancer. Besides, in my opinion, your company's strength for the area of central nervous system is rather the method for advancing clinical trials or administrative method, and by this you have developed such drugs as Cymbalta. What is the strength of your company for the area of central nervous system? And why cancer?

There are several generations for EGFR mutations as you know. Moreover, the resistant mutations have been emerging. Don't you think this looks like infections? If your company can develop drugs that treating all of them, I think it will suite your company's strength.

Although this might be the speak of the devil, I would like to know why you do not address oncology. This is the first question.

Sawada: Personally, oncology is one of my favorite field, but we cannot address this field unless we have many drugs to some extent as well as funds and resources that allow some amounts of investment.

As you know, the potential field involves multiple disciplines and we need to advance each of them at the same time to win the competition. From the standpoint of these issues, we think it is relatively difficult for our company to tackle and focus on this area.

However, on the other hand, as you said, infections and cancer are actually rather similar. At our laboratory, some researchers are studying cancer. Interestingly, although oncology is not our focused area, the researchers advancing the project with an absolutely strong will are doing something quite interesting. I think that this is flowering slightly now.

So when something interesting emerges, we are going to utilize it thoroughly. We feel it's lucky for us about the current oncology.

In particular, we think Professor Sakaguchi is the best partner for us to research Tregs together this time. Including this, we are feeling that something rather interesting has been appearing.

Kotani: Falling short of high expectations is probably an usual practice for people of Osaka. I am sorry to say this, but on the page 26, well, before that I have to ask about regulatory T cells on the page 22. After all, most researches targeting regulatory T cells have not gone well. In short, what we expected most was CCR4, or mogamulizumab, which was highly expected because it attacks only effector regulatory T cells, but consequently it was not so useful in cancer treatment.

To be honest, the only successful research is CTLA-4, although there are still various theories. Why does this project go well? Because the partner is Professor Sakaguchi? Or do you have any other reasons? And, briefly about S-540956. This is an adjuvant of nucleic acid as single agent and on the page 26 is PDX of SCID mice, isn't it? I think this is a xenograft derived from patients, but please explain why this is effective for mice with no immune cells and whether the nucleic acid itself, or adjuvant itself has antitumor effect. This is the final question.

Sawada: With regard to CCR8, after all, Professor Sakaguchi is the best partner for researches on Tregs. The project at the moment is still at a non-clinical phase, and so it is true that we cannot guarantee the 100% clinical success.

However, the key issue concerning Tregs is adverse reactions, various types of actions as expected. We are very concerned about the possibility that Tregs can induce autoimmune diseases and we have been very worried about this from the beginning.

In doing so, the reason why we got very interested in CCR8 is that it expresses only on the Tregs in the tumor tissues. Including this, If we further investigate it to truly re-confirm, it will be a very exciting topic.

The current immune checkpoint inhibitors release the brake, on a premise that CTLs are induced in a sense. However, if the CTLs are basically not induced, the current checkpoint inhibitors do not function. In this regard, now our pipelines are rather aiming to press the accelerator. If all of these 3 pipelines go well, it is best for us, but even if all of these 3 go bad, we think we still can provide a new modality by combining some of them.

Sorry, though I have not checked the experimental results yet, we actually have confirmed the induction of CTLs. It can't have been tested in a setting without T cells. We will answer this question from the laboratory again.

Hashiguchi: I'm Hashiguchi from Daiwa Securities. Between the last year's 8 projects with priority and this year's 8 projects, some of them were replaced. I don't understand what change occurred in the situation. Please explain why you include the project with Tetra this time.

Teshirogi: Tetra initially started working on BPN14770 as Fraile X research. Then in the US, they kicked off clinical trials of this compound intended to investigate it as add-on therapy to donepezil and other existing drugs in patients with MCI and those with mild to moderate Alzheimer's disease. To be honest, in our original timeline, we expected to obtain results from their phase 1 study this coming August or September.

However, as Iwasaki mentioned, the subject enrollment went so smoothly that the phase 2 study was almost completed as of the end of the last year, and Tetra asked us what we desired to do after study completion. Actually, at that time, Tetra was being actively approached by some other interested company, so it was time for us to assess the situation and make the decision to proceed or withdraw.

Iwasaki didn't touch on this much, but we noticed that among the initial subjects, some 260, 270 individuals, PDE4-related gastrointestinal effects, especially nausea and vomiting, were not common, indicating that this investigational drug might have a mechanism of action somewhat different from those of exiting PDE4 inhibitors. We thought that it would be worth proceeding to investigation for the efficacy of this study drug.

