Kyowa Kirin Co., Ltd.

Follow-up Briefing on AAD Conference Presentation on Rocatinlimab

March 10, 2025

Event Summary

[Event Name]	Follow-up Briefing on AAD Conference Presentation on Rocatinlimab	
[Date]	March 10, 2025	
[Number of Speakers]	1	
	Takeyoshi Yamashita	Director, Senior Managing Executive Officer and Chief Medical Officer

Presentation

Moderator: Good morning, ladies and gentlemen. We will begin a briefing for investors and analysts presented by Kyowa Kirin Co., Ltd.

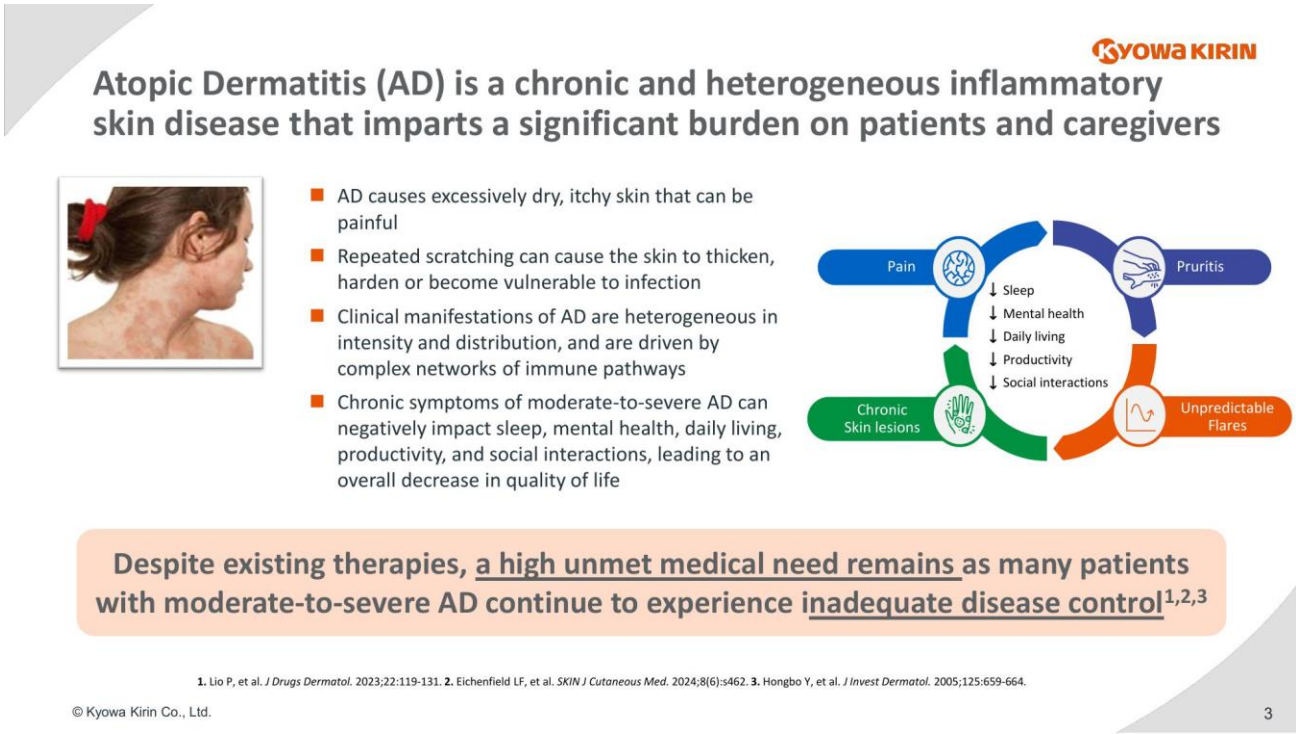
Today's topics include the results of the ROCKET-HORIZON study, a Phase III clinical trial of rocatinlimab for moderate to severe atopic dermatitis, which was presented on March 8, U.S. local time, at the Late-Breaking Session of the American Academy of Dermatology Annual Meeting. We will also provide a follow-up on the top-line data from ROCKET-IGNITE, another Phase III study of rocatinlimab, which was released the day before yesterday.

Before we start, I would like to share a few reminders. Please note that we will keep the names and company names of all participants for today's briefing for a certain period of time as a list of participants. Please note that the content of this presentation will be available on-demand and as a transcript on our website. Keep this in mind when making statements. The information presented today contains forward-looking statements. Please note that there is uncertainty due to various risks.

Today's speaker and in charge of the question-and-answer session is Takeyoshi Yamashita, Director, Senior Managing Executive Officer, and Chief Medical Officer.

This online meeting is scheduled for up to 60 minutes. We will start with our presentation, then proceed to the question-and-answer session.

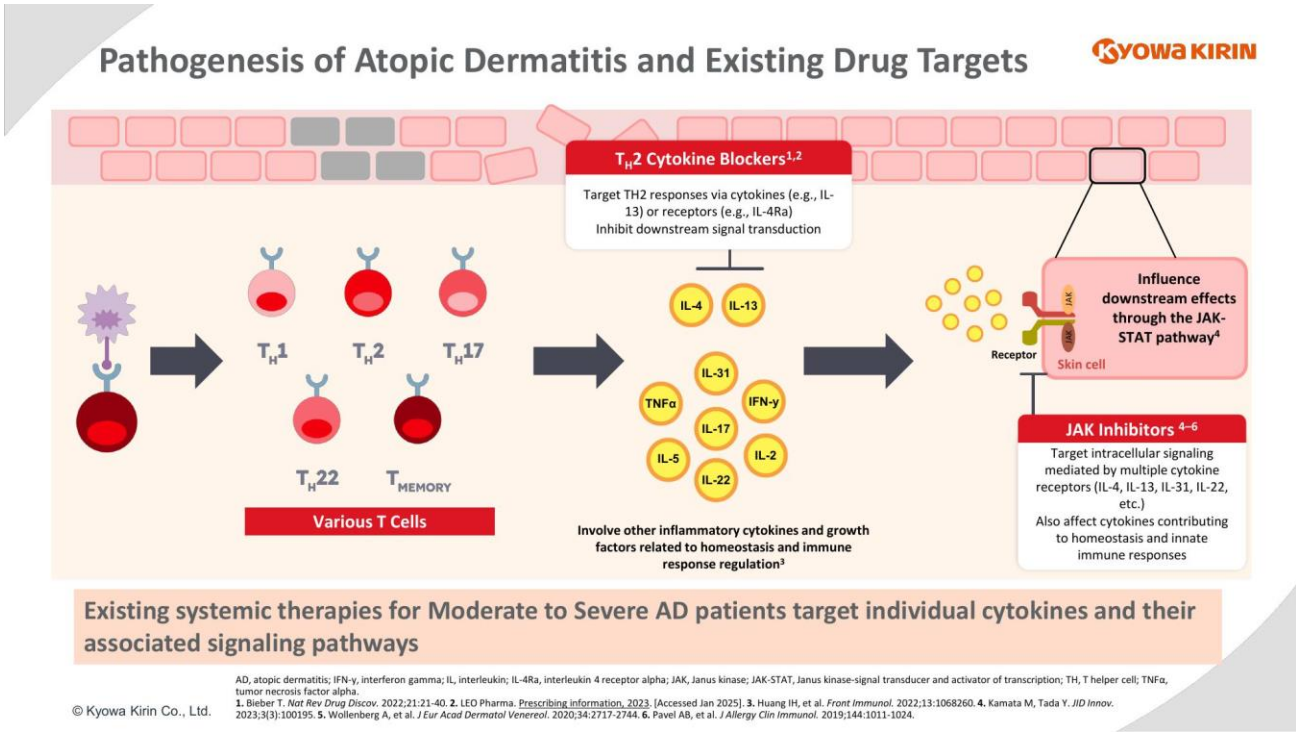
Yamashita: Good morning. My name is Yamashita. Let's get started. I would like to explain using the materials.



Atopic dermatitis imposes a significant physical and mental burden on patients.

Patients with moderate to severe atopic dermatitis not only suffer from itching and pain, but also experience disrupted sleep quality and impaired daily life. The disease's unpredictable flare-ups contribute to emotional distress, affecting patients beyond their skin symptoms.

Although various treatment options are available, disease control remains insufficient, and there is a demand for new therapies that operate through novel mechanisms.

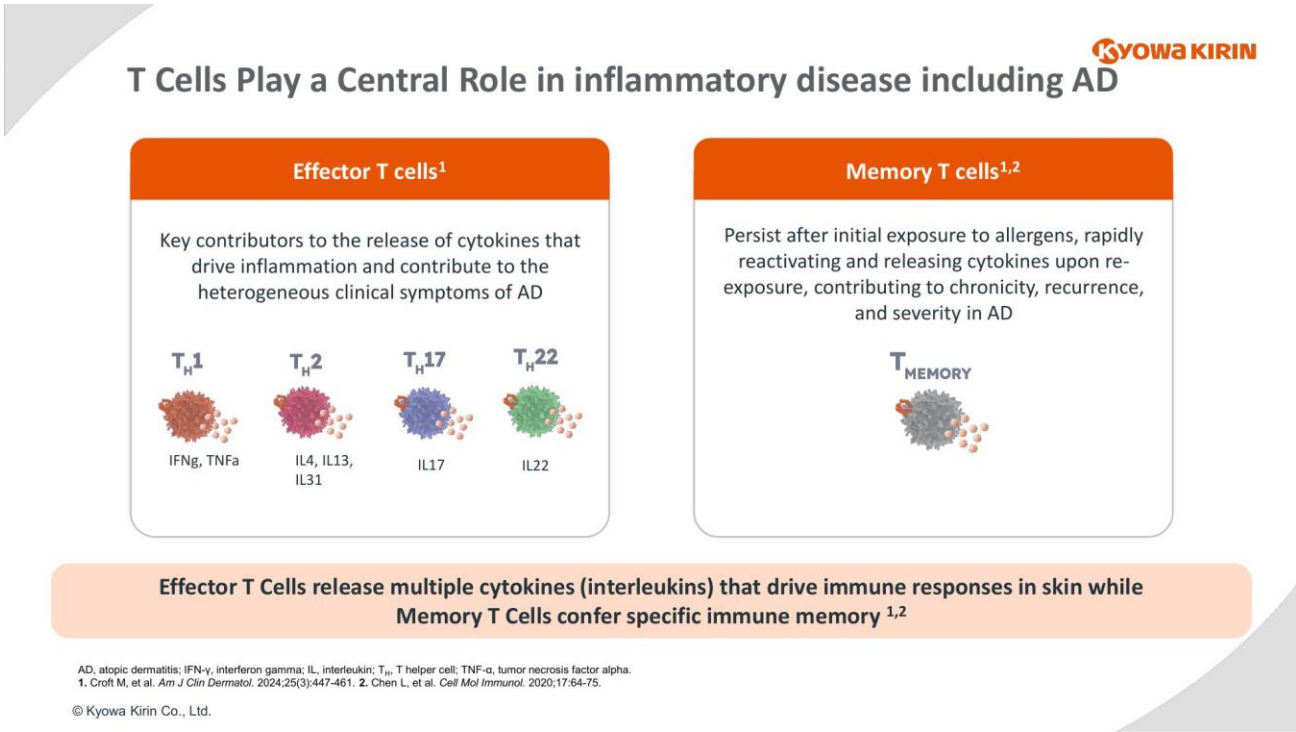


This slide shows the pathogenesis of atopic dermatitis and its relationship with existing systemic treatments.

