

Kyowa Kirin Co., Ltd.

Kyowa Kirin R&D Meeting

December 5, 2022

Event Summary

[Event Name]	Kyowa Kirin R&D Meeting	
[Date]	December 5, 2022	
[Number of Speakers]	1 Yoshifumi Torii	Executive Officer, Vice President, Head of R&D Division

Presentation

Moderator: We will now begin the FY2022 R&D Meeting for Kyowa Kirin.

Please note the following prior to the start of the event. Please be advised that we will keep a list of the names and company names of participants for a certain period of time.

Please note that the content of this presentation will be available on our website as an on-demand video stream and transcript.

The information presented today contains forward-looking statements. Please note that there is uncertainty due to various risks.

Today's speaker is Dr. Yoshifumi Torii, Vice President and Head of the R&D Division. After Torii's presentation, he will be available to answer your questions. Today's session is scheduled for up to 90 minutes.



Torii: Thank you very much for taking the time out of your busy schedule today to participate in the Kyowa Kirin FY2022 R&D Meeting.

Let me begin by explaining the vision we have set forth in our medium-term management plan.

This slide outlines our vision toward 2030. Kyowa Kirin will realize the successful creation and delivery of life-changing value that ultimately makes people smile, as a Japan-based Global Specialty Pharmaceutical company built on the diverse team of experts with shared passion for innovation.

In order to achieve this vision, we have established three strategic pillars, as shown on the right, and are working vigorously on a daily basis.



This slide presents our R&D model.

We aim to create life-changing value with clear competitive advantage by building a technology axis through the evolution of basic drug discovery research and drug discovery modality technologies, and by combining this with a disease axis and the use of open innovation to develop our research and development.

Today's Agenda

- Toward the Creation of Pharmaceuticals for High Unmet Medical Needs - From Our Investigational Products
 - KW-3357 (Preeclampsia)
 - KHK4951 (Tivozanib eye-drop)
- Toward the Successful Creation and Delivery of Life-changing Value - From Early-stage R&D Activities
 - Data-driven drug discovery Collaboration with InveniAI
 - Deepening Kyowa Kirin's Antibody Technology Collaboration with Synaffix
 - The pursuit of innovation with a long-term perspective VC fund investment/CVC activities

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Today I will present these topics described here based on our vision and R&D model.

First, I would like to introduce KW-3357 and KHK4951, two of our products under development, as part of our activities to discover drugs that meet High Unmet Medical Needs.

I would also like to continue by introducing our early-stage R&D activities, which are indispensable for the continuous creation of life-changing value.

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Toward the Creation of Pharmaceuticals for High Unmet Medical Needs - From Our Investigational Products

KW-3357 (Preeclampsia)

KHK4951 (Tivozanib eye-drop)

Then, I would like to introduce some of the products that we have developed as part of our efforts to create drugs that meet high unmet medical needs.

The first is KW-3357, which has already been marketed under the product name ACOALAN[®]. Today, I will present an overview of this product for the indication of preeclampsia, which is currently under development.



Let me begin by introducing preeclampsia.

Preeclampsia is a hypertensive disorders of pregnancy, a serious disease that is triggered by pregnancy and causes hypertension as well as central nervous system disorders, pulmonary edema, liver dysfunction, renal dysfunction, and other complications.

If the onset of the disease is early, the baby is more likely to be premature, so the gestation period is tried to be extended as much as possible. However, since there is currently no effective treatment, the rate of premature births and NICU hospitalization is high. In some cases, for example, when the baby is delivered in the early 20-week gestation period, the newborn may die.

The incidence is reported to be 2.7% of the maternal population in Japan and 2% to 5% globally. The cause of the disease is said to be the failure of placentation in the early stages of pregnancy, followed by an imbalance between neoplastic and inhibitory factors of blood vessels in the middle and later stages of pregnancy.

It has been reported that low antithrombin activity at the onset of preeclampsia is associated with a higher risk of early pregnancy termination. Thus, low antithrombin activity is considered one risk factor for pregnancy termination.

The only definitive curative treatment at present is to end the pregnancy. As I mentioned earlier, if the onset is early, the baby's prematurity becomes a problem. Therefore, it is desirable that the gestational period is extended. However, drugs for hypertension have the potential for adverse effects on fetuses and

placental function by lowering blood pressure. In addition, no other drugs are currently in company-led development.

Thus, preeclampsia is a serious disease that, once developed, is difficult to treat and can be fatal to fetuses, and cause complications for mothers. However, effective treatment has not yet been established.

