



Kyowa Kirin Co., Ltd.

Topline Data from the Phase 2 Study of KHK4951 in Patients with nAMD

September 9, 2026

Event Summary

[Event Name]	Topline Data from the Phase 2 Study of KHK4951 in Patients with nAMD	
[Date]	September 9, 2026	
[Number of Speakers]	1	
	Yoshifumi Torii	Chief Medical Officer

Presentation

Moderator: We would now like to start Kyowa Kirin Co., Ltd.'s online meeting to explain the KHK4951 Phase II study top-line data in nAMD.

Prior to the start of the meeting, let me give you some housekeeping announcements. Today's participants' names and their affiliations will be saved for a certain period of time at the Company as information on the participants. Thank you for your understanding.

Today's meeting will be conducted in Japanese, but you can use the simultaneous translation function on Zoom. If you want to listen to English, please select English from the Zoom translation function. This meeting is going to be available for on-demand streaming and a transcript on our IR website.

Today's explanation includes forward-looking statements. For the details, please refer to the disclaimer in the materials.

Today's participant and the person who's going to respond to questions is Chief Medical Officer, Yoshifumi Torii. We are planning to have this meeting for up to 45 minutes. After the presentation by our Company, we will entertain questions from the audience. Please download the materials from our IR website.

Torii-san, the floor is yours.

Torii: Thank you very much for taking the time to join us today. My name is Torii, and I'm Chief Medical Officer of Kyowa Kirin.

Today, I will present the top-line data from the Phase II study of KHK4951 in patients with neovascular age-related macular degeneration or nAMD. Please note that the data I will show you today are preliminary. A detailed analysis is scheduled to be presented at scientific congresses and publications in due course.

Vision 2030

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

Provide pharmaceuticals for unmet medical needs

We are focused on developing medicines for diseases where there is a clear patient need for new options. We make full use of multiple therapeutic modalities, including biotechnology such as antibody technology, and beyond, building on our Kyowa Kirin established strengths.

Address patient-centric healthcare needs

By applying scientific insights and cutting-edge technologies cultivated through our pharmaceutical business, we aim to create new value that focuses on the needs of people living with diseases.

We will continue to meet society's medical needs through patient-centered innovation.

Retain the trust of society

We pursue world-class product quality and operational excellence to grow our business in ways which build long-term trust with our stakeholders

* Make patients smile through dramatic improvements in quality of life by identifying the unmet medical needs of people battling with medical conditions and by creating and supplying new drugs or services that help them overcome those challenges.

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In Vision 2030, shown here, we state that we are committed to providing pharmaceutical products that address unmet medical needs, and that we aim to create new value—life-changing value—starting from the needs of people living with diseases. KHK4951, which I will report on today, is one of our development assets that seeks to give concrete form to this concept.

As I will describe shortly, what this product aims to offer is a new option, maintenance therapy centered on eye drops distinct from frequent intravitreal injections. Its starting point is nothing other than the unmet needs of patients. By applying our own formulation technology to that need, we're seeking to realize this potential. KHK4951 is one expression of our challenge to address unmet medical needs.

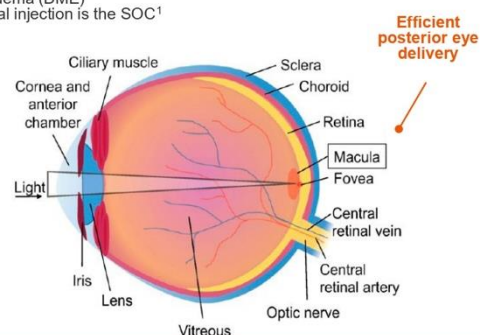
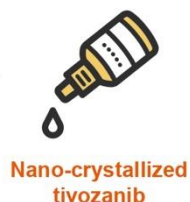
KHK4951

In development for neovascular Age-related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME)
Pursuing the potential to deliver the first anti-VEGF eye drop treatment for diseases where intravitreal injection is the SOC¹



Lancet 2012; 379: 1728-38

KHK4951



Disease areas Ophthalmology	Modalities Small Molecule (Eye drop)	Commercialization Exploring Strategic Partner
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Market Potential	nAMD
Global	Patients 2670k Existing Market Size² 1 Trillion Yen~
Market Potential	DME
Global	Patients 2220k Existing Market Size² 500B~1T yen

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¹ Standard of Care, ² Market size is our own independent estimate based on the total of all products for the disease under development.

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Next slide, please. This is an overview of KHK4951.

The product is a pipeline product currently in Phase II studies in nAMD, neovascular age-related macular degeneration, and in DME, diabetic macular edema. The current standard of care, intravitreal injection, delivers the drug directly into the eye and is therefore highly invasive. By using nano-crystallized tivozanib, we are developing KHK4951 as the only small-molecule kinase inhibitor formulated as an eye drop.

