Kyowa Kirin Co., Ltd.

R&D Day

December 10, 2020

Event Summary

[Event Name]	R&D Day	
[Date]	December 10, 2020	
[Number of Speakers]	2	
	Yoshifumi Torii	Executive Officer, Vice President, Head of R&D Division
	Masamichi Koike	Head of Research Functions and Fellow, R&D Division

Presentation

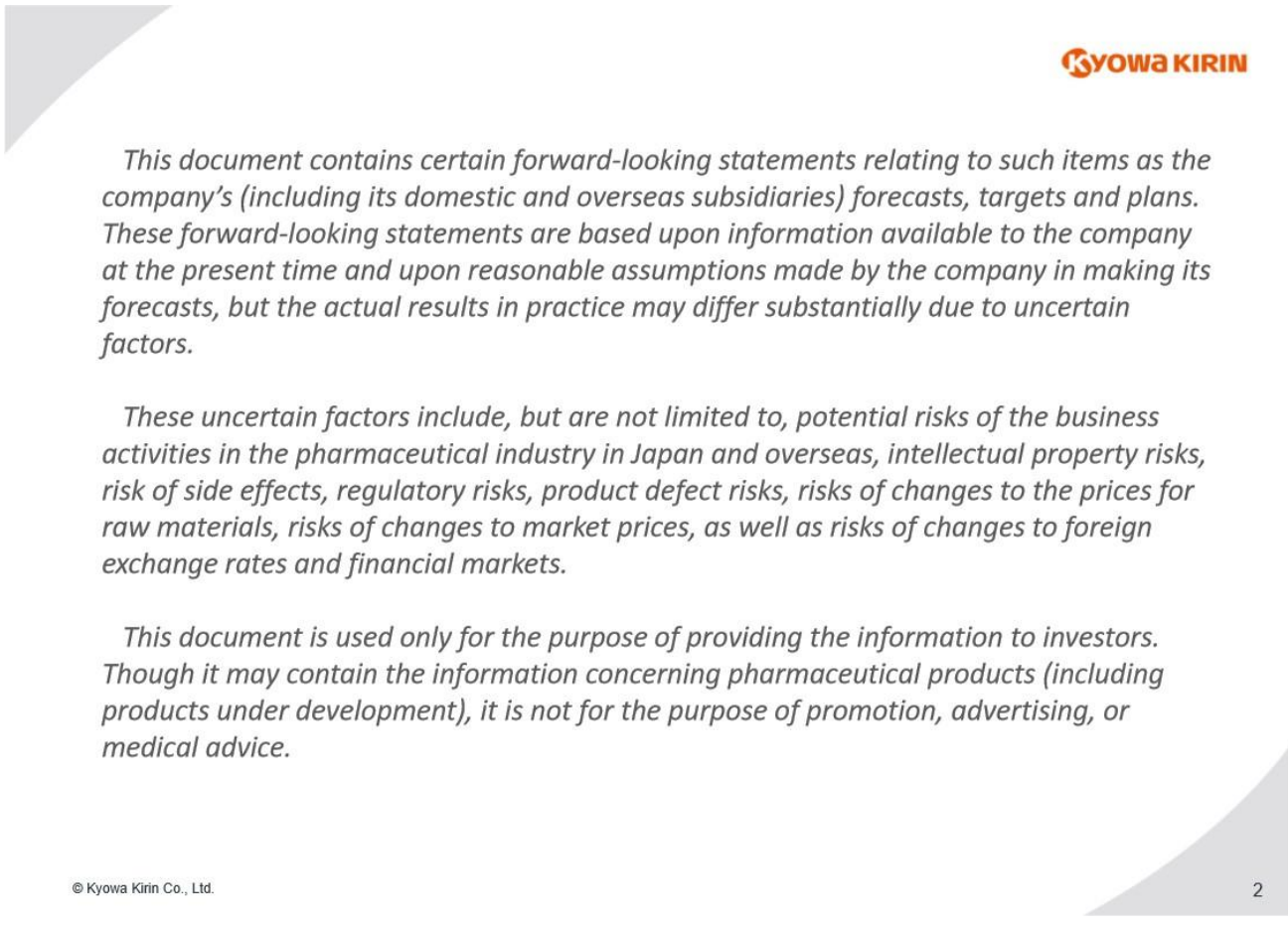
Moderator: We will now hold an R&D Day presentation for Kyowa Kirin Co., Ltd.

In the first half of today's event, Dr. Yoshifumi Torii, Head of the R&D Division, will discuss early-stage development compounds and partnership projects aimed at medium- to long-term drug discovery. In the second half, he will present the most recent progress of the clinical-stage projects.

After the explanation from Dr. Torii, we will accept your questions. Today, from the Research Function of R&D Division, Masamichi Koike, Head of the function and Fellow, and Hiroshi Ishida, Head of the Management Office, will also participate in the Q&A session.

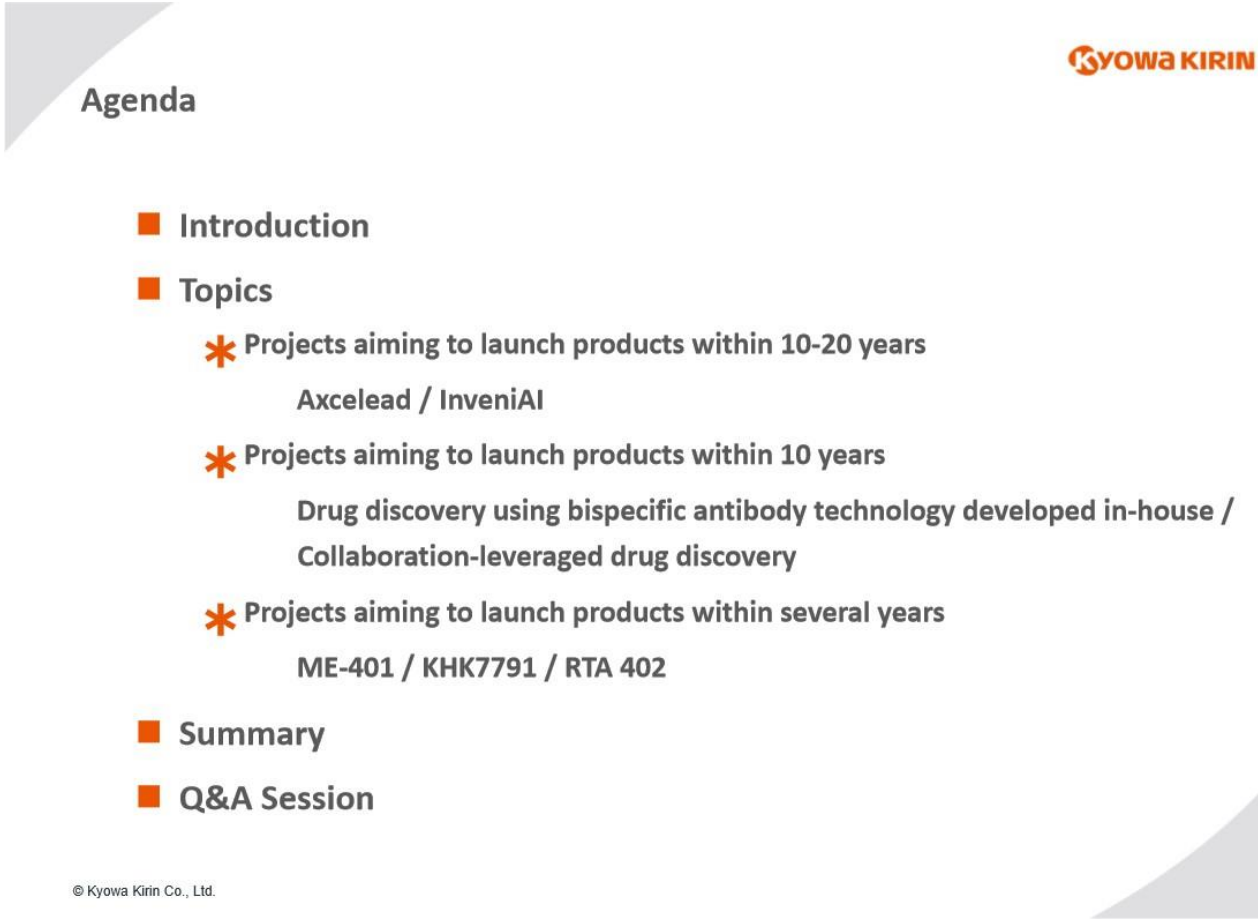
Today's briefing is scheduled to take about 60 minutes. Please review the materials that were uploaded to our IR website at 9 AM today. In addition, a voice recording of the briefing is scheduled to be provided on our IR site. Please use it to check the content of the presentation.

If you have any questions, please contact us at ir@kyowakirin.com.



This is a cautionary statement with respect to forward-looking statements. Please be aware that the content of the forward-looking statements in this discussion today involves various uncertainties.

We will now move to the presentation. Dr. Torii, please go ahead.



Torii: Good morning, ladies and gentlemen. Thank you very much for participating in Kyowa Kirin's R&D Day today.

This is the agenda for today. First, I would like to give an outline of Kyowa Kirin's current R&D activities.

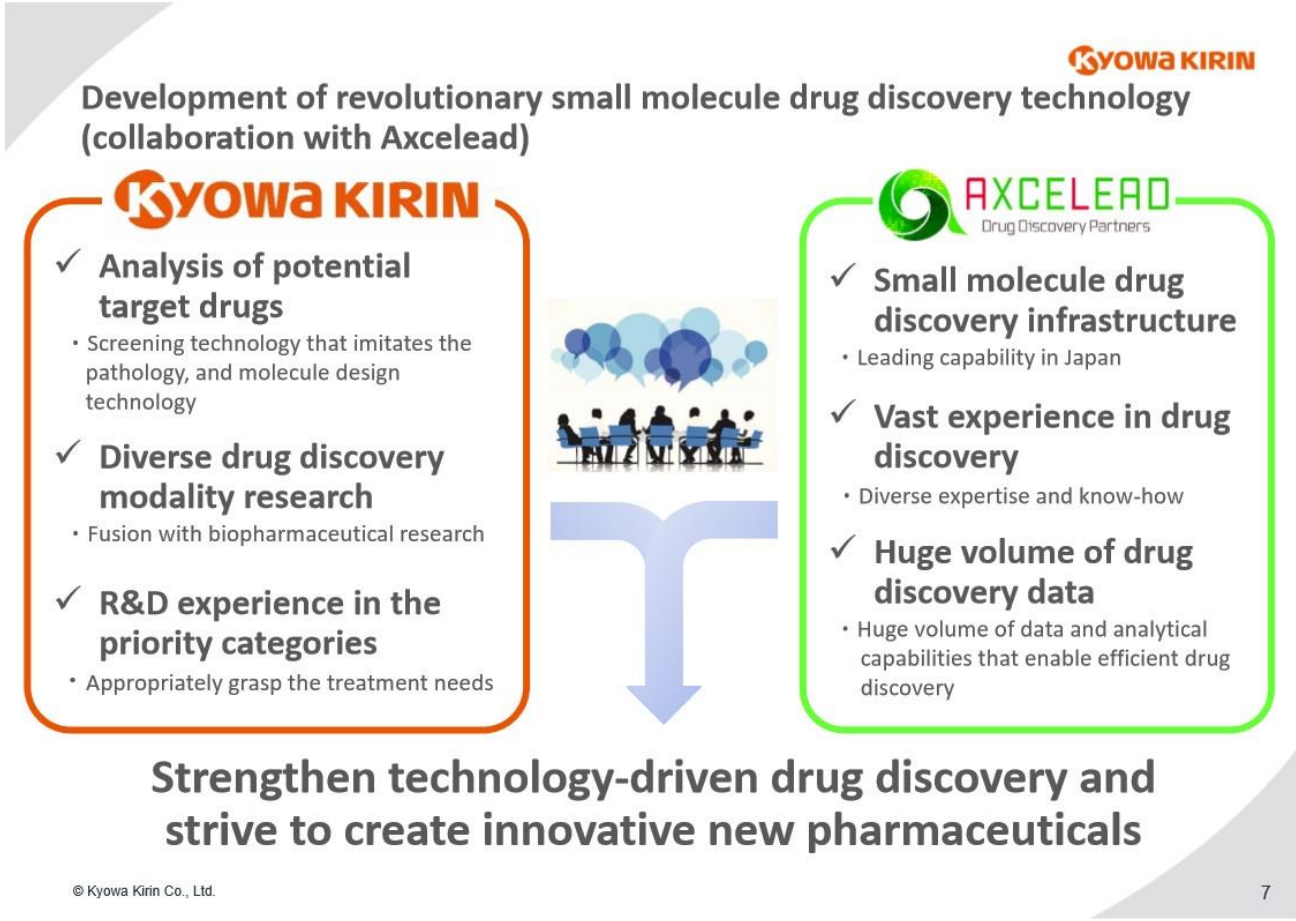
The following topics are divided into three parts, based on the time required for various initiatives: several years from now, 10 years from now, and the period between 10 years to 20 years from now. I will talk about the latest information in terms of each of these time frames.

First, let me briefly explain Kyowa Kirin's approach to R&D activities. In the last five years, we have taken our first steps as a global specialty pharmaceutical company, with three in-house products entering the global market, including in the US and Europe.

In order to continue to develop our experience of nurturing pharmaceuticals in the future, we need to take on the challenge of creating new value by leveraging our proprietary technologies and unique perspectives.

We continue to take on the challenges of technological innovation and medical treatment from two perspectives. As an innovation strategy, we will steadily build platforms that utilize a variety of modalities, including next-generation antibody technologies. In terms of medical treatment strategy, we will play a role in changing the lives of patients by satisfying unmet needs through the integration of technology and knowledge of disease biology.

With these strategies in mind, we are working within the Company as well as partnering with other companies to cultivate product candidates for the future. Of these, today we outline two partnership projects and the concepts of the two initial development themes. Next, I will present the latest information on three projects in the late stages of development.