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KW-3357 Overview

- Generic name: Antithrombin gamma
- Product name (in Japan) : ACOALAN[®] for Intravenous Injection 600, 1800
- Indication: Congenital antithrombin (AT) deficiency-based thrombogenicity and disseminated intravascular coagulation syndrome
- Ph3 study (KOUNO-TORI) underway for preeclampsia
- Features
 - A recombinant human AT pharmaceutical with an amino acid sequence identical to that of human plasmaderived AT
 - Modification to the same type of glycans as human plasma-derived AT by POTELLIGENT[®] leads to its persistence comparable to that of human plasma-derived AT^{*}
 - Manufactured with CHO cells, no other biogenic raw materials used = Low risk of infection + Stable production
 - Exhibits anti-inflammatory effects by binding to heparan sulfate in vascular endothelium and to molecules on neutrophils = **Potential to improve organ damage** in addition to anticoagulation

* It is known that ATs produced with conventional methods shows low-persistence due to the additions of glycans that are different in type from human plasma-derived AT.

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Next, I will give an overview of KW-3357.

The generic name is antithrombin gamma, and the product name is ACOALAN[®]. Existing indications are congenital antithrombin deficiency-based thrombogenicity and disseminated intravascular coagulation syndrome, or DIC. We are currently conducting the Phase III clinical trial for the new indication of preeclampsia in Japan.

KW-3357 is a recombinant human antithrombin (AT) pharmaceutical with an amino acid sequence identical to that of human wild-type AT. The glycans have been modified to the same type as the wild-type one by POTELLIGENT[®], our glycan control technology. This technology gives blood persistence comparable to that of human plasma-derived AT.

In addition, since KW-3357 is manufactured using CHO cells, and no other biologically-derived materials are used, it is less likely to cause infectious diseases than human plasma-derived AT products. Also, since it does not depend on blood donations as human plasma-derived AT does, a stable supply can be ensured.

Regarding the mechanism of action, along with anticoagulation, it has been also reported to exhibit antiinflammatory effects by binding to heparan sulfate on vascular endothelium and the certain molecules on neutrophils, which may reduce organ damage.



This slide explains the bioequivalence to human plasma-derived AT products.

The graph on the left shows the average plasma antithrombin activity of 60 units/kg of human plasmaderived AT versus 72 units/kg of KW-3357 administered intravenously once daily for three days to healthy adult male patients.

As you can see, both drugs showed comparable antithrombin activity.

The pharmacokinetic parameters are shown on the right. These results statistically confirmed the bioequivalence of the two drugs.

Thus, KW-3357 was shown to achieve the same level of plasma AT activity when administered at 1.2 times the dose of human plasma-derived AT.



Finally, I would like to explain the Phase III study, KOUNO-TORI, which we are currently conducting in Japan.

Eligible subjects will be patients with the onset of disease between 24 and 32 weeks gestation, considered clinically significant for prolonged gestation, a diagnosis of severe disease, and confirmed antithrombin activity of less than 100% on the screening test.

The target number of patients is 180, and the actual drug and placebo groups are assigned 1:1. The study design, which is shown here, is to administer KW-3357 or placebo once daily for seven days to patients who are found to be eligible by screening test and follow them until 28 days after end of pregnancy.

The primary endpoint is the number of days of gestational duration, and secondary endpoints are the achievement of up to the number of weeks of gestational age, which is a measure of baby growth, and items that may lead to the elucidation of the mechanism of action and items related to baby growth. The trial is scheduled to be completed at the end of July 2023.

Toward the Creation of Pharmaceuticals for High Unmet Medical Needs - From Our Investigational Products

• KW-3357 (Hypertensive nephropathy of pregnancy)

KHK4951 (Tivozanib eye-drop)

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I will now move on to KHK4951, tivozanib eye drops.



First, let me introduce the disease under development, neovascular age-related macular degeneration, or nAMD.

This is a disease that causes abnormal angiogenesis in the macula at the back of the eye, resulting in vision loss. Currently, the number of patients treated with drugs is estimated to be approximately 200,000 in Japan and 1.6 million globally.

The disease is thought to be caused by the deposition of waste products in the macular retina due to aging. This stimulates the production of a vascular endothelial growth factor called VEGF, resulting in the formation of highly exudative choroidal vessels, which in turn causes retinal edema. This ultimately leads to neuroretinal damage.

Currently, the mainstay of treatment is intravitreal injections of anti-VEGF drugs, as shown here, in which the drugs are administered by injecting them directly into the eye. Since this is a highly invasive treatment that requires continuous hospital visits and surgery, the establishment of a non-invasive treatment method is desired in the medical field.



Next, I will discuss tivozanib, the active pharmaceutical ingredient in KHK4951.

This compound is a small molecule VEGF receptor inhibitor that we created. Tivozanib is currently marketed by our partners in Europe and the United States as FOTIVDA, a treatment for renal cell carcinoma.

This compound is characterized by its high selectivity for VEGF receptors and very potent inhibitory activity, as shown in the figure.



Here is a brief history of tivozanib to date.

In December 2006, the Company at the time licensed the drug to AVEO Pharmaceuticals. Subsequently, in December 2015, EUSA Pharma acquired the European marketing rights for FOTIVDA from AVEO.

On the other hand, in August 2019, Kyowa Kirin bought back from AVEO its development and marketing rights for tivozanib in the non-oncology area. In April 2020, Kyowa Kirin initiated a Phase I study of an eyedrop formulation as KHK4951.