In this disease, TH2 cells and other T cells are activated, releasing various cytokines, which in turn activate the JAK-STAT signaling pathway.

Current medications aim to block the action of these cytokines or inhibit JAK enzymes to control the disease.

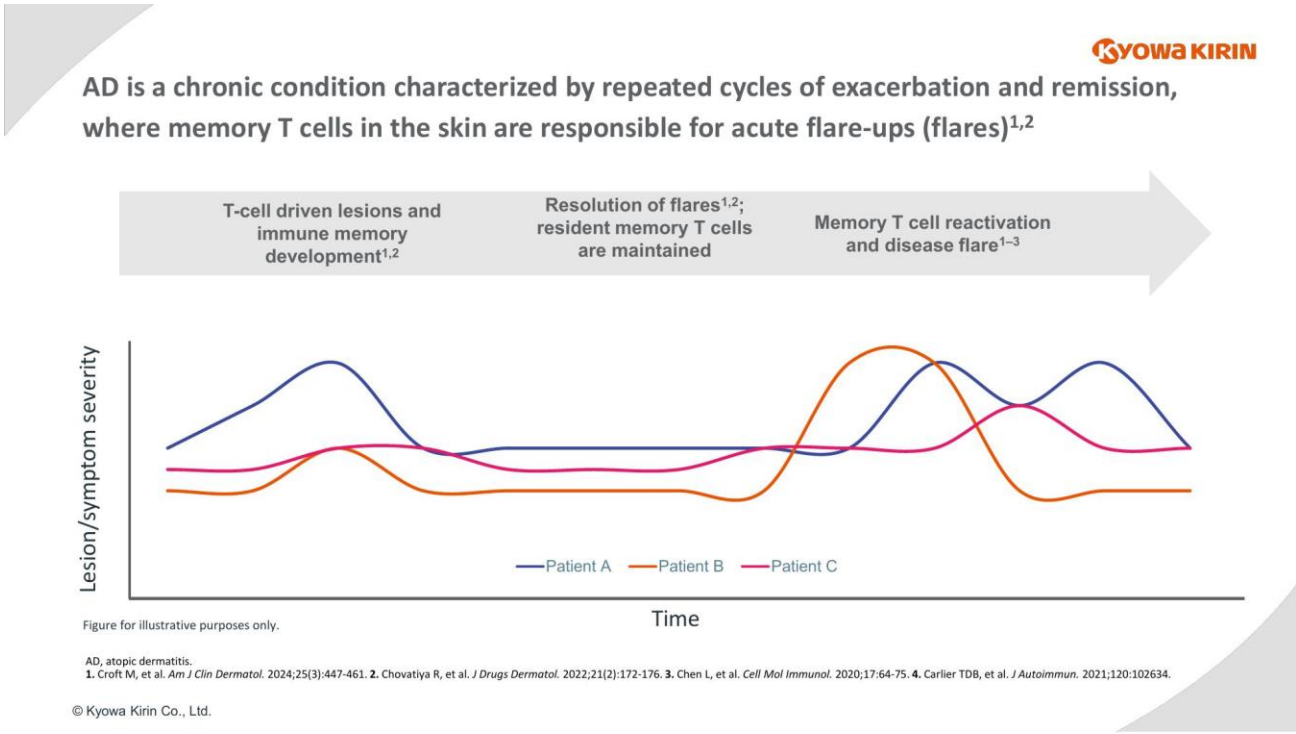
However, the underlying cause of atopic dermatitis is the abnormal activation of T cells, as shown on the left side, and currently there are no effective drugs that directly address this issue.



The abnormally activated T cells in atopic dermatitis are of multiple types, as shown on the left side of the slide, and they release various cytokines. Combinations of these lead to diverse and individualized symptoms.

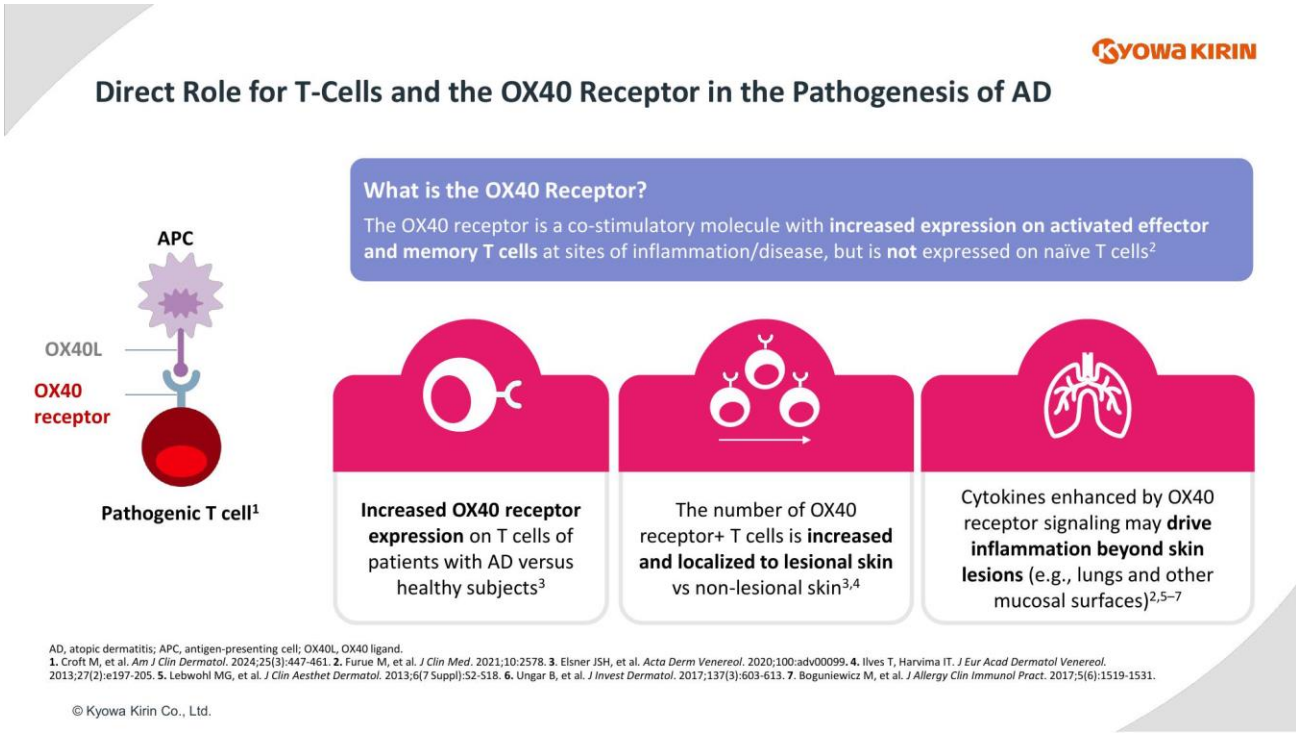
Normally, cells have a lifespan, but some activated T cells enter a state of dormancy. These cells remember the antigens or allergens to which they were exposed during activation and are known as memory T cells.

When these memory T cells encounter the same allergen again, they rapidly reactivate, turning into active T cells and releasing cytokines. This reactivation of memory T cells is believed to be one of the key factors contributing to the chronicity and recurrence of atopic dermatitis.



As illustrated, patients with atopic dermatitis experience repeated cycles of exacerbation and remission of skin flare-ups. This fluctuation is linked to T-cell behavior, as shown earlier.

When symptoms are severe, activated T cells are very active. Even when symptoms temporarily subside, memory T cells remain, which can lead to rapid flare-ups upon encountering new triggers.



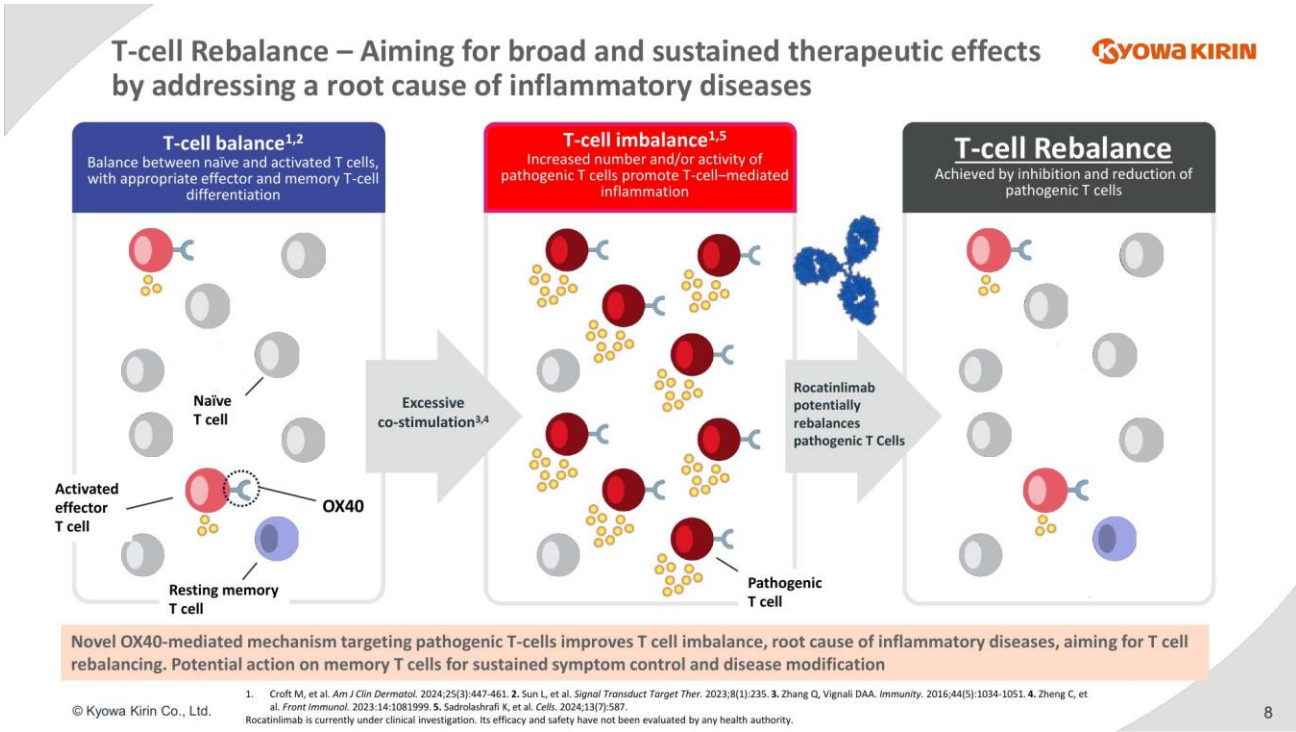
OX40 plays an important role in regulating activated T cells in atopic dermatitis.

