Kyowa Kirin Co., Ltd.

R&D Day

September 26, 2024

Event Summary

[Event Name]	R&D Day	
[Date]	September 26, 2024	
[Number of Speakers]	1	
	Takeyoshi Yamashita	Director, Senior Managing Executive Officer and Chief Medical Officer

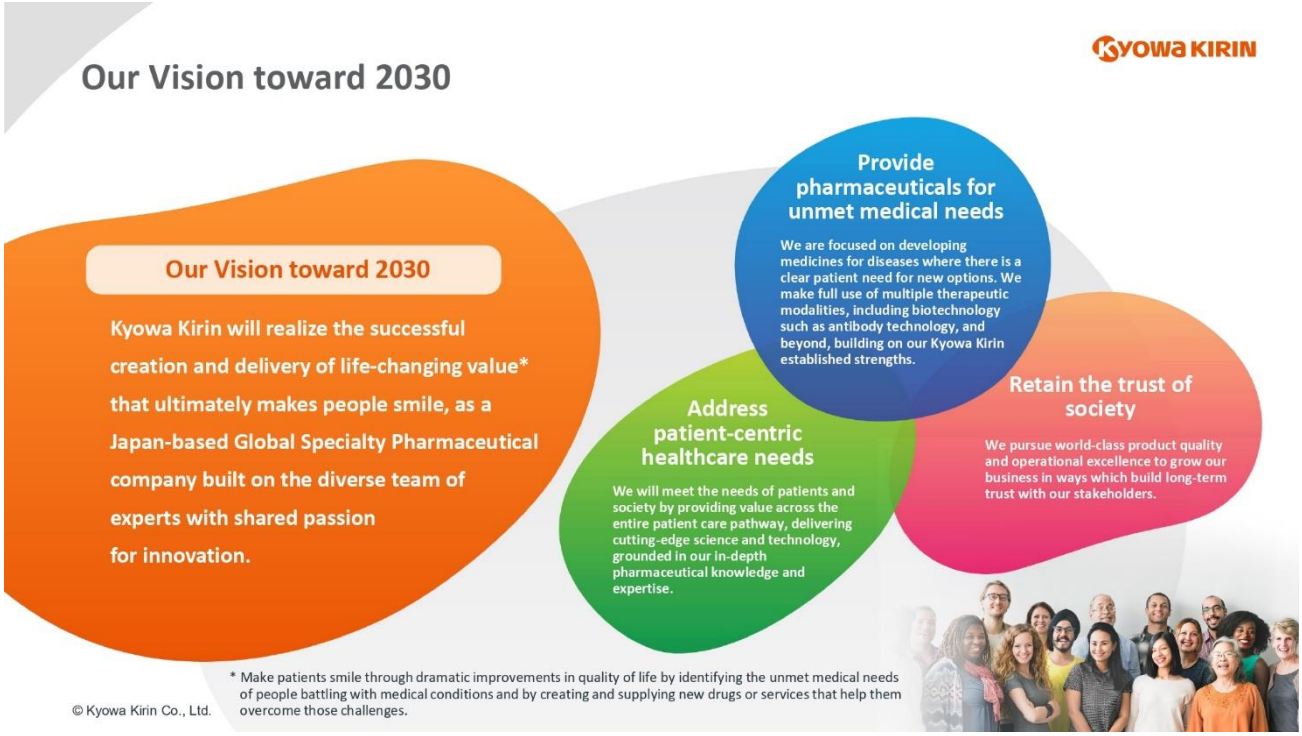
Presentation

Moderator: We will now begin the R&D meeting for FY2024 of Kyowa Kirin Co., Ltd. Please note the following prior to the start of the briefing. Please note that the names and company names of all participants will be kept as a list of participants for a certain period of time. Please note that the content of this presentation will be available on-demand and in transcript form on our website. Please bear in mind when you speak.

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

Today's speaker is Takeyoshi Yamashita, Director of the Board, Senior Managing Executive Officer and Chief Medical Officer. After the presentation, we will be happy to answer any questions you may have. We schedule the meeting for a maximum of 90 minutes.

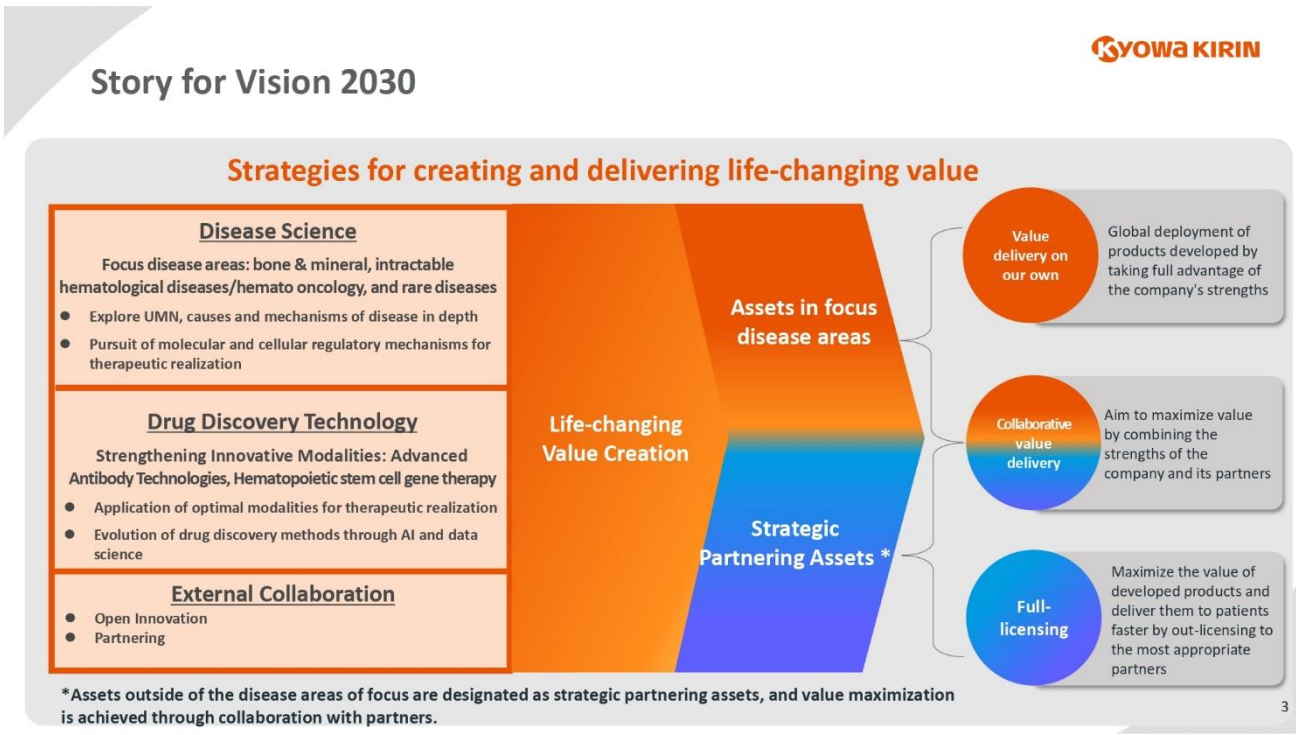
Yamashita: Good morning. My name is Yamashita, Chief Medical Officer. Thank you very much for taking the time out of your busy schedule today to attend the Kyowa Kirin FY2024 R&D meeting. Thank you for your cooperation today.



Let me begin by explaining our vision for 2030.

In 2020, shortly after we entered the global market, we formulated this vision for the year 2030.

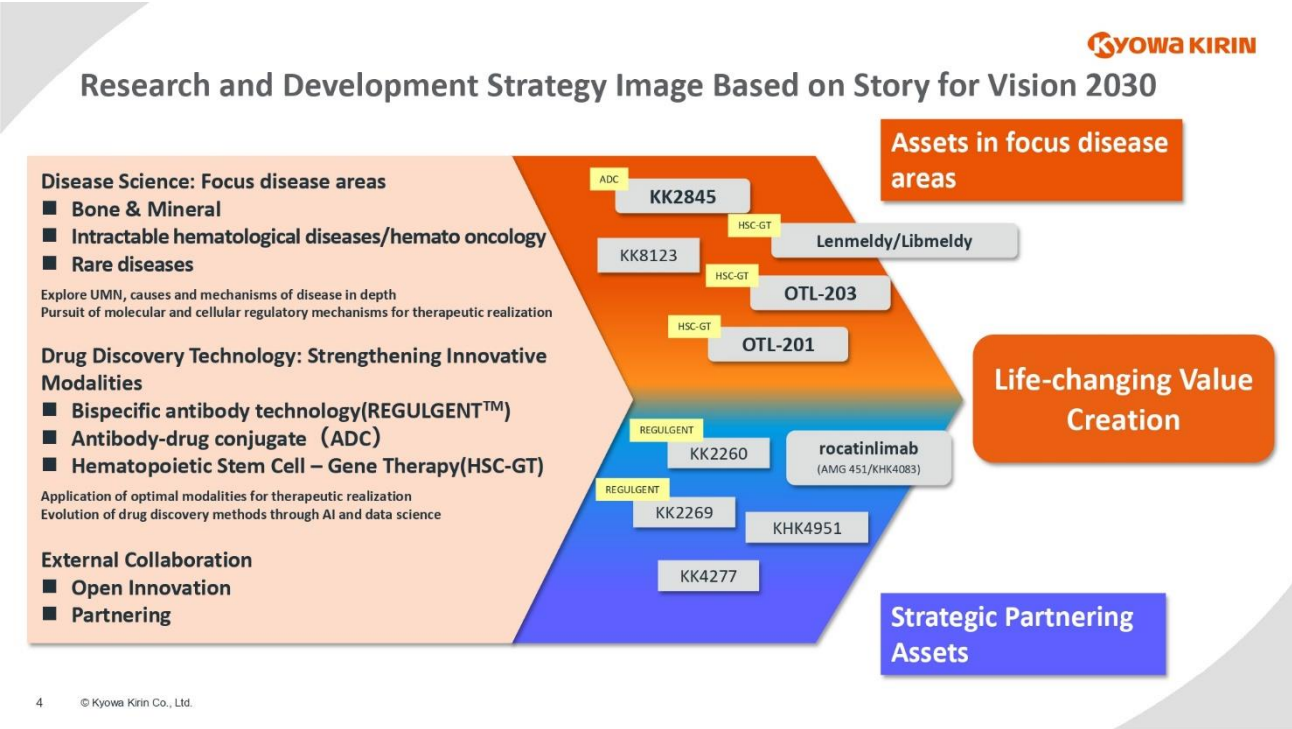
The point is that we create and provide life-changing value to bring smiles not only to patients suffering from illnesses but also to their families and healthcare professionals. Ultimately, it makes us smile. In line with this vision, we have defined a five-year medium-term business plan, which we have been implementing since 2021.



It has been three years have passed since the mid-term business plan was formulated, and we see some changes in the environment and the assumptions made at the time of the plan. Therefore, we refined our mid-term business strategy and created Story for Vision 2030.

In order to vigorously promote our commitment to creating life-changing value, we have designated bone & mineral, intractable hematological diseases/hemato oncology, and rare diseases as areas of focus. In addition, to address more advanced unmet medical needs, we will strengthen drug discovery using innovative modalities such as advanced antibody technology and hematopoietic stem cell gene therapy.

The idea is to increase the pipeline with life-changing value, and to maximize value by appropriately selecting a business model to deliver new value to patients as quickly as possible, either as an asset in a disease area of focus for the company, or as a strategic partnering asset.



When we overlay our main development pipeline onto this diagram, it looks like this. For development products such as rocatinlimab and KHK4951, which are aimed at a large market for a large number of patients, we will seek to maximize their value with the help of third parties as well. For products under development for bone & mineral, intractable hematological diseases/hemato oncology, and rare diseases, we will seek to maximize value in-house.

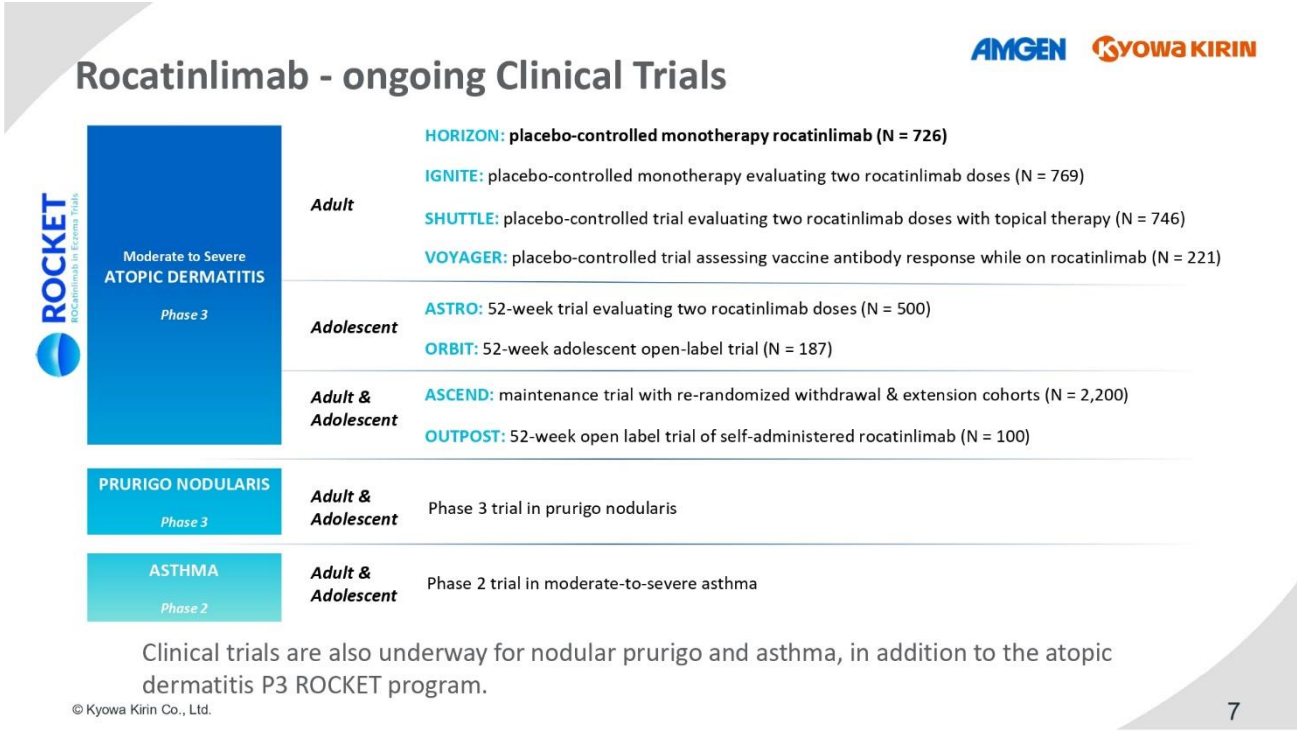
In terms of creating life-changing value to support these products, we are in the process of enhancing our pipeline with innovative technologies such as HSC-GT, REGULGENT (a bispecific antibody), and ADC technology.

Today, as shown in this agenda, we will present the top-line data from the HORIZON study of the ROCKET program for rocatinlimab and the product concept to start with.

Next, we will explain KK2845, our most advanced ADC in our development pipeline.

Next, we will talk about REGULGENT, our proprietary bispecific antibody technology that we have applied to KK2260 and KK2269.