Depending on the results of future studies, we believe this product may be able to offer a treatment option distinct from intravitreal injection, and we would expect it to improve the convenience of pharmaceutical treatment for patients considerably.

KHK4951 Phase 2 Summary of Test Results

Achieved the company's pre-defined product profile targets

Results suggest the potential of an eye drop-centered maintenance treatment strategy

Effectiveness	Primary Evaluation Items	Safety and Tolerability	Secondary Evaluation Items
In all treatment groups, including the low-dose group, 65-69% of subjects maintained their vision within 15 letters decrease in BCVA without any rescue IVT¹ injection at Week 52	The "statistical difference among dose groups in the proportion of patients with a reduction of 15 or more BCVA ² between 8 and 52 weeks" was not observed	No new safety signals were observed in this study	In all groups, BCVA and CST ³ remained stable throughout the treatment period.

1. IVT = Intravitreal; 2. Best-Corrected Visual Acuity; 3. Central Subfield Thickness

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Next slide, please. I will now summarize the results of the Phase II study in nAMD.

We believe that the results obtained have met the target product profile that we set internally and that they suggest the potential of a maintenance therapy strategy centered on eye drops.

As I will explain in more detail shortly, this study comprised three KHK4951 groups, a low-dose group, a medium-dose group, and a high-dose group. In all three treatment groups, between 65% and 69% of subjects maintained their vision at week 52 with a decline in BCVA of fewer than 15 letters and without requiring additional rescue intravitreal injections.

On the other hand, the difference between these dose groups, which was set as the primary endpoint of this study, was not met.

Nevertheless, the secondary endpoints, including the change over time in CST, or central subfield thickness, likewise produced results suggesting the potential of the maintenance therapy strategy centered on eye drops.

With regard to safety, no new safety signals were identified. Taking these findings together, we assess that the study met the targets in the product profile that we established on the basis of market research and other inputs, and we, therefore, regard this as a positive outcome.

Clinical Needs for Eye Drop Maintenance Therapy in nAMD

01

Diseases requiring ongoing treatment

nAMD requires ongoing intravitreal injection therapy with anti-VEGF agents and follow-up to maintain long-term vision

02

Burden of current treatment

Treatment with intravitreal injections places a significant burden on patients and healthcare professionals, including repeated injections, regular visits to specialized medical institutions, patient mobility, and support



The vision the KHK4951 aims for

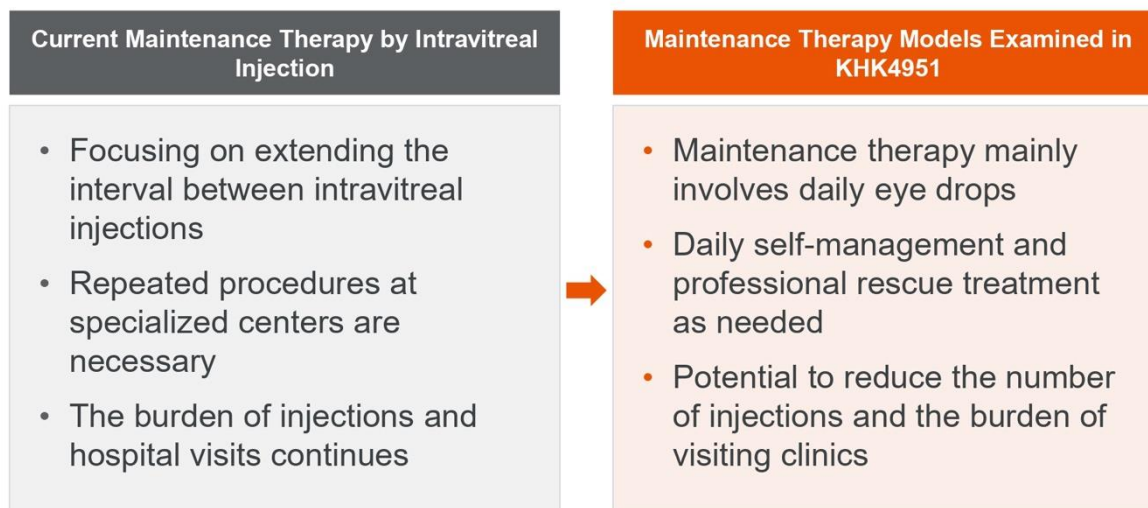
Developing maintenance treatment centered on eye drops after induction with intravitreal injections (maintaining visual acuity, reducing IVT injection count, and providing rescue treatment only when necessary)

I will now explain the unmet medical needs in nAMD in this next slide.

nAMD is a disease in which patients must continue to receive intravitreal injections of anti-VEGF agents together with regular monitoring in order to maintain their vision over the long term. However, in addition to the repeated injections themselves, this treatment places a burden on patients and clinical practice alike, including regular attendance at specialist medical institutions and the travel and support that this entails.