OX40 is not expressed on naive T cells. OX40 is a receptor-like molecule that appears on the surface of T cells during the process in which naive T cells become activated upon receiving antigen presentation.

It is said that OX40 plays a role in maintaining the activated state of effector T cells, as shown earlier. It is also expressed on memory T cells and is thought to be involved in inflammation caused by their reactivation.

In fact, OX40-positive cells are increased in atopic dermatitis patients and are found in abundance in affected skin areas. OX40 is also believed to be involved in inflammation in the lungs and mucosal sites surfaces the skin.

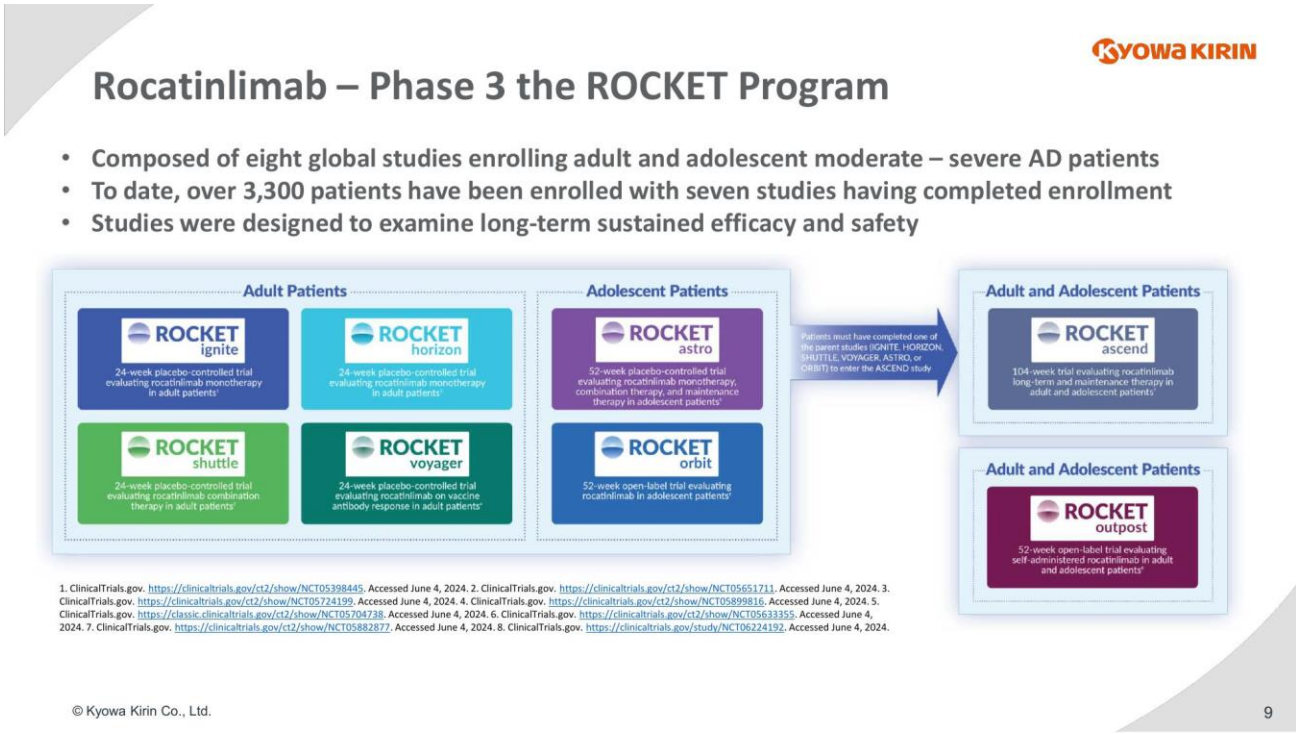
Rocatinlimab is an antibody drug that targets OX40. It blocks the binding of OX40 ligand and, through ADCC activity, reduces the number of cells expressing OX40.



Even in a healthy immune system, various stimuli are continuously present. Therefore, a small number of activated T cells can be found, as shown in the diagram on the left. This is a balanced healthy state of T cells overall.

However, patients with moderate to severe atopic dermatitis are thought to have T-cell imbalance due to chronic activation and a significantly increased number of pathogenic T cells, as illustrated in the middle diagram. This condition is referred to as T-cell imbalance.

Rocatinlimab targets OX40 expressed on pathogenic T cells, reducing the numbers of pathogenic T cells and restoring T-cell balance. We refer to this process as T-cell rebalancing, aiming to correct the underlying T-cell abnormality in patients with atopic dermatitis. By doing so, it aims to control the disease closer to its root cause, resulting to a long-lasting improvement.



This slide provides a reiteration of the overview of the ROCKET program.

The ROCKET program is a large global Phase III trial program comprising eight studies conducted in adults and adolescents with moderate to severe atopic dermatitis.

To date, more than 3,300 patients have participated in clinical trials, and patient enrollment has been completed for seven trials.

The program is designed to evaluate long-term safety and sustained efficacy in patients with chronic atopic dermatitis.

Rocatinlimab – Today's agenda

ROCKET horizon
24-week placebo-controlled trial evaluating rocatinlimab monotherapy in adult patients

Detailed data has been disclosed at the **Late Breaking Abstract** on the afternoon of **March 8, 2025**, US time, at the **American Academy of Dermatology (AAD)**.

ROCKET ignite
24-week placebo-controlled trial evaluating rocatinlimab monotherapy in adult patients

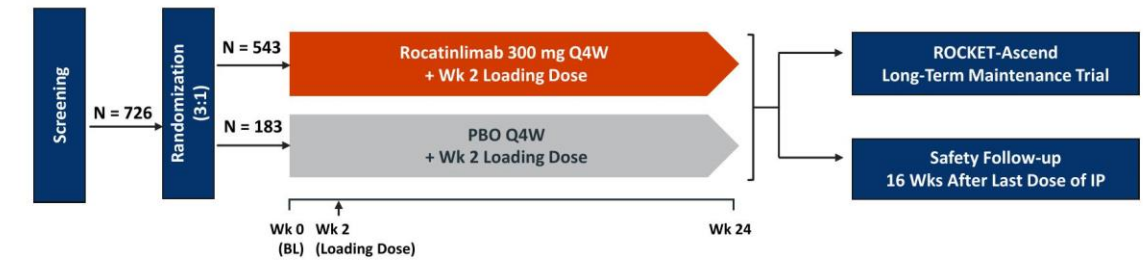
ROCKET shuttle
24-week placebo-controlled trial evaluating rocatinlimab combination therapy in adult patients

ROCKET voyager
24-week placebo-controlled trial evaluating rocatinlimab on vaccine antibody response in adult patients*

Topline data disclosed on March 8, 2025

Today, I will explain four of the eight Phase III trials: the two monotherapy trials, HORIZON and IGNITE, the SHUTTLE trial, which involves combination therapy with topical treatments, and the VOYAGER trial, which evaluates vaccine response.

Phase 3 ROCKET-HORIZON Trial Evaluated Rocatinlimab Monotherapy vs PBO in Adults With Moderate-to-Severe AD



Randomization stratified by:
- Baseline disease severity
- Geographic region

Key Inclusion Criteria
- Age ≥ 18 yrs
- AD diagnosis present for ≥ 12 mo
- vIGA-AD™ of 3 or 4
- EASI ≥ 16
- BSA ≥ 10%
- 7-day recall WP-NRS ≥ 4
- Inadequate response to TCS of medium or higher potency (± TCI) or systemic therapy (after appropriate washout period)

Time course of T cell population measured on Day 1 and Wks 8, 16, and 24

AD, atopic dermatitis; baseline, BL; BSA, body surface area; EASI, Eczema Area and Severity Index; IP, investigational product; mo, month; PBO, placebo; Q4W, every 4 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; vIGA-AD, validated Investigator Global Assessment for AD; Wk, Week; WP-NRS, Worst Pruritis Numerical Rating Scale; yr, year.

First, I will introduce the results of the HORIZON trial, which was presented at AAD.

Here is the trial design. A total of 726 patients participated. They were randomized in a 3:1 ratio into the rocatinlimab treatment group and the placebo group. A loading dose was administered at week two, followed by dosing once every four weeks, for a total of 24 weeks.

The key eligibility criteria are as shown.