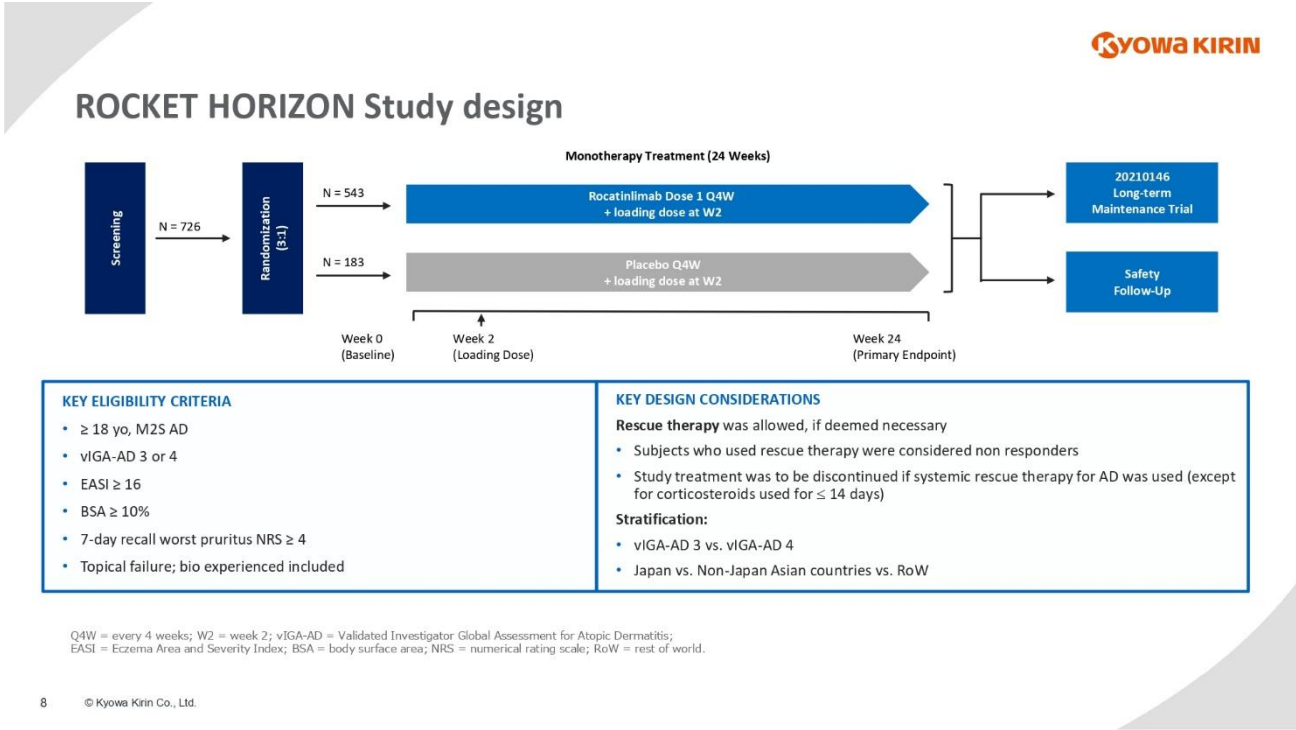
Finally, I will explain about the hematopoietic stem cell gene therapy, HSC-GT, including the data presented at the conference.



First of all, rocatinlimab.

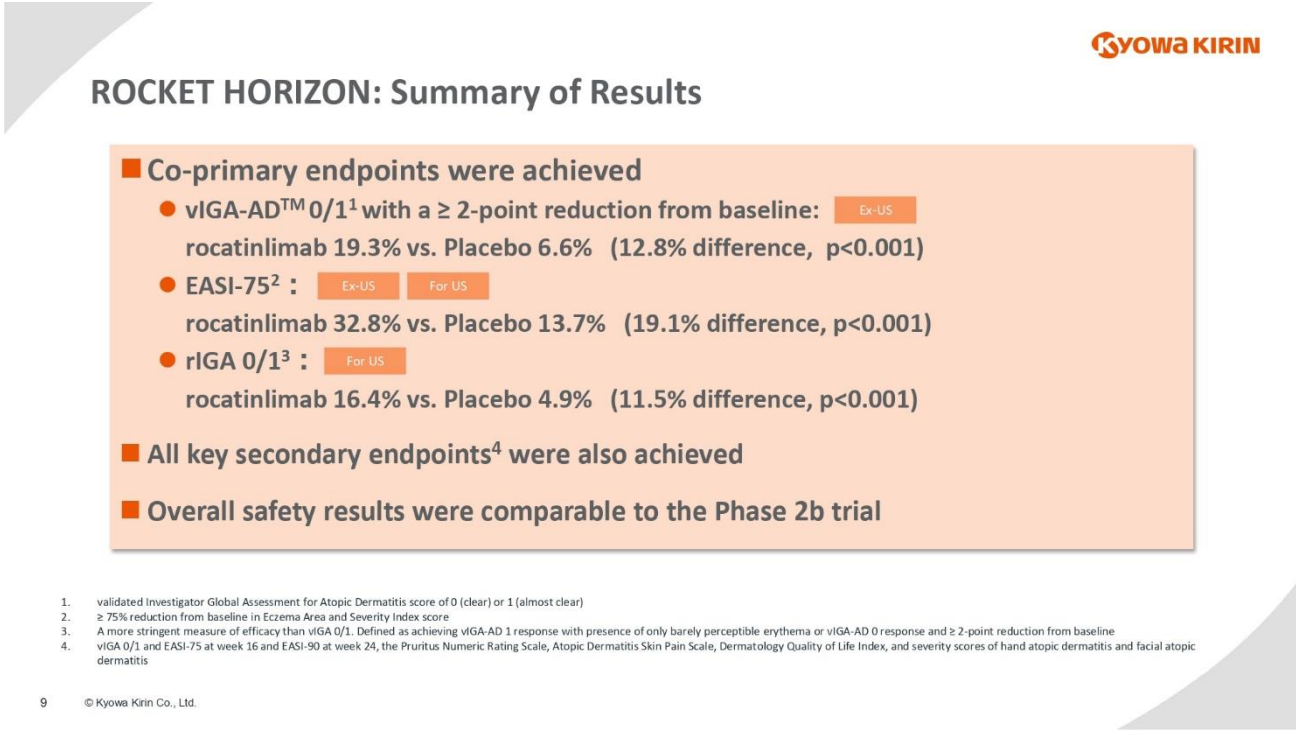
Currently, rocatinlimab is in clinical trials for moderate to severe atopic dermatitis, prurigo nodosa, and asthma. In particular, the ROCKET program is dedicated to characterizing rocatinlimab based on its unique mechanism of action by testing efficacy and safety in eight Phase III studies.

Today, we will discuss the top-line data from the HORIZON study, which is advanced in the ROCKET program. We apologize for the timing discrepancy between Amgen and us in the release of this data, which resulted in a lack of consideration for Japanese investors in particular.



Let me return to the presentation. Here is the design of the HORIZON test.

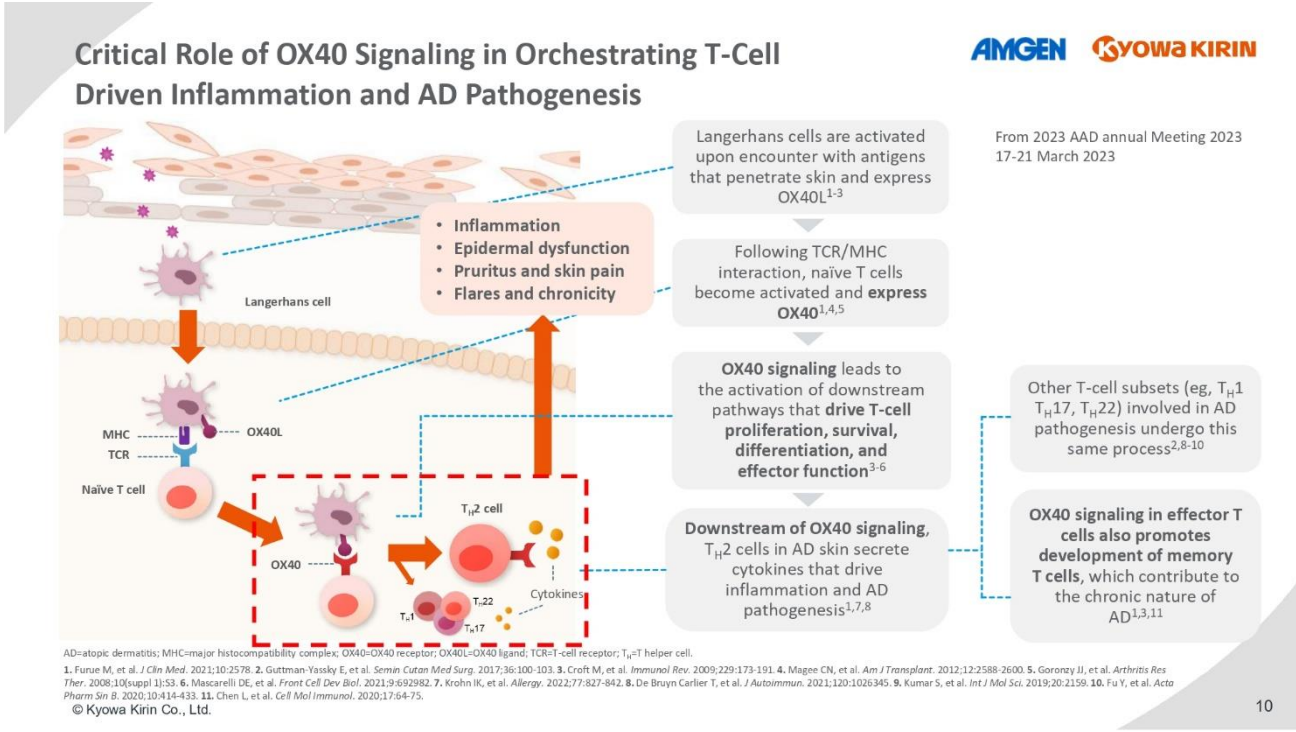
A total of 726 patients were randomized 3:1 to receive rocatinlimab or placebo, with a loading dose at week two, once every four weeks for 24 weeks. Eligibility criteria and considerations are as indicated.



The following is a summary of the results.

The primary endpoint was EASI-75 at week 24 and vIGA or rIGA as the co-primary endpoint. All of these results were achieved with significant improvement over the placebo group. The respective figures are as indicated. In addition, we achieved all major secondary endpoints.

The safety profile was comparable to the Phase IIb study. Further analysis is currently underway, and we anticipate presenting details at a future conference.



We expect rocatinlimab to be a drug with unique characteristics, and I would like to explain it today.

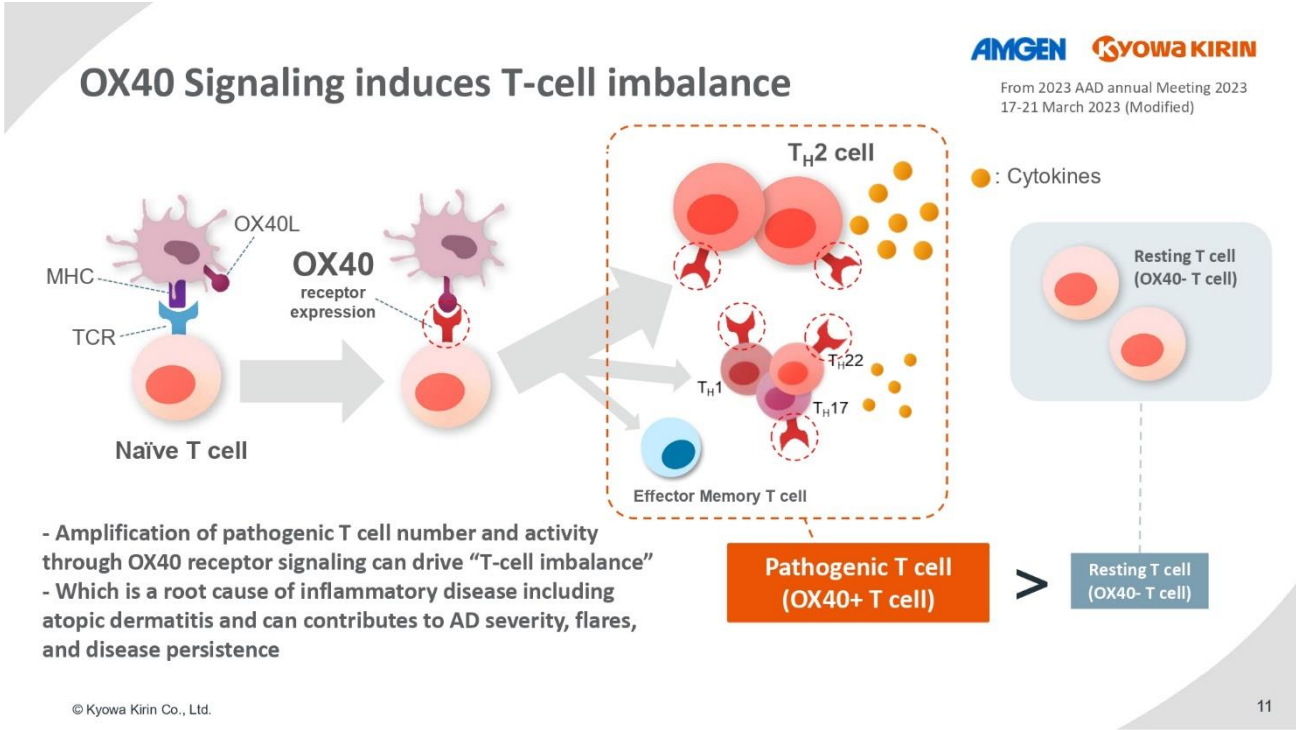
OX40, which is targeted by rocatinlimab, is expressed on activated T cells upon stimulation from antigen-presenting cells.

As shown in the red box, the interaction of OX40 with the OX40 ligand on dendritic cells induces proliferation, survival, and differentiation of various T cells involved in atopic dermatitis.

As a result, ordinary helper T cells, mainly Th2 cells, release various cytokines that promote the pathogenesis of atopic dermatitis, resulting in inflammation, itching, and other symptoms.

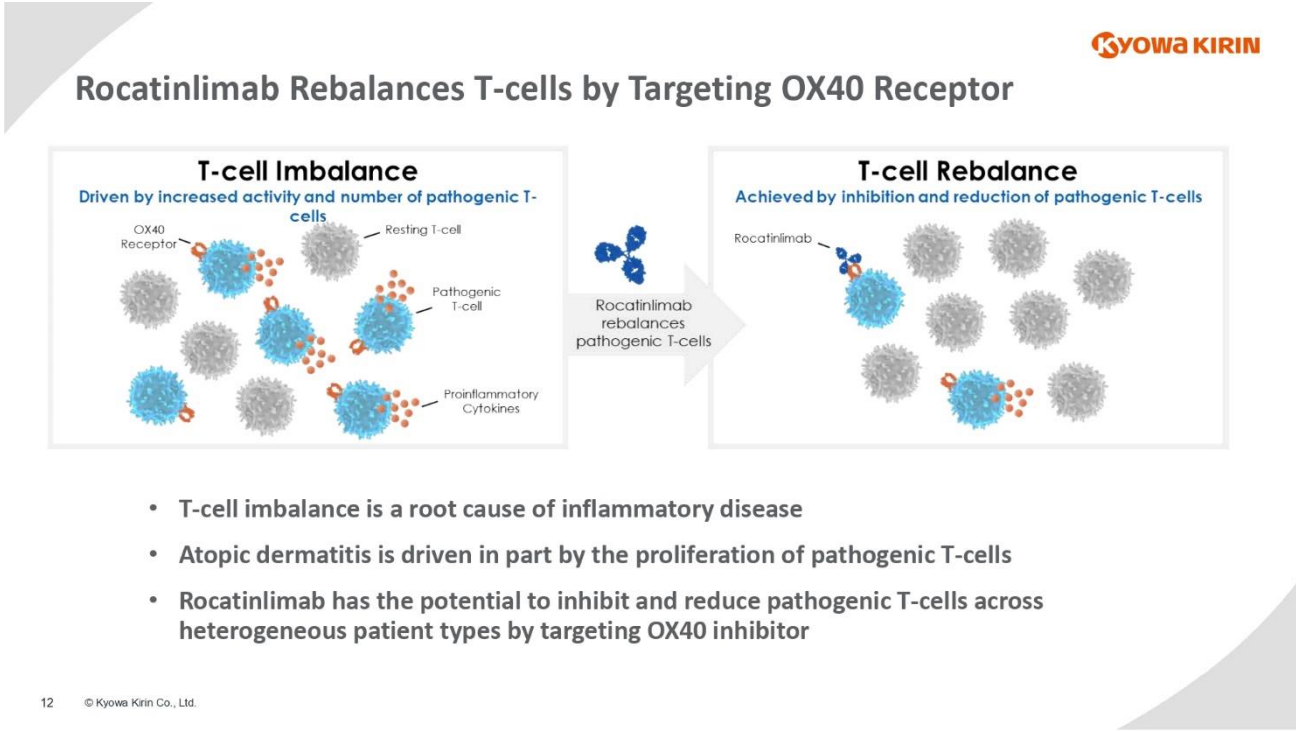
OX40 signaling also induces the formation of memory T cells and contributes to the chronicity of atopic dermatitis symptoms.