What we are aiming to achieve with KHK4951 is a form of treatment in which, following induction therapy with intravitreal injection, vision is maintained through maintenance therapy centered on eye drops, the number of injections is reduced, and rescue treatment, that is, an additional intravitreal injection, is given only when required.

The Concept of KHK4951 as Eye Drop Maintenance Therapy



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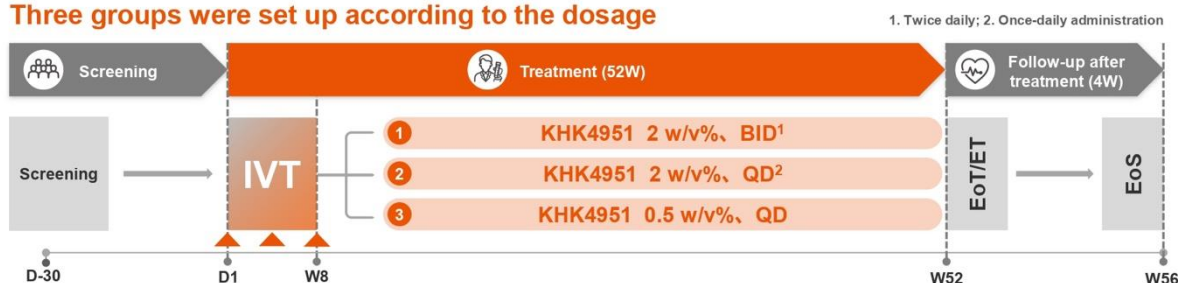
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Maintenance therapy today centers on how far the interval between injections can be extended, and it requires repeated procedures at specialist facilities.

By contrast, in the maintenance therapy model, we are exploring with KHK4951, day-to-day maintenance is carried out by patients themselves using eye drops, with specialist rescue treatment provided as and when required. We believe this may lead to a reduction both in the number of injections and in the burden of hospital attendance.

KHK4951 Design of Phase 2 Trials

Three groups were set up according to the dosage



Overview	
Research Objectives	- Evaluating the efficacy and safety of KHK4951 at different doses - Determining the optimal KHK4951 dose for the Phase 3 study
Primary Evaluation Items	Evaluation of superiority of KHK4951 high dose to low dose: Statistically significant difference in the proportion of patients who lost 15 or more BCVA letters between W8 and W52
Eligible Patients	- Treatment-naïve patients - Patients previously treated with anti-VEGF agents
Sample size	132 patients receiving KHK4951 treatment (no placebo arm)

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1. Twice daily; 2. Once-daily administration; EoT/ET = End of Treatment/Early Termination; EoS = End of Study

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Next slide, please.

The purpose of this study was to evaluate the efficacy and safety of KHK4951 at different doses and to explore the optimal dose for the Phase III study. Following intravitreal injection as an induction therapy, three groups were established: a low-dose group of 0.5% once daily, a medium-dose group of 2.0% once daily, and a high-dose group of 2.0% twice daily, with a treatment period of 52 weeks, followed by a follow-up period after the end of treatment.

The primary endpoint was the difference between the dose groups in the proportion of subjects whose BCVA, best-corrected visual acuity, declined by 15 letters or more between week eight and week 52. The study population comprised both treatment-naïve patients and patients with prior anti-VEGF therapy.

Given that nAMD is a progressive and irreversible disease, no placebo group was included, taking both ethical and clinical considerations into account. The study was conducted in 132 patients.

Approximately 65–69% of cases in all treatment groups maintained their vision within 15 letters decrease in BCVA without any rescue IVT injection

- 15 or more letters decrease in BCVA: **31.1% (2.0% BID), 34.9% (2.0% QD), 31.8% (0.5% QD)**
- No significant differences were observed among dose groups, and the primary endpoint was not met

	KHK4951 0.5 w/v% QD (N = 44)	KHK4951 2.0 w/v% QD (N = 43)	KHK4951 2.0 w/v% BID (N = 45)
Participants Meeting Criteria	14	15	14
Proportion with Exact 95% CI (%)	31.82 (18.610, 47.578)	34.88 (21.008, 50.927)	31.11 (18.166, 46.649)
Difference (%) vs. 0.5 w/v% QD (Reference Dose)	—	3.07	-0.71
Adjusted Difference (%) (Stratified Newcombe 95% CI)	—	2.35 (-17.040, 21.558)	-0.43 (-19.213, 18.360)
p-value	—	NA	0.965

Next page, please. This table shows the primary endpoint results.

The proportion of subjects with a decline in visual acuity of 15 letters or more was 31.8% in the low-dose, 0.5% QD group; 34.9% in the medium-dose, 2.0% QD group; and 31.1% in the high-dose, 2.0% BID group.

No statistically significant difference was observed between the dose groups, and the primary endpoint was not met. However, this means that in each treatment group, including the low-dose group, about 65% to 69% of subjects maintained their vision without a decline in BCVA of 15 letters or more and without requiring rescue therapy and additional IVT injections.