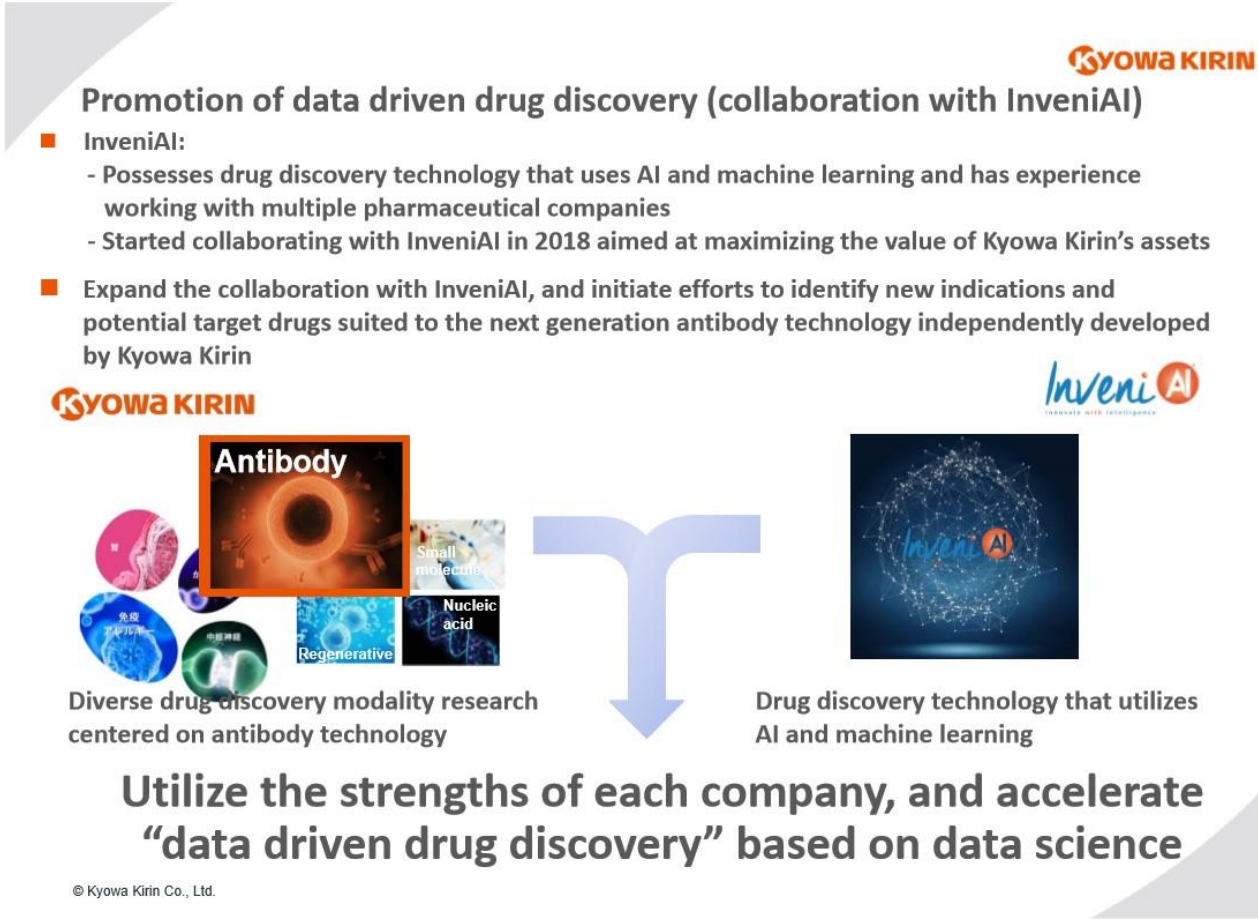
I would like to introduce two partnership projects aiming new drugs to market in the 10- to 20-year time frame that I mentioned just now.

First, let me discuss the alliance with Axcelead Drug Discovery Partners, which we announced on October 2. This partnership has the aim of making technological developments related to innovative small-molecule drugs.

In recent years, there has been significant progress in the technological development of cell-based pharmaceuticals as well as antibodies and other protein formulations, and many companies have been focusing on drug discovery targets and diseases that are difficult to approach with conventional small-molecule pharmaceuticals. On the other hand, these small-molecule compounds still have significant benefits, such as oral administration. Further technological innovation is required in this area.

This time, by forming an alliance with Axcelead, which was established from Takeda Pharmaceutical as a drug discovery platform, we hope to benefit from their top-class domestic small-molecule drug discovery foundation, as well as the vast drug discovery data inherited from Takeda and abundant drug discovery experience.

By integrating their capabilities and Kyowa Kirin's various analytical technologies, diverse modality research know-how based on biotechnology, and the establishment of unmet medical needs through R&D in priority categories, we will strengthen our technology-driven drug discovery style through the development of innovative small-molecule drug discovery technologies. At the same time, we will take on the challenge of innovative drug discovery.

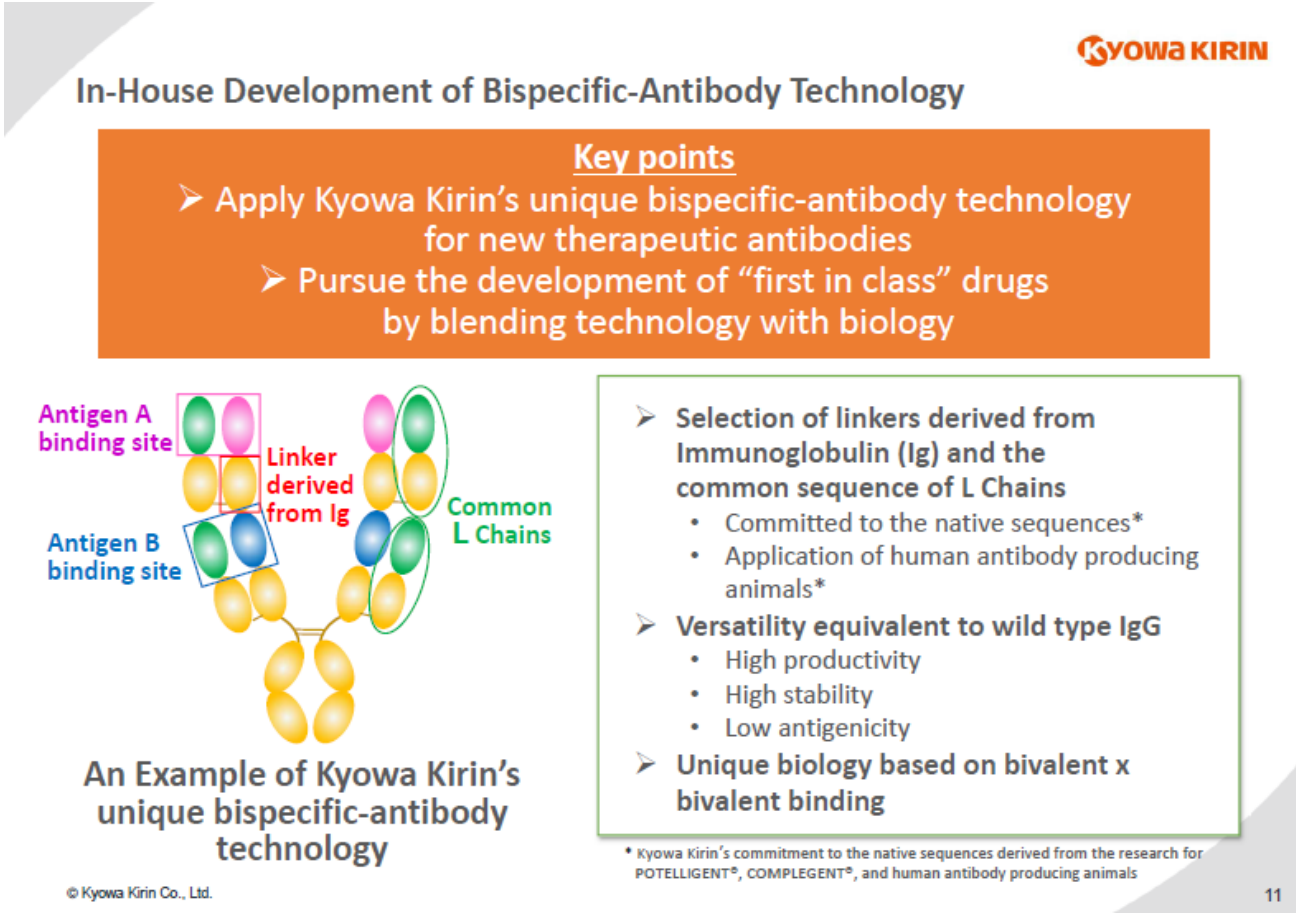


This is about our collaboration with InveniAI, which we announced yesterday, December 9, regarding the search for new targets through AI drug discovery technologies.

InveniAI possesses drug discovery technologies utilizing AI and machine learning and has a track record of collaboration with several pharmaceutical companies, including major foreign companies. Since 2018, we have collaborated to maximize the value of Kyowa Kirin's existing assets, including compounds and R&D information.

This time, the scope of this collaboration will be expanded, and Kyowa Kirin will commence the discovery of target molecular entities and the search for indications that are compatible with the next-generation antibody technologies independently developed by Kyowa Kirin.

As a result, in addition to efforts to create new pipelines by maximizing the value of Kyowa Kirin's existing assets, which we have been working on to date with InveniAI, we will expand the scope of our collaboration to accelerate applied research for next-generation antibody technologies. In this way, we will further accelerate data-driven drug discovery based on data science, combining the strengths in technologies of both companies.



Next, I will present two early-phase compounds that we are aiming to bring to market in the 10-year time frame.

The first is from in-house drug discovery, using our bi-specific antibody technology.

This slide summarizes the applications of our in-house bi-specific antibody technology. We are proceeding with research using our proprietary bi-specific antibodies, with a goal to discover first-in-class drugs that combine technology with biology.

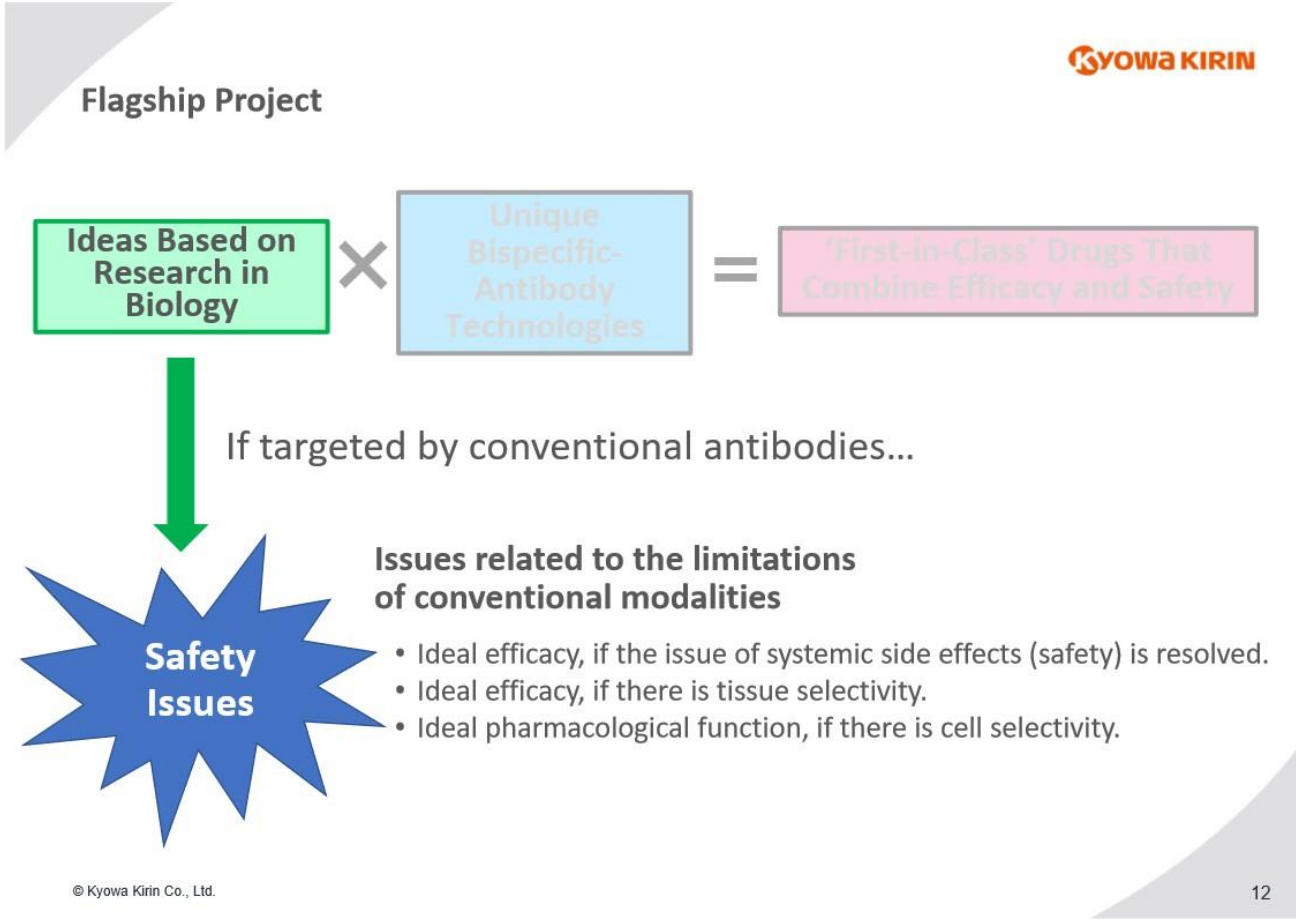
The diagram on the left shows a typical example of Kyowa Kirin's proprietary bi-specific antibody. The antibody has two binding sites for two targets. On the right, we have identified three characteristics of this technology.