In this issue, we will explain in a little more detail the areas circled in the red box.



As shown in the figure here, OX40 signaling triggers the generation of helper T cells, Th2 cells, other helper T cells, and effector memory T cells, which are considered one of the major causes of atopic dermatitis.

This group of cells shown in the dotted line is the group of disease-inducing T-cells, which we will refer to as pathogenic T-cells. And these cells express OX40 on their surface. T-cells are successively activated through these pathways, leading to a state of T-cell imbalance, in which the proportion of pathogenic T-cells is excessively high in the total population. We believe that this T-cell imbalance is one of the underlying causes of inflammatory diseases, including atopic dermatitis, and that correcting this condition is the key to disease treatment.

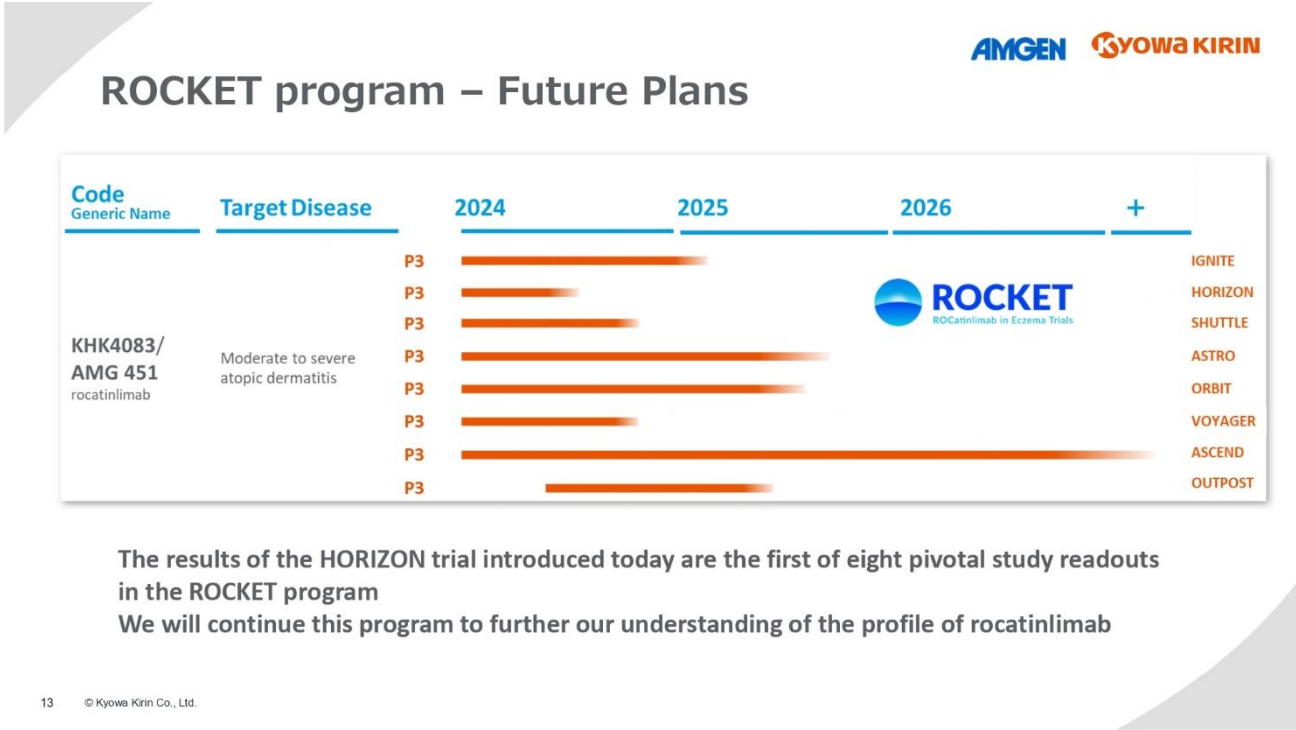


The figure here on the left is a schematic of T-cell imbalance.

Patients with atopic dermatitis are thought to have an increased number of inflammatory pathogenic T-cells, as shown in the figure on the left, and if such a T-cell imbalance persists, the disease is likely to worsen further.

Rocatinlimab acts on OX40, which is specifically expressed on overabundant pathogenic T-cells, inhibiting their function and further selectively reducing the number of such cells. Rocatinlimab does not act on naive or quiescent T cells. In other words, rocatinlimab is thought to correct this T-cell imbalance toward a normal state, or so-called T-cell rebalancing.

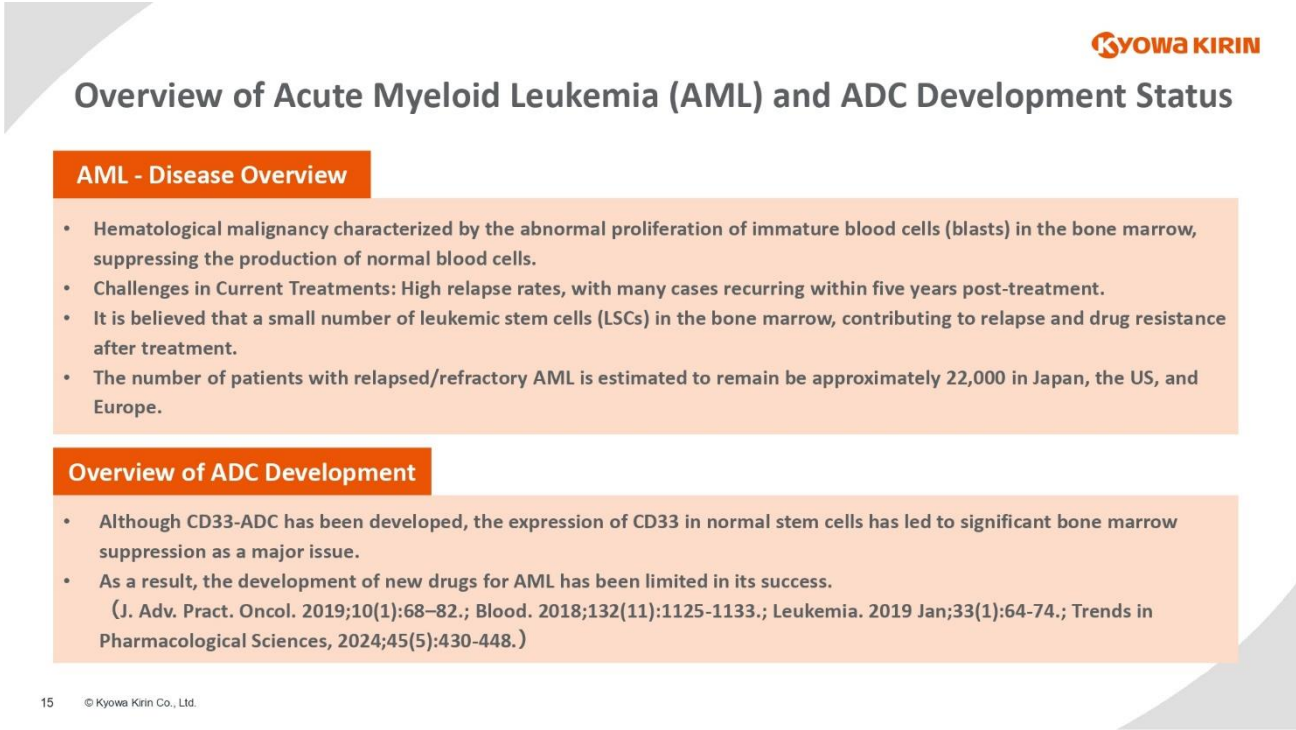
We believe that this restoration of the T-cell balance to a normal state may have a lasting effect on atopic dermatitis. Again, we believe that rocatinlimab may provide a new therapeutic concept to rebalance T-cells by reducing excessive pathogenic T-cells.



We are pleased to present our future plans for the ROCKET program.

We have presented the results of the HORIZON test, which is the ROCKET program, the first of eight trials. We plan to combine the results of the other seven studies to characterize rocatinlimab and its value.

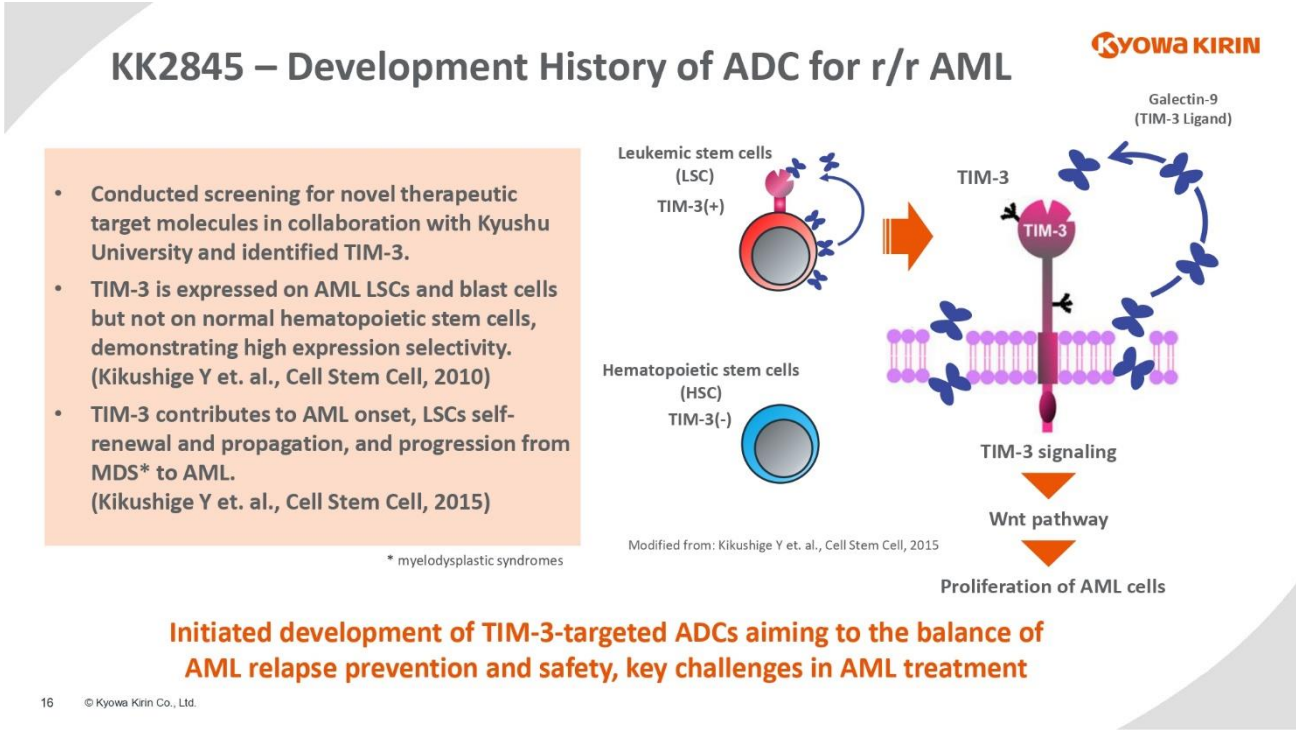
Over the next year, we expect to obtain results from other trials and hope to obtain approval by the end of 2026.



The next one is KK2845. First, let me briefly explain AML, the target disease of this drug.

AML is a hematopoietic malignancy in which immature blood cells in the bone marrow proliferate. Its high relapse rate is a current challenge. Most relapses are thought to be due to leukemia stem cells that remain in the bone marrow after treatment. It is estimated that there are 22,000 patients with relapsed/refractory AML in Japan, the US, and Europe.

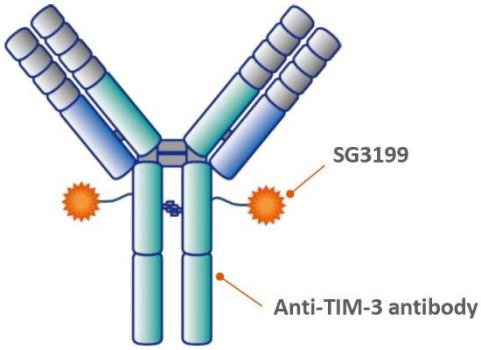
ADCs for AML have been developed that target CD33, which is highly expressed in leukemia cells. However, the side effect of severe myelosuppression has been a challenge. This is likely due to CD33 being widely expressed in normal hematopoietic cells, and the difficulty in separating efficacy and safety has led to limited success in new drug development in the ADC format for AML.



To overcome this challenge, we focused on leukemic stem cells, which are the progenitor cells of leukemia. In collaboration with Kyushu University, we identified TIM-3 as a promising therapeutic target, as it is highly expressed on leukemic stem cells but not on normal blood stem cells.

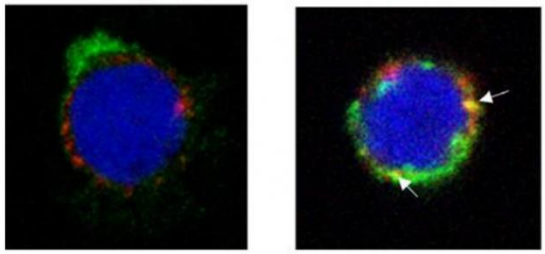
TIM-3 has been found to support the proliferation of leukemic stem cells, contribute to the onset of AML, and drive its progression from myelodysplastic syndrome. KK2845 is an ADC that aims to eliminate AML leukemia cells while circumventing myelosuppression by targeting TIM-3, which is specifically highly expressed in these leukemia stem cells.

KK2845 - Overview



Internalization into cells

Green : KK2845-Alexa488
Red : Lysosome
Blue : Nuclear



Note: The arrows indicate where KK2845 merges with lysosomes

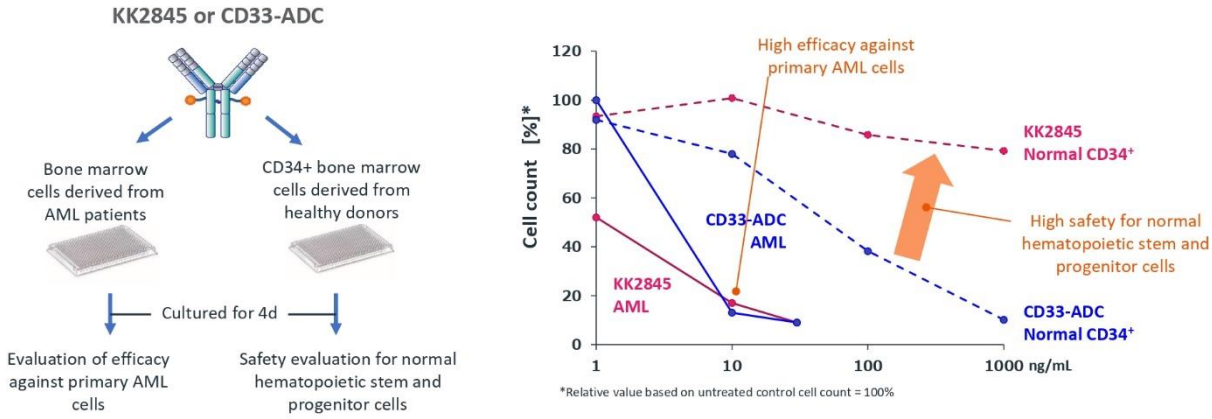
- **Target Molecule : TIM-3** - Aiming to avoid myelosuppression
- **Payload : SG3199** - the PBD molecule also used in marketed drugs, with high expected efficacy

From European Hematology Association (EHA) 13-16 June 2024

17

The monoclonal antibody targeting TIM-3, which is the base of KK2845, is selected to be suitable for ADCs that are efficiently taken up into cells, as shown in the picture on the right. KK2845 is a payload of a PBD called SG3199, which has already been proven as a therapeutic agent, bound to this antibody.