Mean change in BCVA during the KHK4951 dosing period

In all groups, the mean BCVA remained stable from the KHK4951 administration.
No clear differences were observed in the mean BCVA change among dose groups.



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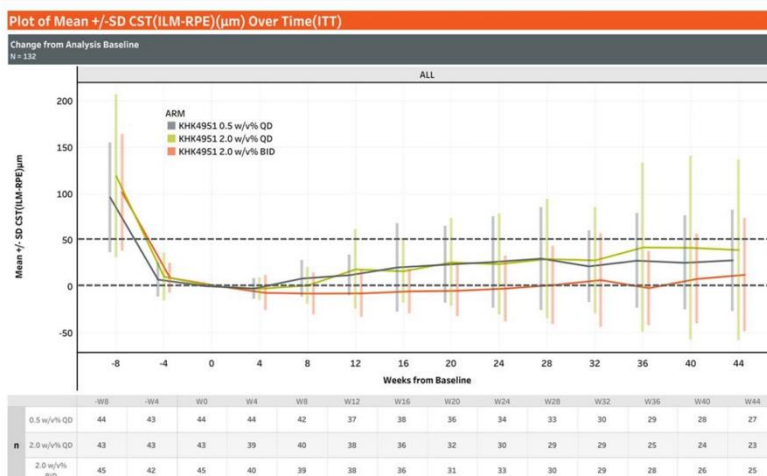
Next page, please. This slide shows the change over time in BCVA.

In all dose groups, mean BCVA remained stable throughout the study period from the end of week eight, at which point induction therapy with intravitreal injection had been completed. No clear difference in the mean change in BCVA was observed between the dose groups.

Mean change in CST during the KHK4951 dosing period

In all groups, the mean CST remained stable from the KHK4951 administration. Meanwhile, no clear differences were observed in the mean CST change among dose groups.

ILM: Internal Limiting Membrane
RPE: Retinal pigment epithelium



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CST, central subfield thickness, which is an anatomical measure, likewise remained broadly stable in each dose group, with no clear dose-related difference. In nAMD, retinal edema associated with neovascularization and exudation leads to a deterioration in vision. We, therefore, consider the fact that CST remained generally stable during the maintenance period with eye drops to be a clinically meaningful finding.

Safety and Tolerability

No new safety signals were observed in this study

Parameter	Main findings
Ocular site	A small number of dry eyes and punctate keratitis were mainly observed in the 2.0% BID cohort
Systemic	No significant new safety signals observed during KHK4951 treatment (e.g., increase in blood pressure)
Study completion	About 70% completed the study. The main reasons for study discontinuation were the need for alternative treatments or progression of nAMD (about 15%)

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With regard to safety, no new safety signals were identified in the study. Locally in the eye, a small number of cases of dry eye and punctate keratitis were observed mainly in the high-dose 2.0% BID group.

As for systemic events, we did not observe any new safety signals, including the increase in blood pressure that is a concern in relation to the inhibition of VEGF signaling. The study completion rate was about 70%, and the principal reasons for discontinuation were the need for additional treatment or progression of nAMD.

Clinical Perspectives on Eye-Drop Maintenance Therapy — KOL Comments

KOLs	Feedbacks
Dr. Pieramici 	Although the absence of a true control group is the study's primary limitation, making it difficult to attribute the observed outcomes directly to the drug, Dr. Pieramici noted that approximately 70% of patients maintained vision (lost less than 3 lines vision or needed rescue) after induction therapy, which may be better than expected from observation alone.
Dr. Iida 	- Dr. Iida agreed Kyowa Kirin's interpretation that this result shows therapeutic effect of KHK4951. - Based on Ph2 result, Ph3 plan should be carefully considered. At this time, non-inferiority study to aflibercept 2 mg with appropriate rescue criteria is reasonable for Ph3 study.
Dr. Murata 	- It is exceeded our expectations that 70% of participants maintained their vision through Week 52 without any intravitreal anti-VEGF injections. This suggests that KHK4951 showed a therapeutic effect. - Even if there is a dose-dependent increase in the frequency of adverse events, these are manageable and acceptable compared to the invasiveness of intravitreal anti-VEGF injections.

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This study did not include a placebo group, which is a limitation in interpreting the results. With that in mind, I would like to share the views of external experts on these findings.

Dr. Pieramici at California Retina Consultants in the United States noted that approximately 70% of patients maintained their vision after induction therapy and observed that this may be a better outcome than would be expected with observation alone without drug intervention.

Next, Dr. Iida at Ageo Central General Hospital agreed with our interpretation that these results demonstrate the efficacy of KHK4951.

In addition, Dr. Murata at Shinshu University Hospital commented that the fact that 70% of subjects maintained their vision through to week 52 without any intravitreal anti-VEGF injections exceeded our expectations, and this suggests that KHK4951 demonstrated a treatment effect.