The first is the selection of native immunoglobulin-derived linkers and L-chain common formats. Kyowa Kirin is always committed to this initiative, and this project will inherit the use of natural array and the application of human antibody-producing animals.

The second point is that it has the same versatility as wild-type antibodies. This technology realizes high productivity, high stability, and low antigenicity, and is an easy-to-use drug format, according to the characteristics described in the first section.

The third point is that distinctive biology can be obtained through the configuration allowing binding to two different antigens in two bivalent and bivalent ways.

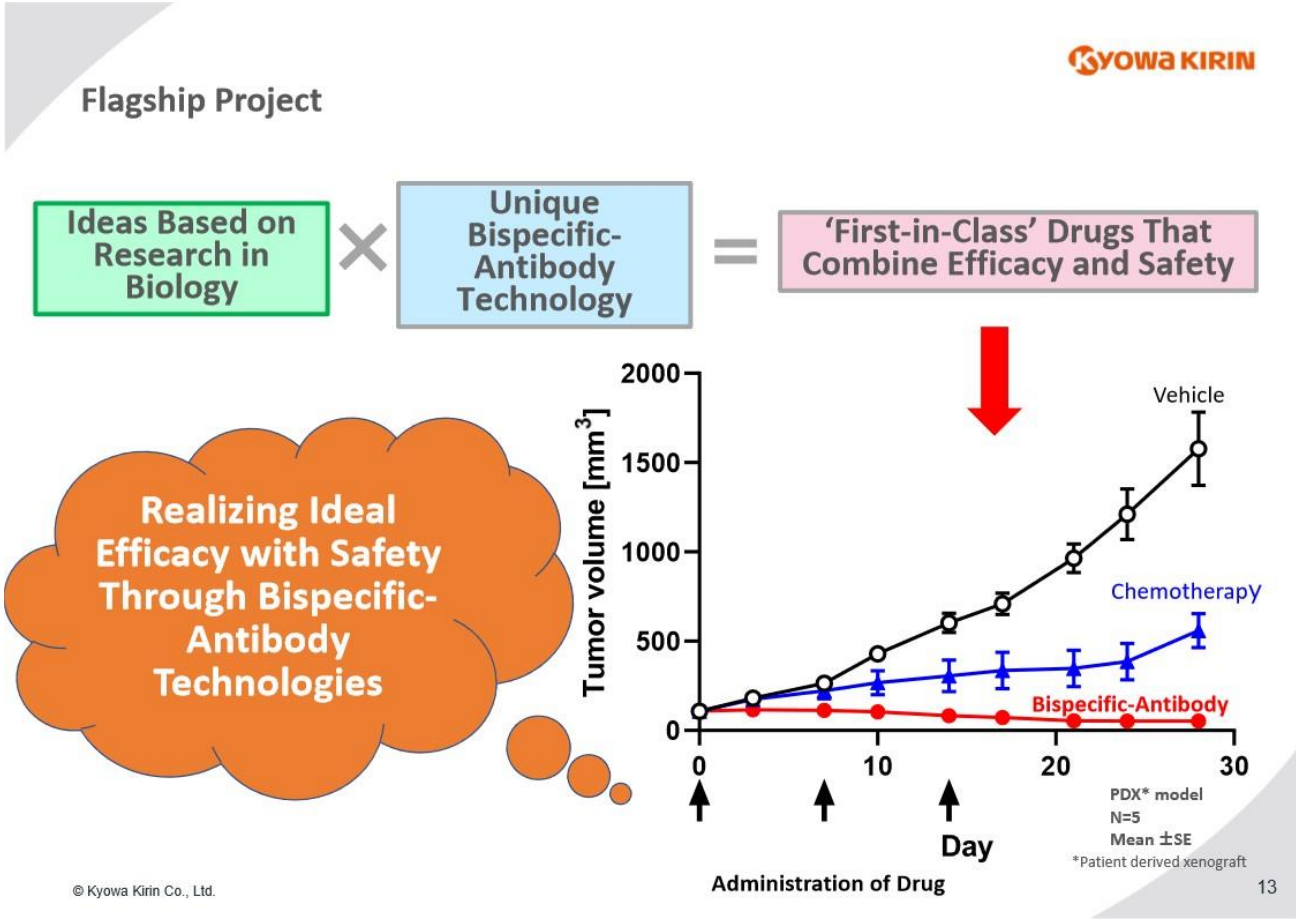
The following is an example of a compound that utilizes these characteristics of the bi-specific antibody technology.



The next few slides are an introduction of a flagship project.

An extremely attractive target was found from the long-standing biology research at Kyowa Kirin's laboratories. However, it has become clear that targeting with conventional types of antibodies presents issues with safety.

If systemic effects and safety can be cleared, if organizational selectivity is available, or if cell selectivity is available, we can expect good pharmacological action and efficacy, but unfortunately, there was a limit to targeting with conventional modalities.

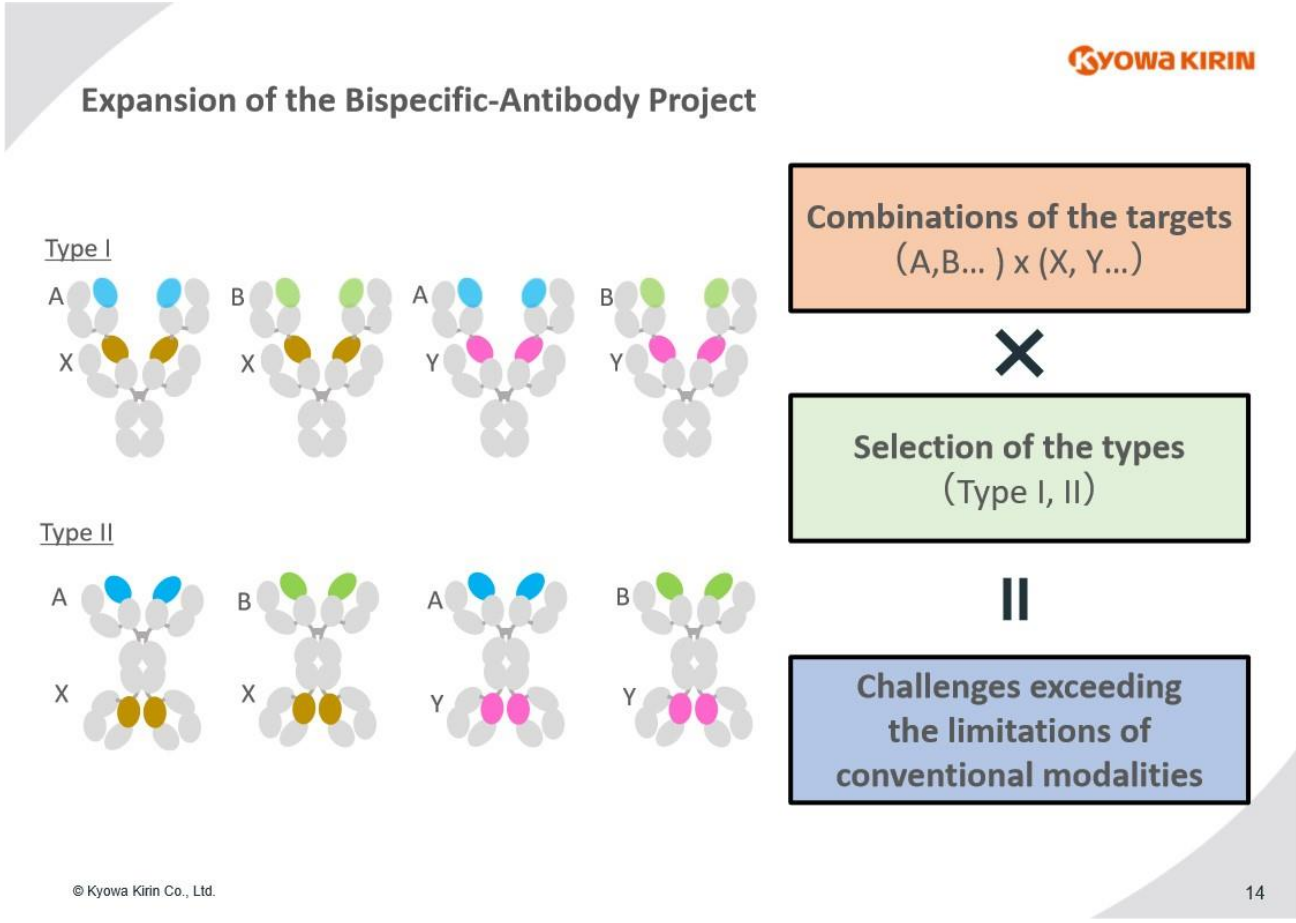


Accordingly, by applying Kyowa Kirin's proprietary bi-specific antibody technology, we succeeded in discovering first-in-class drugs that combine efficacy and safety.

As shown in the figure here, we have confirmed the improved efficacy of a bi-specific antibody in a mouse model transplanted subcutaneously with patient-derived tumor cells.

Furthermore, safety was confirmed since no serious toxicity was found in a high-volume administration of 100 milligrams per kilogram in a toxicity test in cynomolgus monkeys.

Based on these results, we believe that we have succeeded in safely realizing good efficacy through our bi-specific antibody technology.



Following on from the flagship project I now described, we are also actively developing bi-specific antibody projects that apply this technology.

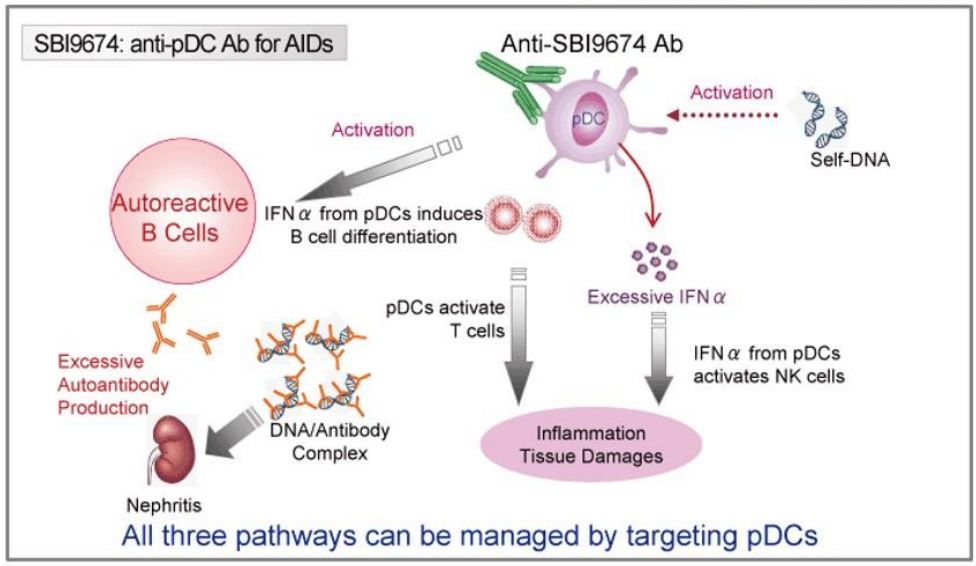
Kyowa Kirin's proprietary bi-specific antibody technology can be produced as a combination of targets such as A, B, X, or Y; or type/frame 1 or 2, as described in the diagram. This selection allows you to create many patterns of bi-specific antibodies.

Through these combinations, we are taking on the challenge of creating distinctive antibodies with life-changing value that we were unable to achieve through conventional modalities. We plan to conduct research in order to begin clinical trials for multiple projects over the next several years.

New antibody that targets pDCs (in-licensed from SBI Biotech)

In 2016 Kyowa Kirin concluded an exclusive licensing agreement with SBI Biotech Co., Ltd. covering development, manufacturing and sales worldwide for SBI-9674, an antibody drug for autoimmune diseases

*** pDC : Plasmacytoid dendritic cell**



Source: SBI Biotech homepage （https://www.sbibiotech.jp/english/pipeline/sbi9674.html）

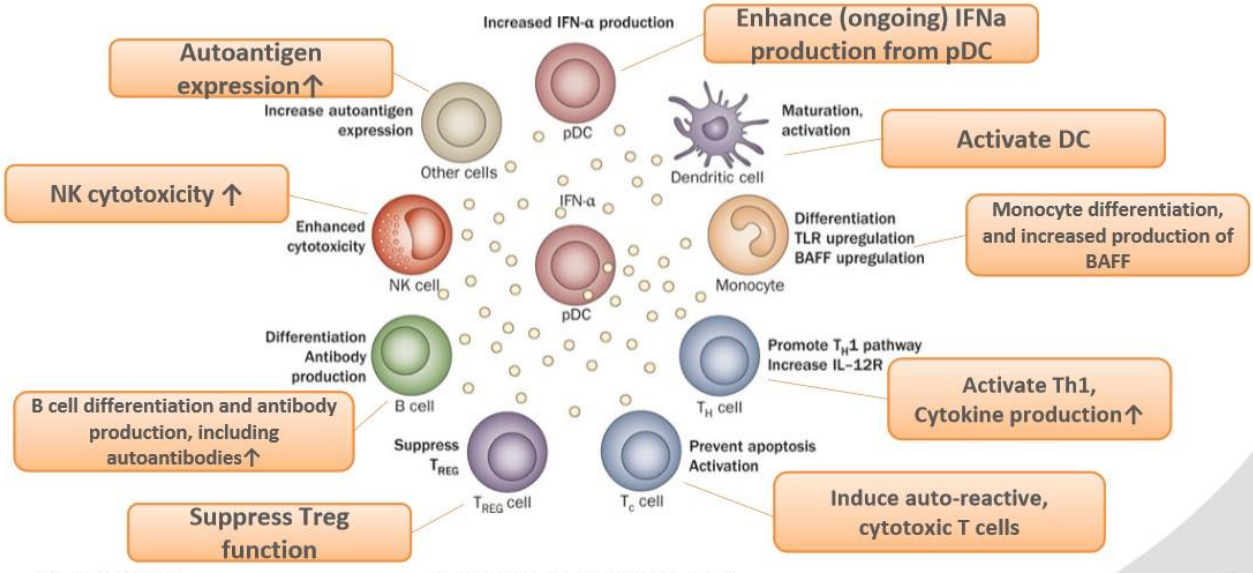
Next, we introduce an example of an early-stage compound in the immunology & allergy field. This discovery is the product of a collaboration with another company.