Evaluation of anti-cellular activity against primary AML cells and normal bone marrow cells



KK2845 demonstrated similar efficacy and higher safety compared to CD33-ADC

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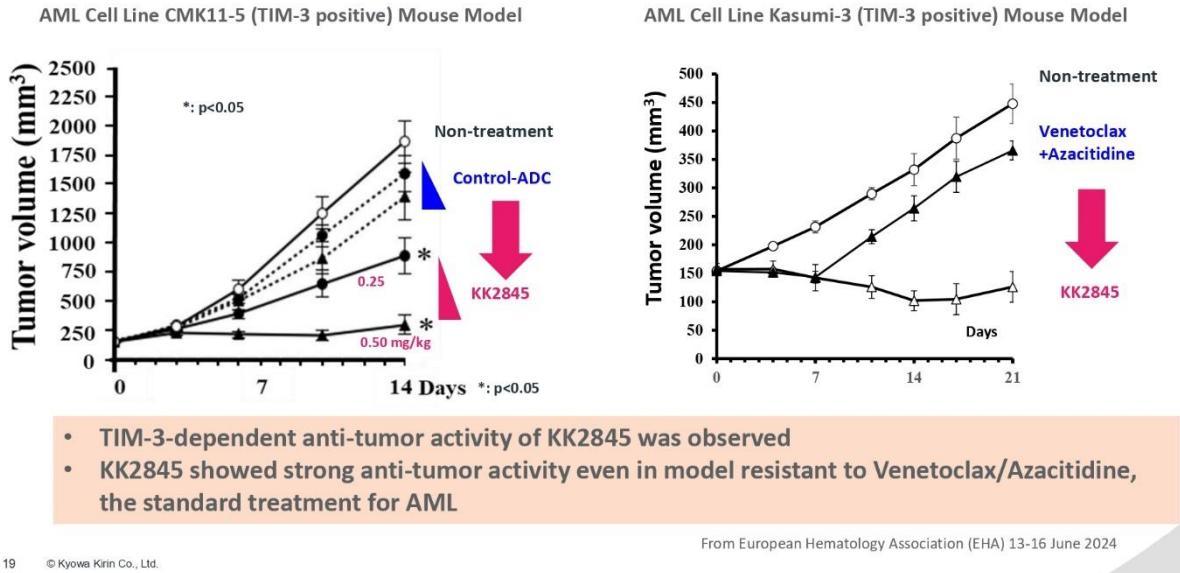
Here are the results of in vitro studies of the effects on AML cells and normal hematopoietic stem cells compared to CD33-ADCs. The cells were added with each antibody and cultured for four days to see how well they reduced AML cells and how well they maintained normal bone marrow cells.

As shown in the graph on the right, KK2845 reduced AML cells from lower concentrations compared to CD33-ADCs. On the other hand, KK2845 maintained cells at high levels for normal hematopoietic cells, while CD33-ADC decreased them.

The results suggest that KK2845 may have higher efficacy and safety compared to CD33-ADCs.

In vivo Anti-tumor Activity Evaluation



- TIM-3-dependent anti-tumor activity of KK2845 was observed
- KK2845 showed strong anti-tumor activity even in model resistant to Venetoclax/Azacitidine, the standard treatment for AML

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Next, the results of an in vivo study.

There was an examination to observe the effect on the growth of tumors formed by transplanting AML cell lines into mice, and the control ADCs showed limited inhibition of tumor growth, as shown in the graph on the left, while KK2845 was able to suppress tumor growth almost completely.

The graph on the right shows a similar study using cells that had developed resistance to Venetoclax/Azacitidine, the standard treatment for AML. In that study, KK2845 was able to demonstrate potent antitumor activity.

We are currently preparing this KK2845 for first-in-human for Phase I trial.

ADC Research and Development Strategy

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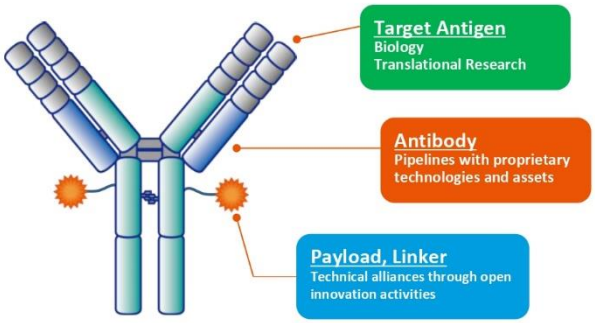
Creation of new drugs in Intractable hematological diseases/hemato oncology through Kyowa Kirin's antibody technologies combined with ADC technologies



#	Current status & Plan
KK2845	2024 Q3 P1 Initiation
ADC-2	Non-clinical/CMC stage; Phase 1 initiation planned for 2025 Q4
ADC-3	Non-clinical/CMC stage
ADC-4	Research stage

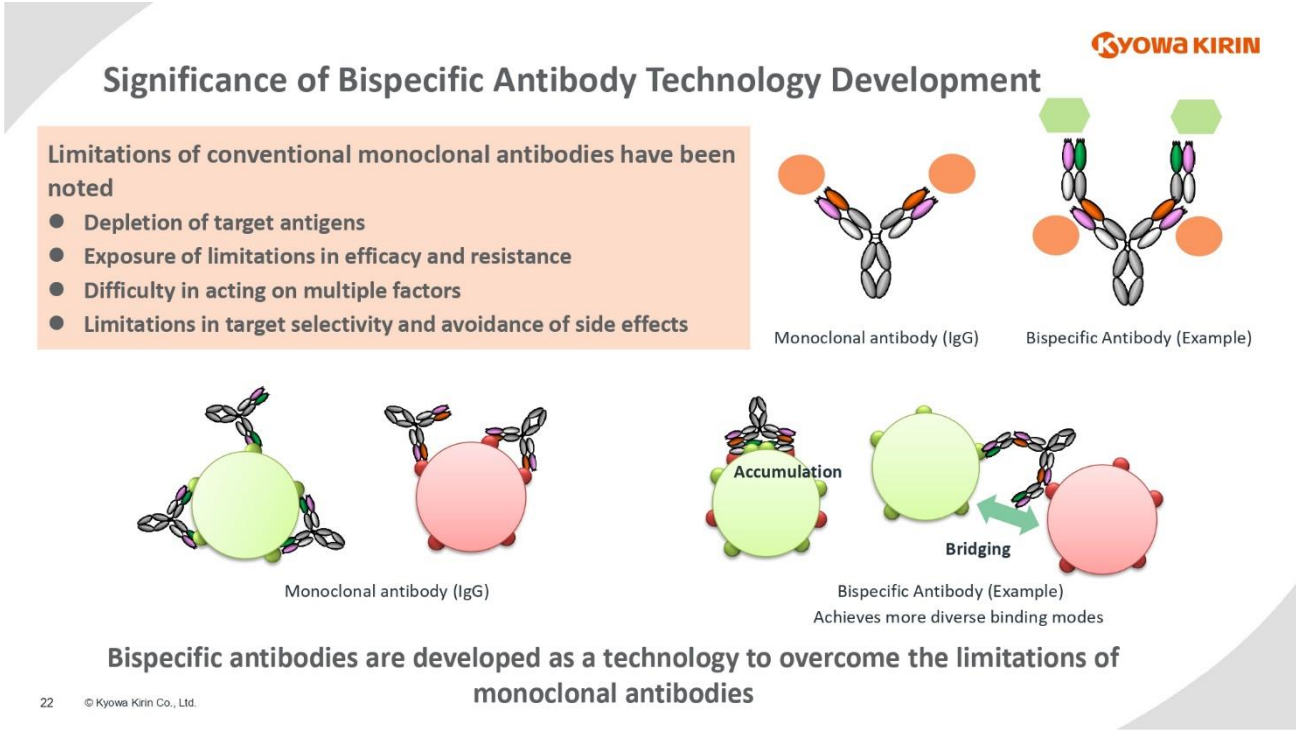
- Collaborative research maximizing antibody technologies of academia and Kyowa Kirin
- Partnering with entities possessing competitive payload technologies for hematological malignancies and refractory diseases
- Collaborating with CDMOs and technology partners to ensure the manufacture of high-quality ADCs

20

We are also engaged in the research and development of ADCs following KK2845.

Focusing on hematologic cancers and refractory blood diseases, our primary areas of expertise, we are committed to continuously developing new drugs in ADC format. Leveraging our strengths in antibody research, our collaboration with Synaffix initiated the year before last, and our proprietary in-house technologies, we are driving innovation in this field.

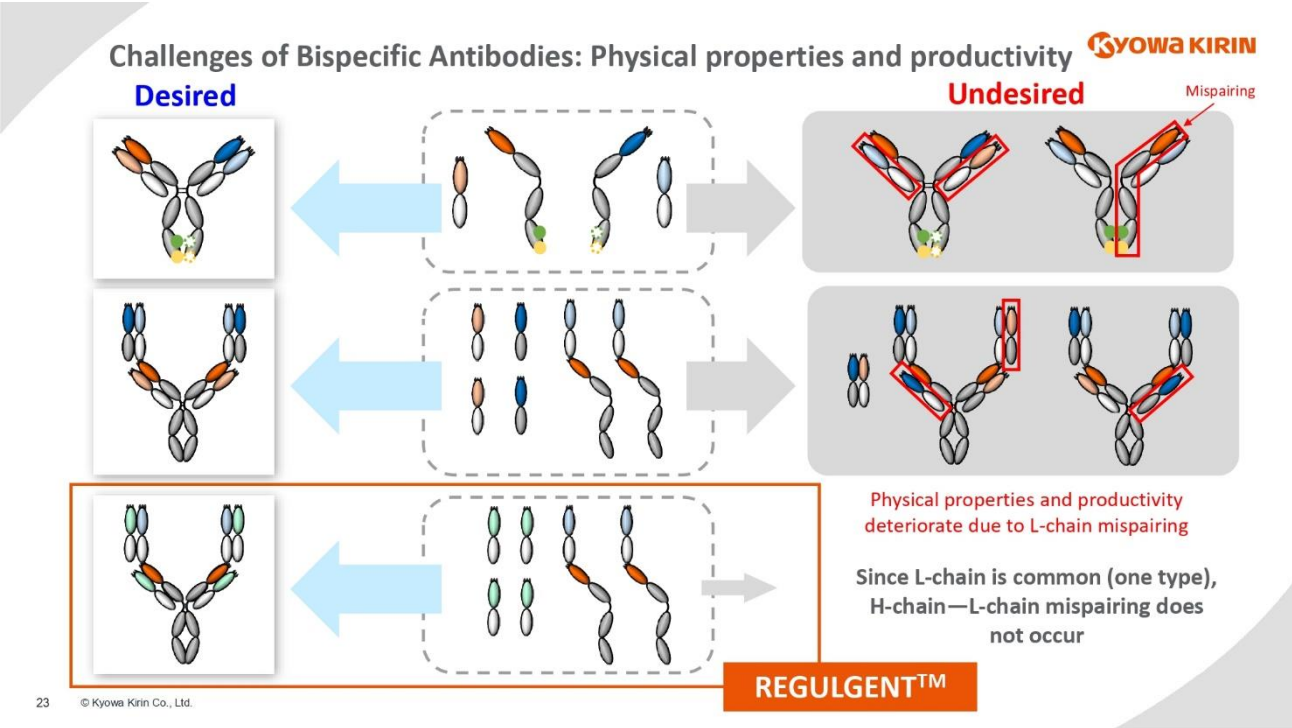
Several projects are currently underway in the non-clinical stage. In terms of ADC manufacturing, we are also working with CDMOs and technical partners to establish a supply system.



Next, we introduce REGULGENT, our proprietary bispecific antibody technology.

Monoclonal antibodies have become established as drugs in a variety of fields. At the same time, the limitations shown here are becoming apparent. As one approach to overcome these challenges, we have focused on bispecific antibody technology and have been working on them.

Monoclonal antibodies target a single molecule, while bispecific antibodies can target two different molecules. This enables the accumulation of distinct targets and facilitates cross-linking between different molecules and cells. This is a drug discovery technology that takes advantage of the benefits of antibody drugs while exceeding the limitations of monoclonal antibodies.

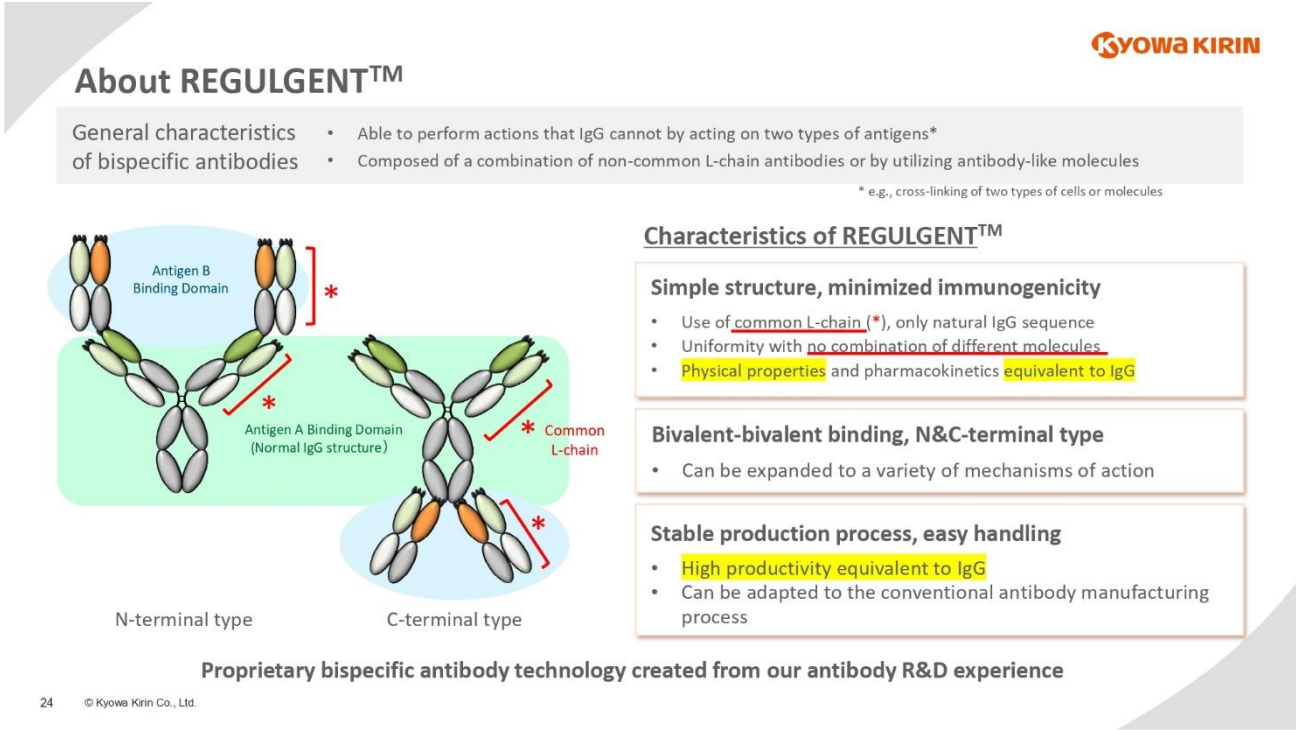


The challenge is to ensure the physical properties related to quality and behavior in the body and stable productivity in terms of manufacturing, as it is an artificial product with a complex structure.

Various forms of bispecific antibodies are available, as shown here. The antigen binding sites of antibodies are formed from a combination of short light chains and long heavy chains. Since the molecule has two different sites for antigen recognition, the L and H chains must each have two different sequences.

On the other hand, since the combination of L and H chains occurs randomly, simply the coexistence of these different L and H chains decreases the probability of obtaining the target antibody, as shown in the left figure. It causes the problem of contamination with non-target products, as shown on the right.