The top management at Tetra was also eager—you could confirm them if you'd like—to go on with this research; they said that Shionogi would make a great partner for them, considering the chemistry between their and our researchers and other factors, and that they could realize what they wanted to accomplish together with us. We felt their passion and decided to get in the same boat. This is how this research has been included in our current projects.

We expect the first readout from their phase 2 study during this March or April at the latest. We would be happy to share the information with you when it is available.

Hashiguchi: One more question, please. It's about CCR8. I understand that a couple of other companies, like AstraZeneca, performed preclinical testing on this. Their studies had negative results while you see some potential in the anti-CCR8 antibody. May I ask what made the difference?

Sawada: We understand some competitors are already preparing for clinical investigations of anti-CCR8 antibodies. These antibodies have become one of the high-profile research targets, so we have no time to waste.

Hashiguchi: Thank you for your answers.

Wakao: I'm Wakao from Mitsubishi.

You showed us some compounds in your pipeline and expected launch timings on page 101.

My first question is about these compounds. I expect you to conduct studies on your own until you obtain POC confirmation. Would you briefly comment on your development strategies beyond that point?

I believe it would be hard time-wise to perform all necessary investigations in-house while excessive outsourcing would be undesirable profit-wise. I think you have been in large part supported by the loyalties from HIV. Under such circumstances, you chose to enter into the US market. Now could you tell us what you plan to and not to undertake in-house in completing the development of your compounds taking your next medium-term management plan into consideration?

Teshirogi: What you said is right. We hope to increase the part we engage in in-house wherever possible in the infectious disease area and also hospital setting treatments—we have just launched cefiderocol—and respiratory filed.

It will be difficult for us to handle marketing ourselves, mainly in the US, of primary-care drugs, for which the presence of salesforce is essential.

Therefore, somewhere in late clinical trial stages, we may seek partnership with a third party or consider something like a licensing-out model. Marketing can be undertaken only in the presence of a considerably large-scale infrastructure, and it can be a too big challenge for us to address single-handedly, especially in the US.

Regarding new markets including China, we have been a very slow starter. We are planning to present a newly formulated medium-term business plan next fiscal year. We intend to construct a business model slightly different from our earlier models; it is going to be a scheme that involves our own participation to some degree.

We think we are fit for the marketing of infectious disease drugs and CNS disease treatments in hospital settings, and this is what we aim at. In line with this strategy, we are going to examine carefully what extent of in-house engagement would generate what value.

Wakao: I see. Then, am I correct assuming that your basic business strategies will remain as they used to be?

Teshirogi: Yes, you are.

Wakao: Thank you for clearing my first question.

My second question concerns adjuvants, including nucleic acid ones, and their production. If my memory serves me right, I think you mentioned the possibility of licensing out your adjuvants in the last fiscal year's R&D meeting or the one before that. I would like to know if that possibility still holds.

I understand that nucleic acid-based drug production is challenging in various aspects, including being technically difficult and time consuming, but you have technical know-how for efficient production of such drugs. I wonder if you are interested in producing nucleic acid-based drugs other than adjuvants for the treatment of additional disease areas—antisense nucleic acids, nucleic acid-based MSI testing, etc., and also the DMD nucleic acid drug, which has become available lately. May I have your comment on this?

Teshirogi: As for nucleic acid-based drugs, our laboratory has been ardently exploring their scientific feasibility; we'll see what will come out. Our approach will depend on the outcomes, but our basic stance is to undertake the effort ourselves required to identify how to utilize nucleic acid-based drugs wherever they are to be used as the therapeutic base for the treatment of infectious diseases.

When it comes to other disease areas, such as tumors, it would be nearly impossible for us to conduct all investigations necessary to enable the use of our adjuvants. Even in the final stage of investigation, for example, individually not effective adjuvants may be found to be effective when given together, for instance, with anti-CCR8-antibody therapy, as Sawada said earlier, but taking account of what it takes to identify such effective combinations and what is entailed in completing large-scale clinical trials that require plenty of various resources,

we won't be able to take care of everything on our own. In such cases, we may consider finding a research partner even for investigations on our adjuvants including S-540956.

Kiyama is here to explain our current status of nucleic acid-based drug development.

Kiyama: We have a research group specialized in nuclear acid-based drugs within our recently established laboratory called Discovery Research Laboratory for Innovative Frontier Medicines. The group is to take over the relevant tasks we have pursued.

Actually, we already have two useful programs under way; we'd be happy to share more details when the time is right.