Subsequently, in 2021, FOTIVDA received approval in the US as an oral treatment for renal cell carcinoma, while this year, the Phase I study of KHK4951 in the ophthalmologic field has reached its last patient out.



I would now like to introduce KHK4951, which we have developed as a new ophthalmic formulation.

Since nAMD is a disease in which retinal tissue is damaged by angiogenesis in the choroid, in the back of the eye, it is very important to deliver the drug to the back of the eye through the administration of this eye drop.

In general, it has proven to be very difficult to deliver drugs to the posterior ocular tissues by ophthalmic administration. Although there have been many attempts to develop eye drops for nAMD in the past, no eye drops have been successfully developed and approved to date.

We therefore investigated new eye-drop formulations and found one that delivers the active pharmaceutical ingredient more efficiently to the posterior ocular tissues than conventional eye-drop formulations, as the information is shown here.

Ph1 Study Synopsis (ID: 4951-001)

ClinicalTrials.gov Identifier: NCT04594681

		Dosing	Subjects	No. of steps	No. of subjects / step
	Cohort 1*	Single administration KHK4951:Placebo=6:2	Healthy volunteers Japanese/White	5	8
Cohort	Cohort 2*	3W administration KHK4951:Placebo=6:2	Healthy volunteers Japanese/White	6	8
Cohort 3**	3W administration KHK4951 only	nAMD patients Japanese	3	6~10	
Endpoint	 Adverse events, Laboratory test, Vital signs, General physical exam, 12-lead electrocardiogram Ophthalmic exam (Visual acuity, IOP, Slit-lamp exam, Fundus exam, OCT) Secondary endpoints: Assessment of pharmacokinetics and efficacy Pharmacokinetics (Serum KHK4951 concentration, Pharmacokinetic parameters) Efficacy CST (Central subfield retinal thickness) BCVA (Best corrected visual acuity) Retinal morphological change with OCT (SRF, IRF, sub-RPE fluid, Dry macula, SHRM) 				

Here is an overview of the Phase I study.

In addition to healthy volunteers, some nAMD patients also participate.

The primary endpoints are safety and tolerability. Secondary endpoints are pharmacokinetics and efficacy.

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Ph1 study results (ID: 4951-001)

- Achieved Last Patient Out
- Safety, pharmacokinetics, and pharmacodynamic data are under analysis
- Received positive feedbacks from global KOLs in discussion regarding the Ph1 data .

Anatomical changes of retina: OCT (Optical Coherence Tomography) image

Note: This is an example when	e KHK4951 was found to be effective
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Step 2 Treatment naïve PCV / Occult with No Classic CNV

In preparation for a publication of the Ph1 data

Here is an excerpt of the Phase I study results.

As I mentioned earlier, the drug has just recently achieved last patient out. The safety, pharmacokinetic, and pharmacodynamic data obtained are currently being analyzed.

Based on the data obtained, discussions have been held with key opinion leaders in Japan, the US, and Europe. Positive feedback has been obtained to date.

In addition, here is a so-called OCT image that shows the anatomical changes in the retina. Of course, please note that this is just an example of an effect that has been observed.

First, the image on the left shows the retina of a patient with nAMD before KHK4951 administration. The arrows show the bump due to leaching from the neovascular vessels. When 4951 is administered, as you can see in the photo on the right, the bump in the arrowhead area disappeared, suggesting that the drug is effective.

We are currently preparing the publication for the results of this study and hope to submit it by the end of 2023.

Based on these results, we are considering conducting Phase II trials in Japan, the US, and other countries. We are currently making preparations for this.



First, I would like to present the progress of our activities to date regarding the collaboration with InveniAI as a challenge toward data-driven drug discovery.

Collaboration with InveniAI to date

1. 2018: <u>Started collaboration</u> Explore new indications for existing pipelines 2022: Obtaining new insights into target molecules a efficacy by confirming preclinical POC	nd disease mechanisms of action suggesting
2. 2020: <u>Expanding collaboration</u> Target exploration for next generation antibody technology	 3. 2021: Expanding collaboration New drug research collaborations signed on several new drugs Access to AlphaMeld[®] and Al Innovation Lab Interaction with Al experts team begins

As mentioned at the 2020 R&D Day, we entered into our first collaboration agreement with InveniAI in 2018 to explore new indications with respect to our existing pipeline.

As of 2022, we have found new insights into target molecules, diseases, and mechanisms of action for specific pipelines, and have confirmed non-clinical POC and obtained data that points to their efficacy.

In 2020, we expanded the scope of our partnership to include joint research on our next-generation antibody technology for the purpose of exploring new targets.

In 2021, we also signed a new collaboration agreement on several new drug researches. In addition to these efforts, we have access to InveniAI's AI platform, AlphaMeld, and AI Innovation Lab, which has enabled us to communicate closely with a team of AI experts.