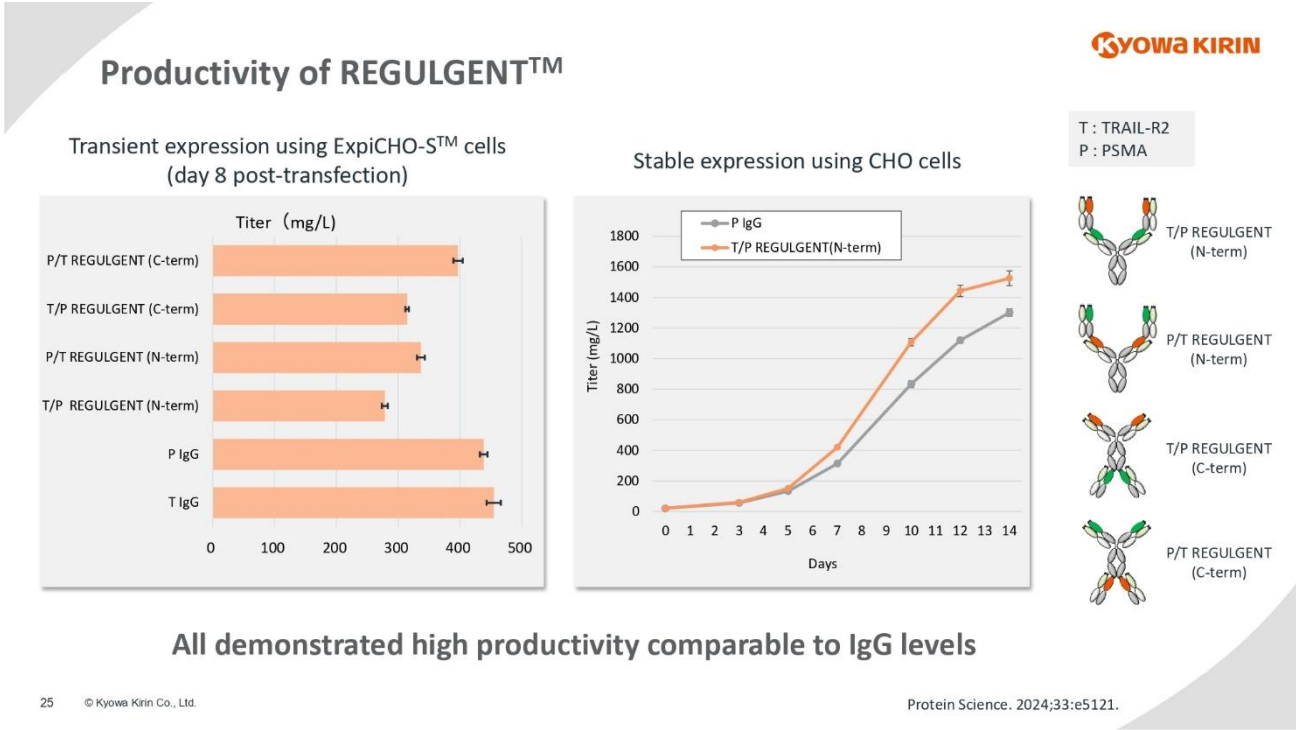
REGULGENT solves this problem with our proprietary technology. Briefly, we chose one type of L-chain that functions in common for the two different binding sites and combined it with a pre-designed H-chain.



Depending on the design of the H chain, REGULGENT antibodies can be offered in two different formats with different antigen binding sites, called N-terminal/C-terminal types, as shown in the figure on the left.

The molecule characteristically contains two antigen recognition sequences and four antigen binding sites, all composed of the same L chain. In addition, the framework is composed of natural-type IgG sequences, which minimizes immunogenicity.

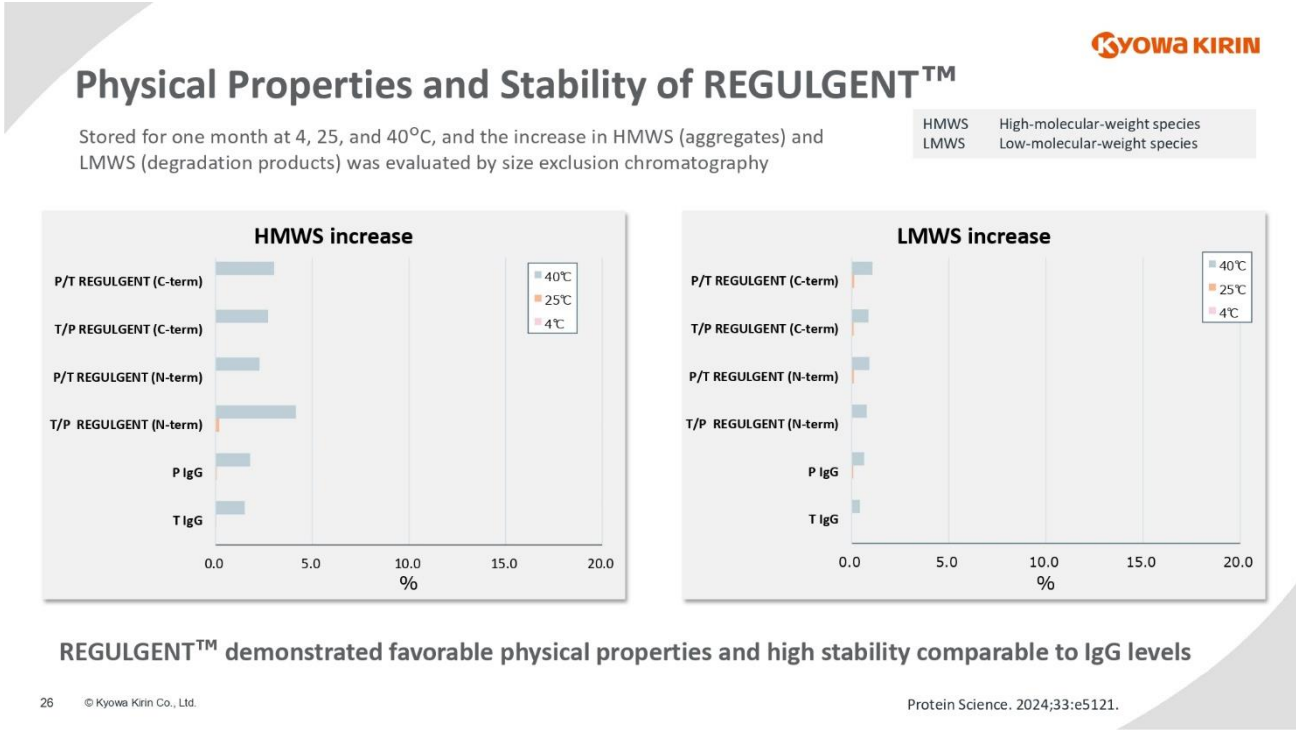
As a result of our in-house studies to date, we have been able to ensure the same physical properties and productivity as monoclonal antibodies. Here is a brief introduction to this point.



The experiment used four different REGULGENT antibodies, each recognizing two distinct molecules, as shown on the far right.

First, here are some data on productivity. Using CHO cells, which are commonly used in monoclonal antibody production, we examined two cases: transient expression and stable expression.

As shown in the figure on the left, the results in the transient expression showed that the productive titer of the REGULGENT antibody was equal to or slightly inferior to that of the monoclonal antibody. On the other hand, in the right stable expression, the data show that the expression titer of REGULGENT rather exceeds that of monoclonal antibodies. In fact, we have confirmed that REGULGENT antibodies are as productive as monoclonal antibodies.



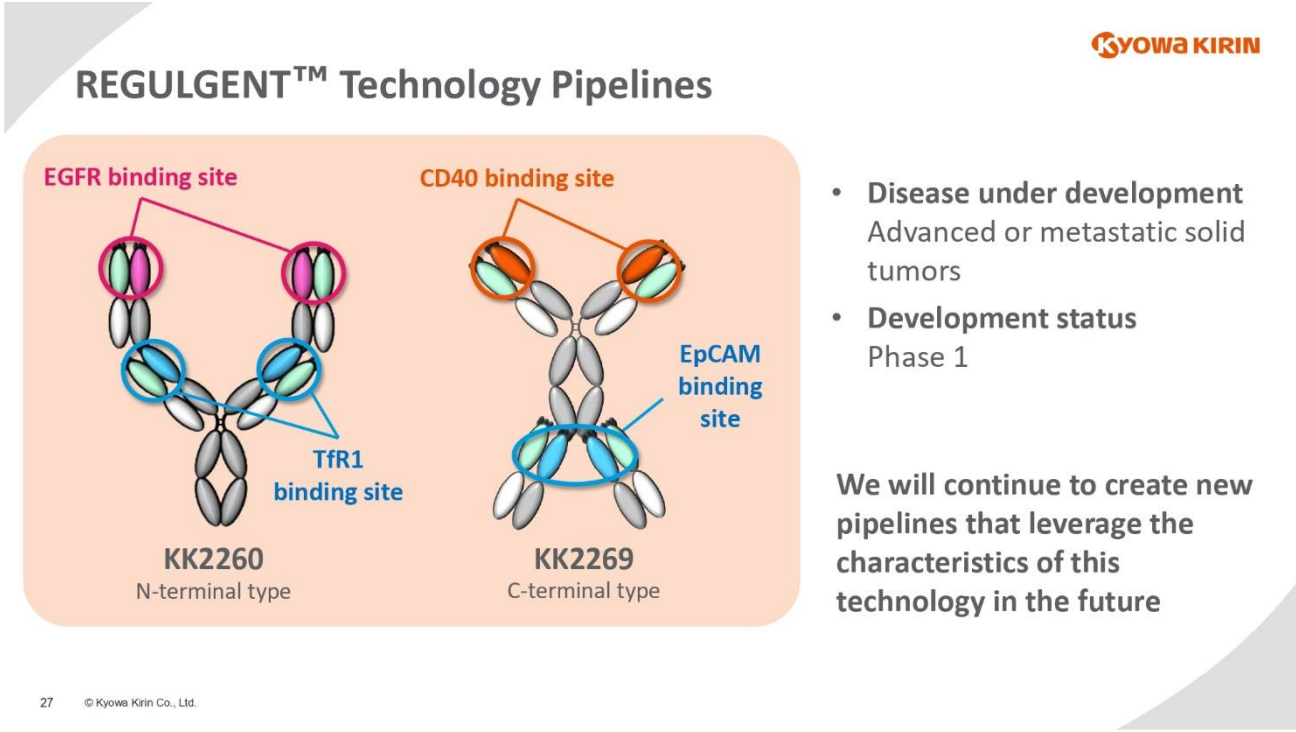
Next, we will present data on physical properties and stability.

Various antibodies were stored at 4, 25, and 40 degrees Celsius for one month to examine whether the molecules aggregate or degrade.

The graph on the left shows an analysis of molecular aggregation, which was virtually undetectable at temperatures below 25 degrees Celsius and less than 5% at 40 degrees Celsius.

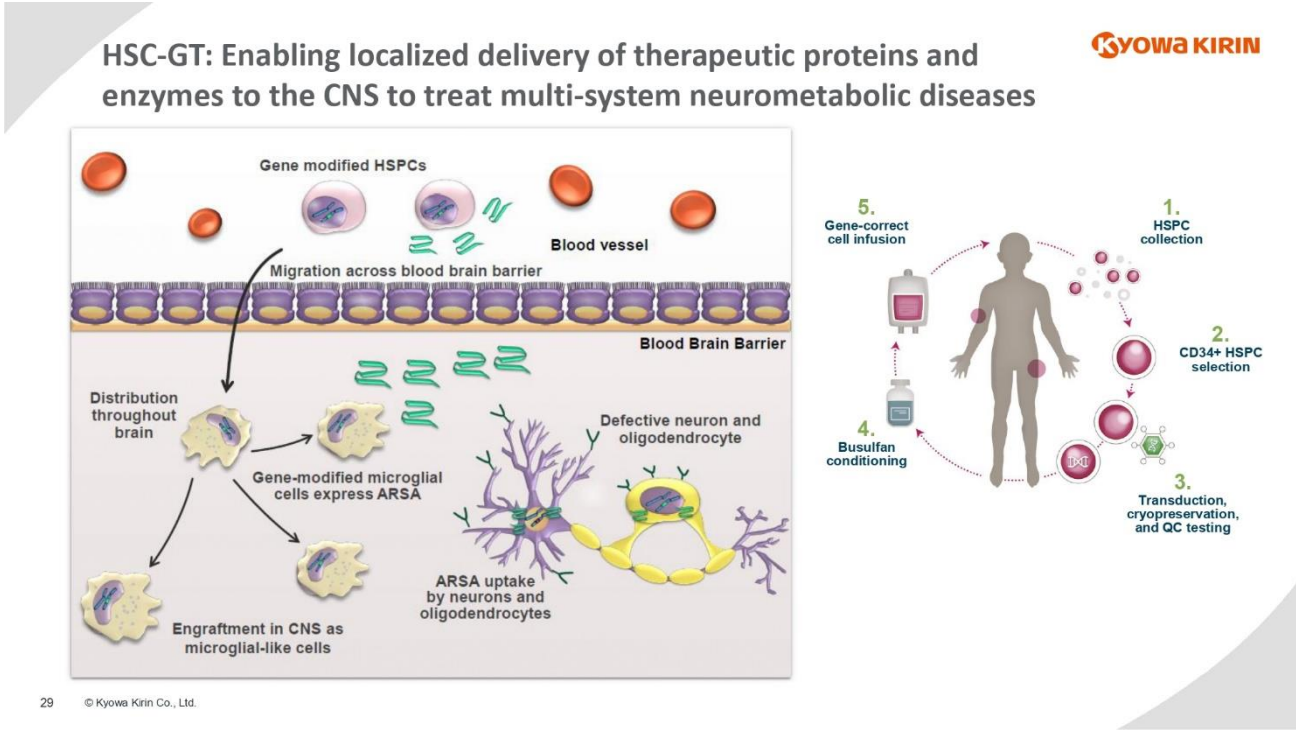
On the right is a study of molecular degradation, again almost undetectable at temperatures below 25 degrees Celsius, and only slightly detectable at 40 degrees Celsius.

As shown in the comparison with monoclonal antibodies, the REGULGENT antibody has good physical properties that are comparable to those of monoclonal antibodies.



Using the REGULGENT technology that shows such favorable properties, we are currently investigating two products in a Phase I study: KK2260 as an N-terminal REGULGENT with binding sites for EGF receptor and transferrin receptor 1, and KK2269 as a C-terminal REGULGENT with binding sites for CD40 and EpCAM. Two products are under Phase I trials.

We will continue to work on creating a new pipeline by taking advantage of the characteristics of this technology.

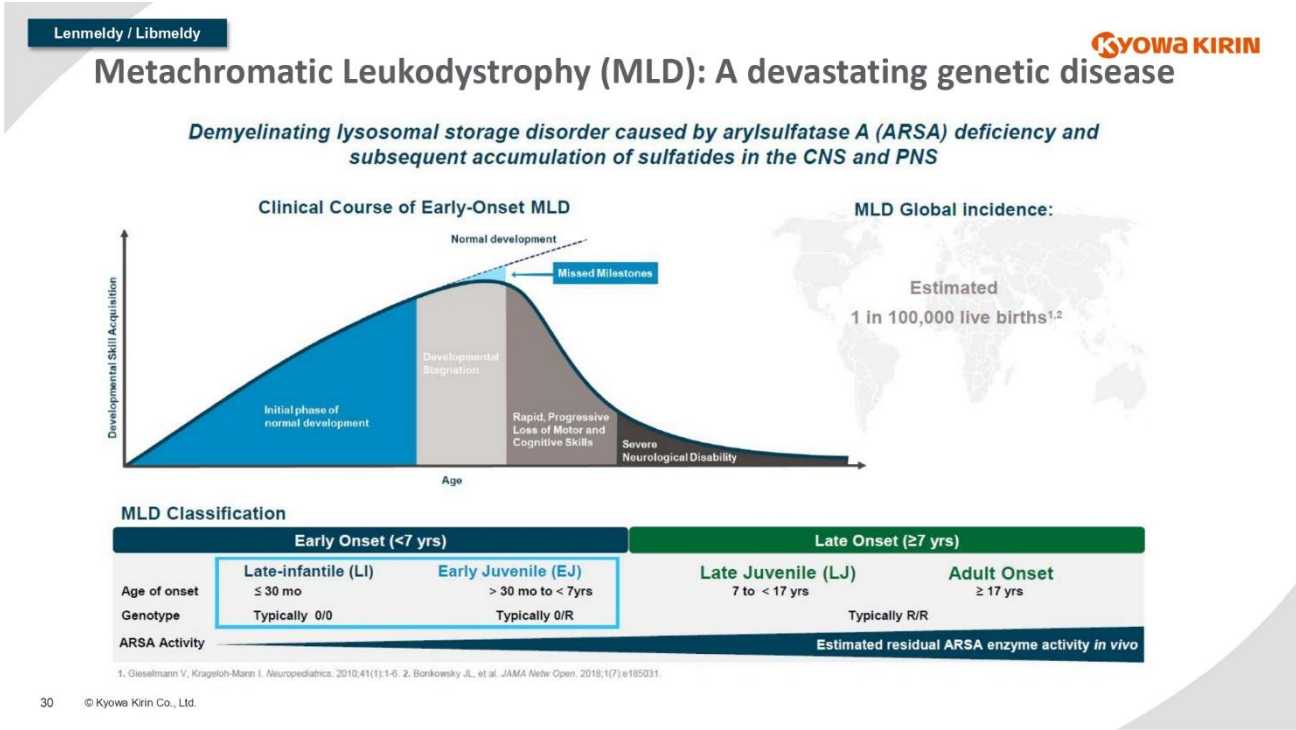


Finally, we will introduce hematopoietic stem cell gene therapy, HSC-GT.