In 2016, we entered into an exclusive worldwide licensing agreement with SBI Biotech for antibodies targeting pDCs, or plasmacytoid dendritic cells.

Kyowa Kirin have focused on pDCs as a target cell for treatment of autoimmunological diseases. However, we came to collaborate on the SBI9674 antibody created by SBI Biotech, believing that by combining Kyowa Kirin's drug discovery modality and R&D capabilities related to antibody drugs, we can expect drug discovery that leverages the strengths of both companies.

New antibody that targets pDCs (in-licensed from SBI Biotech)

- pDCs are known to be the main source of type 1 interferons (Type 1 IFN), which are the cause of various autoimmune diseases
- Type 1 IFN produced from pDCs coordinate immune functions through a variety of mechanisms (see the illustration below)

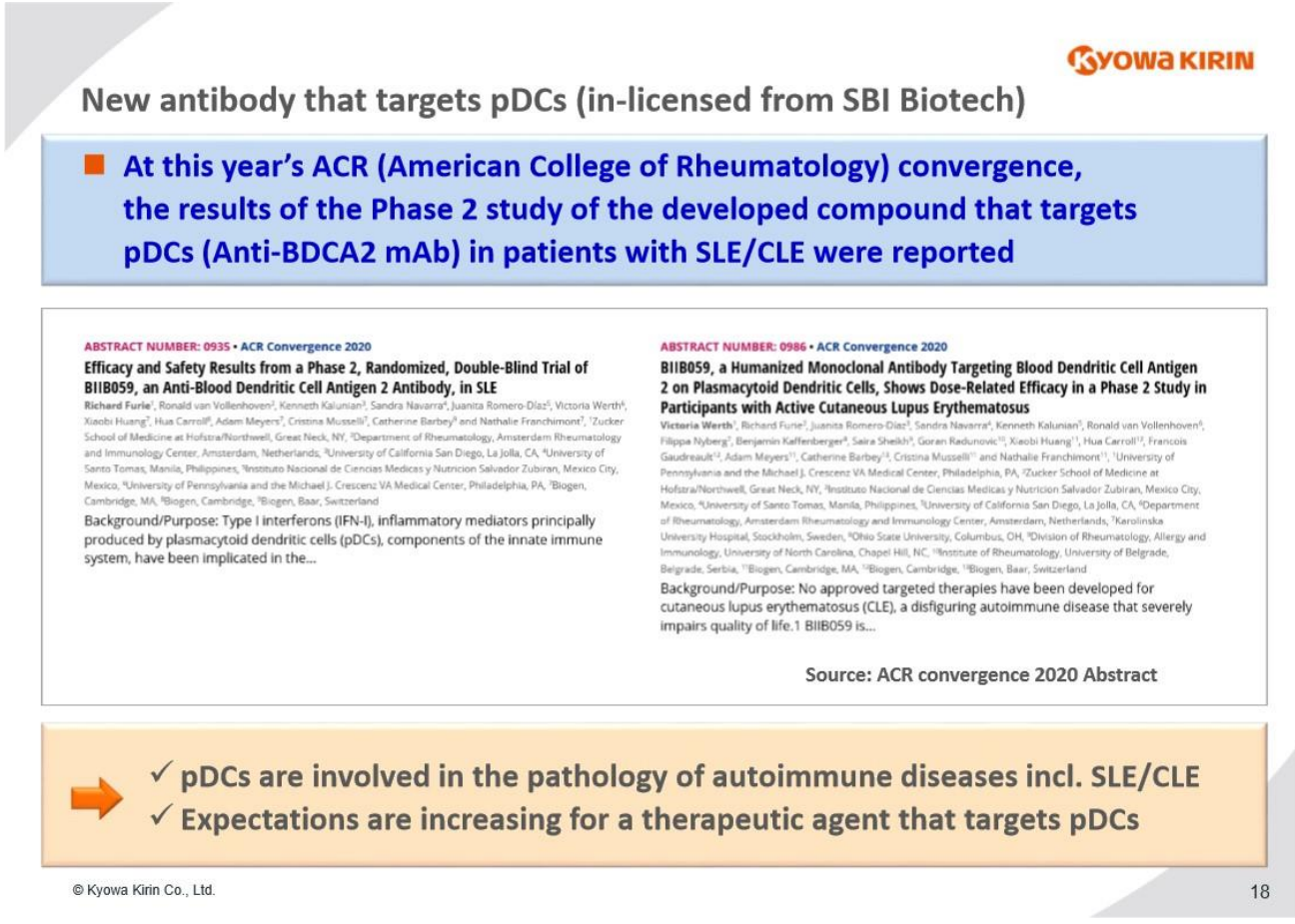


Source: Nat Rev Rheumatol. 2010

The pDC cell type is considered to be the primary cell type involved in production of Type I interferons, which are responsible for SLE and various other autoimmunological diseases.

As shown in the diagram below, Type I interferons produced by pDCs are activating the immunochemistry function through various mechanisms.

Belimumab, a B-cell stimulatory factor inhibitor, was first approved as a biologic for SLE in 2011. However, pDCs are believed to act further upstream of the physiologic functions such as B cell activation and enhanced BAFF production.



Here is an example of preceding development targeting pDCs.

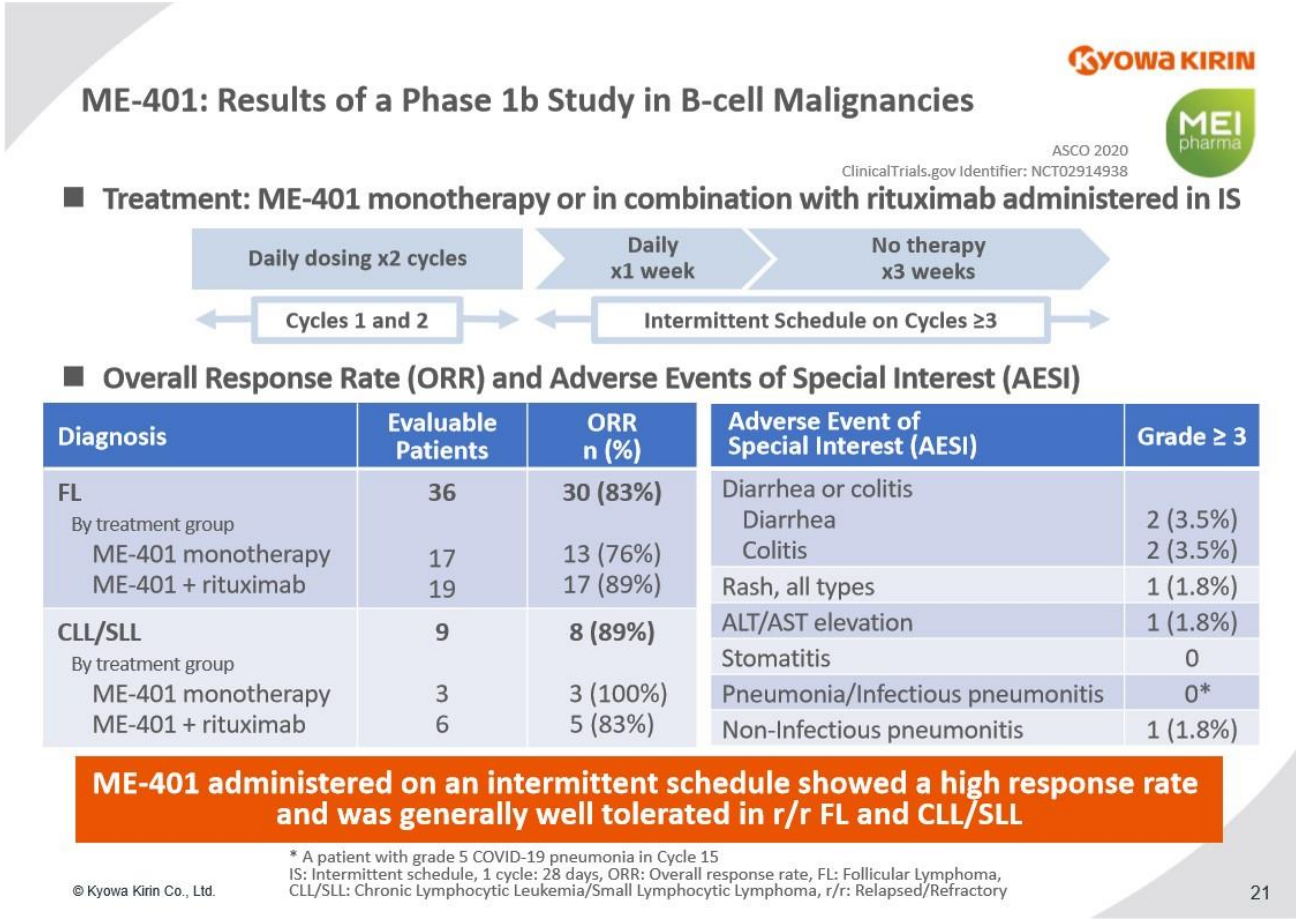
In November of this year, at the American Institute of Rheumatology, Biogen reported on the outcome of a Phase II study for patients in SLE and CLE using an anti-BDCA2 antibody, a development compound targeting pDCs.

This antibody has shown positive results in patients with SLE and CLE, which strongly suggests that pDCs are involved in the development of autoimmune diseases such as SLE and CLE.

In addition, because it is known that high-dose steroids are needed to control the pathway of Type I interferon production, there is a growing sense of hope that this pDC-targeted treatment may reduce the administration of steroids.

Although we cannot discuss our development candidates in detail today, we intend to fully leverage our experience and technological strengths to continue development in this area.

This concludes the section on compounds at the non-clinical stage.



Finally, I would like to introduce updates on three compounds at the clinical stage, which we are aiming to bring to market a few years from now.

The first is ME-401. This section reviews the findings of the Phase Ib trial announced at ASCO in June of this year and introduces the design of the Phase II trial, TIDAL, which is currently underway, and the domestic Phase II Trial, which was commenced in October.

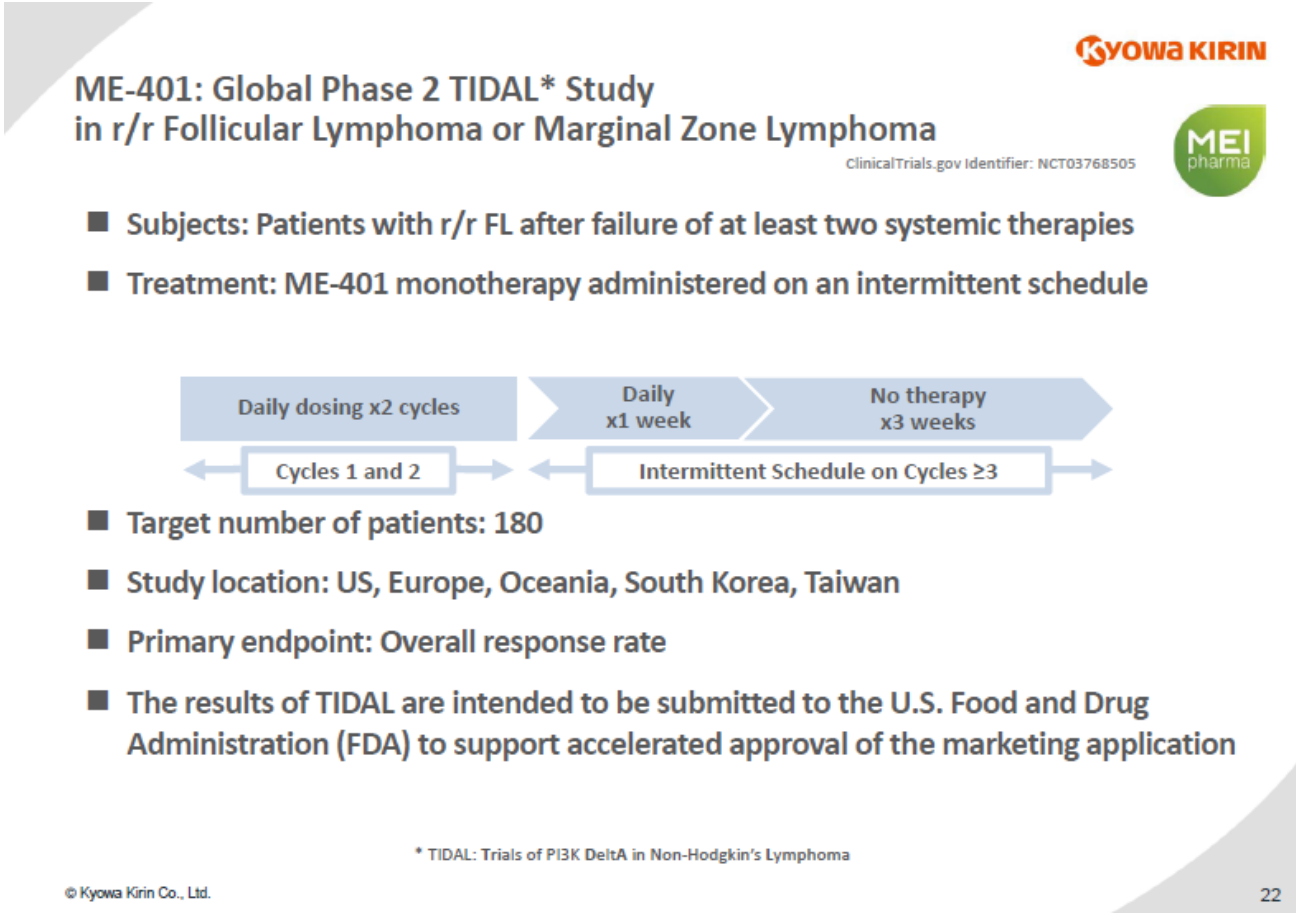
This slide shows the outline and outcome of ME-401 Phase Ib study.