Patient Demographics and Disease Characteristics at Baseline

	ROCA	PBO	Total
Full Analysis Set	**N = 543**	**N = 183**	**N = 726**
Age, yrs, mean (SD)	37.8 (14.6)	40.4 (15.6)	38.4 (14.9)
Female, %	45.7	44.3	45.3
Hispanic/Latino, %	11.6	12.0	11.7
Race, %			
White	59.9	58.5	59.5
Asian	29.7	33.3	30.6
Black	3.5	5.5	4.0
Other[a]	7.0	2.7	5.9
BMI, kg/m², mean (SD)	26.5 (5.4)	28.0 (6.8)	26.9 (5.8)
vIGA-AD score, %			
Moderate (3)	61.9	61.2	61.7
Severe (4)	38.1	38.8	38.3
EASI total score (0–72), mean (SD)	28.5 (10.9)	28.6 (11.1)	28.5 (11.0)
Moderate (> 16 to ≤ 21), %	27.8	30.6	28.5
Severe/Very Severe (> 21), %	70.7	68.9	70.2
Prior use systemic therapy,[b] %	63.0	63.4	**63.1**
Prior use biologic or systemic JAK inhibitors,[b] %	**23.9**	**16.4**	**22.0**

a. Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, and other. b. Prior use to treat AD.
BMI, body mass index; PBO, placebo; ROCA, rocatinlimab; yr, year.

Regarding the baseline characteristics of patients and disease profiles, there were no differences observed between the treatment and placebo groups.

The eligibility criteria targeted patients who were unresponsive to or unsuitable for topical treatments.

However, as shown in the table, many patients had a history of systemic treatment, and a considerable number of patients had prior experience with biologics or JAK inhibitors. This aspect differs somewhat from the background of the Phase IIb trial we conducted previously.

Need for Rescue Therapy Was Reduced in the rocatinlimab Group vs PBO

Full Analysis Set	ROCA 300 mg Q4W N = 543 %	PBO N = 183 %
Any use of rescue therapy by Week 24*	**33.5**	**41.5**
Any use of topical rescue therapy only[a]	**28.7**	**29.5**
Low/medium-potency topical therapy	15.5	13.1
High/super-high–potency topical therapy	13.3	16.4
Any use of systemic rescue therapy[a]	**4.8**	**12.0**
Conventional systemic therapy	3.3	11.5
Biologic or systemic JAK inhibitor	1.5	0.5

*Log-rank *P* value = 0.064

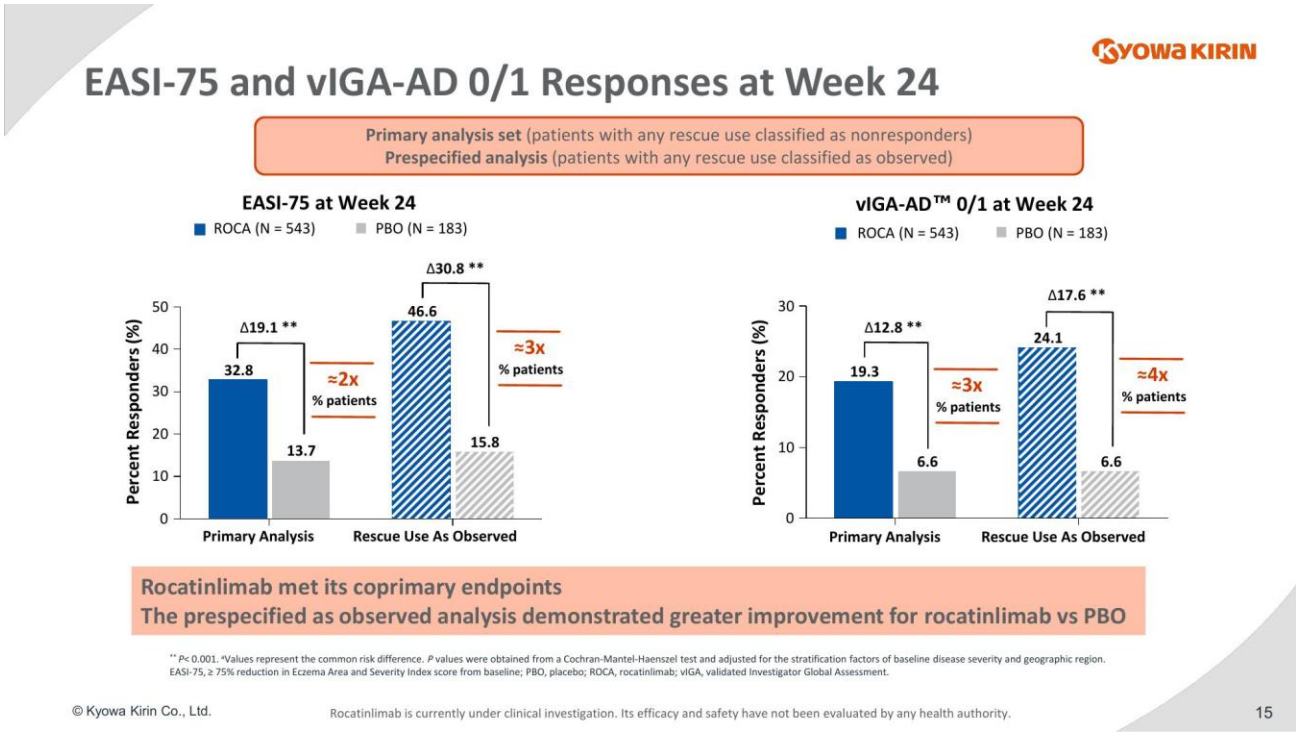
Proportion of patients who used systemic rescue therapy was less in the rocatinlimab group vs PBO

[a]Most advanced line of rescue therapy used for AD. Patients in the systemic rescue therapy group could have also used topical rescue therapy, but patients in the topical rescue therapy group could not have used systemic rescue therapy.

AD, atopic dermatitis; JAK, Janus kinase; PBO, placebo; Q4W, every 4 weeks; ROCA, rocatinlimab.

Additionally, this trial allowed for rescue therapy. It means that rescue treatment could be administered at the physician's discretion.

When comparing the rocatinlimab treatment group with the placebo group, the use of rescue therapy was lower in the rocatinlimab group.



Here are the results as of week 24.

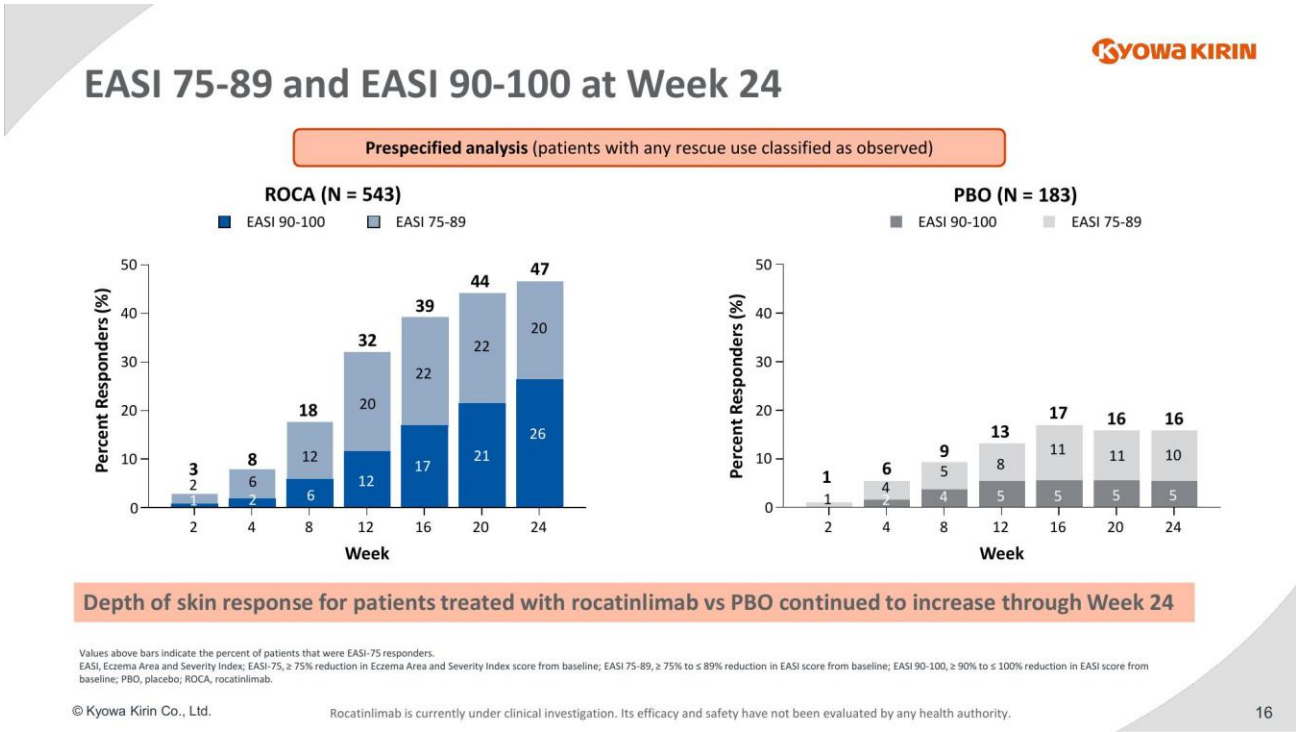
Two sets of data are presented here.

One is the Primary Analysis, which has already been included in the press release. In this analysis, patients who used rescue therapy were statistically treated as non-responders to this drug. Even if they used rescue therapy only slightly, they were classified as: the treatment was ineffective.

In contrast, the Rescue Use As Observed analysis included patients who used rescue therapy but were not classified as non-responders. In this analysis, even if a patient used rescue therapy, they were still counted as having achieved EASI-75 or vIGA.

The figure on the left shows the percentage of subjects achieving EASI-75 at week 24. In both the primary analysis and the Rescue Use As Observed analysis, more patients in the rocatinlimab group achieved EASI-75 compared to the placebo group.

Similarly, in the figure on the right, which represents vIGA, both the primary analysis and the Rescue Use As Observed analysis show that more patients in the rocatinlimab group achieved vIGA-AD 0/1 compared to the placebo group.