Summary and Conclusion

Achieved the company's pre-defined product profile targets

Results suggest the potential of an eye drop-centered maintenance treatment strategy

Efficacy Evaluation

Approximately 65–69% of subjects maintained their vision within 15 letters decrease in BCVA without any rescue IVT injection at Week 52

No difference was observed among dose groups; the primary endpoint was not met

Secondary Endpoints

In all groups, BCVA and CST remained stable throughout the treatment period.

Potential for New Treatment Strategies

Presenting the potential of a maintenance therapy strategy centered on eye drops that could help reduce the burden on patients and healthcare professionals.

Based on the insights gained from this exam, our company will explore various options to maximize the value of this program

Next page, please. Let me summarize.

In each treatment group, about 65% to 69% of subjects maintained their vision at week 52 without a decline in BCVA of 15 letters or more. On the other hand, no difference emerged between the dose groups, and the primary endpoint was not met. Among the patients who completed the study, BCVA and CST remained generally stable, and no new safety signals were identified.

As scientific insight into maintenance therapy centered on eye drops in nAMD, these results provide useful information for future investigation. We believe that they suggest the potential of a new maintenance therapy strategy, one that could reduce the burden on patients and health care professionals. We will continue to consider the options available to us for maximizing the value of this program.

Kyowa Kirin continuously creates Life-changing value by leveraging disease science and drug discovery technology

From Story for Vision 2030

Disease Science

Deeply Exploring Unmet Medical Needs (UMN) of Diseases, Their Causes, and Mechanisms

- Exploring treatment possibilities starting from unmet patient needs

KHK4951: Focusing on UMN in patients with maintenance therapy that does not rely on frequent intravitreal injections

Drug Discovery Technology

Application of the optimal modality for achieving treatment

- Combining research and formulation technology expertise to verify treatment concepts in clinical practice

KHK4951: Pursuing efficient posterior-segment delivery using nanocrystallized tivozanib



Creating
Life-changing
value

KHK4951: Strategic Partnering Assets

Assets beyond our focus areas – Maximizing value through collaboration with partners

Next page. This is the last page. Let me close with one further point.

As I mentioned at the outset, KHK4951 is a development asset that has emerged from our drug discovery strategy and technologies starting from an unmet medical need, deepening our understanding of the disease science, and applying our own drug discovery technologies. Kyowa Kirin will continue to generate distinctive pipeline assets and to deliver life-changing value.

Thank you very much for your attention.

Question & Answer

Moderator [M]: Now, I'd like to move to the Q&A session. If you have a question, please press the raise hand button at the bottom center of your screen and wait. We will call on you in turn, so when the prompt to unmute appears on your screen, please unmute yourself, state your company name and your name, and then ask your question.

So that we can take questions from as many of you as possible, please limit yourself to two questions at a time. Thank you.

Wakao [Q]: Wakao from JPMorgan Securities.

It is true that the primary endpoint was not met, but a certain level of efficacy can be seen in the secondary endpoints, so I personally do not think there is so much to be pessimistic about, and I felt that solid data has been obtained. That said, I have a question.

The first thing I would like to know is this. As you said, no placebo group was included in this study. Without being able to see the true efficacy of tivozanib, just under 70% of patients maintained their vision, and you say that this product has value. I feel there is a gap between the fact that no placebo group was included and that the primary endpoint was missed, on the one hand, and your positive assessment based on just under 70% of patients having maintained their vision, on the other. Could you give us a little more explanation to fill that gap?

For example, it would help if you could say that the fact that 70% of patients maintained their vision over the 44 weeks following the use of Eylea is clearly stronger than maintenance therapy with Eylea, or that the time to the first rescue was clearly longer than under maintenance therapy with Eylea. Could you explain it along those lines so that we can better understand the value of this product as you see it?

Torii [A]: Thank you very much for your question.

As I said, because of ethical considerations, we're not able to set a placebo group. We have to be cautious in interpreting the data.

This is just for your information. But, for example, another company, Ocular Therapeutix, has a TKI hydrogel product or drug product. In that study, after IVT was done, maintenance therapy was not given. If we had set the placebo group, then the regimen would be closer to what I just described.

As I recall, in that study around 44.2% of subjects maintained their BCVA with a decline of less than 15 letters, whereas in our case it was just under 70%. We have to be cautious in interpreting the data, but taking such examples and also the views of KOLs into account, we believe that efficacy can clearly be expected.

As for the future development strategy, this is just preliminary data. We would like to look at the data in more detail for each patient, and then we will collaborate with KOLs and potential partners to come up with the plans. Ultimately, we will talk to the regulatory authorities to reach an agreement on our future development plan.

That's all for me.

Wakao [Q]: A follow-up question. Am I correct in understanding that the time to the first rescue was longer than the interval seen under maintenance therapy with Eylea?

Torii [A]: Well, this is not designed to aim for that. But from the Kaplan-Meier perspective, if you look at our data and real-world data and compare the two, then we could have some expectation or hope from this data, but this is not a comparative study, so we have to be cautious.