This study targeted a total of 57 patients with relapsed or refractory B-cell malignancies who received intermittent doses of ME-401 alone or ME-401 in combination with rituximab.

The administration method was as shown at the top of the slide. After conducting two cycles of this daily administration for a period of 28 days as a cycle, intermittent administration was conducted from the third cycle consisting of daily administration for one week and a suspension for the remaining three weeks.

The overall response rate, ORR, was 83% for relapsed or refractory follicular lymphoma (FL). For chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL), the figure was 89%. In addition, medication was discontinued in 7% of cases due to adverse events.

The results of this study showed that the intermittent administration method of ME-401 was highly effective and well tolerated.



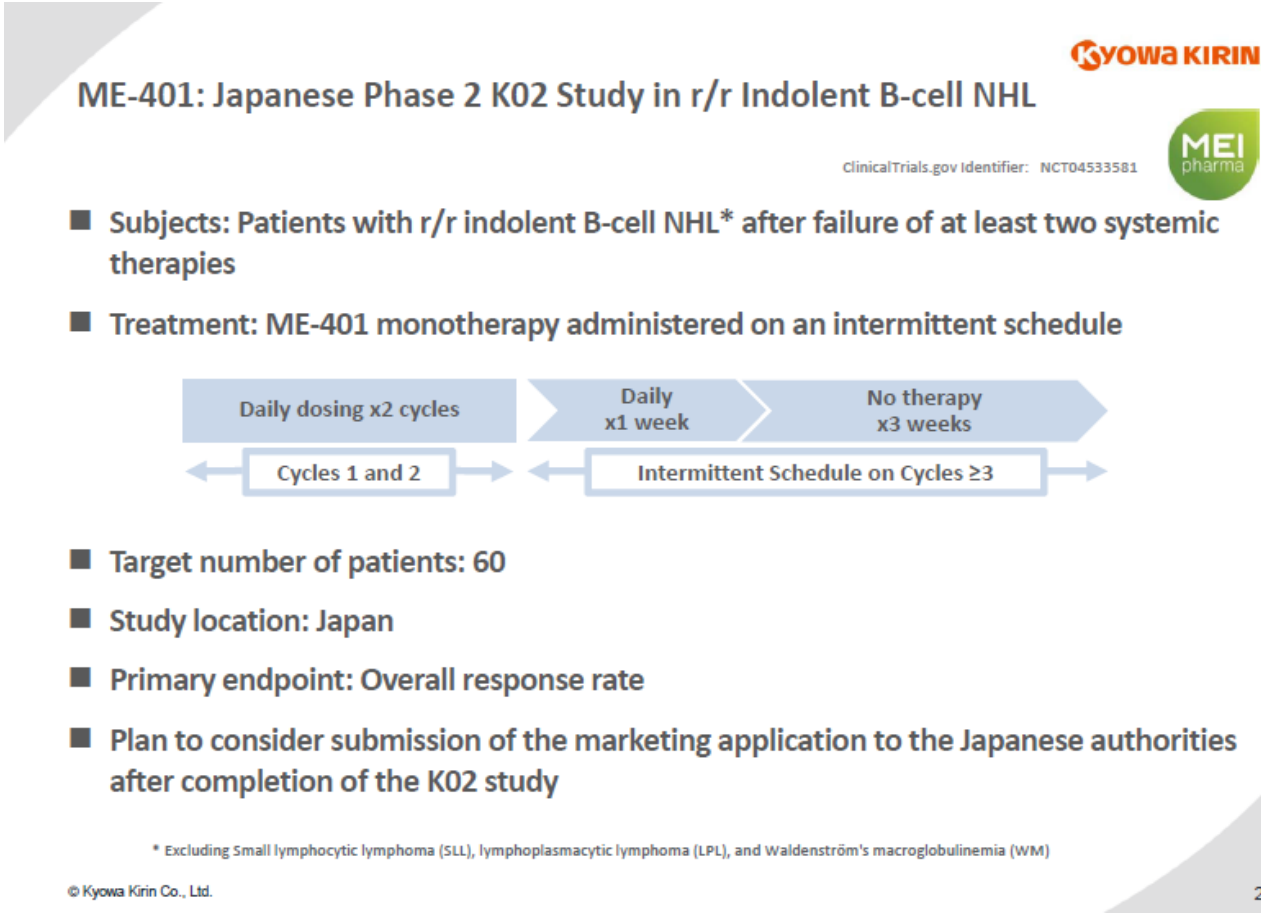
This is a summary of the Phase II TIDAL trial currently underway.

This trial is investigating the efficacy of intermittent administration of ME-401 alone in patients with relapsed and refractory follicular lymphoma who have received two or more prior systemic treatments.

We have recently added a cohort to examine the efficacy in MZL, or marginal zone lymphoma, in addition to FL, or follicular lymphoma.

The administration method of ME-401 is the same as that of Phase Ib, and the trial is a global trial of 180 people, targeting FL and MZL. The main evaluation items are the overall response rate.

As announced at the end of March this year, ME-401 has been designated by the FDA for fast-track program for relapsed or refractory FL. By submitting data from this Phase II trial to the FDA, we will aim for accelerated approval.



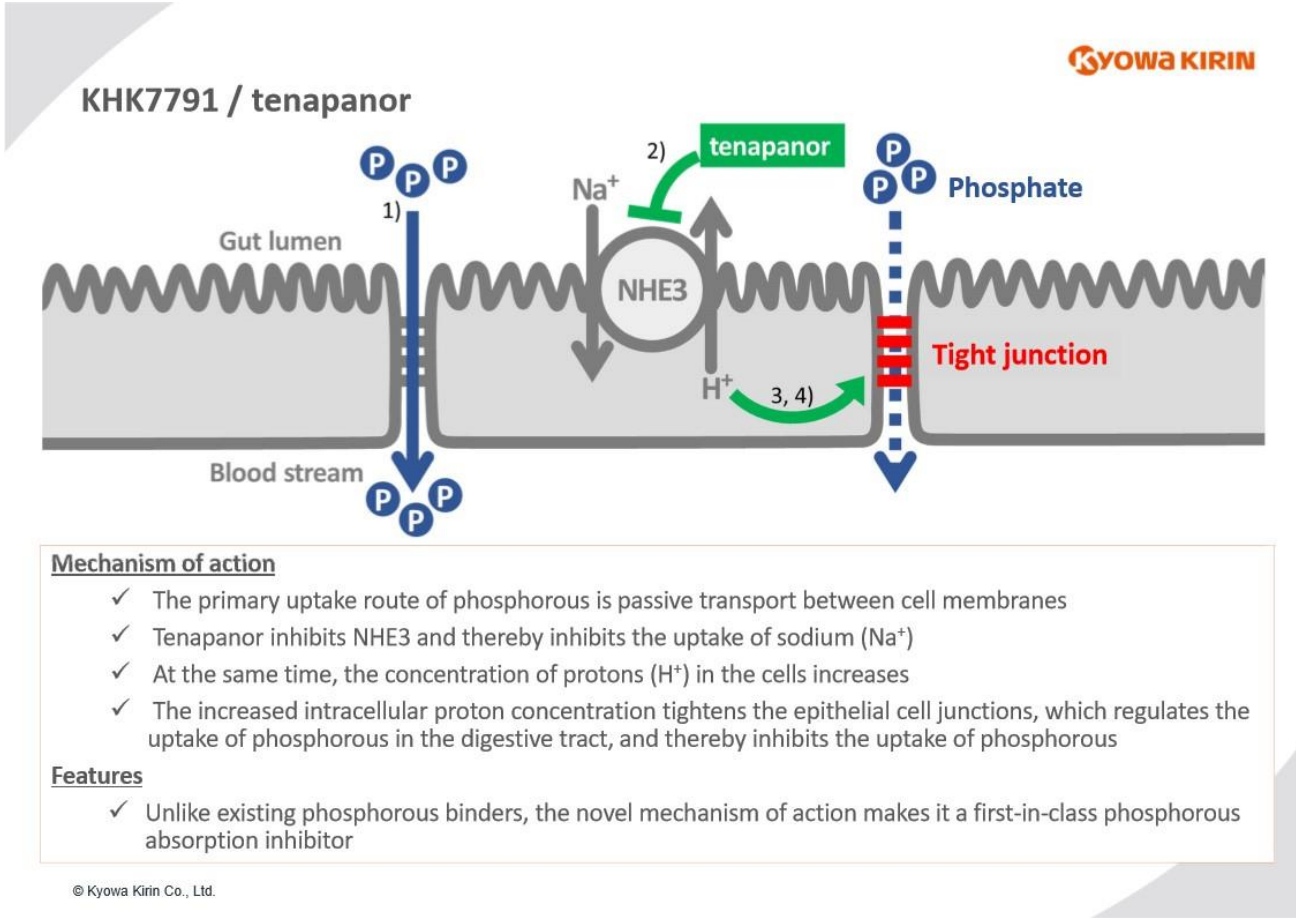
This slide is a summary of the K02 study, a domestic Phase II trial, currently underway, which we announced its commencement on October 2.

This study includes patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma who have received two or more prior systemic treatments.

Specifically, FL and MZL I mentioned before, and patients who cannot be classified as a specific type of B-cell lymphoma, we call it NOS, are enrolled in this trial.

The study design is similar to the ongoing TIDAL study abroad, with a target sample size of 60 patients and overall response rate as the primary endpoint. Based on the data from this Phase II study, we aim to apply for approval in Japan.

In the future, we will continue to develop ME-401, including in combination with other agents, to widely evaluate the usefulness of the drug in various B-cell malignancies.



The second compound is KHK7791.

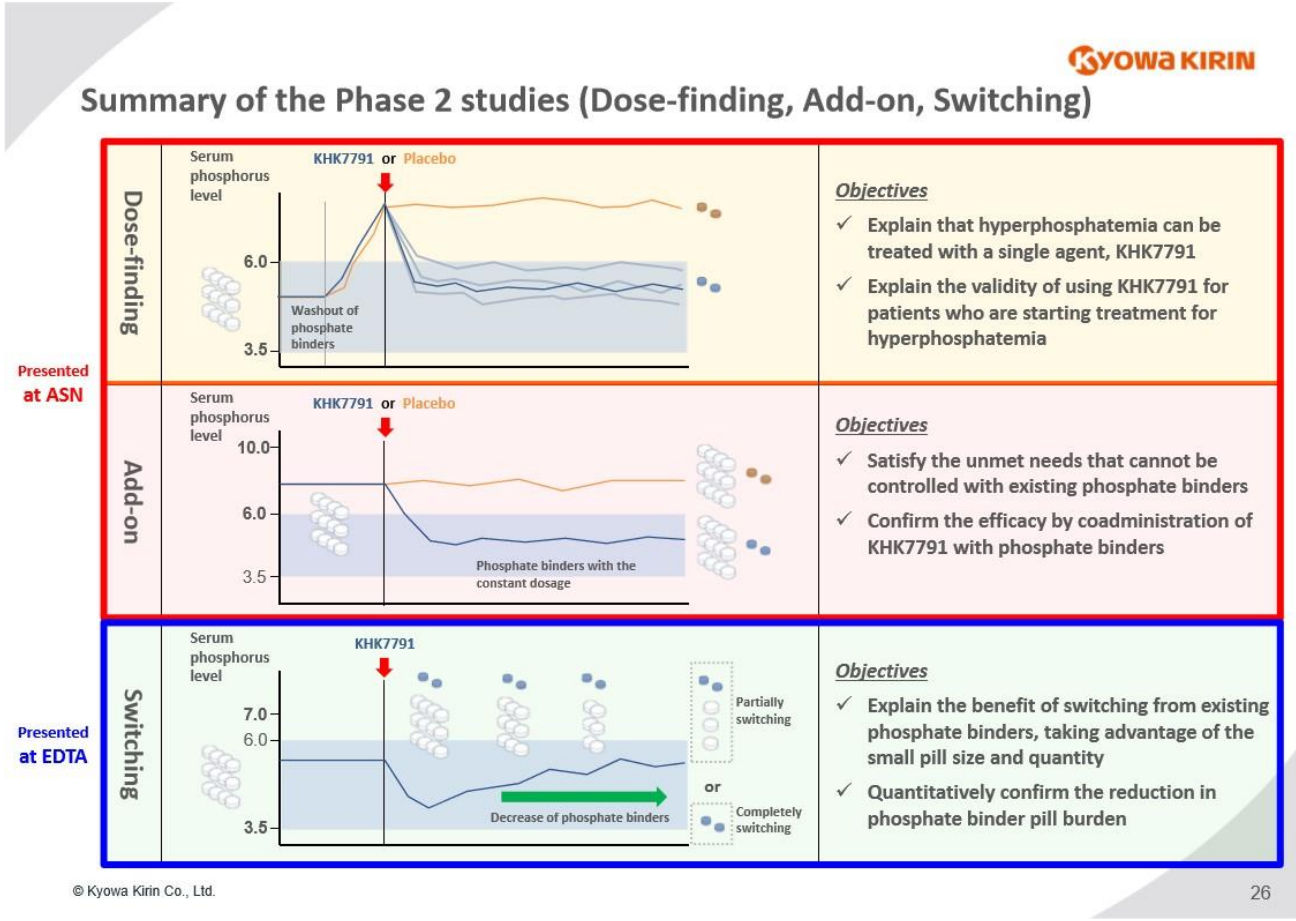
This section presents key data on the results of the three Phase II trials announced at academic conferences in June and October.

Here I will briefly introduce the mechanism of tenapanor, which we in-licensed from the US company Ardelyx in November 2017.

We have many drugs in this nephrology field, but in order to further strengthen our product lineup and meet the enormous needs of dialysis patients and healthcare professionals, we have obtained exclusive development and sales rights in Japan for the field of cardio-renal diseases, including hyperphosphatemia, and are proceeding with development.