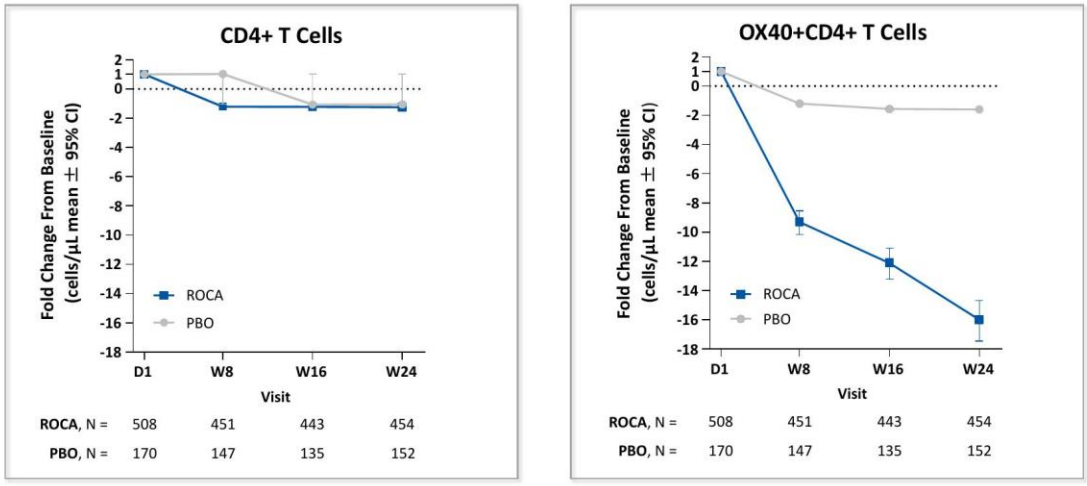
This slide shows the improvement of EASI over time.

As treatment continues, the achievement rate of EASI-75 increases. The achievement rate of EASI-90 also increases. Interestingly, the number of patients who reached EASI-90 to 100 grew linearly and had not yet reached a plateau at week 24.

To understand what happens beyond this point, we need to wait for the results of the ASCEND trial. However, this trend may suggest a unique efficacy profile of rocatinlimab distinct from existing drugs.

The ASCEND trial is designed to evaluate long-term treatment continuation, extended dosing intervals, and off-treatment effects, so we expect it to further clarify the characteristics and benefits of rocatinlimab.

Longitudinal change of T cell number after rocatinlimab treatment



Rocatinlimab Specifically Reduced OX40+ T Cells but Not Conventional T Cells* Over 24 Weeks

*Conventional T cells defined as CD4+ T cell that is not a T regulatory cell; conventional T cells include effector and memory cells.
CD, cluster of differentiation; D, Day; PBO, placebo; ROCA, rocatinlimab; W, Week.

Rocatinlimab is currently under clinical investigation. Its efficacy and safety have not been evaluated by any health authority.

I have explained that rocatinlimab has a mechanism that reduces pathogenic T cells, and this data supports that finding.

Rocatinlimab did not affect the total number of CD4-positive T cells, but it was confirmed that it reduced the number of CD4-positive cells expressing OX40 within that population.

Safety Analysis

Safety Analysis Set	ROCA 300 mg Q4W N = 544[a] %	PBO N = 180[b] %
TEAEs[c]	**68.4**	**63.3**
Mild	28.1	16.1
Moderate	36.8	38.9
Severe	3.5	8.3
Serious adverse events	**1.8**	**4.4**
Fatal adverse events	**0**	**0**
TEAEs leading to discontinuation of IP	**2.6**	**2.8**
Serious	0.2	1.1
Nonserious	2.4	1.7
TEAEs ≥ 4% in Any Treatment Group		
Dermatitis atopic	19.1	26.7
Pyrexia	10.3	1.1
Nasopharyngitis	8.8	11.7
Headache	7.2	3.9
Upper respiratory tract infection	6.3	3.3
Chills	6.1	1.1
COVID-19	4.0	1.1
Aphthous ulcer	4.0	0.6

Pyrexia and chills were predominantly reported and resolved within 48 hours after first dose of IP

[a]Coded using Medical Dictionary for Regulatory Activities version 27.0. [b]One patient in the PBO group received one dose of ROCA at Week 8 in error and thus was included in the ROCA group for safety analyses. [c]Two patients in the PBO group did not receive any IP and were excluded from the safety analyses.
PBO, placebo; Q4W, every 4 weeks; ROCA, rocatinlimab; TEAE, treatment-emergent adverse event.

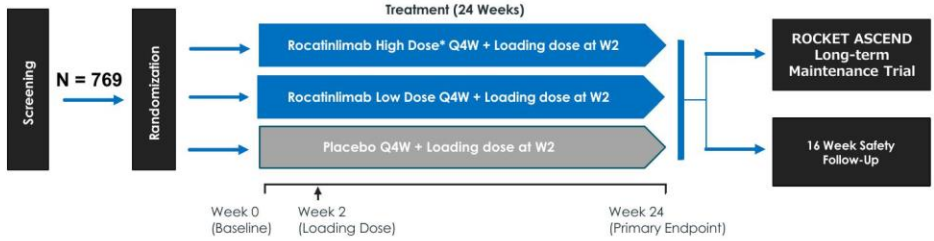
Rocatinlimab is currently under clinical investigation. Its efficacy and safety have not been evaluated by any health authority.

The safety profile of rocatinlimab in this trial was generally consistent with what was observed in the previous Phase IIb trial.

Among adverse events observed in more than 5% of patients in the rocatinlimab group, the most common were fever, chills, and headache. However, fever and chills were reported mainly after the initial dose of the drug and resolved within 48 hours.

That concludes the summary of the HORIZON trial presentation at the conference.

ROCKET-IGNITE Topline Efficacy



Primary Endpoints	ROCA Higher Dose		ROCA Lower Dose	
	%	Difference from PBO (p-value)	%	Difference from PBO (p-value)
EASI-75	42.3	29.5 (p<0.001)	36.3	23.4 (p<0.001)
vIGA-AD 0/1	23.6	14.9 (p<0.001)	19.1	10.3 (p=0.002)
rIGA-0/1	22.7	14.4 (p<0.001)	16.3	8.0 (p=0.01)

ROCKET-Ignite met its co-primary endpoints and all key secondary endpoints, achieving statistical significance for both rocatinlimab doses versus placebo.

*The higher rocatinlimab dose used in IGNITE and SHUTTLE was identical to the dose used in HORIZON.

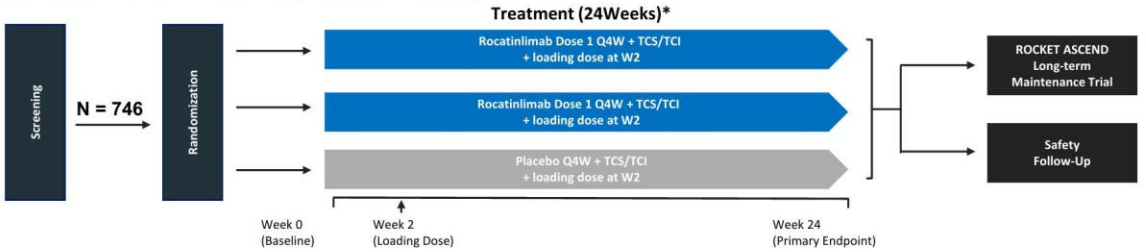
Rocatinlimab is currently under clinical investigation. Its efficacy and safety have not been evaluated by any health authority.

Next, I will introduce the top-line data from the IGNITE trial, which was included in the press release.

Like the previous trial, the IGNITE trial set its eligibility criteria for patients who were unresponsive to topical treatments. This trial included patients with a history of biologic treatment or systemic JAK inhibitor therapy and targeted adults with moderate to severe atopic dermatitis. A total of 769 patients participated.

Rocatinlimab is a 24-week, double-blind, randomized, placebo-controlled trial and administered every four weeks at two doses. As shown here, this trial met all primary and secondary end points, including EASI-75, vIGA-AD 0/1, and rIGA-0/1. Both dose levels demonstrated statistically significant differences compared to the placebo.

ROCKET-SHUTTLE Topline Efficacy



Primary Endpoints	ROCA Higher Dose		ROCA Lower Dose	
	%	Difference from PBO (p-value)	%	Difference from PBO (p-value)
EASI-75	52.3	28.7 (p<0.001)	54.1	30.4 (p<0.001)
vIGA-AD 0/1	26.1	13.8 (p<0.001)	25.8	13.5 (p<0.001)
rIGA-0/1	23.3	11.5 (p<0.001)	22.7	10.9 (p=0.002)

ROCKET-Shuttle met its co-primary endpoints and all key secondary endpoints, achieving statistical significance for both rocatinlimab doses versus placebo.

*The higher rocatinlimab dose used in IGNITE and SHUTTLE was identical to the dose used in HORIZON.

Rocatinlimab is currently under clinical investigation. Its efficacy and safety have not been evaluated by any health authority.

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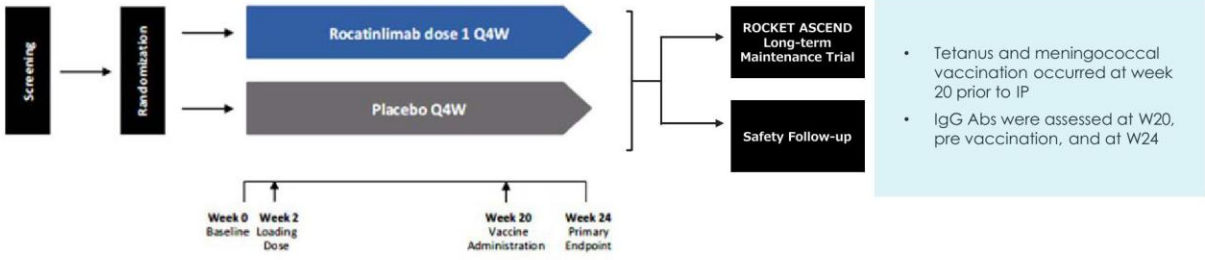
Next is the ROCKET-SHUTTLE trial.

This trial evaluated two dose levels of rocatinlimab in combination with topical steroids or topical calcineurin inhibitors. The study used the same primary end points as the IGNITE trial and included 746 adult patients.

At week 24, both dose levels maintained statistically significant differences compared to the placebo, achieving primary end points, such as EASI-75, vIGA, and rIGA, as well as key secondary end points.

ROCKET-VOYAGER Topline Results



- Tetanus and meningococcal vaccination occurred at week 20 prior to IP
- IgG Abs were assessed at W20, pre vaccination, and at W24

The VOYAGER study successfully demonstrated that rocatinlimab does not interfere with responses to tetanus and meningococcal vaccinations.

Rocatinlimab is currently under clinical investigation. Its efficacy and safety have not been evaluated by any health authority.

Finally, we have the ROCKET-VOYAGER trial.

This study was conducted to evaluate whether rocatinlimab dosing affects the immune response to tetanus and meningococcal vaccines.