Wakao [Q]: The second question: the primary endpoint was missed in this study. But based on this result, in your view, would the future development or partnership be affected?

For example, do you have to run another Phase II study, or, based on the potential partnership discussion, might it take more time to reach an agreement based on the results? How should we interpret the fact that you missed the primary endpoint?

Torii [A]: Honestly speaking, the low-dose group had more efficacy than we had expected. That's why there is no significant difference between the different dose groups.

As I said, for the future plans, the data that we obtained from this study and the DME study, which is another study, will be subject to a more detailed analysis of both studies. Then we will have discussions with potential partners and also talk to the regulatory authorities to study and come up with the future development plans.

Seki [Q]: Thank you for the explanation. Seki from UBS Securities.

First, on your comment that the efficacy in the low-dose group came out more strongly than expected, are you suggesting the possibility that efficacy is already saturated at, for example, 0.5% QD? What was different from your prior assumptions? Could you comment on why dose dependency was not seen more clearly?

Torii [A]: On this point, we have the results on the drug concentrations as well. Including those data, we'd like to look more closely to clarify whether it's saturated or not.

Seki [Q]: Okay. Understood.

Also, regarding the definition of a rescue injection in this Phase II study, I do not know what the final protocol says, but I believe the patent describes a decline of 10 letters or more. Is that understanding correct? If so, I suspect it may differ somewhat from real-world clinical practice. Could you comment on that, and on the comparability of the data with Ocular, which you referred to earlier?

Also, with regard to the Kaplan-Meier curve, should we understand that the declines of 15 letters or more occurred largely in the latter half of the study?

Torii [A]: Regarding the last part of your question, it's throughout the study period that we observed it rather than in the latter half of the study. Regarding the comparison against OTX, we cannot make a stringent comparison. I cannot say more than what I said before.

Going back to your first question, regarding the criteria for rescue therapy, rather than a strict rule under which rescue is given immediately once the measure is met, my understanding is that the investigator judges whether to introduce rescue therapy based on a comprehensive assessment of the degree of disease progression, including the decline in visual acuity, and of the safety situation.

Muraoka [Q]: I'm from Morgan Stanley Securities, Muraoka.

With regard to DME, is the timing of that study, and the dose setting for DME, the same as for nAMD this time, that is, 0.5% QD, 2% QD, and 2% BID? Could you tell us about that?

Torii [A]: As for DME, what I can disclose at this point is no more than what is described on ClinicalTrials.gov, and I would like to refrain from commenting beyond that.

As for when we will disclose the information, I will not go into detail, but as a rough guide, we are making preparations so that we will be able to report to you within around six months to a year. That's all from me.

Muraoka [Q]: Six months, I can understand, but does it take one year?

Torii [A]: I gave you a range in order to be vague about the timing, but we would like to make it public as early as we can.

Muraoka [Q]: Okay.

The reason I have been asking about the dose setting and the study design is that, with only today's nAMD data, we cannot tell at all which dose you will take forward.

Everyone here today feels that they would like some additional information. That is why we believe the DME data will be very important. So let me ask again about the doses. I assume they are probably the same, and it is hard to think of any reason to use different doses for DME, isn't it?

Torii [A]: If I start referring to that, various things would become apparent. That said, as you say, I myself am really looking forward to the DME results. We will judge the nAMD results we have now and the DME results to come in a comprehensive manner as we refine our future development plan.

Muraoka [Q]: The last question. Based on the results from nAMD, if you are to proceed to Phase III, which dose are you going to choose? If you were to choose to go ahead with Phase III, which dose would you choose?

Torii [A]: Including that point, we would like to work through a range of detailed analyses going forward.

Muraoka [Q]: Is more detailed analysis enough?

Torii [A]: We would like to decide comprehensively. There are various perspectives to take into account, so we would like to consider it comprehensively.

Matsubara [Q]: Matsubara from Nomura Securities. I have two questions.

First, regarding the number of doses. In maintenance therapy, injections are given once every two to three months, or, depending on the symptoms, once every four months or even six months, whereas tivozanib is administered every day. Since efficacy was seen even at the low dose this time, is there a possibility of extending the dosing interval, for example to once every two or three days?

Torii [A]: Thank you for your question.

Personally, I think there can be such a possibility. But when it comes to instilling eye drops every day versus once every three days, the question is whether compliance will hold up. We would like to determine the dosing frequency while also taking the real-world situation into account.

Matsubara [Q]: I see. Since patients may forget, every day may be better than once every three days.

Torii [A]: That is one way of looking at it, yes.

Matsubara [Q]: Thank you. My second question concerns the effect of maintenance therapy. Elderly patients may have other ophthalmic conditions in addition to age-related macular degeneration, and I imagine they use a variety of eye drops. Could the concomitant use of other agents affect whether tivozanib penetrates to the posterior segment of the eye and whether its efficacy can be assured? What is your view on this point?