We will present an overview of HSC-GT using the Lenmeldy/Libmeldy example, as well as a review of this technology.

Hematopoietic stem cell HSCs are cells that reside primarily in the bone marrow and are capable of differentiating into a variety of blood cell lineages. HSC-GT takes these blood stem cells and introduces a gene for a specific therapeutic purpose, which is then returned to the body to produce a therapeutic effect.

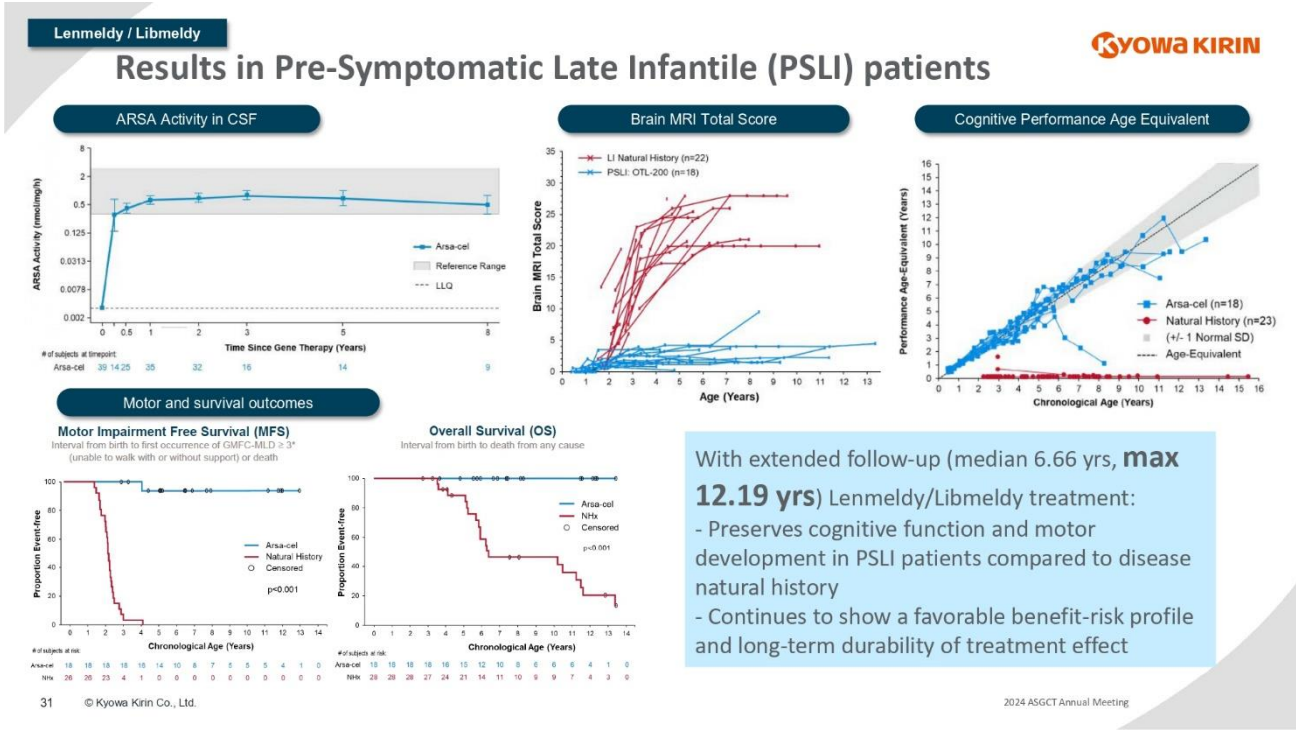
HSCs transfected with the gene for therapeutic purposes can spread throughout the body via self-renewal and differentiation while also crossing the blood-brain barrier, a common obstacle to drug delivery. In the case of Lenmeldy/Libmeldy, HSC-derived cells cross the blood-brain barrier and enter the brain to produce the desired arylsulfatase A in the brain. Then it degrades glycolipids, the causative agent of the disease, thereby demonstrating therapeutic efficacy.



Lenmeldy/Libmeldy's target disease is metachromatic leukodystrophy, MLD. As I showed earlier, the enzyme arylsulfatase A is defective in this disease, and sulfatide accumulates in the cerebral white matter, peripheral nerves, and kidneys, causing motor and cognitive dysfunction.

The center graph shows functional acquisition during postnatal development. At some point, patients with MLD begin to lose motor and cognitive function. By the time abnormal development begins, the accumulation of sulfatide, the causative agent, is already advanced. In order to protect motor and cognitive functions, it is important to treat symptoms before they develop.

To prevent delayed treatment, early diagnosis of newborns, especially right after birth, is crucial. With HSC-GT treatment now established, Orchard Therapeutics is working to implement newborn screening for MLD worldwide to save as many patients as possible.



This slide presents the results of Lenmeldy/Libmeldy treatment in a late infancy case, prior to symptom onset.

The upper left shows enzyme activity in cerebrospinal fluid. Enzyme activity in MLD patients was below the detection limit before treatment. However, it increased quickly after treatment and recovered to the normal range. Brain findings in MRI and cognitive development have been favorable in most cases.

High treatment efficacy was also observed for lower left motor function and overall survival. Long-term follow-up studies are ongoing, including a patient monitored for 12 years after treatment, confirming the lasting effectiveness of this therapy.

OTL-203

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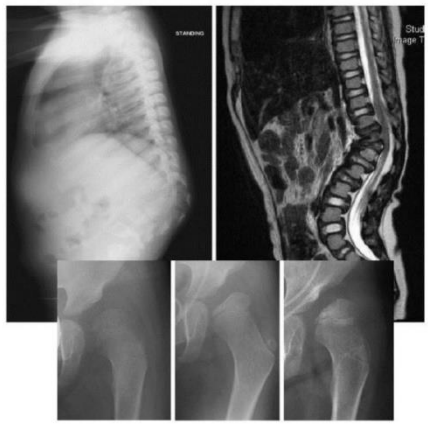
OTL-203 – MPS-IH (Hurler Syndrome) disease background

MPS-IH - Disease snapshot

- Multisystemic neurometabolic condition affecting cognition, growth and skeletal function
- Diagnosed during first 2 years of life; life-expectancy up to 10 yrs.
- Current standard of care: Allogeneic HSCT and/~~or~~ ERT, both of which have significant limitations
- ~1:100,000 live births; NBS established in some geographies, including U.S.



Summary of the proof-of-concept (PoC) study

- Target group: Patients with MPS-IH, without access to a suitable allogeneic donor, preserved neurocognitive function (DQ/IQ ≥70), fit for transplant (N=8)
- Endpoints: IDUA in blood at 1Y, GROWTH VELOCITY at 1, 3 and 5Y, motorfunction, spine MR score at 1, 3 and 5Y.

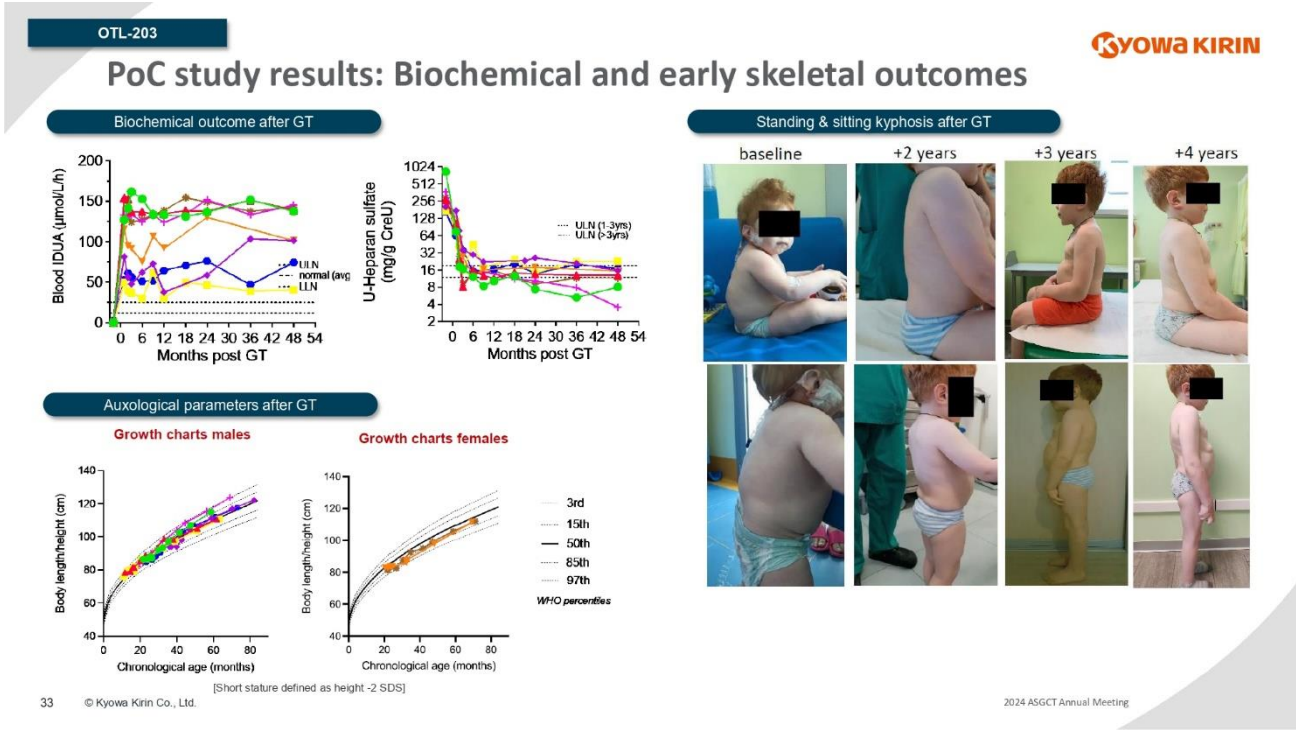
Gentner, ... & Bernardo. N Engl J Med2021

32

Next, we introduce OTL-203.

The target disease is mucopolysaccharidosis type IH, also known as Hurler's syndrome. This is another neurometabolic condition, caused by abnormal accumulation of heparan sulfate due to deficiency of the enzyme's alpha-L-isuronidase and IDUA. It affects cognition, growth, skeletal structure, and function. Life expectancy is ten years, and like MLD. It is a very serious disease.

Currently, blood stem cell transplantation and enzyme replacement therapy exist as standard therapies, but their therapeutic efficacy is limited, and better treatments are needed. The incidence is 1 in 100,000 newborns. Newborn screening is conducted in some areas.

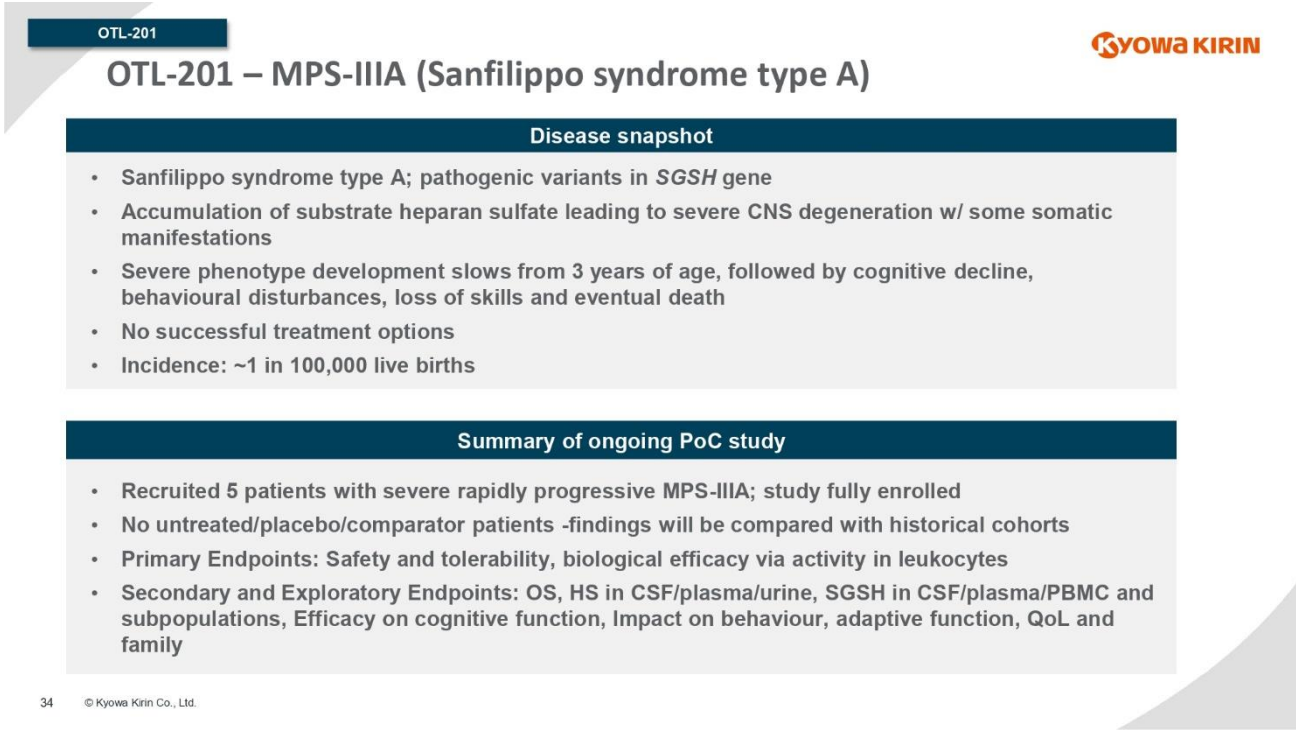


Here, we present the therapeutic effects of HSC-GT in patients who could not undergo standard hematopoietic stem cell transplantation because they could not find a donor.

The upper left graph shows IDUA enzyme activity in blood, which was below the detection limit before treatment. It rose quickly after treatment, reaching levels above the upper limit of the normal range. As shown in the adjacent graph, the enzyme substance heparan sulfate decreased significantly.