The drug is administered as an oral agent, and inhibits intestinal NHE3, reducing the absorption of sodium and phosphate.

It is a first-in-class phosphorus adsorption inhibitor with a novel mechanism of action, which is quite different from conventional phosphorus adsorption agents. It is expected that this inhibitor will provide patients with new treatment options, with benefits such as reduced drug load.



In this slide, I will briefly introduce the design of the three Phase II trials conducted domestically.

The top part is a single-agent study, which is a single-agent dose-response study in which washout is performed in patients who have been controlled with existing phosphorus binders, followed by administration of tenapanor.

The middle part shows a combination study in which tenapanor is added to existing drugs in patients whose phosphate level cannot be controlled with existing drugs.

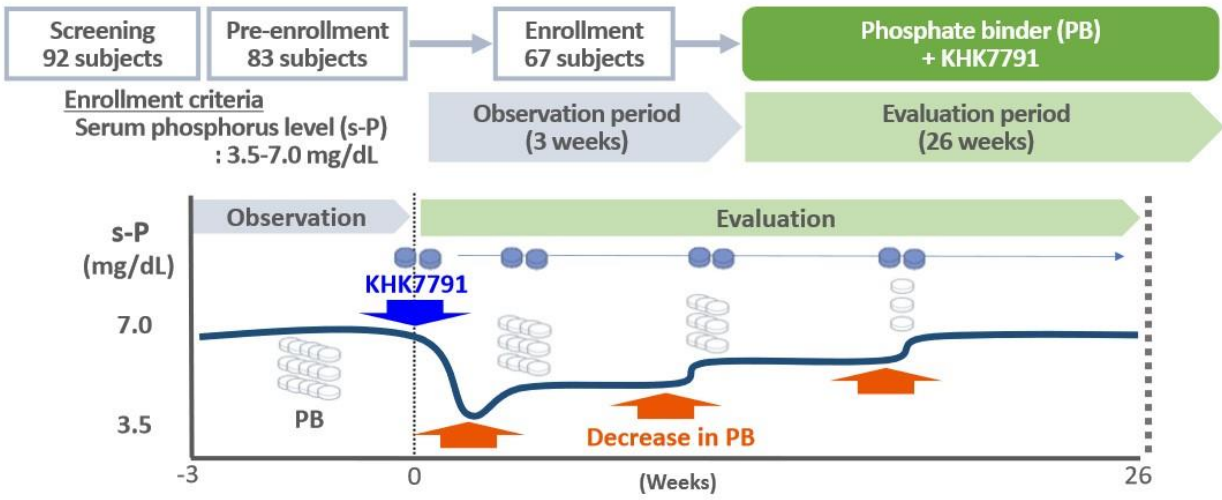
The bottom panel is a switch trial, in which we first add tenapanor to patients who had been controlled with an existing drug, and then gradually reduce the volume of the existing drug according to the change in phosphate level. This evaluates the effectiveness of the drug in reducing the medication burden.

The results of the single-drug and combination trials were announced at the ASN in October of this year, and the results of the switch trials were announced at the European EDTA academic conference in June.

KHK7791: PB switching study design

ClinicalTrials.gov Identifier: NCT03831607

■ Open-label, single-arm, phosphate binder (PB) switch study for hyperphosphatemia patients on hemodialysis



■ Primary endpoint : Achievement of 30% decrease in the mean total tablet number (PB+KHK7791) compared to baseline PB

First of all, we will introduce the switch test.

Many patients need a phosphate-adsorbing drug to control phosohate levels. However, one issue is the large number of tablets that have to be taken. The dose of tenapanor is only two tablets per day. Patients who switch to this drug can expect a reduced medication burden.

In this study, we evaluated the reduction of the medication burden by switching from another phosphate adsorption blocker to tenapanor. As shown on the slide, the primary endpoint is the proportion of subjects with a 30% reduction in the total number of phosphorus-binding agent and tenapanor tablets being taken at 26 weeks from baseline.

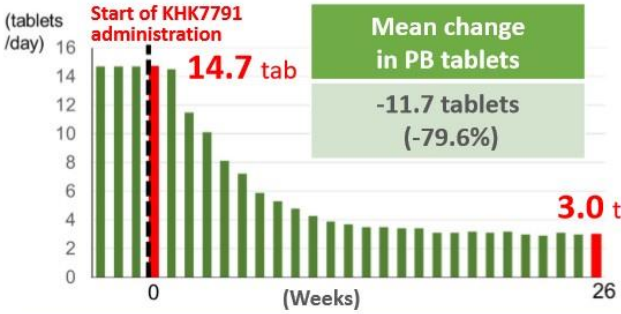
KHK7791: PB switching study results

■ Primary endpoint

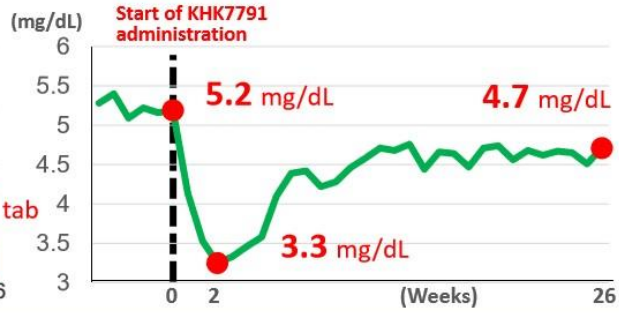
	Achievement ratio	*P* value [95%CI]
30% decrease	71.6% (48/67)	<0.001 [59.3, 82.0]

CI confidence interval.

■ Mean change in total PB tablets over time



■ Mean change in s-P over time

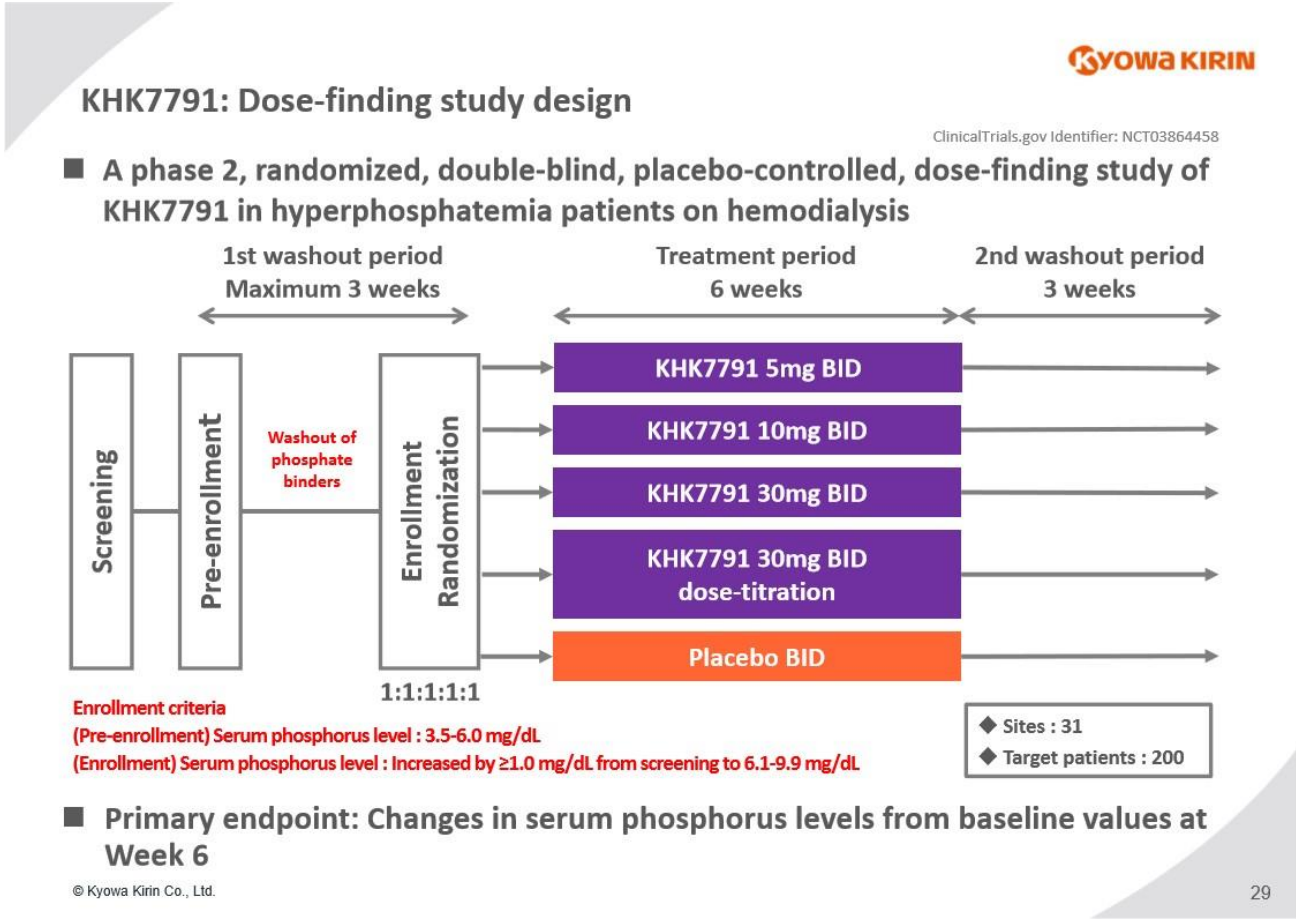


More than 70% patients achieved a 30% decrease in the total number of PB tablets compared to the baseline.

Here is the test result.

As shown in the table at the top, the total number of tablets to be taken in 71.6% of patients was reduced to 30% or less of that from the start of administration.

Specifically, in terms of the average number of tablets taken per day for the phosphate absorption drug, the baseline figure was 14.7 tablets per day, but as of 26 weeks, this figure had been reduced to three tablets. The number of tablets excludes the two tenapanor tablets. Therefore, the number of tablets was 14.7 before the start of administration, but after the start of administration, the number of tablets including tenapanor was reduced to five tablets, a reduction of about two thirds.



Next, we introduce the dosage response tests for single agents.

Total of five groups were set; five milligrams, 10 milligrams, and 30 milligrams of tenapanor, respectively, tapered doses starting at 30 milligrams of tenapanor, and also a placebo group. Approximately 40 patients were assigned to each group for six weeks.

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KHK7791: Dose-finding study results

■ Primary endpoint

		Placebo N=41	KHK7791 5 mg N=42	KHK7791 10 mg N=41	KHK7791 30 mg N=42	KHK7791 30 mg dose-titration N=41
Week 6 Serum phosphorus level (mg/dL)	Mean±SD	0.6±1.6	-0.9±1.7	-1.4±1.5	-1.9±1.2	-2.0±1.1
	Median	0.4	-1.0	-1.5	-2.1	-2.0
	Difference	-	-1.6	-2.0	-2.6	-2.6
	95% CI	-	[-2.3,-0.9]	[-2.7,-1.3]	[-3.2,-2.0]	[-3.2,-2.0]
	p-value	-	<0.001	<0.001	<0.001	<0.001

■ Drug-related TEAEs, discontinued

		Placebo N=41		KHK7791 5 mg N=42		KHK7791 10 mg N=41		KHK7791 30 mg N=42		KHK7791 30 mg dose-titration N=41	
		N	%	N	%	N	%	N	%	N	%
Drug-related TEAEs		7	(17.1)	22	(52.4)	28	(68.3)	32	(76.2)	28	(68.3)
[Gastrointestinal disorders]		5	(12.2)	22	(52.4)	28	(68.3)	32	(76.2)	28	(68.3)
Diarrhea		**4**	**(9.8)**	**21**	**(50.0)**	**27**	**(65.9)**	**32**	**(76.2)**	**27**	**(65.9)**
Severity of diarrhea	Mild	4		21		25		28		24	
	Moderate	0		0		2		4		3	
	Severe	0		0		0		0		0	

KHK7791 significantly decreased serum phosphorus levels from baseline compared with the placebo and decreased serum phosphorus levels in a dose-dependent manner.

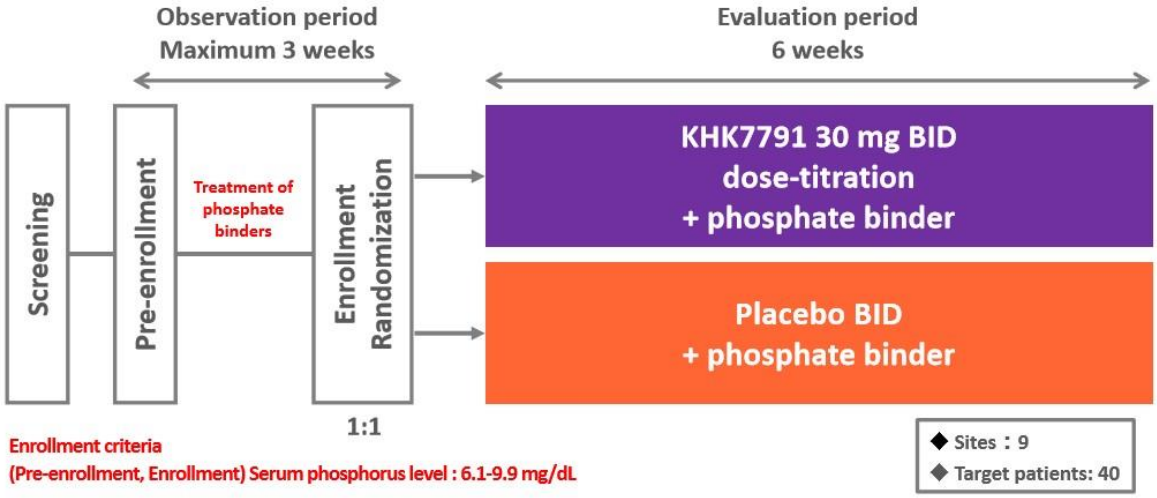
Changes in serum phosphorus, the primary endpoint, were as shown, and dose-dependent decreases in phosphorus concentrations of one to two milligrams per deciliter were observed in all active drug treatment groups.