Wakao: Recently we have seen a number of attempts to treat rare diseases with nucleic acid-based drugs. Considering the small patient population sizes for such diseases, I wonder if you too may be interested in tackling this issue yourselves. I understand that rare disease therapies have not been included in your key areas. Am I correct assuming that basically you are not very much inclined to develop nucleic acid-based drugs to treat rare diseases?

Teshirogi: We are not targeting rare diseases in particular but are willing to address this issue when we have some compounds in our pipeline that could potentially help patients with rare conditions; S-005151, for instance, is a drug candidate to treat epidermolysis bullosa, which is an extremely rare disorder.

Currently, it is not our style to specifically target any rare disease and attempt to design a nucleic acid-based drug or identify an antibody that suits such a need.

Wakao: I see. Thank you for your explanation. That would be all from me.

Kyokawa: Thank you. This is the last question from the floor, please.

Sakai: I am Sakai, Credit Suisse. Please let me ask 2 brief questions.

Everybody here probably knows this question. It is about Cymbalta. Today, I understood well about the HIV cliff in 2028, but I would like to know about the Cymbalta cliff in 2021. I guess it is untouched at all now because of the delay of S-812217. Do you mean we have to wait until the next medium-term management plan? I would like to know more clearly how you are going to make up for that.

Teshirogi: Of course, we will state that in the medium-term management plan in principle, but fundamentally, for example on page 101, you can see that this pipeline has a large dent in the fiscal year of 2021 and 2022. So, how to cover this in the short term is a critical issue also for our company.

That is what the BD team, John in the lead, is frantically tackling to address.

However, as we always say, we have to prepare for the worst-case scenario depending on what we can buy with how much amount of money and how we can materialize them.

I would like to say that I am considering we have to find some way to cover this.

Sakai: Please let me ask one more question about cefiderocol. You said about AMR relating to ESG in the last. In these days, we often hear about the Priority Pathogen List of WHO and CDC, is it correct? Considering the indications of cefiderocol, I think it is probably difficult to make this product a blockbuster, but I think it is very important to be listed in the list of WHO and CDC. Could I have the update around that?

Sawada: As you said, it is the only compound that completely covers in particular, the “Critical” in the Critical Pathogen List of WHO among those in the late development phase or in the market including colistin. Thus, we would like to take that advantage.

However, the unhealthy situation of the AMR market itself is a world concern. So, I do not mean to make use of this pandemic, but I would like to advance a discussion about how we can change the market itself healthier to address the future, more drastic pandemic and would like to continue the activity for that.

Sakai: Thank you.

Kyokawa: Thank you very much. We have 1 or 2 minutes left, but we would like to have only one question from the telephone.

Muraoka: I am Muraoka, Morgan Stanley.

The first question is about a compound from Tetra, in Phase 2 for Alzheimer. I am asking figures after the next term, but if we have a good result with no trouble, to how much extent do we have to be prepared for the increase in R&D budget? This is the first question.

Teshirogi: As Iwasaki told now, we do not consider the phase for prevention. So, the phase 3 program will cover the treatment, that is, treatment from MCI to mild to moderate, and we consider that we can sufficiently manage the program. If we developed a so-called β-amyloid related drug to confirm the prevention of development, the number of patients and the term of the program would be enormous. However, this is not the case and we consider we can make a manageable phase 3

program with a relatively short period, of course, we have to evaluate the safety for 1 year or longer term.

As Wakao-san previously said, we do not think there will be a huge jump, and we think we can proceed following the present strategy.

Muraoka: I understood, thank you very much.

One more question about S-812217, zuranolone. I would like to know the length of the interval period in the figure. Is it 1 month or half a year? It may be related to the design of the clinical study, but could you tell how long it would be?

Iwasaki: Iwasaki answers this.

This is now being evaluated from 3 aspects. Because this is a GABA modulator, one is the interval from the aspect of safety. For example, respiratory depression or dependency. Another is the interval from the aspect of efficacy as a single drug, and the other is the interval from the aspect of coadministration with SSRI or SNRI. The interval period will be determined from these 3 aspects but based on the available data from the phase 2 or non-clinical studies, we could expect 4- to 6-week interval when administered alone.

In addition, from the aspect that how long it could be extended when SSRI or SNRI is added on, we hope we could obtain data about relapse or remission over one year.

Muraoka: I understood, thank you for the clear explanation. No more questions.

Kyokawa: Thank you very much. Now the time is over, so we would like to close the R&D meeting of Shionogi & Co., Ltd.

Teshirogi: Thank you very much for your attention. [End of document]