1. Exploration of new indications for existing pipelines



In the joint research that began in 2018, InveniAI has been searching for new indications for our multiple existing pipelines. The Company has provided InveniAI relevant data linked to its own pipelines, and InveniAI discovered target diseases that Kyowa Kirin had not anticipated.

Regarding one of our pipelines, we were able to obtain a POC following lab-based verification and testing within Kyowa Kirin based on a desk-based hypothesis.

This has shown the possibilities in data-driven drug discovery using AI, giving us the chance of finding new drug discovery hypotheses based on hidden associations and causal relationships that are difficult for humans to notice.

We are currently using the same approach to search for new indications for other pipelines.



In 2020, we expanded the scope of our partnership, using AI analysis to search for two target molecules and disease candidates that could be treated that fit the technical characteristics of our next-generation bispecific antibody technology.

Until now, the pipeline has been created by humans based on literature information. However, by using AI, it will be possible to extract information and hypotheses that are difficult for humans to identify. We expect that this will greatly improve the efficiency of the search for optimal target diseases.

We are planning to apply Al-driven drug discovery to other drug discovery modalities, with antibody as a mainstay, to accelerate the creation of our drug pipeline.

3. Expanding collaboration for implementation of AI drug discovery capabilities



Close interaction between AI experts from InveniAI and Kyowa Kirin's researchers

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AlphaMeld[®] used directly by Kyowa Kirin researchers



Accumulating experience in operating AI platforms to implement functions from both software and hardware perspectives

Implementation of AI drug discovery function is one of the most important issues for DX in pharmaceutical companies We continue to take the challenge for the successful creation and delivery of Lifechanging value by combining biotechnology and digital technology

In 2021, a more comprehensive joint research agreement was signed. In addition to the joint research described so far, this initiative, with the support of InveniAI, will implement an AI drug discovery function, which is one of the key challenges in promoting the digital transformation of pharmaceutical companies.

Specifically, we now have access to InveniAI's AI platform, AlphaMeld, and the AI Innovation Lab, allowing us to communicate closely with InveniAI's team of AI experts.

Going forward, we will take on the challenge of continuously creating life-changing value by integrating our strengths in biology with the digital technology of AI drug discovery.

Toward the successful creation and delivery of Lifechanging value - Early-stage R&D Activities

- Data-driven drug discovery Collaboration with InveniAI
- Deepening Kyowa Kirin's Antibody Technology Collaboration with Synaffix
- The pursuit of innovation with a long-term perspective VC fund investment/CVC activities

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Next, I would like to introduce our collaboration with Synaffix, as an effort to deepen our antibody technology, which is one of our strengths.



We are conducting R&D activities to continuously create and deliver innovative antibody drugs based on inhouse antibody library, our new generation antibody technology, open innovation, and technology knowhow, production ability for antibody development.

Today, I would like to introduce one example of open innovation in this context: our collaboration with Synaffix.



Synaffix, with whom we announced our partnership last year, is a company with proprietary ADC technology.

Synaffix's ADC technology is characterized by the fact that the payload can be loaded by the technology to modify glycans shown here, thus there is no need to modify the amino acid sequence of the antibody. Therefore, as a company with multiple antibody pipelines, we are able to efficiently consider ADC development.

In addition, Synaffix has a wide variety of payloads that can be customized according to the disease we are targeting.

These characteristics led us to enter into a partnership with the company.



As I mentioned earlier, we issued a press release last August announcing the agreement. In June of this year we reported the expansion of this alliance with the addition of one more antibody type.

The preclinical stage studies are currently underway for creation of pipelines of ADC products.



Finally, I would like to introduce our venture capital fund investment and corporate venture capital activities.

Approach to generate more innovations for long-term growth



For an R&D-oriented company such as us to grow over the long term, it is important to know how to continue to innovate in the future.

In order to approach to innovations efficiently, it is important to deepen our knowledge by pursuing our own R&D activities. At the same time, we believe it is important to balance the exploration for knowledge regarding new technologies and new areas that are not part of our own R&D activities.

The VC fund investment and CVC activities that we are introducing here are exactly the kind of activities that we see as part of this search for knowledge.



Outline of Activities

VC Fund Investments

- To keep an eye out for the information related to drug discovery to search for innovative R&D seeds
- We have already invested in three companies to date and through this activity, a joint research agreement was signed with LUCA Science



CVC Activities

- To invest in companies from Kyowa Kirin's perspective while leveraging the experience in VC fund investments
- To enable direct communication with venture companies
- The dedicated team consisting of management and members in charge of practical operations was formed to ensure speedy decision-making and operations.
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As I explained earlier, the purpose of VC fund investment is to collect information that will serve as seeds for creative R&D themes by keeping an eye out for information related to drug discovery in order to create innovation in R&D in the future.

To date, we have invested in the three VC funds shown here. Through this activity, we also concluded a joint research agreement with LUCA Science this year.

Next is CVC activity, the purpose of which is the same as VC fund investment. However, in CVC activities, while utilizing the know-how gained VC fund investments, we select companies from Kyowa Kirin's perspective and directly executes investments. This allows us to communicate more closely with the venture companies in which we invest.