Torii [A]: On that point, honestly speaking, we have not been able to obtain data on what you describe in this clinical study. In part, we designed the study so as not to allow such situations to arise. In Phase III, when we increase the number of cases, such cases may emerge, so we would like to watch that situation and then decide how it should be described in the labeling.

Wada [Q]: Wada from SMBC Nikko Securities.

I would also like to ask about positioning first. I would like to be clear once more about how you expect this drug to be used in real-world clinical practice. In nAMD, long-term compliance with treatment is said to be a challenge. According to the data I have, about 80% of patients are still on treatment at the five-year point, but among elderly patients for whom hospital visits are difficult, 20% to 30% are not attending, and their condition deteriorates as a result. That is said to be a challenge.

Is what you are targeting with tivozanib both reducing, as far as possible, the treatment burden on the 80% who continue treatment, and also addressing those who are not able to continue treatment?

Also, does that mean you are basically envisaging concomitant use with agents such as Eylea?

Torii [A]: On our part, we would like to meet the unmet needs of as many patients as possible. If 80% can continue with the treatment, then we would like to reduce the burden on those patients. That's within our scope.

But the remaining 20%, for various reasons, were not able to carry on or continue with the treatment. By reducing the burden on those patients, we would like to provide more opportunities for them to continue with the treatment.

Wada [Q]: For the 80% of patients who are still on treatment, I think many of them are on T&E, treat-and-extend, so I assume you are aiming to reduce their burden by reducing the number of doses. What concerns me is that, if patients simply keep using the eye drops, they will stop going to the medical institution, and by the time their condition worsens it may be too late. That kind of compliance issue could also arise.

What do you think about that?

Torii [A]: In our understanding, there is no attendance with regard to IVT, but there are regular visits to the hospital. I think this would be continued.

Wada [Q]: One more point, on PK and the basis for the dose setting this time. I would like to ask what you looked at from Phase I when you set these doses.

In Phase I, after all, not much of a dose-response relationship was seen, and it seems to have been the same in Phase II. Through the Phase I and Phase II studies, do you have any placebo-like data, for example data showing that the maintenance rate deteriorates where no treatment is given, or any PK/PD data showing that at these doses the drug is not reaching the posterior segment of the eye at all?

Torii [A]: Not in humans. It is very difficult to measure the concentration in the posterior segment of the eye in humans, so we have obtained that kind of data from animal studies and the like. In addition, at the Phase I stage, we also obtained data in patients.

Initially, in the induction phase, we had thought that we could see some efficacy in the induction phase from this drug, and we looked at that impact. But in terms of induction, it may be a bit challenging. That's why we shifted our aim to maintenance in the Phase II study. That's the background we come from to reach this design for this study.

Wada [Q]: The last question, on a similar point. Would it be ethically possible to set up a placebo-like group such as the one Ocular used?

Torii [A]: As I said earlier, we had a range of discussions with KOLs and with the regulatory authorities, and ultimately we, as a company, decided not to set a placebo group. Since then, cases such as that of Ocular Therapeutix have emerged, so for our future development plan we would like to widen the scope somewhat as we consider the options.

Ueda [Q]: Ueda from Goldman Sachs Securities.

My first question is one I would like to understand better in considering the market potential. Regarding the maintenance of vision in roughly 65% to 69% of patients this time, given that this is a progressive disease that leads to a decline in vision, and that existing treatments such as Eylea have very high efficacy, can this really be said to be sufficient efficacy?

For example, I do think that for a certain proportion of physicians and patients it is better than not using it at all, particularly where the burden of intravitreal injection is very large. In considering the market potential, could you supplement your remarks on the degree of efficacy and on the current unmet need, and share any data of yours that you can?

Torii [A]: Thank you for your question.

As a company, we performed market research, and we have a target product profile. We set the criteria we'd like to achieve based on that. The quantitative criteria specifically cannot be shared, but we are meeting those criteria this time. Based on the market research, to a certain degree, we can meet the needs, and we are able to confirm the efficacy according to our interpretation.

Ueda [Q]: Understood. Secondly, how are you going to proceed from now on? At what point are you going to proceed with this program?

In the press release, you also write that the results require careful interpretation and that further research is called for.

Ueda [Q]: Do you mean that you're not going to enter the Phase III study immediately? And regarding the partnership and out-licensing activities, are there any potential changes compared to what you were thinking?

Torii [A]: There's going to be no major change in principle.

As we explained before, going forward we will have the results from the DME study. Detailed analyses will be performed for both nAMD and DME, and we will hold a range of discussions with KOLs and with potential partners. In the end, we will confirm our approach with the regulatory authorities at an end-of-Phase II meeting so that we can proceed with future development.

Mamegano [Q]: Based on this result, in terms of the product profile, you said that you met the target, but I'm concerned about the criteria. Which criteria did you use to decide that this study was successful?