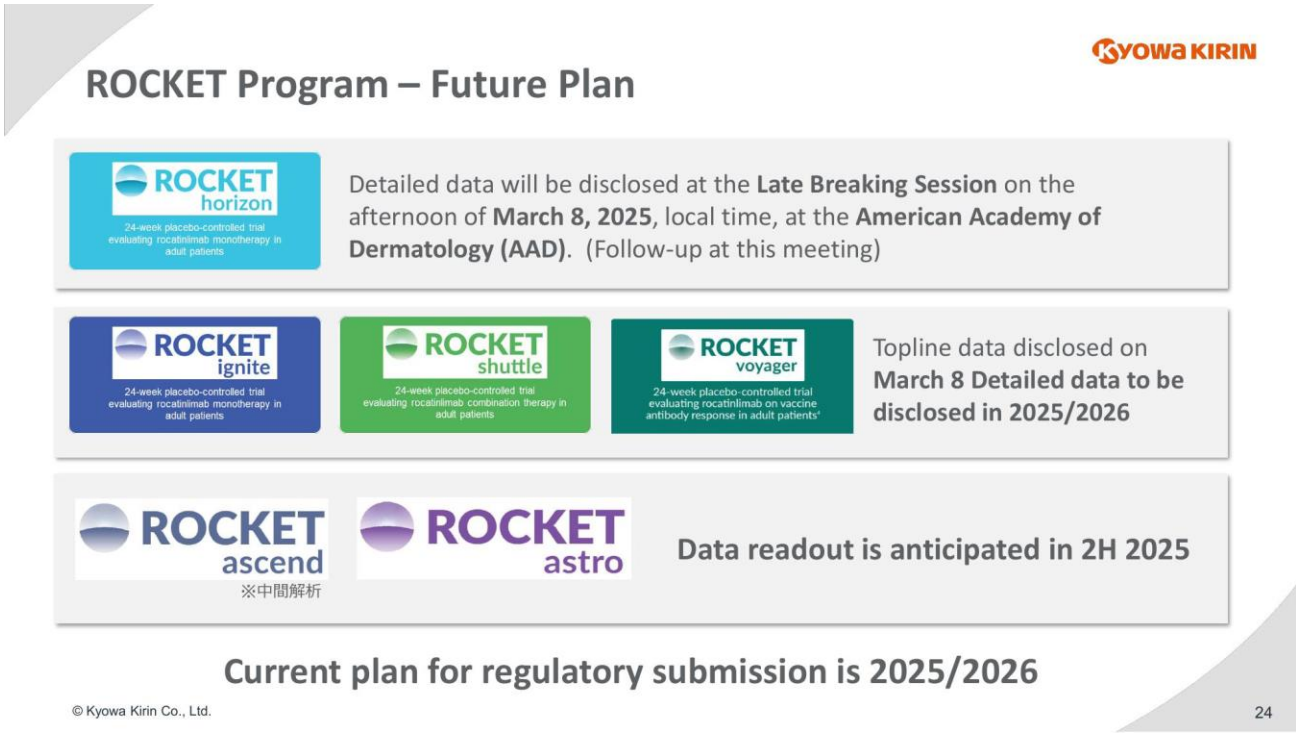
Although we are not presenting detailed data here, the study confirmed that rocatinlimab does not interfere with the immune response to tetanus or meningococcal vaccines.

Here, I have summarized the key points of the trials I explained today.

In summary, there are two main points.

Across the four trials, which included a total of over 2,400 adult patients with atopic dermatitis, all primary and secondary end points were achieved.

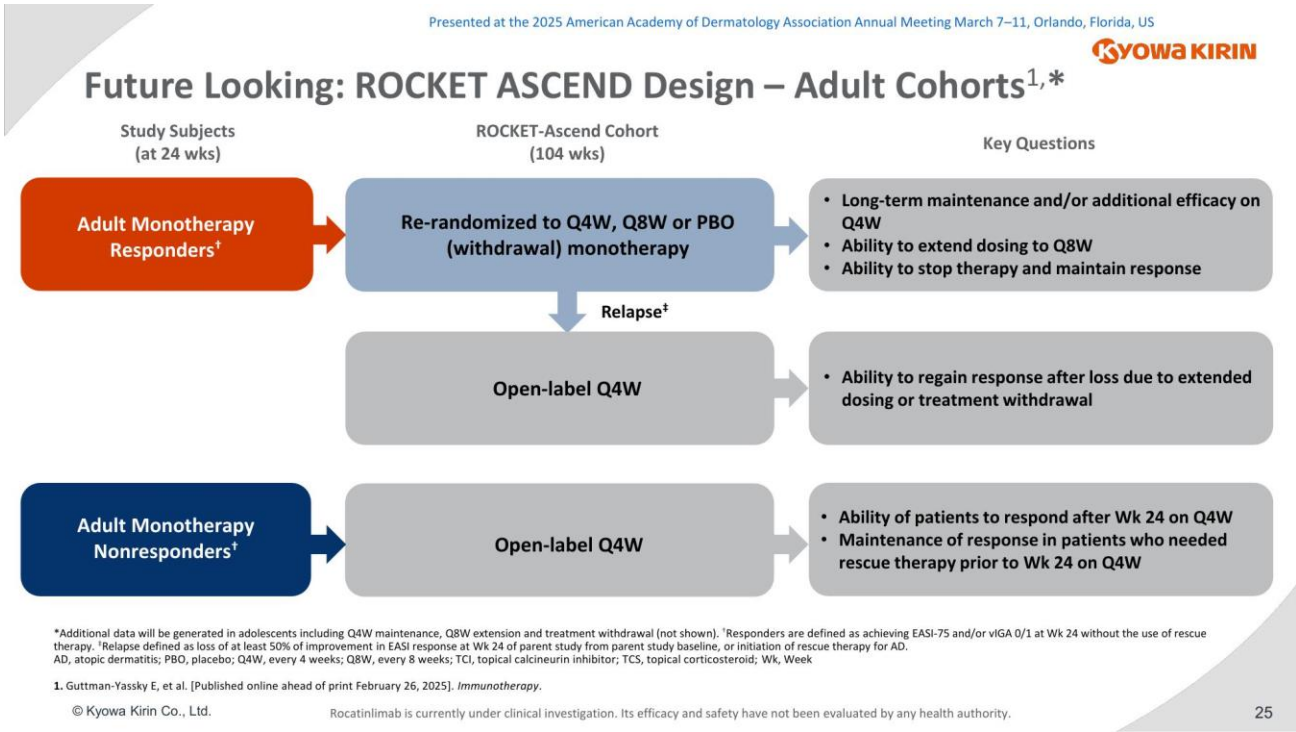
Among adverse events observed in more than 5% of patients in the rocatinlimab group, the most common were fever, chills, and headache. However, fever and chills were reported mainly after the initial dose of the drug and resolved within 48 hours. Additionally, while the incidence was less than 1%, cases of gastrointestinal ulcers were observed at a higher rate in the rocatinlimab group than in the placebo group.



Here are some of our upcoming events.

For the IGNITE trial, of which its top-line data was published on March 8, we plan to disclose detailed data from 2025 to 2026.

Additionally, an interim analysis of the ASCEND trial, which is designed for long-term evaluation, and the ASTRO trial, which focuses on long-term evaluation in adolescent patients, is expected to have a data readout in H2 of 2025.



Now, I will briefly explain a part of the ASCEND trial design using the next slide.

Here is the flowchart of the ASCEND trial.

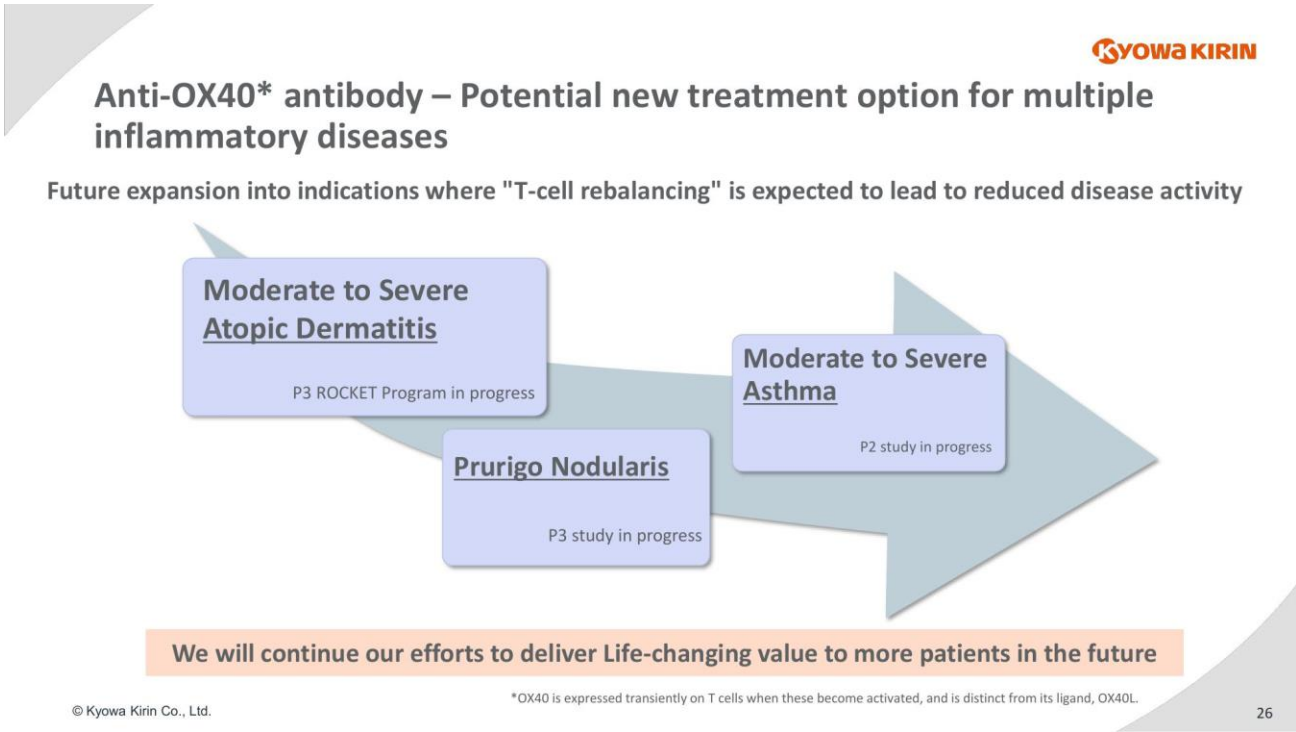
First, the upper section shows patients who responded to treatment in previous trials, such as HORIZON and IGNITE. These patients will be randomized again in the ASCEND trial and assigned to receive dosing every four weeks, dosing every eight weeks, or a placebo. The effects will then be reevaluated under double-blind conditions. If disease relapse occurs, the patients will move to the lower section of the chart.