In this activity, we have organized a specialized team of management and business staff to ensure speedy decision-making and operations. We have reported in a press release that we completed our first investment in October of this year.



These activities are illustrated here.

In the case of an investment in a VC fund, the venture to be invested in is selected according to the VC's own scope.

On the other hand, in CVC activities, we ourselves select companies based on our own proprietary information and the information and expertise we gain from communication with VCs.

As a result, as shown here, we are able to keep an eye out for a wide range of areas.

In addition, as in the case of LUCA Science I mentioned earlier, it is also possible to shift to alliances or joint research with a counterparty for both VC fund investment and CVC activities, depending on the situation.

Summary

- Toward the Creation of pharmaceuticals for High-Unmet Medical Needs
 - From Our Investigational Products
 - KW-3357 (Preeclampsia)
 - KHK4951 (Tivozanib Eye-drop)
- Toward Continuous Creation of Life-changing Value
 - From Early-stage R&D Activities
 - Data-driven drug discovery Collaboration with InveniAI
 - Deepening Kyowa Kirin's Antibody Technology Collaboration with Synaffix
 - The pursuit of innovation with a long-term perspective VC fund investment/CVC activities

Kyowa Kirin will realize the successful creation and delivery of life-changing value that ultimately makes people smile

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This concludes my presentation.

Today, as part of our efforts to create drugs that meet high unmet medical needs, I introduced the development of KW-3357 for preeclampsia. I also presented progress on KHK4951.

As part of our efforts to continuously create life-changing value, I introduced our partnership with InveniAI, which focuses on data-driven drug discovery, and our alliance with Synaffix for ADC drug discovery. I also discussed our VC fund investment and CVC activities.

Also, we have recently started a part of the Phase III study of KHK4083, or rocatinlimab, called the ROCKET program. Some information about this study is available on ClinicalTrials.gov. We are currently in the process of preparing for the resumption of this program. We will provide an overall picture of this trial when we have more information on other trials.

Last but not least, we are engaged in R&D activities such as those introduced here in order to realize our vision "the successful creation and delivery of life-changing value that ultimately makes people smile." Kyowa Kirin will continue to make every effort to realize this vision.

Thank you.

Question & Answer

Yamaguchi [Q]: Yamaguchi from Citigroup Global Markets. Thank you very much.

My first question is about tivozanib. I got the impression that the formulation has been improved and is effective. However, I would just like to confirm that it is indeed a little difficult for your company to achieve the comparable efficacy with the existing injectable formulation. Are you thinking of positioning yours to treat with eye drops to target those with a milder disease severity?

Even though this is still early data, I would like to ask whether this therapy would be suited to that role. Also, can it be expected to be as effective as the existing VEGF injectable drugs?

Torii [A]: Thank you for your question.

As I explained earlier, we are currently in the process of discussion about our future development strategy including its positioning. This process includes discussions with KOLs overseas.

As you mentioned, it would be a bit difficult to achieve the same level of efficacy as injections of VEGF inhibitors. However, periodic treatment is required for patients who are in remission following injections. KOLs in the field are very excited at the possibility that eye drops could fill this role.

Yamaguchi [Q]: I understand. Thank you very much.

Secondly, I hope this is a simple question, but your company's bispecific antibodies were introduced in your R&D event last year or the year before, and I think they were very interesting.

You have mentioned optimization by AI technologies today, but will you be starting the clinical trials of what you are developing now as it is? Or, do you feel that you can go to studies after optimizing bispecifics by AI? I was asking because I am curious about how it would affect the timing of the project, although AI technology could brush up the pipeline much better. Does AI delay the progression of a project? Do you have any thoughts on this?

Torii [A]: Thank you for your question.

As you know, we are planning first-in-human trials for the bi-specific pipelines in the coming year. Those pipelines were under consideration from the stage before we partnered with InveniAI, so it is not really the case that we are using AI technology here.

While continuing to advance the pipelines we developed before our relationship with InveniAI, we are also working in parallel on an attractive pipeline that benefits from AI technology. We are looking at moving forward with development for this part of the pipeline as well.

Yamaguchi [M]: Thank you very much.

Wakao [Q]: Wakao from JPMorgan Securities. Thank you.

First, tell us about tivozanib. In the 15th slide, you explained that there have been various products developed so far. With regard to VEGFR tyrosine kinase inhibitors, is it correct that the concentration of the drug reaching the posterior eye area was low, therefore efficacy was not observed? As for your company's,

am I correct in saying that you are now able to deliver the drug to the posterior compartment with this formulation, and are likely to have good data?

In addition to that, what kind of technology is being used in these new eye drops? Looking at the patents, I noticed that your company has a patent for nanoparticles relating to eye drops. I was wondering if you could tell us as much as you can about this technology as well. This is my first question.

Torii [A]: Thank you for your question.