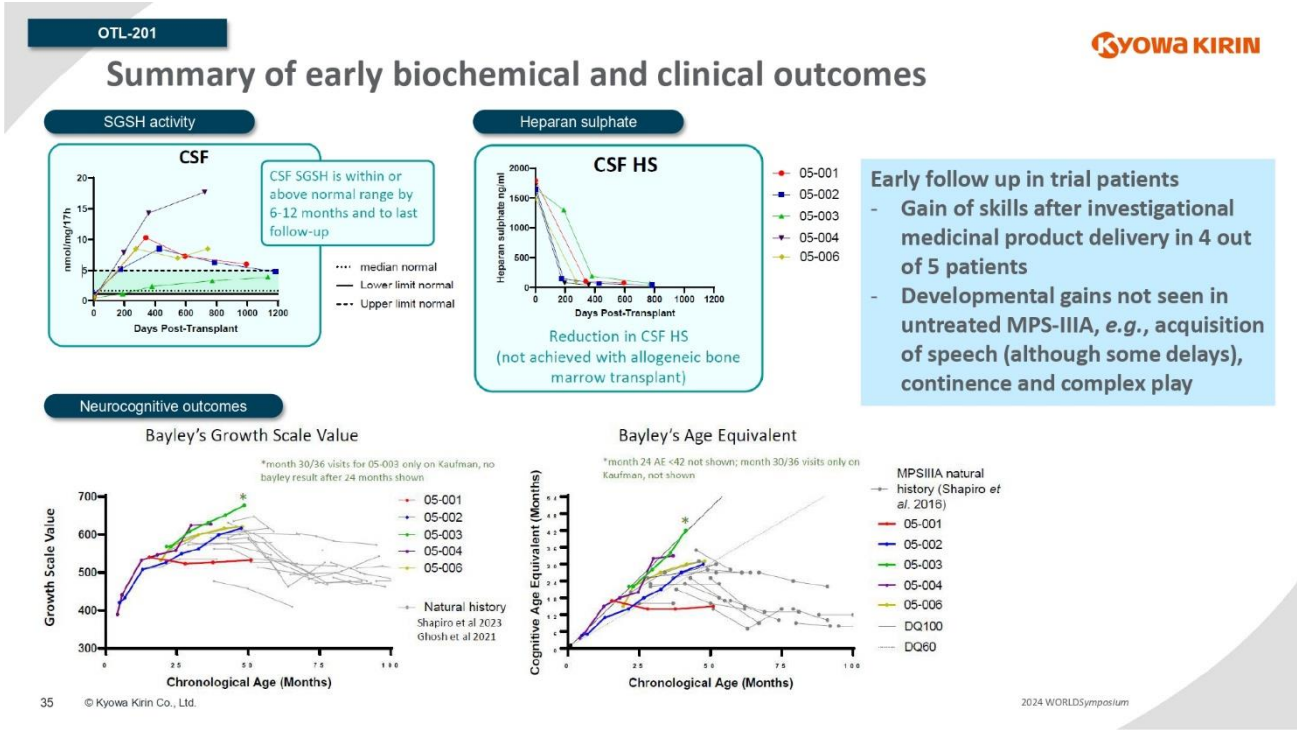
The body growth curve shown on the lower left also maintains the standard range. As shown in the photograph on the right, the physical examination revealed a clear improvement in spinal curvature and healthy skeletal growth.

Having obtained such favorable PoC test results for OTL-203, we are now proceeding with the pivotal study, a validation study, in preparation for submission for approval.



Finally, we would like to introduce OTL-201.

The target disease is mucopolysaccharidosis type IIIA, also known as Sanfilippo syndrome. The condition is believed to be caused by mutations in the SGSH gene, which encodes the enzyme sulfamidase. This leads to the accumulation of heparan sulfate, causing central nervous system degeneration. As the disease progresses, it leads to cognitive decline, behavioral disorders, and eventual death. The incidence is about 1 in 100,000, and there is no effective treatment.

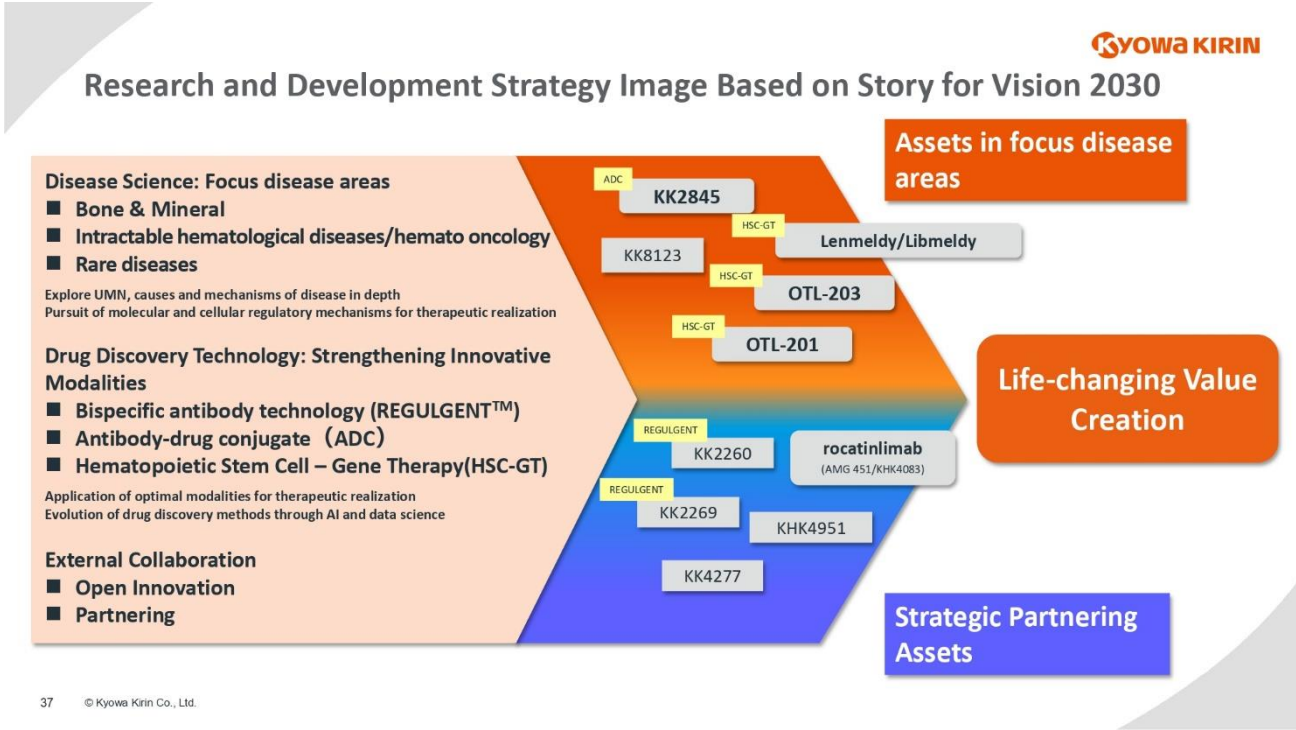


In this issue, we will discuss the results of long-term follow-up cases in a PoC study conducted in patients with severe disease and rapid progression.

The upper left graph shows sulfamidase activity in cerebrospinal fluid, which was below the detection limit before treatment but quickly increased after treatment. In response, the graph on the right demonstrates a significant decrease in heparan sulfate levels in the cerebrospinal fluid.

Four of the five patients in the study showed improvement in cognitive function, consistent with the development of healthy children. Several cases have been able to progress to an advanced cognitive test called the Kaufman test, which is the first case in a severe form of MPS-IIIA cases.

Further follow-up is being conducted to evaluate the degree of improvement in the condition.



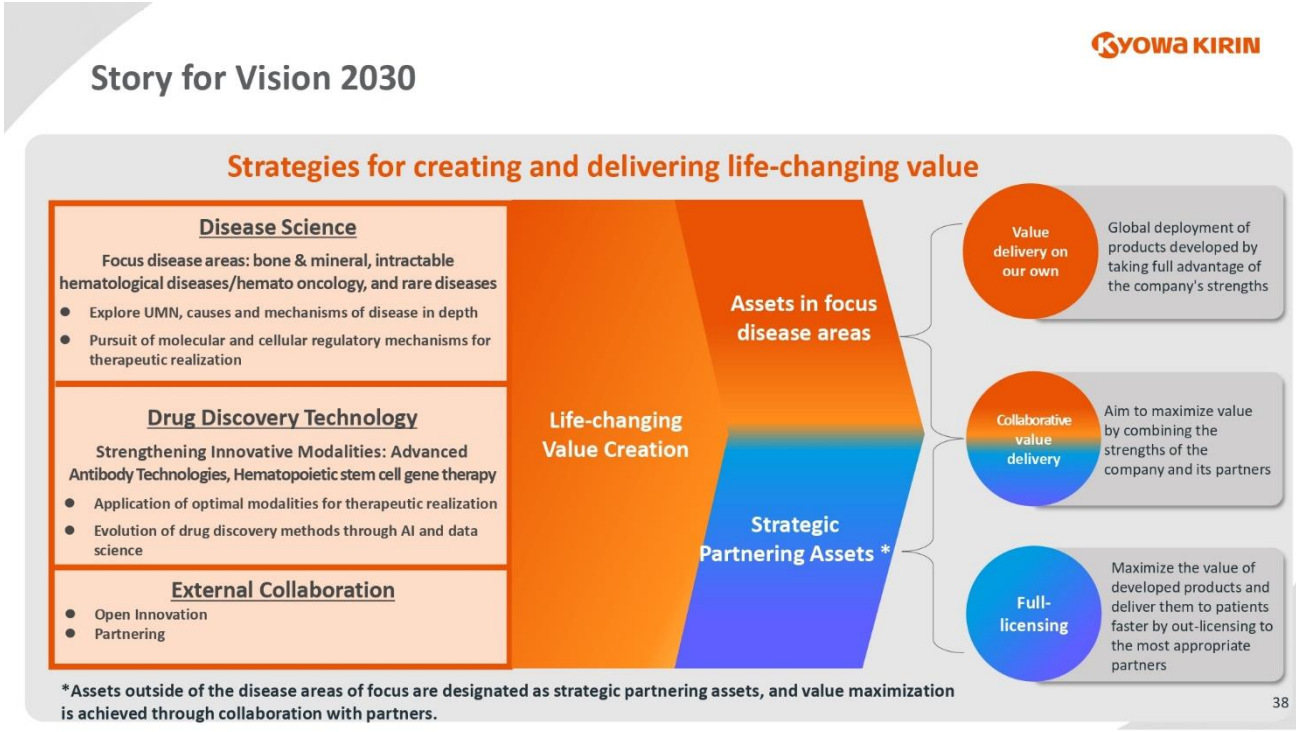
This is the end of the report of our current research and development.

Once again, this slide shows summaries of the key points of today's briefing.

We have reported the results of the first of eight Phase III studies of rocatinlimab. We will continue development with the hope that we can establish the concept of T-cell rebalancing.

Our first ADC, KK2845 which is a advancement of our strength in antibody therapeutics, as well as REGULGENT, which uses our original proprietary bispecific antibody technology. We hope to enrich our pipeline with these technologies in the future.

Finally, we have presented data on HSC-GT pipelines. These projects will serve as a gospel for patients suffering from rare hereditary diseases, and we would like to firmly promote this kind of initiative as a foothold for cellular gene therapy.



Finally, I would like to reiterate the Story for Vision 2030.

We are committed to creating life-changing value and will vigorously engage in research and development to achieve this. Research and development drive our growth, enabling us to create value that we deliver directly to patients. We also collaborate with third parties to maximize this value, ensuring it reaches patients effectively.

By pursuing these strategies, we are committed to continuously creating the life-changing value outlined in our vision. Our goal is to grow as a global specialty pharmaceutical company that ultimately makes people smile.

That is all for today's presentation. Thank you for your attention.

Question & Answer

Moderator [M]: I would now like to move on to the question & answer session.

Muraoka [Q]: Morgan Stanley, this is Muraoka. Thank you very much.

It is about rocatinlimab. I think the data was a bit weaker than Phase IIb, especially EASI-75. I know it all depends on ASCEND, but what are your company's thoughts on this data at this point?

I think it was below the expected range, but what is the understanding and what kind of data can be shown by ASCEND? It would be helpful if you could share your thoughts in this area.

Yamashita [A]: First of all, I think you may be asking if there is a slight difference between the results of the HORIZON and the Phase IIb study.

First of all, we are very positive about the results of this year's evaluation, as we achieved all of the main evaluation items and the secondary items. Certainly, there seems to be a difference between Phase IIb and a little in the figures. However, we are still unable to analyze the details at this time. We would like to investigate the details of these differences in the future.

Instead of directly comparing the HORIZON study with the Phase IIb study, we are evaluating rocatinlimab across various conditions, patient groups, and combinations in the eight Phase III studies. We want to analyze these data carefully and clarify the characteristics of rocatinlimab.

So, we do not have any further information at this time, but we hope to prove the usefulness of rocatinlimab by continuing to advance these trials.

Muraoka [Q]: Dosage is not disclosed, so I think if it were 300 mg instead of 600 mg, it makes sense. Is such an understanding slightly misleading?

Yamashita [A]: There are various conditions and tests for dosage, however we are not disclosing all of them at this time. There are many different settings within these eight tests, and we hope to be able to introduce in a comprehensive manner.

Muraoka [Q]: Okay, thank you. The other question is about KK2845, ADC.

I think payload, or PBD is an ingredient in the second generation PBD family that Daiichi Sankyo has been talking about for some time now. I think this is a highly toxic and highly effective ingredient. I think there are positives and negatives to using it. What is your thought on this matter?

Also, since ADC involves various patents, is there any possibility of royalties to be paid to someone in the future?

Yamashita [A]: Regarding the second point, I would like to ask your understanding that the technical background of this case will not be disclosed.

The advantages and disadvantages of using PBDs for ADCs, are the number of targets, how many are on the cells, and how well the antibodies bind to them with affinity. Next, we consider how many molecules the linker initially binds to in the antibody, as well as the mechanism of how the linker breaks, whether it breaks easily or not. Then, there is the cytotoxicity of the payload. A combination of these will be considered.

We have determined that this payload is suitable for the current target based on various considerations.

Muraoka [Q]: Do you have any ideas about potential side-effect risks with this KK2845?

Yamashita [A]: We need to be cautious about off-target effects with KK2845 or, in general, when these payloads miss their intended mark.

We are aware that the ADC has the problem of strong cytotoxicity when it is taken up by the liver or other organs, even if it binds to antibodies.

We are proceeding with caution in this regard.

Muraoka [M]: Okay, thank you. That is all.

Wakao [Q]: JP Morgan, this is Wakao. Please. Two questions about rocatinlimab, please.

The first is to confirm whether it is correct to understand that the results of this study, especially with regard to EASI-75, were lower than your company's expectations. Also, I am wondering if the patient background is different from Phase II, in terms of HORIZON. I would like to know if there are any differences, if any, regarding the base score of the EASI, or the treatment history of the biologics and such. This is the first question.

Yamashita [A]: In fact, I thought the numbers were a little lower than I thought. To be honest, I expect that the results will fluctuate within a certain range, but I expected to see data like Phase IIb in various patient groups and under various conditions. From that point of view, I think the numbers may be a little low.

As for your other question, the backgrounds of the patients who participated in this study are still undisclosed at this time. We hope to be able to discuss them at an academic conference or similar event in the future.

Wakao [Q]: I understand. For the biologics part. In the case of Phase II, I think it was about 10% to 15%, but as for Phase III, you did not specifically exclude people who were not using biologics. It specified that the patients were those who had been using biologics for a certain period of time, and I don't think you ruled that out. So, is it possible that there are relatively more people with a history of biologics treatment?

Yamashita [A]: We can reasonably assume that what you just pointed out is likely to occur. However, we have not yet been able to conduct an analysis, so this will be one of the points of discussion. We hope to introduce this matter in the future.

Wakao [Q]: I understand. By the way, I think Phase IIb had many Asian patients. This time, there is no bias towards that Asian population, isn’t there?

Yamashita [A]: I think there is a slight difference in the way that we are rolling out the program to a much wider geographical area and enrolling a large number of patients this time.

Wakao [Q]: My understanding is that there are no racial differences in efficacy. Is my understanding correct?

Yamashita [A]: That is how we have been believing and proceeding.

Wakao [Q]: I understand. Second. I believe it is said in the Amgen release that there will be SHUTTLE and IGNITE results at the end of this year or the beginning of the upcoming year. I would like to know the difference between this SHUTTLE, IGNITE and ROCKET program.

As for SHUTTLE, I think it is quite similar to HORIZON because it is on steroids, and as for IGNITE, it is monotherapy. I think the only difference is the inclusion of dose 2. However, I was wondering if you could tell

me if there are any differences, especially in regard to IGNITE and ROCKET, and what I should expect from dose 2.

Yamashita [A]: I would like to respond that we cannot disclose the details of anything beyond what we have disclosed on ClinicalTrials.gov and other sites.

I am in the process of researching the two doses and will introduce them when the time is ripe.