The main side effects were diarrhea, which occurred at a dose-dependent frequency. In almost all cases, it was minor, but in the higher dose groups, it was moderate in a few cases.

KHK7791: Add-on study design

ClinicalTrials.gov Identifier: NCT03864445

■ A phase 2, randomized, double-blind, placebo-controlled, phosphate binder-combination study of KHK7791 in hyperphosphatemia patients on hemodialysis



■ Primary endpoint: Changes in serum phosphorus levels from baseline values at Week 6

Next, we will introduce the combination trial.

In this study, tenapanor is given to patients who cannot be controlled with existing phosphorus absorbers.

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KHK7791: Add-on study results

■ **Primary endpoint and target achievement ratio of serum phosphorus level (3.5～6.0 mg/dL)**

		Placebo N=24	KHK7791 N=23
Week 6 Serum phosphorus level (mg/dL)	Mean±SD	0.1±1.5	-2.0±1.2
	Median	-0.2	-2.1
	Difference	-	-2.1
	95% CI	-	[-2.9,-1.3]
	p-value	-	<0.001
Week 6 Target achievement proportion	% (n/N)	37.5 (9/24)	87.0 (20/23)

■ **Drug-related TEAEs, discontinued**

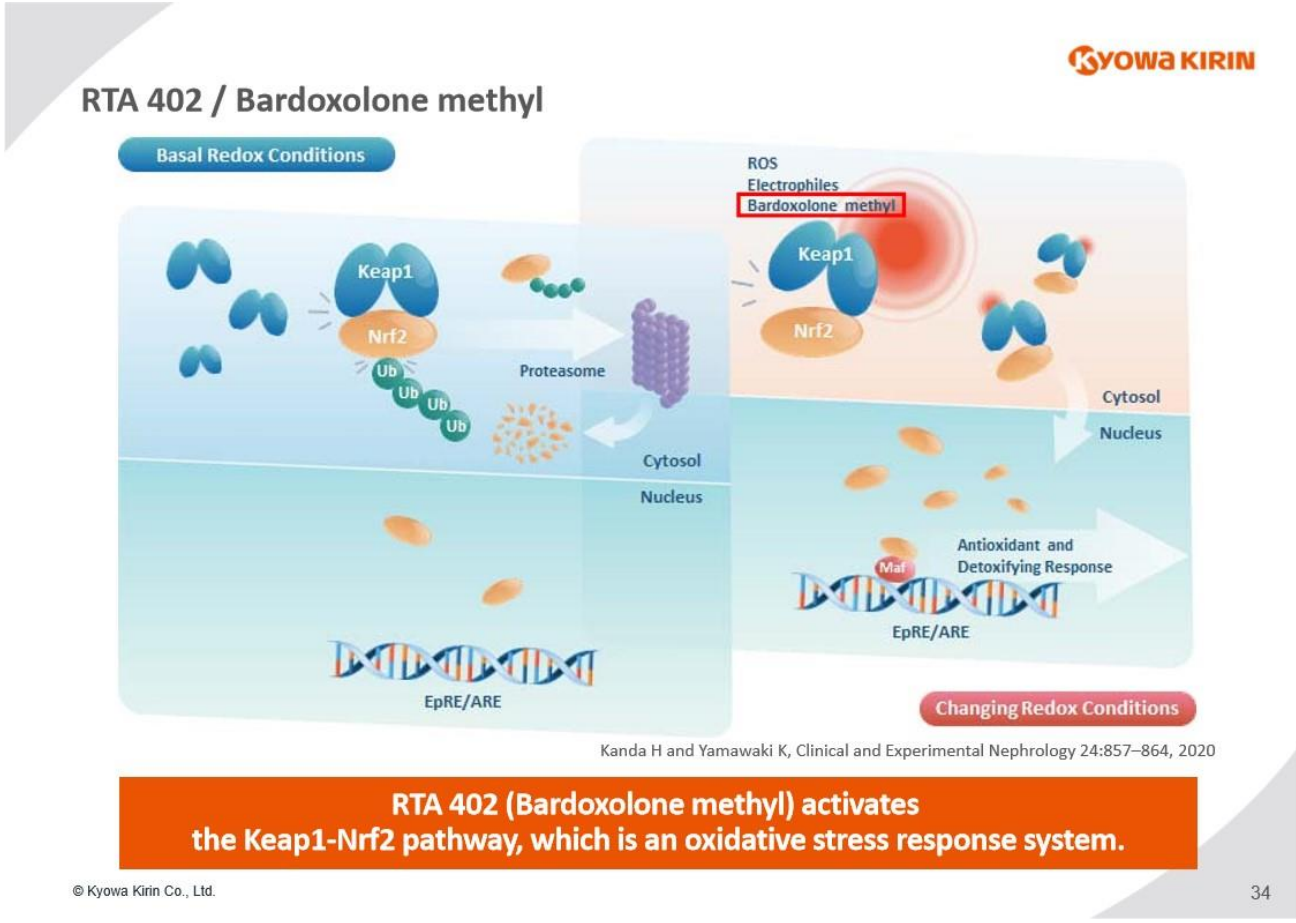
		Placebo N=24		KHK7791 N=23	
		N	%	N	%
Drug-related TEAEs		2	(8.3)	16	(69.6)
[Gastrointestinal disorders]		2	(8.3)	16	(69.6)
Diarrhea		**2**	**(8.3)**	**15**	**(65.2)**
Severity of diarrhea	Mild	2		8	
	Moderate	0		7	
	Severe	0		0	

Adding on KHK7791 resulted in a significant decrease in serum phosphorus levels compared with the placebo.

Changes in serum phosphorus, the primary endpoint, were as shown, with a mean decrease in phosphorus levels of two milligrams per deciliter in the tenapanor group and a statistically significant decrease over placebo.

At week six, 87% of the subjects achieved the targeted levels specified in the domestic CKD-MBD guideline. As same as the single-agent trial, the principal side effect noted was diarrhea.

The efficacy of tenapanor has also been confirmed for patients who cannot be controlled with existing phosphorus absorbers.



Third, I would like to introduce RTA 402.

Regarding trials for Alport Syndrome, we would like to introduce the main data on the results of the Phase III trial announced by Reata in November, as well as our domestic development policy.

RTA 402, or bardoxolone methyl, has the effect of activating the Keap1/Nrf2 pathway, which is an oxide stress response system, and it has been reported that this pathway controls various bio-responses, including antioxidant actions.

RTA 402 is characterized by improved renal glomerular filtration rate, or GFR, which may also be due to activation of the Keap1/Nrf2 pathway.

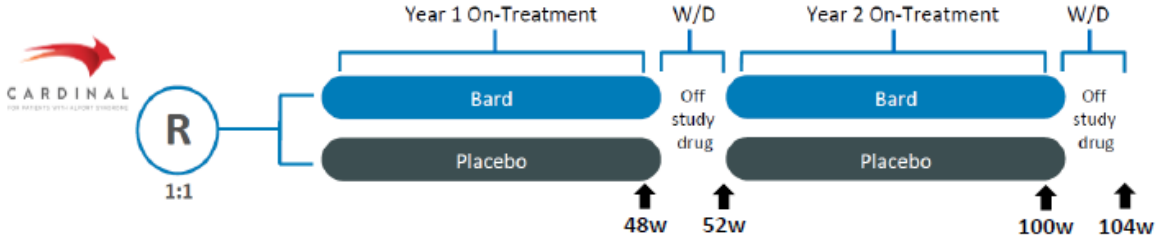
KYOWA KIRIN

RTA 402: CARDINAL Phase 3 for Alport Syndrome patients

What is Alport Syndrome?

Alport Syndrome is a kidney disease caused by genetic mutations in either the type IV collagen α3, α4 or α5 chain. In Japan, Alport Syndrome is certified as designated intractable diseases and specific pediatric chronic diseases. Severe cases have been reported to progress to end-stage kidney disease in the late teens and early 20s. Currently there is no approved treatment for Alport Syndrome as an indication.

- Number of subjects : 157 (Placebo: 80, RTA 402: 77)
- Subjects : 12-70 years, eGFR: 30-90 mL/min/1.73m²
- Primary efficacy endpoint : Change in eGFR from baseline at Week 48 and Week 100
- Key secondary endpoint : Change in eGFR from baseline at Week 52 and Week 104 (4 weeks after withdrawal of drug)
- Region : US, JP, EU, AU



The 2-year study period was completed, and Reata announced the year 2 results on Nov 9th.

https://clinicaltrials.gov/ct2/show/NCT03019185
https://www.reatapharma.com/wp-content/uploads/2019/11/20191112_RETA_YEAR_ONE_TOPLINE_RESULTS_FROM_PIVOTAL_CARDINAL_STUDY_Mgmt_Call.pdf
https://www.reatapharma.com/wp-content/uploads/2020/11/Reata_Third_Quarter_2020_Earnings_Call_Deck.pdf

1-year results were published in Reata's 3Q financial results presentation last November. Both primary/key secondary endpoints have been met.

Last month, the partner company, Reata Pharmaceuticals, announced the result of the CARDINAL trial, the global Phase III trial for Alport Syndrome.

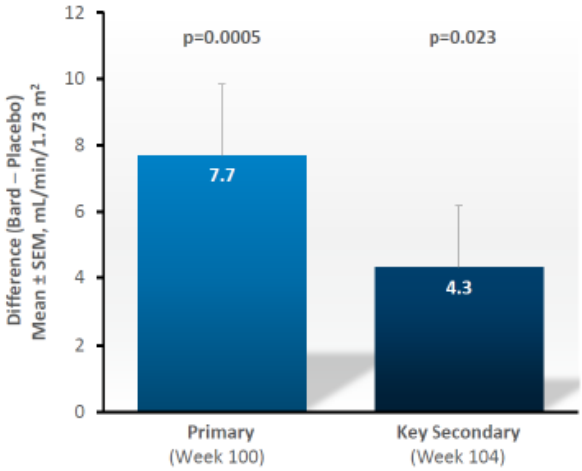
Alport Syndrome is a genetic renal disease resulting from a mutation in a gene that codes for collagen. It affects the kidneys and has been designated as a national intractable disease and a specific pediatric chronic disease in Japan. This is a very serious disease that may shift to end-stage renal failure at a young age. Currently, there is no efficacious treatment approved for treating Alport Syndrome.

The total number of patients enrolled in this trial is 157, including children. The endpoint is change in eGFR, or estimated GFR.

The primary endpoint is eGFR at 48 weeks and at 100 weeks, and the key secondary endpoint is assessment after four weeks of treatment cessation from each point. In addition to the US and Europe, patients were registered for this trial in Japan.

The two-year data were released for this study and are available on the Reata Pharmaceuticals' website.

RTA 402: CARDINAL Phase 3 for Alport Syndrome patients



Mean ± SEM eGFR Change (mL/min/1.73 m²)

Endpoint	Placebo	Bard	Difference (Bard — Placebo)
Primary (ITT)	-8.5 ± 1.5	-0.8 ± 1.6	7.7 ± 2.1 (p=0.0005)
Primary (mITT)	-9.6 ± 1.5	1.7 ± 1.6	11.3 ± 2.2 (p<0.0001)
Key Secondary (ITT)	-8.8 ± 1.4	-4.5 ± 1.4	4.3 ± 1.9 (p=0.023)

ITT: Intent to treat
mITT: modified-ITT, analysis assesses the effect of receiving treatment by excluding values after patients discontinued treatment

Both primary/key secondary endpoints were met.
The results also show a favorable safety profile.

https://www.reatapharma.com/wp-content/uploads/2020/11/Reata_Third_Quarter_2020_Earnings_Call_Deck.pdf

This is the result for the primary and key secondary endpoint.

As you can see, there were significant improvements in eGFR in the bardoxolone methyl group compared with the placebo-treated group.

The details are omitted here, but good results were also shown for the safety profile.

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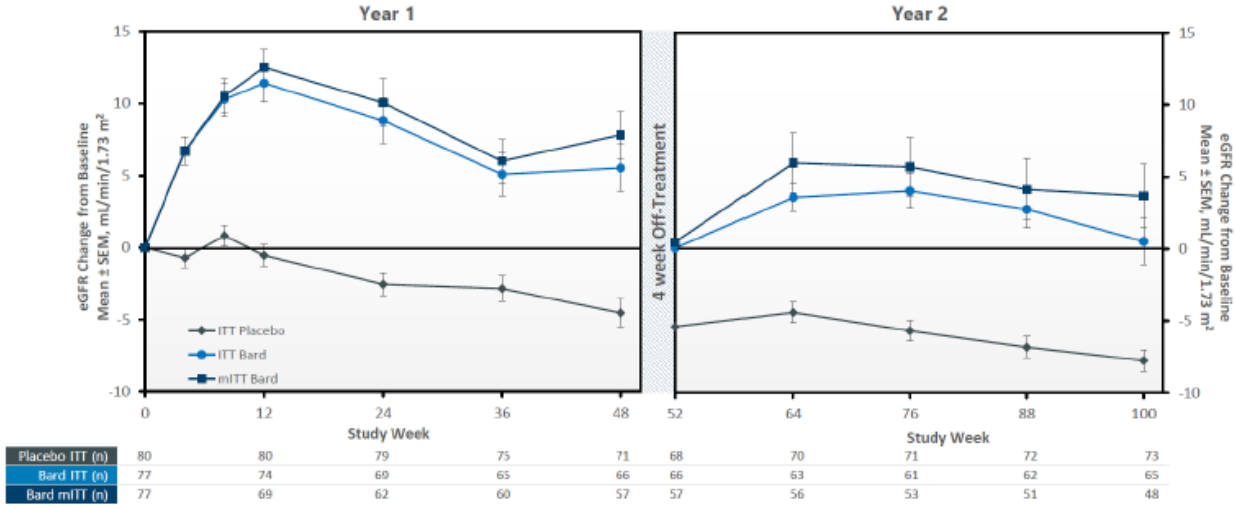
RTA 402: CARDINAL Phase 3 for Alport Syndrome patients



Placebo ITT (n)	80	80	79	75	71	68	70	71	72	73
Bard ITT (n)	77	74	69	65	66	66	63	61	62	65
Bard mITT (n)	77	69	62	60	57	57	56	53	51	48

Effect for eGFR was observed over the study period in the RTA 402 group.