We do not have a detailed understanding of the development of eye drops by other companies, but in developing our own eye drops, we checked the profiles of various other companies' products and obtained preliminary data that it is difficult to deliver drugs to the posterior compartment of the eye even if our technology is used. We guess that is one of the reasons other candidates are not going well.

Regarding the technology, we are using several technologies to develop this eye drop formulation. Nanoparticle is one of the elements, but please understand that I am not able to disclose any details at this time.

Wakao [Q]: I understand. If so, does that mean that there are other issues besides delivery to the posterior eye? Are there any difficulties?

Torii [A]: Drug development is quite a complex process, considering the balance of safety, delivery, pharmacokinetics, and formulation stability, etc. We have comprehensively taken these factors into consideration as we are being able to develop KHK4951 into a therapy that could deliver benefits to patients.

Wakao [Q]: I understand. Incidentally, I understand that the technology used in this project is your own technology, is that correct?

Torii [A]: Yes. The technology has been set up in-house.

Wakao [Q]: I understand. Thank you very much.

Secondly, I would like to talk about ADC technology, which is introduced in the 25th slide. Now, when it comes to ADCs, I have an impression that Daiichi Sankyo is in very successful situation, but I was not able to understand the technology of loading payloads by modifying glycans. Could you please tell me the advantages of this technology compared to the existing ADC technology, and if there are any disadvantages?

Torii [A]: As I explained a little earlier, Synaffix has several technologies, but one thing I find very attractive is that there is no need to modify amino acids.

In addition, Synaffix has a number of candidate payloads, that is the "poison" part, so we can select the most appropriate payload for each of our antibody profiles and target disease conditions. We decided to collaborate with Synaffix because we believe that these two factors are very attractive.

Wakao [Q]: I understand now that if this is an existing one, you would have to modify the amino acid sequence to attach a payload or something like that, but what is the problem with modifying the amino acid sequence? Does the structure of the antibody change and does it change its activity in any way?

Torii [A]: One risk is a change in activity or antigenicity by changing its structure. Another is that, in the case of Synaffix, ADC can be selectively attached only at certain points.

In general, ADCs are not easily controlled in terms of how many payloads are assigned to a single antibody molecule, and they can be distributed stochastically. However, compared to such cases, Synaffix technology

can achieve high degree of purifying or, for example, they can achieve high rate of ADCs where certain number of payloads assigned to each molecule. That means it is convenient to handle from the CMC point of view.

Wakao [M]: I understand. Thank you very much. That is all.

Muraoka [Q]: Hello. Morgan Stanley MUFG Securities, Muraoka. Thank you very much.

I would also like to ask about tivozanib. You introduced there was one case where you saw the efficacy in the OCT photo slide, but do you mean that out of 6 to 10 patients, you saw this kind of efficacy only in one case? Or did you mean that there were several cases, and this image is one of them?

Torii [A]: Thank you.

The case I showed was one of several cases where efficacy was observed.

Muraoka [Q]: I understand. Of the 6 to 10 patients, in how many was an effect observed? Was it something like three or four patients?

Torii [A]: Yes.

Muraoka [Q]: I understand. Thank you very much.

How will you organize the next phase, which I think is Phase II? Will you go straight into maintenance purpose for patients? Also, in terms of the frequency of administration, based on the current formulation and Phase I, will it only need to be administered about once a day, or will it need to be administered quite frequently?

Torii [A]: Thank you.

We are currently discussing the development strategy for Phase II, including with overseas KOLs. We will introduce the details when the time is right, so please refer to that. Administration will be daily.

Muraoka [Q]: For eye drops, some medications have a frequency of six times a day or so, but is once a day sufficient for this treatment?

Torii [A]: We are testing a number of doses, and we would like to make a decision based on that data and detailed analysis.

Muraoka [Q]: Can you give any hints about this today?

Torii [A]: Based on this Phase I data alone, we have not yet reached a decision on what frequency and concentration to use, so we would like to confirm the actual efficacy of several dosages in the next round of testing.

Muraoka [Q]: I understand. But my impression is that it would be at least once a day, is that right?

Torii [A]: Yes, that is correct.

Muraoka [Q]: Thank you very much.

I would also like to ask about Acoalan. I would guess that the number of patients is in the tens of thousands. Would the market indeed be quite large?

Torii [A]: There were 800,000 births this year, and there are about 20,000 patients in Japan, I believe. Of those patients, I think about 20% might meet the criteria for the Phase III KOUNO-TORI study. This is still in flux based on various assumptions, but that is how I see the scale of the patient numbers.

Muraoka [Q]: How about in terms of unit cost? Sorry, I have not checked the drug prices.

Torii [M]: Do you mean the drug price for the current indication?

Muraoka [Q]: Yes. At the current NHI price, how much would be a price for PE?

Torii [A]: I am sorry, but I do not have the data on the NHI price at hand, so please understand that I cannot give you an answer today.

Muraoka [M]: I understand. I will look into it myself. That is all. Thank you very much.

Torii [M]: Thank you very much.