Wakao [Q]: I understand. Am I correct in understanding that steroids are loaded on SHUTTLE and IGNITE has two dosages and is relatively different from ROCKET?

Yamashita [M]: Do you mean it is close to HORIZON?

Wakao [M]: Yes, HORIZON.

Yamashita [A]: As I mentioned earlier, the patient's background and other factors may influence the final treatment outcome. However, Among the criteria established this time, the differences in the dosage you just mentioned are the differences between the two studies that we are disclosing.

Wakao [Q]: I understand. I don't think dose dependency was not seen in Phase IIb in the first place. Against this background, I am still not sure what the intention of dose one and dose two is. Can you give us some more clues in there?

That being said, is it possible that by separating the high and low doses, we might see some difference?

Yamashita [A]: We are currently designing the Phase III study based on the results of Phase IIb, which includes eight different doses, to determine the optimal dose for approval of this treatment to get an approval.

The two types of dosages and dosing intervals mentioned are embedded in each of these trials, as is the discussion of concomitant use and so on. I can't give you any specifics right now.

Wakao [M]: Okay, thank you very much. That is all.

Ueda [Q]: My name is Ueda from Goldman Sachs. Thank you very much.

I also would like to ask about rocatinlimab, as well. It may be difficult to comment on the trial results at this stage, but looking at the Phase II data, do you notice any hypotheses or trends, such as differences in efficacy based on previous treatments, as you mentioned? Can you comment on this?

I this moisturizer was used in Phase II. Is it okay to assume that the conditions have not changed in this area.

Yamashita [A]: We have not yet been able to analyze the results of this study in terms of whether or not there was prior treatment, so we do not have an answer to that question at this time.

Then let me confirm about the moisturizer.

Ueda [Q]: Thank you very much. Incidentally, is it okay to understand that there is no particular difference in the pre-treatment that you are aware of up to the Phase II stage?. For example, do you have any analysis that shows a tendency of any sort for the patients who use biologics in their previous treatment?

Yamashita [A]: In the limited scope of Phase II, no significant differences have been observed.

Ueda [Q]: Okay, thank you. Second question. I would like to know about the characteristics of your company's ADC technology.

In your introduction, you mentioned the partnership with Synaffix, along with collaborations in the linker and payload areas. How do you see your strengths coming into play within these partnerships?

You also referred to the antibodies earlier. Could you explain the characteristics of the linker, payload, antibodies, and their combinations?

Yamashita [A]: I mentioned earlier some of the key points of ADCs. First of all, when we are considering ADCs, we can thoroughly examine the behavior of antibodies, and I think that is a great advantage.

As I mentioned earlier, we have been conducting long-term research on antibody drugs, focusing on target selection, the required level of drug delivery for cytotoxicity, and the concentration of targets and antibodies on the cell surface. These things have been central to our antibody drug research for many years. I think we have strengths in those areas.

We have been challenging linkers and payloads for a surprisingly long time, and I think we are well aware of the challenges. That is where we are gaining experience through various experiments.

While we have a few initiatives to develop high-quality linkers or payloads in-house, as I mentioned earlier, to accelerate the creation of the best ADC, we should combine our strengths with those of third parties, as with Synaffix. Rather than managing every component ourselves, we focus on leveraging our partners' expertise and, when needed, selecting antibodies that complement their strengths. I think this is one of the strengths of our ADC.

Ueda [M]: Understood. Thank you very much. That is all from me.

Sakai [Q]: This is Sakai, UBS. This may be a bit of an overlay to Ueda-san’s question.

I think there were many questions about patient treatment history at the Amgen conference call. I am wondering if those incoming patients are properly washed out, right?

Since the condition is moderate to severe, I am not sure whether it is possible to wash them out or not. I think there will naturally be some variation if the washout is not perfect. Do you have any information on that area?

Yamashita [A]: We look into the history of previous treatment in the eligibility criteria for patients, and a certain interval is set.

Sakai [Q]: How long is that fixed interval? Am I correct in understanding that it depends on the individual patient?

Yamashita [A]: It depends on the treatment. Type of treatment.

Sakai [Q]: If so, how much is it, as an image?

Yamashita [A]: Basically, it's a washout. So, it means it's been set up in a way that the effects of previous treatment were eliminated.

Sakai [Q]: So, the washout period is slightly longer for biologics, is that right? Suppose you are using it on that patient.

So, this protocol is properly and entirely applied, right? I am afraid this is an obvious question.

Yamashita [A]: I think so. There may be various cases there, such as whether the previous treatment is working to some extent or no longer working, but basically, the patient is enrolled in such a setting.

Sakai [Q]: So, if the previous treatment did not do anything wrong, that would be fine. The result of this is that the results are straightforward.

Yamashita [A]: I think that's right.

Sakai [Q]: Then there is a table on page 20. Payload and linker, I guess, are the main ones. I think I understand your explanation of the technical aspects very well. In the section on target antigens, you mention biology and translational research. As you mentioned in your comment, what kind of targets or antigens are expressed on the surface of the cells? I think it would not be possible without cooperation with academia, which is outside of your company. I would like to know what stage your company is at in this regard.

The ADC field, in particular, is getting very competitive, especially with regard to intellectual property rights from a technology aspect. In terms of competitiveness, I think the difference will depend on how you develop or promote the target area. How about this point?

Yamashita [A]: We have been conducting research on antibodies that induce cell death using POTELLIGENT technology. At that time, antibodies accumulate in large numbers in the target cells. Unlike with ADCs, we have been focused on identifying the best target antigen for a long time, operating under the assumption that effector cells will come to the site and kill the target cell without the antigen being internalized.

We also examine for antigens expressed on specific cells at the gene or protein level. Once such model cells are obtained, we can count the number of antigens on the cell surface, as mentioned earlier. We can also examine whether the cells are easily taken up or not within the company.

Therefore, we believe that our research experience and achievements are quite useful in narrowing down the target of antibody research using POTELLIGENT, which is a little like an application of we have done so far.

Sakai [Q]: How many targets do you realistically have in your company? This may be a long time ago, but I have heard that the number of targets has been increasing from 100 or so to 300 or so in recent years. Do you have anything to share in this regard?

Yamashita [M]: Do you mean the number of types now? Or do you mean the number of molecules?

Sakai [Q]: I mean the type.

Yamashita [A]: Regarding the type, there are various patterns depending on the cell. We have been searching for antigens that exist only in the targeted cells for a long time, and we are using the same technology to search ADC antigens.

Sakai [Q]: I understand. You mean you are doing it in-house, is it not?

Yamashita [A]: Yes, that's right. Existing ones are in various forms, and those that have been reported can now be examined in-house. For those that are still completely new or those that are being discovered for the first time in the joint research with Kyushu University, we are still working on them either in-house or through joint research.

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

Wada [Q]: SMBC Nikko Securities, this is Wada. Thank you very much. I would also like to ask one question about rocatinlimab and another question about ADC.

Regarding rocatinlimab, I would like to go over the positioning one more time. On page 12, you mention T-cell imbalance. I would like to ask you what kind of patients you are targeting with these different mechanisms of action.

I would like to know if you are targeting patients like DUPIXENT failure. I would like to hear once again about the severity of the disease and the treatment line.

Yamashita [A]: We are still trying to find out how rocatinlimab can be very effective in the eight trials I mentioned earlier.

Let me start by talking about the mechanism. The pro-inflammatory cytokines produced by the pathogenic T-cells, as shown in the T-cell imbalance section, include IL-4, IL-13, and others. So, the biologics that are widely used today are targeting these cytokines, although they are suppressing the molecules that ultimately drive the pathology.

As for this OX40, we are trying to control the cells that produce such cytokines upstream. We expect that by targeting the cells that produce inflammatory cytokines, rather than specific cytokines, we can suppress various types of inflammation across a wide range of areas.

We anticipate that such a mechanism exists primarily in conditions like atopic dermatitis. I also believe that in other inflammatory diseases, the therapeutic effect of controlling OX40 in chronic T-cell imbalances will be to bring them closer to the normal state, as shown on the right side.

We think we can differentiate ourselves from existing treatment in those areas.

Wada [Q]: Thank you very much. As an additional note, it seems to me that rebalancing these T cells will make it easier to induce remission.

I understand that in the ASCEND trial, after administering rocatinlimab, you switch to a placebo, thereby creating a group of patients who stop receiving the treatment altogether. Do you have any indication that such effects will continue in the long term in animal studies?

Yamashita [A]: We concluded that it is effective; however, animal studies have limitations in accurately replicating atopic dermatitis, and we did not anticipate confirming long-term effects at the animal testing stage.

When the drug actually progressed to Phase IIb, we were able to see a real sustained effect. So, this time, we focused on the mechanism targeting OX40 and came to the assumption that this is what is happening now.

Wada [Q]: Okay, thank you very much. Also, regarding KK2845 in the ADCs, I would like to ask you about the pros and cons of applying ADCs to blood cancers.

Basically, ADCs are being developed mainly for solid tumors. Since AML is a bone marrow cancer, by targeting TIM-3, which is shown on page 17, they are targeting blood cells or active bone marrow cells. Or cancerization in another way.

I would like to ask two points that since it has a bystander effect, that it may destroy the surrounding bone marrow as well, and if you are taking any measures to avoid this, and if you think it can be applied to other blood cancers.

Yamashita [A]: As a concept of recurrence of AML, we can knock down leukemia cells that have been greatly increased by drugs, but we have not been able to knock down leukemia stem cells, which are the main source of leukemia cells. That is what we are assuming.

We are now using TIM-3 to selectively hit these cells, and we will continue to monitor the results of future trials. We are hoping that we can eliminate the leukemia stem cells after reducing leukemia cells, rather than just hitting them out. We are hopeful that the results of the upcoming trials will be promising.

We would like to investigate the balance between the use of this ADC and the risks associated with its use, as you mentioned in your question earlier. We would like to confirm this through clinical trials.

As for the bystander effect, as I mentioned earlier about turnover on cells, it depends on the actual distribution and turnover in the body. So, I would like to address this issue through clinical trials.

Wada [Q]: On pages 18 and 19, there are experiments on animals and cells. For example, in the two of cell experiment on page 18, I believe normal bone marrow cells and two leukemia cells could be mixed and tested to see that the bone marrow cells are not damaged. I think you can tell whether or not bone marrow suppression is occurring by examining the blood of animal cells. Do you have data in this regard?

Yamashita [A]: Although I don't have any data on mixing cells, I feel that if we wanted to do it, we could probably achieve the desired effect.

We are conducting long-term toxicity studies on the product's safety in animal models before advancing to clinical trials. So, we have confirmed that it is unlikely to cause issues in terms of its behavior within the body at the animal level.

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

Tsuzuki [Q]: My name is Tsuzuki from Mizuho Securities. Thank you very much for your explanation today. I would like to know one point each about rocatinlimab and ADC.

First, you mentioned that the data on rocatinlimab was lower than expected in your assumption this time. I think you mentioned that detailed analysis will be done in the future, but how long will it take for this kind of detailed data to be released in the future? Is there a timeline for this?

Yamashita [A]: We are still analyzing the data, so I cannot provide an exact timeline. One consideration is that we need to thoroughly review the trial, and we believe the data should be presented at an academic conference.

I am also feeling that as data becomes available for subsequent tests, we will be able to interpret them more broadly and accurately. Regarding the timing, it is unrealistic to expect an announcement by the end of the year. From there, we will focus on submitting the data to conferences. We would like to consider targets with this image in mind.

Tsuzuki [Q]: Okay, thank you. Also, I think you mentioned SHUTTLE and IGNITE. it is shown as active, not recruiting or something like that, so am I correct in understanding that you have decided to make this public in the future?

Yamashita [A]: I think Amgen disclosed that rough estimate of the lead-out timing. However, there are many things to be considered as whether it would be better to release a single release each time or to include a discussion of the results together with the previous tests. Therefore, we have not set up the timing of release at this time.

Tsuzuki [Q]: Okay, thank you. In that sense, I think SHUTTLE and IGNITE are gaining attention. As for patient background, as far as I can see, it looks the same at EASI or BSA. Is there a big difference here in terms of recruiting conditions? It doesn't look like there are any, though.

Yamashita [A]: As you mentioned, we are narrowing down the range from moderate to severe based on the EASI score and BSA level. I think that there is not much difference in the background of the patients in the form of largely specific populations. Sorry, I am a little uncertain.

Tsuzuki [Q]: No, no, I understand very well. One more point: You announced KK2845 in the ADC area this time. Are you considering launching another ADC next year, building on the linker and payload as a platform? Will this linker or payload be the next ADC with one more renewal? What are your thoughts on this area?

I wonder if you will do it as a platform base, or if the linker and payload are changing, or rather optimized, each time. What kind of image should I have? Please let me know just this point.

Yamashita [A]: Hopefully, if it becomes a platform, we can create a pipeline like a magic mallet.

As I mentioned earlier, there is a talk about whether the strongest payload is really good or not, depending on the target.

Rather than fixing a certain linker and payload, we would like to combine the optimal linker and payload with our knowledge of antibodies.

Tsuzuki [Q]: I understand. In that sense, from your current answer, it is my understanding that these two, three, and four are a little different from KK2845, is that correct?

Yamashita [A]: I will explain when we are able to disclose it.

Tsuzuki [M]: I understand. That is all, thank you very much.

Sawada [Q]: My name is Sawada, and I am from JP Morgan Asset Management. I, too, would like to ask you one question at a time about rocatinlimab and ADC.

If you check ClinicalTrials.gov about rocatinlimab, I think those who were using biologics are supposed to enter with a 12-week washout. However, all treated and previously treated patients can enter just all seven of these trials.

I think ebglyss, for example, is doing Phase III focused on bio-naive. Why are you not doing any bio-naïve focused trials at all? It may be difficult for your company to say something, but I would like to ask you if you have a comment on it.

Yamashita [A]: Of course, I don't think we are trying to prevent bio-naive patients from coming in. However, I think that if we focus only on those patients, the exam will take a little longer. There are so many patients who are undergoing various types of treatment now.

In this context, I hope you understand that we have not set up a specific area for this test, as we expect to obtain a variety of information by running many tests.

Sawada [Q]: I understand. Then, in essence, since quite a few of the current patients are not bio-naive, in that sense, you have done so in accordance with the patient's situation, is that correct?

Yamashita [M]: I don't know about that. Sorry, you mean bio-naive.

Sawada [Q]: Is it correct to say that the number of bio-naive patients is very small so you are doing this way? The bottom line is that narrowing down to bio-naive takes time, which means there are already fewer bio-naive.

Yamashita [A]: I was referring to bio-naive patients when I said that there are very few of them. There are some patients who are enrolled in this study who have used biologics as a previous treatment in terms of bio-naive. However, recently, it has become common for patients to enter this study after using Janus kinase inhibitors.

In a sense, they can be said to be bio-naive. As I mentioned earlier, when we look at the totality of these tests, I think we can evaluate the popularity of these products quite well.

Sawada [Q]: I understand. Then, I have one more question about ADC.

The payload, SG3199, is also used in the approved ADC, Zinlonta, which I believe targets blood cancer. However, AbbVie's Rova-T and other similar drugs failed to develop due to the hepatotoxicity associated with this payload.

In that sense, this SG3199, while there are certainly some products that have been commercialized, I don't think they are necessarily all doing well. In that sense, I think the reason your company chose SG3199 is because it is a publicly known substance, and there is no patent fee. I wonder if there is anything you can tell us about the reasons why you chose SG3199.

I believe Zinlonta also has skin toxicity, but I am not sure if you have any major concerns about that.

Yamashita [A]: As I mentioned earlier, the balance between the affinity of the antibody and the number of targets and the payload of cytotoxic activity is very important for ADCs.

When the target population is small or the dosage is low, but the killing power is high, using a potent payload is an option. However, when the target is large and the dosage is high with high killing power, I am concerned about potential toxicity.

It is often reported that the most likely cause of toxicity is nonspecific toxicity in the liver. So, we have decided to proceed with clinical trials using this molecule while taking this into consideration.

Sawada [M]: Okay, thank you. That is all.

Moderator [M]: No one else seems to have any other questions. Since the closing time is approaching, we conclude the presentation.

Thank you very much for attending our R&D presentation today. Thank you for your continued support of Kyowa Kirin.

[END]