You said that you cannot share the specific criteria. But is there, for example, any historical data on what happens when patients are simply observed without treatment after induction therapy? This time the figure was around 30% in the low-dose group, and I would like to know the reason you judged that this demonstrates efficacy. With no placebo group in this study, on what basis did you make that judgment?

Torii [A]: As I said, we conducted a variety of market research, and we set part of the criteria on that basis. In addition, although it is not a direct comparison, there is the case of OTX that I mentioned earlier, as well as other clinical study results that serve as references. We set the criteria for the target product profile by comparing these comprehensively, and this time we met them.

Mamegano [Q]: But there's no dose-response relationship. Even then, you said that there is efficacy.

Torii [A]: Well, the proportion of patients who were able to maintain their vision, that part was met. For future development, how we can address the dose-response relationship is a challenge.

Mamegano [Q]: The comments from KOLs were shared with us. Dr. Iida said that if we are to do the Phase III study, non-inferiority is one of the options. But when you did the Phase II study, the Eylea group was not included. Is there any reason for that?

Torii [M]: Just to confirm, do you mean an Eylea arm in the sense of a negative control, or as a positive control?

Mamegano [Q]: As a positive control. In the Phase II study, in order to gauge the efficacy of KHK4951 to some extent, I think it would have been better to have something to compare it against. A placebo would have been best, but you said that was not possible for ethical reasons. Eylea, on the other hand, is the standard of care, so I would like to ask why you did not include that arm.

Torii [A]: As for Eylea data as a positive control, there are various clinical data, and it is clear that patients can maintain their vision well. From that perspective, we did not set an Eylea arm.

Hashiguchi [Q]: Hashiguchi from Daiwa Securities.

My first question is as follows. You said that you achieved the targets in the product profile, but 30% of the patients could not complete the study, and 15% of the patients required an alternative treatment or experienced disease progression. Can that really be described as an achievement?

Given that failure of treatment carries a risk of blindness, and that the disease may progress to this extent, I think patients will still need to attend hospital regularly to be examined for progression. In that case, from the patient's standpoint, it might be more convenient to receive an injection when they visit. Since they have to visit for an examination in any case, how much need do you think there is for daily eye drops rather than injections?

Torii [A]: Thank you very much for a very important question.

More than we assume, IVT's invasiveness is very significant. We are discussing this with KOLs and investigators, and we think that just reducing the frequency is going to be very clinically meaningful. When they visit, receiving an IVT is not an easy procedure, in my view. There is high clinical significance.

Hashiguchi [Q]: Secondly, this study looked at maintenance with eye drops alone, without IVT. What about the possibility of reframing the treatment concept so that the drug can be given in combination with IVT while monitoring the patient's condition, with the main target being a reduction in the number of IVTs compared with a control arm that does not receive KHK4951?

Torii [A]: We, too, think that what you describe may well arise in actual clinical practice. There may be some patients who can be maintained over the long term on our drug alone, but that is not something we would expect in all patients. In patients with severe disease, I imagine the picture will be one of long-term maintenance using our drug in combination with IVT.

Hashiguchi [Q]: In that case, rather than moving straight on to Phase III, I feel it might be better to explore once more in a Phase II study the dosing approach you have just described for real-world clinical practice, including the optimal dosage and administration. What is your view?

Torii [A]: On that point as well, as I have said repeatedly, we would like to take a variety of data into comprehensive consideration in determining our development plan.

Kawamura [Q]: SBI, Kawamura. There's not much time, so just one question.

In this study, no dose-response or dose-dependent relationship was seen. In the trial, was there any mechanism to check whether each patient was properly instilling the eye drops, in other words whether adherence was being ensured? You commented that the low dose came out more strongly than expected, but could it be that the high dose turned out to be unexpectedly less effective because the drops were not instilled properly? Unless that is firmly addressed, I feel it will be hard to get a clear picture of the dose next time as well. Could you comment on whether the overall trial design incorporates anything to that effect?

Torii [A]: Compliance is one of the challenges for us, and my understanding is that measures to enhance compliance have been incorporated into the design. Also, while it is not possible to measure the concentration in the posterior segment of the eye, we do measure the systemic concentration, so I believe we are able to confirm that the drug has been properly administered. We would like to double-check that point going forward as well.

Kawamura [Q]: Understood. Should we take it that, including whether the highest-dose group really is the highest dose in practice, we will have to wait for the data to come?

Torii [A]: We would like to analyze the detailed data and present it at academic congresses and in papers.

Moderator [M]: Due to time constraints, we are sorry that we have not been able to take all of your questions. For any questions we were unable to take, please contact our IR team.

The audio of today's meeting will be made available for on-demand streaming on our IR website. A transcript, including the Q&A session, will also be published, so please take a look at that as well. Thank you very much for joining us today. We look forward to your continued support of Kyowa Kirin.

[END]