Kohtani [Q]: This is Kohtani, Nomura Securities.

My first question is about KW-3357. This was skipped over a little bit, but a clinical trial using antithrombin, the pAT trial in Japan, was successful. However, the drug was not approved at that time because it did not eliminate the risk of parvovirus infection. Next, in the US, in the 2010s, there was the PRESERVE-1 trial, which did not show an increase in gestational length. Some weaknesses of the PRESERVE-1 trial were that it includes patients with less severe disease, and those with no antithrombin lowering.

This time, in this trial, antithrombin is being administered to those who are found to have low antithrombin, which seems to be more likely to succeed. However, I still think that if antithrombin is administered to those with low antithrombin, something like thrombosis can be cured, but I am not sure if it is possible to solve the problem of hypertension. Can you please provide me with the scientific evidence that this can be resolved? This is my first question.

Torii [A]: Thank you for your question.

The concern you mentioned are certainly logical, but it would be difficult to consider these issues in a nonclinical trial setting. Therefore, we would like to proceed with caution in clinical trials to ensure safety and avoid risks.

Kohtani [Q]: In terms of the probability of success, can you tell us why hypertension can be cured, and how confident you are?

Torii [A]: We can also think about what you said earlier about focusing on targets that are easy for us to show the success, but as I mentioned earlier, in the case of this disease, there are no other treatment options. So, from this perspective, we are now in the process of developing such evidence for patients who can be expected to benefit more from the product, and we hope to deliver the benefits to them.

While doing so, we would also like to continue to discuss the possibilities related to the surrounding areas.

It is true that we are developing the product with limited information, so, as I mentioned earlier, we are now proceeding with development from this perspective, carefully cooperating with KOLs and the investigator.

Kohtani [Q]: I understand.

My second question relates to KHK4951. My understanding is that the nanoparticles probably enter capillaries or something in the back of the posterior eye and slowly release the drug there, so that the fact that this effect in the posterior eye was recognized is an invention that has never been seen before.

But then, as it says on page 13, I thought that perhaps a drug with a similar spectrum would have a similar effect, but the idea of making it into nanoparticles itself is still the biggest thing. I am wondering if a similar TKIs like axitinib might be actually effective. At the same time, I am wondering what the concentration would be. After all, when the concentration is high, the nose and eyes are connected, so I wonder if systemic side effects might be an issue.

Side effects of FOTIVDA include diarrhea and other gastrointestinal symptoms. I'm sure the dosage is very different from that, so I probably don't have to worry about that, but I still feel very uncomfortable if patients get diarrhea after using the eye drops. What can you tell us about your investigation to date of the safety of the product? Thank you.

Torii [A]: Thank you for your question.

As I think I explained a little earlier, we have examined our ophthalmic formulation with low molecular weight compounds from other companies. In this context, we have confirmed that other companies' compounds are not effective. We believe that complex factors are involved here, such as the compatibility of compounds, although it is difficult to make detailed assumptions.

As for the concentration, as you mentioned, the oral form has been approved for renal cell carcinoma, but one of the side effects is hypertension due to inhibition of angiogenesis. If the drug enters the bloodstream at high levels and the concentration increases, there is a possibility of side effects similar to those seen when the drug is administered orally. Therefore, we proceeded with the development of Phase I while carefully monitoring cardiovascular indicators.

Kohtani [Q]: Am I correct in my understanding that no such issue has come up so far?

Torii [A]: We have received positive comments from overseas KOLs, including data on side effects, and we are now preparing for Phase II.

Kohtani [M]: I understand. Thank you very much.

Sakai [Q]: This is Sakai from Credit Suisse. Thank you.

Regarding KW-3357, did you say the number of patients in Japan, or the number of pregnant women who could receive this medication, is 20,000? Is this correct?

Torii [A]: It is about 20% of those 20,000 people.

Sakai [Q]: I understand. 20% of the 20,000 people could be taking this medication.

So, this time, you also administered a placebo, right?

Torii [A]: Yes.

Sakai [Q]: I assume it would take a lot of hard work to incorporate a placebo into clinical trials. I understand that the protocol is on ClinicalTrials.gov, but as of now, is there any progress or anything you can update us on?

Torii [A]: Thank you for your question.

As for the placebo effect, I think it is limited. It is not about setting a placebo in place of a drug that has a standard therapy, so there is no ethical problem with using a placebo for this disease, since there is no cure for this disease.

Regarding the schedule, the coronavirus pandemic is having an effect. Due to COVID-19, some clinical trial sites are closed or do not accept new patients. As reported in the news, the birth rate has decreased during the COVID-19 period. Due to these factors, we are behind schedule compared to our original plan. However, as I mentioned earlier, we will welcome the last patient in next year, and if the results are favorable, we would like to start working on the domestic application.

Sakai [Q]: I understand. For the placebo, is a totally fake drug being used?

Torii [A]: Yes, that is my understanding.

Sakai [Q]: Thank you very much.