Based on the current results, KKC also plans to submit a marketing approval application for the indication of Alport Syndrome in Japan.

https://www.reatapharma.com/wp-content/uploads/2020/11/Reata_Third_Quarter_2020_Earnings_Call_Deck.pdf

This is a graph showing change in eGFR from the beginning of administration. As you can see, the effect was observed throughout the two-year study, compared to the placebo.

Based on these results, Kyowa Kirin intends to proceed with preparations for a domestic marketing application for the indication of Alport Syndrome.

This concludes the update of development projects on clinical stage.

Today, we have introduced the contents shown in bold on the slides.

We will continue to steadily conduct clinical trials for candidates under development, which have already progressed to Phase II or Phase III. Regarding non-clinical compounds, we aim to collect the necessary data and enter the clinical stage as soon as possible.

Furthermore, with an eye toward the long term, considering 20 years from now, we will steadily identify candidate compounds and target diseases where new technologies can be fully utilized.

By advancing these initiatives in parallel, we will continue to take on the challenge of providing value through the creation of new drugs that are unique to Kyowa Kirin in order to help bring patients life-changing treatment in the future.

Although we have not been able to introduce it today, we plan to introduce the review of the current medium-term management plan and details of the R&D strategy in the new medium-term management plan starting in 2021 at the briefing on the new medium-term management plan scheduled to be held on February 5 next year.

Summary (2): Challenging the creation of new value in R&D

This is our ideal as members of the Kyowa Kirin R&D team: R&D spirits.

Be the Best in Science. Passion for Innovation. Every Challenge, a Step to Success. This is me. This is our team. We are constantly aware of and practice this R&D spirits and are committed to bringing smiles to patients through Kyowa Kirin products.

Thank you for your attention.

Question & Answer

Moderator: I would now like to move on to the question-and-answer session. In addition, in order to be able to receive as many questions as possible, we will limit the number of questions to up to two at a time.

Yamaguchi: This is Yamaguchi from Citigroup. Thank you very much. First of all, I would like to know a few things about bi-specific.

There are various forms, and I think this is a little different from the typical bi-specific, so I was wondering if you could tell us about the merits and disadvantages of using this form. In particular, are there any difficulties in production? Please tell us about the advantages and disadvantages of this antibody compared to the other companies' antibodies.

And, I found the patent information such as CD40 and EpCAM, as well as TRAIL2 and PSMA, and I guess they are anti-cancer drug projects. Your concept is that one side of antibody has tissue selectivity and another side induces immune cell, is it correct?

Torii: Thank you for your question.

First of all, as I explained earlier, we are pretty particular about the native sequence. We are able to use technologies we have developed for other antibodies in producing these, so yields are good. With this variety of forms, the range of applications is considerably wider than standard monovalent-plus-monovalent bi-specifics.

The second question, regarding CD40 and EpCAM, these are components of the immune system that exert their effects, and if they have too much effect at the systemic level, they increase the risk for an adverse effect. In order to limit this effect, they can be used only at the target point, and in this way an effect can be achieved.

The bivalent-plus-bivalent bi-specific has a wide range of applications, so we are continuing to conduct research, including the targets you mentioned earlier, as well as other targets.

Yamaguchi: Thank you. Recruiting T-cells with CD3 is a popular technique at the moment, but your company is not doing this, right?

Torii: No comment.

Yamaguchi: Okay. Thank you very much.

Hashiguchi: This is Hashiguchi from Daiwa Securities. Thank you. I would also like to ask about bi-specific antibodies.

It was said that there were multiple projects. Could you please say a little more about what kind of projects you have? You mentioned in your explanation that these are differentiated from conventional antibodies, but I think many other pharmaceutical companies have established various technologies and are taking various approaches.

Would it be correct to say that your company has used its own approach to solve the problems faced by other companies in this process, and that this is a point of differentiation for you? Or is this something that other companies could arrive at with their technologies, and produce a somewhat similar product?

Torii: Thank you for your question. Regarding whether or not we are aiming for specific targets, I am sorry, but I would like to leave it undisclosed from a strategic standpoint.

In the second question, regarding what is our advantage of our antibodies while other companies are also developing variety of bi-specifics, the issue is not only binding but also activity. It is a little bit difficult to explain in detail here, but as I have just mentioned, it is not enough to simply attach two different things together, but the degree of their activity must also be controlled delicately. This is the point where we intend to gain an advantage.

Hashiguchi: Thank you very much. The second question is how would you think of the safety of targeting pDCs as a treatment for autoimmune diseases? Also, what is the point of differentiation against the Biogen's antibody, to which you have rights?

Torii: You mean the superiority of our developed candidate to Biogen's?

Hashiguchi: That's right.

Torii: Understood. First of all, with regard to the safety part, I think that we should proceed very cautiously. As I mentioned a bit in the previous explanation, the pDCs that we are aiming for this time will work on a fairly upstream site, so in the area of efficacy, it will be very positive. On the other hand, as you said, we intend to proceed with development while carefully considering safety.

As for a comparison with Biogen's, we believe that our antibody will act even more upstream than Biogen's, so we can expect greater efficacy.

Hashiguchi: Thank you very much.

Tanaka: This is Tanaka from Mizuho Securities. Thank you very much. I would like to ask you about bi-specific antibodies. This focus on native sequences means that productivity is high. I believe that another important feature is that antigenicity is low?

Torii: Yes. Again, as the size of artificial regions increases, the possibility of an immune response against the antibodies increases, and with it the risk of antibodies being produced against the treatment. In this sense, something that is similar to what is found in the human body can be expected to have low antigenicity. We believe this is positive from the viewpoint of safety.

Tanaka: This is quite a way off yet, I think you mentioned 10 years or 20 years, but do you have any idea when you would plan to enter into clinical trials?

Torii: Although it is difficult to answer accurately, I would like to accelerate the pace as much as possible. Ideally, we will be in a position to find out the possibilities during the period of the next medium-term management plan.

Tanaka: This is the second question about ME. I think ME have received the fast-track designation, and the submission of same type of drug, I think it's TG Therapeutics', was accepted by the FDA in August. I believe that the third-line for MZL obtained certainly a priority review, FL got a regular review, and two PDUFA dates were confirmed.

If this phase II, which your company is doing, works well, do you think this is likely to be a priority review for both of them?

Torii: We are not able to comment on the part of other companies that you just mentioned. Regarding our co-operation with MEI Pharma, the situation with FL is continued, and we aim to add MZL cohort in the future. I anticipate that accelerated approval will be a possibility for both of these.

Tanaka: Okay. Thank you very much.

Ueda: This is Ueda from Goldman Sachs. Thank you very much. First of all, you outlined some long-term projects being undertaken by your company today. Could you tell us about the strengths of the field of basic research by being in the Kirin Group?

In March of this year, at Kirin Holdings' investor day, I think that there was an explanation of the Kirin Group's joint research in the R&D Division. What initiatives are you implementing? Also, could you tell us about when you have been undertaking such initiatives and what results you can expect?

Torii: Thank you for your question. As you know, Kirin Holdings is engaged in food-centered health care. We are a pharmaceutical company that is somewhat segregated. Looking ahead, I think there will be some areas in which the division will overlap considerably.

The fact that Kirin Holdings is approaching the field of pharmaceuticals to a considerable extent and handles a variety of projects while sharing information means that I expect we will be able to collaborate in a variety of ways in the near future.

At this stage, I'm sorry but I'd like to leave it undisclosed, especially with regard to specific cases.

Ueda: Thank you very much. I would also like to ask about bi-specific antibodies. This time, you talked about some anticancer agents. I think that there will be many applications of bi-specifics as anticancer agents. What strategy and features will you be addressing with this area?

Torii: Thank you very much. In the case of ordinary antibodies, it is rare to have both high efficacy and a good safety profile. I think that there are very many cases where this can be a bottleneck.

We believe that our bi-specific antibodies can perform well on both points, and on this basis we intend to develop a pipeline presence with our bi-specific technology.

Ueda: Okay. Thank you very much. That is all.

Muraoka: This is Muraoka from Morgan Stanley MUFG Securities. I'm sorry, this is a bit of a deviation from the scientific talk. My question relates to the midium-term plan to be released in February.

In view of the five-year medium-term plan for the three items, ME, bardoxolone methyl, and tenapanor, which are scheduled to be launched within the next few years, I think you will present a plan that clearly shows the contribution of these to the business.

Torii: That's right. We have three products I have introduced today. And also, as for revenue, I cannot say whether or not it will be in time for the next medium-term management plan, but what is extremely important for our R&D is that we are making steady progress on KHK4083 or KW-6356, which we plan to proceed with trials globally in the future. We recognize it as a major goal.

Muraoka: Thank you. For ME, MEI has stated a peak figure of 1 billion dollars, but it is only FL. Do you have such a large figure in mind?

Torii: It is difficult to comment on the other company's statement. As I mentioned earlier, ME-401 on intermittent administration is considerably safer than the preceding PI3K drugs. We are aiming not only for

monotherapy, but also for use in combination with a variety of drugs, so we expect that the range of indications will expand considerably. I would very much like to make it closer to the levels that MEI Pharma are saying.

Muraoka: Thank you very much.

Sakai: This is Sakai from Credit Suisse Securities. Thank you very much. The first question is regarding an alliance with Axcelead, but I understand that you are looking 10 years or 20 years into the future. For the time being, will you focus on small-molecule drugs? Judging from today's presentation, I don't think there was much to add to the release on October 2. Which areas will you focus on? Or is the arrangement still completely open? If you already have some ideas of strategy for the area, could you say a little about it?

Torii: Thank you for your question. Would the area of your question now be the therapeutic area?

Sakai: That's right.

Torii: What we are aiming for now is a pretty basic or fundamental part. We believe that this is not limited to specific therapeutic areas but can be applied to all types of diseases when truly successful. In that sense, the answer is that we have not narrowed down our areas.

Sakai: Understood. The other question is about bi-specific antibodies. No targets have been disclosed, which I think is understandable. Conversely, though, I think that when a target is not set, perhaps that might hamper research. With that in mind, and this is a question I ask all companies, but how many potential target antigens as the cause of the diseases are you considering?

Even your personal thoughts on this question would be very helpful to me.

Torii: Thank you for your question. As I mentioned earlier, several projects are already underway targeting different antigens. These targets were selected by Kyowa Kirin researchers through various surveys. With regard to targets, there is considerable potential, although there is a limit to investigating with human power, which is the basis for our alliance with InveniAI. Therefore, we are using AI and machine learning to investigate in a fairly comprehensive manner what is considered to be the target of our next-generation antibodies. In that part, we expect a considerable number of potential targets to hit.

However, if too many targets were found, that will also be an issue. So, we intend to proceed with development after narrowing down to those we think have a considerable chance of success, based on our knowledge of disease biology.

Sakai: Then, it is possible to think there will be targets outside immunology and oncology? I think this is also the case of the small molecule initiatives with Axcelead you mentioned earlier. Would this be a valid assessment?

Torii: Well, at present, we are focusing on four therapeutic areas. The risks increase to some extent if we go out of our area of expertise.

However, as the number of drug discovery targets has become considerably smaller, we will boldly take on challenges when necessary, after conducting various surveys, in the event that such potential arises in areas other than the four therapeutic areas that we are currently working in.

Sakai: Thank you very much.

Wakao: This is Wakao from JP Morgan. Thank you. The first question is about bi-specifics. In terms of safety, immunogenicity is important, I think. My understanding is that a fully human antibody has been regarded as suitable for its low immunogenicity. But recently, there have been efforts to reduce immunogenicity further.

In the case of your bi-specific antibodies, are you aiming for a lower immunogenicity than fully human antibodies?

In your presentation, you mentioned that controlling the degree of activity is the key, but is it correct to understand that this can only be done by this type of your company, and it cannot be done by ordinary antibodies or the bi-specific antibodies of other companies?

Torii: Thank you very much. I would like to pass this question to Dr. Koike.

Koike: Thank you for your question. Generally, as you might know, you can reduce the immunogenicity from antibodies by removing the specific sequences recognized as T-cell epitopes.

In this regard, it is common to design an antibody that has even lower immunogenicity than human antibodies, by incorporating modern technology. This, of course, is being applied, and I hope you will understand that this is our bi-specific format.

Regarding activity, it is not necessarily true that, if it is a bi-specific antibody, one will have similar activity as other bi-specific antibodies. I'm surprised to see, however, that different combinations of epitopes produce a variety of different activities.

Simply converting antibodies A and B into bi-specifics does not mean that everything will show activity in the same way. I personally feel that this is the know-how of each researcher or company and that good and unique things will come from the benefit of experience.

Wakao: Thank you. Secondly, when I hear what you are saying today, I think that various platforms, such as bi-specific antibodies, have a lot of promise. Do you feel that the productivity of drug discovery will improve further in the future? From the perspective of the number of projects that will be in the clinical phase, could you see that the number of projects will increase steadily in the future? Can you comment on the productivity perspective and the number of projects that will be in the clinical stage in the future?

Torii: Thank you for your question. As you have just mentioned, this antibody type has a fairly attractive pipeline. Small-molecule entities may take a little more time, but by proceeding both of in-house and partnering initiatives, we are committed to achieving the establishment of the fundamental technologies to develop a bundle of pipelines that will eventually emerge in this area.

Wakao: Thank you. Could you tell us what the target values are for the future, for example, at a briefing session on the medium-term management plan?

Torii: I still want to refrain from disclosing any numeric objectives at this stage.

Wakao: Okay. Thank you, that's all.

Moderator: Thank you very much. Time is up, so I will now bring to an end today's R&D Day. Thank you very much for participating in our event today.

We look forward to your continued support of Kyowa Kirin. Thank you very much.

[END]