For patients who were assigned to the placebo group and had their treatment discontinued, we will examine what happens when treatment is reintroduced after relapse. Various scenarios are expected, such as cases where relapse occurs at week eight. In these situations, we plan to further verify the treatment's effects as a backup to the evaluations conducted in the upper section.

Additionally, patients who were initially classified as non-responders due to the use of rescue therapy will continue treatment every four weeks, as shown in the bottom section.

Even for patients who did not respond in the HORIZON trial, the trial is designed to evaluate the potential effectiveness of continued rocatinlimab treatment.

By integrating the four trials introduced today with the data from the ASCEND trial, we aim to further clarify the effectiveness of rocatinlimab across a diverse range of patient conditions.



Finally, I will introduce the development status of rocatinlimab targeting the receptor-type molecule OX40 in indications beyond atopic dermatitis.

We believe that the T-cell imbalance I mentioned earlier is present in various inflammatory diseases and that rocatinlimab may be effective in these conditions.

Among them, we are currently conducting global Phase III trials for prurigo nodularis. A Phase II study is also underway for moderate to severe asthma.

We will continue our efforts to deliver life-changing value to more patients.

That is all for my presentation today.

Question & Answer

Moderator [M]: We will move on to the question-and-answer session.

Yamaguchi [Q]: Good morning. I am Yamaguchi from Citigroup Global Markets.

The first question is a simple one. The simple difference between the placebo and EASI is 19 for HORIZON but others are much higher, almost in 30. The backgrounds of each trial are different and so are the doses. I wonder what are the reasons for this significant difference in EASI-75, although it depends on factors. Is it background or rescue treatment? I would appreciate if you can comment on it.

Yamashita [A]: We are not sure of the details until we have analyzed the situation thoroughly. We introduced rescue therapy in this HORIZON. Rocatinlimab appears to act somewhat more slowly compared to cytokine blockers.

Even after starting administration, the onset of efficacy was delayed, which may have led to the early use of topical rescue therapy, as some may have felt that the treatment was not working. It is unclear how this information was conveyed in later trials, but during the course of this study, some differences were observed in trial settings.

Moving forward, we intend to conduct further analysis and consideration of this aspect.

Yamaguchi [Q]: A quick addition. Regarding the inclusion of rescue therapy, whenever rescue therapy is used in all current trials, the patient is classified as a non-responder, correct? This has been consistently applied since the Phase II trials, hasn't it?

Yamashita [A]: Yes, that's correct.

Yamaguchi [Q]: So, your view has not changed, but you think the impact may have been significant this time.

Yamashita [A]: Yes, that's right. When the trial expanded from Phase II to Phase III, it included patients from more countries and a wider range of medical institutions. It is common for treatment practices to be somewhat inconsistent in such cases, and we believe that may have contributed to the situation.

Yamaguchi [Q]: One more question. You have previously explained the difference between OX40 antibodies and OX40 ligand antibodies. Just to confirm once again, when targeting OX40, your drug can attack pathogenic T cells. However, when targeting the ligand, it can still attack T cells and circulating ligands, but it cannot attack pathogenic T cells. Is my understanding correct?

Yamashita [A]: Yes, that's right. I don't think there is that much difference conceptually in terms of the OX40 ligand and OX40 interaction this time in terms of blocking and suppressing OX40 signaling.

However, our rocatinlimab has the effect of attaching to OX40-expressing cells, and this antibody has ADCC activity, reducing the number of bound cells by what might be called a cellular killing function. This cannot be achieved by OX40 ligand antibodies.

Yamaguchi [M]: Thank you. That is all.

Muraoka [Q]: Thank you very much. I am Muraoka from Morgan Stanley.

I have a question about something that was not included on the slides. Dupilumab is thought to be less effective or weaker in improving symptoms on the face and hands. This was not addressed in the HORIZON details, but was there any update?

Yamashita [A]: We are not able to disclose that part yet. We can say at this moment that Phase II has shown its effectiveness in such areas.

Muraoka [Q]: Is it possible that findings not included in this detailed presentation at AAD will be released in the future?

Yamashita [A]: As I mentioned earlier, with the inclusion of the ASCEND trial, we will not only look at the results up to 24 weeks, but also examine how the drug performs beyond that. Additionally, by varying the dosing intervals and dosage levels, we expect to gather a large amount of data on the differences that emerge.

By comparing these outcomes, we believe we can gain a clearer understanding of the drug's characteristics. We believe that more data will be available.

Muraoka [Q]: Rather than looking at symptoms on the face and hands in individual trials like HORIZON, it may be that these aspects will become clearer, may be with the interim analysis of ASCEND, as the N numbers increases. In other words, we should expect more insights in the fall. Is that correct?

Yamashita [A]: Yes, that's correct. This time, we are only introducing the important part in terms of getting regulatory approval. Naturally, the drug's characteristics is an area of interest for both you and us. Once we have sufficient data, we will be able to provide a well-grounded message about the drug's characteristics.

Muraoka [Q]: One more point, I believe it was on slide 16. Over time, the number of patients in the darker-colored EASI range, specifically EASI-90 to EASI-100, has been steadily increasing. On the other hand, the proportion of patients in the EASI-75 to EASI-89 range has remained unchanged. This suggests that the number of patients responding exceptionally well continues to increase over time and that the treatment effect has not yet plateaued, which I find quite interesting.

Thinking ahead, how do you plan to incentivize physicians to adopt this drug given its characteristics? It does not work immediately, and the percentage of patients requiring rescue therapy is somewhat high. For reference, dupilumab's rate was around 21%, meaning that more patients may need rescue therapy. However, as treatment continues gradually, the number of patients achieving EASI-90 to EASI-100 increases.

While I understand this concept, it is difficult to imagine how to effectively convey this to physicians and patients. Could you provide a more concrete explanation?

Yamashita [A]: One point we introduced today is the slide about flare-ups.

Scientifically, we anticipate that rocatinlimab may reduce memory T cell formation and activation. If this effect is realized, it could mean that the therapeutic benefits are maintained over the long term. Or, if memory T cells are eliminated, there may be a possibility that patients can maintain a good condition even with extended dosing intervals or after discontinuation of treatment.

The steady increase in the percentage of patients achieving EASI-90 and above is something we find very intriguing to know what is actually happening there. If this drug demonstrates characteristics distinct from cytokine blockers or JAK inhibitors, it could lead to better relapse prevention and long-term disease control.

Muraoka [Q]: In other words, the drug works exceptionally well with prolonged use. However, in the short term, more patients may require rescue therapy, so it becomes important to convince physicians to continue treatment patiently.

Yamashita [A]: Yes. That is why we introduced concepts such as T-cell imbalance and rebalance today. If the drug can truly normalize a root cause, it may lead to the ability to modify the disease. This is the concept behind our expectations for this treatment's effects.

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

Barker [Q]: I'm Stephen Barker from Jefferies. Thank you very much.

On page 15, I understand that patients who receive rescue are classified as non-responders, but I would like to know if a similar analysis was conducted in the SOLO1 and SOLO2 trials for Dupixent. If so, could you please share the results?

Yamashita [A]: I am very sorry. We are not prepared to answer to your question at this time.

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

Wakao [Q]: My name is Wakao from JPMorgan. Thank you for taking my questions.

First, I would like to know about the results of the SHUTTLE trial. Looking at the placebo-adjusted EASI-75 levels, they do not seem very different from the EASI-75 levels observed in IGNITE or in HORIZON, which also included non-responders.

I thought adding steroids should enhance efficacy normally, but that effect does not seem to be apparent. How do you interpret this data?

Yamashita [A]: Thank you for your question.

We do see a considerable additive effect, but I understand your point that the numbers could have been even higher.

Earlier, I briefly mentioned the patient enrollment process. One factor is that the eligibility criteria included patients who were already unresponsive to topical steroids. Additionally, many participants had undergone systemic therapies. Given this, I feel that the patient backgrounds in this trial were quite different.

However, beyond this, anything I say would be speculative, so it is difficult to provide a definitive answer without further analysis.

Wakao [Q]: My second question overlaps somewhat with Muraoka's earlier question. My understanding is that the drug has a slow onset of efficacy, but it is expected that efficacy will strengthen over time. Since it is a new mechanism, more findings will emerge, including from ASCEND.

In this context, is ASCEND alone sufficient as data when considering marketing? Since this is a very new mechanism, I expect many unexpected findings to emerge. I wonder it would be necessary to conduct more marketing-focused trials, similar to Phase IV studies. If there are already any considerations on this at this point, I would like to know.

Yamashita [A]: I don't have any details to disclose on that point yet. We will naturally consider such possibilities in the future. For now, it is crucial for ASCEND to clearly identify the characteristics that distinguish this drug.

Beyond just the interim analysis, we will continue to follow up after regulatory submission. Depending on the situation, we may further investigate these aspects or perhaps look into its effects on new patient populations. That said, at this moment, we are not in a position to disclose any details.

Wakao [Q]: So, as you mentioned earlier, the key message for now is whether the drug can secure regulatory approval. At the same time, when considering the long-term outlook, it seems like building up sales will take a considerable amount of time. Is that also your perspective?

Yamashita [A]: As I have been saying, if the characteristics of this drug become clearer, it may align with what we refer to as unmet medical needs. Given the diverse nature of atopic dermatitis patients, this drug could be a good fit for many of them, and I think there is a possibility that it will generate considerable interest and be widely used. I also think that we can accumulate a substantial amount of real clinical data in such a situation.

To reiterate, it is important to clearly define the drug's characteristics and further strengthen the data supporting it. Ideally, we hope this will be recognized as a highly attractive drug and generate widespread interest.

Wakao [M]: I understand very well. Thank you for taking my questions. That is all.

Wada [Q]: I am Wada from SMBC Nikko Securities. Thank you for taking my questions.

I would like to ask about the background behind the dosing regimen, the data points, and the decision to set the observation period at 24 weeks. The dosing this time was 300 mg.

In Phase IIb, I believe doses of 150 mg and 600 mg were evaluated with Q4W dosing. Also, from my understanding, IGNITE uses a high dose of 600 mg. Could you share why and how these doses were chosen?