Regarding tivozanib, in the table on page 15 on the right side, I understand the data for the new eye drops is from a rat model, is that correct? I am not sure if I should call it eye reproducibility, but I would like to ask your company's thoughts on this and your experience to date, if you studied by rats, how much reproducibility can be achieved when taken to humans.

Torii [A]: Thank you.

The species difference is a very important point, and we are not only examining data from rats, but also from rabbits and other animal species. We are proceeding in a way because we think we can expect the same results in humans, considering the results as a whole.

Sakai [Q]: You just mentioned rabbits, rabbits are used quite a bit.

Torii [A]: Yes.

Sakai [M]: I understand. Thank you very much.

Yamaguchi [Q]: Thank you. This is my second time.

The first question is about tivozanib. I think you mentioned that you are preparing for phase2 trials in Japan, the US and other countries. I know that your company is not independently developing ophthalmic agents overseas, but is your company willing to do the overseas work in-house too?

Torii [A]: Thank you for your question.

As for 4951, we are working with KOLs and other contracted development companies in this area. I think the Company's main objective is to maximize the value of this drug and to deliver it to as many patients as possible. We are considering a strategic option without ruling it out partnering with a company that has such experience.

Yamaguchi [Q]: Thank you.

Second, this is also about 4083, which you mentioned at the beginning of the presentation. It is true that one open-label test has been announced, but from the outside standpoint, I wonder how it will go if only one piece of information is released. Is it correct to say that the ROCKET program is on schedule to be ready by the end of this year, even though it is not ready today?

Torii [A]: Thank you.

As for the timing of the restarting of the program, the situation has remained the same. We are aiming for some time between the end of this year and the beginning of the new year. As you know, we will be running six trials.

Basically, our disclosure policy is to disclose when we have achieved first patient in status. We are hoping to achieve first patient in status in these six trials and provide an overall overview at the next financial announcement.

Yamaguchi [Q]: As for Phase III, you have a plan in place but have not disclosed it because there is no first patient in.

Torii [A]: Indeed.

Yamaguchi [M]: I understand. Thank you very much. That is all.

Kohtani [Q]: Kohtani, Nomura Securities.

I would like to ask you about Synaffix. This is actually something I have wondered about for a little while now, and this technique can be used to create the ADCs that are specific to DAR4 or 2, right? This is the kind of technology that can be attached to a specific site and for example it only works for 4.

Torii [A]: Yes, it is a technology that can also control DAR with a great deal of precision.

Kohtani [Q]: Various companies are doing this kind of conjugation behind the scenes, including Pfizer and other Japanese companies. Eisai is using a similar technology for a preclinical drug called MORAb-109.

But I don't think it has never worked. Do you know what the common points are? I still think that a single DAR would certainly be more advantageous when applying for approval, but in fact, I think that there is a view that it would actually be better to have a variety of DARs that are quite discrete, as in the case of Enhertu. Do you have any background on this type of technology, something that has been talked about a lot but not quite worked out?

Torii [A]: I am not aware of the details of that, but we are also considering various other technologies in addition to Synaffix's.

As for the question of increasing the DAR, the fact that the efficacy of the drug is enhanced by increasing the DAR is a benefit. However, depending on the target or disease, there may be cases where the balance

between efficacy and safety is disrupted. From the CMC perspective, if the DAR is increased too much, a complex or unstable situation may occur.

Synaffix's technology, which I did not explain in detail today, is unique in the linker that connects the antibody to the payload. When this ADC is administered in vivo, depending on the technology, it may break off immediately in the bloodstream before it is delivered to the target site, resulting in more toxicity. Synaffix's linker is very stable when it enters the body, so I am not sure about other companies, but I think they may be struggling with the issues I just mentioned.

Kohtani [Q]: I understand.

Secondly, I think the ROCKET-Orbit for KHK4083 is out. This was a study in adolescents, and moreover, it is a safety study, so it is good that it is administered once a month, but I have the expectation that it will be tested a little more in adults, is that right?

Torii [A]: Yes, that is correct.

As I mentioned earlier, I am hoping to be able to outline the details at the next financial results briefing, so I hope you will wait until then.

Kohtani [Q]: In the end, if we think about what it takes to compete with dupilumab, then it is 100% correct what Regeneron said, and in the end, atopy alone is not enough to compete. I think it would be difficult to compete without controlling atopic disease, asthma, and other atopic diseases, all of which are also complications. Are you also expecting this pattern from 4083?

Torii [A]: Yes, that's right. Theoretically, it is possible to suppress not only the IL-13 strain but also other strains in the case of 4083, so we expect stronger effectiveness in this area than in other competitors.

On the other hand, there are concerns about side effects and high risks associated with this, which we will carefully assess in the upcoming Phase III.

Kohtani [M]: I understand. Thank you very much.

Moderator [M]: Thank you very much.

Since there appear to be no further questions, I will conclude the briefing.

Thank you very much for attending our R&D presentation today. The content of the briefing will be distributed on our IR website. Please check the contents on this page.

Thank you very much for your participation today.

[END]