Additionally, regarding the data points, Phase II had a 16-week observation period, whereas Phase III extends it to 24 weeks. Looking at slide 16, which shows EASI-75 and EASI-90 data, it seems that the drug's efficacy appears later compared to existing treatments.

Given that, I understand why 24 weeks was chosen, but you do not know yet when the drug reaches its peak effect based on the long-term analysis from Phase II? I would appreciate your comment on it.

Yamashita [A]: Thank you for your question.

First, regarding dose setting, Phase II was conducted with around four different treatment arms, varying both the dosing period and the dose, making the study somewhat complex. In this context, we ran simulations and determined that 300 mg Q4W would likely be a key candidate and proceeded with it. With that as the baseline, IGNITE was designed to test two different dose levels.

As for the 24-week period, we believe that by this time point, we can sufficiently demonstrate that the drug is effective to some extent. As you mentioned, Phase II data suggested a long-acting effect, which is why we designed ASCEND to be evaluated as a set with this study to provide long-term data. The actual results will need to be awaited.

Regarding to your question whether Phase II provided insights into the long-term effects, since it was still in the Phase II trial, follow-up was discontinued partway through. In hindsight, we think it would have been beneficial to collect longer-term data, but this trial is now designed to address that area.

Wada [Q]: I have asked about this before, but my understanding is that one of the major issues with DUPIXENT and other existing biologics is the recurrence of flare-ups, as you illustrated on the slides. Many patients struggle to stay in remission, which is a key concern.

Have you conducted any estimates for how many patients fall into this category? Do you have any data on this?

Yamashita [A]: We are not in a position to estimate it yet. As you pointed out, we do believe there is an unmet medical need in this area. It may be possible to make a rough estimate.

However, our approach is more focused on identifying the segments or patients with the backgrounds that align best with rocatinlimab's characteristics. Once we define these patient backgrounds, we will consider how many patients fall into this category and what treatment approaches are needed.

At this point, we do not have a rough estimate, as mentioned in your question.

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

Moderator [M]: Thank you very much.

The next question is from Mr. Hashiguchi of Daiwa Securities. Mr. Hashiguchi, please ask your questions.

Hashiguchi [Q]: I am Hashiguchi. Thank you for taking my questions.

Regarding the slide on page 17, I would like to hear your thoughts on what can be inferred about the long-term safety. On the right side, OX40-positive T cells continue to decrease over time, whereas on the left side, the total number of CD4-positive cells remains unchanged.

Does the left side represent only OX40-negative cells, or is it that while OX40-positive cells are decreasing, the number of OX40-negative and CD4-positive cells are increasing? As a result, there is no overall change in the total CD4-positive cell count? I would like to understand how to interpret this and what considerations can be made from this finding.

In addition, fever and chills, that's on the next page. They were reported mainly after the initial dose. What do you think is the cause of this? If OX40-positive cells are contributing to these adverse events, the difference from the placebo should continue to widen, meaning these adverse events could be observed beyond the first dose. I would like to hear your thoughts on why these events were concentrated only after the first administration.

Yamashita [A]: Thank you for your question.

First, regarding the figure on page 17, the left side shows the total CD4-positive T cells. I believe this data includes OX40-positive.

The key difference here is that the population sizes are entirely different and the numbers are completely different. When we talk about CD4-positive T cells, they make up about 30% to 50% or half of all T cells, meaning we are looking at a significant proportion of the body's total T cell count. If this number were to fluctuate dramatically, it would indicate a substantial impact on the immune system.

On the other hand, OX40, CD4 T cells are much smaller in number compared to the total CD4 population. Despite being a small subset, they are highly active, producing large amounts of cytokines. The right-side figure shows how they are reduced.

Regarding your second question about the transient reaction of fever and chills, it is somewhat similar to what is commonly observed as so-called infusion reactions when administering biologics. You specifically mentioned OX40's long-term effects and their relation, but I believe they are unlikely to be involved in this reaction. Instead, I suspect this is a temporary immune response triggered by the introduction of a new biologic, though it is unclear whether it occurs because it targets OX40 or not.

I think it is possible that the sudden introduction of a large amount of new proteins causes a temporary response. Then, this reaction seems to be effectively managed and disappears quickly.

Hashiguchi [M]: Thank you very much. That is all.

Ueda [Q]: My name is Ueda from Goldman Sachs.

My first question is about how much we should consider patient backgrounds when comparing the results of the Phase II trial and the HORIZON trial. At the beginning of your explanation, you suggested that differences in treatment practices may have had a significant impact.

I assume there were also differences in factors such as prior biologic treatment history and racial distribution between Phase II and HORIZON. Do you think these factors may have influenced the results? If there are any insights from subgroup analyses, could you share them?

Yamashita [A]: Thank you for your question.

We do not yet have data available to present, but as I briefly mentioned earlier, Phase IIb was conducted around 2018. At that time, JAK inhibitors were not yet available, and DUPIXENT was just launched.

By the time we conducted the HORIZON trial, these treatments had become widely used. Although our eligibility criteria included patients who were unresponsive to topical steroids or topical treatments, many of them had already moved on to biologics or JAK inhibitors or systemic treatments, such as systemic steroids, when topical treatments failed.

We believe the proportion of patients previously treated with biologics and JAK inhibitors has significantly increased in systemic treatments. As previously mentioned, T cells send out various signals, and when new cytokine blockers or JAK inhibitors disrupt these pathways, how this disturbance occurs and what kind of disordered state results can vary widely from patient to patient.

Because of this, we believe that the proportion of patients with more complex treatment backgrounds was higher compared to Phase IIb.

That is about all I can answer now.

Ueda [Q]: Second, I would like to ask about safety. In this trial, fever and chills were observed only after the initial dose. Aside from that, were there any aspects of the safety profile that could be a concern in real clinical practice?

Earlier, it was mentioned that the number of OX40-positive cells is relatively low. However, given the increase in upper respiratory infections and COVID-19, have there been any actual cases where these infections have been affected? That said, since this treatment is for atopic dermatitis, would this not be considered a major concern? I would like to hear your thoughts on how this is perceived in clinical practice.

Yamashita [A]: I am not fully aware of how this has been received in clinical practice, but based on the incidence rates of adverse events, I do not believe infections like the ones you mentioned are a level of concern.

We plan to further investigate rocatinlimab's role in immune regulation and assess the impact of treatment. However, at this stage, I have not heard of any signs of problems.

Ueda [M]: Understood. That's all from me. Thank you for taking my questions.

Matsubara [Q]: I am Matsubara from Nomura Securities. Thank you for taking my questions.

I would like to know your company's current position on page 15. My first question is about patients who received rescue therapy. In the placebo group, there was not a significant difference between EASI-75 and vIGA-AD. I would like to understand this area.

My second question is regarding the additional effect of rocatinlimab administration. You have stopped this for now, but was the observed improvement purely due to rocatinlimab itself? Or is there an add-on effect with rescue therapy? Can you tell us your view?

Looking at the placebo numbers, I don't think there's a significant improvement in the Rescue Use As Observed compared to the Primary Analysis. For EASI-75, it's 13.7 versus 15.8, and for vIGA-AD, it remains at 6.6 for both. I'd like to ask about two points: first, the background as to why the rescue use didn't have much effect in the placebo group, and second, whether there's an additional effect from rocatinlimab, or if these results are solely due to rocatinlimab's effect on its own.

Yamashita [A]: Thank you very much.

First, regarding the placebo group, the patients included in this trial were already unresponsive to topical treatments. Since most rescue therapies involved topical treatments, it is likely that these patients did not see much effect, even with rescue therapy. This is one reason.

Then again, some patients are receiving biologic treatments, and minor improvements may have been seen in them.

As for rocatinlimab, we expect that its effect is quite significant. As mentioned earlier, since the onset of efficacy is somewhat delayed, some patients may have used rescue therapy in the early stages based on their condition. I think it may be that after some time, rocatinlimab started to take effect for those patients, and the treatment response improved.

Matsubara [M]: I understand. Thank you for taking my questions.

Wakao [Q]: I just have one thing to confirm regarding how to interpret the presence or absence of prior treatment history in the latest results compared to the initial ROCKET-HORIZON results.

When the initial HORIZON results were released, I understood that prior biologic treatment history was suggested as one possible factor influencing the outcome and was a key point of discussion.

However, based on the results this time, rather than prior biologic treatment itself being a major factor, it seems that the way patients were enrolled amid evolving treatment options did not align exactly with your initial expectations. In other words, I interpreted it as prior biologic use not having a significant impact on treatment efficacy. Is my understanding correct?

Yamashita [A]: I would like to refrain from giving an answer at this time, as some of the analysis is still in progress.

In discussing prior treatment history and why there was a difference between the Phase II trial and HORIZON, as I mentioned earlier, the treatment landscape has changed over time, and the content of prior treatments has also shifted significantly. That is what we have assumed so far.

That possibility still remains, and as we assess rocatinlimab's efficacy, we would like to continue discussing it comprehensively, including the ASCEND trial, as I have mentioned earlier.

Wakao [Q]: In Phase II, prior treatment history was around 10% to 16%, and the prior biologic treatment history is not significantly higher even in Phase III. So, I assume you think it may not be a major concern. We still don't know the impact of biologics, but it is not necessarily the only factor at play, is it?

Yamashita [A]: Well, when considering factors like the duration of prior treatment, simple percentage comparisons may not be enough. We think these aspects also need to be examined further.

Wakao [M]: I understand very well. That is all.

Yamaguchi [Q]: May I confirm one thing? Thank you.

I think Sanofi has mentioned that suppressing the immune system could lead to side effects like chills and other symptoms. Based on today's discussion, would it be correct to say that this is not the case? Regarding nausea and chills, they seem to occur initially, like an infusion reaction, and then subside. Do you think your company can demonstrate that these symptoms are not due to continuous immune suppression?

Yamashita [A]: Thank you very much.

I am not sure what exactly Sanofi has stated, but as I mentioned earlier, these symptoms seem to be transient. We also believe firmly that suppressing OX40 is not associated with events related to its long-term effects.

Yamaguchi [M]: I think you should emphasize this point. That is all. Thank you.

Yamashita [M]: Thank you very much.

Moderator [M]: Thank you very much.

This concludes the online presentation about rocatinlimab.

Thank you very much for your participation today. Thank you for your continued support of Kyowa Kirin.

[END]